VARIOUS COLORS OF RESILIENCE

IN THE FACE OF DISEASE-RELATED CHALLENGES

Sabine E.I. van der Laan

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CHAPTER 1

GENERAL INTRODUCTION

PART I: RESILIENCE IN THE FACE OF INCREASING PREVALENCE OF CHRONIC CONDITIONS IN YOUTH

Increasing prevalence of chronic conditions among youth

In recent decades, the prevalence of chronic conditions among youth has substantially increased: nowadays, one in four individuals under the age of twenty-five face one or more chronic conditions [1,2]. A chronic condition is defined as a clinically established diagnosis with persistent or recurring symptoms lasting more than three to six months or occurring more than three times per year, requiring long-term use of medications, treatments, or supportive devices [1]. Among Dutch youth aged 0-25 years, the five most common chronic conditions are: asthma (4.6%), anxiety and mood disorders (4.1%), attention deficit hyperactivity disorder (3.6%), stomach ache/fecal issues (2.8%), and eczema (2.8%) [1]. Youth living with a chronic condition often experience physical and psychosocial challenges, due to symptom distress, demanding therapeutic regimens, periods of hospitalization, uncertainty about the future, social exclusion, and the inability to fully participate in school or society [3–7]. Moreover, youth with a chronic condition are more likely to experience depressive symptoms and behavioral problems, compared to their healthy peers [8,9]. Adolescents, in particular, might be susceptible to these challenges, as adolescence is not only marked as a time period in which numerous mental health disorders first emerge, but also as a formative period for neurocognitive and social development [10–12].

A paradigm shift away from disease-focused towards health-focused research

As the prevalence of chronic conditions is increasing, it is important to rethink how health and disease are conceptualized. The definition of health adopted by the World Health organization (WHO) in 1948 and still in use today is that "health is a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity" [13]. This definition seems, nowadays, to be outdated and contributes to medicalization: the requirement for complete health would render most individuals unhealthy most of the time and would label people with chronic diseases and conditions as chronically ill. This labeling may diminish the ability to adapt to the evolving physical, emotional, and social challenges introduced by the chronic condition, thereby undermining people to live their lives with a sense of fulfillment and wellbeing despite the presence of chronic condition or disability [14]. For these reasons, Huber et al. proposed to change the WHO's definition of health to a new dynamic concept, namely "the ability to adapt and self-manage in the face of social, physical and emotional challenges" [14]. This new concept initiated a paradigm shift away from disease-focused towards health-focused care [14,15]. Paralleling this shift, in pediatric healthcare and research, there has been increasing attention to resilience of youth with a chronic condition. However, rather than painting a consistent pattern of resilience, research highlights that resilience in adolescents with chronic conditions has many facets.

The concept of resilience

Yet, what exactly does the term "resilience" encompass? Resilience is a multifaceted concept that takes on varying forms depending on the scientific discipline in which it is explored. To illustrate: in material sciences, resilience is commonly defined as the material's capability to absorb and store energy [16]. When approached from a biological perspective, a resilient microbiome has the capacity to restore its original state following a disruptive event, such as the introduction of antibiotics [17]. In medical sciences, physical resilience is often thought of as "the ability to physically recover or optimize function in the face of disease or age-related losses" [18]. In the field of psychology, resilience is often referred to as the phenomenon of maintaining or regaining mental health after or during exposure to an adversity [15]. This thesis focuses on psychological resilience, referred to as 'resilience' throughout. Through the integration of resilience research into pediatric healthcare, it holds the promise of providing valuable insights for preventing the deterioration of mental health in youths with chronic conditions and identifying potential targets for treatment and interventions to enhance mental health.

Over the years, however, resilience researchers have portrayed resilience in various colors [15]: some have regarded resilience purely as a trait [19,20], others have described it as a complex combination of multiple factors [21,22], including various traits, skills, beliefs, and behaviors. Moreover, resilience is not only conceptualized as a dynamic process [23], but also as an ultimate outcome [15]. These different conceptualizations of resilience have led to a variety in definitions, study designs, and measurements of resilience, making it challenging to compare findings of resilience research [15]. Also within the medical field, these different colors of resilience have impeded comprehensive analyses and implores us to delve deeper into the intricate concept of resilience [3,24]. An overview of resilience definitions and measurement in the pediatric research field is needed to gain clarity, aiding in recommendations for adopting a specific definition and using particular measurement tools.

Various adversities in relation to chronic conditions

Given that resilience only emerges during or after the experience of an adversity, it is logical to conclude that resilience cannot be measured in the absence of such adversity. Therefore, resilience researchers within the medical field should consider the specific context and severity of the experienced adversity. In pediatric healthcare, there is a wide range of adversities related to chronic conditions, including -but not limited to- receiving a diagnosis of a severe disease, feeling or appearing different from peers due to the condition, enduring restrictive symptoms like pain or fatigue, or encountering difficulties associated with treatment. Furthermore, some patients may view even positive opportunities, such as access to promising new treatments, as adversities, as these opportunities may contradict their previous identities, habits, or beliefs.

To better understand the various colors of resilience in adolescents with a chronic condition, this thesis investigates the impact of disease-related challenges on adolescent mental wellbeing through three distinct studies, each focusing on a specific disease-related challenge.

1. New challenges for people with cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR)-protein. In the Netherlands around 1600 people live with CF [25]. CF is characterized by dysfunction of multiple organs, including the lungs, pancreas, gastro-intestinal tract, the reproductive system, and sweat glands [26]. People with CF experience varying degrees of CF-related symptoms, with pulmonary manifestations being the most severe and progressive [27,28]. Aside from a reduced life expectancy, individuals with CF also face substantial comorbidities and undergo intensive treatments [29]. These factors significantly impact their mental and social wellbeing, daily functioning, identity and life goals [29].

The introduction of CFTR modulators, the first of which received approval in 2012, has marked a new era in the management of CF. They fundamentally altered the perception of CF from a life-threatening condition to a chronic condition characterized by improved disease manifestation and expected improved life expectancy [27,30]. Especially the triple combination of elexacaftor/ tezacaftor/ ivacaftor (ETI), which has been available in the Netherlands since January 2022 [31], significantly improves lung function and reduces pulmonary exacerbations [27,32]. Gaining access to ETI therapy is, therefore, considered a positive and major life event [33]. Unexpectedly, several case series reported that a subset of individuals experienced a decline in their mental health following initiation of ETI therapy [34–36].

Long term longitudinal studies systematically investigating changes in mental health after initiation of ETI are not available yet. Conducting longitudinal research is important to gain a clear picture of changes in mental wellbeing after ETI therapy. Moreover, it has the potential to identify subgroups that experience different changes concerning their mental wellbeing after ETI therapy.

2. The impact of having asthma on mental wellbeing during adolescence

In 2019, asthma was the most common chronic disease among Dutch youth aged 0-25 years (4.6%) [1]. The severity of asthma can vary greatly between individuals; for some people, asthma symptoms may be mild and infrequent, while for others, asthma symptoms can be severe, having a significant impact on their daily life. Especially during adolescence, asthma symptoms and disease control is variable over time [1,37] and as mental wellbeing generally decreases [38,39], making it more complex to investigate the impact of having asthma on mental wellbeing. Unfortunately, much of the current literature on the

association between asthma and mental wellbeing is cross-sectional in design, limiting the ability to draw inferences about the effect of asthma on mental wellbeing during adolescence [40–43].

3. The impact of self-reporting having a chronic condition on psychosocial functioning
Population-representative studies revealed that approximately 5% of adolescents aged 11 to 16 years reported having a chronic condition [44]. These adolescents reported poorer outcomes in a wide range of psychosocial wellbeing domains [44]. In contrast to the 5% prevalence of self-reported chronic conditions, based on healthcare records approximately 25% of the youth have been clinically diagnosed with at least one chronic somatic or psychiatric condition [1,45]. Youth with a physician diagnosed chronic condition generally report a significantly lower quality of life, are more prone to develop psychosocial problems, often show delays in achieving psychosocial milestones, and are less likely to be (financially) independent in young adulthood, compared to their healthy peers [1,46,47]. It remains unknown what the difference is between those who self-report their condition ('reporters'), and those who do not ('non-reporters'), in relationship to their clinical diagnosis and psychosocial wellbeing.

PART II: RESILIENCE IN THE FACE OF THE CORONAVIRUS DISEASE 2019 (COVID-19) PANDEMIC

In late 2019, in the second year of my PhD, a local outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan and rapidly spread to numerous countries worldwide [48]. The WHO declared a Public Health Emergency of International Concern on January 30, 2020, and officially labeled the outbreak as the Coronavirus Disease 2019 (COVID-19) pandemic on March 11, 2020 [49]. Governments, including in the Netherlands, implemented stringent measures to control the spread of the virus. Due to lockdown measures, such as school closures, quarantine and social distancing, millions of people worldwide faced unprecedented periods of social isolation and stress [48]. Many families, and children in particular, were affected in multiple ways; school closures disrupted the structure of daily life and social interaction for all affected children and adolescents, and resulted in parents having to juggle homeschooling and work [50]. At that time, numerous experts considered the pandemic and its associated measures as a significant threat to the mental health of young individuals and therefore underscored the need for empirical research focusing on the tracking mental wellbeing of youth to evaluate the effects of the pandemic [51–54].

Moreover, little was known about the effects of the pandemic on the mental wellbeing of youth with chronic conditions; a subgroup who faces more challenges and often has a lower mental wellbeing on average compared to their healthy peers [3–5,55]. Nonetheless, narrative insights from child and adolescent clinical practice suggested that due to the lockdown

measures, certain individuals with a chronic condition and their families experienced a reduction in and even an improvement in mental wellbeing due to the lockdown measures [56]. Researching differences in mental wellbeing between adolescents with and without chronic conditions could give us insights in who might function more resiliently during the pandemic.

A bit of context
The ongoing WHISTLER population-birth-cohort [68], which I coordinated at that time, had to be stopped due to the pandemic. However, by that point, we had already collected data on the mental wellbeing of 224 adolescents. We have continued the assessment of their mental wellbeing through online questionnaires throughout the first year of the pandemic. This provided the opportunity to respond to the experts' call and to actually investigate changes in the mental wellbeing of adolescents during the COVID-19 pandemic compared to before.

Through close collaboration between the WHISTLER cohort and the PROactive cohort [69] (which gathers data about psychosocial health of youth with a chronic condition, based at the Wilhelmina Children's Hospital), we were able to examine whether adolescents with or without a chronic condition exhibit greater resilience during the pandemic.

AIM AND OUTLINE OF THIS THESIS

To better understand the various colors of resilience in adolescents with a chronic condition and in adolescents during the COVID-19 pandemic, this thesis tracks their mental wellbeing before, during and/or after facing disease-related adversities. By gaining a deeper understanding of if and how adolescents adapt to these disease-related challenges, we can potentially mitigate future mental health problems among adolescents, especially those with chronic conditions.

The upcoming chapters will strive to address the knowledge gaps raised above.

Chapter 2 presents a scoping review focusing on the definition and measurement of resilience in youth with chronic conditions, including suggestions for optimizing the definition and measurement of resilience in future research. Building upon the insights gained from Chapter 2, **Chapter 3** introduces the study protocol for the Resilience Impacted by Positive Stressful Events (RISE) study, examining if and how mental wellbeing of people with CF changes after starting ETI therapy. The secondary objectives of the RISE study include, among others, investigating underlying biological and psychosocial factors associated with a change in mental wellbeing of people with CF after starting ETI therapy. Moreover, Chapter 3 describes in detail the study design and statistical methods of the RISE study. **Chapter 4** presents the key findings of the prospective longitudinal RISE study,

focusing on the observed changes in mental wellbeing following ETI therapy, including the identification of subgroups who may be more susceptible to mental health issues and should therefore be monitored more closely. Transitioning from a rare chronic disease among adolescents and adults to the most common condition in youth, I assess the impact of asthma on mental wellbeing and perceived general health during adolescence in **Chapter 5**. I investigate whether adolescents with asthma experience lower mental wellbeing and perceived general health compared to their peers without asthma. **Chapter 6** focuses on adolescents with a clinically defined chronic condition and examines differences in psychosocial wellbeing between adolescents who report having a chronic condition and those who do not report having a chronic condition.

Chapter 7 investigates changes in adolescent mental wellbeing following the implementation of lockdown measures, with a specific focus on gender differences and the association between COVID-19-related stressors and mental wellbeing. **Chapter 8** examines the trajectory of adolescent mental wellbeing during the first year of the pandemic and compares these levels with pre-pandemic data to gain insight into the timing and extent of the impact on mental wellbeing. **Chapter 9** delves into the comparison of mental wellbeing of adolescents with and without a chronic condition during the COVID-19 pandemic.

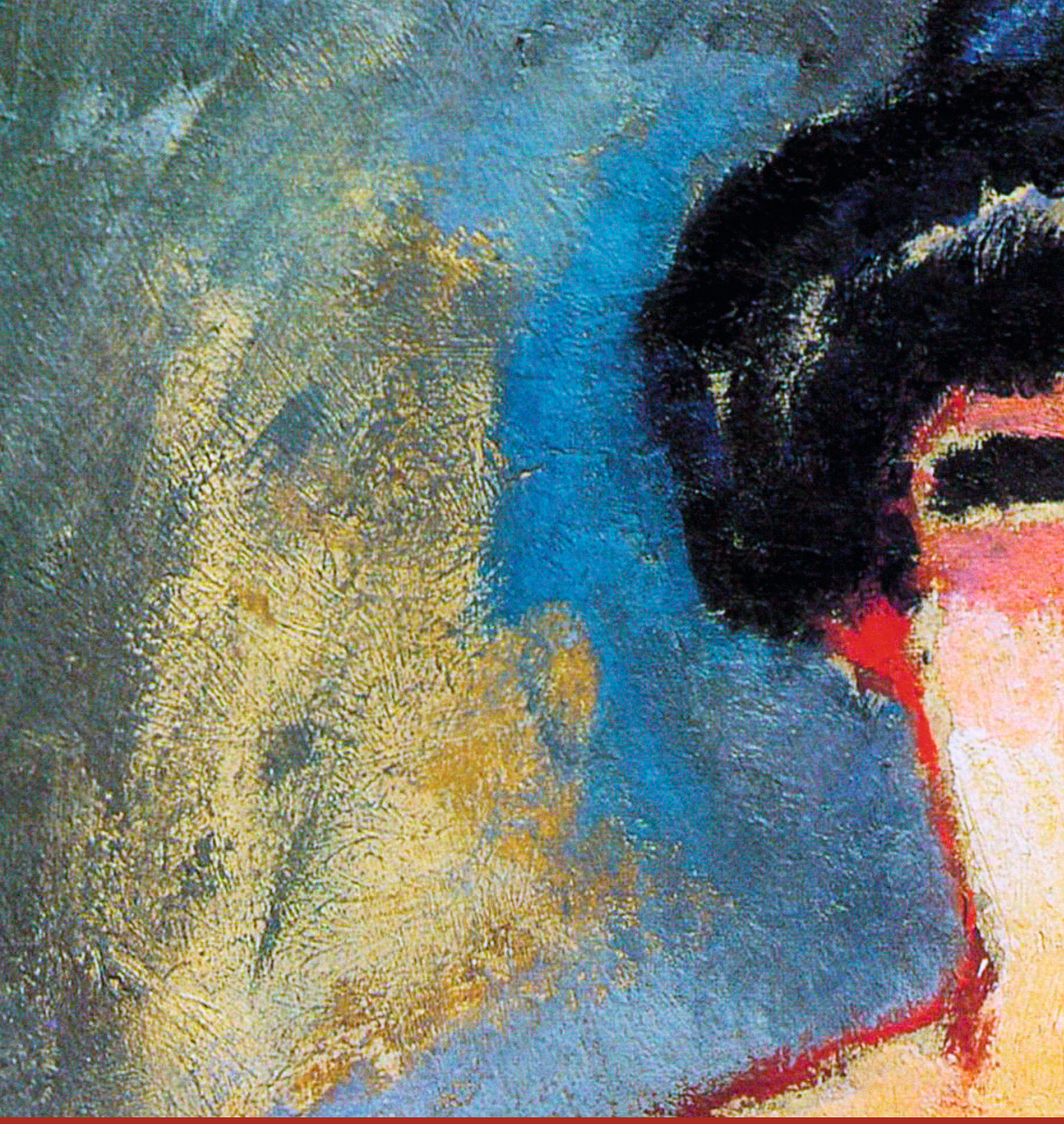
Finally, **Chapter 10** includes a layman-blog on the concept of resilience with a case study on resilience in the COVID-19 pandemic, and **Chapter 11** concludes this thesis with a general discussion, including directions for future research.

REFERENCES

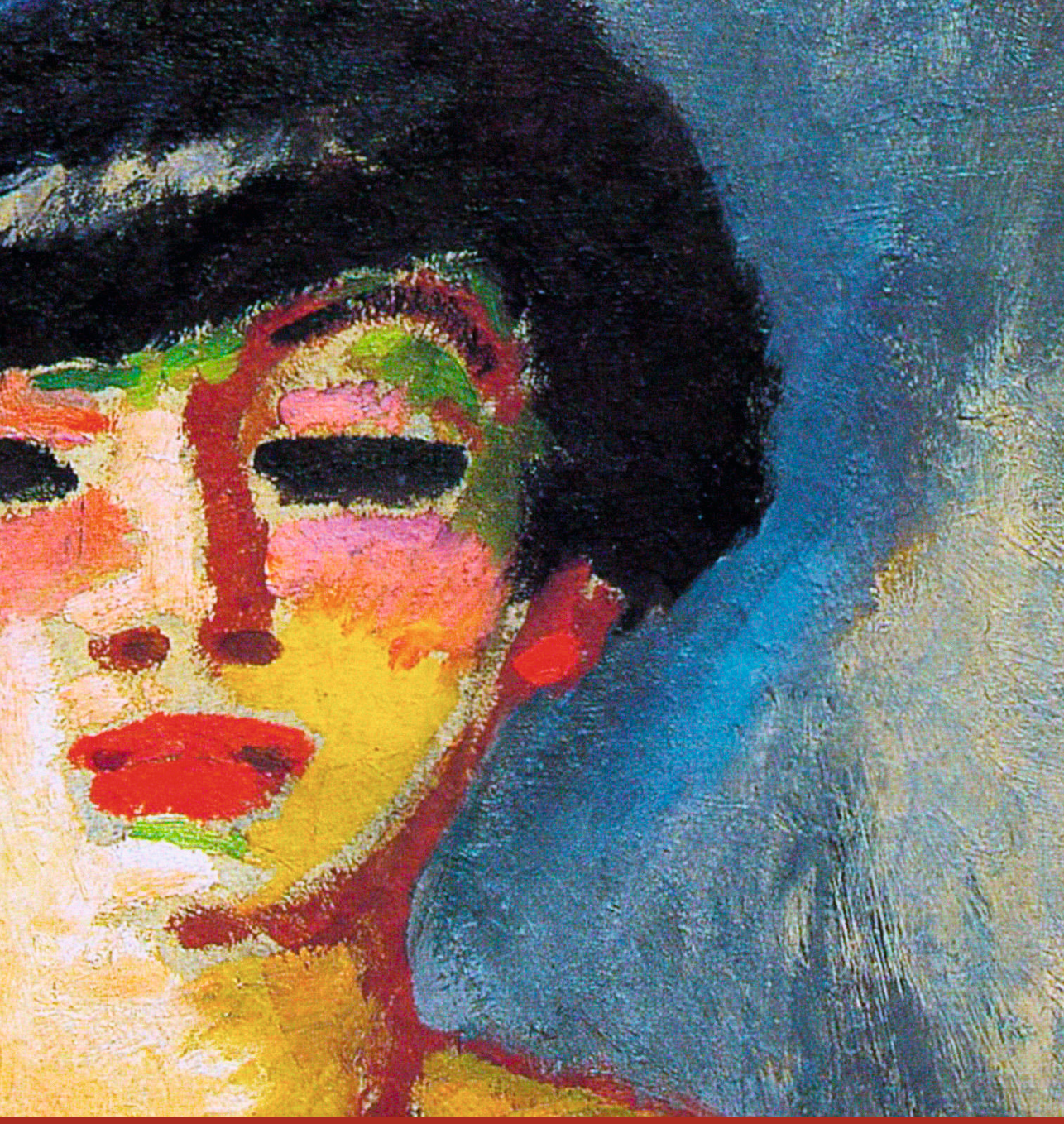
1. van Hal L, Tierolf B, van Rooijen M, van der Hoff M. *Een Actueel Perspectief Op Kinderen En Jongeren Met Een Chronische Aandoening in Nederland. Omvang , Samenstelling En Participatie*.; 2019.
2. van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. *JAMA - Journal of the American Medical Association*. 2010;303(7):623-630. doi:10.1001/jama.2010.104
3. Perfect MM, Frye SS. Resiliency in pediatric chronic illness: Assisting youth at school and home. *Resilience interventions for youth in diverse populations*. Published online 2014:423-446.
4. Compas BE, Jaser SS, Dunn MJ, Rodriguez EM. Coping with Chronic Illness in Childhood and Adolescence. *Annu Rev Clin Psychol*. 2012;8(1):455-480. doi:10.1146/annurev-clinpsy-032511-143108
5. Michaud PA, Suris JC, Viner R. The adolescent with a chronic condition. Part II: Healthcare provision. *Arch Dis Child*. 2004;89(10):943-949. doi:10.1136/adc.2003.045377
6. Pinquart M. Achievement of developmental milestones in emerging and young adults with and without pediatric chronic illness--a meta-analysis. *J Pediatr Psychol*. 2014;39(6):577-587.
7. Pinquart M, Teubert D. Academic, physical, and social functioning of children and adolescents with chronic physical illness: A meta-analysis. *J Pediatr Psychol*. 2012;37(4):376-389. doi:10.1093/jpepsy/jsr106
8. Pinquart M, Shen Y. Behavior problems in children and adolescents with chronic physical illness: A meta-analysis. *J pediatr Psychol*. 2011;36(9):1003-1016.
9. Pinquart M, Shen Y. Depressive Symptoms in Children and Adolescents with Chronic Physical Illness: An Updated Meta-Analysis. *J Pediatr Psychol*. 2011;36(4):375-384. doi:10.1093/jpepsy/jsq104
10. Blakemore S jayne. The art of medicine Adolescence and mental health. *The Lancet*. 2019;393(10185):2030-2031. doi:10.1016/S0140-6736(19)31013-X
11. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of. *Arch Gen Psychiatry*. 2005;62:593-602. doi:10.1001/archpsyc.62.6.593
12. Blakemore SJ, Mills KL. Is Adolescence a Sensitive Period for Sociocultural Processing? *Annu Rev Psychol*. 2014;65:187-207. doi:10.1146/annurev-psych-010213-115202
13. World Health Organisation. *Basic Documents: Forty-Ninth Edition (Including Amendments Adopted up to 31 May 2019)*.; 2020.
14. Huber M, Knottnerus AJ, Green L, et al. How should we define health? *BMJ (Online)*. 2011;343(7817):1-3. doi:10.1136/bmj.d4163
15. Kalisch R, Baker DG, Basten U, et al. The resilience framework as a strategy to combat stress-related disorders. *Nat Hum Behav*. 2017;1(11):784-790. doi:10.1038/s41562-017-0200-8
16. Guha S. Quantification of inherent energy resilience of process systems for optimization of energy usage. *Environ Prog Sustain Energy*. 2020;39(2). doi:10.1002/ep.13308
17. Dogra SK, Doré J, Damak S. Gut Microbiota Resilience: Definition, Link to Health and Strategies for Intervention. *Front Microbiol*. 2020;11. doi:10.3389/fmicb.2020.572921
18. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical Resilience in Older Adults: Systematic Review and Development of an Emerging Construct. *J Gerontol A Biol Sci Med Sci*. 2016;71(4):489-495. doi:10.1093/gerona/glv202
19. Block JH, Block J. The role of ego-control and ego-resiliency in the organization of behavior. In: *Development of Cognition, Affect, and Social Relations*. Erlbaum; 1980:39-101.
20. Kobasa SC. Stressful life events, personality, and health: An inquiry into hardiness. *J Pers Soc Psychol*. 1979;37(1):1-11. doi:10.1037/0022-3514.37.1.1
21. Masten AS, Garmezy N. Risk, vulnerability, and protective factors in developmental psychopathology. In: Lahey BB, Kazdin AE, eds. *Advances in Clinical Child Psychology*. Vol 8. Plenum Press; 1985:1-52.
22. Werner E, Smith R. *Vulnerable but Invincible: A Lonogitudinal Study of Resilient Children and Youth*. Adams, Bannister and Cox; 1982.
23. Luthar SS, Cicchetti D, Becker B. The Construct of Resilience: A Critical Evaluation and Guidelines for Future Work. *Child Dev*. 2000;71(3):543-562.
24. Hilliard ME, McQuaid EL, Nabors L, et al. Resilience in Youth and Families Living With Pediatric Health and Developmental Conditions: Introduction to the Special Issue on Resilience. *J Pediatr Psychol*. 2015;40(9):835-839.
25. Nederlandse Cystic Fibrosis Stcihting. Taaislijmziekte: de basis. www.ncfs.nl. Published 2023. Accessed July 11, 2023. https://ncfs.nl/over-taaislijmziekte/cf-de-basis/

26. Férec C, Scotet V. Genetics of cystic fibrosis: Basics. *Archives de Pediatrie*. 2020;27:eS4-eS7. doi:10.1016/S0929-693X(20)30043-9
27. Bierlaagh MC, Muilwijk D, Beekman JM, van der Ent CK. A new era for people with cystic fibrosis. *Eur J Pediatr*. 2021;180(9):2731-2739. doi:10.1007/s00431-021-04168-y
28. Elborn JS. Cystic fibrosis. *The Lancet*. 2016;388(10059):2519-2531. doi:10.1016/S0140-6736(16)00576-6
29. Jamieson N, Fitzgerald D, Singh-Grewal D, et al. Children's experiences of cystic fibrosis: a systematic review of qualitative studies. *Pediatrics*. 2014;133:1683-1697.
30. McBennett KA, Davis PB, Konstan MW. Increasing life expectancy in cystic fibrosis: Advances and challenges. *Pediatr Pulmonol*. 2022;57(S1). doi:10.1002/ppul.25733
31. Rijksoverheid. Kaftrio als behandeling van taaislijmziekte toegelaten tot basispakket. Rijksoverheid.nl. Published 2021. https://www.rijksoverheid.nl/actueel/nieuws/2021/12/09/kaftrio-als-behandeling-van-taaislijmziekte-toegelaten-tot-basispakket
32. Goetz DM, Savant AP. Review of CFTR modulators 2020. *Pediatr Pulmonol*. 2021;56(12):3595-3606. doi:10.1002/ppul.25627
33. Kapouni N, Moustaki M, Douros K, Loukou I. Efficacy and Safety of Elexacaftor-Tezacaftor-Ivacaftor in the Treatment of Cystic Fibrosis: A Systematic Review. *Children*. 2023;10(3):554. doi:10.3390/children10030554
34. Spoletini G, Gillgrass L, Pollard K, et al. Dose adjustments of Elexacaftor/Tezacaftor/Ivacaftor in response to mental health side effects in adults with cystic fibrosis. *Journal of Cystic Fibrosis*. 2022;21:1061-1065. doi:10.1016/j.jcf.2022.05.001
35. Heo S, Young DC, Safirstein J, et al. Mental status changes during elexacaftor/tezacaftor / ivacaftor therapy. *Journal of Cystic Fibrosis*. 2022;21(2):339-343. doi:10.1016/j.jcf.2021.10.002
36. Tindell W, Su A, Oros SM, Rayapati AO, Rakesh G. Trikafta and Psychopathology in Cystic Fibrosis: A Case Report. *Psychosomatics*. 2020;61:735-738. www.psychosomaticsjournal.org
37. Petsios KT, Priftis KN, Hatziagorou E, et al. Determinants of quality of life in children with asthma. *Pediatr Pulmonol*. 2013;48(12):1171-1180. doi:10.1002/ppul.22768
38. Okelo SO, Wu AW, Krishnan JA, et al. Emotional quality-of-life and outcomes in adolescents with asthma. *Journal of Pediatrics*. 2004;145(4):523-529. doi:10.1016/j.jpeds.2004.06.043
39. KyngÄs HA, Kroll T, Duffy ME. Compliance in adolescents with chronic diseases: a review. *Journal of Adolescent Health*. 2000;26(6):379-388. doi:10.1016/s1054-139x(99)00042-7
40. Määttä H, Hurtig T, Taanila A, et al. Childhood chronic physical condition, self-reported health, and life satisfaction in adolescence. *Eur J Pediatr*. 2013;172(9):1197-1206. doi:10.1007/s00431-013-2015-6
41. Cui W, Zack M, Zahran H. Health-Related Quality of Life and Asthma among United States Adolescents. *Physiol Behav*. 2016;176(1):139-148. doi:10.1016/j.physbeh.2017.03.040
42. Mohangoo AD, Sc M, Koning HJ De, et al. Health-Related Quality of Life in Adolescents with Wheezing Attacks. 2007;41:464-471. doi:10.1016/j.jadohealth.2007.06.002
43. Matterne U, Schmitt J, Diepgen TL, Apfelbacher C. Children and adolescents' health-related quality of life in relation to eczema, asthma and hay fever: results from a population-based cross-sectional study. *Qual Life Res*. 2011;20:1295-1305.
44. Berkelbach van der Sprenkel EE, Nijhof SL, Dalmeijer GW, et al. Psychosocial functioning in adolescents growing up with chronic disease: The Dutch HBSC study. *Eur J Pediatr*. 2022;181(2):763-773. doi:10.1007/s00431-021-04268-9
45. Van Cleave J. Dynamics of Obesity and Chronic Health Conditions Among Children and Youth. *JAMA*. 2010;303(7):623. doi:10.1001/jama.2010.104
46. Maurice-Stam H, Nijhof SL, Monninkhof AS, Heymans HSA, Grootenhuis MA. Review about the impact of growing up with a chronic disease showed delays achieving psychosocial milestones. *Acta Paediatrica, International Journal of Paediatrics*. 2019;108(12):2157-2169. doi:10.1111/apa.14918
47. Mokkink LB, Van Der Lee JH, Grootenhuis MA, Offringa M, Van Praag BMS, Heymans HSA. Omvang en gevolgen van chronische aandoeningen bij kinderen. *Tijdschr Kindergeneeskd*. 2007;75(4):138-142. doi:10.1007/bf03061684
48. World Health Organisation. Q&A on coronaviruses (COVID-19). World Health Organization. Published 2020. Accessed March 27, 2020. www.who.int
49. World Health Organisation. Coronavirus disease (COVID-19) pandemic. https://www.who.int/. Published 2023. Accessed June 23, 2023. https://www.who.int/europe/emergencies/situations/covid-19
50. Fegert JM, Vitiello B, Plener PL, Clemens V. Challenges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: a narrative review to highlight clinical and research needs in the acute phase and the long return to normality. *Child Adolesc Psychiatry Ment Health*. 2020;14(1):1-11. doi:10.1186/s13034-020-00329-3

51. The Alliance For Child Protection In Humanitarian. *Technical Note : Protection of Children during the Corona Pandemic.*; 2020.
52. Liu JJ, Bao Y, Huang X, Shi J, Lu J. Mental health considerations for children quarantined because of COVID-19. *The Lancet*. 2020;4(20):347-349. doi:10.1016/S2352-4642(20)30096-1
53. Fegert JM, Vitiello B, Plener PL, Clemens V. Challenges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: a narrative review to highlight clinical and research needs in the acute phase and the long return to normality. *Child Adolesc Psychiatry Ment Health*. 2020;14(1):1-11. doi:10.1186/s13034-020-00329-3
54. Golberstein E, Gonzales G, Meara E. How do economic downturns affect the mental health of children? Evidence from the National Health Interview Survey. *Health Economics (United Kingdom)*. 2019;28(8):955-970. doi:10.1002/hec.3885
55. Maurice-Stam H, Nijhof SL, Monninkhof AS, Heymans HSA, Grootenhuis MA. Review about the impact of growing up with a chronic disease showed delays achieving psychosocial milestones. *Acta Paediatr*. 2019;108(12):2157-2169.
56. Bruining H, Bartels M, Polderman TJC, Popma A. COVID-19 and child and adolescent psychiatry: an unexpected blessing for part of our population? *Eur Child Adolesc Psychiatry*. 2021;30(7):1139-1140. doi:10.1007/s00787-020-01578-5
57. Mokkink LB, Van Der Lee JH, Grootenhuis MA, Offringa M, Heymans HSA. Defining chronic diseases and health conditions in childhood (0-18 years of age): National consensus in the Netherlands. *Eur J Pediatr*. 2008;167:1441-1447. doi:10.1007/s00431-008-0697-y
58. Masten AS. Resilience in children threatened by extreme adversity: Frameworks for research, practice, and translational synergy. *Dev Psychopathol*. 2011;23(2):493-506. doi:10.1017/S0954579411000198
59. Oles M. Resilience and quality of life in chronically ill youth. *Health Psychol Rep*. 2015;3(3):220-236.
60. Van Breda A. A critical review of resilience theory and its relevance for social work. *Soc Work*. 2018;54(1). doi:10.15270/54-1-611
61. Ioannidis K, Dahl Askelund A, Kievit RA, al E. The complex neurobiology of resilient functioning after childhood maltreatment. *BMC Med*. 2020;18(32). doi:10.13140/RG.2.2.17380.48005
62. Fritz J, de Graaff AM, Caisley H, al E. A Systematic Review of Amenable Resilience Factors That Moderate and/or Mediate the Relationship Between Childhood Adversity and Mental Health in Young People. *Front Psychiatry*. 2018;9(June). doi:10.3389/fpsyt.2018.00230
63. Rutter M. Resilience in the face of adversity: protective factors and resistance to psychiatric disorders. *British Journal of Psychiatry*. 1985;147:598-611. doi:10.1192/bjp.147.6.598
64. van Harmelen AL, Kievit RA, Ioannidis K, Al E. Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychol Med*. 2017;47(13):2312-2322. doi:10.1017/S0033291717000836
65. Afifi TO, MacMillan HL. Resilience following child maltreatment: A review of protective factors. *Canadian Journal of Psychiatry*. 2011;56(5):266-272. doi:10.1177/070674371105600505
66. Liebenberg L, Ungar M, van d.V.jver F. Validation of the Child and Youth Resilience Measure-28 (CYRM-28) Among Canadian Youth. *Res Soc Work Pract*. 2012;22(2):219-226.
67. Sollie P. On Uncertainty in Ethics and Technology. In: Sollie P, Düwell M, eds. *Evaluating New Technologies - Methodological Problems for the Ethical Assessment of Technology Developments*. Vol 3. Springer Science+Business Media B.V.; 2009:141-158. doi:10.1007/978-90-481-2229-5
68. Katier N, Uiterwaal CSPM, De Jong BM, et al. The Wheezing Illnesses Study Leidsche Rijn (WHISTLER): Rationale and design. *Eur J Epidemiol*. 2004;19(9):895-903. doi:10.1023/B:EJEP.0000040530.98310.0c
69. Nap-van Der Vlist MM, Hoefnagels JW, Dalmeijer GW, et al. The PROactive cohort study: rationale, design, and study procedures. *Eur J Epidemiol*. 2022;37:993-1002.



PART I



RESILIENCE IN THE FACE OF INCREASING PREVALENCE OF CHRONIC CONDITIONS IN YOUTH

CHAPTER 2

DEFINING AND MEASURING RESILIENCE IN CHILDREN WITH A CHRONIC DISEASE:

A SCOPING REVIEW

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ABSTRACT

More than 25% of all children grow up with a chronic disease. They are at higher risk for developmental and psychosocial problems. However, children who function resiliently manage to adapt positively to these challenges. We aim to systematically review how resilience is defined and measured in children with a chronic disease. A search of PubMed, Cochrane, Embase and PsycINFO was performed on December 9, 2022, using resilience, disease and child/adolescent as search terms. Two reviewers independently screened articles for inclusion according to predefined criteria. Extraction domains included study characteristics, definition, and instruments assessing resilience outcomes, and resilience factors. Fifty-five out of 8,766 articles were identified as relevant. In general, resilience was characterized as positive adaptation to adversity. The included studies assessed resilience by the outcomes of positive adaptation, or by resilience factors, or both. We categorized the assessed resilience outcomes into three groups: personal traits, psychosocial functioning, and disease-related outcomes. Moreover, myriad of resilience factors were measured, which were grouped into internal resilience factors (cognitive, social, and emotional competence factors), disease-related factors, and external factors (caregiver factors, social factors, and contextual factors). Our scoping review provides insight into the definitions and instruments used to measure resilience in children with a chronic disease. More knowledge is needed on which resilience factors are related to positive adaptation in specific illness-related challenges, which underlying mechanisms are responsible for this positive adaptation, and how these underlying mechanisms interact with one another.

INTRODUCTION

The diagnosis and treatment of childhood diseases have advanced significantly in recent decades, which has also led to an improved life expectancy among children with a chronic disease [1]. Recent studies showed that more than 25% of children and young adults under the age of twenty-five suffer from a chronic disease, both in the Netherlands as well as in the USA [2,3]. In light of the increasing prevalence of chronic diseases, Huber (2011) proposed to change the concept of health from "a state of complete physical, mental and social well-being" [4] to a new dynamic approach focusing more on disease management than pathology, namely "the ability to adapt and self-manage in the face of social, physical and emotional challenges" [5].

It has been shown that children with a chronic disease suffer from more physical as well as psychosocial challenges due to symptom distress, demanding therapeutic regimens, periods of hospitalization, uncertainty about the future, social exclusion, and the inability to fully participate in school or society [6–8]. However, there are large inter-individual differences and not all children with a similar chronic disease experience (similar) difficulties: while some children do not adapt or even adapt negatively and develop more serious problems, many children manage to positively adapt to these challenges. This phenomenon, *positive adaptation within the context of significant adversity by maintaining or regaining mental health or psychosocial functioning*, is often referred to as resilience [9–12]. Different concepts of resilience are described, such as -but not limited to- physical resilience and psychological resilience. Physical resilience is often thought of as "the ability to physically recover or optimize function in the face of disease or age-related losses " [13]. As clinician-scientists, our research focus is on identifying the factors that contribute to differences in functioning among children with chronic diseases. Specifically, we aim to investigate why some children with the same chronic disease are able to adapt and integrate into society, while others experience difficulties in this regard. Thus, in this review, our focus is on the psychological aspect of resilience, which we refer to as 'resilience' throughout this paper.

In pediatric healthcare, increased awareness of the importance of positive adaptation to stress has led to an increased focus on resilience research [14]. Resilience is a complex concept and various resilience frameworks have been developed to clarify the concept [14]. As a result, definitions and instruments used to assess resilience in pediatric healthcare research vary greatly between studies and might lead to lack of clarity within the field [6,14]. Some investigators defined and measured resilience as an outcome by assessing outcomes of positive adaptation to adversity (i.e., disease), for instance, in terms of psychosocial functioning (e.g., mental wellbeing, QoL, lack of mental health problems, cognitive abilities) [15]. Others tried to explain why individuals are able to positively adapt and maintain good mental wellbeing, and therefore focus on the factors that facilitate positive

adaptation to adversity. These factors are generally referred to as resilience factors [12,15]. These resilience factors can be roughly divided into internal factors and external factors. The first group consists of factors that can be related to the child's biology but also to the child's behavior, emotions, and cognition [16,17]. External factors relate to various aspects of the child's environment, such as relationships with parents and friends [18–20], but also contextual factors such educational, and cultural environment [21].

The aim of the present review is to provide an overview of definitions and instruments used to assess resilience in children with a chronic disease. Hereby, we seek to identify commonalities and differences between these definitions of childhood resilience. Moreover, we provide an overview of resilience *outcomes* and resilience *factors* in the field of pediatric care. Identifying these outcomes and factors can improve the care of children with chronic illness by providing insights for interventions and preventive strategies aimed at adapting best to the challenges posed by chronic illness.

METHODS

Search strategy

A systematic review of the available literature was conducted on December 9, 2022, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Extension for Scoping Reviews [22]. An electronic search of PubMed, Cochrane, Embase and PsycINFO was performed to identify relevant peer-reviewed articles. The search terms included resilience, (chronic) disease, and child/adolescent – in combination with the corresponding Medical Subject Headings (MeSH) terms and synonyms. The complete search strings were approved by a medical librarian at the University Medical Centre Utrecht and can be found in Supplement 1. This review is registered in PROSPERO, the international prospective register of systematic reviews (ID:147023).

Selection criteria

Our pre-defined study selection criteria were the following: (1) pediatric sample; (2) having a physical chronic disease; (3) with self-reported measurement(s) of resilience; (4) published in English in a peer-reviewed journal; (5) available in full text. Exclusion criteria were: (1) articles that mentioned resilience in the text but did not measure resilience; (2) articles in which resilience was merely defined as 'not having a disease'; (3) parental-reported resilience; (4) qualitative research (e.g., interviews); (5) studies with only a limited number of participants (e.g., case-reports); (6) studies that provide too little or no details on the quantitative methods and/or results (conference abstracts, protocols); (7) articles that focused on children with medically unexplained symptoms; (8) articles that focused on children with psychiatric disorders; (9) articles that used the exact same study population as previously studied articles (in that case, we retained the first published article); (10) studies validating a resilience instrument; and (11) articles that

focused on resilience related to the COVID-19 pandemic of children with a chronic disease instead of resilience of children with a chronic disease. There was no restriction in terms of publication date of the included articles.

A pediatric chronic disease was defined as "a condition that occurs between the age of 0-18 years, was diagnosed by a professional based on medical scientific knowledge using valid methods and instruments, is not (yet) curable and has existed for more than three months" [1].

We only included self-reported measurements of resilience, as children and their parents or caregivers may experience certain (internal) resilience factors in a different way. For example, research shows that parents overestimate their children's optimism and underestimate their worries [23]. When included studies used proxy-reported, or qualitive instruments (besides self-reported measurements of resilience), we did not present these in our overviews (Table 1, Figure 2, Supplement 3, Figure 3, and Supplement 4). Some studies used blood tests to measure metabolic control (as a resilience outcome) next to self-reported questionnaire methods [24–27], we also presented the blood test as this test is a qualitative instrument.

Study selection

All identified articles were uploaded in Rayyan QCRI, a web-based tool, in which titles and abstracts were independently reviewed by two researchers (SvdL, EBvdS). Each researcher assigned the article to one of three categories: include, exclude or maybe. Articles with labels 'include' and 'maybe' were selected for full-text screening. Those articles were evaluated for eligibility according to the inclusion and exclusion criteria, again independently by the same two researchers (SvdL, EBvdS). In 85% of all included articles, the researchers agreed that the articles met the inclusion criteria. In the remaining 15%, consensus was reached through discussion.

Article review and data extraction

For each article, the following characteristics were extracted: first author, year of publication, diagnosis, sample size, age of study population, country, study design, definition of resilience (when provided), and instruments measuring resilience outcomes and/or resilience factors (see Supplement 2). To further examine the instruments used by the included articles, the following characteristics of the instruments were extracted: items, response, and range (Supplement 3 and 4). A risk of bias assessment was not performed, as the findings of the individual studies were not the primary interest of this review. The Figure 2 and Figure 3 presented in this study were created using Datylon, a data visualization software [28].

RESULTS

Search and baseline characteristics

A total of 8,766 articles were identified through the literature search. After removal of duplicates, the remaining 8,101 articles were uploaded to Rayyan QCRI [29]. A total of 362 articles were identified for full text review and evaluated according to the inclusion criteria. In total, 55 articles were included. The flow diagram is shown in Figure 1.

Articles represented study populations from fourteen different countries, and 25 (45%) studies were conducted in the USA. The articles were published between 2009-2022, and encompassed the following chronic diseases: malignancies (n=12), type 1 or type 2 diabetes (n=8), atopic diseases (n=4), nonmalignant neurological diseases (n=5), congenital heart disease (CHD) (n=4), auto-immune disorders (n=4), nonmalignant hematological diseases (n=4), Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (n=2), obesity (n=2), otolaryngology problems (n=2) or, other or combination of the aforementioned (n=8) (see Supplement 2). Table 1 presents a general definition and specific aspects of resilience summarizing all included definitions. Additionally, Table 1 provides information on how often resilience was measured as an outcome, as resilience factors, or as both. Supplement 2 demonstrates the specific characteristics of all included articles.

Definition of resilience in the context of childhood chronic diseases

Various definitions of the concept of resilience were found in the included articles. In total, 46 (84%) of the articles) provided a definition of resilience. Of all definitions, the definition provided by Luthar et al. (2000) was cited most frequently (n=6): "*Resilience refers to a dynamic process encompassing positive adaptation within the context of significant adversity*" [9]. The other definitions (n=40) are presented in Supplement 2. In the presented definitions, resilience was characterized as emerging in times of stress or emergency to ensure maintenance of health, psychological and/or social well-being, and was often considered an adaptation process to a stressor. In total, 15 (27%) articles described resilience as a personal trait or skill, whereas 11 (20%) articles characterized resilience as a multi-dimensional concept. The majority of the included articles (n=29, 53%) did not explicitly mention (or gave no definition at all) whether resilience was seen as a personal trait or multi-dimensional concept (Table 1).

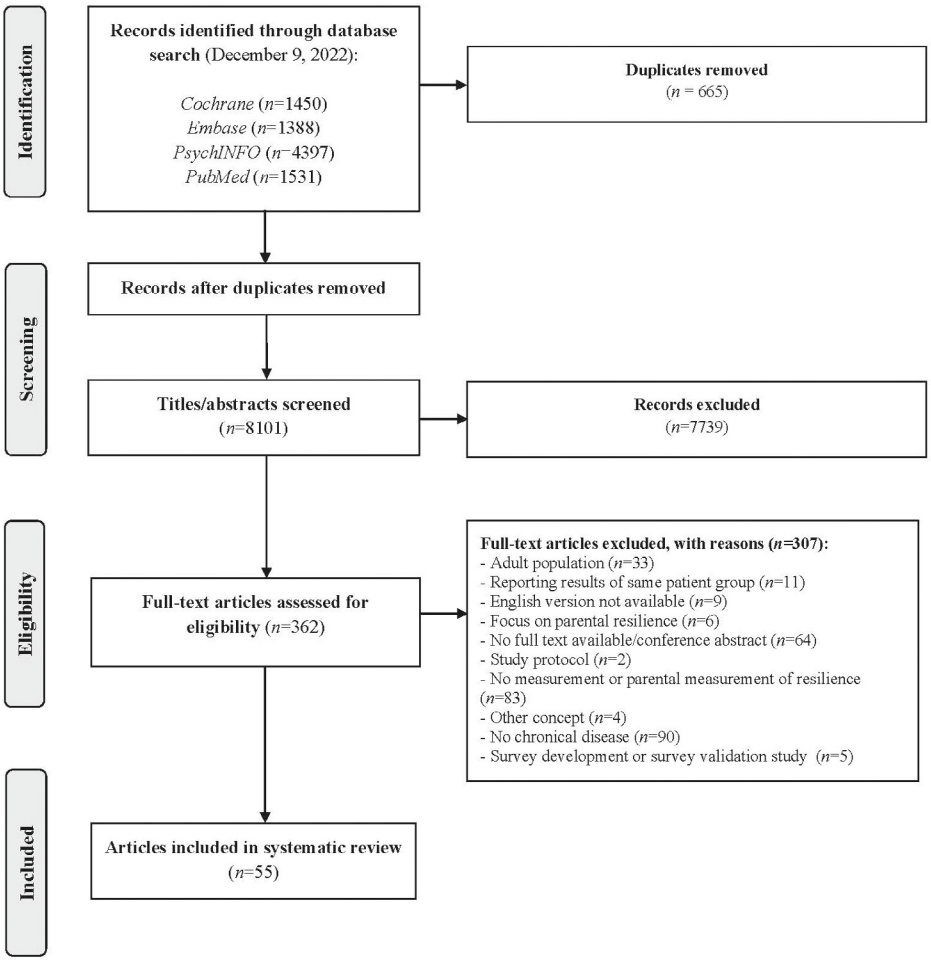

Figure 1: PRISMA flow diagram of selection process

Table 1: Definition and measurement of resilience, as presented in the included studies

DEFINITION OF RESILIENCE		
Total included: n = 55	**No definition provided**	9 (16%) [24,30–37]
	Definition provided	46 (84%) [25,27,38–81]
In the presented definitions, resilience was characterized as emerging in times of stress or emergency to ensure maintenance of health, psychological and/or social well-being, and was often considered an adaptation process to a stressor.		
Aspects of resilience definition *Some examples are described below*		
Personal trait/skill n = 15 (27%) [27,41,44,47,49–51,55,62,64,65,70,74,78,80]	• "The ability to adapt to situations and environments through self-regulation." *Gheshlagh (2016)*[82] • "Resilience is defined as an individual's strength and ability to moderate the negative effects of stress, promote adaptation, and maintain mental well-being in the face of adversity." *Wagnild (1993)*[83], *Davydov (2003)*[84] • "(…) a universal construct describing an individual's capacity to maintain psychological and/or physical well-being in the face of stress and is a good candidate to buffer the negative impact of serious illness among multiple populations of adolescents and young adults." *Haase (2004)*[85], *Southwick & Charney (2012)*[86] • "Psychological resilience is mentioned among the various psychological resources facilitating beneficial adaptation to illness. Resilience is revealed in the context of coping with negative life events and difficulties. In this sense, resilience can be viewed as an indicator of mental strength. Thanks to it, despite adversities, a person can develop and maintain mental health. (…) When it comes to a chronic illness, psychological resilience is a resource that promotes adaptation to the circumstances of the illness and the limitations generated by it." Rutter (2012)[87], Kim (2019)[88]	
Multi-dimensional concept n = 11 (20%) [38,40,48,54,57,58,60,61,71,73,81]	• "A process of harnessing resources needed to sustain individual well-being." *Haase (1999)*[89], *Southwick (2014)*[90], *Rosenberg (2014)*[74] • "(…) 'a dynamic process encompassing positive adaptation within the context of significant adversity'. Resilience is 'the ability to maintain a stable equilibrium' (…) It is not a particular personality trait but a process by which positive adaptation occurs despite adversity." *Werner (1989)*[91] • "Resilience refers to the family's ability to withstand stressful experiences and rebound from them by creating new, healthy ways of functioning." *Walsh (2003)*[92] • "(…) a capacity of a dynamic system that helps individuals to overcome the negative effects, recover from adverse circumstances while maintaining normal development. It is not a quality that is always present in every situation, but a process of harnessing new and existing resources to maintain well-being during and after any stressor." *Masten (2014)*[93], *Rosenberg (2016)*[94]	
Not explicitly mentioned n = 29 (53%) [24,25,30–37,39,42,43,45,46,52,53,56,59,63,66–69,72,75–77,79,95]	• "A dynamic process encompassing positive adaptation within the context of significant adversity." *Luthar (2020)*[9] • "The ability to function with healthy responses despite the presence of significant stress and adversity." *Masten (1988)*[96] • "The protective factors that dynamically allow one to have a good outcome, over-coming stress and adversity, while sustaining normal psychological and physical functioning." *Wu (2013)*[97], *Masten (2001)*[98] • "A positive psychological adjustment in the face of adversity which is associated with improved health outcomes in patients with chronic conditions." *Wu (2016)*[99]	
RESILIENCE MEASURED AS		
Outcome, n(%)*	**Factor, n(%)****	**Outcome and factor, n(%)**
12 (22%)[30,40,48,54,59,60,63,65,69,74–76]	7 (13%)[43,56,61,67,70,73,78]	36 (65%)[24,25,27,31–39,41,42,44–47,49–53,55,57,58,62,64,66,68,71,72,77,79–81]

*Please see Figure 2 and Supplement 3; **Please see Figure 3 and Supplement 4.

Measurement of resilience in children with a chronic disease

In this scoping review, we analyzed which resilience outcomes (Figure 2, Supplement 3) and which resilience factors (Figure 3, Supplement 4) were measured in the included articles. To identify the specific topics that were being assessed by each instrument, we reviewed the corresponding or background articles (for references, see Supplements 3 and 4). The topics were then quantified and categorized, and the resultant distribution was depicted in Figures 2 and 3. It should be noted that not all articles explicitly reported the topics that were assessed by an instrument. To offer a comprehensive overview of the resilience outcomes and factors examined in the literature, we retrieved all themes from the source file and included them in the figures separately.

In total, 36 (65%) studies measured both a resilience outcome as well as resilience factors, and statistically tested whether certain resilience factors were significantly associated with the resilience outcome. For example, Willard et al. (2018) assessed if connectedness to the social environment (such as connectedness to friends and family) influenced social functioning in children with brain tumors [33]. In this case, the researchers considered social functioning as a resilience outcome and connectedness as resilience factor. Of the remaining 19 studies, 12 (22%) measured only one or more resilience outcome, without assessing resilience factors. For instance, Rosenberg et al. (2014), Lee et al. (2017), and Rosenberg et al. (2018) conducted a randomized controlled trial (RCT) and assessed whether the resilience outcome(s) improved after the intervention [48,54,74]. Moreira et al. (2015), Lee et al. (2020), and Zimmerman et al. (2021) compared resilience scores (as an outcome of resilience) of children with a (specific) chronic disease and a control group [60,75,76]. Additionally, Kaewkong et al. (2020) examined whether demographics such as sex and age were associated with the resilience outcome [100]. The remaining 7 (13%) studies assessed resilience factors only. To illustrate, Whiteley et al. (2019) and Hood et al. (2018) conducted RCTs with the aim to assess whether their intervention improved certain resilience factors, such as treatment motivation, of the participants [56,70].

Resilience outcomes

A myriad of resilience outcomes has been assessed in the included studies (see Figure 2). For each instrument, we examined which topic(s) was/were being measured by searching the corresponding or background articles (for references see Supplement 3). This examination resulted in three categories: personal traits, psychosocial functioning, and disease-related outcomes. In total 34 instruments were used: 9 (26,5%) instruments assessed resilience by means of outcomes related to personal traits [47,83,101–107], 9 (26,5%) instruments appraised resilience by outcomes of psychosocial functioning [40,108–115], 13 (38%) instruments consisted of disease-related outcomes [25,37,116–124], 2 (6%) instruments measured both personal traits and psychosocial functioning [125,126], and 1 (3%) instrument assessed both personal traits and disease-related outcomes [103]. Examples of personal traits are self-efficacy measured by the General self-efficacy questionnaire (GFE-10) [47], responsibility measured by the Social-

Emotional Assets and Resilience Scales (SEARS) [106], and affect measured by the Positive and Negative Affect Scale for Children (PANAS-c) [111]. Examples of psychosocial functioning are quality of life measured by the Pediatric Quality of Life Inventory (PedsQL) [112], (absence of) internalizing symptoms measured by the Center for Epidemiologic Studies Depression Scale (CESDS) [110], and (absence of) post-traumatic stress disorder symptoms measured by the UCLA PTSD Reaction Index for DSM-IV (PTSDI) [113]. Examples of disease-related outcomes are disease-related quality of life measured by the disease specific modules of the PedsQL [122] and benefit finding in illness measured by the Benefit Finding Scale for Children (BFSC) [117].

In total, 13 (24% of all included) studies used a resilience instrument to measure positive adaptation to stress (resilience outcome) by calculating a total resilience score per participant rather than assessing each topic separately. Examples of the scales used to derive total resilience scores are the Connor-Davidson resiliency questionnaire (CD-RISC) [48,60,74,77], the Wagnild and Young Resilience Scale (RS) [43,49,50,52,54,76,127], the Healthy Kids Resilience Assessment Module [35], and the Family Resilience Assessment Scale (FRAS-C) [61].

When focusing on the resilience outcomes regarding psychosocial functioning, both positive and negative outcomes were assessed; concerning the latter, participants were considered resilient when they reported an absence of mental health problems.

All included instruments were questionnaires, except for the HbA1c which is a blood test, used to assess metabolic control [25].

Resilience factors

We categorized the resilience factors into 'internal factors', 'disease-related factors', and 'external factors'. Internal factors comprised of cognitive, emotional, social competence factors. External factors comprised of caregiver factors, peer factors, and contextual factors. Disease-related factors could be both internal and external factors (Figure 3, Supplement 4).

In total, 66 different instruments were used to measure resilience factors. Overall, 33 (50%) instruments assessed internal factors, 15 (23%) instruments assessed disease-related factors, 11 (17%) instruments assessed external factors, and 7 (10%) instruments assessed a combination of internal, disease-related, or external factors (Supplement 4). Figure 3 shows which resilience factors were measured. With regard to internal factors, examples of cognitive, social, and emotional competence factors were measured, such as coping [70,128–132], social skills [21,107,108,133], and self- efficacy [102,134,135]. Some examples of the disease-related factors were acceptance of the disease [136,137], social support promoting adherence [138,139], and disease-related coping [140–142]. With regard to external resilience factors, caregiver factors focused, among others, on family cohesion and connectedness [133,143–146], peer factors

focused, among others, on peer relations [21,104,106,135,147], and contextual factors, focused, among others, on spiritual, educational, and cultural environment [21].

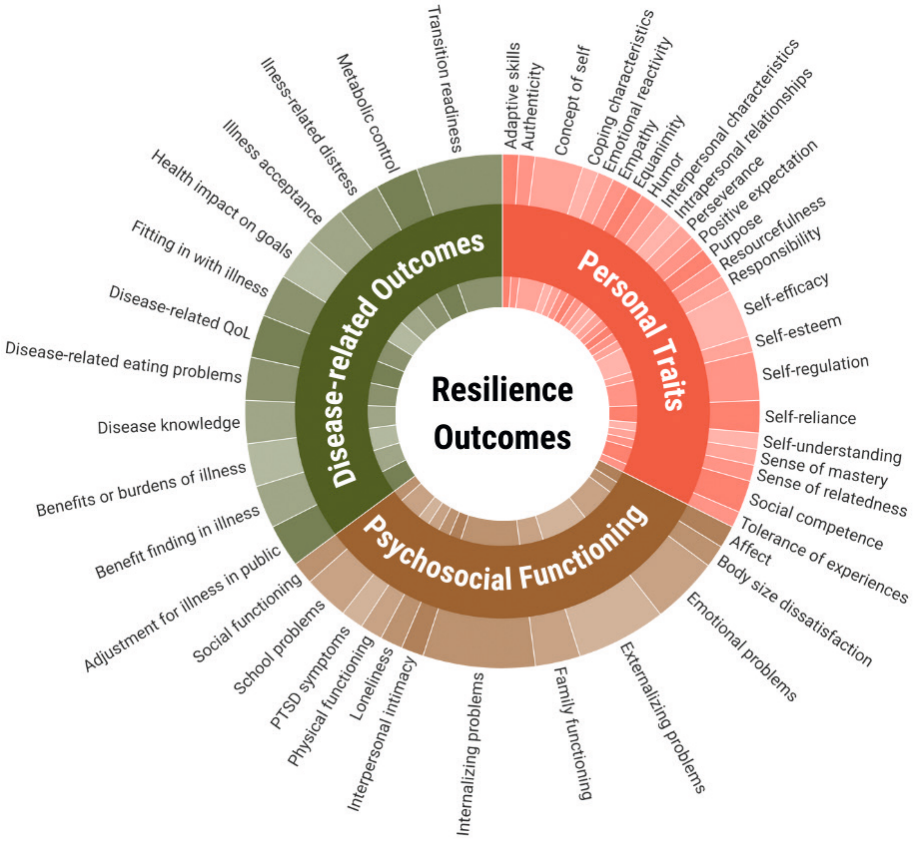

Figure 2: Pie chart illustrating the variety and distribution of resilience outcomes (n = 69) measured by 34 instruments in the included studies (see Supplement 3). The chart presents three main categories: personal traits, psychosocial functioning, and disease-related outcomes - with slice and category sizes corresponding to the proportion of total amount of reported resilience outcomes.

Out of all included studies, 10 (18%) employed a resilience instrument as a resilience factor by calculating a total resilience score per participant, as opposed to measuring individual domains separately. Examples of the scales used to derive total resilience scores as resilience factor are the resilience measurement instrument for children with chronic illness [39], the Wagnild and Young Resilience Scale (RS) [43,51], the Connor-Davidson resiliency questionnaire (CD-RISC) [47,77], Haase Adolescent Resilience in Illness Scale (HARIS) [55], 7Cs tool [66], The Neil and Dias Resilience Scale [71], Diabetes Strengths and Resilience measure for adolescents (DSTAR) [36], and the Child and Youth Resilience Measure (CYRM-28) [79].

Figure 3: Pie chart illustrating the heterogeneity of resilience factors (n=155) assessed by 66 instruments from the included studies (see Supplement 4). The chart shows three overarching categories: internal, external and disease-related factors. Internal factors encompassed of cognitive, emotional, social competence factors. External factors were further classified into caregiver factors, peer factors, and contextual factors. Slice as well as category size indicate the proportion of the total amount of reported resilience factors.

DISCUSSION

The aim of this scoping review was to provide an overview of definitions and instruments used to assess resilience in children with a chronic disease. In total, 55 articles were included. Resilience was often conceptualized as a dynamic concept that signals a positive adaptive response to stress or adversity. The included studies either assessed resilience by the outcomes of positive adaptation, or by resilience factors. Most studies (65%), however, measured both resilience outcomes and resilience factors simultaneously, and examined whether resilience factors were associated with an resilience outcome. We categorized the assessed resilience outcomes into three groups: personal traits, psychosocial functioning,

and disease-related outcomes. Moreover, myriad of resilience factors were measured, which were grouped into internal resilience factors (cognitive, social, and emotional competence factors), disease-related factors, and external factors (caregiver factors, social factors, and contextual factors). Disease-related factors could be both internal and external factors.

Even though resilience has been a topic of interest in scientific research since the 1970s, the articles that met our inclusion criteria were relatively recent (2009-2022) [1,48]. We did not add restriction in terms of publication date as exclusion criteria in the search. The relatively recent publication dates of the included articles suggest that resilience has recently gained more (scientific) attention in pediatric healthcare research.

Although we observed many commonalities between the used definitions, this review identified that one cannot simply compare 'resilience' in one paper with 'resilience' in other papers. Therefore, just as the new agreement on the concept of health, a global definition and agreement on terminology of resilience would be helpful in crossing the boundaries between medical research and other relevant disciplines to enhance our understanding of general, trans-diagnostic, and disease-specific aspects of resilience factors and outcomes. By differentiating between factors and outcomes, and between internal, disease-related factors, and external factors, this scoping review makes a first attempt to reach a consensus on the conceptualization of resilience. The resilience definition of Luthar et al. (2000) was cited most frequently by the articles included in this review: "*Resilience refers to a dynamic process encompassing positive adaptation within the context of significant adversity*" [9]. In our opinion, however, it would be helpful to employ a definition that also identifies (one) measurable outcome(s) of positive adaptation.

Various resilience outcomes have been measured by the included studies. Resilience outcomes reflected positive adaptation to stress, which was measured, for example, by pediatric QoL, child competence, and (lack of) mental health problems. Although resilience is defined as a positive adaptation to stress, many mental health instruments measured (the absence of) negative outcomes, such as emotional and behavioral problems [34,39,100], anxiety and depressive symptoms [53,62], loneliness [53], or posttraumatic stress symptoms [31]. Children were identified as being resilient when they did not experience these symptoms or problems. Measuring a resilience outcome as the absence of negative outcomes introduces several challenges, leading one to question whether positive adaptation to a stressor should be measured as such. First, there are limitations to assessing binary outcomes. By examining continuous scores, we can advance our understanding of, for instance, clinical and sub-threshold problems. Both clinical and sub-threshold problems can be debilitating in the everyday life of children with a chronic disease. Therefore, focusing on absence versus presence of certain disorders is not an ideal resilience outcome. Secondly, we might be careful using the absence of negative outcomes, because not having

a disorder/symptom/problem does not necessarily imply that one has a good mental health. To illustrate, the definition of wellbeing is: life satisfaction, the presence of positive affect and the absence of negative affect. The presence of positive affect does not mean that negative affect is absent or vice versa. Positive and negative affect are—although negatively correlated—partly independent dimensions of wellbeing [149–152]. How could researchers measure resilience outcomes in a positive manner and which outcomes can be used to do so? In recent decades, the outlook on health has shifted from an approach merely focusing on (the absence of) physical health to a more dynamic and all-encompassing concept assessing various dimensions of well-being and psychosocial functioning: the ability to adapt and self-manage in the face of social, physical and emotional challenges [5]. In total, six dimensions have been described that influence adaption: bodily functions, mental functions and perceptions, spiritual dimension, quality of life, social and societal participation, and daily functioning [153]. All dimensions, except bodily functions, might be used as positive resilience outcomes regarding psychosocial functioning and positive mental health. When measuring only improvement or adaptation of bodily functions, one focuses on physical resilience [13]. Although we selected articles focusing on psychological resilience, some of the included studies combined physical and psychological resilience [25,27]. As an example, Jaser et al. explored how the use of specific coping strategies impacts resilience (defined as quality of life, competence, and metabolic control) among adolescents with Type 1 diabetes [25]. To do so, they incorporated both psychological and physical resilience outcomes, conceptualizing that physical and psychological resilience are intertwined.

Most of the internal and external resilience factors, measured in the current scoping review, have also been reported in other (systematic) reviews focusing on resilience factors associated with different adversities, such as childhood maltreatment, war, and poverty [17,20,154]. Noteworthy, in the current scoping review many disease-related factors were also identified as resilience factors. These factors might be new targets for psychosocial interventions to improve children's positive adjustment to their chronic disease. Moreover, in previous literature, multiple levels of the environment are described [155]: proximal levels, which include the child's direct relationships, such as relationships with parents and friends [18–20], and more distal levels such as characteristics of the neighborhood or culture of society [155]. When focusing on the external factors measured by the studies in this review, most of these factors were related to proximal levels of the environment and included the child's relationships with caregivers (caregiver factors) and with peers (peer factors). Although some factors seemed to be more distal, such as expectations at school or connectedness with the neighborhood [145,156] (contextual factors), all factors focused on the child's perception of the school or neighborhood. This is the result of including only self-reported instruments in this review. Although the more distal factors, such as cultural norms or the effect of time on the adversity, are not easily measured with questionnaires, these elements could be very important for positive adaptation to a chronic disease. For

instance, the organizational culture of hospitals may have an impact on the shared ways of thinking, feeling, and behaving of doctors, which might influence prevailing views on patient needs and therefore the openness of doctors to their patients' input [157]. Huber showed that adult patients' views on health are much broader than that of doctors: patients give equal importance to bodily functions as QoL, spirituality, and mental state, while doctors focus predominantly on bodily functions [153]. When medical professionals are used to invite (paediatric) patients to express their feelings and experiences not only about their bodily functions, but also about other important aspects of their lives (e.g., friendships, and mental wellbeing), adaptation to their disease might be enhanced. Furthermore, positive adaptation to a chronic disease may change or develop over time, and therefore, researchers might consider when and over which time frame resilience should be measured. Disease severity and the frequency of relapses or exacerbations might be taken into consideration too, as these aspects of a chronic disease could play a role in the adaptation process. Finally, many leading resilience researchers acknowledge that not only internal factors and external factors facilitate resilience, but also emphasize the importance of interaction between the child and their environment [12,16,90,158].

Several strengths of our review deserve mentioning. First, we conducted a broad literature search across multiple electronic databases. This resulted in a diverse sample of articles, half of which were published in the last decade, representing many different chronic diseases in various countries across the world. Furthermore, this search offered a comprehensive overview of definitions, and how resilience is measured: as an outcome of positive adaptation to a stressor, as resilience factor(s), or both. Moreover, our scoping review a first attempt to reach a consensus on the conceptualization of resilience by categorizing resilience measurements by between factors and outcomes. Some limitations need to be mentioned. Our inclusion criteria involved resilience, (chronic) disease, and children – in combination with the corresponding MESH terms. We did not add terms that describe the functions of resilience such as 'buffering' or 'adaptation' to the search string. This might have resulted in missing potentially relevant articles. Additionally, some articles identified by the used search terms described they researched resilience, but lacked information on how resilience was operationalized. These articles were also not included in this review. We hope that our review will stimulate future investigations that include research describing the functions of resilience. Furthermore, as we chose to only include self-report measurements, we implicitly excluded studies with children younger than six years old, as well as the parental perspective on resilience. Research indicates that children are able to report on their health-related quality of life from the age of 5 years [159], and most resilience questionnaires are deemed appropriate for self-reporting from the age of 8 years [160,161] (see Supplement 2, indicating the age of the populations studied).

It was beyond the scope of this review to evaluate whether the resilience factors were actually (significantly) associated with the resilience outcome. Therefore, we are

unable to conclude whether these factors contribute to positive adaptation to stress. Notwithstanding, this provides several interesting avenues for further research. First, the biological mechanisms underpinning resilience factors. In this systemic review, we did not report on the working mechanism of a resilience factor and therefore we were unable to answer why the identified resilience factors facilitated positive adaptation to disease-related challenges in children with a chronic disease. Multiple mechanisms explaining resilience in the face of childhood adversity have been described, involving biomedical processes at the genetic, inflammation and brain level, and involving processes in external levels [12,162,163]. Future research in pediatric healthcare could examine if these mechanisms also explain positive adaptation of disease-related challenges. Furthermore, it is acknowledged that positive adaptation to stress is not facilitated by one resilience factor only, but rather is an interplay between multiple factors. Therefore, insight into how these underlying mechanisms across internal and external levels interact would also enhance our understanding of resilience in children with a chronic disease. Furthermore, it should be further elucidated whether underlying mechanisms differ across different diseases. A second aspect is disease-specific associations. As chronic diseases vary in terms of predictability, treatment regimen, side effects, life-expectancy, disability, and impact on daily functioning, it is conceivable that resilience factors have a different contribution to positive adaptation in different disease-related challenges. For instance, self-efficacy of treatment management and self-esteem were identified in this review as internal factors that contribute to resilience. However it is possible that the degree to which these factors facilitate positive adaptation differs per disease. To illustrate: when looking at resilience in pediatric cancer patients more emphasis may be on decreased self-esteem due to changes in physical appearance, whereas self-efficacy of treatment management might be less challenged as cancer treatment is typically administered in hospital settings. To gain more insight into which factors are related to positive adaptation to specific disease-related challenges, it might be useful to use instruments that include questions on disease-specific challenges. Lastly, a third aspect revolves around disease severity. Several articles acknowledged that having a chronic disease or experiencing symptoms of the disease is a stressor, however, the severity of the disease was not often taken into account in the analyses. Van Harmelen et al. showed that taking the severity of the stressor into taking is of importance while researching resilient functioning [19,164]. They quantified resilient functioning as the degree to which the child shows better or worse psychosocial functioning than expected, given their experienced adversity. The researchers define psychosocial functioning as an outcome of positive adaptation to adversity. They identified the resilience factors ‘parent support’ and ‘friendships’ that were significantly more present in children that functioned better than expected given their experienced stress, than children who functioned worse than expected given their experienced stress [19].

In short, our scoping review on resilience in children with a chronic disease provides insight into the variety of definitions and the multidimensionality of resilience outcomes and resilience factors in pediatric healthcare research. Research may profit from a shared definition that facilitates comparability and enhances our understanding of resilience in the pediatric healthcare field. Moreover, future research might focus on which resilience factors are related to positive adaptation in specific disease-related challenges, which underlying mechanisms are responsible for this positive adaptation, and how these underlying mechanisms interact with one another. These insights could be used to develop new psychosocial interventions to stimulate resilience of children with a chronic disease.

REFERENCES

1. Mokkink LB, Van Der Lee JH, Grootenhuis MA, Offringa M, Heymans HSA. Defining chronic diseases and health conditions in childhood (0-18 years of age): National consensus in the Netherlands. *Eur J Pediatr*. 2008;167:1441-1447. doi:10.1007/s00431-008-0697-y
2. van Hal L, Tierolf B, van Rooijen M, van der Hoff M. *Een Actueel Perspectief Op Kinderen En Jongeren Met Een Chronische Aandoening in Nederland. Omvang , Samenstelling En Participatie*.; 2019.
3. van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. *JAMA - Journal of the American Medical Association*. 2010;303(7):623-630. doi:10.1001/jama.2010.104
4. World Health Organisation. *Basic Documents: Forty-Ninth Edition (Including Amendments Adopted up to 31 May 2019)*.; 2020.
5. Huber M, Knottnerus AJ, Green L, et al. How should we define health? *BMJ (Online)*. 2011;343(7817):1-3. doi:10.1136/bmj.d4163
6. Perfect MM, Frye SS. Resiliency in pediatric chronic illness: Assisting youth at school and home. *Resilience interventions for youth in diverse populations*. Published online 2014:423-446.
7. Compas BE, Jaser SS, Dunn MJ, Rodriguez EM. Coping with Chronic Illness in Childhood and Adolescence. *Annu Rev Clin Psychol*. 2012;8(1):455-480. doi:10.1146/annurev-clinpsy-032511-143108
8. Michaud PA, Suris JC, Viner R. The adolescent with a chronic condition. Part II: Healthcare provision. *Arch Dis Child*. 2004;89(10):943-949. doi:10.1136/adc.2003.045377
9. Luthar SS, Cicchetti D, Becker B. The Construct of Resilience: A Critical Evaluation and Guidelines for Future Work. *Child Dev*. 2000;71(3):543-562. doi:10.1111/1467-8624.00164
10. Masten AS. Resilience in children threatened by extreme adversity: Frameworks for research, practice, and translational synergy. *Dev Psychopathol*. 2011;23(2):493-506. doi:10.1017/S0954579411000198
11. Oles M. Resilience and quality of life in chronically ill youth. *Health Psychol Rep*. 2015;3(3):220-236.
12. Kalisch R, Baker DG, Basten U, et al. The resilience framework as a strategy to combat stress-related disorders. *Nat Hum Behav*. 2017;1(11):784-790. doi:10.1038/s41562-017-0200-8
13. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical Resilience in Older Adults: Systematic Review and Development of an Emerging Construct. *J Gerontol A Biol Sci Med Sci*. 2016;71(4):489-495. doi:10.1093/gerona/glv202
14. Hilliard ME, McQuaid EL, Nabors L, et al. Resilience in Youth and Families Living With Pediatric Health and Developmental Conditions: Introduction to the Special Issue on Resilience. *J Pediatr Psychol*. 2015;40(9):835-839.
15. Van Breda A. A critical review of resilience theory and its relevance for social work. *Soc Work*. 2018;54(1). doi:10.15270/54-1-611
16. Ioannidis K, Dahl Askelund A, Kievit RA, al E. The complex neurobiology of resilient functioning after childhood maltreatment. *BMC Med*. 2020;18(32). doi:10.13140/RG.2.2.17380.48005
17. Fritz J, de Graaff AM, Caisley H, al E. A Systematic Review of Amenable Resilience Factors That Moderate and/or Mediate the Relationship Between Childhood Adversity and Mental Health in Young People. *Front Psychiatry*. 2018;9(June). doi:10.3389/fpsyt.2018.00230
18. Rutter M. Resilience in the face of adversity: protective factors and resistance to psychiatric disorders. *British Journal of Psychiatry*. 1985;147:598-611. doi:10.1192/bjp.147.6.598
19. van Harmelen AL, Kievit RA, Ioannidis K, Al E. Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychol Med*. 2017;47(13):2312-2322. doi:10.1017/S0033291717000836
20. Afifi TO, MacMillan HL. Resilience following child maltreatment: A review of protective factors. *Canadian Journal of Psychiatry*. 2011;56(5):266-272. doi:10.1177/070674371105600505
21. Liebenberg L, Ungar M, van d.V.jver F. Validation of the Child and Youth Resilience Measure-28 (CYRM-28) Among Canadian Youth. *Res Soc Work Pract*. 2012;22(2):219-226.
22. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 2018;169(7):467-473. doi:10.7326/M18-0850
23. Lagattuta KH, Sayfan L, Bamford C. Do you know how I feel? Parents underestimate worry and overestimate optimism compared to child self-report. *J Exp Child Psychol*. 2012;113(2):211-232. doi:10.1016/j.jecp.2012.04.001
24. LeBovidge JS, Strauch H, Kalisch LA, Al E. Assessment of psychological distress among children and adolescents with food allergy. *J ALLERGY CLIN IMMUNOL*. 2009;124(6). doi:10.1016/j.jpsychores.2014.10.005

25. Jaser SS, White LE. Coping and resilience in adolescents with type 1 diabetes. *Child Care Health Dev.* 2011;37(3):335-342.
26. Santos FRM, Bernardo V, Gabbay MAL, et al. The impact of knowledge about diabetes, resilience and depression on glycemic control: a cross-sectional study among adolescents and young adults with type 1 diabetes. *Diabetol Metab Syndr.* 2013;5(1).
27. Yi-Frazier JP, Yaptangco M, Semana S, et al. The association of personal resilience with stress, coping, and diabetes outcomes in adolescents with type 1 diabetes: variable- and person-focused approaches. *J Health Psychol.* 2015;20(9):1196-1206.
28. Datylon. Supercharge your chart designs! https://insights.datylon.com/auth/join. Published 2023. Accessed February 24, 2023. https://insights.datylon.com/auth/join
29. Rayyan QCRI. Rayyan QCRI. https://rayyan.qcri.org/reviews/77948.
30. Tang Y, Chen W, Li J, et al. A disease-targeted picture book for children with Henoch-Schonlein purpura nephritis: A quasi-experimental study. *J Ren Care.* Published online 2022. doi:10.1111/jorc.12451
31. Sharp KMH, Willard VW, Okado Y, et al. Profiles of connectedness: Processes of resilience and growth in children with cancer. 2015;40(9):904-913. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc12&NEWS=N&AN=2015-45524-008
32. Schwartz LA, Brumley LD. What a Pain: The Impact of Physical Symptoms and Health Management on Pursuit of Personal Goals Among Adolescents with Cancer.pdf. *J Adolesc Young Adult Oncol.* 2017;6(1).
33. Willard VW, Russell KM, Long A, Al E. The impact of connectedness on social functioning in youth with brain tumors. *Pediatr Blood Cancer.* 2018;66(5).
34. Sharp C, Penner F, Marais L, Lochner S. School connectedness as psychological resilience factor in children affected by HIV/AIDS. *AIDS Care.* 2018;30(4):34-41.
35. Santos T, de Matos MG, Marques A, Simoes C, Leal I, Machado M do C. Adolescent's subjective perceptions of chronic disease and related psychosocial factors: highlights from an outpatient context study. *BMC Pediatr.* 2016;16(1):211.
36. Araia E, King RM, Pouwer F, Speight J, Hendrieckx C. Psychological correlates of disordered eating in youth with type 1 diabetes: Results from diabetes MILES Youth—Australia. *Pediatr Diabetes.* 2020;21(4):664-672. doi:10.1111/pedi.13001
37. Huston SA, Bloun RL, Heidsec T. Resilience, emotion processing and emotionexpression among youth with type 1 diabetes. *Pediatr Diabetes.* 2016;17:623-631.
38. Im YJ, Kim DH. Factors associated with the resilience of school-aged children with atopic dermatitis. *J Clin Nurs.* 2012;21(1):80-88.
39. Kim DH, Im YJ. Resilience as a protective factor for the behavioral problems in school-aged children with atopic dermatitis. *J Child Health Care.* 2014;18(1):47-56.
40. Nabors LA, Graves ML, Fiser KA, Merianos AL. Family resilience and health among adolescents with asthma only, anxiety only, and comorbid asthma and anxiety. *Journal of Asthma.* 2021;58(12):1599-1609. doi:10.1080/02770903.2020.1817939
41. Carlsen K, Haddad N, Gordon J, et al. Self-efficacy and Resilience Are Useful Predictors of Transition Readiness Scores in Adolescents with Inflammatory Bowel Diseases. *Inflamm Bowel Dis.* 2017;23(3):341-346.
42. Beeckman M, Hughes S, van Ryckeghem D, et al. Resilience factors in children with juvenile idiopathic arthritis and their parents: The role of child and parent psychological flexibility. *Pain Medicine (United States).* 2019;20(6):1120-1131. doi:10.1093/pm/pny181
43. Gmuca S, Sonagra M, Xiao R, et al. Suicidal risk and resilience in juvenile fibromyalgia syndrome: a cross-sectional cohort study. *Pediatric Rheumatology.* 2021;19(1). doi:10.1186/s12969-020-00487-w
44. Kim DH, Yoo IY. Factors associated with resilience of school age children with cancer. *J Paediatr Child Health.* 2010;46(7):431-436.
45. Wu LM, Sheen JM, Shu HL, et al. Predictors of anxiety and resilience in adolescents undergoing cancer treatment. *J Adv Nurs.* 2013;69(1):158-166.
46. Robb SL, Burns DS, Stegenga KA, et al. Randomized clinical trial of therapeutic music video intervention for resilience outcomes in adolescents/young adults undergoing hematopoietic stem cell transplant: a report from the Children's Oncology Group. *Cancer.* 2014;120(6):909-917.
47. Bahryni S, Bermas H, Tashvighi M. The self-efficacy forecasting based on hope to life and resiliency in adolescents suffering from cancer. *Biomedical and Pharmacology Journal.* 2016;9(3):1147-1156.
48. Rosenberg AR, Bradford MC, McCauley E, et al. Promoting resilience in adolescents and young adults with cancer: Results from the PRISM randomized controlled trial. *Cancer.* 2018;124(19):3909-3917. doi:10.1002/cncr.31666

49. Wu W, Chang J, Tsai S, Liang S. Assessing Self-concept as a Mediator between Anger and Resilience in Adolescents with Cancer in Taiwan. *Cancer Nurs*. 2018;41(3):210-217.
50. Lee JY, Jeong DC, Chung NG, Lee S. The effects of illness cognition on resilience and quality of life in korean adolescents and young adults with leukemia. *J Adolesc Young Adult Oncol*. 2019;8(5):610-615. doi:10.1089/jayao.2018.0152
51. Chung JOK, Li WHC, Cheung AT, et al. Relationships among resilience, depressive symptoms, self-esteem, and quality of life in children with cancer. *Psychooncology*. 2021;30(2):194-201. doi:10.1002/pon.5548
52. Lee S, Kim S, Young Choi J. Coping and resilience of adolescents with congenital heart disease. *J Cardiovasc Nurs*. 2014;29(4):340-346.
53. Rassart J, Luyckx K, Goossens E, Al E. A big five personality typology in adolescents with congenital heart disease: Prospective associations with psychosocial functioning and perceived health. *Int J Behav Med*. 2016;23(3):310-318.
54. Lee S, Lee J, Choi JY. The effect of a resilience improvement program for adolescents with complex congenital heart disease. *Eur J Cardiovasc Nurs*. 2017;16(4):290-298.
55. Huang HR, Chen CW, Chen CM, et al. A positive perspective of knowledge, attitude, and practices for health-promoting behaviors of adolescents with congenital heart disease. *European Journal of Cardiovascular Nursing*. 2018;17(3):217-225.
56. Whiteley L, Brown LK, Mena L, Craker L, Arnold T. Enhancing health among youth living with HIV using an iPhone game. *AIDS Care*. 2018;30(sup4):21-33. doi:10.1080/09540121.2018.1503224
57. Fee RJ, Hinton VJ. Resilience in children diagnosed with a chronic neuromuscular disorder. *J Dev Behav Pediatr*. 2011;32(9):644-650.
58. Rainone N, Chiodi A, Lanzillo R, Al E. Affective disorders and Health-Related Quality of Life (HRQoL) in adolescents and young adults with Multiple Sclerosis (MS): The moderating role of resilience. *Quality of Life Research*. 2017;26(3):727-736.
59. Arruda MA, Arruda R, Landeira-Fernandez J, Anunciação L, Bigal ME. Resilience and vulnerability in adolescents with primary headaches: A cross-sectional population-based study. *Headache*. 2021;61(3):546-557. doi:10.1111/head.14078
60. Zimmerman K, May B, Barnes K, et al. Post-Traumatic Stress Symptoms in Caregivers and Children with Hydrocephalus. *World Neurosurg*. 2021;148:e66-e73. doi:10.1016/j.wneu.2020.12.008
61. Cui C, Shuang-zi L, Cheng W jin, Wang T. Mediating effects of coping styles on the relationship between family resilience and self-care status of adolescents with epilepsy transitioning to adult healthcare: A cross-sectional study in China. *J Pediatr Nurs*. 2022;63:143-150. doi:10.1016/j.pedn.2021.11.021
62. Simon K, Barakat LP, Patterson CA, Al E. Symptoms of depression and anxiety in adolescents with sickle cell disease: The role of intrapersonal characteristics and stress processing variables. 2009;40(2):317-330.
63. Kaewkong P, Boonchooduang N, Charoenkwan P, Louthrenoo O. Resilience in adolescents with thalassemia. *Pediatr Hematol Oncol*. 2020;38(2):124-133. doi:10.1080/08880018.2020.1821140
64. Wright LA, Cohen LL, Gise J, Shih S, Sil S, Carter, S. Pain and QOL in pediatric sickle cell disease: Buffering by resilience processes. *J Pediatr Psychol*. 2021;46(8):1015-1024. doi:10.1093/jpepsy/jsab034
65. Parviniannasab AM, Rakhshan M, Momennasab M, Soltanian M, Rambod M, Akbarzadeh M. The mediating role of Courageous coping in the relations between spirituality and social support with resilience among adolescents with hemophilia. *Clin Child Psychol Psychiatry*. 2022;27(4):1141-1154. doi:10.1177/13591045211055081
66. Borinsky S, Gaughan JP, Feldman-Winter L. Perceived overweight/obesity, low resilience, and body size dissatisfaction among adolescents. *Obes Res Clin Pract*. 2019;13(5):448-452. doi:10.1016/j.orcp.2019.08.002
67. Li MK, Patel BP, Chu L, Strom M, Hamilton JK. Investigating resilience and its association with stress, anthropometrics, and metabolic health in adolescents with obesity: a pilot study. *Psychol Health Med*. Published online 2022. doi:10.1080/13548506.2022.2059094
68. Ruff RR, Sischo L, Broder H. Resiliency and socioemotional functioning in youth receiving surgery for orofacial anomalies. *Community Dent Oral Epidemiol*. 2016;44(4):371-380.
69. Adibsereshki N, Hatamizadeh N, Kazemnejad A, Sajedi F. RESILIENCE INTERVENTION TO STRENGTHEN SELF-REGULATION IN ADOLESCENT STUDENTS WITH HEARING LOSS. *European Journal of Mental Health*. 2021;16(2):76-98. doi:10.5708/EJMH.16.2021.2.4
70. Hood KK, Iturralde E, Rausch J, et al. Preventing diabetes distress in adolescents with type 1 diabetes: Results 1 year after participation in the STePS program. *Diabetes Care*. 2018;41(8):1623-1630.

71. Lukacs A, Mayer K, Sasvari P, Al E. Health-related quality of life of adolescents with type 1 diabetes in the context of resilience. *Pediatr Diabetes*. 2018;19(8):1481-1486.
72. J. M, A. D, B. W, et al. Determinants of Readiness for Adopting Healthy Lifestyle Behaviors Among Indigenous Adolescents with Type 2 Diabetes in Manitoba, Canada: A Cross-Sectional Study. *Obesity*. 2018;26(5):910-915.
73. Shapiro JB, Bryant FB, Holmbeck GN, Hood KK, Weissberg-Benchell J. Do baseline resilience profiles moderate the effects of a resilience-enhancing intervention for adolescents with type I diabetes? *Health Psychology*. 2021;40(5):337-346. doi:10.1037/hea0001076
74. Rosenberg AR, Yi-Frazier JP, Eaton L, et al. Promoting resilience in stress management: A pilot study of a novel resilience-promoting intervention for adolescents and young adults with serious illness. *J Pediatr Psychol*. 2014;40(9):992-999.
75. Moreira JM, Bouissou Morais Soares CM, Teixeira AL, Simoes e Silva AC, Kummer AM. Anxiety, depression, resilience and quality of life in children and adolescents with pre-dialysis chronic kidney disease. *Pediatr Nephrol*. 2015;30(12):2153-2162.
76. Lee S, Chung NG, Choi JY. Comparison of resilience and quality of life between adolescent blood cancer survivors and those with congenital heart disease: A cross sectional study. *Health Qual Life Outcomes*. 2020;18(1):1-7. doi:10.1186/s12955-020-01487-w
77. Verma T, Rohan J. Examination of transition readiness, medication adherence, and resilience in pediatric chronic illness populations: A pilot study. *Int J Environ Res Public Health*. 2020;17(6):4-14. doi:10.3390/ijerph17061905
78. Biernacka M, Jakubowska-Winecka A, Kalicí nski P. Influence of Parental Attitudes on Formation of Psychological Resilience and Adherence to Medical Regime in Adolescents after Liver or Renal Transplantation. Published online 2021. doi:10.3390/children
79. Kully-Martens K, Pei J, McNeil A, Rasmussen C. Resilience Resources and Emotional and Behavioral Functioning Among Youth and Young Adults with Fetal Alcohol Spectrum Disorder. *Int J Ment Health Addict*. Published online 2021. doi:10.1007/s11469-021-00652-6
80. Tomlinson RM, Bax KC, Ashok D, McMurtry CM. Health-related quality of life in youth with abdominal pain: An examination of optimism and pain self-efficacy. *J Psychosom Res*. 2021;147. doi:10.1016/j.jpsychores.2021.110531
81. Lau N, Yi-Frazier JP, Bona K, Baker KS, McCauley E, Rosenberg AR. Distress and resilience among adolescents and young adults with cancer and their mothers: An exploratory analysis. *J Psychosoc Oncol*. 2020;38(1):118-124. doi:10.1080/07347332.2019.1656317
82. Gheshlagh R, Ebadi A, Dalvandi A. A systematic study of resilience in patients with chronic physical diseases. *Nurs Midwifery Stud*. 2016;6(2).
83. Wagnild GM, Young HM. Development and psychometric evaluation of the Resilience Scale. *J Nurs Meas*. 1993;1(2):165-178.
84. Davydov DM, Stewart R, Ritchie K, Chaudieu I. Resilience and mental health. *Clin Psychol Rev*. 2010;30(5):479-495. doi:10.1016/j.cpr.2010.03.003
85. Haase JE. The adolescent resilience model as a guide to interventions. *Journal of Pediatric Oncology Nursing*. 2004;21(5):289-299.
86. Southwick SM, Charney DS. The Science of Resilience: Implications for the Prevention and Treatment of Depression. *Science (1979)*. 2012;338(October):79-83.
87. Rutter M. Resilience as a dynamic concept. *Dev Psychopathol*. 2012;24(2):335-344. doi:10.1017/S0954579412000028
88. Kim GM, Lim JY, Kim EJ, Park S. Resilience of patients with chronic diseases: A systematic review. *Health Soc Care Community*. 2019;27(4):797-807. doi:10.1111/hsc.12620
89. Haase J, Heiney S, Ruccione K, Stutzer C. Research triangulation to derive meaning-based quality-of-life theory: adolescent resilience model and instrument development. *Int J Cancer Suppl*. 1999;12:125-131.
90. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: Interdisciplinary perspectives. *Eur J Psychotraumatol*. 2014;5. doi:10.3402/ejpt.v5.25338
91. Werner EE. Children of the Garden Island. *Sci Am*. 1989;260(4):106-111.
92. Walsh F. Family resilience: A framework for clinical practice. *Fam Process*. 2003;42(1):1-18. doi:10.1111/j.1545-5300.2003.00001.x
93. Masten AS. Global Perspectives on Resilience in Children and Youth. *Child Dev*. 2014;85(1):6-20.
94. AR Rosenberg, Yi-Fraizer J. Commentary: resilience defined: an alternative perspective. *J Pediatr Psychol*. 2016;41(5):506-509.

95. Tang S, Xiang M, Cheung T, Xiang YT. Mental health and its correlates among children and adolescents during COVID-19 school closure: The importance of parent-child discussion. *J Affect Disord*. 2021;279(October 2020):353-360. doi:10.1016/j.jad.2020.10.016
96. Masten AS, O'Connor MJ. Vulnerability, stress and resilience in the early development of a high risk child. *American Academy of Child and Adolescent Psychiatry*. 1988;28:274-278.
97. Wu G, Feder A, Cohen H, et al. Understanding resilience. *Front Behav Neurosci*. 2013;7.
98. Masten AS. Ordinary magic. Resilience processes in development. *AM Psychol*. 2001;56(3):227-238.
99. Wu Z, Liu Y, Li X, Li X. Resilience and Associated Factors among Mainland Chinese Women Newly Diagnosed with Breast Cancer. *PLoS One*. 2016;11(12).
100. Kaewkong P, Boonchooduang N, Charoenkwan P, Louthrenoo O. Resilience in adolescents with thalassemia. *Pediatr Hematol Oncol*. 2020;38(2):124-133. doi:10.1080/08880018.2020.1821140
101. Dias PC, del Castillo JAG, Moilanen KL. The Adolescent Self-Regulatory Inventory (ASRI) Adaptation to Portuguese Context. *Paidéia (Ribeirão Preto)*. 2014;24(58):155-164. doi:10.1590/1982-43272458201403
102. Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the connor–davidson resilience scale (CD-RISC): Validation of a 10-item measure of resilience. *J Trauma Stress*. 2007;20(6):1019-1028.
103. Kim DH, Yoo IY. Development of a Questionnaire to Measure Resilience in Children with Chronic Diseases. *J Korean Acad Nurs*. 2010;40(2):236. doi:10.4040/jkan.2010.40.2.236
104. Haase JE, Kintner EK, Monahan PO, Robb SL. The resilience in illness model, part 1: exploratory evaluation in adolescents and young adults with cancer. *Cancer Nurs*. 2014;37(3):E1-12.
105. Prince-Embury S. Resiliency Scales for Children and Adolescents: A Profile of Personal Strengths. *Can J Sch Psychol*. 2007;22(2):255-261.
106. Merell KW. SEARS. Published online 2011. Accessed August 21, 2020. https://www.parinc.com/Products/Pkey/406
107. Achenbach TM, Rescorla LA. *Manual for the ASEBA School-Age Forms and Profiles*. University of Vermont, Research Centre for Children, Youth and Families; 2001.
108. Achenbach TM. *The Manual for the Child Behavior Checklist/4-18 and 1991 Profile*. University of Vermont, Department of Psychiatry; 1991.
109. Thompson M, Gray J. Development and validation of a new body-image assessment scale. *J Pers Assess*. 1995;64(2):258-269.
110. Bouma J, Ranchor A, Sanderman R, van Sonderen E. *Het Meten van Symptomen van Depressie Met de CESD: Een Handleiding [The Measurement Ofsymptoms Ofdepression with the CESD: A Manual]*.; 1995.
111. Laurent J, Catanzaro J, Joiner T, et al. A measure of positive and negative affect for children: Scale development and preliminary validation. *Psychol Assess*. 1999;11(3):236-238.
112. Varni J, Seid M, Rode C. The PedsQL™ measurement model for the pediatric quality of life inventory. *Med Care*. 1999;3:126-139.
113. Pynoos R, Rodriquez N, Steinberg A, Stuber M, Frederick C. *The University of California at Los Angeles Posttraumatic Stress Disorder Reaction Index (UCLA-PTSD RI) for DSM-IV (Revision 1)*.; 1998.
114. Goodman R. The strengths and difficulties questionnaire: A research note. *J Child Psychol Psychiatry*. 1997;38(5):581-586. doi:10.1111/j.1469-7610.1997.tb01545.x
115. Roberts R, Lewinsohn P, Seeley J. A brief measure of loneliness suitable for use with adolescents. *Psychol Rep*. 1993;72:1379-1391.
116. Currier J, Hermes S, Phipps S. Children's response to serious illness: Perceptions of bene-fit and burden in a pediatric cancer population. *J Pediatr Psychol*. 2009;34(1129-1134).
117. Phipps S, Long AM, Ogden J. Benefit finding scale for children: preliminary findings from a childhood cancer population. *J Pediatr Psychol*. 2007;32(10):1264-1271.
118. Markowitz J, Butler D, Volkening L, Antisdel J, Anderson B, Laffel L. Brief screening tool for disordered eating in diabetes: inter- nal consistency and external validity in a contemporary sample of pediatric patients with type 1 diabetes. *Diabetes Care*. 2010;33(3):495-500.
119. Schwartz L, Drotar D. Health-related hindrance of personal goal pursuit and well-being of young adults with cystic fibrosis, pediatric cancer survivors, and peers without a history of chronic illness. *J pediatr Psychol*. 2009;34(9):954-965.
120. Yang H, Chen Y, Wang J. Measuring knowledge of patients with congenital heart disease and their parents: Validity of the 'Leuven Knowledge Questionnaire for Congenital Heart Disease.' *Eur J Cardiovasc Nurs*. 2012;11:77-84.
121. Welch G, Jacobson A, Polonsky W. The problem areas in diabetes scale: An evaluation of its clinical utility. *Diabetes Care*. 1997;20:760-766.

122. Varni J, Seid M, Kurtin P. Pediatric health-related quality of life measurement technology: a guide for health care decision makers. *Journal of Clinical Outcomes Management*. 1999;6:33-40.
123. Fenton N, Ferris M, Ko Z, Javalkar K, Hooper S. The relationship of health care transition readiness to disease-related characteristics, psychosocial factors, and health care outcomes: Preliminary findings in adolescents with chronic kidney disease. *J pediatr Rehabil Med*. 2015;8:13-22.
124. Wood D, Sawicki G, Miller M, et al. The Transition Readiness Assessment Questionnaire (TRAQ): its factor structure, reliability, and validity. *Acad Pediatr*. 2014;14:415-422.
125. Reynolds C, Kamphaus R. *Behavior Assessment System for Children Manual*. 2nd ed. AGS Publishing; 2004.
126. Beck J, Beck A, Jolly J, Steer R. *Beck Youth Inventories for Children and Adolescents*. NCS Pearson, Inc; 2005.
127. Moreira JM, Bouissou Morais Soares CM, Teixeira AL, al E. Anxiety, depression, resilience and quality of life in children and adolescents with pre-dialysis chronic kidney disease. *Pediatr Nephrol*. 2015;30(12):2153-2162.
128. Sandler IN, Tein JY, Wolchik S, al E. Coping Efficacy and Psychological Problems of Children of Divorce. *Child Dev*. 2000;71(4):1099-1118.
129. Carver CS. You want to measure coping but your protocol's too long: Consider the Brief COPE. *Int J Behav Med*. 1997;4:92-100.
130. Endler N, Parker J. *Coping Inventory for Stressful Situations (CISS): Manual*. 2nd ed. Multi-Health Systems; 1999.
131. Jalowiec A. Psychometric assessment of the Jalowiec Coping Scale. *Nurs Res*. 1984;33:157-161.
132. Barger J, Vitale P, Gaighan J, Feldman-Winter L. Measuring resilience in the adolescent population: a succinct tool for outpatient adolescent health. *J Pediatr2*. 2017;189:201-206.
133. Gartland D, Bond L, Olsson CA, Buzwell S, Sawyer SM. Development of a multi-dimensional measure of resilience in adolescents: the Adolescent Resilience Questionnaire. *BMC Med Res Methodol*. 2011;11:134.
134. Connor KM, Davidson JRT. Development of a new Resilience scale: The Connor-Davidson Resilience scale (CD-RISC). *Depress Anxiety*. 2003;18(2):76-82.
135. Martins MH. *Contribuições Para a Análise de Crianças e Jovens Em Situação de Risco - Resiliência e Desenvolvimento [Contributions for the Analysis of Children and Adolescentes in Risky Situations – Resilience and Development]*. Universidade do Algarve; 2005.
136. McCracken L, Gauntlett-Gilbert J, Eccleston C. Acceptance of pain in adolescents with chronic pain: Validation of an adapted assessment instrument and preliminary correlation analyses. *Eur J Pain*. 2010;14(3):316-320.
137. Evers A, Kraaimaat F. Illness Cognition Questionnaire. www.andreaevers.nl. Published 2009. Accessed May 6, 2021. https://www.andreaevers.nl/uploads/bestanden/ICQ18-En.pdf
138. Cutrona CE, Russel DW. The provisions of social relationships and adaptation to stress. *Advances in personal relationships*. 1987;1(37-67).
139. Fisher JD, Fisher WA, Amico KR, Harman JJ. An information-motivation-behavioral skills model of adherence to antiretroviral therapy. *Health Psychology*. 2006;25(4):462-473. doi:10.1037/0278-6133.25.4.462
140. Gil KM, Williams DA, Thompson RJ, et al. Sickle Cell Disease in Children and Adolescents: The Relation of Child and Parent Pain Coping Strategies to Adjustment. *J Pediatr Psychol*. 1991;16(5):643-663.
141. Wu L, Chin C, Chen C, Lai F, Tseng Y. Development and validation of the paediatric cancer coping scale. *J Adv Nurs*. 2011;67(5):1142-1152.
142. Connor-Smith JK, Compas BE, Wadsworth ME, al E. Responses to stress in adolescence: measurement of coping and involuntary stress responses. *J Consult Clin Psychol*. 2000;68:976-992.
143. Lim J, Lee K, Oh M, Kwak K, Lee H, Yoon B. A study on reliability and validity of FACES. *J Korean Acad Fam Med*. 1990;11:8-17.
144. Olson D. *Family Inventories*. Family Social Science, University of Minnesota; 1985.
145. Karcher MJ. *The Hemingway: Measure of Adolescent Connectedness: A Manual for Scoring and in-Terpretation. Unpublished Manuscript*. University of Texas; 2005.
146. Karcher MJ, Sass D. A multicultural assessment of adolescent connectedness: Testing measurement invariance across gender and ethnicity. *J Couns Psychol*. 2010;57:274-289.
147. Hilliard ME, Iturralde E, Weissberg-Benchell J, Hood KK. The Diabetes Strengths and Resilience Measure for Adolescents With Type 1 Diabetes (DSTAR-Teen): Validation of a New, Brief Self-Report Measure. *J Pediatr Psychol*. 2017;42(9):995-1005.

148. Zolkoski SM, Bullock LM. Resilience in children and youth: A review. *Child Youth Serv Rev*. 2012;34(12):2295-2303.

149. Smith AJ, Moreno-López L, Davidson E, et al. REACT study protocol: resilience after the COVID-19 threat (REACT) in adolescents. *BMJ Open*. 2021;11(1):e042824. doi:10.1136/bmjopen-2020-042824

150. Diener E. Subjective Well-being. *Psychol Bull*. 1984;95(3):542-575.

151. Weich S, Brugha T, King M, et al. Mental well-being and mental illness: findings from the Adult Psychiatric Morbidity Survey for England 2007. *British Journal of Psychiatry*. 2011;199(1):23-28. doi:10.1192/bjp.bp.111.091496

152. Rao SK, Wallace LMK, Theou O, Rockwood K. Is it better to be happy or not depressed? Depression mediates the effect of psychological well-being on adverse health outcomes in older adults. *Int J Geriatr Psychiatry*. 2017;32(9):1000-1008. doi:10.1002/gps.4559

153. Huber M, Van Vliet M, Giezenberg M, et al. Towards a "patient-centred" operationalisation of the new dynamic concept of health: A mixed methods study. *BMJ Open*. 2016;6(1):1-11. doi:10.1136/bmjopen-2015-010091

154. Gartland D, Riggs E, Muyeen S, et al. What factors are associated with resilient outcomes in children exposed to social adversity? A systematic review. *BMJ Open*. 2019;9(4):1-14. doi:10.1136/bmjopen-2018-024870

155. Bronfenbrenner U. *The Ecology of Human Development*. Harvard University Press; 1979.

156. McNeely C, Nonnemaker J, Blum R, al E. Promoting school connectedness: Evidence from the National Longitudinal Study of Adolescent Health. *Journal of School Health*. 2002;72:138-146.

157. Mannion R, Davies H. Understanding organisational culture for healthcare quality improvement. *BMJ (Online)*. 2018;363(November):1-4. doi:10.1136/bmj.k4907

158. Masten AS. Pathways to Integrated Resilience Science. *Psychol Inq*. 2015;26(2):187-196. doi:10.1080/1047840X.2015.1012041

159. Varni J, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life?: An analysis of 8,591 children across age subgroups with the PedsQL™ 4.0 Generic Core Scales. *Health Qual Life Outcomes*. 2007;5(1):1. doi:10.1186/1477-7525-5-1

160. Vannest KJ, Ura SK, Lavadia C, Zolkoski S. Self-report Measures of Resilience in Children and Youth. *Contemp Sch Psychol*. 2021;25(4):406-415. doi:10.1007/s40688-019-00252-1

161. King L, Jolicoeur-Martineau A, Laplante DP, Szekely E, Levitan R, Wazana A. Measuring resilience in children: a review of recent literature and recommendations for future research. *Curr Opin Psychiatry*. 2021;34(1):10-21. doi:10.1097/YCO.0000000000000663

162. Ioannidis K, Dahl Askelund A, Kievit R, et al. The complex neurobiology of resilient functioning after childhood maltreatment. *Preprint*. 2018;(March):1-38. doi:10.13140/RG.2.2.17380.48005

163. Kalisch R, Cramer AOJ, Binder H, et al. Deconstructing and Reconstructing Resilience: A Dynamic Network Approach. *Perspectives on Psychological Science*. 2019;14(5):765-777. doi:10.1177/1745691619855637

164. van Harmelen AL, Blakemore SJ, Goodyer IM, Kievit RA. The Interplay Between Adolescent Friendship Quality and Resilient Functioning Following Childhood and Adolescent Adversity. *Advers Resil Sci*. Published online 2020. doi:10.1007/s42844-020-00027-1

SUPPLEMENT 1:

Search strings (search performed on December 9, 2022)

PubMed (items = 1531):
("Chronic Disease"[MeSH] OR "disease"[MeSH] OR "disease*"[tiab] OR "illness*"[tiab] OR "condition*"[tiab] OR "sickness*"[tiab] OR "disorder*"[tiab]) AND ("child"[MeSH] OR "adolescent"[MeSH] OR "child*"[tiab] OR "adolescen*"[tiab] OR "minor*"[tiab] OR "juvenile*"[tiab] OR "kid*"[tiab] OR "young*"[tiab] OR pediatrics[MESH] OR pediatri* [tiab] OR paediatri*[tiab] OR boy[tiab] OR boys[tiab] OR girl[tiab] OR girls[tiab] OR schoolchild*[tiab] OR school child*[tiab]] OR youth[tiab] OR youths[tiab] OR teen[tiab] OR teens[tiab] OR teenager[tiab]) AND ("Resilience, Psychological"[MeSH] OR "resilien*"[tiab])

Embase (items = 1388):
('chronic disease'/exp OR 'diseases'/exp OR disease*.ti,ab,kw OR illness*.ti,ab,kw OR condition*.ti,ab,kw OR sickness*.ti,ab,kw OR disorder*.ti,ab,kw) AND ('child'/exp OR 'adolescent'/exp OR adolescen*.ti,ab,kw OR minor*.ti,ab,kw OR juvenile*.ti,ab,kw OR kid*. ti,ab,kw OR young*.ti,ab,kw OR pediatri*.ti,ab,kw OR paediatri*.ti,ab,kw OR boy.ti,ab,kw OR boys.ti,ab,kw OR girl.ti,ab,kw OR girls.ti,ab,kw OR schoolchild*.ti,ab,kw OR child*.ti,ab,kw OR youth.ti,ab,kw OR youths.ti,ab,kw OR teen.ti,ab,kw OR teens.ti,ab,kw OR teenager. ti,ab,kw) AND ('psychological resilience'/exp OR resilien*.ti,ab,kw)

PsycINFO (items = 4397):
(exp Chronic Illness/ or disease.mp. or (disease* or illness* or condition* or sickness* or disorder*).ti,ab.) and (child.mp. or adolescent.mp. or (child* or adolescen* or minor* or juvenile* or kid* or young* or pediatric* or paediatri* or boy or boys or girl or girls or schoolchild or youth or youths or teen or teens or teenager).ti,ab.) and (exp "Resilience (Psychological)"/ or resilien*.ti,ab.)

Cochrane (items = 1450):
((MeSH descriptor: [Chronic Disease] explode all trees) OR (MeSH descriptor: [Disease] explode all trees) OR ((disease*):ti,ab,kw OR (illness*):ti,ab,kw OR (condition*):ti,ab,kw OR (sickness*):ti,ab,kw OR (disorder*):ti,ab,kw)) AND ((MeSH descriptor: [Child] explode all trees) OR (MeSH descriptor: [Adolescent] explode all trees) OR ((child*):ti,ab,kw OR (adolescen*):ti,ab,kw OR (minor*):ti,ab,kw OR (young*):ti,ab,kw OR (kid*):ti,ab,kw)) AND ((MeSH descriptor: [Resilience, Psychological] explode all trees) OR ((resilien*):ti,ab,kw))

SUPPLEMENT 2:

Study characteristics, resilience definition, and assessment of resilience of the included studies

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Atopic diseases								
LeBovidge (2009)[1] *Food allergy*	Cross-sectional	141	8-17	USA	No definition	NA	● Behavior Assessment System for Children Self-Report of Personality (BASC-2 SRP)	● Child Attitude Toward Illness Scale (CATIS)
Im (2012)[2] *Atopic dermatitis*	Cross-sectional	102	7-15	South Korea	"(...) individuals may overcome difficulties and adapt better using their positive capacities and available resources even under the risky and challenging situation, such as diagnosing a chronic disease interfering the child and family's life."	Davis (2004)[3]	● Resilience measurement instrument for children with chronic illness	● Childrearing Behavior Questionnaire
Kim (2014)[4] *Atopic dermatitis*	Cross-sectional	120	7-13	South Korea	"(...) the ability to function with healthy responses despite the presence of significant stress and adversity"	Masten & O'Connor (1988)[5]	● Child Behavior Checklist (K-CBCL)	● Resilience measurement instrument for children with chronic illness
Nabors (2021)[6] *Asthma*	Cross-sectional	2383	12-17	USA	"Family resilience involves adjustment or rebounding in the face of stress. Family resilience can involve problem-solving, interacting positively with each other, and at the same time be influenced by a multitude of environmental stressors experienced by family members."	Buehler (2020)[7], Walsh (2016)[8], Traub (2017)[9]	● Family Resilience: NSCH-subscale 'family flourishing'	
Auto-immune disorders								
Carlsen (2017)[10] *Inflammatory Bowel Diseases*	Cross-sectional	87	16-23	USA	"One's ability to bounce back from obstacles."	Iacoviello (2014)[11]	● Transition Readiness Assessment Questionnaire (TRAQ)	● Connor-Davidson resiliency questionnaire (CD-RISC-10)

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Beeckman (2019)[12] *Juvenile idiopathic arthritis*	Cross-sectional	59	13.8 ± 2.67	Belgium	"(...) resilience factors is crucial if we are to understand how, why, and in which contexts some individuals function well despite pain whereas others do not."	Goubert (2017)[13], Cousins (2015)[14], Sturgeon (2010)[15]	● Pediatric Quality of Life Inventory (PedsQL) ● Positive and Negative Affect Scale for Children (PANAS-C)	● Psychological flexibility: Avoidance and Fusion Questionnaire for Youth (AFQ-Y) ● Dutch Chronic Pain Acceptance Questionnaire– Adolescent version (CPAQ-A)
Gmuca (2021)[16] *Juvenile fibromyalgia syndrome*	Cross-sectional	31	12-17	USA	"Resilience serves as an important protective factor against psychological distress. Resilience can be defined as a dynamic process of positive adaptation or continued development in the context of adversity (e.g. chronic pain)."	Masten (2001)[17], Luthar (2000)[18]		●14-item Resilience Scale (RS-14)
Tang (2022)[19] *Henoch Schonlein purpura nephritis*	Longitudinal	60	9.15 ± 1.59	China	No definition	NA	● Chronic Illness Children's Resilience Scale (CICRS)	
					Malignancies			
Kim (2010)[20] *Cancer (nfs)*	Cross-sectional	74	10-15	South Korea	"The concept of resilience came from the paradigm that individuals could overcome difficulties and adapt better by utilising strengths and abilities that they already have."	NR	● Resilience measurement instrument for children with chronic illness	● Family Adaptability and Cohesion Scale (FACES III) ● Relationship with friends: Personal Relationship Measurement ● Relationship with teachers: School Adjustment Test

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Wu (2013)[21] *Cancer (nfs)*	Cross-sectional	131	11–19	Taiwan	"(…) the ability to recover from or overcome negative events in terms of mental health, functional capacity, and social competence"	Hunter & Chandler (1999)[22]	● Haase Adolescent Resilience in Illness Scale (HARIS)	● Pediatric Cancer Coping Scale (PCCS)
Robb (2014)[23] *Hematopoietic Stem Cell Transplant*	RCT	113	11–24	USA	"The process of identifying or developing resources and strengths to flexibly manage stressors to gain a positive outcome, a sense of confidence, mastery, and self-esteem."	Haase (2004)[24]	● Haase Adolescent Resilience in Illness Scale (HARIS)	● McCorkcle Symptom Distress Scale ● Mishel Uncertainty in Illness Scale ● Jalowiec Coping Scale-Revised ● Reed Spiritual Perspective Scale ● Perceived social support from healthcare providers, friends and family: Perceived Social Support ● Family adaptability/Cohesion Scale II ● Parent-Adolescent Communication Scale ● Family Strengths Scale ● Hope-Derived Meaning: Herth Hope Index
Howard Sharp (2015)[25] *Cancer (nfs)*	Cross-sectional case-control	254	8–19	USA	No definition	NA	● UCLA PTSD Reaction Index for DSM-IV (PTSDI) ● Benefit Finding/Burden Scale for Children (BBSC)	● Hemingway Measure of Adolescent Connectedness (HMAC)
Bahryni (2016)[26] *Cancer (nfs)*	Cross-sectional	120	NR	Iran	"(…): resiliency is defined as human adaptability in confrontation with overwhelming disasters or pressures, overcoming and even get strengthen by them. It can be said that resiliency is an individual's ability to make bio-psycho balance in dangerous conditions."	Diener (2003)[27], Connor & Davidson (2003)[28]	● General self-efficacy questionnaire (GSE-10)	● Connor-Davidson resiliency questionnaire (CD- RISC-25)

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Schwartz (2017)[29] *Cancer (nfs)*	Cross-sectional case-control	199	13-19	USA	No definition	NA	● Health-related Hindrance Inventor	● Brief Coping Orientation to Problems Experienced (COPE)¶ ● Cowen Self-Efficacy Scale ● Childen's Hope Scale (CHS) ● Family Assessment Device ● Perceived Social Support Scale
Rosenberg (2018)[30] *Cancer (nfs)*	RCT	92	12-25	USA	"The process of harnessing resources to sustain physical and emotional well-being in the face of significant stress."	Bonnano (2011)[31]	● Coping Orientation to Problems Experienced (CD-RISC-10)	
Willard (2018)[32] *Brain tumor*	Prospective study	53	13.11 ± 2.31	USA	No definition	NA	● Social-Emotional Assets and Resilience Scales (SEARS¶)	● Hemingway Measure of Adolescent Connectedness (HMAC)
Wu (2018)[33] *Cancer (nfs)*	Cross-sectional	40	10-18	Taiwan	"(...) the capacity of individuals to successfully maintain their psychosocial well-being in the face of adversity, is a positive health concept that may be used to improve psychosocial well-being and quality of life in adolescents with cancer."	Stewart (2011)[34], Haase (2014)[35]	● The Wagnild and Young Resilience Scale (RS)	● Beck Self- Concept Inventory (BSCI-Y)
Lee (2019)[36] *Leukemia*	Cross-sectional	72	13-20	South Korea	"The ability to adapt to situations and environments through self-regulation."	Gheshlagh (2016)[37]	● The Wagnild and Young Resilience Scale (RS)	● Illness Cognition Questionnaire (ICQ)
Lau (2020)[38] *non-central nervous system cancer*	Longitudinal	14	14-25	USA	"(...) a process of harnessing resources needed to sustain individual well-being."	Haase (1999)[39-41], Southwick (2014), Rosenberg (2014)	● Connor-Davidson resiliency questionnaire (CD-RISC-10¶)	● Parental distress: Kessler-6 psychological distress scale (K6)

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or **mean** ± **SD (years)**	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Chung (2021)[42] *Leukemia, lymphoma, brain tumor, osteosarcoma, kidney tumor*	Cross-sectional	138	7-14	China	"Resilience is defined as an individual's strength and ability to moderate the negative effects of stress, promote adaptation, and maintain mental well-being in the face of adversity."	Wagnild (1993)[43], Davydov (2003)[44]	● Pediatric Quality-of-Life Inventory Cancer Module version 3.0 (PedsQL Cancer Module)	● 14-item Resilience Scale (RS-14)
					Congenital Heart Disease			
Lee (2014)[45]	Cross-sectional	103	14-20	South Korea	"(...) a dynamic process encompassing positive adaptation within the context of significant adversity; it is the ability to sustain adaptive functioning and positive growth and development in the face of significant stress."	Luthar (2000)[18], Compas (2006)[46], Mandleco (2000)[47]	● The Wagnild and Young Resilience Scale (RS)	● Coping Inventory for Stressful Situations (CISS)
Rassart (2016)[48]	Prospective study	366	15-20	Belgium	"Ego-resiliency refers to the tendency to respond flexibly to environmental demands."	Block (1980)[49]	● Depression: Center for Epidemiologic Studies Depression Scale (CESDS) ● UCLA loneliness scale ● Pediatric Quality of Life Inventory (PedsQL) ● Cardiac module of the Pediatric Quality of Life Inventory (PedsQL)	● Personality Typology: Quick Big Five
Lee (2017)[50]	Controlled trial	60	14-22	South Korea	"(...) a dynamic process that encompasses positive adaptations to critical adversity, which is essentially the ability to maintain a pattern of positive responses and development in the face of crisis." "Resilience is associated with five psychosocial factors: (1) positive emotions (including optimism and humor), (2) cognitive flexibility (including positive explanatory style, positive appraisal and acceptance), (3) meaning (including religion, spirituality and altruism), (4) social support (including role models) and (5) an active coping style (including exercise and training)."	Luthar (2000)[18], Compas (2006)[46], Southwick (2005)[51]	● The Wagnild and Young Resilience Scale (RS)	

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Huang (2018)[52]	Cross-sectional	320	12–18	Taiwan	"(…) the ability of an individual to successfully manage his or her life, and to successfully adapt to change and stressful events in healthy and constructive ways."	Dent (2008)[53]	● Health promoting behavior: Leuven Knowledge Questionnaire for Congenital Heart Disease (LKQCHD) ● Haase Adolescent Resilience in Illness Scale (HARIS)	
Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome								
Sharp (2018)[54]	Cross-sectional	750	7–11	USA	No definition	NA	● Behavioral and emotional problems: Strength and Difficulties Questionnaire (SDQ) ● School Connectedness Scale (SCS) ● Scale of Satisfaction with Social Support (SSS)	
Whiteley (2019)[55]	RCT	61	14–26	USA	"Resilience, broadly defined as the capacity and skills to confront life challenges, can be a target for prevention and intervention programs for youth. Interventions can focus on resilience factors that can be measured and improved, such as self-efficacy, motivation, and support seeking."	Furniss (2014)[56], Johnson (2003)[57], among others	● Self-efficacy for ART use ● ART motivation ● Social support	
Nonmalignant hematological diseases								
Simon (2009)[58] *Sickle Cell Disease*	Cross-sectional	44	12–18	USA	" (…) resilience factors such as cognitive appraisals (i.e., hope and coping strategies) and intrapersonal characteristics (i.e., self-esteem and sense of inadequacy). The interplay among all these factors is thought to account for the variation in adaptation among adolescents with a chronic illness."	Wallander (1998)[59]	● Internalizing symptoms: Behavior Assessment System for Children (BASC) ● Children's Attributional Style Questionnaire-Revised (CASQ-R) ● Children's Hope Scale (CHS) ● Coping Strategies Questionnaire for Sickle Cell Disease (CSQ)	
Kaewkong (2020)[60] *Thalassemia*	Cross-sectional	120	10–18	Thailand	"(…) a dynamic ability to adapt successfully in the face of adversity, trauma, or significant threat."	Chmitorz (2018)[61], Masten (2014)[62]	● Behavioral and emotional problems: Strengths and Difficulties Questionnaire (SDQ)	

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Wright (2021)[63] *Sickle cell disease*	Cross-sectional	93	12–18	USA	"The process of resilience—an individual's ability to respond effectively to risk or adversity- (…)."	Masten (2001)[17]	● Pediatric Quality of Life Inventory (PedsQL)	● Child and Adolescent Mindfulness Measure (CAMM) ● Chronic Pain Acceptance Questionnaire (CPAQA)
Parviniannasab (2022) [64] *Hemophilia*	Cross-sectional	372	11–21	Iran	"(…) using one's strength and capacity to adapt to stressful situations. Resilience is the ability and a personality characteristic which helps patients maintain their mental health when facing hardship and physical illnesses."	Connor & Davidson (2003)[28], Haase (1999)[39]	● Connor-Davidson resiliency questionnaire (CD-RISC-10)	
					Nonmalignant neurological diseases			
Fee (2011)[65] *Duchenne Muscular Dystrophy*	Retrospective	165	6–14	USA	"(…) 'a dynamic process encompassing positive adaptation within the context of significant adversity'. Resilience is 'the ability to maintain a stable equilibrium' (…) It is not a particular personality trait but a process by which positive adaptation occurs despite adversity."	Werner (1989)[66]	● General psychosocial adjustment: Child Behavior Checklist (CBCL) ● IQ: Peabody Picture Vocabulary Test—Third Edition (PPVT-III) ● Social support: Child Behavior Checklist (CBCL)-social scale	
Rainone (2017)[67] *Multiple Sclerosis*	Cross-sectional	53	14–24	Italy	"A process through which the impact of a critical event is mitigated by the ability to overcome it by using and negotiating resources."	NR	● Pediatric Quality of Life Inventory (PedsQL) ● Ego-Resiliency Scale ● Child and Youth Resilience Measures-28 (CYRM-28)	
Arruda (2021)[68] *Primary headaches*	Cross-sectional	339	10–18	Brazil	"Childhood resilience is a dynamic developmental process that reflects positive adaptation despite significant life adversities."	Luthar (2000)[18]	● Resilience Scale for Children and Adolescents (RSCA)	

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Zimmerman (2021)[69] *Hydrocephalus*	Cross-sectional	40	7–21	USA	"(…) the process by which individuals use available resources to maintain well-being in the face of stress."	Bonanno (2011)[70]	● Connor-Davidson resiliency questionnaire (CD-RISC-10)	
Cui (2022)[71] *Epilepsy*	Cross-sectional	1238	12–18	China	"Resilience refers to the family's ability to withstand stressful experiences and rebound from them by creating new, healthy ways of functioning."	Walsh (2003)[72]		● Family Resilience Assessment scale (FRAS-C)
Obesity								
Borinsky (2019)[73]	Cross-sectional	85	13–21	USA	"(…) the protective factors that dynamically allow one to have a good outcome, over-coming stress and adversity, while sustaining normal psychological and physical functioning."	Wu (2013)[74], Masten (2001)[17]	● Body size dissatisfaction: Contour Drawing Rating Scale (CDRS)	● Resilience: 7Cs tool
Li (2022)[75] *Metabolically healthy obesity (MHO)* *Metabolically unhealthy obesity (MUO)*	Cross-sectional	39	MHO: 15.7 ±0.5 MUO: 15.3±0.4	Canada	"A positive psychological adjustment in the face of adversity which is associated with improved health outcomes in patients with chronic conditions."	Wu (2016)[76]		● Adolescent Resilience Questionnaire (ARC)
Otolaryngology problems								
Ruff (2016)[77] *Orofacial anomalies*	Longitudinal study	1196	7.5–18.5	USA	"(…) an important factor among individuals facing potential adversity, and emotional and social functioning are critical for future development."	NR	● Psychosocial functioning: Beck Youth Inventory for Emotional and Social Impairment (2nd edition)	● Resilience Scale for Children and Adolescents (RSCA)
Adibsereshki (2021)[78] *Hearing loss*	Experimental	122	12–15	Iran	"Resilience refers to a dynamic process wherein individuals show positive adaptation despite experiences of significant adversity."	Luthar (2000)[18]	● The Adolescent Self-Regulatory Inventory (ASRI)	

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Type 1 Diabetes/ Type 2 Diabetes								
Jaser (2011)[79] *Type 1 Diabetes*	Cross-sectional	30	10-16	USA	"(...) factors that promote successful adaptation to type 1 diabetes. These positive outcomes in the context of a potentially adverse environment may be considered indicators of resilience."	Luthar (2000)[18], Masten (2007)[80]	● Child Competence: Youth Self Report (YSR) ● Pediatric Quality of Life Inventory (PedsQL) ● Metabolic control: HbA1c¥	● Responses to Stress Questionnaire (RSQ)
Yi-Frazier (2015)[81] *Type 1 Diabetes*	Pilot study	50	13-18	USA	"(...) is a construct describing an individual's capacity to maintain psychological and/or physical well-being in the face of stress." "(...) personal resilience embodies combined personal resources including self-esteem, optimism, and self-efficacy."	Rew and Horner (2003)[82] Connor & Davidson (2003)[28] Yi (2008)[83]	● Problem Areas in Diabetes Scale (PAID) ● Diabetes Self-Management Profile (DSMP) ● Pediatric Quality of Life Inventory (PedsQL) ● Metabolic control: HbA1c	● Optimism: Life Orientation Test ● Rosenberg Self-Esteem Scale ● Self-efficacy for diabetes (SED)
Huston (2016)[84] *Type 1 Diabetes*	Cross-sectional	243	11-16	USA	No definition	NA	● Benefit Finding Scale for Children (BFSC) ● Diabetes acceptance, fitting in, and comfort in adjusting for diabetes in public*	● Emotion processing and regulation: Emotional Approach & Coping Scale (EAC)
Hood (2018)[85] *Type 1 Diabetes*	RCT	264	14-18	USA	"Resilience consists of the following four key constructs: a sense of hopefulness, an optimistic explanatory style, effective coping strategies, and positive problem-solving skills."	Gillham (2006)[86]		● Resilience Scale for Children and Adolescents (RSCA) ● Automatic Thoughts Questionnaire (ATQ) ● Coping Efficacy Questionnaire (CEQ) ● Diabetes Strengths and Resilience measure for adolescents (DSTAR-Teen) ● Social Problem-Solving Inventory-Revised short form (SPSI-R:S)

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Lukács (2018)[87] *Type 1 Diabetes*	Prospective cohort study	229	13-19	Hungary	"(...) a capacity of a dynamic system that helps individuals to overcome the negative effects, recover from adverse circumstances while maintaining normal development. It is not a quality that is always present in every situation, but a process of harnessing new and existing resources to maintain well-being during and after any stressor."	Masten (2014)[88], Rosenberg (2016)[89]	● PedsQL Diabetes module	● The Neil and Dias Resilience Scale
McGavock (2018)[90] *Type 2 Diabetes*	Cross-sectional	162	10-25	Canada	"(...) a hedge against poor mental health"	Dray (2017)[91]	● Resilience Scale for Children and Adolescents (RSCA)	● Patient-Based Assessment and Counseling for Physical Activity and Nutrition-Adolescent assessment forms (PACE-Adolescent)
Araia (2019)[92] *Type 1 Diabetes*	Cross-sectional	477	16 ± 2	Australia	No definition	NA	● Diabetes Eating Problem Survey-Revised (DEPS-R)	● Diabetes Strengths and Resilience measure for adolescents (DSTAR)
Shapiro (2021)[93] *Type 1 Diabetes*	Longitudinal	264	14-18	USA	"Resilience refers to achieving positive emotional, behavioral, or health outcomes in the face of adversity, such as managing a complex medical condition. Resilience processes refer to protective skills and assets that contribute to optimal health and psychological outcomes when exposed to risk or adversity. Resilience processes for youth with type 1 diabetes are multi-faceted, spanning individual, familial, and contextual systems, and some can be modified through intervention to improve resilience."	Hilliard (2013)[94]		● The Coping Efficacy Scale ● The Social Problem-Solving Inventory – Revised (SPSI-R) ● Automatic Thoughts Questionnaire (ATQ) ● Hopelessness Scale for Children (HSC) ● Diabetes Family Conflict Scale-Revised (DFCS-R)

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Other or combination of chronic diseases (for *diagnosis* see column author)								
Rosenberg (2014)[41] *Type 1 Diabetes, cancer*	RCT	30	12–25	USA	"(…) a universal construct describing an individual's capacity to maintain psychological and/or physical well-being in the face of stress and is a good candidate to buffer the negative impact of serious illness among multiple populations of adolescents and young adults."	Haase (2004)[95], Southwick& Charney (2012)[96]	● Connor-Davidson resiliency questionnaire (CD-RISC-10)	
Moreira (2015)[97] *Chronic Kidney Disease*	Cross-sectional	28	9–18	Brazil	"Resilience refers to an adaptive behavior associated with either internal states of well-being or adequate functioning in the environment and can be also defined as "a dynamic, multidimensional process, which results in positive adaptation in adverse contexts"."	Luthar (2000)[18]	● The Wagnild and Young Resilience Scale (RS)	
Santos (2016)[98] *Type 1 Diabetes, allergic diseases, neurological diseases*	Cross-sectional	135	11–17	Portugal	No definition	NA	● Healthy Kids Resilience Assessment Module	● Connectedness to school: Scale of Satisfaction with Social Support (SSSS)
Lee (2020)[99] *Congenital Heart Disease, Leukemia*	Cross-sectional	175	12–20	South Korea	"(…) the process of effectively negotiating, adapting to, or managing a significant source of stress or trauma."	Windle (2011)[100]	● The Wagnild and Young Resilience Scale (RS)	
Verma (2020)[101] *Various chronical diseases*	Cross-sectional	50	13–21	USA	"(…) a measure of adaptability to stress and ability to overcome challenges."	Seligman (2011)[102], Luthar (2000)[18], among others	● Self-Management and Transition to Adulthood with Rx (STARx)	● Connor-Davidson resiliency questionnaire (CD-RISC-25)

Study characteristics, resilience definition, and assessment of resilience of the included studies (continued)

First Author (year), *Disease*	Study design	n	Age range or mean ± SD (years)	Country	Definition of resilience	Originally defined by	Assessment of resilience	
							● *Resilience outcome*	● *Resilience factor(s)*
Biernacka (2021)[103] *Liver or Renal transplantation*	Cross-sectional	96	12–18	Switzerland	"Psychological resilience is mentioned among the various psychological resources facilitating beneficial adaptation to illness. Resilience is revealed in the context of coping with negative life events and difficulties. In this sense, resilience can be viewed as an indicator of mental strength. Thanks to it, despite adversities, a person can develop and maintain mental health. (...) When it comes to a chronic illness, psychological resilience is a resource that promotes adaptation to the circumstances of the illness and the limitations generated by it."	Rutter (2012)[104], Kim (2019)[105]		● Resilience Assessment Scale for Children and Adolescents (SPP-18)
Kully-Martens (2021)[106] *Fetal Alcohol Spectrum Disorder*	Cross-sectional	19	13–23	Canada	"Resilience is a phenomenon defined by competent (or developmentally typical) adaptation amidst adversity."	Masten and Cicchetti (2016)[107]	● Behavioral Assessment System for Children (BASC-2)	● Child and Youth Resilience Measure (CYRM-28)
Tomlinson (2021)[108] *Functional gastrointestinal disorders or organic gastrointestinal disorders*	Cross-sectional	98	8–17	Canada	(...) protective factor model of resilience in which personal assets serve as buffers between risk factors and negative outcomes (...).	Fergus (2005)[109]	● Pediatric Quality of Life Inventory (PedsQL)	● Youth Life Orientation Test (YLOT), optimism subscale ● Child Self-Efficacy Scale (CSES)

NA = not applicable; NR = not reported; nfs = not further specified; RCT = Randomized Controlled Trial
*no validated questionnaire; ¥ this is not a questionnaire

REFERENCES

1. LeBovidge JS, Strauch H, Kalisch LA, Al E. Assessment of psychological distress among children and adolescents with food allergy. *J ALLERGY CLIN IMMUNOL*. 2009;124(6). doi:10.1016/j.jpsychores.2014.10.005
2. Im YJ, Kim DH. Factors associated with the resilience of school-aged children with atopic dermatitis. *J Clin Nurs*. 2012;21(1):80-88.
3. Davis D. *Child Development: A Practitioner's Guide*. 2nd ed. The Guilford Press; 2004.
4. Kim DH, Im YJ. Resilience as a protective factor for the behavioral problems in school-aged children with atopic dermatitis. *J Child Health Care*. 2014;18(1):47-56.
5. Masten AS, O'Connor MJ. Vulnerability, stress and resilience in the early development of a high risk child. *American Academy of Child and Adolescent Psychiatry*. 1988;28:274-278.
6. Nabors LA, Graves ML, Fiser KA, Merianos AL. Family resilience and health among adolescents with asthma only, anxiety only, and comorbid asthma and anxiety. *Journal of Asthma*. 2021;58(12):1599-1609. doi:10.1080/02770903.2020.1817939
7. Buehler C. Family Processes and Children's and Adolescents' Well-Being. *Journal of Marriage and Family*. 2020;82(1):145-174. doi:10.1111/jomf.12637
8. Walsh F. Family resilience: a developmental systems framework. *European Journal of Developmental Psychology*. 2016;13(3):313-324. doi:10.1080/17405629.2016.1154035
9. Traub F, Boynton-Jarett R. Modifiable Resilience Factors to Childhood Adversity for Clinical Pediatric Practice. *Pediatrics*. 2017;139(5).
10. Carlsen K, Haddad N, Gordon J, et al. Self-efficacy and Resilience Are Useful Predictors of Transition Readiness Scores in Adolescents with Inflammatory Bowel Diseases. *Inflamm Bowel Dis*. 2017;23(3):341-346.
11. Iacoviello BM, Charney DS. Psychosocial facets of resilience: implications for preventing posttrauma psychopathology, treating trauma survivors, and enhancing community resilience. *Eur J Psychotraumatol*. 2014;5:1-10.
12. Beeckman M, Hughes S, van Ryckeghem D, et al. Resilience factors in children with juvenile idiopathic arthritis and their parents: The role of child and parent psychological flexibility. *Pain Medicine (United States)*. 2019;20(6):1120-1131. doi:10.1093/pm/pny181
13. Goubert L, Trompetter H. Towards a science and practice of resilience in the face of pain. *Eur J Pain*. 2018;21(8):1301-1315.
14. Cousins L, Kalapurakkel S, Cohen L, Simons L. Topical review: Resilience resources and mechanisms in pediatric chronic pain. *J pediatr Psychol*. 2015;40(9):840-845.
15. Sturgeon J, Zautra A. Resilience: A new paradigm for adaptation to chronic pain. *Curr Pain Headache rep*. 2010;14(2):105-114.
16. Gmuca S, Sonagra M, Xiao R, et al. Suicidal risk and resilience in juvenile fibromyalgia syndrome: a cross-sectional cohort study. *Pediatric Rheumatology*. 2021;19(1). doi:10.1186/s12969-020-00487-w
17. Masten AS. Ordinary magic. Resilience processes in development. *AM Psychol*. 2001;56(3):227-238.
18. Luthar SS, Cicchetti D, Becker B. The Construct of Resilience: A Critical Evaluation and Guidelines for Future Work. *Child Dev*. 2000;71(3):543-562. doi:10.1111/1467-8624.00164
19. Tang Y, Chen W, Li J, et al. A disease-targeted picture book for children with Henoch-Schonlein purpura nephritis: A quasi-experimental study. *J Ren Care*. Published online 2022. doi:10.1111/jorc.12451
20. Kim DH, Yoo IY. Factors associated with resilience of school age children with cancer. 2010;46(7):431-436.
21. Wu LM, Sheen JM, Shu HL, et al. Predictors of anxiety and resilience in adolescents undergoing cancer treatment. *J Adv Nurs*. 2013;69(1):158-166.
22. Hunter A, Chandler G. Adolescent resilience. *IMAGE: Journal of Nursing Scholarship*. 1999;31(3243-247).
23. Robb SL, Burns DS, Stegenga KA, et al. Randomized clinical trial of therapeutic music video intervention for resilience outcomes in adolescents/young adults undergoing hematopoietic stem cell transplant: a report from the Children's Oncology Group. *Cancer*. 2014;120(6):909-917.
24. Haase JE. Resilience. In: *Middle Range Theories: Application to Nursing Research*. Lippincott; 2004:125.
25. Sharp KMH, Willard VW, Okado Y, et al. Profiles of connectedness: Processes of resilience and growth in children with cancer. 2015;40(9):904-913. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc12&NEWS=N&AN=2015-45524-008

26. Bahryni S, Bermas H, Tashvighi M. The self-efficacy forecasting based on hope to life and resiliency in adolescents suffering from cancer. *Biomedical and Pharmacology Journal*. 2016;9(3):1147-1156.
27. Diener E, Oishi S, Lucas RE. Personality, Culture, and Subjective Well-Being: Emotional and Cognitive Evaluations of Life. *Annu Rev Psychol*. 2003;54(1):403-425.
28. Connor KM, Davidson JRT. Development of a new Resilience scale: The Connor-Davidson Resilience scale (CD-RISC). *Depress Anxiety*. 2003;18(2):76-82.
29. Schwartz LA, Brumley LD. What a Pain: The Impact of Physical Symptoms and Health Management on Pursuit of Personal Goals Among Adolescents with Cancer.pdf. *J Adolesc Young Adult Oncol*. 2017;6(1).
30. Rosenberg AR, Bradford MC, McCauley E, et al. Promoting resilience in adolescents and young adults with cancer: Results from the PRISM randomized controlled trial. *Cancer*. 2018;124(19):3909-3917. doi:10.1002/cncr.31666
31. Bonanno GA, Westphal M, Mancini AD. Resilience to Loss and Potential Trauma. *Annu Rev Clin Psychol*. 2011;7(1):511-535.
32. Willard VW, Russell KM, Long A, Al E. The impact of connectedness on social functioning in youth with brain tumors. *Pediatr Blood Cancer*. 2018;66(5).
33. Wu W, Chang J, Tsai S, Liang S. Assessing Self-concept as a Mediator between Anger and Resilience in Adolescents with Cancer in Taiwan. *Cancer Nurs*. 2018;41(3):210-217.
34. Stewart DE, Yuen T. A Systematic Review of Resilience in the Physically Ill. *Psychosomatics*. 2011;52(3):199-209. doi:10.1016/j.psym.2011.01.036
35. Haase JE, Kintner EK, Monahan PO, Robb SL. The resilience in illness model, part 1: exploratory evaluation in adolescents and young adults with cancer. *Cancer Nurs*. 2014;37(3):E1-12.
36. Lee JY, Jeong DC, Chung NG, Lee S. The effects of illness cognition on resilience and quality of life in korean adolescents and young adults with leukemia. *J Adolesc Young Adult Oncol*. 2019;8(5):610-615. doi:10.1089/jayao.2018.0152
37. Gheshlagh R, Ebadi A, Dalvandi A. A systematic study of resilience in patients with chronic physical diseases. *Nurs Midwifery Stud*. 2016;6(2).
38. Lau N, Yi-Frazier JP, Bona K, Baker KS, McCauley E, Rosenberg AR. Distress and resilience among adolescents and young adults with cancer and their mothers: An exploratory analysis. *J Psychosoc Oncol*. 2020;38(1):118-124. doi:10.1080/07347332.2019.1656317
39. Haase J, Heiney S, Ruccione K, Stutzer C. Research triangulation to derive meaning-based quality-of-life theory: adolescent resilience model and instrument development. *Int J Cancer Suppl*. 1999;12:125-131.
40. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: Interdisciplinary perspectives. *Eur J Psychotraumatol*. 2014;5. doi:10.3402/ejpt.v5.25338
41. Rosenberg AR, Yi-Frazier JP, Eaton L, et al. Promoting resilience in stress management: A pilot study of a novel resilience-promoting intervention for adolescents and young adults with serious illness. *J Pediatr Psychol*. 2014;40(9):992-999.
42. Chung JOK, Li WHC, Cheung AT, et al. Relationships among resilience, depressive symptoms, self-esteem, and quality of life in children with cancer. *Psychooncology*. 2021;30(2):194-201. doi:10.1002/pon.5548
43. Wagnild GM, Young HM. Development and psychometric evaluation of the Resilience Scale. *J Nurs Meas*. 1993;1(2):165-178.
44. Davydov DM, Stewart R, Ritchie K, Chaudieu I. Resilience and mental health. *Clin Psychol Rev*. 2010;30(5):479-495. doi:10.1016/j.cpr.2010.03.003
45. Lee S, Kim S, Young Choi J. Coping and resilience of adolescents with congenital heart disease. *J Cardiovasc Nurs*. 2014;29(4):340-346.
46. Compas BE. Psychobiological processes of stress and coping: Implications for resilience in children and adolescents - Comments on the papers of Romeo & McEwen and Fisher et al. *Ann N Y Acad Sci*. 2006;1094:226-234.
47. Mandleco BL, Peery JC. An organizational framework for conceptualizing resilience in children. *Child Adolesc Psychiatr Nurs*. 2000;13:99-111.
48. Rassart J, Luyckx K, Goossens E, Al E. A big five personality typology in adolescents with congenital heart disease: Prospective associations with psychosocial functioning and perceived health. *Int J Behav Med*. 2016;23(3):310-318.
49. Block JH, Block J. *The Role of Ego-Control and Ego- Resiliency in the Origination of Behavior*. Vol 13. WA Collings (red.). The Minnesota Symposia on Child Psychology.; 1980.
50. Lee S, Lee J, Choi JY. The effect of a resilience improvement program for adolescents with complex congenital heart disease. *Eur J Cardiovasc Nurs*. 2017;16(4):290-298.

51. Southwick SM, Vythilingam M, Charney DS. The Psychobiology of Depression and Resilience to Stress: Implications for Prevention and Treatment. *Annu Rev Clin Psychol*. 2005;1(1):255-291.
52. Huang HR, Chen CW, Chen CM, et al. A positive perspective of knowledge, attitude, and practices for health-promoting behaviors of adolescents with congenital heart disease. *European Journal of Cardiovascular Nursing*. 2018;17(3):217-225.
53. Dent M. *Promoting Resilience in the Millennial Adolescent: The Lighthouse Model.*; 2008.
54. Sharp C, Penner F, Marais L, Lochner S. School connectedness as psychological resilience factor in children affected by HIV/AIDS. *AIDS Care*. 2018;30(4):34-41.
55. Whiteley L, Brown LK, Mena L, Craker L, Arnold T. Enhancing health among youth living with HIV using an iPhone game. *AIDS Care*. 2018;30(sup4):21-33. doi:10.1080/09540121.2018.1503224
56. Furniss D, Barber N, Lyons I, al E. Unintentional non-Adherence: Can a spoon full of resilience help the medicine go down? *BMJ Qual Saf*. 2014;23(2):95-98.
57. Johnson MO, Catz SL, Remien RH, et al. Theory-Guided, Empirically Supported Avenues for Intervention on HIV Medication Nonadherence: Findings from the Healthy Living Project Downloaded. *AIDS Patient Care*. 2003;17(12).
58. Simon K, Barakat LP, Patterson CA, Al E. Symptoms of depression and anxiety in adolescents with sickle cell disease: The role of intrapersonal characteristics and stress processing variables. 2009;40(2):317-330.
59. Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. *J Child Psychol Psychiatry*. 1998;39(1):29-46.
60. Kaewkong P, Boonchooduang N, Charoenkwan P, Louthrenoo O. Resilience in adolescents with thalassemia. *Pediatr Hematol Oncol*. 2020;38(2):124-133. doi:10.1080/08880018.2020.1821140
61. Chmitorz A, Kunzler A, Helmreich I. Intervention studies to foster resilience: a systematic review and proposal for a resilience framework in future intervention studies. *Clin Psychol Rev*. 2018;59:78-100.
62. Masten AS. Global Perspectives on Resilience in Children and Youth. *Child Dev*. 2014;85(1):6-20. doi:10.1111/cdev.12205
63. Wright LA, Cohen LL, Gise J, Shih S, Sil S, Carter, S. Pain and QOL in pediatric sickle cell disease: Buffering by resilience processes. *J Pediatr Psychol*. 2021;46(8):1015-1024. doi:10.1093/jpepsy/jsab034
64. Parviniannasab AM, Rakhshan M, Momennasab M, Soltanian M, Rambod M, Akbarzadeh M. The mediating role of Courageous coping in the relations between spirituality and social support with resilience among adolescents with hemophilia. *Clin Child Psychol Psychiatry*. 2022;27(4):1141-1154. doi:10.1177/13591045211055081
65. Fee RJ, Hinton VJ. Resilience in children diagnosed with a chronic neuromuscular disorder. *J Dev Behav Pediatr*. 2011;32(9):644-650.
66. Werner EE. Children of the Garden Island. *Sci Am*. 1989;260(4):106-111.
67. Rainone N, Chiodi A, Lanzillo R, Al E. Affective disorders and Health-Related Quality of Life (HRQoL) in adolescents and young adults with Multiple Sclerosis (MS): The moderating role of resilience. *Quality of Life Research*. 2017;26(3):727-736.
68. Arruda MA, Arruda R, Landeira-Fernandez J, Anunciação L, Bigal ME. Resilience and vulnerability in adolescents with primary headaches: A cross-sectional population-based study. *Headache*. 2021;61(3):546-557. doi:10.1111/head.14078
69. Zimmerman K, May B, Barnes K, et al. Post-Traumatic Stress Symptoms in Caregivers and Children with Hydrocephalus. *World Neurosurg*. 2021;148:e66-e73. doi:10.1016/j.wneu.2020.12.008
70. Bonanno GA, Westphal M, Mancini AD. Resilience to Loss and Potential Trauma. *Annu Rev Clin Psychol*. 2011;7(1):511-535. doi:10.1146/annurev-clinpsy-032210-104526
71. Cui C, Shuang-zi L, Cheng W jin, Wang T. Mediating effects of coping styles on the relationship between family resilience and self-care status of adolescents with epilepsy transitioning to adult healthcare: A cross-sectional study in China. *J Pediatr Nurs*. 2022;63:143-150. doi:10.1016/j.pedn.2021.11.021
72. Walsh F. Family resilience: A framework for clinical practice. *Fam Process*. 2003;42(1):1-18. doi:10.1111/j.1545-5300.2003.00001.x
73. Borinsky S, Gaughan JP, Feldman-Winter L. Perceived overweight/obesity, low resilience, and body size dissatisfaction among adolescents. *Obes Res Clin Pract*. 2019;13(5):448-452. doi:10.1016/j.orcp.2019.08.002
74. Wu G, Feder A, Cohen H, et al. Understanding resilience. *Front Behav Neurosci*. 2013;7.
75. Li MK, Patel BP, Chu L, Strom M, Hamilton JK. Investigating resilience and its association with stress, anthropometrics, and metabolic health in adolescents with obesity: a pilot study. *Psychol Health Med*. Published online 2022. doi:10.1080/13548506.2022.2059094

76. Wu Z, Liu Y, Li X, Li X. Resilience and Associated Factors among Mainland Chinese Women Newly Diagnosed with Breast Cancer. *PLoS One*. 2016;11(12).
77. Ruff RR, Sischo L, Broder H. Resiliency and socioemotional functioning in youth receiving surgery for orofacial anomalies. *Community Dent Oral Epidemiol*. 2016;44(4):371-380.
78. Adibsereshki N, Hatamizadeh N, Kazemnejad A, Sajedi F. RESILIENCE INTERVENTION TO STRENGTHEN SELF-REGULATION IN ADOLESCENT STUDENTS WITH HEARING LOSS. *European Journal of Mental Health*. 2021;16(2):76-98. doi:10.5708/EJMH.16.2021.2.4
79. Jaser SS, White LE. Coping and resilience in adolescents with type 1 diabetes. *Child Care Health Dev*. 2011;37(3):335-342.
80. Masten AS. Resilience in developing systems: Progress and promise as the fourth wave rises. *Dev Psychopathol*. 2007;19(3):921-930.
81. Yi-Frazier JP, Yaptangco M, Semana S, et al. The association of personal resilience with stress, coping, and diabetes outcomes in adolescents with type 1 diabetes: variable- and person-focused approaches. *J Health Psychol*. 2015;20(9):1196-1206.
82. Rew L, Horner SD. Youth resilience framework for reducing health-risk behaviors in adolescents. *J Pediatr Nurs*. 2003;18(6):379-388. doi:10.1016/S0882-5963(03)00162-3
83. Yi JP, Vitaliano PP, Smith RE, et al. The role of resilience on psychological adjustment and physical health in patients with diabetes. 2008;13(Pt 2):311-325.
84. Huston SA, Bloun RL, Heidsec T. Resilience, emotion processing and emotionexpression among youth with type 1 diabetes. *Pediatr Diabetes*. 2016;17:623-631.
85. Hood KK, Iturralde E, Rausch J, et al. Preventing diabetes distress in adolescents with type 1 diabetes: Results 1 year after participation in the STePS program. *Diabetes Care*. 2018;41(8):1623-1630.
86. Gillham JE, Hamilton J, Freres DR, al E. Preventing depression among early adolescents in the primary care setting: A randomized controlled study of the Penn Resiliency Program. *J Abnorm Child Psychol*. 2006;34(2):203-219.
87. Lukacs A, Mayer K, Sasvari P, Al E. Health-related quality of life of adolescents with type 1 diabetes in the context of resilience. *Pediatr Diabetes*. 2018;19(8):1481-1486.
88. Masten AS. Global Perspectives on Resilience in Children and Youth. *Child Dev*. 2014;85(1):6-20.
89. Rosenberg AR, Yi-Frazier JP. Commentary: Resilience defined: An alternative perspective. *J Pediatr Psychol*. 2016;41(5):506-509. doi:10.1093/jpepsy/jsw018
90. J. M, A. D, B. W, et al. Determinants of Readiness for Adopting Healthy Lifestyle Behaviors Among Indigenous Adolescents with Type 2 Diabetes in Manitoba, Canada: A Cross-Sectional Study. *Obesity*. 2018;26(5):910-915.
91. Dray J, Bowman J, Campbell E, et al. Systematic Review of Universal Resilience-Focused Interventions Targeting Child and Adolescent Mental Health in the School Setting. *J Am Acad Child Adolesc Psychiatry*. 2017;56(10):813-824.
92. Araia E, King RM, Pouwer F, Speight J, Hendrieckx C. Psychological correlates of disordered eating in youth with type 1 diabetes: Results from diabetes MILES Youth—Australia. *Pediatr Diabetes*. 2020;21(4):664-672. doi:10.1111/pedi.13001
93. Shapiro JB, Bryant FB, Holmbeck GN, Hood KK, Weissberg-Benchell J. Do baseline resilience profiles moderate the effects of a resilience-enhancing intervention for adolescents with type I diabetes? *Health Psychology*. 2021;40(5):337-346. doi:10.1037/hea0001076
94. Hilliard ME, Holmes CS, Chen R, Maher K, Robinson E, Streisand R. Disentangling the roles of parental monitoring and family conflict in adolescents' management of type 1 diabetes. *Health Psychology*. 2013;32(4):388-396. doi:10.1037/a0027811
95. Haase JE. The adolescent resilience model as a guide to interventions. *Journal of Pediatric Oncology Nursing*. 2004;21(5):289-299.
96. Southwick SM, Charney DS. The Science of Resilience: Implications for the Prevention and Treatment of Depression. *Science (1979)*. 2012;338(October):79-83.
97. Moreira JM, Bouissou Morais Soares CM, Teixeira AL, Simoes e Silva AC, Kummer AM. Anxiety, depression, resilience and quality of life in children and adolescents with pre-dialysis chronic kidney disease. *Pediatr Nephrol*. 2015;30(12):2153-2162.
98. Santos T, de Matos MG, Marques A, Simoes C, Leal I, Machado M do C. Adolescent's subjective perceptions of chronic disease and related psychosocial factors: highlights from an outpatient context study. *BMC Pediatr*. 2016;16(1):211.
99. Lee S, Chung NG, Choi JY. Comparison of resilience and quality of life between adolescent blood cancer survivors and those with congenital heart disease: A cross sectional study. *Health Qual Life Outcomes*. 2020;18(1):1-7. doi:10.1186/s12955-020-01487-w

100. Windle G. What is resilience? A review and concept analysis. *Rev Clin Gerontol*. 2011;21(2):152-169. doi:10.1017/S0959259810000420
101. Verma T, Rohan J. Examination of transition readiness, medication adherence, and resilience in pediatric chronic illness populations: A pilot study. *Int J Environ Res Public Health*. 2020;17(6):4-14. doi:10.3390/ijerph17061905
102. Seligman M. Building resilience. *Harv Bus Rev*. 2011;89:100-106.
103. Biernacka M, Jakubowska-Winecka A, Kalicí nski P. Influence of Parental Attitudes on Formation of Psychological Resilience and Adherence to Medical Regime in Adolescents after Liver or Renal Transplantation. Published online 2021. doi:10.3390/children
104. Rutter M. Resilience as a dynamic concept. *Dev Psychopathol*. 2012;24(2):335-344. doi:10.1017/S0954579412000028
105. Kim GM, Lim JY, Kim EJ, Park S. Resilience of patients with chronic diseases: A systematic review. *Health Soc Care Community*. 2019;27(4):797-807. doi:10.1111/hsc.12620
106. Kully-Martens K, Pei J, McNeil A, Rasmussen C. Resilience Resources and Emotional and Behavioral Functioning Among Youth and Young Adults with Fetal Alcohol Spectrum Disorder. *Int J Ment Health Addict*. Published online 2021. doi:10.1007/s11469-021-00652-6
107. Masten A, Cicchetti D. Resilience in development: Progress and transformation. . In: *Developmental Psychopathology* . Vol 4. 3rd ed. John Wiley & Sons; 2016.
108. Tomlinson RM, Bax KC, Ashok D, McMurtry CM. Health-related quality of life in youth with abdominal pain: An examination of optimism and pain self-efficacy. *J Psychosom Res*. 2021;147. doi:10.1016/j.jpsychores.2021.110531
109. Fergus S, Zimmerman M. ADOLESCENT RESILIENCE: A Framework for Understanding Healthy Development in the Face of Risk. *Annu Rev Public Health*. 2005;26:399-419.

SUPPLEMENT 3:

Instruments measuring resilience outcomes

Instruments	Previously used in youth with diagnosis*	Items	Response	Range [a]	Instrument measures: Personal trait	Instrument measures: Psychosocial functioning	Instrument measures: Disease-related outcomes
The Adolescent Self-Regulatory Inventory (ASRI)[1]	Hearing loss	36	5-point Likert scale	36–180	● Short term self-regulation ● Long term self-regulation		
Behavior Assessment System for Children 2nd edition (BASC-2)[2]	Food allergy SCD Asthma	36	4-point Likert scale	36–144	● Adaptive skills	● Behavioral symptoms index ● Externalizing problems ● Internalizing problems ● School problems	
Beck Youth Inventory for Emotional and Social Impairment (2nd edition)[3]	Orofacial anomalies	100	NR	NR		● Depression ● Anxiety ● Concept of self	
Benefit Finding/Burden Scale for Children (BBSC)[4]	Cancer	20	5-point Likert scale	NR			● Potential benefits or burdens of illness
Benefit Finding Scale for Children (BFSC)[5]	T1D	10	5-point Likert scale	NR			● Benefit finding in illness
Child Behavior Checklist ((K-) CBCL)[6]	DMD, atopic dermatitis	118	3-point Likert scale	0–236		● Emotional problems ● Behavioral problems	
Connor-Davidson resiliency questionnaire (CD-RISC-10)[7]	IBD, cancer, T1D	10	5-point Likert scale	0–40	● Perceived ability to tolerate experiences ● Humor ● Self-efficacy		

Instruments measuring resilience outcomes (continued)

Instruments	Previously used in youth with diagnosis*	Items	Response	Range [a]	Instrument measures
					Personal trait / Psychosocial functioning / Disease-related outcomes
Contour Drawing Rating Scale (CDRS)[8]	Obesity	2	9 options	NA	Psychosocial functioning: Body size dissatisfaction
Center for Epidemiologic Studies Depression Scale (CESDS)[9]	CHD	20	4-point Likert scale	0-60	Psychosocial functioning: Depressive symptoms
Chronic illness children's resilience scale (CICRS)[10]	Henoch Schonlein purpura nephritis	32	4-point Likert scale	32-128	Personal trait: Interpersonal characteristics; Coping characteristics; Intrapersonal relationships
Diabetes Eating Problem Survey-Revised (DEPS-R)[11]	T1D	16	6-point Likert scale	0-80	Disease-related outcomes: Disordered eating
Diabetes acceptance[12]**	T1D	3	NR	NR	Disease-related outcomes: Illness acceptance
Diabetes, fitting in [12]**	T1D	5	NR	NR	Disease-related outcomes: Fitting in with illness
Diabetes, comfort in adjusting for diabetes in public [12]**	T1D	3	NR	NR	Disease-related outcomes: Comfort in adjusting for illness in public
Family resilience (NSCH)[13]	Asthma	4	4-point Likert scale	4-16	Psychosocial functioning: Family flourishing
General self-efficacy questionnaire (GFE-10) [14]	Cancer	10	4-point Likert scale	10-40	Personal trait: General self-efficacy; Social self-efficacy

Instruments measuring resilience outcomes (continued)

Instruments	Previously used in youth with diagnosis*	Items	Response	Range [a]	Instrument measures		
					Personal trait	Psychosocial functioning	Disease-related outcomes
Haase Adolescent Resilience in Illness Scale (HARIS)[15]	Cancer, CHD, HSCT	13	6-point Likert scale	13-78	● Self-esteem ● Sense of mastery ● Positive expectation		
Health-related Hindrance Inventory[16]	Cancer	10	7 point-Likert scale	0-60			● Impact of health on personal goals
Leuven Knowledge Questionnaire for Congenital Heart Disease (LKQCHD)[17]	CHD	34 (female) 31 (male)	3-point Likert scale	NR			● Level of disease knowledge
Metabolic control (HbA1c)[18]¥	T1D	NA	NA	NA			● Metabolic control
Problem Areas in Diabetes Scale (PAID)[19]	T1D	20	5-point Likert scale	0-80			● Illness related distress
Positive and Negative Affect Scale for Children (PANAS-c)[20]	JIA	27	5-point Likert scale	5-135		● Positive and negative affect	
Pediatric Quality of Life Inventory (PedsQL)[21]	CHD	23	5-point Likert scale	0-92		● Physical functioning ● Emotional functioning ● Social functioning ● School-related functioning	
Pediatric Quality of Life Inventory (PedsQL) [22] ***Cardiac module*** ***Diabetes module***	T1D	27 33	5-point Likert scale	0-108 0-132			● Disease-related quality of life
UCLA PTSD Reaction Index for DSM-IV (PTSDI[23]	Cancer	22	5-point Likert scale	0-88		● PTSD symptoms	

Instruments measuring resilience outcomes (continued)

Instruments	Previously used in youth with diagnosis*	Items	Response	Range [a]	Instrument measures
					Personal trait / Psychosocial functioning / Disease-related outcomes
Resilience measurement instrument for children with chronic illness [24]	Atopic dermatitis, cancer	32	4-point Likert scale	32-128	Self-understanding; Self-reliance; Resourcefulness; Perception of family relationships; Perception of interpersonal intimacy
The Wagnild and Young Resilience Scale (RS)[25]	CHD, CKD, T1D, cancer	25	7-point Likert scale	25-175	Purpose; Perseverance; Self-reliance; Equanimity; Authenticity
Resilience Scale for Children and Adolescents (RSCA)[26]	T1D, Orofacial anomalies	64	5-point Likert scale	0-256	Self-perception of skills and competences; Emotional reactivity; Sense of relatedness
Strengths and Difficulties Questionnaire (SDQ)[27]	HIV/AIDS	25	3-point Likert scale	0-50	Emotional problems; Behavioral problems
Social-Emotional Assets and Resilience Scales (SEARS)[28]	Cancer	35	4-point Likert scale	NR	Self-regulation; Responsibility; Empathy; Social Competence
Self-Management and Transition to Adulthood with Rx (STARx)[29]	Various chronic diseases	18	5-point Likert scale	0-90	Transition readiness

Instruments measuring resilience outcomes (continued)

Instruments	Previously used in youth with diagnosis*	Items	Response	Range [a]	Instrument measures: Personal trait / Psychosocial functioning / Disease-related outcomes
Transition Readiness Assessment Questionnaire (TRAQ)[30]	IBM	20	5-point Likert scale	20-100	Transition readiness
UCLA loneliness scale[31]	CHD	8	5-point Likert scale	8-40	Loneliness
Youth Self Report (YSR)[32]	T1D	112 20	3-point Likert scale	0-224 0-40	Perception of competence Perception of social competence

Legend

Disease or therapy	CHD = Congenital Heart Disease; CKD = Chronic Kidney Disease; DMD = Duchenne Muscular Dystrophy; HIV = Human Immunodeficiency Virus; HSCT = Hematopoietic Stem Cell Transplant; IBD= Inflammatory Bowel Diseases; SCD = Sickle Cell Disease; T1D = Type 1 Diabetes.
Study design	RCT = Randomized Controlled Trial
Other	NA = not applicable; NR = not reported; pr= parents reported ¥ = this is not a questionnaire [a] = raw scores, not transformed

REFERENCES

1. Dias PC, del Castillo JAG, Moilanen KL. The Adolescent Self-Regulatory Inventory (ASRI) Adaptation to Portuguese Context. *Paidéia (Ribeirão Preto)*. 2014;24(58):155-164. doi:10.1590/1982-43272458201403
2. Reynolds C, Kamphaus R. *Behavior Assessment System for Children Manual*. 2nd ed. AGS Publishing; 2004.
3. Beck J, Beck A, Jolly J, Steer R. *Beck Youth Inventories for Children and Adolescents*. NCS Pearson, Inc; 2005.
4. Currier J, Hermes S, Phipps S. Children's response to serious illness: Perceptions of bene-fit and burden in a pediatric cancer population. *J Pediatr Psychol*. 2009;34(1129-1134).
5. Phipps S, Long AM, Ogden J. Benefit finding scale for children: preliminary findings from a childhood cancer population. *J Pediatr Psychol*. 2007;32(10):1264-1271.
6. Achenbach TM. *The Manual for the Child Behavior Checklist/4-18 and 1991 Profile*. University of Vermont, Department of Psychiatry; 1991.
7. Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the connor–davidson resilience scale (CD-RISC): Validation of a 10-item measure of resilience. *J Trauma Stress*. 2007;20(6):1019-1028.
8. Thompson M, Gray J. Development and validation of a new body-image assessment scale. *J Pers Assess*. 1995;64(2):258-269.
9. Bouma J, Ranchor A, Sanderman R, van Sonderen E. *Het Meten van Symptomen van Depressie Met de CESD: Een Handleiding [The Measurement Ofsymptoms Ofdepression with the CESD: A Manual]*.; 1995.
10. Kim DH, Yoo IY. Development of a Questionnaire to Measure Resilience in Children with Chronic Diseases. *J Korean Acad Nurs*. 2010;40(2):236. doi:10.4040/jkan.2010.40.2.236
11. Markowitz J, Butler D, Volkening L, Antisdel J, Anderson B, Laffel L. Brief screening tool for disordered eating in diabetes: inter- nal consistency and external validity in a contemporary sample of pediatric patients with type 1 diabetes. *Diabetes Care*. 2010;33(3):495-500.
12. Huston SA, Bloun RL, Heidsec T. Resilience, emotion processing and emotionexpression among youth with type 1 diabetes. *Pediatr Diabetes*. 2016;17:623-631.
13. Nabors LA, Graves ML, Fiser KA, Merianos AL. Family resilience and health among adolescents with asthma only, anxiety only, and comorbid asthma and anxiety. *Journal of Asthma*. 2021;58(12):1599-1609. doi:10.1080/02770903.2020.1817939
14. Bahryni S, Bermas H, Tashvighi M. The self-efficacy forecasting based on hope to life and resiliency in adolescents suffering from cancer. *Biomedical and Pharmacology Journal*. 2016;9(3):1147-1156.
15. Haase JE, Kintner EK, Monahan PO, Robb SL. The resilience in illness model, part 1: exploratory evaluation in adolescents and young adults with cancer. *Cancer Nurs*. 2014;37(3):E1-12.
16. Schwartz L, Drotar D. Health-related hindrance of personal goal pursuit and well-being of young adults with cystic fibrosis, pediatric cancer survivors, and peers without a history of chronic illness. *J pediatr Psychol*. 2009;34(9):954-965.
17. Yang H, Chen Y, Wang J. Measuring knowledge of patients with congenital heart disease and their parents: Validity of the 'Leuven Knowledge Questionnaire for Congenital Heart Disease.' *Eur J Cardiovasc Nurs*. 2012;11:77-84.
18. Jaser SS, White LE. Coping and resilience in adolescents with type 1 diabetes. *Child Care Health Dev*. 2011;37(3):335-342.
19. Welch G, Jacobson A, Polonsky W. The problem areas in diabetes scale: An evaluation of its clinical utility. *Diabetes Care*. 1997;20:760-766.
20. Laurent J, Catanzaro J, Joiner T, et al. A measure of positive and negative affect for children: Scale development and preliminary validation. *Psychol Assess*. 1999;11(3):236-238.
21. Varni J, Seid M, Rode C. The PedsQL™ measurement model for the pediatric quality of life inventory. *Med Care*. 1999;3:126-139.
22. Varni JW, Seid M, Kurtin PS. Pediatric health-related quality of life measurement technology: a guide for health care decision makers. *Journal of Clinical Outcomes Management*. 1999;6:33-40.
23. Pynoos R, Rodriquez N, Steinberg A, Stuber M, Frederick C. *The University of California at Los Angeles Posttraumatic Stress Disorder Reaction Index (UCLA-PTSD RI) for DSM-IV (Revision 1)*.; 1998.
24. Kim DH, Yoo IY. Development of a Questionnaire to Measure Resilience in Children with Chronic Diseases. *J Korean Acad Nurs*. 2010;40(2):236.

25. Wagnild GM, Young HM. Development and psychometric evaluation of the Resilience Scale. *J Nurs Meas*. 1993;1(2):165-178.
26. Prince-Embury S. Resiliency Scales for Children and Adolescents: A Profile of Personal Strengths. *Can J Sch Psychol*. 2007;22(2):255-261.
27. Goodman R. The strengths and difficulties questionnaire: A research note. *J Child Psychol Psychiatry*. 1997;38(5):581-586. doi:10.1111/j.1469-7610.1997.tb01545.x
28. Merell KW. SEARS. Published online 2011. Accessed August 21, 2020. https://www.parinc.com/Products/Pkey/406
29. Fenton N, Ferris M, Ko Z, Javalkar K, Hooper S. The relationship of health care transition readiness to disease-related characteristics, psychosocial factors, and health care outcomes: Preliminary findings in adolescents with chronic kidney disease. *J pediatr Rehabil Med*. 2015;8:13-22.
30. Wood D, Sawicki G, Miller M, et al. The Transition Readiness Assessment Questionnaire (TRAQ): its factor structure, reliability, and validity. *Acad Pediatr*. 2014;14:415-422.
31. Roberts R, Lewinsohn P, Seeley J. A brief measure of loneliness suitable for use with adolescents. *Psychol Rep*. 1993;72:1379-1391.
32. Achenbach TM, Rescorla LA. *Manual for the ASEBA School-Age Forms and Profiles*. University of Vermont, Research Centre for Children, Youth and Families; 2001.

SUPPLEMENT 4:

Instruments measuring resilience factors

Instruments	Previously used in youth with diagnosis	Items	Response	Range [a]	Assessment of resilience factors				
					Internal	Disease	External		
					Cognitive, social, and emotional competence factors	Disease-related factors	Caregiver factors	Peer factors	Contextual factors
Adolescent Resilience Questionnaire [1]	Obesity	77	5-point Likert scale	77-385	• Confidence • Emotional insight • Negative cognition • Empathy • Social skills		• Family connectedness • Family availability	• Peer connectedness • Peer availability	• Supportive school environment • School connectedness • Community connectedness
Antiretroviral treatment (ART) motivation [2]	HIV/AIDS	NR	4-point Likert scale	NR		• Therapy motivation (personal/social)			
Automatic Thoughts Questionnaire (ATQ) [3]	T1D	30	5-point Likert scale	30-150	• Personal maladjustment • Self-concepts and expectations • Low self-esteem • Helplessness				
Avoidance and Fusion Questionnaire for Youth (AFQ-Y) [4]	JIA	17	5-point Likert scale	0-86	• Psychological flexibility				
Beck Self- Concept Inventory (BSCI-Y) [5]	Cancer	20	4-point Likert scale	0-60	• Positive self-worth • Self-esteem • Potency • Competency				

Instruments measuring resilience factors (continued)

Instruments	Previously used in youth with diagnosis	Items	Response	Range [a]	Assessment of resilience factors				
					Internal	Disease	External		
					Cognitive, social, and emotional competence factors	Disease-related factors	Caregiver factors	Peer factors	Contextual factors
Child and Adolescent Mindfulness Measure (CAMM) [6]	Sickle cell disease	10	4-point Likert scale	0-40	• Mindfulness				
Child Attitude Toward Illness Scale (CATIS) [7]	Food allergy	13	5-point Likert scale	13-65		• Attitudes toward having a condition			
Children's Attributional Style Questionnaire-Revised (CASQ-R) [8]	CHD	24	2-point Likert scale	NR	• Attributional style				
Child Behavior Checklist (CBCL) [9]	DMD	118	3-point Likert scale	0-236	• Internalizing behaviors • Externalizing behaviors • Social competence				
Child self-efficacy scale (CSES) [10]	Gastrointestinal disorders	7	5-point Likert Scale	7-35		• Self-efficacy despite pain			
Connor-Davidson resiliency questionnaire (CD-RISC-10/25) [11,12]	IBD, cancer, T1D	10 25	5-point Likert scale	0-40 0-100	• Perceived ability to tolerate experiences • Humor • Self-efficacy				
Coping Efficacy Questionnaire (CEQ) [13,14]	T1D	7	4-point Likert scale	NR	• Coping skills				
Children's Hope Scale (CHS) [15]	SCD	6	6-point Likert scale	6-36	• Agency as related to achieving goals				

Instruments measuring resilience factors (continued)

Instruments	Previously used in youth with diagnosis	Items	Response	Range [a]	Assessment of resilience factors				
					Internal	Disease	External		
					Cognitive, social, and emotional competence factors	Disease-related factors	Caregiver factors	Peer factors	Contextual factors
Childrearing behavior Questionnaire[16]	Atopic dermatitis	30	4-point Likert scale	30-120					
					• Warmth acceptance • Rejection-restriction • Permissiveness non-intervention				
Coping Orientation to Problems Experienced (COPE)[17]	T1D	28	4-point Likert scale	28-112					
					• Coping (problem-focused, emotion-focused, avoidant)				
Coping Inventory for Stressful Situations (CISS)[18]	CHD	48	5-point Likert scale	48-240					
					• Coping (task-oriented, emotion-oriented, avoidance oriented)				
Chronic Pain Acceptance Questionnaire (CPAQA)[19]	JIA, SCD	20	5-point Likert scale	0-80					
					• Pain acceptance				
Coping Strategies Questionnaire for Sickle Cell Disease (CSQ)[20]	SCD	80	7-point Likert scale	0-480					
					• Coping with sickle cell disease-related pain				
Child and Youth Resilience Measures-28 (CYRM-28)[21]	MS	28	5-point Likert scale	28-140					
					• Personal skills • Social skills • Physical caregiving • Psychological caregiving • Peer support • Spiritual context • Educational context • Cultural context				

Instruments measuring resilience factors (continued)

Instruments	Previously used in youth with diagnosis	Items	Response	Range [a]	Assessment of resilience factors				
					Internal	Disease	External		
					Cognitive, social, and emotional competence factors	Disease-related factors	Caregiver factors	Peer factors	Contextual factors
Coping Efficacy Scale (CSE) [22]	T1D	8	4-point Likert scale	8-32	Perceived ability to cope with stress				
Diabetes Family Conflict Scale-Revised (DFCS-R)[23]	T1D	19	3-point Likert scale	19-57		Diabetes-related family conflict			
Diabetes Strengths and Resilience measure for adolescents (DSTAR-teen)[24]	T1D	12	5-point Likert scale	12-60		Managing and adapting to illness		Availability and support from others	
Emotional Approach & Coping Scale (EAC)[25]	T1D	16	4-point Likert scale	4-64	Emotional processing Emotion expression				
Ego-Resiliency Scale[26,27]	MS	14	4-point Likert scale	14-56	Adaptive flexibility				
Family Adaptability and Cohesion Scale (FACES II/III)[28]	Cancer	20	5-point Likert scale	10-50			Family cohesion Family adaptability		
Family Resilience Assessment scale (FRAS-C)[29]	Epilepsy	32	4-point Likert scale	32-128	Maintaining a positive outlook		Family communication and problem solving	Utilizing social resources	
Family Strengths Scale[30]	Cancer	12	5-point Likert scale	12-60			Interactional patterns Family values Family coping strategies Family commitment Resource mobilization skills		

Instruments measuring resilience factors (continued)

Instruments	Previously used in youth with diagnosis	Items	Response	Range [a]	Assessment of resilience factors				
					Internal	Disease	External		
					Cognitive, social, and emotional competence factors	Disease-related factors	Caregiver factors	Peer factors	Contextual factors
Haase Adolescent Resilience in Illness Scale (HARIS)[31]	Cancer, CHD, HSCT	13	6-point Likert scale	13-78	• Self-esteem • Sense of mastery • Positive expectation				
Herth Hope Index[32]	Cancer	4 4	5-point Likert scale	1-20 1-20	• Hope-derived meaning • Positive readiness and expectancy • Sense of interconnectedness				
Hemingway Measure of Adolescent Connectedness (HMAC)[33,34]	Cancer	57	5-point Likert scale	57-285	• Self-connection • Family connectedness • Peer connectedness • School connectedness				
Healthy Kids Resilience Assessment Module (HKRM) [35]	T1D, allergic or neurological diseases	18	4-point Likert scale	18-72	• Achievement motivation • Communication • Empathy • Problem-solving • Self-efficacy • Self-awareness				
Hopelessness Scale for Children (HSC)[36]	T1D	17	True/false items	0-17	• Negative expectations about the future				
Illness Cognition Questionnaire (ICQ)[37]	Leukemia	18	4-point Likert scale	4-72		• Helplessness • Acceptance • Perceived benefit			
Jalowiec Coping Scale-Revised[38]	Cancer	32	4-point Likert scale	0-96	• Coping (emotive, evasive, confrontive, optimistic, supporting)				

Instruments measuring resilience factors (continued)

Instruments	Previously used in youth with diagnosis	Items	Response	Range [a]	Assessment of resilience factors				
					Internal	Disease	External		
					Cognitive, social, and emotional competence factors	Disease-related factors	Caregiver factors	Peer factors	Contextual factors
Kessler-6 psychological distress scale (K6)[39]	Cancer	6	5-point Likert scale	6-30	• Psychological distress				
Life Orientation Test (LOT)[40]	T1D	8	5-point Likert scale	0-40	• Optimism • Confidence in one's own ability				
McCorkcle Symptom Distress Scale[41]	Cancer	11	5-point Likert scale	11-55		• Symptom distress			
Mishel Uncertainty in Illness Scale[42]	Cancer	28	5-point Likert scale	28-140		• Uncertainty in illness			
Parent-Adolescent Communication Scale[30]	Cancer	20	5-point Likert scale	20-100			• Open communication • Communication problems		
Pediatric Quality of Life Inventory (PedsQL)[43]	T1D	23	5-point Likert scale	0-92	• Physical functioning • Emotional functioning		• School-related functioning	• Social functioning	
Pediatric Quality of Life Inventory (PedsQL), diabetes module [43]	T1D	33	5-point Likert scale	0-132		• Disease-related quality of life			
Patient-Based Assessment and Counseling for Physical Activity and Nutrition-Adolescent assessment forms (PACE-Adolescent)[44–46]	T2D	NR	5-point Likert scale	NR	• Readiness for behavior change				

Instruments measuring resilience factors (continued)

Instruments	Previously used in youth with diagnosis	Items	Response	Range [a]	Assessment of resilience factors				
					Internal	Disease	External		
					Cognitive, social, and emotional competence factors	Disease-related factors	Caregiver factors	Peer factors	Contextual factors
Pediatric Cancer Coping Scale (PCCS)[47]	Cancer	33	3-point Likert scale	0–66	Coping style (cognitive, problem-oriented, and defensive)				
Perceived social suppor[t48]	Cancer	60	5-point Likert scale	NR	Perceived social support from healthcare providers Perceived social support from family Perceived social support from friends				
Personal Relationship Measurement[49]	Cancer	14	5-point Likert scale	NR	Friendship				
Peabody Picture Vocabulary Test—Third Edition (PPVT-III)[50]	DMD	204	4-point Likert scale	NR	Verbal intelligence				
Quick Big Five[51]	CHD	30	7-point Likert scale	NR	Personality type (extraversion, agreeableness, conscientiousness, emotional stability, openness)				
Reed Spiritual Perspective Scale[52]	Cancer	10	6-point Likert scale	10–60	Spiritual frequency and beliefs				
Resilience measurement instrument for children with chronic illness [53]	Atopic dermatitis, cancer	32	4-point Likert scale	32–128	Self-understanding Self-reliance Resourcefulness Family relationships Interpersonal intimacy				
Resilience Scale for Children and Adolescents (RSCA)[54]	T1D, Orofacial anomalies	64	5-point Likert scale	0–256	Self-perception of skills and competences Emotional reactivity Sense of relatedness				

Instruments measuring resilience factors (continued)

Instruments	Previously used in youth with diagnosis	Items	Response	Range [a]	Assessment of resilience factors				
					Internal	Disease	External		
					Cognitive, social, and emotional competence factors	Disease-related factors	Caregiver factors	Peer factors	Contextual factors
Resilience Assessment Scale for Children and Adolescents (SPP-18) [55]	Liver or renal transplantation	18	5-point Likert scale	0–72	• Sense of mastery • Sense of relatedness • Emotional reactivity				
Resilience Scale (RS), Wagnild and Young [56]	CHD, CKD, T1D, cancer	25	7-point Likert scale	25–175	• Purpose • Perseverance • Self-reliance • Equanimity • Authenticity				
Resilience Scale, 14-item (RS-14) [57]	Cancer	10	4-point Likert scale	10–40	• Sense of purpose and meaning • Authenticity • Equanimity • Self-reliance • Perseverance				
Responses to Stress Questionnaire (RSQ)[58]	T1D	57	4-point Likert scale	57–171		• Coping strategies in response to illness-related stressors • Involuntary stress response in response to illness-related stressors			
Rosenberg Self-Esteem Scale[59]	Cancer, T1D	10	4-point Likert scale	NR	• Self-esteem • Self-worth/self-acceptance				
School Connectedness Scale (SCS)[60,61]	HIV/AIDS	6	4-point Likert scale	6–24				• Connectedness to peers • Connectedness to the school • Connectedness to adults in schools	

Instruments measuring resilience factors (continued)

Instruments	Previously used in youth with diagnosis	Items	Response	Range [a]	Assessment of resilience factors				
					Internal	Disease	External		
					Cognitive, social, and emotional competence factors	Disease-related factors	Caregiver factors	Peer factors	Contextual factors
Self-efficacy for antiretroviral treatment use[2]	HIV/AIDS	NR	5-point Likert scale	NR					
					• Self-efficacy for medication				
Self-efficacy for diabetes (SED)[62]	T1D	35	6-point Likert scale	35-175					
					• Self-efficacy in relation to diabetes management				
Social support[63]	HIV/AIDs	6	4-point Likert scale	NR					
					• Social support promoting therapy adherence				
Social Problem-Solving Inventory-Revised short form (SPSI-R:S)[64,65]	T1D	25	5-point Likert scale	0-100					
					• Problem solving				
School Support Scale (SSS)[66]	HIV/AIDS	5	5-point Likert scale	5-25					
					• School liking				
Scale of Satisfaction with Social Support (SSSS)[67,68]	T1D, allergic or neurological diseases	12	5-point Likert scale	18-72					
					• Satisfaction with social support • Activities connected to social support				
School Adjustment Test[69]	Cancer	8	5-point Likert scale	NR					
					• Relationship with teachers				
The Neil and Dias Resilience scale[70]	T1D	15	7-point Likert scale	15-105					
					• Personal competence • Acceptance				

Instruments measuring resilience factors (continued)

Instruments	Previously used in youth with diagnosis	Items	Response	Range [a]	Assessment of resilience factors				
					Internal	Disease	External		
					Cognitive, social, and emotional competence factors	Disease-related factors	Caregiver factors	Peer factors	Contextual factors
Youth Self Report (YSR)[71]	T1D	20	3-point Likert scale	0-40	• Perception of competence • Perception of social competence				
7Cs Tool[72]	Obesity	7	3-point Likert scale	0-2	• Competence • Confidence • Character • Connection • Caring • Coping • Control				

Legend Disease CHD = Congenital Heart Disease; CKD = Chronic Kidney Disease; DMD = Duchenne Muscular Dystrophy; HIV = Human Immunodeficiency Virus; IBD = Inflammatory Bowel Diseases; JIA = juvenile idiopathic arthritis; MS = Multiple Sclerosis; SCD = Sickle Cell Disease; T1D = Type 1 diabetes; T2D = Type 2 diabetes.

Other NA = not applicable; NR = not reported

REFERENCES

1. Gartland D, Bond L, Olsson CA, Buzwell S, Sawyer SM. Development of a multi-dimensional measure of resilience in adolescents: the Adolescent Resilience Questionnaire. *BMC Med Res Methodol*. 2011;11(1):134. doi:10.1186/1471-2288-11-134
2. Fisher JD, Fisher WA, Amico KR, et al. An information-motivation-behavioral skills model of adherence to antiretroviral therapy. *Health Psychology*. 2006;25(4):462-473.
3. Hollon SD, Kendall PC. Cognitive self-statements in depression: Development of an automatic thoughts questionnaire. *Cognit Ther Res*. 1980;4(4):383-395. doi:10.1007/BF01178214
4. Greco L, Lambert W, Baer R. Psychological inflexibility in childhood and adolescence: Development and evaluation of the avoidance and fusion questionnaire for youth. *Psychol Assess2*. 8AD;20(2):93-102.
5. Cho S, Hung L, Su C, Chen H. A research of the Chinese version Beck Youth Inventories. *Psychol Test*. 2009;56(4).
6. Greco LA, Baer RA, Smith GT. Assessing mindfulness in children and adolescents: Development and validation of the Child and Adolescent Mindfulness Measure (CAMM). *Psychol Assess*. 2011;23(3):606-614. doi:10.1037/a0022819
7. Austin JK, Huberty TJ. Development of the Child Attitude Toward Illness Scale. *J Pediatr Psychol*. 1993;18:467-480.
8. Kaslow NJ, Tannenbaum RL, Seligman MEP. *The KASTAN: A Children's Attributional Style Questionnaire.*; 1978.
9. Achenbach TM. *The Manual for the Child Behavior Checklist/4-18 and 1991 Profile*. University of Vermont, Department of Psychiatry; 1991.
10. Bursch B, Tsao JCI, Meldrum M, Zeltzer LK. Preliminary validation of a self-efficacy scale for child functioning despite chronic pain (child and parent versions). *Pain*. 2006;125(1):35-42. doi:10.1016/j.pain.2006.04.026
11. Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the connor–davidson resilience scale (CD-RISC): Validation of a 10-item measure of resilience. *J Trauma Stress*. 2007;20(6):1019-1028.
12. Connor KM, Davidson JRT. Development of a new Resilience scale: The Connor-Davidson Resilience scale (CD-RISC). *Depress Anxiety*. 2003;18(2):76-82.
13. Sandler IN, Tein JY, Wolchik S, al E. Coping Efficacy and Psychological Problems of Children of Divorce. *Child Dev*. 2000;71(4):1099-1118.
14. Hood KK, Iturralde E, Rausch J, et al. Preventing diabetes distress in adolescents with type 1 diabetes: Results 1 year after participation in the STePS program. *Diabetes Care*. 2018;41(8):1623-1630.
15. Snyder CR, Hoza B, Pelham WE, et al. The Development and Validation of the Children's Hope Scale. *J Pediatr Psychol*. 1997;22(3):399-421.
16. Park Y. *The Relationships between Parental Childrearing Behaviors and Sibling Relations and Children's Self- Esteem.*; 1995.
17. Carver CS. You want to measure coping but your protocol's too long: Consider the Brief COPE. *Int J Behav Med*. 1997;4:92-100.
18. Endler N, Parker J. *Coping Inventory for Stressful Situations (CISS): Manual*. 2nd ed. Multi-Health Systems; 1999.
19. McCracken L, Gauntlett-Gilbert J, Eccleston C. Acceptance of pain in adolescents with chronic pain: Validation of an adapted assessment instrument and preliminary correlation analyses. *Eur J Pain*. 2010;14(3):316-320.
20. Gil KM, Williams DA, Thompson RJ, et al. Sickle Cell Disease in Children and Adolescents: The Relation of Child and Parent Pain Coping Strategies to Adjustment. *J Pediatr Psychol*. 1991;16(5):643-663.
21. Liebenberg L, Ungar M, van d.V.jver F. Validation of the Child and Youth Resilience Measure-28 (CYRM-28) Among Canadian Youth. *Res Soc Work Pract*. 2012;22(2):219-226.
22. Sandler I, Tein J, Wolchik S, et al. Coping Efficacy and Psychological Problems of Children of Divorce. *Child Dev*. 2000;71(4):1099-1118.
23. Hood KK, Butler DA, Anderson BJ, Laffel LMB. Updated and Revised Diabetes Family Conflict Scale. *Diabetes Care*. 2007;30(7):1764-1769. doi:10.2337/dc06-2358

24. Hilliard ME, Iturralde E, Weissberg-Benchell J, Hood KK. The Diabetes Strengths and Resilience Measure for Adolescents With Type 1 Diabetes (DSTAR-Teen): Validation of a New, Brief Self-Report Measure. *J Pediatr Psychol*. 2017;42(9):995-1005.
25. Huston SA, Bloun RL, Heidsec T. Resilience, emotion processing and emotionexpression among youth with type 1 diabetes. *Pediatr Diabetes*. 2016;17:623-631.
26. Prince-Embury S. The Ego-Resiliency Scale by Block and Kremen (1996) and Trait Ego-Resiliency. In: *Prince-Embury S., Saklofske D. (Eds) Resilience in Children, Adolescents, and Adults*. Springer; 2013.
27. Block JH, Block J. *The Role of Ego-Control and Ego- Resiliency in the Origination of Behavior*. Vol 13. WA Collings (red.). The Minnesota Symposia on Child Psychology.; 1980.
28. Lim J, Lee K, Oh M, Kwak K, Lee H, Yoon B. A study on reliability and validity of FACES. *J Korean Acad Fam Med*. 1990;11:8-17.
29. Li Y, Lu PW, Sun J. Research on post-traumatic growth status and influencing factors of adolescent patients with chronic diseases. *Journal of Chinese Nursing Management*. 2016;7:914-919.
30. Olson D. *Family Inventories*. Family Social Science, University of Minnesota; 1985.
31. Haase JE, Kintner EK, Monahan PO, Robb SL. The resilience in illness model, part 1: exploratory evaluation in adolescents and young adults with cancer. *Cancer Nurs*. 2014;37(3):E1-12.
32. Herth K. Abbreviated instrument to measure hope: development and psychometric evaluation. *J Adv Nurs*. 1992;17:1251-1259.
33. Karcher MJ. *The Hemingway: Measure of Adolescent Connectedness: A Manual for Scoring and in-Terpretation. Unpublished Manuscript*. University of Texas; 2005.
34. Karcher MJ, Sass D. A multicultural assessment of adolescent connectedness: Testing measurement invariance across gender and ethnicity. *J Couns Psychol*. 2010;57:274-289.
35. Martins MH. *Contribuições Para a Análise de Crianças e Jovens Em Situação de Risco - Resiliência e Desenvolvimento [Contributions for the Analysis of Children and Adolescentes in Risky Situations – Resilience and Development]*. Universidade do Algarve; 2005.
36. Kazdin AE, Rodgers A, Colbus D. The Hopelessness Scale for Children: Psychometric characteristics and concurrent validity. *J Consult Clin Psychol*. 1986;54(2):241-245. doi:10.1037/0022-006X.54.2.241
37. Evers A, Kraaimaat F. Illness Cognition Questionnaire. www.andreaevers.nl. Published 2009. Accessed May 6, 2021. https://www.andreaevers.nl/uploads/bestanden/ICQ18-En.pdf
38. Jalowiec A. Psychometric assessment of the Jalowiec Coping Scale. *Nurs Res*. 1984;33:157-161.
39. Kessler R, Green J, Gruber M, et al. Screening for serious mental illness in the general population with the K6 screening scale: results from the WHO World Mental Health (WMH) survey initiative. *Int J Methods Psychiatr Res*. 2010;19:4-22.
40. Scheier M, Carver C. Dispositional optimism and physical well-being: The influence of generalized outcome expectancies on health. *J Pers*. 1987;55(2):169-210.
41. McCorkle R. The measurement of symptom distress. *Semin Oncol Nurs*. 1987;3:248-256.
42. Mishel M. The measurement of uncertainty in illness. *Nurs Res*. 1982;30:258-263.
43. Varni J, Seid M, Kurtin P. Pediatric health-related quality of life measurement technology: a guide for health care decision makers. *Journal of Clinical Outcomes Management*. 1999;6:33-40.
44. Prochaska J, Sallis J, Long B. A physical activity screening measure for use with adolescents in primary care. *Arch Adolesc Med*. 2001;155:554-559.
45. Prochaska J, Sallis J. Reliability and validity of a fruit and vegetable screening measure for adolescents. *Adoles Health*. 2004;33:163-165.
46. Hagler A, Calfas K, Norman G, Sallis J, Patrick K. Construct validity of physical activity and sedentary behaviors staging measures for adolescents. *Ann Behav Med*. 2006;31:186-193.
47. Wu L, Chin C, Chen C, Lai F, Tseng Y. Development and validation of the paediatric cancer coping scale. *J Adv Nurs*. 2011;67(5):1142-1152.
48. Procidano M, Heller K. Measures of perceived social support from friends and from family: three validation studies. *Am J Community Psychol*. 1983;11(1-24).
49. Kim J. The relation between daily stress and emotional experience on the adjustment of middle-aged women: impacts of psychological and social resources. *J Korean Psychol Assoc*. 1992;4:54-68.
50. Dunn LM, Dunn DM. *Peabody Picture Vocabulary Test*. Fourth edi. Pearson Assessments; 2007.
51. Vermulst AA, Geriis JRM. *QBF: Quick Big Five Persoonlijkheidstest Handleiding [Quick Big Five Personality Test Manual]*. LDC Public.; 2005.
52. Reed PG. Spirituality and well-being in terminally ill hospitalized adults. *Research in Nursing Health*. 1987;10(5):344-355.
53. Kim DH, Yoo IY. Development of a Questionnaire to Measure Resilience in Children with Chronic Diseases. *J Korean Acad Nurs*. 2010;40(2):236.

54. Prince-Embury S. Resiliency Scales for Children and Adolescents: A Profile of Personal Strengths. *Can J Sch Psychol*. 2007;22(2):255-261.
55. Ogińska-Bulik N, Juczyński Z. "Prężność u dzieci i młodzieży: charakterystyka i pomiar–polska skala SPP-18." *Polskie Forum Psychologiczne*. 2011;16(1).
56. Wagnild GM, Young HM. Development and psychometric evaluation of the Resilience Scale. *J Nurs Meas*. 1993;1(2):165-178.
57. Wagnild GM, Young HM. Development and psychometric evaluation of the Resilience Scale. *J Nurs Meas*. 1993;1(2):165-178.
58. Connor-Smith JK, Compas BE, Wadsworth ME, al E. Responses to stress in adolescence: measurement of coping and involuntary stress responses. *J Consult Clin Psychol*. 2000;68:976-992.
59. Rosenberg M. *Conceiving the Self*. Basic Books; 1979.
60. McNeely C, Nonnemaker J, Blum R, al E. Promoting school connectedness: Evidence from the National Longitudinal Study of Adolescent Health. *Journal of School Health*. 2002;72:138-146.
61. Resnick MD, Bearman PS, Blum R, al E. Protecting adolescents from harm: Findings from the National Longitudinal Study on Adolescent Health. *Journal of American Medical Association*. Published online 1997:823-832.
62. Grossman HY, Brink S, Hauser ST. Self-efficacy in adolescent girls and boys with insulin-dependent diabetes mellitus. *Diabetes Care*. 1987;10(3):324-329.
63. Cutrona CE, Russel DW. The provisions of social relationships and adaptation to stress. *Advances in personal relationships*. 1987;1(37-67).
64. Maydeu-Olivares A, D'Zurilla T. A factor analytic study of the social problem-solving inventory: an integration of theory and data. *Cognit Ther Res*. 1996;20:115-133.
65. Weissberg-Benchell J, Rausch J, Iturralde E, et al. A randomized clinical trial aimed at preventing poor psychosocial and glycemic outcomes in teens with type 1 diabetes (T1D). *Contemp Clin Trials*. 2016;49(24):78-84.
66. Hanson TL, Kim JO. *Measuring Resilience and Youth Development: The Psychometric Properties of the Healthy Kids Survey.*; 2007.
67. Gaspar T, Robeiro J, Matos M, Leal I, Ferreira A. Psychometric Properties of a Brief Version of the Escala de Satisfação com o Suporte Social for Children and Adolescents. *Span J Psychol*. 2009;12(1):360-372.
68. Ribeiro J. Escala de Satisfação com o Suporte Social (ESSS) [Satisfaction with Social Support Scale]. *Analise Psicologica*. 1999;3(17):547-558.
69. Im J. *The Relationships between Dependency and School Adjustment of Children (Master Thesis)*. Korea National University of Education; 1993.
70. Neill JT, Dias KL. Adventure education and resilience: The double-edged sword. *Journal of Adventure Education & Outdoor Learning*. 2001;1(2):35-42.
71. Achenbach TM, Rescorla LA. *Manual for the ASEBA School-Age Forms and Profiles*. University of Vermont, Research Centre for Children, Youth and Families; 2001.
72. Barger J, Vitale P, Gaighan J, Feldman-Winter L. Measuring resilience in the adolescent population: a succinct tool for outpatient adolescent health. *J Pediatr2*. 2017;189:201-206.

CHAPTER 3

THE RISE STUDY PROTOCOL:

RESILIENCE IMPACTED BY POSITIVE STRESSFUL EVENTS FOR PEOPLE WITH CYSTIC FIBROSIS

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ABSTRACT

Introduction

For people with cystic fibrosis (pwCF), gaining access to elexacaftor/tezacaftor/ivacaftor (ETI) therapy, a new modulator drug combination, is perceived as a positive life event. ETI leads to a strong improvement of disease symptoms. However, some pwCF experience a deterioration in mental well-being after starting ETI therapy. The primary objective of this study is to investigate if and in which direction mental well-being of pwCF, defined as quality of life (QoL), changes after starting ETI therapy. Our secondary objectives include, among others, investigation of underlying biological and psychosocial factors associated with a change in QoL of pwCF after starting ETI therapy.

Methods and analysis

The Resilience lmpacted by positive Stressful Events (RISE) study is a single arm, observational, prospective longitudinal cohort. It has a timeframe of 60 weeks: 12 weeks before, 12 weeks after, 24 weeks after, and 48 weeks after start ETI therapy. The primary outcome is the mental well-being, measured on each of these four time points. Patients are eligible when aged 12 years or older, qualifying for ETI therapy based on their CF-mutation, and being a patient in the University Medical Center Utrecht. Data will be analyzed using a covariance pattern model with a general variance covariance matrix.

Ethics

The RISE study was classified by the Institutional Review Board as exempt from the Medical Research Involving Human Subjects Act. Informed consent was obtained by both the child (12 to 16 years) and their caregivers or only provided by the participants themselves when aged 16 years and older.

INTRODUCTION

Cystic Fibrosis (CF) is a common autosomal recessive disease manifested by dysfunction of multiple organs, including the lungs, pancreas, gastro-intestinal tract, the male reproductive system, and sweat glands [1]. CF is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR)-protein, resulting in impaired water and salt transport through epithelial cell membranes [1]. People with CF (pwCF) have varying severity of CF-related symptoms and many different CFTR mutations and phenotypes are described [2]. Nevertheless, pulmonary manifestations are usually most severe and progressive [3]. In addition to a shortened life expectancy, pwCF also have significant comorbidities and high impact treatments [4]. The combination of these factors affects their daily functioning, identity and life goals [4]. Additionally, regarding mental and social health, a systematic review revealed that youth with CF experience a sense of vulnerability, loss of independence and opportunities, and disempowerment [4]. New therapies (CFTR modulators in particular), however, decreased CF- related disease expression and have greatly improved the life expectancy of pwCF. These new therapies changed CF from a life threatening disease into a chronic disease with a normal life expectancy [2,3,5–7].

From January 2022, the newest CFTR-modulator combination elexacaftor/tezacaftor/ivacaftor (ETI) is available to pwCF aged 12 years and older in the Netherlands [8]. ETI is a modulator drug combination that impacts the CFTR protein resulting in improvement of the CFTR chloride and bicarbonate channel function [2,9]. ETI is a very effective drug combination that leads to a strong reduction of disease expression and severity [2,9]. Therefore getting access to ETI is considered to be a positive, major life event and seen as a game changer for pwCF [10]. Nonetheless, several articles report a deterioration in mental health, primarily expressed as increased symptoms of anxiety and/or depression after starting a CFTR-modulator [11–13]. Moreover, when specifically focused on ETI , a minority of the patients also experienced a deterioration in mental health after starting ETI [14–16]. Multiple mechanisms, which might co-exist, on why mental health might worsen after starting these novel CFTR modulators are described, including: 1) the psychological effect of starting a potentially life-changing drug; 2) direct effects of CFTR modulators on the functioning of the central nervous system (CNS); 3) interaction of the CFTR modulator with psychotropic medication; and/or 4) no direct relationship with the CFTR modulator, but the change in mental health is provoked by typical triggers of depression and anxiety such as stress, pain, and inflammation [12,14,17,18].

There have been no longitudinal studies focusing on a possible change in mental well-being after starting with ETI therapy. Additionally, as significant improvements of CF-related symptoms are often experienced, some patients might feel resistance to discontinue their ETI therapy and consequently, under-report side effects regarding their mental health [14,19]. By multiple measurements of mental well-being, we aim to gain a better picture of

the incidence of deterioration of mental health. Furthermore, by incorporating multiple variables of mental well-being, we might be able to epidemiologically analyze potential associations between the severity of mental health problems and CFTR modulators and draw conclusions on how mental well-being changes after starting ETI therapy [12,16]. Therefore, we will assess inter-individual differences in mental well-being both before and after gaining access to ETI therapy. Although we are aware that in addition to psychological effects of starting a CFTR modulator, all mechanisms might concomitantly affect mental well-being of pwCF. In this manuscript, we will mainly focus on mechanism 1 (the psychological effect of starting a potentially life-changing drug). We hypothesize that most of the pwCF manage to positively adapt to the renewed life-possibilities, while some do not adapt or even adapt negatively and develop more serious problems concerning their mental health.

It is important to understand why pwCF respond differently to ETI therapy, especially to grasp why one person is able to adapt positively and function resiliently, and another is not. The phenomenon, *positive adaptation within the context of a significant stressor by maintaining or regaining mental health*, is often referred to as resilience [20–22]. Many factors on biological, psychosocial, and environmental levels facilitating positive adaptation to adversity have been described: these factors are generally referred to as resilience or protective factors [22–24]. Factors can involve the individual's biology (e.g., brain structure or genes) [24], one's behavior, emotions, and cognition [25–27], one's environment such as relationships with family and friends [28–30], and one's attitude towards religion [22,23,31]. In this study we will take illness perception (including acceptance), illness identity, and the personal competence to handle stress into account (e.g. the ability to bounce back). Resilience factors could give insight in the mechanisms behind change in mental well-being after gaining access to ETI therapy and might allow physicians and other caregivers to identify resilient functioning pwCF but also potentially vulnerable pwCF at an earlier stage. Through support and interventions, healthcare professionals, family members, caregivers, significant others, and pwCF themselves could promote resilience potentially resulting in better mental well-being taking ETI therapy or equivalent medication.

Objectives

The primary objective of the 'Resilience lmpacted by positive Stressful Events for people with cystic fibrosis' (RISE) study is to investigate if and in which direction mental well-being of pwCF changes after initiation of ETI therapy.

Our exploratory secondary objectives include investigating which underlying resilience factors are associated with the change in mental well-being of pwCF after starting ETI therapy. Moreover, we also investigate change of other indicators of mental well-being, such as anxiety and depressive symptoms, after initiation of ETI therapy.

METHODS AND ANALYSIS

Study design

RISE is a single-arm, observational, prospective longitudinal cohort study which follows people with CF aged ≥12 years over a time frame of 60 weeks. A control arm was not considered ethically feasible, as in general ETI therapy has been demonstrated to be a very effective drug combination that leads to a strong reduction of disease expression and severity [9]. The primary outcome is measured at each of the four time points.

Eligibility and recruitment

Inclusion criteria for the RISE study are 1) people with CF aged ≥12 years, 2) who qualify for ETI therapy based on their CF-mutation (homozygous for the F508del-mutation or heterozygous with a F508del-mutation and any other mutation), and 3) are patients at the University Medical Center Utrecht (UMCU)/Wilhelmina Children's Hospital (Utrecht, the Netherlands). Potential participants are excluded if they are not able to read and understand Dutch and/or when their medical condition is perceived as unfit for ETI therapy, evaluated by the treating physician.

The listing and invitation of eligible patients from the UMCU for the medical introduction consults is done by the secretariat of the Pediatric Pulmonology Department, Wilhelmina Children's Hospital and Cystic Fibrosis Centre of the UMCU. Patients are informed through an invitation letter regarding the start of ETI therapy and the RISE study by their treating physician. A few weeks after sending the patient information letters, patients (and, when aged <16 years, their parents) are contacted by phone, in order to answer questions if necessary and to ask for verbal informed consent for participation in the study. If patients need more time to decide, another appointment is planned. When a patient consents verbally to participate in the study, an appointment is scheduled for the regular medical consultation and the additional study act (completing questionnaires) for the RISE study at baseline (T0). Patients who do not want to participate in the RISE study are still invited for the medical consultation at T0, but do not complete the RISE questionnaires. These patients receive a different package of questionnaires. These questionnaires are conducted and used in the context of medical care.

Time schedule

Over 60 weeks, at four time points, we collected data. The first time point was before the participants started ETI. We call this moment baseline (T0). We then collected data at 12 weeks (T1), 24 weeks (T2) and 48 weeks (T3) after starting ETI. Questionnaires were sent at all four time points (T0, T1, T2 and T3). At T0 and T2, participants attended medical consultations (Table 1).

Table 1: Timing of measurements

	12 weeks before start	12 weeks after start	24 weeks after start	48 weeks after start
Timing	***T0***	***T1***	***T2***	***T3***
Type of measurement	Medical consultation Questionnaires RISE	Questionnaires RISE	Medical consultation Questionnaires RISE	Questionnaires RISE

Procedure

Both before starting ETI therapy (T0) and after using ETI therapy (T2), all participants are invited to the UMCU for a medical consultation. All measurements are performed by physicians and experienced research nurses. During this medical consultation we measure lung function, nutrition status, sweat chloride concentration and faecal elastase. Moreover, information about CF-related comorbidities (CF-related diabetes and CF-related liver disease), colonisation with *Pseudomonas aeruginosa*, intravenous antibiotics and maintenance therapy, including psychotropic drugs, is collected from the electronic patient file.

At every time point (T0–T4), participants are asked to complete the RISE questionnaires. The questionnaires are sent *via* Castor, an e-clinical data management platform, and participants receive a personalized and secure link to the questionnaires (www.castoredc.com).

Because participants are already in the UMCU for a medical consultation at T0 and T2, they complete the questionnaires at the hospital at these time points. At T1 and T3, the participants complete the questionnaires at any place of their choice. Completing the research questionnaires will take participants ~20 min. Completing all questionnaires, including those conducted in the context of medical care, will take participants ~1 h. Table 2 shows which questionnaires are conducted for RISE and which questionnaires are conducted in the context of medical consultation.

Table 2: Summary of used instruments

Questionnaires	Content/subscales	Items	Values	In context of
B-IPQ[32]* Illness perception	· consequence · timeline · personal control · treatment control · identity score · coherence · emotional representation · illness concern	8	· score 0 (best possible) to 10 (worst possible) · higher score = more threatening view of the illness	research
BMLSS[33]* Multidimensional Life Satisfaction	· overall life satisfaction, myself	*1*	· very low satisfaction; low satisfaction; neutral; satisfaction; high satisfaction · score 0-5: higher score = more life satisfaction	medical care
BRS[34] Resilience Scale	The ability to bounce back	6	· strongly disagree, disagree, neutral, agree, strongly agree · score 1-5: higher score = more ability to bounce back	medical care
Cantril ladder[35,36] General life satisfaction	How do you feel about your life?	*1*	· score 0 (worst possible life) to 10 (best possible life)	medical care
CFQ-R[37] Cystic Fibrosis, health related quality of life	· physical · role · vitality · emotion · social · body · eat · treat · health · weight · respiratory · digestion	*50*	· always, often, sometime, never · score 0-100: higher scores = better health related quality of life	medical care
GAD-7[38] Generalized anxiety	Generalized anxiety	7	· not at all, several days, more than half the days, nearly every day · score 0-21: higher score = more symptoms	medical care
Gastro-Intestinal module of the PedsQL[39] Gastro-intestinal symptoms	Gastro-intestinal symptoms · gastro intestinal symptoms · worries about symptoms · communication about symptoms	15	· never, almost never, sometimes, often, almost always	medical care

Table 2: Summary of used instruments (continued)

Questionnaires	Content/subscales	Items	Values	In context of
IIQ [40] Illness identity	· rejection · engulfment · acceptance · enrichment	*25*	· score 1 (strongly disagree) to 5 (strongly agree)on every subscale · high scores on subscales rejection and engulfment are related to maladaptive psychological and physical functioning. · high scores on subscales acceptance and enrichment are related to adaptive psychological and physical functioning	research
PedsQl 4.0 [41–43] Pediatric quality of life	· physical functioning · emotional functioning · social functioning · school functioning	*23*	· never, almost never, sometimes, often, almost always · score 0-100: higher score = higher quality of life	research
PHQ-9 [44] Health Questionnaire	Major depressive disorder	*9*	· not at all, several days, more than half the days, nearly every day · score 0-27: mild depression = 5 points; moderate depression = 10 points; severe depression = 15 points; very severe depression = 20 points.	medical care
PSS[45] Perceived stress	Perceived stress in the last month	*10*	· never, almost never, sometimes, often, very often · score 0-40: when one scored above 14 points, than one is more stressed than average	medical care
RCADS[46] Internalizing symptoms	· Separation anxiety disorder · Social phobia · Generalized anxiety disorder · Panic disorder · Obsessive compulsive disorder · Major depressive disorder	*47*	· never, sometimes, often, always · score 0-141: higher score = more severe symptoms	medical care
SDQ[47] Emotional and behaviour problems	· Emotional symptoms · Conduct problems · Hyperactivity/inattention · Peer problems · Prosocial behavior	*25*	· not true, somewhat true, certainly true · score 0-40: higher score = more severe symptoms	research

Table 2: Summary of used instruments (continued)

Biological measurements	Measured by	Research/ medical care
Lung function	FVC, FEV1 and predicted %FEV1	medical care
Nutrition status	Length, weight: body mass index in kg/m^2	medical care
Sweat chloride	Chloride concentration mMol/L	medical care
Fecal elastase	Microgram/gram	medical care
CF related diabetes	Electronic patient file	medical care
CF related liver disease	Electronic patient file	medical care
Colonization with Pseudomonas Aeruginosa	Electronic patient file	medical care
IV antibiotics: Used in the previous year before To of the RISE study	Electronic patient file	medical care
Maintenance therapy	Electronic patient file	medical care

B-IPQ = Brief Illness Perception Questionnaire; BRS = Brief Resilience Scale; BMLSS = Brief Multidimensional Life Satisfaction Scale; CFQ-R = Cystic Fibrosis Questionnaire Revised; GAD = Generalized Anxiety Disorder-7; IIQ = Illness Identity Questionnaire; PedsQL 4.0 = Pediatric Quality of Life Inventory 4.0; PHQ-9 = Patient Health Questionnaire-9; PSS = perceived stress scale; RCADS = Revised Child Anxiety and Depression Scale; SDQ = Strengths and Difficulties Questionnaire

*not all subscales of the original questionnaire are used. The used subscales in the RISE study are presented in this table

Data collection and statistical methods

Data are collected simultaneously in two ways. First, in the context of research we ask the participants to complete questionnaires. Moreover, multiple biological measurements and questionnaires are already incorporated into the medical consultation, and due to overall UMCU CF patient consent based on the Central Cystic Fibrosis Research (CCFR) cohort 16/668, we will be able to use this information. All questionnaires are completed by the participants themselves and are thus self-reported. Additionally, all selected RISE questionnaires are related to our study aims. The questionnaires used in the context of medical care will be used for the exploratory secondary objectives. The overview of used instruments in both research and the medical consultation is shown in Table 2.

Measurements in context of research

In the RISE study, we only use questionnaires with validated concepts and (sub)scales that will enable us to compare the outcomes to other studies with participants from population cohorts or people with other diseases. The measurement of mental wellbeing is primarily based on the outcome of the Pediatric Quality of Life Inventory 4.0. (PedsQL) versions for adolescents and adults. This questionnaire is frequently used and has validated versions for children, adolescents and adults [48]. The PedsQL 4.0 generic core scales consists of four scales: physical functioning (eight items), emotional functioning (five items), social functioning (five items) and school/study/work functioning (five items). Three standardised summary scores can be calculated from these four core scales: a total quality-of-life score, a physical health summary score (based on the physical functioning items) and a psychosocial health summary score (a combination of emotional, social and school/study/work items). Current research shows that the outcome measures of the PedsQL psychosocial health dimension correspond with mental wellbeing [49]. This dimension is our primary outcome. We define significant change in mental well-being as minimal clinically important difference of 4.4 points after starting ETI therapy [50].

Additionally, we assess illness identity with the Illness Identity Questionnaire (IIQ) [40], illness perception with the Brief Illness Perception Questionnaire (B-IPQ) [32], and emotional and behavior problems with the Brief Strengths and Difficulties Questionnaire (SDQ) [51] (see Table 2).

Measurements in the context of medical care

During the medical consultation, we measure nutrition status with body mass index in $kg{\cdot}m^{-2}$, clinical sweat chloride with chloride concentration in $mmol{\cdot}L^{-1}$ and lung function in forced expiratory volume in 1 s (FEV_1), FEV_1 % predicted and forced vital capacity. Moreover, from the electronic patient file we extract information about CF-related diabetes, CF-related liver disease, colonization with *P. aeruginosa*, maintenance therapy and *i.v.* antibiotics in the year prior to T0 of the RISE study.

Additionally, a number of questionnaires are conducted in the context of medical care. These questionnaires are: Cantril Ladder [52], Brief Multidimensional Life Satisfaction Scale [53] (BMLSS), Generalized Anxiety Disorder-7 (GAD-7) [54], Cystic Fibrosis Questionnaire Revised (CFQ-R) [55], Revised Child Anxiety and Depression Scale (RCADS) [56], Patient Health Questionnaire-9 (PHQ-9) [57], the Perceived Stress Scale (PSS) [58], the Brief Resilience Scale (BRS) [34], and the Gastro-Intestinal module of the PedsQL [39] (Table 2).

Most of the questionnaires used in the RISE study are not CF-specific, as we aimed for a holistic and broad interpretation of the concept of mental health. If a questionnaire is not validated in people with CF, we believe it may still be appropriate for this study because we are also examining disease-nonspecific concepts. In the supplementary material, we specify whether the questionnaire is validated in general and validated in Dutch, has been validated in people with CF, and/or has been used previously in people with CF. Moreover, we have included an explanation of why we chose to include the questionnaire in the RISE study. We did not perform a systematic review, and therefore this overview is not complete, *e.g.* when a questionnaire was used often, we did not present all studies. In summary, all questionnaires are validated, almost all questionnaires are validated in Dutch, and some questionnaires are validated in people with CF.

Statistical analysis of results

Descriptive baseline characteristics of the cohort will be presented as n (%), mean±sd or median (interquartile range). Psychosocial health summary score (PedsQL) scores, measured on the four visits, will be treated as continuous and analysed using a covariance pattern model with a general (*i.e.* unrestricted) variance covariance matrix. The test of primary interest is the likelihood-ratio test (α=0.05) comparing the model with a fixed effect of "visit" (included in the model as a discrete variable) against the intercept-only model, thus testing the null hypothesis of equality of the four visit-specific means. For a more detailed assessment of the results, regression coefficient estimates and visit-specific estimated marginal means will be provided along with 95% confidence intervals.

The study data will also be used for more exploratory secondary analyses. Secondary analyses include 1) subgroup comparisons for the primary outcome variable; for instance, analysis will be stratified on age groups: adolescents aged 12–24 years and adults aged ≥25 years; 2) in accordance with the analysis of the primary outcome variable, we will also analyze the secondary variables as an outcome variable; 3) an assessment of pairwise correlations between all primary and secondary outcome variables (per visit); and 4) evaluation/description of subjects who experience a decline in primary outcome variable at one of the post-baseline visits.

Sample size considerations

A priori, it was conservatively estimated that, in this rare-disease setting, ~100 subjects would be eligible and willing to participate in this observational study. With n=100, the expected width of the confidence interval around a sample mean will be roughly equal to 0.4 times the standard deviation in the population. In this respect, *i.e.* in terms of precision, a sample size of 100 is considered adequate for the purpose of this study. However, to also obtain an approximation of the power of the primary analysis, simulations were performed. In the simulations, data were drawn from a multivariate normal distribution with correlations following a spatial-power correlation function. A range of setting was explored, varying 1) the correlation between the repeated measurements (ranging from very "pessimistic" to very "optimistic"); 2) the visit(s) on which the mean would differ from the other visits; and 3) the size of the difference. Overall, the results indicate that, with n=100, it is very plausible to assume that the power will be sufficient (*i.e.* close to or exceeding 0.80) to detect a difference of 0.4 times the population standard deviation at any or all post-baseline visits, which is considered satisfactory for the purpose of this study. With very high test–retest correlations, the power will also be sufficient for differences of 0.3 or even 0.2 times the standard deviation.

Handling missing data

Missing data are expected to be rare, given the intertwined nature of care and research. For this reason, a complete case analysis is considered appropriate. We will report the number and percentage of missed visits (*e.g.* due to dropouts), as well as the total number and percentage of data rows to be removed for each analysis. Additionally, also the reason for dropout and/or missingness will be noted. Analyses that require a substantial portion (>10%) of the data rows to be removed due to missing data will be reanalyzed using multiple imputation.

Patient and public involvement

We have been awarded a grant for this research: Corno Fonds Onderzoek Subsidie 2022 by the Dutch Cystic Fibrosis Society. Both people with CF and scientists individually reviewed and assessed the research plan and provided feedback on the work. It was scored on scientific properties (from goal to feasibility) and relevance to people with CF. We believe this feedback strengthened our research plan.

Ethics

The RISE study was classified by the institutional review board as exempt from the Medical Research Involving Human Subjects Act (code METC: 21/626). This study was and will be performed in line with the principles of the Declaration of Helsinki. Informed consent was provided by both the children (aged 12–16 years) and their parent(s)/representative(s), or only provided by the participants themselves when aged >16 years, and comprised the use of data from the questionnaires for research and to extract data from the electronic patient

records for those patients that provided their consent for this extraction in the CCFR study. The CCFR study was also classified as exempt from the Medical Research Involving Human Subjects Act (code METC 16/668). We ensured that all participants were aware that their participation was voluntary and that they could withdraw at any time. When a patient decides not to participate in the RISE study, the patient will under no circumstances be excluded from receiving the drug combination ETI and will still be invited for the medical consultation at T0 and T2.

The time burden associated with participation in the RISE study is minimal. There are no additional study visits beyond regular CF care visits. Each quarter during the first year of ETI use, the study population will be asked to complete questionnaires digitally. We see no risks associated with participation in this study.

Data management

Handling and storage of data and documents

The RISE study has a data management plan, supported by a data manager of the UMCU. In short, all data of included participants will be handled confidentially. All participants will have a unique RISE study number, which is not based on the patient initials nor birthdate. Decoding can only be done by the investigator. All collected data will be kept in a secured database in the UMCU, only accessible for the researcher or a person who is authorized by the researcher.

Data sharing

De-identified participant data and the data dictionary can be provided by the corresponding author upon reasonable request, with a signed data access agreement.

Dissemination of results

The results of the RISE study will be disseminated through 1) publications in scientific peer-reviewed journals; 2) presentations on relevant scientific conferences and meetings, such as the European Cystic Fibrosis Society and the North American Cystic Fibrosis Conference; and 3) publications and presentations for the general public and through the Dutch Cystic Fibrosis Society.

CURRENT STATUS

The RISE study started in September 2021 and data collection of T0 was completed in January 2022. From January 2022 onwards, ETI therapy became available in the Netherlands. All participants completed the baseline measurements at T0 before they started with ETI therapy. Our aim was to measure all participants 12 weeks before starting with ETI. To have a 12-week gap between T0 and T1 for all participants was practically impossible. As a result, not all participants had a 12-week gap between their baseline

measurement at T0 and the follow-up measurement at T1. Nonetheless, all participants have baseline measurements before start with ETI and all were measured at T1 ~12 weeks after start of ETI therapy.

In total, 177 participants signed the RISE study informed consent forms; 174 (98%), 146 (85%), 141 (80%) and 142 (80%) participants completed the questionnaires at T0, T1, T2 and T3, respectively (Figure 1). Not all questionnaires were 100% completed.

We are aware that we have included more participants than our sample size indicated. Inclusion was easier than anticipated, and because there were minimal risks or efforts for the participants, we decided not to stop inclusion upon reaching the minimum number of subjects.

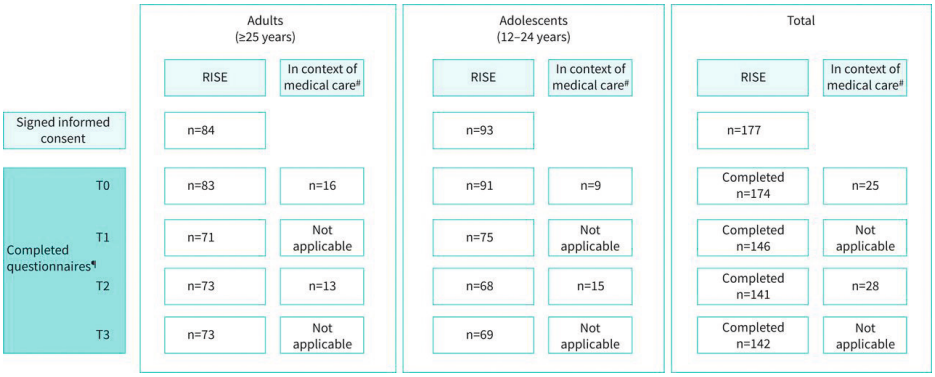

Figure 1: Follow-up chart (2 May 2023). RISE: Resilience Impacted by Positive Stressful Events study; T0: 12 weeks before starting elexacaftor/tezacaftor/ivacaftor (ETI); T1: 12 weeks after starting ETI; T2: 24 weeks after starting ETI; T3: 48 weeks after starting ETI. #: questionnaires used in medical care with Central Cystic Fibrosis Research consent; these questionnaires will only be used for exploratory secondary objectives; ¶: not all questionnaires have been 100% completed.

DISCUSSION

No longitudinal studies focusing on a possible change in mental wellbeing after starting ETI therapy compared to mental wellbeing before starting ETI therapy have been conducted. Most patients experience significant physical improvements in their CF-related symptoms. Some patients may be reluctant to report adverse events regarding their mental health, being scared that their ETI therapy could be discontinued as a result. Consequently, there is no clear picture of the incidence of deterioration of mental health after the start of ETI therapy. Therefore, the primary objective of the RISE study is to investigate whether and in which direction mental wellbeing of people with CF changes after starting ETI therapy in order to gain a better picture of resilient functioning. Our exploratory secondary objectives include investigation of which underlying biological and psychosocial factors

are associated with the change in mental wellbeing of people with CF after starting ETI therapy. These factors may be of value in the development of current or new interventions to build resilience and thereby preventing the deterioration of mental wellbeing after starting ETI therapy. Moreover, we also investigate change of other indicators of mental wellbeing, such as anxiety and depressive symptoms, after initiation of ETI therapy to get a more complete picture of mental wellbeing change.

Strengths and limitations

The RISE study will provide a comprehensive evaluation of change in mental wellbeing after starting ETI therapy, with the unique added value of a pre–post longitudinal design. Through this design, we will be able to examine intra-individual changes in mental wellbeing. Using an integrated biopsychosocial model, we will be able to examine the relationships and interrelationships of disease severity, CF-related comorbidities, attitude towards illness, illness perception and illness identity in predicting mental wellbeing. We will use standardized and validated instruments to measure our outcomes and determinants. As we combine our research with standard CF care, the effort for people with CF will be minimal. A longer follow-up period may be needed to detect a long-lasting change or, conversely, stability in mental wellbeing after starting ETI therapy.

REFERENCES

1. Férec C, Scotet V. Genetics of cystic fibrosis: Basics. *Archives de Pediatrie*. 2020;27:eS4-eS7. doi:10.1016/S0929-693X(20)30043-9
2. Bierlaagh MC, Muilwijk D, Beekman JM, van der Ent CK. A new era for people with cystic fibrosis. *Eur J Pediatr*. 2021;180(9):2731-2739. doi:10.1007/s00431-021-04168-y
3. Elborn JS. Cystic fibrosis. *The Lancet*. 2016;388(10059):2519-2531. doi:10.1016/S0140-6736(16)00576-6
4. Jamieson N, Fitzgerald D, Singh-Grewal D, et al. Children's experiences of cystic fibrosis: a systematic review of qualitative studies. *Pediatrics*. 2014;133:1683-1697.
5. Spoonhower KA, Davis PB. Epidemiology of Cystic Fibrosis. *Clin Chest Med*. 2016;37(1):1-8. doi:10.1016/j.ccm.2015.10.002
6. Scotet V, L'hostis C, Férec C. The changing epidemiology of cystic fibrosis: Incidence, survival and impact of the CFTRGene discovery. *Genes (Basel)*. 2020;11(6). doi:10.3390/genes11060589
7. Stephenson AL, Stanojevic S, Sykes J, Burgel PR. The changing epidemiology and demography of cystic fibrosis. *Presse Medicale*. 2017;46(6P2):e87-e95. doi:10.1016/j.lpm.2017.04.012
8. Rijksoverheid. Kaftrio als behandeling van taaislijmziekte toegelaten tot basispakket. Rijksoverheid.nl. Published 2021. https://www.rijksoverheid.nl/actueel/nieuws/2021/12/09/kaftrio-als-behandeling-van-taaislijmziekte-toegelaten-tot-basispakket
9. Goetz DM, Savant AP. Review of CFTR modulators 2020. *Pediatr Pulmonol*. 21AD;56(12):3595-3606.
10. Kapouni N, Moustaki M, Douros K, Loukou I. Efficacy and Safety of Elexacaftor-Tezacaftor-Ivacaftor in the Treatment of Cystic Fibrosis: A Systematic Review. *Children*. 2023;10(3):554. doi:10.3390/children10030554
11. McKinzie CJ, Goralski JL, Noah TL, Retsch-Bogart GZ, Prieur MB. Worsening anxiety and depression after initiation of lumacaftor/ivacaftor combination therapy in adolescent females with cystic fibrosis. *Journal of Cystic Fibrosis*. 2017;16(4):525-527. doi:10.1016/j.jcf.2017.05.008
12. Talwalkar JS, Koff JL, Lee HB, Britto CJ, Mulenos AM, Georgiopoulos AM. Cystic Fibrosis Transmembrane Regulator Modulators: Implications for the Management of Depression and Anxiety in Cystic Fibrosis. *Psychosomatics*. 2017;58(4):343-354. doi:10.1016/j.psym.2017.04.001
13. Havermans T, Willem L. Prevention of anxiety and depression in cystic fibrosis. *Curr Opin Pulm Med*. 2019;25(6):654-659. doi:10.1097/MCP.0000000000000617
14. Heo S, Young DC, Safirstein J, et al. Mental status changes during elexacaftor/tezacaftor / ivacaftor therapy. *Journal of Cystic Fibrosis*. 2022;21(2):339-343. doi:10.1016/j.jcf.2021.10.002
15. Tindell W, Su A, Oros SM, Rayapati AO, Rakesh G. Trikafta and Psychopathology in Cystic Fibrosis: A Case Report. *Psychosomatics*. 2020;61:735-738. www.psychosomaticsjournal.org
16. Spoletini G, Gillgrass L, Pollard K, et al. Dose adjustments of Elexacaftor/Tezacaftor/Ivacaftor in response to mental health side effects in adults with cystic fibrosis. *Journal of Cystic Fibrosis*. 2022;21:1061-1065. doi:10.1016/j.jcf.2022.05.001
17. Schneider E, McQugde R, Ortega V, et al. The potentially beneficial central nervous system activity profile of ivacaftor and its metabolites. *ERJ Open Res*. 2018;4(1).
18. Guo Y, Su M, McNutt M, Gu J. Expression and distribution of cystic fibrosis transmembrane conductance regulator in neurons of the human brain. *Journal of Histochemistry and Cytochemistry*. 2009;57(12):1113-1120.
19. Aspinall SA, Mackintosh KA, Hill DM, Cope B, McNarry MA. Evaluating the Effect of Kaftrio on Perspectives of Health and Wellbeing in Individuals with Cystic Fibrosis. *Int J Environ Res Public Health*. 2022;19(10):6114. doi:10.3390/ijerph19106114
20. Luthar SS, Cicchetti D, Becker B. The Construct of Resilience: A Critical Evaluation and Guidelines for Future Work. *Child Dev*. 2000;71(3):543-562.
21. Masten AS. Resilience in children threatened by extreme adversity: Frameworks for research, practice, and translational synergy. *Dev Psychopathol*. 2011;23(2):493-506. doi:10.1017/S0954579411000198
22. Kalisch R, Baker DG, Basten U, et al. The resilience framework as a strategy to combat stress-related disorders. *Nat Hum Behav*. 2017;1(11):784-790. doi:10.1038/s41562-017-0200-8
23. Van Breda A. A critical review of resilience theory and its relevance for social work. *Soc Work*. 2018;54(1). doi:10.15270/54-1-611
24. Ioannidis K, Dahl Askelund A, Kievit RA, al E. The complex neurobiology of resilient functioning after childhood maltreatment. *BMC Med*. 2020;18(32). doi:10.13140/RG.2.2.17380.48005

25. Casier A, Goubert L, Theunis M, et al. Acceptance and well-being in adolescents and young adults with cystic fibrosis: a prospective study. *2011*. 36:476-487.
26. Mitmansgruber H, Smrekar U, Rabanser B, Beck T, Eder J, Ellemunter H. Psychological resilience and intolerance of uncertainty in coping with cystic fibrosis. *Journal of Cystic Fibrosis*. 2016;15(5):689-695. doi:10.1016/j.jcf.2015.11.011
27. Sawicki G, Sellers D, Robinson W. Associations between illness perceptions and health-related quality of life in adults with cystic fibrosis. *J Psychosom Res*. 2011;70(161-167).
28. Rutter M. Resilience in the face of adversity: protective factors and resistance to psychiatric disorders. *British Journal of Psychiatry*. 1985;147:598-611. doi:10.1192/bjp.147.6.598
29. Afifi TO, MacMillan HL. Resilience following child maltreatment: A review of protective factors. *Canadian Journal of Psychiatry*. 2011;56(5):266-272. doi:10.1177/070674371105600505
30. van Harmelen AL, Kievit RA, Ioannidis K, Al E. Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychol Med*. 2017;47(13):2312-2322. doi:10.1017/S0033291717000836
31. Lee S, Lee J, Choi JY. The effect of a resilience improvement program for adolescents with complex congenital heart disease. *Eur J Cardiovasc Nurs*. 2017;16(4):290-298.
32. Broadbent E, Petrie KJ, Main J, Weinman J. The Brief Illness Perception Questionnaire. *J Psychosom Res*. 2006;60(6):631-637. doi:10.1016/j.jpsychores.2005.10.020
33. Levin KA, Currie C. Reliability and Validity of an Adapted Version of the Cantril Ladder for Use with Adolescent Samples. *Soc Indic Res*. 2014;119(2):1047-1063. doi:10.1007/s11205-013-0507-4
34. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: Assessing the ability to bounce back. *Int J Behav Med*. 2008;15(3):194-200. doi:10.1080/10705500802222972
35. Cantril H. *The Pattern of Human Concern*. Rutgers University press; 1965.
36. Szkultecka-Dębek M, Dzielska A, Drozd M, Małkowska-Szkutnik A, Mazur J. What does the Cantril Ladder measure in adolescence? *Archives of Medical Science*. 2018;14(1):182-189. doi:10.5114/aoms.2016.60718
37. Cronly JA, Duff AJ, Riekert KA, et al. Health-related quality of life in adolescents and adults with cystic fibrosis: Physical and mental health predictors. *Respir Care*. 2019;64(4):406-415. doi:10.4187/respcare.06356
38. Abbott J, Havermans T, Jarvholm S, et al. Mental Health screening in cystic fibrosis centres across Europe. *Journal of Cystic Fibrosis*. 2019;18(2):299-303. doi:10.1016/j.jcf.2018.09.003
39. Boon M, Claes I, Havermans T, et al. Assessing gastro-intestinal related quality of life in cystic fibrosis: Validation of PedsQL GI in children and their parents. *PLoS One*. 2019;14(12):1-14. doi:10.1371/journal.pone.0225004
40. Van Bulck L, Luyckx K, Goossens E, Oris L, Moons P. Illness identity: Capturing the influence of illness on the person's sense of self. *European Journal of Cardiovascular Nursing*. 2019;18(1):4-6. doi:10.1177/1474515118811960
41. Boon M, Claes I, Havermans T, et al. Assessing gastro-intestinal related quality of life in cystic fibrosis: Validation of PedsQL GI in children and their parents. *PLoS One*. 2019;14(12):1-14. doi:10.1371/journal.pone.0225004
42. Beverung LM, Varni JW, Panepinto JA. Clinically meaningful interpretation of pediatric health-related quality of life in sickle cell disease. *J Pediatr Hematol Oncol*. 2015;37(2):128-133. doi:10.1097/MPH.0000000000000177
43. Varni J. Pediatric Quality of Life Inventory™ (PedsQL™). Mapi Research Trust. Published 2022. Accessed August 2, 2022. https://eprovide.mapi-trust.org/instruments/pediatric-quality-of-life-inventory
44. Abbott J, Havermans T, Jarvholm S, et al. Mental Health screening in cystic fibrosis centres across Europe. *Journal of Cystic Fibrosis*. 2019;18(2):299-303. doi:10.1016/j.jcf.2018.09.003
45. Chan SF, La Greca AM. Perceived Stress Scale (PSS). *Encyclopedia of Behavioral Medicine*. Published online 2020:1646-1648. doi:10.1007/978-3-030-39903-0_773
46. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
47. Gariepy G, McKinnon B, Sentenac M, Elgar FJ. Validity and Reliability of a Brief Symptom Checklist to Measure Psychological Health in School-Aged Children. *Child Indic Res*. 2016;9(2):471-484. doi:10.1007/s12187-015-9326-2
48. Varni JW, Limbers CA. The PedsQL™ 4.0 Generic Core Scales Young Adult Version. *J Health Psychol*. 2009;14(4):611-622. doi:10.1177/1359105309103580
49. Organisation WH. WHO Adolescent Mental Health 17 november 2021. Published 2021. https://www.who.int/news-room/fact-sheets/detail/adolescent-mental-health

50. Varni JW, Limbers CA. The Pediatric Quality of Life Inventory: Measuring Pediatric Health-Related Quality of Life from the Perspective of Children and Their Parents. *Pediatr Clin North Am*. 2009;56(4):843-863. doi:10.1016/j.pcl.2009.05.016
51. Goodman A, Goodman R. Strengths and difficulties questionnaire as a dimensional measure of child mental health. *J Am Acad Child Adolesc Psychiatry*. 2009;48(4):400-403. doi:10.1097/CHI.0b013e3181985068
52. Levin KA, Currie C. Reliability and Validity of an Adapted Version of the Cantril Ladder for Use with Adolescent Samples. *Soc Indic Res*. 2014;119(2):1047-1063. doi:10.1007/s11205-013-0507-4
53. Huebner ES, Suldo S, Valois RF, Drane JW, Zullig K. Brief Multidimensional Students' Life Satisfaction Scale: Sex, Race, and Grade Effects for a High School Sample. *Psychol Rep*. 2004;94(1):351-356. doi:10.2466/pr0.94.1.351-356
54. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder. *Arch Intern Med*. 2006;166(10):1092. doi:10.1001/archinte.166.10.1092
55. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and Validation of the Cystic Fibrosis Questionnaire in the United States. *Chest*. 2005;128(4):2347-2354. doi:10.1378/chest.128.4.2347
56. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
57. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *J Gen Intern Med*. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x
58. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983;24(4):385-396.

SUPPLEMENT 1:

Information about the used questionnaires

Questionnaires	Validated Questionnaire and validated in Dutch?	Validated in people with CF?	Earlier use in people with CF?	Reason for inclusion in RISE
B-IPQ Illness perception	The B-IPQ is validated in Dutch[1], and in adults and adolescents in different diseases (asthma, renal patients, diabetes and myocardial infarction patients) [2].	In CF populations, the IPQ-Revised is validated in adults and in adolescents with CF and their healthy peers [3,4]. We use the B-IPQ, but there are moderate to good associations -Pearson correlations range from 0.32 to 0.63 - between the B-IPQ and the IPQ-Revised [2,5].	The B-IPQ has not previously been used in CF populations.	We will use the B-IPQ in the RISE study for one of our secondary aims: "(d) evaluation/description of subjects who experience a decline in primary outcome variable at one of the post-baseline visits" We are wondering if certain illness perceptions are associated with a higher mental well-being, meaning that illness perception can be perceived as a resilience factor.
BMLSS Multidimensional Life Satisfaction	The BMLSS is validated in adults with chronic diseases (among which cancer, chronic pain conditions and depressive disorders) and in healthy adults. Additionally, the BMLSS is validated in healthy adolescents [6–8]. The used item (outlook on future) is unfortunately not been officially translated in Dutch, therefore, we translated this question ourselves.	The BMLSS is not validated in CF-populations.	The BMLSS has not previously been used in CF populations.	We will use the BMLSS in the RISE study for one of our secondary aims: "(d) evaluation/description of subjects who experience a decline in primary outcome variable at one of the post-baseline visits" to gain a better picture on why some people with CF experience a (negative/positive) change in mental well-being after starting ETI therapy. We are wondering that if pwCF have a positive outlook on their future they might experience a higher mental well-being. We also want to know if this outlook on the future changes after starting ETI therapy.
BRS Resilience as ability to bounce back	The BRS is validated in Dutch language [9], and the BRS is validated in adolescents and adults with a chronic disease (cardiac and chronic pain conditions) and in healthy controls [10–12].	The BRS is not validated in CF-populations.	The BRS has not previously been used in CF populations.	The BRS is part of the Standard Protocol of the ETI therapy introduction in the Dutch CF centers. We will use the BRS in the RISE study for one of our secondary aims: "(d) evaluation/description of subjects who experience a decline in primary outcome variable at one of the post-baseline visits" to gain a better picture on why some people with CF experience a (negative/positive) change in mental well-being after starting ETI therapy.

Information about the used questionnaires (continued)

Questionnaires	Validated Questionnaire and validated in Dutch?	Validated in people with CF?	Earlier use in people with CF?	Reason for inclusion in RISE
Cantril ladder Life satisfaction	The Cantril ladder is validated in the general population of adolescents and adults, and the Cantril Ladder is used over decades in the Health Behaviour in School-Aged Children Study (HBSC) in the Netherlands [13–15].	The Cantril ladder is not validated in CF-populations.	The Cantril ladder was used to measure life satisfaction in a longitudinal study in which children and adolescents with a chronic disease (including youth with CF pwCF) [16].	We will use the Cantril ladder in the RISE study for two of our secondary aims: "(b) in accordance with the analysis of the primary outcome variable, we will also analyze the secondary variables as an outcome variable; and (c) an assessment of pair-wise correlations between as primary and secondary outcome variables (per visit)" to gain a better picture on change in mental well-being in general after ETI therapy.
CFQ-R Cystic Fibrosis health related Quality of life	See 'Validation in pwCF'.	The CFQ-R is the disease-specific, internationally and in Dutch validated, used and recognized in the medical care of CF, health related quality of life measure with developmentally appropriate version for children, adolescents and adult [17–20].	The CFQ-R is used in numerous CF-related studies. (References are not noted, as this questionnaire is used in numerous studies.)	The CFQ-R is part of the Standard Protocol of the ETI therapy introduction in the Dutch CF centers. We will use the CFQ-R in the RISE study for two of our secondary aims: "(b) in accordance with the analysis of the primary outcome variable, we will also analyze the secondary variables as an outcome variable; and (c) an assessment of pair-wise correlations between as primary and secondary outcome variables (per visit)" to get a better picture on change in mental well-being in general after ETI therapy.
GAD-7 Generalized anxiety	The GAD-7 is validated in Dutch [21], in the general population of adolescents and adults [22].	The GAD-7 is not validated in CF-populations.	The GAD-7 is used in numerous studies into generalized anxiety in pwCF and recommended as a screening instrument in the guidelines on mental health in CF by the CFF/ECFS International Committee on Mental Health in CF in 2015 [23–29].	We use the GAD-7 in accordance with 'standards of care' after introduction of ETI therapy, defined by the ECFS in 2022 [27]. Moreover the GAD-7 is part of the Standard Protocol of the ETI therapy introduction in the Dutch CF centers in 2022. We will use the GAD-7 in the RISE study for two of our secondary aims: "(b) in accordance with the analysis of the primary outcome variable, we will also analyze the secondary variables as an outcome variable; and (c) an assessment of pair-wise correlations between as primary and secondary outcome variables (per visit) " to get a better picture on change in mental well-being after ETI in general

Information about the used questionnaires (continued)

Questionnaires	Validated Questionnaire and validated in Dutch?	Validated in people with CF?	Earlier use in people with CF?	Reason for inclusion in RISE
IIQ Illness identity	This questionnaire has been validated in several chronic illnesses (among which congenital heart disease, multisystem connective tissue disorders and refractory epilepsy) in adolescents and adults [30–33]. Although this questionnaire is used in Dutch, data on its development have not been published [34].	The IIQ is not validated in CF-populations.	The ILQ has not previously been used in CF populations.	We will use the IIQ in the RISE study for one of our secondary aims: "(d) evaluation/description of subjects who experience a decline in primary outcome variable at one of the post-baseline visits" to gain a better picture on why some people with CF experience a (negative/positive) change in mental well-being after starting ETI therapy. We are wondering if certain illness identities are associated with higher mental well-being meaning that illness perception might be perceived as a resilience factor. And we are wondering whether this identity might change over time [35].
PedsQL 4.0 Pediatric Quality of Life	The PedsQL is adapted and validated in Dutch [36], in teens, adolescents and adults [37–39].	The PedsQL 4.0 is not validated in CF-populations.	In addition to the use in several international studies in pwCF, the PedsQL was used to measure QoL and mental well-being in the a longitudinal study in which children and adolescents with a chronic disease (including youth with CF) were followed [16,40–43].	The psychosocial health dimension (sum score of the dimensions emotional, social and school/study/work) of the PedsQL is our primary outcome: to investigate if and in which direction mental well-being of pwCF changes after initiation of ETI therapy.
PedsQL 4.0 GI Gastro intestinal symptoms	The PedsQL 4.0 GI is validated in Flemish [38], in children and adolescents with various GI disorders (among which irritable bowel syndrome, functional dyspepsia, Crohn disease, ulcerative colitis) [44].	The gastro-intestinal QoL module of the PedsQL, was validated in children with CF and their parents [38].	The PedsQL 4.0 GI is used in children with CF [45].	We use the PedsQL 4.0 GI to assess gastro-intestinal symptoms and GI QoL, and we research whether this changes over time after starting ETI therapy.
PHQ-9 Health questionnaire	The PHQ-9 questionnaire is validated in the general population in adolescents and adults [46].	The PHQ-9 is not validated in CF-populations.	The PHQ-9 is used in numerous studies focusing on depression in adolescents and adults with CF. (References are not noted, as this questionnaire is used in numerous studies.) Moreover, the PHQ-9 is recommended as a screening instrument in the guidelines on mental health in CF by the CFF/ECFS International Committee on Mental Health in CF in 2015 [23–25,27,28,47].	We use the PHQ-9 in accordance with 'standards of care' after introduction of ETI therapy defined by the ECFS in 2022 [27]. Moreover, the PHQ-9 is part of the Standard Protocol of the ETI therapy introduction in the Dutch CF centers in 2022. We will use the PHQ-9 in the RISE study for two of our secondary aims: "(b) in accordance with the analysis of the primary outcome variable, we will also analyze the secondary variables as an outcome variable; and (c) an assessment of pair-wise correlations between as primary and secondary outcome variables (per visit)" to get a better picture on change in mental well-being in general after ETI therapy.

Information about the used questionnaires (continued)

Questionnaires	Validated Questionnaire and validated in Dutch?	Validated in people with CF?	Earlier use in people with CF?	Reason for inclusion in RISE
PSS Perceived stress	The PSS is a validated psychological instrument for measuring the perception of stress in the general population as of approximately 12 years of age and widely used in the Dutch language [48–51].	The PSS is not validated in CF-populations.	The PSS has not previously been used in CF populations.	We will use the PSS in the RISE study for two of our secondary aims: "(b) in accordance with the analysis of the primary outcome variable, we will also analyze the secondary variables as an outcome variable; and (c) an assessment of pair-wise correlations between as primary and secondary outcome variables (per visit)" to get a better picture on change in mental well-being in general after ETI therapy. We chose the PSS because of the generic nature of the scale which is deemed to be fit for measuring the experienced level of stress in people with a disease [50].
RCADS Internalizing symptoms	The RCADS measures depression and anxiety is validated in Dutch [52] and in children, adolescents and adults in the general population [53–55].	The RCADS is not validated in CF-populations.	The RCADS has been used in studies to measures symptoms of depression and anxiety in pwCF [56,57].	We will use the RCADS in the RISE study for two of our secondary aims: "(b) in accordance with the analysis of the primary outcome variable, we will also analyze the secondary variables as an outcome variable; and (c) an assessment of pair-wise correlations between as primary and secondary outcome variables (per visit) " to get a better picture on change in mental well-being in general after ETI therapy.
SDQ Emotional and behavior problems	The SDQ is a validated generic, psychological instrument for measuring social, emotional and behavioral functioning in children, adolescents and adults in the general population. The SDQ youth questionnaires are validated in Dutch [58–60]. The adult versions were not available nor validated in Dutch, therefore, we translated the questions ourselves.	The SDQ is not validated in CF-populations.	The SDQ was used in to investigate the psychological changes in children and adults with a chronic disease (among which CF) [61].	We will use the SDQ in the RISE study for two of our secondary aims: "(b) in accordance with the analysis of the primary outcome variable, we will also analyze the secondary variables as an outcome variable; and (c) an assessment of pair-wise correlations between as primary and secondary outcome variables (per visit)" to get a better picture on change in mental well-being after ETI in general.

B-IPQ = Brief-Illness Perception Questionnaire; BMLSS = Brief Multidimensional Life Satisfaction Scale; BRS = Brief Resilience Scale; CF = cystic fibrosis; CFF = Cystic Fibrosis Foundation; CFQ-R = Cystic Fibrosis Quality of Life Questionnaire-Revised; ECFS = European Cystic Fibrosis Society; GAD-7 = Generalized Anxiety Disorder Scale; IIQ = Illness Identity Questionnaire; PedsQL 4.0 = Pediatric Quality of Life Inventory Generic Core Scales 4.0; PedsQL 4.0 GI = Pediatric Quality of Life Inventory Generic Core Scales 4.0 Gastrointestinal Symptoms Scales and Module; PHQ-9 =Patient Health Questionnaire for Depression; PSS = Perceived stress scale; pwCF = people with cystic fibrosis. RCADS = Revised Child Anxiety and Depression Scale; SDQ = Strengths and Difficulties Questionnaire

REFERENCES

1. Timmermans I, Versteeg H, Meine M, Pedersen SS, Denollet J. Illness perceptions in patients with heart failure and an implantable cardioverter defibrillatorDimensional structure, validity, and correlates of the brief illness perception questionnaire in Dutch, French and German patients. *J Psychosom Res*. 2017;97:1-8. doi:10.1016/j.jpsychores.2017.03.014
2. Broadbent E, Petrie KJ, Main J, Weinman J. The Brief Illness Perception Questionnaire. *J Psychosom Res*. 2006;60(6):631-637. doi:10.1016/j.jpsychores.2005.10.020
3. Beinke K, O'Callaghan F, Morrissey S. Illness Perceptions of Cystic Fibrosis: A Comparison of Young Adults with CF and Same-Aged Peers. *Behavioral Medicine*. 2017;43(1):40-46. doi:10.1080/08964289.2015.1045824
4. Sawicki G, Sellers D, Robinson W. Associations between illness perceptions and health-related quality of life in adults with cystic fibrosis. *J Psychosom Res*. 2011;70(161-167).
5. Witteman C, Bolks L, Hutschemaekers G. Development of the illness perception questionnaire mental health. *Journal of Mental Health*. 2011;20(2):115-125. doi:10.3109/09638237.2010.507685
6. Huebner ES, Suldo S, Valois RF, Drane JW, Zullig K. Brief multidimensional students' life satisfaction scale: Sex, race, and grade effects for a high school sample. *Psychol Rep*. 2004;94(1):351-356. doi:10.2466/pr0.94.1.351-356
7. Fischer J, Haller A, Heusser P, Ostermann T, Matthiessen PF. Validation of the Brief Multidimensional Life Satisfaction Scale in Patients with Chronic Diseases. Published online 2009:171-177.
8. Büssing A, Poier D, Lauche R, Dobos G, Cramer H. Validation of an Instrument to Measure Patients' Intentions and Ability to Change Attitudes and Behavior. *Complement Med Res*. 2017;24(4):246-254. doi:10.1159/000477720
9. Soer R, Six Dijkstra MWMC, Bieleman HJ, et al. Measurement properties and implications of the Brief Resilience Scale in healthy workers. *J Occup Health*. 2019;61(3):242-250. doi:10.1002/1348-9585.12041
10. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: Assessing the ability to bounce back. *Int J Behav Med*. 2008;15(3):194-200. doi:10.1080/10705500802222972
11. Consten C. Measuring Resilience with the Brief Resilience Scale: Factor Structure, Reliability and Validity of the Dutch Version of the BRS (BRSnl). Published online 2016.
12. Soer R, Six Dijkstra MWMC, Bieleman HJ, et al. Measurement properties and implications of the Brief Resilience Scale in healthy workers. *J Occup Health*. 2019;61(3):242-250. doi:10.1002/1348-9585.12041
13. Zubaida SD, Cantril H. The Pattern of Human Concerns. *Br J Sociol*. 1967;18:212. doi:10.2307/588624
14. Mazur J, Szkultecka-dębek M, Dzielska A, Drozd M. What does the Cantril Ladder measure in adolescence ? Published online 2018. doi:10.5114/aoms.2016.60718
15. Health Behaviour in School-aged Children. About HBSC. http://www.hbsc.org/about/index.html. http://www.hbsc.org/about/index.html
16. Nap- van der Vlist MM, Hoefnagels JW, Dalmeijer GW, et al. The PROactive cohort study: rationale, design, and study procedures. *Eur J Epidemiol*. 2022;37(9):993-1002. doi:10.1007/s10654-022-00889-y
17. Quittner AL, Sawicki GS, McMullen A, et al. Psychometric evaluation of the cystic fibrosis questionnaire-revised in a national sample. *Quality of Life Research*. 2012;21(7):1267-1278. doi:10.1007/s11136-011-0036-z
18. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of the cystic fibrosis questionnaire in the United States: A health-related quality-of-life measure for cystic fibrosis. *Chest*. 2005;128(4):2347-2354. doi:10.1378/chest.128.4.2347
19. Cronly JA, Duff AJ, Riekert KA, et al. Health-related quality of life in adolescents and adults with cystic fibrosis: Physical and mental health predictors. *Respir Care*. 2019;64(4):406-415. doi:10.4187/respcare.06356
20. Klijn PH, van Stel HF, Quittner AL, et al. Validation of the Dutch cystic fibrosis questionnaire (CFQ) in adolescents and adults. *Journal of Cystic Fibrosis*. 2004;3(1):29-36. doi:10.1016/j.jcf.2003.12.006
21. Donker T, van Straten A, Marks I, Cuijpers P. Quick and easy self-rating of Generalized Anxiety Disorder: Validity of the Dutch web-based GAD-7, GAD-2 and GAD-SI. *Psychiatry Res*. 2011;188(1):58-64. doi:10.1016/j.psychres.2011.01.016

22. Löwe B, Decker O, Müller S, et al. Validation and standardization of the generalized anxiety disorder screener (GAD-7) in the general population. *Med Care*. 2008;46(3):266-274. doi:10.1097/MLR.0b013e318160d093
23. Abbott J, Havermans T, Jarvholm S, et al. Mental Health screening in cystic fibrosis centres across Europe. *Journal of Cystic Fibrosis*. 2019;18(2):299-303. doi:10.1016/j.jcf.2018.09.003
24. Landau EC, Verkleij M, Graziano S, et al. Mental health screening in Cystic Fibrosis as an intervention: Patient and caregiver feedback on improving these processes. *Respir Med*. 2022;202(August). doi:10.1016/j.rmed.2022.106955
25. Duff AJA, Bowmer G, Waldron R, Cammidge S, Peckham D, Latchford G. 257 Administering the PHQ8 and GAD7 in routine UK CF care in situ utilisation in a paediatric and an adult centre. *Journal of Cystic Fibrosis*. 2015;14:S124. doi:10.1016/s1569-1993(15)30432-x
26. Quittner AL, Goldbeck L, Abbott J, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: Results of the International Depression Epidemiological Study across nine countries. *Thorax*. 2014;69(12):1090-1097. doi:10.1136/thoraxjnl-2014-205983
27. Southern KW, Castellani C, Lammertyn E, et al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. *Journal of Cystic Fibrosis*. 2022;(xxxx). doi:10.1016/j.jcf.2022.10.002
28. Havermans T, Willem L. Prevention of anxiety and depression in cystic fibrosis. *Curr Opin Pulm Med*. 2019;25(6):654-659. doi:10.1097/MCP.0000000000000617
29. Ratnayake I, Ahern S, Ruseckaite R. A systematic review of patient-reported outcome measures (PROMs) in cystic fibrosis. *BMJ Open*. 2020;10(10):e033867. doi:10.1136/bmjopen-2019-033867
30. Van Bulck L, Luyckx K, Goossens E, Oris L, Moons P. Illness identity: Capturing the influence of illness on the person's sense of self. *European Journal of Cardiovascular Nursing*. 2019;18(1):4-6. doi:10.1177/1474515118811960
31. Luyckx K, Oris L, Raymaekers K, et al. Illness identity in young adults with refractory epilepsy. *Epilepsy and Behavior*. 2018;80:48-55. doi:10.1016/j.yebeh.2017.12.036
32. Oris L, Luyckx K, Rassart J, et al. Illness Identity in Adults with a Chronic Illness. *J Clin Psychol Med Settings*. 2018;25(4):429-440. doi:10.1007/s10880-018-9552-0
33. Weinman J, Petrie KJ, Moss-Morris R, Horne R. The illness perception questionnaire: A new method for assessing the cognitive representation of illness. *Psychol Health*. 1996;11(3):431-445. doi:10.1080/08870449608400270
34. Oris L, Rassart J, Prikken S, et al. Illness identity in adolescents and emerging adults with type 1 diabetes: Introducing the illness identity questionnaire. *Diabetes Care*. 2016;39(5):757-763. doi:10.2337/dc15-2559
35. Jamieson N, Fitzgerald D, Singh-Grewal D, Hanson CS, Craig JC, Tong A. Children's experiences of cystic fibrosis: A systematic review of qualitative studies. *Pediatrics*. 2014;133(6). doi:10.1542/peds.2014-0009
36. Bastiaansen D, Koot HM, Bongers IL, Varni JW, Verhulst FC. *Measuring Quality of Life in Children Referred for Psychiatric Problems: Psychometric Properties of the PedsQL TM 4.0 Generic Core Scales-18; PedsQL TM 4.0-Pediatric Quality of Life Inven-Tory TM Version 4.0; QoL-Quality of Life; YSR-Youth Self-Report*.
37. Beverung LM, Varni JW, Panepinto JA. Clinically meaningful interpretation of pediatric health-related quality of life in sickle cell disease. *J Pediatr Hematol Oncol*. 2015;37(2):128-133. doi:10.1097/MPH.0000000000000177
38. Boon M, Claes I, Havermans T, et al. Assessing gastro-intestinal related quality of life in cystic fibrosis: Validation of PedsQL GI in children and their parents. *PLoS One*. 2019;14(12):1-14. doi:10.1371/journal.pone.0225004
39. Varni J. Pediatric Quality of Life Inventory™ (PedsQL™). Mapi Research Trust.
40. Nap-Van Der Vlist MM, Dalmeijer GW, Grootenhuis MA, et al. Fatigue among children with a chronic disease: A cross-sectional study. *BMJ Paediatr Open*. 2021;5(1):1-10. doi:10.1136/bmjpo-2020-000958
41. Cheney J, Vidmar S, Gailer N, Wainwright C, Douglas TA. Health-related quality-of-life in children with cystic fibrosis aged 5-years and associations with health outcomes. *Journal of Cystic Fibrosis*. 2020;19(3):483-491. doi:10.1016/j.jcf.2020.02.022
42. Driscoll KA, Modi AC, Filigno SS, et al. Quality of life in children with CF: Psychometrics and relations with stress and mealtime behaviors. *Pediatr Pulmonol*. 2015;50(6):560-567. doi:10.1002/ppul.23149
43. Schwarzenberg SJ, Palermo JJ, Ye W, et al. Health-related Quality of Life in a Prospective Study of Ultrasound to Detect Cystic Fibrosis-related Liver Disease in Children. *J Pediatr Gastroenterol Nutr*. 2022;75(5):635-642. doi:10.1097/MPG.0000000000003605

44. Varni JW, Bendo CB, Denham J, et al. PedsQL gastrointestinal symptoms module: Feasibility, reliability, and validity. *J Pediatr Gastroenterol Nutr*. 2014;59(3):347-355. doi:10.1097/MPG.0000000000000414
45. Boon M, Calvo-Lerma J, Claes I, et al. Use of a mobile application for self-management of pancreatic enzyme replacement therapy is associated with improved gastro-intestinal related quality of life in children with Cystic Fibrosis. *Journal of Cystic Fibrosis*. 2020;19(4):562-568. doi:10.1016/j.jcf.2020.04.001
46. Kocalevent RD, Hinz A, Brähler E. Standardization of the depression screener Patient Health Questionnaire (PHQ-9) in the general population. *Gen Hosp Psychiatry*. 2013;35(5):551-555. doi:10.1016/j.genhosppsych.2013.04.006
47. Verkleij M, de Winter D, Hurley MA, Abbott J. Implementing the International Committee on Mental Health in Cystic Fibrosis (ICMH) guidelines: Screening accuracy and referral-treatment pathways. *Journal of Cystic Fibrosis*. 2018;17(6):821-827. doi:10.1016/j.jcf.2018.02.005
48. Chan SF, La Greca AM. Perceived Stress Scale (PSS). *Encyclopedia of Behavioral Medicine*. Published online 2020:1646-1648. doi:10.1007/978-3-030-39903-0_773
49. Cohen S. Perceived Stress Scale scoring and questions. *Psychology*. Published online 1994:1-3.
50. Cohen, Sheldon; Kamarck, Tom; Mermelstein R. A Global Measure of Perceived Stress Authors (s): Sheldon Cohen , Tom Kamarck and Robin Mermelstein Source : Journal of Health and Social Behavior , Vol . 24 , No . 4 (Dec ., 1983), pp . 385-396 Published by : American Sociological Association Stable. 2016;24(4):385-396.
51. Baas KD, Cramer AOJ, Koeter MWJ, van de Lisdonk EH, van Weert HC, Schene AH. Measurement invariance with respect to ethnicity of the Patient Health Questionnaire-9 (PHQ-9). *J Affect Disord*. 2011;129(1-3):229-235. doi:10.1016/j.jad.2010.08.026
52. Kösters MP, Chinapaw MJM, Zwaanswijk M, van der Wal MF, Koot HM. Structure, reliability, and validity of the revised child anxiety and depression scale (RCADS) in a multi-ethnic urban sample of Dutch children. *BMC Psychiatry*. 2015;15(1). doi:10.1186/s12888-015-0509-7
53. McKenzie K, Murray A, Freeston M, Whelan K, Rodgers J. Validation of the Revised Children's Anxiety and Depression Scales (RCADS) and RCADS short forms adapted for adults. *J Affect Disord*. 2019;245(November 2018):200-204. doi:10.1016/j.jad.2018.10.362
54. Kösters MP, Chinapaw MJM, Zwaanswijk M, van der Wal MF, Koot HM. Structure, reliability, and validity of the revised child anxiety and depression scale (RCADS) in a multi-ethnic urban sample of Dutch children. *BMC Psychiatry*. 2015;15(1). doi:10.1186/s12888-015-0509-7
55. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
56. Lord L, McKernon D, Grzeskowiak L, Kirsa S, Ilomaki J. Depression and anxiety prevalence in people with cystic fibrosis and their caregivers: a systematic review and meta-analysis. *Soc Psychiatry Psychiatr Epidemiol*. Published online 2022. doi:10.1007/s00127-022-02307-w
57. Nap-van Der Vlist MM, Hoefnagels JW, Dalmeijer GW, et al. The PROactive cohort study: rationale, design, and study procedures. *Eur J Epidemiol*. 2022;37:993-1002.
58. Muris P, Meesters C, Van den Berg F. The Strengths and Difficulties Questionnaire (SDQ) further evidence for its reliability and validity in a community sample of Dutch children and adolescents. *Eur Child Adolesc Psychiatry*. 2003;12(1):1-8. doi:10.1007/s00787-003-0298-2
59. Vostanis P. Strengths and Difficulties Questionnaire: Research and clinical applications. *Curr Opin Psychiatry*. 2006;19(4):367-372. doi:10.1097/01.yco.0000228755.72366.05
60. sdqinfo.org. Accessed December 14, 2022. https://sdqinfo.org/Adult/
61. Goldbeck L, Hölling I, Schlack R, West C BT. The impact of an inpatient family-oriented rehabilitation program on parent-reported psychological symptoms of chronically ill children. *n Padiatr 2011 Mar;223(2):79-84*. Published online 2010. doi:0.1055/s-0030-1262831

CHAPTER 4

PSYCHOSOCIAL HEALTH CHANGES IN PEOPLE WITH CYSTIC FIBROSIS AFTER INITIATION OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR THERAPY: INSIGHTS FROM THE RISE STUDY

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Submitted

ABSTRACT

Introduction

Starting elexacaftor/tezacaftor/ivacaftor (ETI) is a positive life event for people with Cystic Fibrosis (pwCF). Nevertheless, some individuals report decline in mental health after commencing ETI. This study aimed to determine if and how psychosocial health of pwCF changed after ETI. To identify those potentially more vulnerable, we investigated possible differences in psychosocial health among subgroups based on age, sex, lung function at baseline, earlier use of any other CFTR modulator, and use of psychotropic medication at baseline.

Methods

This is a prospective 60-week cohort study with questionnaire-based measurements of psychosocial health 12 weeks before (T0) and 12, 24 and 48 weeks after starting ETI (T1, T2, and T3, respectively). Data were analyzed using a covariance pattern model with a general variance covariance matrix.

Results

In total, 177 subjects participated, with a mean age of 25.90 years, 44.07% female, and 174 (98%), 146 (85%), 141 (80%), and 142 (80%) participants (partially) completed the questionnaires at T0, T1, T2, and T3, respectively. PedsQL psychosocial health scores improved following ETI ($p<0.0001$), especially between T0 and T1 ($p<0.0001$). No differences in psychosocial health after following ETI were observed between subgroups. People using psychotropic medications at baseline, however, reported structural lower psychosocial health, compared to those not using this medications ($p=0.047$).

Conclusions

PwCF experienced a relevant improvement in psychosocial health following ETI. We could not identify subgroups potentially more vulnerable in terms of their psychosocial health, as we did not observe clear significant differences in psychosocial health between the subgroups.

INTRODUCTION

The advent of cystic fibrosis transmembrane conductance regulator (CFTR) modulators has marked a new era in the management of cystic fibrosis (CF), leading to a shift in the perception of CF from a life-threatening to a chronic disease with more favorable disease expression and expected improved life expectancy [1,2]. Especially the elexacaftor/ tezacaftor/ ivacaftor (ETI) combination significantly improves lung function and reduces pulmonary exacerbations [2,3]. For many people with CF (pwCF) gaining access to ETI is therefore considered a positive and major life event [4]. Two randomized controlled studies (>12 years, n=405 [5], n=113 [6]) to confirm ETI's safety and efficacy found a significant improvement in the Cystic Fibrosis Questionnaire - Revised (CFQ-R) respiratory domain [5,6] and improvements in practically all other health-related quality of life domains [7].

Unexpectedly, several case series reported a subset of individuals experiencing a deterioration in their mental health following initiation of ETI, expressed in various symptoms such as insomnia, depressive and anxiety symptoms, brain fog, and concentration problems [8–10]. Several mechanisms underlying this deterioration in mental health have been suggested: compounds of ETI can affect mental health through direct effects on the central nervous system or through interactions with (psychotropic) medications [9–12]. Also the psychological impact of starting a potentially life-changing drug might affect mental health [11]. Individuals with a prior history of mental health problems might be more susceptible to recurrence of these problems [13], but literature showed that both individuals with and without a history of mental health problems experienced worsening of their mental health after ETI [8–10,14].

Remarkable improvements in physical health may cause patients reluctance to discontinue ETI, potentially resulting in underreporting of mental health-related side effects [9,15]. However, long term longitudinal studies systematically investigating changes in mental health after initiation of ETI are not available yet. Such research may identify subgroups more susceptible to these mental adverse effects and can open avenues for prevention.

The primary objective of the 'Resilience Impacted by positive Stressful Events for people with cystic fibrosis' (RISE) study was to investigate if and how psychosocial health of pwCF changes after initiation of ETI. The secondary objective included investigation of differences in psychosocial health among subgroups to identify subgroups that are potential more susceptible for a diminished mental health after starting ETI.

METHODS

Study population and ethics

Inclusion criteria were: pwCF 1) of ≥12 years, 2) who started ETI based on their CFTR-mutation, and 3) being a patient in the University Medical Center Utrecht (UMCU)/ Wilhelmina Children's Hospital, the Netherlands. Participants were excluded when they were not able to read and understand Dutch. This study was conducted in accordance with the principles of the Declaration of Helsinki and classified by the Institutional Review Board as exempt from the Medical Research Involving Human Subjects Act (code METC: 21/626 and 16/668).

Study design and procedures

The design of the RISE study has been described in detail elsewhere [16]**.** In short, the RISE study is a single arm, observational, longitudinal cohort study which follows pwCF over a time frame of 60 weeks collecting data at four time points. The baseline assessment (T0 – September 2021) was circa 12 weeks prior to starting ETI and at 12 (T1), 24 (T2) and 48 weeks (T3) after starting ETI. A package of multiple questionnaires was sent at all four time points. At T0 and T2, participants also attended medical consultations.

A sample size of 100 participants was considered adequate for the purpose of this study [16].

Definition of variables

The primary outcome variable was measured by the psychosocial health scale of the Pediatric Quality of Life Inventory 4.0 (PedsQL), combining the emotional, social, and school/study/work PedsQL's subscales [17]. This psychosocial health scale corresponds with mental wellbeing [18]. The PedsQL has been validated for children, adolescents, and adults [17,19]. A significant change in psychosocial health was defined as a minimal clinically important difference (MCID) of 4.4 points [20]. By choosing this generic scale of psychosocial health -instead of a disease-specific scale-, applicable to various age categories, we aim to assess overall psychosocial health in general, across different age groups.

The clinical study variables at T0 and T2 were lung function (in percentage predicted forced expiratory volume in 1 second (FEV_1pp)), body mass index (BMI), sweat chloride concentration (SCC), and fecal elastase. Moreover, by using the electronic patient files, we counted the frequency of pulmonary exacerbations (PEx) requiring intravenous (IV) antibiotic treatment in the year prior to the first visit (T0), defined as IV-treated PEx. Additionally, we verified the CFTR-genotype, and collected information maintenance therapy including psychotropic medications. The presence of psychotropic medications in the baseline data indicated that the participants had used such medications in the six months before or by T0. Psychotropic medications used by the participants were

antipsychotics, hypnotics, antidepressants, and stimulants. Finally, at T2 we noted side effects, next to changes in use of psychotropic medications.

Statistical analyses

Descriptive baseline characteristics of the cohort were presented as counts with percentages, means with standard deviations (SD) or medians with interquartile range (IQR). The PedsQL psychosocial health scores were treated as continuous and analyzed using a covariance pattern model with a general (i.e., unrestricted) variance covariance matrix. The test of primary interest was the likelihood-ratio test (α=0.05) comparing the model with a fixed effect of 'visit' against the intercept-only model, thus testing whether there was a difference in the mean psychosocial health score at one of the four time points. Visit-specific estimated marginal means (EMM) was provided along with 95% confidence intervals.

To identify those potentially more vulnerable to diminished mental health after starting ETI, we conducted subgroup analyses. Subgroups were defined based on clinical practice and literature and categorized into age (<25 years and ≥25 years, as adolescence is defined as ranging from 10 up to and including 24 year [21]), sex (female and male), lung function at baseline (≤70 and >70%), earlier use of any other CFTR modulator (yes and no), and use of psychotropic medication at baseline (yes and no). We first analyzed whether we observed a difference in EMM of PedsQL psychosocial health scores between the subgroups by testing the full model, including visit, the main effect of the subgroup and the interaction between the main effect and visit, against a model only including the effect of the visit using likelihood-ratio tests. To assess the results in more detail, we tested whether differences were structural and/or represented a differential change over time between the subgroups. We tested for structural difference by using a likelihood-ratio test comparing a model including both a visit term as well as the main effect of the subgroup versus a model with only the visit-effect. We tested for a differential change over time by using likelihood-ratio test on comparison between the full model versus the model without the interaction term. Furthermore, we evaluated visit-specific contrasts in PedsQL psychosocial health scores between the subgroups. Lastly, we also reported the physical changes in BMI, FEV_1pp, and SCC by using a covariance pattern model with a general (i.e., unrestricted) variance covariance matrix.

We have multiple imputed data using multivariate imputation, using chained equations with the R package mice v3.15.0 [22]; 100 data sets were imputed (using 100 iterations in each) - for more information, see Supplement 1. The baseline table shows the original data, all other results are based on multiple imputation data sets; for comparison between results we refer to Supplement 2.

Significance levels were set at 0.05. All statistical analyses were performed with R version 4.2.2: besides the packages mice cited above, we used the packages miceadds v3.16-18 [23], nlme v3.1-161 [24], and package emmeans v1.8.4-1 [25].

RESULTS

Study population

In total, 177 subjects participated in the study, of which the mean age was 25.90 years, 44.07% was female, and 79.00% had a F508del/F508del mutation (Table 1). In total 174 (98.31%), 146 (82.49%), 141 (79.66%), and 142 (80.23%) participants completed or partially completed the RISE questionnaires at T0, T1, T2, and T3, respectively (more information, see Supplement 3). Altogether, 66.10% of the participants completed the RISE questionnaires at all four time points, 84.70% at three time points, and 90.30% at least at two time points. One person was excluded for the RISE study. Seven participants dropped out of the study cohort: three without an explicit explanation, one was admitted to the psychiatric ICU and is still using ETI, two discontinued ETI (one due to liver problems, the other without providing a reason) and one participant was transferred to another medical center and was lost to follow-up.[1]

Changes in psychosocial health scores after initiation of ETI

The EMM of the PedsQL psychosocial health scores were 72.30 (95% CI: 70.11;74.49) at T0, 77.35 (95% CI: 75.10;79.61) at T1, 78.64 (95% CI: 76.39;80.89) at T2, and 79.81 (95% CI: 77.50;82.12) at T3, showing a significant difference between the four time points ($p < 0.0001$) (Table 2, Figure 1). Post-hoc tests identified that this change is mainly from T0 to T1 ($p<0.0001$). Although psychosocial health further increased at T2 and T3, these changes were not significant (from T1 to T2, $p=0.11$; from T2 to T3, $p=0.14$).

1 The participants admitted to the psychiatric ICU and those who discontinued ETI accidentally dropped out of the study; these participants should have remained enrolled.

Table 1: Baseline characteristics of study population

Participant characteristics and medical information	**T0**
n	177 (100)
Age at baseline	25.80 ±8.79
Adolescents: 12-24 years	94 (53.11)
Adults: ≥25 years	83 (46.89)
Male	99 (55.93)
Female	78 (44.07)
Genotype	
F508del/F508del	140 (79.10)
F508del/any other mutation	37 (20.90)
BMI	21.12 ±2.68
FEV_1pp	73.18 ±19.62
<40	6 (3.39)
40-70	67 (37.85)
70-90	64 (36.16)
>90	40 (22.60)
SCC ($mmol{\cdot}L^{-1}$)	84.27 ±17.3
Missing¶	6 (3.39)
Pancreatic function	
Insufficient (fecal elastase <200 $\mu g{\cdot}g^{-1}$)	157 (88.70)
Sufficient (fecal elastase ≥200 $\mu g{\cdot}g^{-1}$)	3 (1.69)
Missing	17 (9.60)
Use of CFTR modulator before ETI	
Yes	141 (79.66)
No	36 (20.34)
IV- treated PEx (7/1/2021 – 7/1/2022)	
None	137 (77.40)
One or more	40 (22.60)
Use of psychotropic medication	
Yes	16 (9.00)
No	161 (91.00)
Questionnaires	**T0**
RISE questionnaires (partially) completed*	174 (98.31)
Psychosocial health [0-100] n=173	72.48 (14.73)

Data are presented as n, median (interquartile range), n (%) or mean±SD.
*BMI: Body Mass Index; CFRD: Cystic Fibrosis Related Diabetes, CFLD: Cystic Fibrosis related Liver Disease, CFTR: cystic fibrosis transmembrane conductance regulator, FEV_1pp: forced expiratory volume in 1 s, % predicted, IV: intravenous, NA: not applicable, PedsQL: Pediatric Quality of Life Inventory 4.0, PEx: pulmonary exacerbations, SCC: sweat chloride concentration. ¶Insufficient sweat collection, *not all questionnaires 100% completed, [0]we used validated versions adolescents and adults. Original data is used for this table.*

Subgroup analyses on differences in psychosocial health scores

Comparing for subgroup age, the EMM for the adolescents (<25 years old) were consistently higher than those for the adults (≥25 years old) (Figure 2a). However, no significant difference was observed between subgroups (p=0.46), nor did we find a significant main difference between subgroups (p=0.33), nor a differential change over time (p=0.58) (Table 2). Visit-specific contrasts, however, showed significant subgroup differences at T0 (p=0.04) and T2 (p=0.05), but not on T1 (p=0.26) and T3 (p=0.08) (Supplement 4).

With respect to the subgroup sex, the EMM were consistently higher for males compared to females (Figure 2b). We did not find significant differences in the PedsQL psychosocial health, nor did we identify significant differences in visit-specific contrasts between these subgroups.

Comparing subgroups based on baseline lung function, the EMM of the PedsQL psychosocial health scores for the subgroup with FEV_1pp values >70 were consistently higher than those for the subjects with FEV_1pp <70 (Figure 2c). However, no significant differences were observed between the subgroups. With respect to the visit-specific contrasts, only the contrast in PedsQL psychosocial health scores at T0 was significantly different between the subgroups (p=0.006) (p=0.33 at T1, p=0.22 at T2, and p=0.15 at T3 (Supplement 4)).

Comparing the EMM for subgroup 'early use of CFTR modulator', the EMM were consistently higher for participants that already used CFTR-modulators (Figure 2d). We did not find significant differences in the PedsQL psychosocial health, nor did we identify significant differences in visit-specific contrasts between these subgroups.

Comparing subgroups based on baseline psychotropic medication use, the EMM were consistently higher for participants not using psychotropic medication (Figure 2e). No significant difference was observed between the subgroups in general (p=0.13). People using psychotropic medications have reported lower psychosocial health compared to those not using these medication (p=0.047), yet no differential change over time was observed (p=0.76) (Table 2). Visit-specific contrasts showed significant subgroup differences at all timepoints (p=0.003 at T0, p=0.01 at T1, p=0.03 at T2, and p=0.009 at T3 (Supplement 4).

Clinical changes after ETI

Regarding clinical changes after ETI, we identified that the EMM of BMI increased with 0.64 kg/m^2 (p< 0.0001; 95% CI 0.43 to 0.85), the EMM of FEV_1pp increased with 12.46% (p< 0.0001; 95% CI 10.48 to 14.45), and the EMM of SCC decreased with -49.97 $mmol{\cdot}L^{-1}$ (p< 0.0001; 95% CI -54.31 to -45.63) at T2 (Table 3). For more clinical changes after ETI, please refer to Supplement 5.

Table 2: Changes in psychosocial health on group level and subgroup level

Primary outcome	T0		T1		T2		T3		p-values			
	EMM	(95% CI)	EMM	(95% CI)	EMM	(95% CI)	EMM	(95% CI)	Overall	*Post-hoc tests*		
										T0-T1	*T1-T2*	*T2-T3*
PedsQL Psychosocial health scores [0-100]	72.30	(70.11;74.49)	77.35	(75.10;79.61)	78.64	(76.39;80.89)	79.81	(77.50;82.12)	<0.0001	<0.0001	0.11	0.14
Subgroups analyses on psychosocial health	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**Difference in visits**	***Post-hoc tests***		
										Main Difference	***Differential change***	
Age at To												
<25 years	74.44	(71.43;77.45)	78.55	(75.32;81.79)	80.72	(77.66;83.78)	81.67	(78.58;84.77)	0.46	0.33	0.58	
≥25 years	69.88	(66.73;73.03)	76.00	(72.88;79.12)	76.29	(73.07;79.51)	77.70	(74.35;81.05)				
Sex												
Female	70.58	(67.25;73.91)	76.40	(73.04;79.77)	76.77	(73.26;80.27)	78.24	(74.51;81.96)	0.77	0.53	0.69	
Male	73.65	(70.75;76.56)	78.10	(75.11;81.10)	80.12	(77.23;83.02)	81.05	(78.16;83.94)				
Lung function at To												
FEV_1pp ≤70	68.99	(65.93;72.05)	76.12	(72.82;79.41)	77.10	(73.68;80.51)	77.92	(74.33;81.52)	0.11	0.15	0.16	
FEV_1pp >70	74.97	(71.98;77.95)	78.35	(75.27;81.44)	79.89	(76.93;82.85)	81.33	(78.38;84.29)				
Earlier use of CFTR modulator												
Yes	73.05	(70.62;75.49)	77.81	(75.33;80.30)	79.29	(76.75;81.83)	80.16	(77.58;82.74)	0.82	0.72	0.77	
No	69.35	(64.37;74.33)	75.55	(70.37;80.74)	76.11	(71.30;80.84)	78.45	(72.99;83.91)				
Use psychotropic medications at To												
Yes	62.60	(55.85;69.36)	67.60	(59.48;75.73)	70.43	(62.52;78.34)	69.24	(60.86;77.61)	0.13	0.047	0.76	
No	73.26	(71.00;75.53)	78.38	(76.00;80.64)	79.46	(77.14;81.78)	80.86	(78.51;83.22)				

CFTR: cystic fibrosis transmembrane conductance regulator, EMM: estimated marginal means. Multiple imputation data is used for this table.

Table 3: clinical changes after initiation of ETI

Clinical parameters	T0, EMM	T2, EMM	Difference	(95% CI)	p-value
BMI (kg/m²)	21.12	21.76	0.64	(0.43;0.85)	<0.0001
FEV_1pp	73.18	85.64	12.46	(10.48;14.45)	<0.0001
SCC (mmol·L⁻¹)	84.05	34.07	-49.97	(-54.31;-45.63)	<0.0001

EMM: estimated marginal means, FEV_1pp: forced expiratory volume in 1 s, % predicted, SCC: sweat chloride concentration. Multiple imputation data is used for this table.

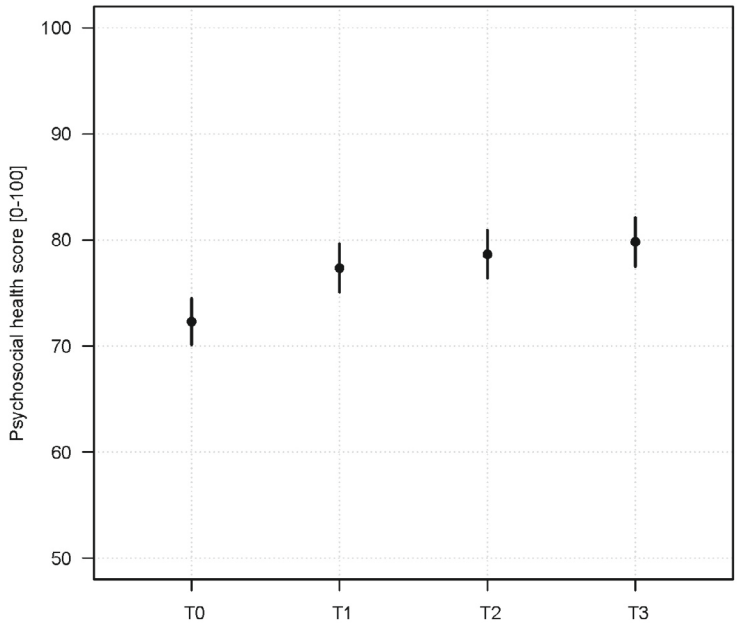

Figure 1: Estimated marginal means with 95% confidence intervals at T0, T1, T2 and T3 of PedsQL psychosocial health scores, using multiple imputation data

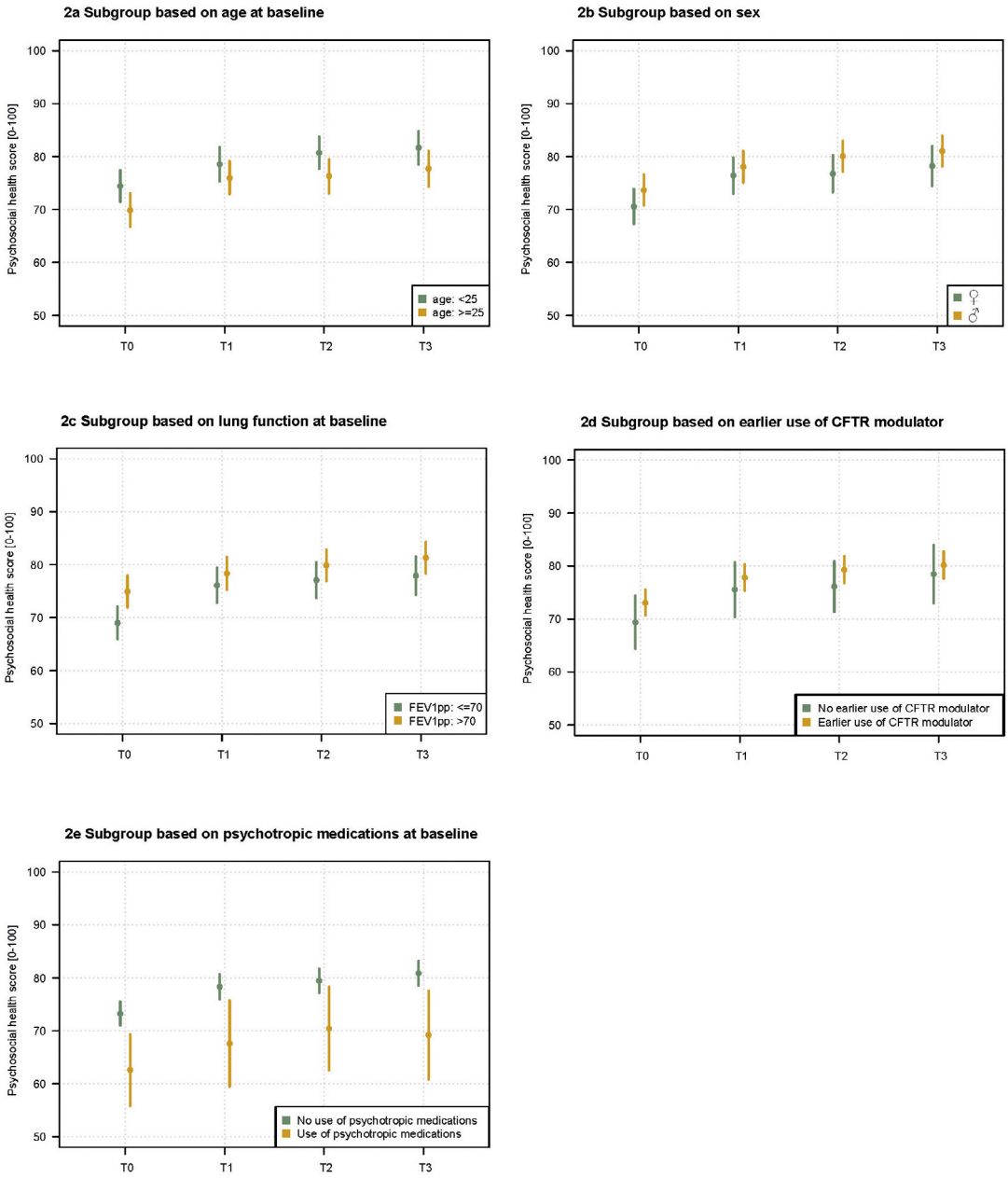

Figure 2: Estimated Marginal Means of PedsQL psychosocial health scores and 95% confidence intervals of psychosocial health scores at T0, T1, T2 and T3, of subgroups based at age at T0, sex, earlier use of CFTR-modulator, FEV_1pp at T0, and use of psychotropic medication at T0, using multiple imputation data

DISCUSSION

The RISE study demonstrated a significant and clinically relevant mean improvement in psychosocial health following the initiation of ETI, with the most substantial change occurring between three months before and three months after use of ETI. No clear differences in psychosocial health scores after start of ETI were observed between subgroups based on age, sex, lung function at baseline and earlier use of any other CFTR modulator. People using psychotropic medications at baseline, however, reported structural lower psychosocial health both before and after initiation of ETI, compared to those not using these medications.

The improvement in psychosocial health after starting ETI on group level of the RISE study is in line with existing studies [5,6,26]. These studies identified the improvement of CFQ-R (respiratory domain) in four weeks after starting ETI [5,6] and remained high over 24 weeks [5], matching the pace of improvement in biological outcomes. The RISE study showed that, on group level, psychosocial health remained high till 48 weeks after ETI. Moreover, previous literature has shown that older age, being female and having a lower FEV_1pp are generally associated with lower levels of mental health in adults in general [27]. We could not confirm this, as we did not identify differences in psychosocial health scores on subgroup level. However, the likelihood-ratio tests and the tests based on visit-specific contrasts for subgroup analyses on age and lung function, led to apparently conflicting results, complicating their interpretation. Where the likelihood-ratio tests did not indicate any significant findings, the visit-specific contrasts did. We interpreted the findings as inconclusive as to whether there was a true difference and, if so, whether that difference existed on baseline only or remained constant over time.

Individuals with a history of psychiatric illness or use of psychotropic medications might be more likely to experience a worsening of their mental health after ETI [8–10,14]. Although people using psychotropic medications at baseline seem to report lower psychosocial health scores, based on the post-hoc test and visit-specific contrasts, compared to those who do not use these medications, we did not find differential changes in psychosocial health scores following ETI between these subgroups. This means that both subgroups regarding psychotropic medications had an equal improvement in psychosocial health following ETI.

To compare our psychosocial health scores with those of the general population, we used normative data on PedsQL psychosocial health scores of Dutch adolescents and young adults aged 12-30 [28,29]. Although our study group in general experienced an improved average psychosocial health scores after ETI (79.85 (95% CI 77.57;82.14) at T3), healthy adults (n=512) seem to score higher on psychosocial health with a mean average score of

83.89 (95% CI 82.78;85.00) [29].[2] Our adolescent subgroup, however, demonstrated a mean score of 83.71 (95% CI 78.73;88.69) after ETI (at T3), while the average psychosocial health of healthy adolescents (n=185) is 80.23 (95% CI 78.76; 81.70) [28].[3] The improvement and high state of psychosocial health after ETI, especially in adolescents with CF, is remarkable. It is possible this increase was influenced not only by the physical changes but also by factors such as hope, a positive outlook on the future, and illness identity, particularly during adolescence when the future outlook is predominantly uncertain [30]. Future research is needed to disentangle the contributions of these factors and their underlying mechanisms, to better understand how these adolescents are able to adapt.

The strength of this study lay in its longitudinal prospective design with four time waves of data collection, including a baseline assessment prior starting ETI and a long follow-up period.. We assessed that a sample size of 100 is acceptable for the aim of this study [16], however as inclusion was easier than expected and there were low risks or efforts for the participants, we opted not to end inclusion, resulting in 177 study participants. These study participants included both sexes , adolescents and adults with varying degrees of disease severity, which enhances the generalizability of the findings. Some limitations deserved mentioning. We anticipated missing data to be rare [16], but experienced a lower response-rate than expected. During the visits, we noticed that some adolescents lacked motivation and/or concentration to complete the questionnaires, primarily attributed to the length of the complete set of questionnaires. We aimed to mitigate potential biased effects by using multiple imputation techniques. Nevertheless, if participants did not complete questionnaires as a result of mental health issues, we might have overestimated the improvement of psychosocial health following ETI. Yet, attrition bias seemed to be limited (Supplement 6). Secondly, some adolescents sought assistance from their parents during the completion, which might have influenced their answers in the questionnaires. Moreover, we cannot establish a causal relationship between ETI and psychosocial health as we did not perform a randomized controlled trial and external factors or unrelated other life events could therefore possibly influenced our results. Furthermore, we did not correct for multiple testing, which prevented us from excluding false positives. Furthermore, we have not noted any changes in ETI dosing for individuals. Finally, the most seriously ill pwCF may have been on an ETI compassionate use program and were not included in this study.

We were unable to identify any subgroups experiencing lower psychosocial functioning after the initiation of ETI, hence leaving unanswered who these patients are. Patients could be part of multiple subgroups (e.g., having a low lung function, being of age, and taking psychotropic medications), and the deterioration of mental health might not be

2 95% CI calculated by $\bar{x} \pm z\frac{s}{\sqrt{n}}$

3 95% CI calculated by $\bar{x} \pm z\frac{s}{\sqrt{n}}$

solely facilitated by a single (biological) factor. Instead, this deterioration may be the result of an interplay among various biological, pharmacological, and psychological factors on individual level. Gaining insight into how these underlying factors collectively affect mental health would enhance our understanding of why some people experience a diminished mental health after ETI.

CONCLUSIONS

The RISE study underlined that pwCF experienced a significant and clinically relevant improvement in psychosocial health following ETI. No differences in psychosocial health scores after starting ETI were observed between subgroups, except for people using psychotropic medications at baseline. They reported structural lower psychosocial health scores, compared to those not using these medications. We were unable to identify a subgroup more susceptible to reduced mental health after starting ETI, for we did not find differential changes in psychosocial health scores following ETI between subgroups. Future studies are needed to further investigate the underlying biological, pharmacological, and psychological mechanisms at the individual level to better understand why individuals react differently to ETI in terms of their mental health.

REFERENCES

1. McBennett KA, Davis PB, Konstan MW. Increasing life expectancy in cystic fibrosis: Advances and challenges. *Pediatr Pulmonol.* 2022;57(S1). doi:10.1002/ppul.25733
2. Bierlaagh MC, Muilwijk D, Beekman JM, van der Ent CK. A new era for people with cystic fibrosis. *Eur J Pediatr.* 2021;180(9):2731-2739. doi:10.1007/s00431-021-04168-y
3. Goetz DM, Savant AP. Review of CFTR modulators 2020. *Pediatr Pulmonol.* 2021;56(12):3595-3606. doi:10.1002/ppul.25627
4. Kapouni N, Moustaki M, Douros K, Loukou I. Efficacy and Safety of Elexacaftor-Tezacaftor-Ivacaftor in the Treatment of Cystic Fibrosis: A Systematic Review. *Children.* 2023;10(3):554. doi:10.3390/children10030554
5. Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *New England Journal of Medicine.* 2019;381(19):1809-1819. doi:10.1056/NEJMoa1908639
6. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet.* 2019;394(10212):1940-1948. doi:10.1016/S0140-6736(19)32597-8
7. Fajac I, Daines C, Durieu I, et al. Non-respiratory health-related quality of life in people with cystic fibrosis receiving elexacaftor/tezacaftor/ivacaftor. *Journal of Cystic Fibrosis.* 2023;22(1):119-123. doi:10.1016/j.jcf.2022.08.018
8. Spoletini G, Gillgrass L, Pollard K, et al. Dose adjustments of Elexacaftor/Tezacaftor/Ivacaftor in response to mental health side effects in adults with cystic fibrosis. *Journal of Cystic Fibrosis.* 2022;21:1061-1065. doi:10.1016/j.jcf.2022.05.001
9. Heo S, Young DC, Safirstein J, et al. Mental status changes during elexacaftor/tezacaftor / ivacaftor therapy. *Journal of Cystic Fibrosis.* 2022;21(2):339-343. doi:10.1016/j.jcf.2021.10.002
10. Tindell W, Su A, Oros SM, Rayapati AO, Rakesh G. Trikafta and Psychopathology in Cystic Fibrosis: A Case Report. *Psychosomatics.* 2020;61:735-738. www.psychosomaticsjournal.org
11. Talwalkar JS, Koff JL, Lee HB, Britto CJ, Mulenos AM, Georgiopoulos AM. Cystic Fibrosis Transmembrane Regulator Modulators: Implications for the Management of Depression and Anxiety in Cystic Fibrosis. *Psychosomatics.* 2017;58(4):343-354. doi:10.1016/j.psym.2017.04.001
12. Purkayastha D, Agtarap K, Wong K, et al. Drug-drug interactions with CFTR modulator therapy in cystic fibrosis: Focus on Trikafta®/Kaftrio®. *Journal of Cystic Fibrosis.* Published online January 2023. doi:10.1016/j.jcf.2023.01.005
13. Burcusa SL, Iacono WG. Risk for recurrence in depression. *Clin Psychol Rev.* 2007;27(8):959-985. doi:10.1016/j.cpr.2007.02.005
14. Zhang L, Albon D, Jones M, Bruschwein H. Impact of elexacaftor/tezacaftor/ivacaftor on depression and anxiety in cystic fibrosis. *Ther Adv Respir Dis.* 2022;16:175346662211442. doi:10.1177/17534666221144211
15. Aspinall SA, Mackintosh KA, Hill DM, Cope B, McNarry MA. Evaluating the Effect of Kaftrio on Perspectives of Health and Wellbeing in Individuals with Cystic Fibrosis. *Int J Environ Res Public Health.* 2022;19(10):6114. doi:10.3390/ijerph19106114
16. van der Heijden E, van den Bor RM, van der Ent CK, Nijhof SL, van der Laan SEI. The RISE study protocol: resilience impacted by positive stressful events for people with cystic fibrosis. *ERJ Open Res.* 2023;9(3):00535-02022. doi:10.1183/23120541.00535-2022
17. Varni J, Seid M, Rode C. The PedsQL™ measurement model for the pediatric quality of life inventory. *Med Care.* 1999;3:126-139.
18. WHO Adolescent Mental Health 17 november 2021.
19. Varni JW, Limbers CA. The PedsQL™ 4.0 Generic Core Scales Young Adult Version. *J Health Psychol.* 2009;14(4):611-622. doi:10.1177/1359105309103580
20. Varni JW, Limbers CA. The Pediatric Quality of Life Inventory: Measuring Pediatric Health-Related Quality of Life from the Perspective of Children and Their Parents. *Pediatr Clin North Am.* 2009;56(4):843-863. doi:10.1016/j.pcl.2009.05.016
21. Sawyer SM, Azzopardi PS, Wickremarathne D, Patton GC. The age of adolescence. *Lancet Child Adolesc Health.* 2018;2(3):223-228. doi:10.1016/S2352-4642(18)30022-1
22. Buuren S van, Groothuis-Oudshoorn K. MICE: Multivariate Imputation by Chained Equations in R. *J Stat Softw.* 2011;45(3). doi:10.18637/jss.v045.i03

23. Robitzsch A, Grund S. miceadds: Some Additional Multiple Imputation Functions, Especially for "mice." https://CRAN.R-project.org/package=miceadds. Accessed May 1, 2023. https://CRAN.R-project.org/package=miceadds
24. Pinheiro J, Bates D, R Core Team. nlme: Linear and Nonlinear Mixed Effect Models. https://cran.r-project.org/web/packages/nlme/index.html. Published 2022. Accessed May 1, 2023. https://cran.r-project.org/web/packages/nlme/index.html
25. Lenth R. emmeans: Estimated Marginal Means, aka Least-Squares. https://CRAN.R-project.org/package=emmeans. Published 2023. Accessed May 1, 2023. https://CRAN.R-project.org/package=emmeans
26. DiMango E, Spielman DB, Overdevest J, et al. Effect of highly effective modulator therapy on quality of life in adults with cystic fibrosis. *Int Forum Allergy Rhinol*. 2021;11(1):75-78. doi:10.1002/alr.22700
27. Quittner AL, Goldbeck L, Abbott J, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries. *Thorax*. 2014;69(12):1090-1097. doi:10.1136/thoraxjnl-2014-205983
28. Engelen V, Haentjens MM, Detmar SB, Koopman HM, Grootenhuis MA. Health related quality of life of Dutch children: Psychometric properties of the PedsQL in the Netherlands. *BMC Pediatr*. 2009;9:68. doi:10.1186/1471-2431-9-68
29. Limperg PF, Haverman L, van Oers HA, van Rossum MAJ, Maurice-Stam H, Grootenhuis MA. Health related quality of life in Dutch young adults: Psychometric properties of the PedsQL generic core scales young adult version. *Health Qual Life Outcomes*. 2014;12(1). doi:10.1186/1477-7525-12-9
30. Laranjeira C, Querido A. Hope and Optimism as an Opportunity to Improve the "Positive Mental Health" Demand. *Front Psychol*. 2022;13. doi:10.3389/fpsyg.2022.827320

SUPPLEMENT 1

More information about the imputation model

Imputations were performed with the data in wide format. Corresponding to the default options, imputations were based on predictive mean matching (numeric variables) or logistic regression (binary variables). However, using the default predictor matrix (i.e. using all variables as predictors) resulted in numerical issues for one of the variables with missing data (sweat chloride at t2). Therefore, the quickpred() function (with default specifications) was used to simplify the model for this specific variable. No issues were logged in the function's event log, and no abnormalities were identified during the inspection of trace plots. Rubin's rules were used to pool estimates from the imputed data sets. Likelihood ratio test statistics were pooled using the 'D2' method (using the function micombine.chisquare() from the R package miceadds v3.16-18[1]. Pooled confidence intervals for estimated marginal means are based on normal approximations.

List of variables included in the imputation model

Variables	Variables are treated as numeric unless indicated otherwise
t0_ApprAgeAtBaseline	
t0_pat_sex	Binary
t0_CFTR_modulator	Binary
t0_genotype_Cat	Binary
t0_BMIAtBaseline	
t0_baseline_sweatchloride	
t0_baseline_FEV1_pp	
t0_baseline_fecal_elastase	Binary (Dichotomized: 0 vs >0) *fecal elastase at t2 was not included, because only one observation exceeded 0.
t0_total_dur_IV_AB	Binary (Dichotomized: 0 vs >0)
t0_clin_CFRD	Binary
t0_clin_CFLD	Binary
t0_baseline_psychfarm	Binary
t0_PedsQL_PsychSoc_total	
t0_BIPQ_total	
t0_IIQ_Rejection	
t0_IIQ_Acceptance	
t0_IIQ_Engulfment	
t0_IIQ_Enrichment	
t0_PSS_total	
t0_GAD7_total	
t0_PHQ9_total	

List of variables included in the imputation model (continued)

Variables	Variables are treated as numeric unless indicated otherwise
t0_RCADS_Overall_total	
t0_Cantril	
t0_CFQR_Resp	
t0_BRS_total	
t0_SDQ_Difficulties_total	
t1_PedsQL_PsychSoc_total	
t1_BIPQ_total	
t1_IIQ_Rejection	
t1_IIQ_Acceptance	
t1_IIQ_Engulfment	
t1_IIQ_Enrichment	
t1_PSS_total	
t1_GAD7_total	
t1_PHQ9_total	
t1_RCADS_Overall_total	
t1_Cantril	
t1_CFQR_Resp	
t1_BRS_total	
t1_SDQ_Difficulties_total	
t2_BMIAtFollowup	
t2_followup_sweatchloride	
t2_followup_FEV1_pp	
t2_sum_unresolved_ sideeffects	
t2_followup_psychfarm	Binary
t2_PedsQL_PsychSoc_total	
t2_BIPQ_total	
t2_IIQ_Rejection	
t2_IIQ_Acceptance	
t2_IIQ_Engulfment	
t2_IIQ_Enrichment	
t2_PSS_total	
t2_GAD7_total	
t2_PHQ9_total	
t2_RCADS_Overall_total	
t2_Cantril	

List of variables included in the imputation model (continued)

Variables	Variables are treated as numeric unless indicated otherwise
t2_CFQR_Resp	
t2_BRS_total	
t2_SDQ_Difficulties_total	
t3_PedsQL_PsychSoc_total	
t3_BIPQ_total	
t3_IIQ_Rejection	
t3_IIQ_Acceptance	
t3_IIQ_Engulfment	
t3_IIQ_Enrichment	
t3_PSS_total	
t3_GAD7_total	
t3_PHQ9_total	
t3_RCADS_Overall_total	
t3_Cantril	
t3_CFQR_Resp	
t3_BRS_total	
t3_SDQ_Difficulties_total	

REFERENCES

1. Robitzsch A, Grund S. miceadds: Some Additional Multiple Imputation Functions, Especially for "mice." https://CRAN.R-project.org/package=miceadds. Accessed May 1, 2023. https://CRAN.R-project.org/package=miceadds

SUPPLEMENT 2

Results based on original data and multiple imputed data sets

Table 1 : Changes in psychosocial health after initiation of ETI therapy on group level and subgroup level, results presented in original data and after use of multiple imputation data

Part 1	**T0**				**T1**			
	Original		**MI**		**Original**		**MI**	
Primary outcome	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**
PedsQL Psychosocial health [0-100]	72.24	(70.02;74.46)	72.30	(70.10;74.49)	77.41	(75.16;79.67)	77.33	(75.05;79.62)
Subgroups analyses on psychosocial health scores	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**
Age at To								
<25 years	79.38	(74.66;84.10)	74.42	(71.42;77.42)	81.61	(76.12;87.09)	78.46	(75.20;81.72)
≥25 years	70.78	(68.34;73.22)	69.89	(66.74;73.04)	76.60	(74.14;79.05)	76.06	(72.90;79.22)
Sex								
Female	70.47	(67.02;73.93)	70.60	(67.25;73.95)	76.14	(72.82;79.46)	76.41	(72.99;79.83)
Male	73.65	(70.69;76.61)	73.63	(70.73;76.53)	78.47	(75.40;81.54)	78.06	(75.03;81.09)
Lung function at To								
≤70	68.85	(65.66;72.04)	68.99	(65.92;72.05)	76.20	(72.80;79.59)	76.12	(72.79;79.46)
>70	74.96	(71.98;77.94)	74.96	(71.97;77.95)	78.28	(75.23;81.33)	78.31	(75.24;81.37)
Earlier use of CFTR modulator								
Yes	72.95	(70.49;75.42)	73.05	(70.61;75.48)	77.96	(75.49;80.43)	77.79	(75.27;80.31)
No	69.57	(64.37;74.76)	69.35	(64.39;74.32)	75.37	(69.90;80.85)	75.54	(70.35;80.74)
Use psychotropic med To								
Yes	64.01	(56.76;71.26)	66.63	(60.33;72.92)	67.46	(58.20;76.72)	72.26	(64.46;80.06)
No	73.09	(70.72;75.45)	73.13	(70.80;75.46)	78.21	(75.89;80.53)	78.08	(75.73;80.43)

Part 2	T2				T3				p-values	
	Original		MI		Original		MI		Original	MI
Primary outcome	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**EMM**	**overall**	**EMM**	**(95% CI)**	**overall**	**overall**
PedsQL Psychosocial health [0-100]	79.26	(77.04;81.47)	78.75	(76.50;81.00)	79.92	<0.0001	79.85	(77.57;82.14)	<0.0001	<0.0001
Subgroups analyses on psychosocial health scores	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**EMM**	**(95% CI)**	**Difference in visits**	
									Original	**MI**
Age at To										
<25 years	84.56	(79.59;89.53)	80.85	(77.80;83.90)	84.82	(80.00;89.65)	81.62	(78.57;84.67)	0.07	0.43
≥25 years	78.18	(75.74;80.62)	76.36	(73.11;79.62)	78.91	(76.32;81.50)	77.85	(74.49;81.21)		
Sex										
Female	77.18	(73.79;80.58)	76.94	(73.39;80.48)	78.24	(74.43;82.05)	78.34	(74.60;82.09)	0.50	0.64
Male	80.86	(77.94;83.79)	80.17	(77.30;83.04)	81.27	(78.35;84.20)	81.04	(78.20;83.89)		
Lung function at To										
≤70	77.41	(73.86;80.96)	77.15	(73.76;80.54)	77.90	(74.02;81.77)	78.01	(74.43;81.58)	0.01	0.09
>70	80.75	(77.93;83.57)	80.03	(77.09;82.98)	81.66	(78.89;84.44)	81.34	(78.45;84.24)		
Earlier use of CFTR modulator										
Yes	80.02	(77.55;82.49)	79.42	(76.89;81.95)	80.30	(77.74;82.86)	80.20	(77.66;82.74)	0.76	0.83
No	76.33	(71.34;81.32)	76.11	(71.35;80.87)	78.52	(73.02;84.02)	78.49	(73.15;83.83)		
Use psychotropic med at To										
Yes	70.88	(62.30;79.45)	72.83	(65.33;80.34)	68.04	(58.99;77.08)	72.98	(64.97;80.99)	0.08	0.40
No	80.01	(77.71;82.31)	79.62	(77.28;81.95)	81.03	(78.67;83.39)	80.87	(78.55;83.18)		

Part 3	p-values					
Primary outcome	**Post-hoc tests**					
	T0-T1		**T1-T2**		**T2-T3**	
	Original	**MI**	**Original**	**MI**	**Original**	**MI**
PedsQL Psychosocial health scores [0-100]	<0.0001	<0.0001	0.01	0.07	0.25	0.14
Subgroups analyses on psychosocial health	**Post-hoc tests**			
	Main difference		**Differential change**	
	Original	**MI**	**Original**	**MI**
Age at T0				
<25 years	0.05	0.31	0.36	0.45
≥25 years				
Sex				
Female	0.29	0.47	0.76	0.68
Male				
Lung function at T0				
FEV_1pp ≤70	0.02	0.17	0.08	0.17
FEV_1pp >70				
Earlier use of CFTR modulator				
Yes	0.67	0.77	0.62	0.76
No				
Use psychotropic medications at T0				
Yes	0.05	0.15	0.35	0.82
No				

Data are presented as n, median (interquartile range), n (%) or mean±SD. CFTR: cystic fibrosis transmembrane conductance regulator .

Original Supplement 4: Results based on original and multiple imputation visit-specific contrasts

Supplement 4	**p-values**							
Subgroups analyses on psychosocial health	**Visit-specific contrasts**							
	T0		**T1**		**T2**		**T3**	
	Original	**MI**	**Original**	**MI**	**Original**	**MI**	**Original**	**MI**
Age at To								
<25 years	0.04	0.04	0.16	0.29	0.02	0.05	0.05	0.10
≥25 years								
Sex								
Female	0.16	0.18	0.31	0.47	0.11	0.16	0.21	0.26
Male								
Lung function at To								
FEV_1pp ≤70	0.006	0.006	0.36	0.34	0.15	0.20	0.12	0.15
FEV_1pp >70								
Earlier use of CFTR modulator								
Yes	0.24	0.19	0.39	0.44	0.19	0.23	0.56	0.57
No								
Use psychotropic medications at To								
Yes	0.02	0.06	0.03	0.16	0.04	0.09	0.008	0.06
No								

CFTR: cystic fibrosis transmembrane conductance regulator

Original Supplement 5: clinical changes after initiation of ETI therapy, results presented in original data and after use of multiple imputation data

	Original	MI	Original	MI	Original		MI		Original	MI
Clinical parameters	**T0, EMM**	**T0, EMM**	**T2, EMM**	**T2, EMM**	**Difference**	**(95% CI)**	**Difference**	**(95% CI)**	**p-value**	**p-value**
BMI (kg/m^2)	21.12	21.12	21.79	21.77	0.67	(0.48; 0.85)	0.65	(0.43;0.86)	<0.0001	<0.0001
FEV_1pp	73.18	73.18	86.27	85.51	13.10	(11.39;14.81)	12.34	(10.26;14.41)	<0.0001	<0.0001
SCC (mmol·L^{-1})	84.27	84.05	34.93	34.01	-49.34	(-53.03; -45.64)	-50.04	(-54.46;-45.61)	<0.0001	<0.0001

Data are presented as n, median (interquartile range), n (%) or mean±SD. BMI: Body Mass Index; FEV_1pp: forced expiratory volume in 1 s, % predicted, SCC: sweat chloride concentration.

SUPPLEMENT 3:

Response rate regarding the RISE-questionnaires

Questionnaires								
Time points	**T0**		**T1**		**T2**		**T3**	
Medical consultation (%)	177	**(100)**			151	(83)		
Completed (%)	174	(98.3)	146	(82.5)	141	(79.7)	142	(80.2)
· *100% completed*	158		140		137		139	
· *partially completed*	16		6		4		3	
· *missing*	3		31		36		35	

Data are presented as n, or n (%).

SUPPLEMENT 4:

Visit-specific contrasts

Subgroups analyses on psychosocial health	p-values			
	Visit-specific contrasts			
	T0	T1	T2	T3
Age at To				
<25 years	0.04	0.26	0.05	0.08
≥25 years				
Sex				
Female	0.17	0.46	0.15	0.24
Male				
Lung function at To				
FEV_1pp ≤70%	0.006	0.33	0.22	0.15
FEV_1pp >70%				
Earlier use of CFTR modulator				
Yes	0.19	0.44	0.25	0.58
No				
Use psychotropic medications at To				
Yes	0.003	0.01	0.03	0.009
No				

CFTR: cystic fibrosis transmembrane conductance regulator

SUPPLEMENT 5:

Clinical changes after ETI therapy

Of the 177 people at T0, 152 (85.88%) participants attended the medical consultation on T2. Only 74 participants had their sweat chloride concentration measured at T2 due to a lack of sweat chloride tests (an international event beyond the control of the study team).[27] In total, 146 participants completed questionnaires about side effect, of which 119 have experienced them in the last six months, since use of ETI therapy. Of the 119 participants, 48 (40%) subjects reported coughing, 69 (58%) sputum increase, 30 (25%) headache, 18 (15%) diarrhea, 27 (23%) abdominal pain, 3 (3%) hemoptysis, 26 (22%) fatigue, 14 (12%) rhinorrhea, 6 (5%) hoarseness, 7 (6%) sore throat, 20 (17%) rash, 13 (11%) mood changes. Side effects reported in open answer format: obstipation (n=8, 7%), sleep problems (n=6, 5%), dry eyes or other eye related symptoms (n=6, 5%), being dizzy (n=5, 4%), tinnitus (n=5, 4%), skin-related problems (n=4, 3%), cold-like symptoms (n=3, 3%), concentration problems, restless or forgetful (n=3, 3%), different sputum production (n=3, 3%), fever (n=3, 3%), liver function problems (n=3, 3%), gall or kidney stones (n=2, 2%), nausea (n=2, 2%), shortness of breath (n=2, 2%), weight gain (n=2, 2%), diaphragmatic pain (n=1, 1%), hypertension (n=1, 1%), having more energy (n=1, 1%), headache (n=1, 1%), hot flash (n=1, 1%), more hungry (n=1, 1%), more often getting stung by mosquitoes (n=1, 1%), and pain in testicles (n=1, 1%). At T2, 24 (20.16%) participants were still experiencing one side effect, twelve (10.1%) participants experienced two side effects, five (4.20%) participants experienced three side effects, and two (1.68%) participants experienced four side effects at T2. We do not have any data on side effects at T1 and T3. In terms of psychotropic medication use, 15 participants (8.47%) reported baseline usage at T0, decreasing to 11 (6.21%) at T2. Among them, nine continued usage, while two started taking medication during the study.

SUPPLEMENT 6:

Analysis of attrition bias

Participants who completed the RISE questionnaires at T3 did not exhibit significant differences in baseline values for age, lung function, and baseline psychosocial health scores compared to those who did not. This suggests limited attrition bias.

Completing RISE questionnaires at T3	Variable at baseline	Mean	(SD)	Median	(interquartile range)
No	Age	23.87	(8.04)	21.85	(17.78; 29.39)
No	FEV_1pp	75.29	(16.74)	76.50	(66.75; 87.50)
No	Psychosocial health score	72.45	(14.91)	74.17	(62.92; 85.00)
Yes	Age	26.32	(8.93)	25.33	(19.30; 31.45)
Yes	FEV_1pp	72.74	(20.32)	73.50	(57.25; 89.00)
Yes	Psychosocial health score	72.48	(14.74)	73.33	(61.67; 83.33)

FEV_1*pp: forced expiratory volume in 1 s, % predict*

CHAPTER 5

MENTAL WELLBEING AND GENERAL HEALTH IN ADOLESCENTS WITH ASTHMA:

THE PIAMA BIRTH COHORT STUDY

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ABSTRACT

Objectives

To assess whether adolescents with asthma experience a lower mental wellbeing and lower general health than their non-asthmatic peers.

Study design

Data from the Prevention and Incidence of Asthma and Mite Allergy study were used. At the ages of 11, 14, 17, and 20 years, 2651, 2522, 2094, and 2206 participants, respectively, completed questionnaires. Their parents completed questionnaires at the ages of 11 (n = 2660), 14 (n = 2338), and 17 years (n = 1872). Asthma was defined according to the Mechanisms of the Development of Allergy criteria. Mental wellbeing was measured using the Mental Health Index-5 and was reported by the adolescents. General health, measured on a 4-point Likert scale, was reported by the adolescents and their parents. We estimated associations of asthma with mental wellbeing and perceived general health using generalized estimating equations.

Results

At ages 11, 14, 17, and 20 years, 6.7%, 6.9%, 5.0%, and 6.6%, respectively, of the adolescents had asthma. Adolescents with asthma did not score differently on the Mental Health Index than their peers without asthma. Adolescents with asthma were less likely to experience good or excellent health than their peers without asthma (aOR, 0.37; 95% CI, 0.26-0.51 for intermittent asthma and 0.33; 95% CI, 0.25-0.41 for persistent asthma). These results remain similar across the different ages.

Conclusions

The mental wellbeing of adolescents with asthma is similar to that of their peers without asthma, although adolescents with asthma are less likely to perceive a good or excellent general health.

INTRODUCTION

In the US one-fourth of youth have a chronic disease [1]. Similarly, in the Netherlands 26% of the children and adolescents grow up with a chronic disease [2]. In Dutch youth aged 0-25 years, asthma is the most common chronic disease (4.6%), followed by anxiety and mood disorder (4.1%), attention deficit hyperactivity disorder (3.6%), stomach ache/fecal issues (2.8%), eczema (2.8%), learning disorder (2.0%), congenital skeleton deformities (1.5%), migraine (1.4%), morbid obesity (1.4%), and autism spectrum disorders (1.1%) [2].

Children and adolescents with a chronic disease face more challenges in daily life compared with their healthy peers, often resulting in fatigue, participating less in sports, worrying more about their future, and being more prone to dropping out of school [2–4]. Therefore, quality care for affected youth encompasses more than only treating physical symptoms, it also includes looking after their overall wellbeing [2,5]. The positive health concept defines health as being able to adapt and to self-manage, instead of defining health as the absence of a disease [6–8]. Positive health focuses on resilience and therewith on positive challenges, such as maintaining mental wellbeing and a good perceived general health [7].

Investigating wellbeing and health in adolescents is important, knowing that these aspects strengthen essential developmental tasks, including maturation of emotional and cognitive abilities to become independent, completion of education, and transition to employment, civic engagement, and establishment of lifelong relationships [9]. Adolescence is a key developmental time period marked by rapid neurocognitive and social developmental changes, as well as the first emergence of mental health disorders [10–12]. In general, previously published studies reported that youth with asthma perceived a lower general health compared with their peers without asthma [13,14]. Additionally, prior research mainly focused on the association between asthma and quality of life (QoL). Silva et al reported that youth with asthma presented an overall lower QoL compared with healthy controls [15].

However, QoL is a broader concept than mental wellbeing, including multiple domains such as physical, psychological, emotional, and social and school functioning. Some studies used a QoL instrument, such as the health-related QoL questionnaire, that explicitly measure mental wellbeing as a separate domain. Studies using these instruments presented different results: some studies reported a lower mental wellbeing in adolescents with asthma, others observed a similar mental wellbeing for adolescents with asthma and adolescents without asthma [14,16,17].

Asthma severity and medication use are seen as predictors of mental being in patients with asthma [18]. Moreover, adolescence could influence the course of asthma, and overall

wellbeing [2,19,20]. Therefore, repeated measurements within the same individual during adolescence, and also testing for interaction effects of "asthma and age" and "asthma and gender" will give more robust results than using only one measurement at one time point. Longitudinal data were not available in most of the previously mentioned studies [13,14,16,21]. Our study used a large adolescent sample from a national birth cohort with data from age 11 to 20 years; using longitudinal data, we aim to investigate whether adolescents with asthma experience a lower mental wellbeing and lower general health compared with their peers without asthma.

METHODS

Study design and study population

Data were obtained from the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. In 1996/1997, pregnant women were recruited from the general population and their children (n = 3963 at baseline) have been followed since [22]. The study protocol was approved by the medical ethics committees of the participating institutes and all parents gave written informed consent. For this study, we used data that was collected when the adolescents were 11, 14, 17, and 20 years of age. At these years, respectively 2651, 2522, 2094, and 2206 participants completed questionnaires about health, lifestyle, and environment. Parents completed questionnaires at the participants' ages of 11 (n = 2660), 14 (n = 2338), and 17 years (n = 1872).

Definition of outcome

Our outcome measures were mental wellbeing as reported by adolescents, and general health as reported by adolescents and their parents. Mental wellbeing was measured by the Mental Health Index-5 (MHI-5) [23,24]. The MHI-5 is a short, simple set of 5 questions and is widely used as an instrument to assess mental wellbeing in large questionnaire-based population studies [25]. The MHI-5 contained the question "How often during the last 4 weeks, did you feel: nervous, calm and peaceful, downhearted and blue, happy, and so down in the dumps that nothing could cheer you up?". For each of these 5 items, answers could be given on a 5-point Likert scale: all the time, mostly, often, sometimes, and never. These answers were converted in a score, ranging from 0 to 100. This questionnaire was completed by the adolescent himself or herself at the ages of 11, 14, 17, and 20 years.

Perceived general health was measured by the question: "What do you think about your health?" and for the parents: "Would you describe your child's health in general as excellent, good, fair or poor?". A 4-point Likert scale was used: excellent, good, fair, or poor. The number of participants in the poor category was very low in all age categories (adolescents with asthma and adolescents without asthma combined): 0.1%, 0.8%, 1.5%, and 2.2%, at ages 11, 14, 17, and 20 years respectively. Therefore, we decided to construct 3 categories, in which the categories poor and fair were combined. The question was

answered by the adolescent at the ages of 11, 14, 17, and 20 years and by their parents at the participants' ages of 11, 14, and 17 years.

Definition of exposure variables

The exposure variable of interest was asthma (severity). Asthma was defined as reported presence of at least 2 of the 3 following criteria: (1) doctor diagnosed asthma ever, (2) wheezing or whistling in the chest in the last 12 months, and (3) prescribed asthma medication during the last 12 months. This asthma definition has been developed by a panel of experts within the Mechanisms of the Development of ALLergy consortium [26]. To obtain the needed information, we used data from questionnaires completed by the parents at the participants' ages of 11, 14, and 17 years and data reported by the 20-year-old participants. Asthma severity varies and as differences in asthma severity could influence our outcome measure, we created an asthma variable with 3 categories, based on medication use: (0) no asthma, (1) intermittent asthma, and (2) persistent asthma. Adolescents with asthma using no medication, or using only short- acting bronchodilators or antihistamine were classified as having intermittent asthma. Adolescents with asthma using (in addition to their short acting bronchodilators or antihistamine) either (inhalation) corticosteroids, long-acting bronchodilators, and/or leukotriene receptor antagonists were classified as having persistent asthma (Supplement 1). Intermittent asthma is considered to be a milder asthmatic phenotype, whereas persistent asthma is assumed to be more severe. The classification of asthma severity was based on Global Initiative for Asthma and Guidelines of the US National Heart, Lung and, Blood Institute [27,28]. The asthma severity classification could vary (for one specific individual) over time as medication use (of this individual) could vary over time.

Potential confounders

Based on literature and clinical reasoning we a priori selected potential confounders: sex (male/female), age (11, 14, 17, and 20 years), parental allergy, pubertal development, ethnicity, parental educational level as an indicator for family socioeconomic status, and educational level of the adolescents themselves. Parental allergy is a strong risk factor for having a child with asthma and parents with allergy/asthma are more used to self-management of asthma [29]. It might be conceivable that parental allergy could affect mental wellbeing of the child. Pubertal development changes the prevalence of asthma [30].

The ethnicity of the child was divided into Dutch, non-Dutch Western, and non-Western, based on the country of birth of both parents. Pubertal development was assessed using the self-administrated rating scale for pubertal development [31]. An overall score, based on puberty characteristics, was calculated and divided into 4 categories: puberty has not yet started, barely started, definitely started, and is complete. We classified the latter 2 as puberty started. Parental educational level was categorized into low, intermediate, and high. Low was defined as primary school, lower vocational or lower secondary education;

intermediate as intermediate vocational education or intermediate/higher secondary education; and high as higher vocational education and university. The educational level of the adolescents themselves was also categorized into low, intermediate, and high, where low was defined as prevocational secondary education or secondary vocational education, intermediate as higher general secondary education, and high as preuniversity education, higher vocational education, and university.

Statistical analyses

Descriptive statistics were used to summarize the characteristics of the study population. We estimated associations of asthma severity with mental wellbeing and perceived general health using generalized estimating equations (GEE). The GEE estimate associations of asthma with the outcome measures, taking correlations within participants into account. While using the GEE, we chose an independent correlation structure that enables the GEE to handle time-dependent variables (in our case asthma) to change over time. In this way, valid inferences can be ensured [32]. We used the GEE with an identity link function to estimate the associations between asthma severity and MHI scores (continuous outcome) and the GEE with a logit link function to estimate associations between asthma severity and general health (categorical outcome). For the outcome measure general health, reported by parents, we used data of 3 time points (at 11, 14, and 17 years). Associations with the MHI-5 score were expressed as differences (βs) and associations with general health were expressed as odds ratios, with no asthma as the reference category.

As secondary analyses, we tested for interactions between sex and asthma severity, and between age (11, 14, 17, and 20 years of age) and asthma severity. For an interaction term, we considered a *P* value of less than .1 as significant. We adjusted for a priori selected potential confounders (see subhead Potential Confounders). A *P* value of less than .05 was considered statistically significant. Both crude and adjusted differences or odds ratios are reported. All analyses were done with SPSS 25.0 (SPSS Inc).

RESULTS

Study population

The study participants of the PIAMA birth cohort were followed over time. For this study, we used data of 11-, 14-, 17-, and 20-year-old adolescents. Asthma data of at least one of the 4 measurement points was available for 3051 participants. Asthma data at least 3 of the four measurement points was available for 2022 participants.

Figure 1 shows the follow-up flowchart of the PIAMA birth cohort study. The number of complete cases could differ from the number of available questionnaires in age categories 11, 14, 17, and 20 years old, because a complete case is composed of a combination of variables. shows the characteristics of the study population; adolescents in age categories

11, 14, 17, and 20 years old, of which 6.7%, 6.9%, 5.0%, and 6.6%, respectively had asthma according to the Mechanisms of the Development of ALLergy definition. As is well-known from the previous literature and clinical practice, the prevalence of asthma was greater in boys than in girls up to the age of 14 years [33]. At ages 17 and 20 years, girls had a higher prevalence of asthma. Table 2 shows the outcome measures—the self-reported score on the MHI-5, and self- and parent-reported general health—per age category for adolescents with and without asthma. In both adolescents with asthma and adolescents without asthma, the MHI score and perceived general health decreased with age.

Associations between asthma severity and MHI-5 score

Adolescents with intermittent asthma scored 0.51 point (95% CI: -1.49 to2.52) higher on the MHI-5 than non-asthmatic adolescents, whereas adolescents with persistent asthma scored -0.50 points (95% CI: -2.24 to1.25) lower on the MHI-5 than non-asthmatic adolescents (Table 3). On the MHI-5 scale of 0-100, these differences are very small and they were not statistically significant. Secondary analyses did not reveal differences in the association of asthma with score on the MHI between boys and girls ($p_{interaction}$=0.75), and between different ages ($p_{interaction}$ =0.86) More information about the interaction term, age specific associations and sex specific association is shown in Supplement 2.

Associations between asthma severity and general health: self- and parent-reported

Adolescents with asthma were less likely to experience good or excellent health than their peers without asthma (adjusted OR: 0.37; 95% CI: 0.26 to 0.51 for intermittent asthma and 0.33; 95% CI: 0.25 to 0.41 for persistent asthma) (Table 3). Secondary analyses identified no differences in the associations of asthma with perceived general health between boys and girls ($p_{interaction}$ =0.69) and between different ages ($p_{interaction}$ =0.74) (Supplement 2).

A comparable pattern emerges when we analyzed the parental reports. Parents of adolescents with asthma were less likely to rate their child's health as good or excellent, compared to parents of non-asthmatic adolescents (adjusted OR: 0.26; 95% CI: 0.17 to 0.41 for intermittent asthma, and 0.21; 95% CI: 0.15 to 0.28 for persistent asthma respectively) (Table 3). Secondary analyses identified no differences in the associations of asthma with parent-reported general health between boys and girls ($p_{interaction}$ =0.99) and between different ages ($p_{interaction}$ =0.18) (Supplement 2).

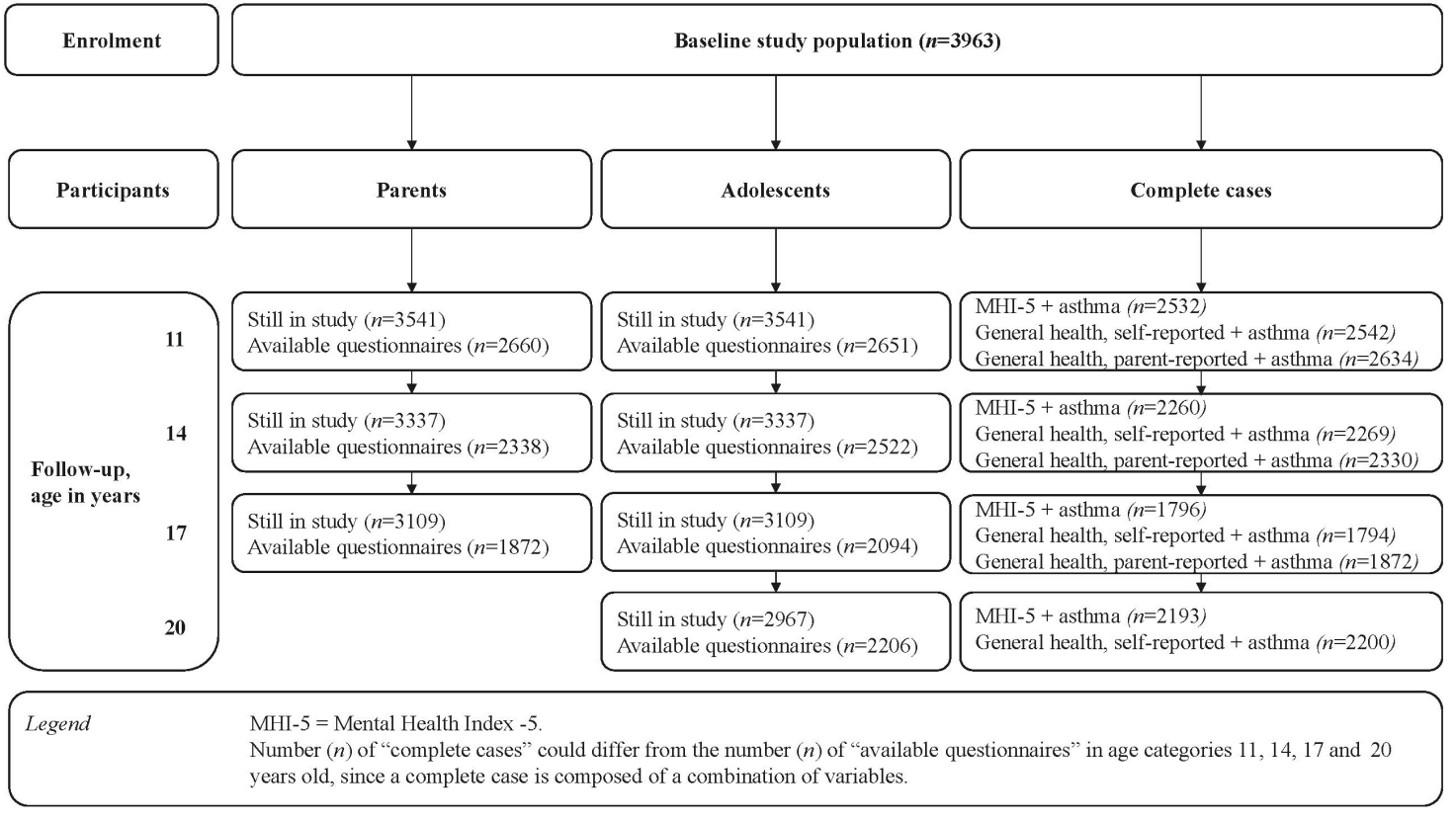

Figure 1: Follow-up flowchart of the PIAMA birth cohort study. The number (n) of complete cases could differ from the n of available questionnaires in age categories 11, 14, 17, and 20 year of age, because a complete case is composed of a combination of variables.

Table 1: Characteristics of study population according to asthma status at ages 11, 14, 17, and 20 years.

		Adolescents with asthma (%)								*Adolescents without asthma (%)*							
Age category (years)		**11**		**14**		**17**		**20**		**11**		**14**		**17**		**20**	
N (% of total per age category)		178	(6.7)	160	(6.9)	94	(5.0)	165	(6.6)	2464	(93.3)	2172	(93.1)	1778	(94.9)	2036	(93.4)
Age in years, mean (SD)		11.4	(0.3)	14.8	(0.3)	17.7	(0.3)	20.9	(0.4)	11.3	(0.3)	14.8	(0.3)	17.7	(0.3)	20.9	(0.3)
*Asthma**	Intermittent	44	(24.7)	58	(36.3)	36	(38.3)	86	(52.1)	na		na		na		na	
	Persistent	134	(75.3)	102	(63.7)	58	(61.7)	79	(47.9)	na		na		na		na	
Gender	Girl	69	(38.8)	74	(46.3)	55	(58.5)	95	(57.6)	1214	(49.3)	1076	(49.5)	887	(49.9)	1062	(52.2)
	Boy	109	(61.2)	85	(53.1)	39	(41.5)	70	(42.4)	1247	(50.6)	1094	(50.4)	887	(49.9)	970	(47.6)
Ethnicity	Dutch	158	(88.7)	138	(86.3)	82	(87.2)	143	(86.7)	2242	(91.0)	1978	(91.1)	1621	(91.2)	1845	(90.6)
	Western	8	(4.5)	12	(7.5)	8	(8.5)	10	(6.1)	106	(4.3)	95	(4.4)	79	(4.4)	93	(4.6)
	Non-Western	6	(3.4)	6	(3.8)	4	(4.3)	8	(4.8)	62	(2.5)	55	(2.5)	44	(2.5)	56	(2.8)
Education	Low	37	(20.6)	35	(21.7)	18	(18.8)	41	(24.8)	483	(19.7)	377	(17.4)	299	(16.9)	377	(18.6)
Mother	Intermediate	73	(40.8)	70	(43.5)	36	(37.5)	66	(40.0)	1027	(41.8)	899	(41.5)	708	(40.0)	823	(40.6)
	High	68	(38.0)	55	(34.2)	40	(41.7)	58	(35.2)	948	(38.6)	890	(41.1)	763	(43.1)	825	(40.7)
Father	Low	42	(23.5)	41	(25.8)	24	(25.0)	42	(25.5)	561	(23.0)	464	(21.6)	360	(20.4)	440	(21.9)
	Intermediate	59	(33.7)	60	(37.3)	25	(26.3)	61	(37.0)	816	(33.1)	712	(33.3)	574	(32.6)	669	(33.3)
	High	73	(41.7)	57	(35.8)	44	(45.8)	59	(35.8)	1065	(43.6)	971	(45.2)	828	(48.0)	900	(44.8)
Adolescent	Low	na		64	(40.0)	27	(28.7)	48	(29.1)	na		722	(33.2)	532	(32.3)	497	(24.4)
	Intermediate	na		36	(22.5)	13	(13.8)	29	(17.6)	na		593	(27.3)	288	(16.2)	271	(10.3)
	High	na		56	(35.0)	46	(48.9)	59	(35.8)	na		781	(36.0)	819	(46.1)	815	(40.0)
Puberty started	Girl	21	(11.7)	70	(98.6)	55	(100.0)	86	(100.0)	412	(16.7)	1020	(97.8)	886	(99.9)	1062	(100.0)
	Boy	6	(3.4)	69	(81.2)	39	(100.0)	79	(100.0)	70	(2.8)	924	(87.7)	885	(99.8)	970	(100.0)

Abbreviations: na=not applicable. *See supplement 1 for classification asthma severity

Table 2: Mental Health Index and perceived general health according to asthma status at ages 11, 14, 17, and 20 years.

		Adolescents with asthma (%)								*Adolescents without asthma (%)*							
Age category (years)		**11**		**14**		**17**		**20**		**11**		**14**		**17**		**20**	
N (% of total per age category)		178	(6.7)	160	(6.9)	94	(5.0)	165	(6.6)	2464	(93.3)	2172	(93.1)	1778	(94.9)	2036	(93.4)
Age in years, mean (SD)		11.4	(0.3)	14.8	(0.3)	17.7	(0.3)	20.9	(0.4)	11.3	(0.3)	14.8	(0.3)	17.7	(0.3)	20.9	(0.3)
MHI-5: 0-100, mean (SD)		79.7	(11.4)	77.6	(13.0)	74.7	(14.1)	70.2	(17.6)	80.1	(10.5)	77.4	(12.7)	74.2	(14.5)	71.9	(15.6)
General health, self-reported	Excellent	34	(19.1)	24	(15.0)	13	(13.8)	14	(8.5)	1017	(41.3)	838	(38.6)	548	(30.8)	497	(24.4)
	Good	126	(70.8)	110	(68.8)	62	(66.0)	123	(74.5)	1294	(52.5)	1205	(55.5)	1046	(58.8)	1367	(67.1)
	Fair/poor	15	(8.4)	22	(13.8)	14	(14.9)	28	(16.0)	55	(2.2)	69	(3.2)	110	(6.2)	171	(8.4)
General health, parent-reported	Excellent	35	(19.7)	27	(16.9)	13	(10.6)	na		1349	(54.7)	1114	(51.3)	743	(41.8)	na	
	Good	132	(74.2)	116	(72.5)	64	(68.1)	na		1079	(43.8)	1000	(46.0)	941	(53.0)	na	
	Fair/poor	11	(6.2)	17	(10.6)	17	(18.1)	na		27	(1.1)	55	(2.5)	93	(5.2)	na	

Abbreviations: MHI = Mental Health Index; na=not applicable.

Table 3: Mental Health Index and perceived general health: differences and associations between adolescents with no asthma (reference), mild asthma and severe asthma.

	MHI-5, self-reported			
Asthma status	**Crude β**	**(95% CI)**	**Adj. β**	**(95% CI)**
No asthma	ref	-	ref	-
Intermittent asthma	-0.37	(-2.44;1.70)	0.51	(-1.49;2.52)
Persistent asthma	-0.51	(-2.37;1.36)	-0.50	(-2.24;1.25)
	General health, self-reported			
Asthma status	**Crude OR**	**(95% CI)**	**Adj. OR**	**(95% CI)**
No asthma	ref	-	-	-
Intermittent asthma	0.32	(0.23;0.44)	0.37	(0.26;0.51)
Persistent asthma	0.32	(0.25;0.41)	0.33	(0.25;0.41)
	General health, parent-reported			
Asthma status	**Crude OR**	**(95% CI)**	**Adj. OR**	**(95% CI)**
No asthma	ref	-	-	-
Intermittent asthma	0.24	(0.16;0.36)	0.26	(0.17;0.41)
Persistent asthma	0.21	(0.16;0.28)	0.21	(0.15;0.28)

Abbreviations: Adj.= adjusted. MHI=mental health index. Adjusted for: sex, age, parental allergy, pubertal development, ethnicity, parental educational level, educational level of the adolescents themselves.

DISCUSSION

This study, using data from a general population-based cohort, showed no significant differences in mental wellbeing between adolescents with asthma and their peers without asthma. However, adolescents with asthma and their parents were both less likely to perceive the adolescent's health as good or excellent than adolescents without asthma and their parents. All associations were similar for boys and girls and across different ages. Our findings provide insight into adolescents' experience with asthma and are hopeful and highlight the positive health approach: having asthma does not restrain them from feeling mentally well during adolescence.

Despite differences in asthma definition, previous studies also reported that asthmatic youth perceived a lower general health [13,14]. However, the MHI-5 has not been used in previously published studies to measure mental wellbeing in adolescents with asthma and we therefore could not compare our results directly. In the previously published literature, much attention has been paid to the association between asthma and QoL. With a meta-analysis in their systematic review on QoL in pediatric patients with asthma, Silva et al analyzed the association of asthma with psychological functioning [15]. Because overall mental wellbeing is part of the definition of psychological functioning, next to individual's

behavior, emotions, and social skills, we compared the results of this meta-analysis with our results [34]. A slightly lower psychological functioning was reported for the adolescents with asthma aged 11–18 years (mean difference −2.73 on a scale from 0 to 100; 95% CI, −5.38 to −0.09) compared with controls without asthma [15]. This meta-analysis included 4 studies from Turkey, Sri Lanka, Finland, and Germany, and all studies had a cross-sectional study design [21,35–37]. The latter study used a QoL-instrument that measured mental wellbeing (in the meta-analysis interpreted as psychological functioning) as one of their domains and found no differences in mental wellbeing between adolescents with and without asthma [21]. Two studies that were not included in this meta-analysis, both using a QoL instrument that explicitly measures mental wellbeing as a separate domain, reported (just as the meta-analysis) a lower mental wellbeing in adolescents with asthma [14,16]. In our study, we observed no differences in mental wellbeing between asthmatic and adolescents without asthma.

Some studies have stated that adolescents are more mature and, therefore, may experience the emotional impact of asthma differently resulting in an improvement of mental wellbeing during the transition from childhood to adolescence [20]. Other investigators state that adolescence goes along with a negative impact on mental wellbeing because treatment adherence is often a problem in adolescents with asthma [38]. In our study, we did not see any interactions between asthma and age, and therefore could not confirm the suggestion that the association between asthma and mental wellbeing might change in the course of adolescence.

Our results showed that adolescents with asthma and their parents were less likely to perceive the adolescent's health as good or excellent than the adolescents without asthma and their parents. The association between asthma and perceived general health was stronger for the parent-reported general health than for the self-reported general health. Parents and children often have different perceptions of the child's wellbeing, especially when it comes to emotional and social domains. Chronically ill children and adolescents generally score higher on these domains than their parents [39,40]. In contrast, healthy adolescents report lower scores on emotional and social domains than their parents [41]. In our study, the latter observation could explain why the association was stronger for parent-reported general health. Parents of children without asthma perceived their children's general health more often as excellent or good than the children did themselves (shown in Table 1).

This study had several strengths. We prospectively collected data in a large study population and we took the severity of asthma into account, which is a potential influencer of mental wellbeing and perceived general health. Furthermore, we used repeated measurements of mental wellbeing and general health during adolescence and therefore, did not draw conclusions based on 1 measurement at 1 time point. Last, we analyzed both

self- and parent-reported outcomes, which are highly relevant as parents and children often report differently on these outcomes [39,40].

The participants of the PIAMA cohort were recruited from the general population from several parts from the Netherlands [42]. However, in the PIAMA birth cohort and therefore in this study, parents from non-Western countries were under-represented. This factor implies that our results may not be generalizable to populations with different ethnic or cultural backgrounds.

The prevalence of chronic diseases among youth is high [1,2]. Adolescents with and without asthma may (also) have non-asthmatic chronic illnesses that might (negatively) impact their mental wellbeing and perceived general health. However, we think that our results are not affected by the presence of non-asthmatic chronic illnesses specifically in the participants without asthma, because it is unlikely that these non-asthmatic illnesses are more prevalent in adolescents without asthma than in the adolescents with asthma.

In long-term follow-up studies, selective loss to follow-up of low socioeconomic status participants is a common phenomenon. Attrition bias could, therefore, be introduced. The percentage of participants with highly educated parents was only slightly higher at age 20 years than at baseline; 40.3% of the mothers and 44.2% of the fathers were highly educated at the participants age of 20 years, whereas 35.0% of the mothers and 39.7% of the fathers were highly educated at baseline (Supplement 3). This finding indicates that selective loss to follow-up of participants from low socioeconomic status families has been limited and is, therefore, unlikely to have biased our results.

In our study, the severity of asthma was defined by medication use [43–45]. Having asthma symptoms under control, irrespective of frequency, type, or dose of medication, might have a favorable effect on the burden of disease and subsequently on perceived mental and general health. This finding would suggest that asthma severity would be best defined by the level of asthma control. We do think that the type of asthma medication is a good proxy to define asthma severity. Strong asthma medication, prescribed for persistent asthma, can cause side effects and might provoke a feeling of dependency on the medication in the patient. This could have a negative effect on perceived mental and general health and will be less prominent in adolescents with intermittent asthma using milder medication such as short acting bronchodilators.

Our conclusions on mental wellbeing are based on the MHI-5, which assesses anxiety and depressed moods well, but it is less suitable as an indicator of behavioral and addiction problems [24,25,46]. The MHI-5 is not designed to establish a clinical diagnosis. The MHI-5 is well-known and often used as a measure of general mental wellbeing and it has been shown that the MHI-5 performs remarkably well against other often-used and longer mental

health questionnaires, such as the Mental Health Component Summary, the General Health Questionnaire (GHQ-12)[47], and the Hopkins Symptom Checklist (SCL-25) [25,48,49].

This study highlights the positive health approach by showing that despite growing up with asthma, affected adolescents can still experience a good mental wellbeing.

REFERENCES

1. Van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. *JAMA*. 2010;303:623-630. doi:10.1001/jama.2010.104
2. van Hal L, Tierolf B, van Rooijen M, van der Hoff M. *Een Actueel Perspectief Op Kinderen En Jongeren Met Een Chronische Aandoening in Nederland. Omvang , Samenstelling En Participatie*.; 2019.
3. Secinti E, Thompson E, Richards M, Gaysina D. Research Review: Childhood chronic physical illness and adult emotional health – a systematic review and meta-analysis. *J Child Psychol Psychiatry*. 2017;58:753-769.
4. Nap-Van Der Vlist M, Dalmeijer G, Grootenhuis M, et al. Fatigue in childhood chronic disease. *Arch Dis Child*. Published online 2019:1-6. doi:10.1136/archdischild-2019-316782
5. Michaud PA, Suris JC, Viner R. The adolescent with a chronic condition. Part II: Healthcare provision. *Arch Dis Child*. 2004;89(10):943-949. doi:10.1136/adc.2003.045377
6. Huber M, André Knottnerus J, Green L, et al. How should we define health? *BMJ (Online)*. 2011;343:1-3. doi:10.1136/bmj.d4163
7. Huber M, Van Vliet M, Giezenberg M, et al. Towards a "patient-centred" operationalisation of the new dynamic concept of health: A mixed methods study. *BMJ Open*. 2016;6:1-11. doi:10.1136/bmjopen-2015-010091
8. WHO. Constitution of the World Health Organization. World Health Organization Chronicle.
9. Patton GC, Sawyer SM, Santelli JS, et al. Our future: a Lancet commission on adolescent health and wellbeing. *The Lancet*. 2016;387:2423-2478. doi:10.1016/S0140-6736(16)00579-1
10. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet*. 2012;379:1056-1067. doi:10.1016/S0140-6736(11)60871-4.Depression
11. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of. *Arch Gen Psychiatry*. 2005;62:593-602. doi:10.1001/archpsyc.62.6.593
12. Blakemore SJ, Mills KL. Is Adolescence a Sensitive Period for Sociocultural Processing? *Annu Rev Psychol*. 2014;65:187-207. doi:10.1146/annurev-psych-010213-115202
13. Määttä H, Hurtig T, Taanila A, Honkanen M, Ebeling H, Koivumaa-Honkanen H. Childhood chronic physical condition, self-reported health, and life satisfaction in adolescence. *Eur J Pediatr*. 2013;172:1197-1206. doi:10.1007/s00431-013-2015-6
14. Cui W, Zack M, Zahran H. Health-Related Quality of Life and Asthma among United States Adolescents. *Physiol Behav*. 2016;176:139-148. doi:10.1016/j.physbeh.2017.03.040
15. Silva N, Carona C, Crespo C, et al. Quality of life in pediatric asthma patients and their parents : a meta-analysis on 20 years of research. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15:499-519. doi:10.1586/14737167.2015.1008459
16. Mohangoo AD, Sc M, Koning HJ De, et al. Health-Related Quality of Life in Adolescents with Wheezing Attacks. 2007;41:464-471. doi:10.1016/j.jadohealth.2007.06.002
17. Matterne U, Schmitt J, Diepgen TL, Apfelbacher C. Children and adolescents' health-related quality of life in relation to eczema, asthma and hay fever: results from a population-based cross-sectional study. *Qual Life Res*. 2011;20:1295-1305.
18. Petsios KT, Priftis KN, Hatziagorou E, Tsanakas JN, Antonogeorgos G, Matziou VN. Determinants of quality of life in children with asthma. *Pediatr Pulmonol*. 2013;48:1171-1180. doi:10.1002/ppul.22768
19. Kyngäs HA, Kroll T, Duffy ME. Compliance in adolescents with chronic diseases: a review. *Journal of Adolescent Health*. 2000;26:379-388. doi:10.1016/s1054-139x(99)00042-7
20. Okelo SO, Wu AW, Krishnan JA, Rand CS, Skinner EA, Diette GB. Emotional quality-of-life and outcomes in adolescents with asthma. *Journal of Pediatrics*. 2004;145:523-529. doi:10.1016/j.jpeds.2004.06.043
21. Matterne U, Schmitt J, Diepgen T, Apfelbacher C. Children and adolescents' health-related quality of life in relation to eczema, asthma and hay fever: results from a population-based cross-sectional study. *Qual Life Res*. 2011;20:1295-1305.
22. Brunekreef B, Smit J, de Jongste J, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatric allergy and immunology*. 2002;13(15):55-60.
23. Veit CT, Ware JE. The structure of psychological distress and well-being in general populations. *J Consult Clin Psychol*. 1983;51:730-742. doi:10.1037/0022-006X.51.5.730
24. Berwick DM, Murphy JM, Goldman PA, Ware JE, Barsky AJ, Weinstein MC. Performance of a Five-Item mental Health Screening Test. *Med Care*. 1991;29.

25. Rivera-riquelme M, Piqueras JA, Cuijpers P. The Revised Mental Health Inventory-5 (MHI-5) as an ultra-brief screening measure of bidimensional mental health in children and adolescents. *Psychiatry Res*. 2019;274:247-253. doi:10.1016/j.psychres.2019.02.045
26. Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: A population-based cohort study. *Lancet Respir Med*. 2014;2:131-140. doi:10.1016/S2213-2600(13)70277-7
27. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018.
28. National Institutes of Health, National Heart Lung and Blood Institue. *Expert Panel Report 3 : Guidelines for the Diagnosis and Management of Asthma. Full Report 2007*.; 2007.
29. Dold S, Wjst M, Von Mutius E, Reitmeir P, Stiepel E. Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. *Arch Dis Child*. 1992;67:1018-1022. doi:10.1136/adc.67.8.1018
30. Fuhlbrigge A, Jackson B, Wright R. Gender and asthma. *Immunology and Allergy clinicals of North America*. 2002;22:753-789.
31. Carskadon M, Acebo C. A self-administered rating scale for pubertal development. *Journal of Adolescent Health*. 1993;518:4491-4512. doi:10.1002/cne.22466
32. Pepe MS, Anderson GL. A cautionary note on inference for marginal regression models with longitudinal data and general correlated response data. *Commun Stat Simul Comput*. 1994;23:939-951.
33. Tollefsen E, Langhammer A, Romundstad P, Bjermer L, Johnson R, Holmen TL. Female gender is associated with higher incidence and more stable respiratory symptoms during adolescence. *Respir Med*. 2007;101:896-902. doi:10.1016/j.rmed.2006.09.022
34. Preedy V, Watson R. Psychological Functioning. In: *Handbook of Disease Burdens and Quality of Life Measures*. Springer; 2010.
35. Altiparkmak S, Altiparmak O, Sari HY. Asthma and quality of life in adolescents in Manisa, Turkey. *Int J Adolesc Med Health*. 2011;23:217-221.
36. Danansuriya M, Rajapaksa L. Psychometric properties of the Sinhala version of the PedsQL™ 4.0 Generic Core Scales in early adolescents in Sri Lanka. *Health Qual Life Outcomes*. 2012;4.
37. Merikallio V, Mustalahti K, Remes S, Valovirta E, Kaila M. Comparison of quality of life between asthmatic and healthy school children. *Pediatric Allergy Immunol*. 2005;16:332-340.
38. De Benedictis D, Bush A. The challenge of asthma in adolescence. *Pediatr Pulmonol*. 2007;42:683-692. doi:10.1002/ppul.20650
39. Janse A, Sinnema G, Uiterwaal C, Kimpen J, Gemke R. Quality of life in chronic illness: Children, parents and paediatricians have different, but stable perceptions. *Acta Paediatrica, International Journal of Paediatrics*. 2008;97:1118-1124. doi:10.1111/j.1651-2227.2008.00847.x
40. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. *Quality of Life Research*. 2001;10:347-357. doi:10.1023/A:1012253723272
41. Waters E, Stewart-Brown S, Fitzpatrick R. Agreement between adolescent self-report and parent reports of health and well-being: Results of an epidemiological study. *Child Care Health Dev*. 2003;29:501-509. doi:10.1046/j.1365-2214.2003.00370.x
42. Wijga AH, Kerkhof M, Gehring U, et al. Cohort profile: The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort. *Int J Epidemiol*. 2014;43:527-535. doi:10.1093/ije/dys231
43. Colice GL. Categorizing asthma severity: an overview of national guidelines. *Clin Med Res*. 2004;2:155-163. doi:10.3121/cmr.2.3.155
44. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018.
45. National Institutes of Health, National Heart Lung and Blood Institue. *Expert Panel Report 3 : Guidelines for the Diagnosis and Management of Asthma. Full Report 2007*.; 2007.
46. Rumpf H, Meyer C, Hapke U, John U. Screening for mental health : validity of the MHI-5 using DSM-IV Axis I psychiatric disorders as gold standard. 2001;105:243-253.
47. Goldberg D, Williams P. *A User's Guide to the General Health Questionnaire: GHQ*. NFER-Nelson; 1988.
48. Strand B, Dalgard O, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population : A comparison of the instruments SCL-25 , SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry*. 2009;57:113-118. doi:10.1080/08039480310000932
49. Kelly MJ, Dunstan FD, Lloyd K, Fone DL. Evaluating cutpoints for the MHI-5 and MCS using the GHQ-12 : a comparison of five different methods. 2008;36:1-9. doi:10.1186/1471-244X-8-10

SUPPLEMENT 1:

Asthma severity, based on medication use

Intermittent asthma: no medication use OR Airomir, Bricanyl, Salbutamol, Terbutaline, Ventolin, Atrovent, Ipratropium, Berodual, Combivent, Cromoglicinezuur, Lomudal, Natriumcromoglicaat, Nedocromil, Tilade. At age of 17: Grazax, Oralair

Persistent asthma: Aerobec, Alvesco, Beclometaso, Budesonide, Ciclesonide, Flixotide, Fluticason, Pulmicort, Qvar, Foradil, Formoterol, Oxis, Salmeterol, Servent, Seretide, Symbicort, Tiotropium, Spiriva, Montelukast, Singulair. At age of 17 and 20: Depo-medrol, Dexamethason, Di-adreson F, Kenacort, Oradexon, Prednisolon, Triamcinolon

SUPPLEMENT 2:

Test of Effect Models

Table 4: Test of Effect Models, p values of the interaction terms

	MHI-5, self-reported		
Interaction term	**Wald χ2**	**df**	**p value**
*sex*asthma severity*	0.3	2	0.86
*age*asthma severity*	3.4	6	0.75
	General health, self-reported		
Interaction term	**Wald χ2**	**df**	**p value**
*sex*asthma severity*	0.7	2	0.69
*age*asthma severity*	3.5	6	0.74
	General health, parent-reported		
Interaction term	**Wald χ2**	**df**	**p value**
*sex*asthma severity*	0.003	2	0.998
*age*asthma severity*	6.3	4	0.18

MHI-5=Mental Health Index-5

Table 5: Mental Health Index and perceived general health: age specific associations between adolescents with no asthma (reference), mild asthma and severe asthma.

Age category (years)	**11**		**14**		**17**		**20**	
MHI-5	**Adj. β**	**(95% CI)**	**Adj. β**	**(95% CI)**	**Adj. β**	**(95% CI)**	**Adj. β**	**(95% CI)**
No asthma	ref		ref		ref		ref	
Intermittent asthma	1.03	(-2.31;4.38)	1.07	(-1.86;4.00)	1.12	(-3.46;5.69)	-0.44	(-4.09;3.21)
Persistent asthma	-1.22	(-3.62;1.16)	-0.81	(-3.55;1.93)	2.04	(-1.34;5.22)	-0.85	(-5.15;3.45)
GH, self-reported	**Adj. OR**	**(95% CI)**	**Adj. OR**	**(95% CI)**	**Adj. OR**	**(95% CI)**	**Adj. OR**	**(95% CI)**
No asthma	ref		ref		ref		ref	
Intermittent asthma	0.40	(0.29;0.82)	0.28	(0.14;0.55)	0.48	(0.22;1.04)	0.40	(0.24;0.65)
Persistent asthma	0.28	(0.18;0.42)	0.29	(0.18;0.43)	0.40	(0.22;1.73)	0.43	(0.26;0.69)
GH, parent-reported	**Adj. OR**	**(95% CI)**	**Adj. OR**	**(95% CI)**	**Adj. OR**	**(95% CI)**		
No asthma	ref		ref		ref		na	
Intermittent asthma	0.42	(0.21;0.85)	0.60	(0.08;0.31)	0.34	(0.15;0.77)	na	
Persistent asthma	0.17	(0.12;0.26)	0.24	(0.16;0.36)	0.22	(0.12;0.40)	na	

Abbreviations: Adj.= adjusted; GH=general health; MHI-5=Mental Health Index-5; na=not applicable. Adjusted for gender (boy/girl), family history of atopic disease in mother/ father, puberty scale, ethnicity, highest attained education of parents and education of the children/adolescents themselves

Table 6: Mental Health Index and perceived general health: sex specific associations between adolescents with no asthma (reference), mild asthma and severe asthma.

	Boys		Girls	
MHI-5	**Adj. β**	**(95% CI)**	**Adj. β**	**(95% CI)**
No asthma	ref		ref	
Intermittent asthma	-0.10	(-2.70;2.49)	1.20	(-1.89;4.29)
Persistent asthma	-0.85	(-3.18;1.49)	-0.12	(-2.69;2.46)
GH, self-reported	**Adj. OR**	**(95% CI)**	**Adj. OR**	**(95% CI)**
No asthma	ref		ref	
Intermittent asthma	0.42	(0.25;0.68)	0.33	(0.22;0.50)
Persistent asthma	0.34	(0.24;0.47)	0.31	(0.21;0.45)
GH, parent-reported	**Adj. OR**	**(95% CI)**	**Adj. OR**	**(95% CI)**
No asthma	ref		ref	
Intermittent asthma	0.26	(0.15;0.46)	0.27	(0.14;0.52)
Persistent asthma	0.21	(0.14;0.29)	0.21	(0.13;0.32)

Abbreviations: Adj.= adjusted; GH=general health; MHI-5=Mental Health Index-5; na=not applicable. Adjusted for gender (boy/girl), family history of atopic disease in mother/ father, puberty scale, ethnicity, highest attained education of parents and education of the children/adolescents themselves

SUPPLEMENT 3:

Follow-up rate within the PIAMA study

Table 7: Participant characteristics for all participants and those who completed the 20-year follow-up

	Baseline		*20-year follow-up*	
Variable	**n/N**	**(%)**	**n/N**	**(%)**
Female sex	2053/3963	(51.8)	1040/2201	(47.3)
Maternal asthma and/or hay fever	963/3923	(24.5)	505/2181	(23.2)
Paternal asthma and/or hay fever	980/3928	(24.9)	546/2181	(25.0)
Dutch nationality	3327/3684	(90.3)	1971/2159	(91.3)
High maternal education	1331/3807	(35.0)	883/2190	(40.3)
High paternal education	1493/3761	(39.7)	959/2171	(44.2)

CHAPTER 6

CHRONIC CONDITIONS AND ADOLESCENTS' PSYCHOSOCIAL WELLBEING:

THE IMPACT OF SELF-REPORTING

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ABSTRACT

Objective

This study explores psychosocial wellbeing in adolescents with a physician diagnosed chronic condition, with emphasis on the disparity between adolescents who self-report their condition and those who do not.

Methods

This cross-sectional study included participants from the Dutch PROactive cohort aged 12-18 years with clinical diagnosis of chronic disease: auto-immune disease, cystic fibrosis, congenital heart disease, nephrological condition, or a general pediatric condition. Psychosocial wellbeing was assessed using self-reported indicators of life satisfaction, self-rated health, psychosomatic symptoms, pediatric quality of life, anxiety, and depression. We examined differences in psychosocial wellbeing among reporters and non-reporters, both at a group level and within distinct disease categories. Potential moderating effects of age, sex and socio-economic status (SES) on the association between reporting status and psychosocial wellbeing outcomes were assessed.

Results

Of the 1,009 adolescents (mean age 15.4 ± 1.6 years; 67.4% girls) 26.8% self-reported having a chronic condition. Reporters consistently indicated worse psychosocial wellbeing across all assessed sub-domains. When stratified for disease, this pattern was not always replicated; similar deficits in wellbeing were only observed for the populations with an auto-immune disease or a general pediatric condition. No clear moderating effects were found for sex, age, and SES on the association between self-reporting of chronic disease and psychosocial wellbeing.

Conclusions

Only a minority of adolescents with a physician diagnosed chronic condition self-report as having a chronic disease. Adolescents with a self-reported chronic condition indicated a lower psychosocial wellbeing, a pattern that seems to hold across some, but not all, disease groups.

INTRODUCTION

Population-representative studies revealed that approximately 5% of adolescents aged 11 to 16 years reported having a chronic condition [1]. These adolescents reported poorer outcomes in a wide range of psychosocial wellbeing domains [1]. Moreover, previous research showed that being female, being older, and having a lower socioeconomic status (SES) has a negative effect on psychosocial wellbeing [2–4]. However, the lack of information on the established clinical diagnoses of the adolescents in this sample limited our ability to understand the relationship between self-reporting versus a physician diagnosed chronic condition.

In contrast to the 5% prevalence of self-reported chronic conditions, based on healthcare records approximately 25% of the youth have been clinically diagnosed with at least one chronic somatic or psychiatric condition [5,6]. A chronic condition is defined as a clinically established diagnosis with persistent or recurring symptoms lasting more than three to six months or occurring more than three times per year, requiring long-term use of medications, treatments, or supportive devices [6]. Youth with a physician diagnosed chronic condition generally report a significantly lower quality of life, are more prone to develop psychosocial problems, often show delays in achieving psychosocial milestones, and are less likely to be (financially) independent in young adulthood, compared to their healthy peers [6–8]. It remains unknown what the difference is between those who self-report their condition ('reporters'), and those who do not ('non-reporters'), in relationship to their clinical diagnosis and psychosocial wellbeing.

In this study we focused on adolescents with a physician diagnosed chronic condition and examined differences in psychosocial wellbeing between reporters and non-reporters. Secondly, to explore whether the clinical diagnosis played a role, we compared psychosocial wellbeing of reporters and non-reporters across specific disease groups. Lastly, we investigated whether sex, age, and SES moderated the associations between self-report of a chronically condition and psychosocial wellbeing.

METHODS

Study design and study population

The PROactive cohort study is an ongoing longitudinal study that commenced in 2016 at the Wilhelmina Children's Hospital, part of the University Medical Center Utrecht, the Netherlands focusing on fatigue, daily life participation, and psychosocial wellbeing [9,10]. Data is collected from children, aged 2-18 years, with a chronic condition. Children are respectively included at least one year post-diagnosis of the chronic condition, or when they present with complaints of long-lasting fatigue or pain [9]. The current study included the cross-sectional baseline data collected from participants aged 12-18 years, resulting

in 1,009 inclusions. This specifically refers to the initial set of questionnaires adolescents completed between December 2018 and March 2022.

The PROactive study was classified by the institutional review board as exempt of the Medical Research Involving Human Subjects Act (16-707/C) and adhered to all local laws and the declaration of Helsinki [9].

Measures

Reporting having a chronic condition

Information about the medical diagnosis of each participant was derived from the hospital electronic health record. To assess presence of self-reported chronic conditions, we used a question from the Dutch Health Behaviour in School-aged Children (HBSC) 2017 questionnaire [11]: "*Is there someone in your home (the house or family where you are most of the time) who has been physically and/or mentally ill or disabled for more than three months?*" followed by a list of examples: "*Examples of diseases and disabilities include: cancer, diabetes, heart disease, depression, addiction, autism, intellectual disability.*". Adolescents reported whether they themselves or someone else in their household had a condition. Based on this answer, the adolescents were divided into two groups: adolescents with a medical diagnosis who self-reported having a chronic condition (reporters), and adolescents with a medical diagnosis who did not self-report having a chronic condition (non-reporters).

Psychosocial wellbeing

Psychosocial wellbeing was assessed using multiple indicators, including life satisfaction [12,13], self-rated health [14], psychosomatic health [15], health-related quality of life [16], and symptoms of anxiety and depression [17].

Life satisfaction was assessed with the Cantril ladder using the question "*How do you feel about your life as a whole right now?*" using a ladder analogy and possible answers range from 0 (worst life you can imagine) to 10 (best life you can imagine). However, in the PROactive study, the response options ranged from 1 to 10. The Cantril ladder is considered a valid and reliable instrument for measuring life satisfaction in adolescents [18–20].

Self-rated health (SRH) was assessed using the HBSC-question '*What do you think of your own health*?' with response categories from 1 (excellent) to 4 (bad) [14]. This construct is widely employed globally and relates to the self-perception of health. It serves as a valid predictor of both mortality and morbidity in adults [21,22].

Psychosomatic health was assessed using the HBSC-SCL, and it was expressed as a mean score indicating how frequently specific symptoms were experienced. In total 10 symptoms are assessed (e.g., having a headache, being nervous, or feeling dizzy), and the mean score over these 10 symptoms is calculated [15]. A five-point Likert-scale was used to measure the

frequency of the symptoms: from 1 (about every day) to 5 (rarely or never). The HBSC-SCL has good psychometric properties and has also been validated in Dutch [23,24].

Health-related quality of life (QoL) is measured using the Pediatric Quality of Life Generic Core Scale 4.0 (PedsQL GCS), comprising 23 items rated on a 5-point Likert scale. The response options range from 0 (never a problem) to 4 (almost always a problem) [25]. The PedsQL GCS assesses four domains: physical functioning, emotional functioning, social functioning, and school functioning. Answers were reverse coded to create a scale ranging from 0 to 100, where higher scores reflect a higher quality of life.

The severity of self-reported anxiety symptoms and depressive symptoms was evaluated using the Revised Child Anxiety and Depression Scale (RCADS), based on anxiety disorders and depression criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders-IV [26]. The questionnaire consists of 47 items, rated on a 4-point Likert scale, ranging from 0 (never) to 3 (always). To assess anxiety symptoms, we used the total anxiety subscale, based on 37 items, with a total score ranging from 0 to 111. To assess depressive symptoms, we used the major depressive disorder subscale, based on 10 items, with a total score ranging from 0-30. A higher score indicated more anxiety or depressive symptoms [26]. Raw scores were transformed into normative T-scores based on sex and age and assessed as a continuous measure where <65 = normal, 65-70 = borderline, >70 = clinical [27].

Individual characteristics

Age, sex, disease group, and SES were included as individual characteristics. The disease groups were auto-immune disease, cystic fibrosis (CF), congenital heart disease (CHD), nephrological conditions, and general pediatrics conditions.

The SES-score is calculated by the Statistics Netherlands, and based on the financial prosperity, educational level, and recent employment history of residents of a neighborhood administrative unit (four-digit postal code) [28]. The SES-score is freely available and presented in coefficients ranging from -7.0 to 3.1, with a higher coefficient indicating higher SES [29]. We ascertained the SES-score of our participants by referencing their four-digit postal code as of January 1, 2019.

Statistical analysis

We used descriptive statistics to summarize the characteristics of the study population - for the total population, and separately for the reporters and the non-reporters. To evaluate demographic differences between reporters and non-reporters, we performed $\chi 2$ tests for categorical data, and for continuous data we used independent t-tests when the data were normally distributed or Mann-Whitney-U tests for skewed distributed data. Spearman's rank correlation coefficients were used to examine the correlations between different psychosocial wellbeing measures (Supplement 1).

To assess differences in psychosocial wellbeing outcomes between reporters and non-reporters, we used the same tests described above. To gain more insight into the relationship between reporting status and psychosocial wellbeing in specific types of chronic conditions, we performed these analyses stratified by disease group. Secondary analyses were conducted to explore the potential moderation effects of the associations between reporting status and psychosocial wellbeing outcomes by age, sex and SES. We used generalized linear models with psychosocial wellbeing as the dependent variable (each outcome analyzed separately), and two-way interaction terms between reporting (yes, no) and potential moderators as the independent variables. Z-scores were employed for the continuous variables (age and SES) in order to facilitate standardized comparisons.

We presented the beta with 95% confidence intervals for the main effects of reporting status, age, sex, and SES. Significance levels were set at alpha < 0.05. In total, we ran four tests on the same psychosocial wellbeing outcome: one test for our primary analyses, and three tests -analyzing the associations with the outcome measure for each potential effect moderator- as secondary analyses. To account for multiple comparisons in all analyses, a post-hoc Bonferroni correction was applied. Consequently, for our outcomes, results with a p-value of 0.0125 or lower were considered statistically significant. All analyses were performed with SPSS 27.0 (IBM, Armonk, NY).

RESULTS

In total, 1,009 adolescents were included, with a mean age of 15.4 years (σ =1.6), of which 67.4% were girls. Out of the total sample, 57.0% were patients with a general pediatric condition, 26.4% had an auto-immune disease, 9.0% had a CHD, 5.1% had CF, and 2.7% had a nephrological condition. Of the patients with a general pediatric condition, 89.5% of 574 adolescents experienced persistent somatic symptoms (mostly pain or fatigue). Of these, 59.8% also had another chronic condition. The remaining 10.5% without persistent somatic symptoms had another chronic condition, such as asthma, obesity, or a mood disorder.

Reporting status

In general, 26.8% (n = 270) reported having a chronic condition (Table 1). Individual characteristics such as age, sex, disease group, and SES did not significantly differ between reporters and non-reporters (Table 1). Among specific disease groups, the percentage of reporters ranged from 23% (CHD) to 44% (nephrological conditions).

Differences in psychosocial wellbeing between reporters and non-reporters

Reporters demonstrated lower scores on all separate psychosocial wellbeing outcomes (p-values ranging from <0.001 to 0.009) compared to non-reporters (Table 2). To be more specific, reporters reported significantly lower life satisfaction (μ = 6.3, σ = 1.9) than non-reporters (μ = 7.0, σ = 1.7; p <0.001), poorer health (μ = 3.1, σ = 0.8) compared

to non-reporters (μ = 2.8, σ = 0.8; p <0.001), and lower levels of psychosomatic health (μ = 3.1, σ = 0.9) than non-reporters (μ = 3.3, σ = 0.9; p <0.001). In terms of health-related QoL, reporters scored lower at the total score and each individual subscale, compared to non-reporters (total score 62.8, σ = 18.4, compared to total score 70.5, σ = 16.3, p <0.001, for subscale details, refer to Table 2). Finally, reporters reported more anxiety (μ = 42.6, σ = 11.8) and depressive symptoms (μ = 54.4, σ = 13.9) compared to non-reporters (anxiety: μ = 40.2, σ = 9.9, p = 0.009; depressive symptoms: μ = 49.8, σ = 13.0, p < 0.001).

Relation between reporting status and psychosocial wellbeing across chronic conditions

When stratifying the analysis based on disease groups, similar results were observed among adolescents with an auto-immune disorder (n = 266) and a general pediatric condition (n = 574): reporters exhibited a lower psychosocial wellbeing in comparison to non-reporters (Supplement 2). No significant differences were found in the psychosocial wellbeing of reporters compared to non-reporters for adolescents with CF, CHD, and nephrological conditions.

Moderating effects of sex, age and SES on the association between reporting status and psychosocial wellbeing

The analyses exploring the moderating effects of demographic factors included main effects and interactions with moderators. Replicating the results of the direct comparisons, the main effects of reporters were negatively associated with psychosocial wellbeing, meaning that reporters had worse psychosocial wellbeing compared to non-reporters (Table 3). There was one exception: being an reporter was not associated with a higher degree of anxiety (p = 0.03), when was tested for moderating effect of sex on reporting status and anxiety symptoms. The main effect of sex was significant for all outcomes. Girls were more likely to experience worse psychosocial wellbeing than boys. The main effect age was only significant for the outcomes life satisfaction, self-rated health, and psychosomatic health, indicating that older adolescents had worse outcomes on these domains. No main effect for SES was found across all psychosocial wellbeing outcomes. In general, no moderating effects for sex, age, and SES were found. We found indications of an interaction between sex and reporting status on psychosomatic health (p = 0.03) and on depressive symptoms (p = 0.04), although those results did not survive correction for multiple comparisons.

Table 1: Baseline characteristics for study population and stratified by reporting status

Individual characteristics		Total		Reporters		Non-reporters		*p*-value
		n=1009		*n*=270		*n*=739		
Age at baseline	*n*=1009	15.4	±1.6	15.5	±1.6	15.3	±1.6	0.16
Sex	*n*=1002							0.40
Male		322	(32.1)	92	(34.2)	230	(31.4)	
Female		680	(67.9)	177	(65.8)	503	(68.6)	
Disease group								0.29
Auto-immune		266	(26.4)	72	(26.7)	194	(26.3)	
Cystic fibrosis		51	(5.1)	14	(5.2)	37	(5.0)	
Congenital heart disease		91	(9.0)	21	(7.8)	70	(9.5)	
General pediatric conditions		574	(57.0)	151	(55.9)	423	(57.2)	
Nephrological conditions		27	(2.7)	12	(4.4)	15	(2.0)	
Socioeconomic status [1]	*n*=975	0.1	±0.2	0.1	±0.2	0.1	±0.2	0.49

Data are presented as *n*, mean ± standard deviation or *n* (%). [1] Range -7.0 to 3.1.

Table 2: Differences in psychosocial wellbeing between reporters and non-reporters

Psychosocial wellbeing outcomes		Total		Reporters		Non-reporters		*p*-value
		n=1009		*n*=270		*n*=739		
Life satisfaction [range 1-10]	*n*=1009	6.8	±1.8	6.3	±1.9	7.0	±1.7	<0.001
Self-rated health [range 1-4]	*n*=1009	2.9	±1.6	3.1	±0.8	2.8	±0.8	<0.001
Psychosomatic health [range 1-5]	*n*=1009	3.3	±0.9	3.1	±0.9	3.3	±0.9	<0.001
Health-related QoL [range 1-100]	*n*=802	68.5	±17.2	62.8	±18.4	70.5	±16.3	<0.001
Physical		66.6	±23.5	59.2	±26.0	69.1	±22.1	<0.001
Emotional		68.8	±21.1	64.6	±21.1	70.3	±20.9	0.001
Social		79.7	±17.0	74.2	±19.6	81.6	±15.6	<0.001
School		60.0	±21.0	55.3	±21.4	61.7	±20.7	<0.001
Internalizing symptoms [t-score] [1]	*n*=932							
Anxiety symptoms		40.8	±10.5	42.6	±11.8	40.2	±9.9	0.009
Depressive symptoms		51.1	±13.4	54.4	±13.9	49.8	±13.0	<0.001

Data are presented as *n* or mean ± standard deviation. [1] Raw scores were converted to normative T-scores based on sex and age, where <65 = normal, 65-70 = borderline, >70 = clinical. QoL = Quality of Life.

Table 3: Moderating effects of sex, age and SES on the association between reporting status and psychosocial wellbeing

Sex					Age					SES				
Variables	**β**	**SE**	**95% CI**	**p**	**Variables**	**β**	**SE**	**95% CI**	**p**	**Variables**	**β**	**SE**	**95% CI**	**p**
Life satisfaction[1]														
Reporter	-0.65	0.15	(-0.94;-0.35)	<0.001	Reporter	-0.64	0.12	(-0.87;-0.40)	<0.001	Reporter	-0.68	0.12	(-0.92;-0.43)	<0.001
Sex*	0.64	0.08	(0.37;0.90)	<0.001	Age●	-0.30	0.06	(-0.43;-0.18)	<0.001	SES●	-0.01	0.06	(-0.14;0.12)	0.87
Interaction	-0.11	0.26	(-0.62;0.39)	0.66	Interaction	0.06	0.12	(-0.18;0.30)	0.66	Interaction	0.09	0.12	(-0.16;0.33)	0.49
Self-rated health[2]														
Reporter	0.37	0.07	(0.22;0.51)	<0.001	Reporter	0.36	0.06	(0.24;0.47)	<0.001	Reporter	0.39	0.06	(0.27;0.50)	<0.001
Sex*	-0.38	0.07	(-0.51;-0.25)	<0.001	Age●	0.15	0.03	(0.09;0.21)	<0.001	SES●	-0.006	0.03	(-0.07;0.06)	0.85
Interaction	0.04	0.12	(-0.20;0.29)	0.74	Interaction	0.02	0.06	(-0.09;0.14)	0.71	Interaction	0.02	0.06	(-0.10;0.13)	0.81
Psychosomatic health[3]														
Reporter	-0.21	0.07	(-0.36;-0.06)	0.005	Reporter	-0.27	0.06	(-0.40;-0.15)	<0.001	Reporter	-0.30	0.06	(-0.43;-0.17)	<0.001
Sex*	0.63	0.07	(0.49;0.76)	<0.001	Age●	-0.11	0.03	(-0.17;-0.05)	0.001	SES●	0.009	0.03	(-0.06;0.07)	0.79
Interaction	-0.28	0.13	(-0.54;-0.03)	0.03	Interaction	0.02	0.06	(-0.10;0.15)	0.73	Interaction	0.02	0.06	(-0.10;0.15)	0.71
Health-related QoL[4]														
Reporter	-7.06	1.65	(-10.29;-3.83)	<0.001	Reporter	-7.62	1.36	(-10.28;-4.95)	<0.001	Reporter	-7.59	1.38	(-10.30;-4.88)	<0.001
Sex*	9.68	1.43	(6.87;12.48)	<0.001	Age●	-0.69	0.67	(-2.01;0.64)	0.31	SES●	-0.16	0.71	(-1.54;1.22)	0.82
Interaction	-2.45	2.77	(-7.89;2.99)	0.38	Interaction	-0.31	1.35	(-2.96;2.34)	0.82	Interaction	1.32	1.40	(-1.43;4.07)	0.35
Anxiety symptoms[5]														
Reporter	1.96	0.93	(0.14;3.77)	0.03	Reporter	2.38	0.77	(0.86;3.89)	0.002	Reporter	2.42	0.78	(0.89;3.94)	0.002
Sex*	-4.37	0.85	(-6.05;-2.70)	<0.001	Age●	0.22	0.40	(-0.57;1.01)	0.59	SES●	0.76	0.41	(-0.04;1.55)	0.06
Interaction	1.63	1.61	(-1.53;4.78)	0.31	Interaction	-0.08	0.78	(-1.61;1.45)	0.92	Interaction	-0.01	0.77	(-1.52;1.50)	0.99
Depressive symptoms[6]														
Reporter	3.28	1.17	(0.98;5.57)	0.005	Reporter	4.49	0.98	(2.57;6.40)	<0.001	Reporter	4.69	0.99	(2.75;6.62)	<0.001
Sex*	-6.25	1.08	(-8.36;-4.14)	<0.001	Age●	0.10	0.51	(-0.90;1.10)	0.85	SES●	0.57	0.51	(-0.43;1.58)	0.27
Interaction	4.13	2.03	(0.15;8.12)	0.04	Interaction	0.16	0.99	(-1.78;2.10)	0.87	Interaction	-0.75	0.98	(-2.66;1.16)	0.44

β = unstandardized β; 95% CI = 95% confidence intervals; SE = standard error; SES = socioeconomic status. *Estimate for male, reference is female. ●Z-score is used, when this Z-score is used in the independent variable, it is also used in the interaction term; [1] Higher score indicated better life satisfaction; [2]Lower score indicated better self-rated health; [3] Higher score indicated better psychosomatic health; [4]Higher score indicated better quality of life; [5]Higher score indicated more anxiety symptoms; [6]Higher score indicated more depressive symptoms.

DISCUSSION

The present study aimed to investigate differences in psychosocial wellbeing among adolescents with a physician diagnosed chronic condition who self-report or do not self-report having a chronic condition. Out of the 1009 included adolescents with a clinical diagnosis, 270 (26.7%) were reporters. Our findings revealed that reporters had significantly worse outcomes in all psychosocial domains assessed. When stratified by disease group, reporters with general pediatric conditions or with an auto-immune disease indicated a significantly lower psychosocial wellbeing than non-reporters. No significant differences between reporters and non-reporters were found for the adolescents with CF, a CHD, and a nephrological condition. In general, no clear moderating effects of sex, age, or SES, on the relationship between reporting status and psychosocial wellbeing, were identified.

This study confirmed that reporting is associated with impaired psychosocial wellbeing, consistent with previous population studies, while also extending their findings by incorporating medical data from the study population [1]. Interestingly, the majority (73.2%) of adolescents with a physician diagnosed chronic condition did not self-report having a chronic condition. The percentage of self-reporters varied among disease groups, ranging from 23% (CHD) to 44% (nephrological conditions). Several hypotheses can be proposed regarding factors that might influence reporting status. First of all, reporters may experience more severe disease symptoms. Moreover, the extent to which one reports having a chronic condition might be associated with the degree of perceived burden, irrespective of the disease severity. Furthermore, environmental factors, including parents and friends, can influence adolescents' self-reporting of chronic conditions. Factors such as disease knowledge, awareness, conversations about the illness, and social stigma or acceptance within one's social circles have been found significant in the context of self-report [30–32]. Lastly, illness identity – how individuals construct or reestablish a new sense of self, wherein the condition becomes integrated in their identity- might also have influenced the decision to report having a chronic condition [33,34]. The PROactive cohort structure with preset questionnaires limits detailed examination of these specific concepts related to self-report, marking this study as an initial exploration and emphasizing the need for more comprehensive research.

The negative correlation between reporting and psychosocial wellbeing prompts inquiry. The hypotheses regarding self-report of a chronic condition could also be relevant here. Factors such as increased disease severity, higher perceived burden, heightened stigmatization, and negative illness identities may contribute to lower psychosocial wellbeing. It is, for instance, recognized that individuals who share similar experiences may interpret or evaluate those experiences differently [35,36]. The level of *perceived* burden influences subsequent stress responses [37,38]. Furthermore, psychosocial wellbeing and

reporting status could also be related with how adolescents evaluate their overall health. In a previous study, children defined health as 'feeling good about yourself' and 'being able to participate'. Through interviews, six domains of health were identified, each with various related aspects: body, feelings and thoughts, now and in the future, feeling good about yourself, participation, and daily life [39]. This aligns with the contemporary societal perspective on health, characterized by a shift from a disease-centric perspective to a broader, more all-encompassing approach to health with an increased emphasis on self-management and the ability to adapt [40]. It is conceivable that non-reporting in our study reflects perceived control over other health domains irrespective of the condition – and is thus also related with better psychosocial wellbeing overall.

To gain a deeper understanding of the relationship between the medical diagnosis of a chronic condition, reporting status and psychosocial wellbeing, further exploration involving larger sample sizes including diverse disease groups with corresponding severity measures is essential. The complex interplay among individual characteristics, environmental factors, and the broader healthcare system demands additional in-depth research. Capturing this complexity might pose a challenge for quantitative studies alone, underscoring the potential utility of a mixed-methods approach. Enhancing our understanding in this area will contribute to shifting the healthcare professionals' focus towards a more patient-centered model of care with a broader perspective on health, moving beyond traditional disease-centered paradigms.

In the present study, we evaluated a comprehensive sample drawn from a large academic pediatric hospital in the Netherlands, encompassing adolescents with diverse disease types. Owing to the known medical information, we were able to further illuminate the previously delineated discrepancies between the prevalence of physician diagnosed and self-reported chronic conditions. Several limitations of this study warrant acknowledgment. First, the cross-sectional design precludes causal inferences between reporting status and psychosocial wellbeing. Additionally, the representativeness of the PROactive cohort may be limited due to the recruitment of patients from an academic hospital, characterized by specific diagnoses, post-establishment of chronic disease diagnosis, and a relatively elevated SES in contrast to the broader population. Besides that, the proportion of patients with a general pediatric condition, a heterogeneous group, adds complexity to our findings. However, the diversity in disease types, age, and sex within the sample may mitigate this limitation to some extent. Lastly, the neighborhood-based SES measure might not fully reflect individual socio-economic nuances.

CONCLUSION

This study revealed that only a minority of adolescents with a physician diagnosed chronic condition self-report as having a chronic disease. Reporters indicated a lower psychosocial wellbeing, a pattern that seems to hold across some, but not all, disease groups. The findings of this study underscore the need to adopt a multidimensional healthcare perspective that emphasizes the transition from a disease-centric toward a more individual-centric approach.

REFERENCES

1. Berkelbach van der Sprenkel EE, Nijhof SL, Dalmeijer GW, et al. Psychosocial functioning in adolescents growing up with chronic disease: The Dutch HBSC study. *Eur J Pediatr*. 2022;181(2):763-773. doi:10.1007/s00431-021-04268-9
2. Pinquart M, Shen Y. Behavior Problems in Children and Adolescents With Chronic Physical Illness: A Meta-Analysis. *J Pediatr Psychol*. 2011;36(9):1003-1016. doi:10.1093/jpepsy/jsr042
3. Spencer NJ, Blackburn CM, Read JM. Disabling chronic conditions in childhood and socioeconomic disadvantage: a systematic review and meta-analyses of observational studies. *BMJ Open*. 2015;5(9):e007062. doi:10.1136/bmjopen-2014-007062
4. Suris JC, Michaud PA, Viner R. The adolescent with a chronic condition. Part I: developmental issues. *Arch Dis Child*. 2004;89(10):938-942. doi:10.1136/adc.2003.045369
5. Van Cleave J. Dynamics of Obesity and Chronic Health Conditions Among Children and Youth. *JAMA*. 2010;303(7):623. doi:10.1001/jama.2010.104
6. van Hal L, Tierolf B, van Rooijen M, van der Hoff M. *Een Actueel Perspectief Op Kinderen En Jongeren Met Een Chronische Aandoening in Nederland. Omvang , Samenstelling En Participatie*.; 2019.
7. Maurice-Stam H, Nijhof SL, Monninkhof AS, Heymans HSA, Grootenhuis MA. Review about the impact of growing up with a chronic disease showed delays achieving psychosocial milestones. *Acta Paediatrica, International Journal of Paediatrics*. 2019;108(12):2157-2169. doi:10.1111/apa.14918
8. Mokkink LB, Van Der Lee JH, Grootenhuis MA, Offringa M, Van Praag BMS, Heymans HSA. Omvang en gevolgen van chronische aandoeningen bij kinderen. *Tijdschr Kindergeneeskd*. 2007;75(4):138-142. doi:10.1007/bf03061684
9. Nap-van Der Vlist MM, Hoefnagels JW, Dalmeijer GW, et al. The PROactive cohort study: rationale, design, and study procedures. *Eur J Epidemiol*. 2022;37:993-1002.
10. Nijhof SL, van de Putte EM, Hoefnagels JW. PROactive Cohort Study. DataverseNL. Published 2021. Accessed November 10, 2022. https://dataverse.nl/dataset.xhtml?persistentId=doi:10.34894/FXUGHW
11. Stevens G, Dorsselaer S Van, Boer M, et al. *HBSC 2017*.; 2017.
12. Szkultecka-Dębek M, Dzielska A, Drozd M, Małkowska-Szkutnik A, Mazur J. What does the Cantril Ladder measure in adolescence? *Archives of Medical Science*. 2018;14(1):182-189. doi:10.5114/aoms.2016.60718
13. Cantril H. *The Pattern of Human Concern*. Rutgers University press; 1965. https://ia801900.us.archive.org/27/items/in.ernet.dli.2015.139016/2015.139016.The-Pattern-Of-Human-Concerns.pdf
14. Schnohr CW, Gobina I, Santos T, et al. Semantics bias in cross-national comparative analyses: Is it good or bad to have "fair" health? *Health Qual Life Outcomes*. 2016;14(1). doi:10.1186/s12955-016-0469-8
15. Ravens-Sieberer U, Erhart M, Torsheim T, et al. An international scoring system for self-reported health complaints in adolescents. *Eur J Public Health*. 2008;18(3):294-299. doi:10.1093/eurpub/ckn001
16. Engelen V, Haentjes MM, Detmar SB, Koopman HM, Grootenhuis MA. Health related quality of life of Dutch children: psychometric properties of the PedsQL in the Netherlands. *BMC Pediatr*. 2009;9(68).
17. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
18. Levin KA, Currie C. Reliability and Validity of an Adapted Version of the Cantril Ladder for Use with Adolescent Samples. *Soc Indic Res*. 2014;119(2):1047-1063. doi:10.1007/s11205-013-0507-4
19. Szkultecka-Dębek M, Dzielska A, Drozd M, Małkowska-Szkutnik A, Mazur J. What does the Cantril Ladder measure in adolescence? *Archives of Medical Science*. 2018;14(1):182-189. doi:10.5114/aoms.2016.60718
20. Cantril H. *The Pattern of Human Concern*. Rutgers University press; 1965.
21. Idler EL, Benyamini Y. *Self-Rated Health and Mortality: A Review of Twenty-Seven Community Studies*. Vol 38.; 1997.
22. Benjamins MR, Hummer RA, Eberstein IW, Nam CB. Self-reported health and adult mortality risk: An analysis of cause-specific mortality. *Soc Sci Med*. 2004;59(6):1297-1306. doi:10.1016/j.socscimed.2003.01.001

23. Erhart M, Ottova V, Gaspar T, et al. Measuring mental health and well-being of school-children in 15 European countries using the KIDSCREEN-10 Index. *Int J Public Health*. 2009;54(SUPPL. 2):160-166. doi:10.1007/s00038-009-5407-7
24. Ravens-Sieberer U, Erhart M, Torsheim T, et al. An international scoring system for self-reported health complaints in adolescents. *Eur J Public Health*. 2008;18(3):294-299. doi:10.1093/eurpub/ckn001
25. Engelen V, Haentjes MM, Detmar SB, Koopman HM, Grootenhuis MA. Health related quality of life of Dutch children: psychometric properties of the PedsQL in the Netherlands. *BMC Pediatr*. 2009;9(68).
26. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
27. Revised Children's Anxiety and Depression Scale (and Subscales) (RCADS). Accessed November 24, 2023. https://www.corc.uk.net/outcome-experience-measures/revised-childrens-anxiety-and-depression-scale-rcads/
28. Centraal Bureau voor de Statistiek. Sociaal-economische status per postcode, 2019. CBS. Published July 1, 2022. Accessed July 14, 2023. https://www.cbs.nl/nl-nl/maatwerk/2022/26/sociaal-economische-status-per-postcode-2019
29. Centraal Bureau voor de Statistiek. SES-WOA scores per wijk en buurt. CBS.nl. Published 2023. Accessed July 14, 2023. https://www.cbs.nl/nl-nl/onze-diensten/methoden/onderzoeksomschrijvingen/korte-onderzoeksomschrijvingen/ses-woa-scores-per-wijk-en-buurt
30. Pathmalingam T, Moola FJ, Woodgate RL. Illness conversations: Self-disclosure among children and youth with chronic illnesses. *Chronic Illn*. 2023;19(3):475-494. doi:10.1177/17423953221110152
31. Caqueo-Urízar A, Urzúa A, Villalonga-Olives E, et al. Children's Mental Health: Discrepancy between Child Self-Reporting and Parental Reporting. *Behavioral Sciences*. 2022;12(10):401. doi:10.3390/bs12100401
32. Whitmore C, Markle-Reid M, McAiney C, Fisher K, Ploeg J. How do individual, social, environmental, and resilience factors shape self-reported health among community-dwelling older adults: a qualitative case study. *BMC Geriatr*. 2023;23(1):8. doi:10.1186/s12877-023-03726-3
33. Leventhal H, Idler EL, Leventhal EA. The impact of chronic illness on the self system. In: *Self, Social Identity, and Physical Health*. Vol 2. Ocford University Press; 1999:185-208.
34. Charmaz K. The Body, Identity, and Self: Adapting To Impairment. *Sociol Q*. 1995;36(4):657-680. doi:10.1111/j.1533-8525.1995.tb00459.x
35. Rutter M. Resilience in the face of adversity: protective factors and resistance to psychiatric disorders. *British Journal of Psychiatry*. 1985;147:598-611. doi:10.1192/bjp.147.6.598
36. Rutter M. Resilience as a dynamic concept. *Dev Psychopathol*. 2012;24(2):335-344. doi:10.1017/S0954579412000028
37. van Wingen GA, Geuze E, Vermetten E, Fernández G. Perceived threat predicts the neural sequelae of combat stress. *Mol Psychiatry*. 2011;16(6):664-671. doi:10.1038/mp.2010.132
38. van Harmelen AL, Kievit RA, Ioannidis K, Al E. Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychol Med*. 2017;47(13):2312-2322. doi:10.1017/S0033291717000836
39. de Jong-Witjes S, Kars MC, van Vliet M, et al. Development of the My Positive Health dialogue tool for children: a qualitative study on children's views of health. *BMJ Paediatr Open*. 2022;6(1):e001373. doi:10.1136/bmjpo-2021-001373
40. Huber M, Knottnerus JA, Green L, et al. How should we define health? *BMJ*. 2011;343. doi:10.1136/bmj.d4163

SUPPLEMENT 1:

Correlations between the domains of psychosocial wellbeing

Correlations		PedsQL, total score	PedsQL, subscale physical funct.	PedsQL, subscale emotional funct.	PedsQL, subscale social funct.	PedsQL, subscale school funct.	RCADS, depression score	RCADS, total anxiety score	Cantril ladder, life satisfaction	Self-rated health	HBSC-SCL, Psychosomatic health
PedsQL, total score	Spearman's rho	1									
	Sig. (2-tailed)										
	n	802									
PedsQL, subscale physical funct.	Spearman's rho	.89	1								
	Sig. (2-tailed)	<0.001									
	n	802	802								
PedsQL, subscale emotional funct.	Spearman's rho	.75	.50	1							
	Sig. (2-tailed)	<0.001	<0.001								
	n	802	802	802							
PedsQL, subscale social funct.	Spearman's rho	.78	.63	.52	1						
	Sig. (2-tailed)	<0.001	<0.001	<0.001							
	n	802	802	802	802						
PedsQL, subscale school funct.	Spearman's rho	.78	.56	.56	.51	1					
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001						
	n	802	802	802	802	802					
RCADS, the major depressive disorder score	Spearman's rho	-.77	-.61	-.74	-.55	-.66	1				
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001					
	n	755	755	755	755	755	932				

Correlations between the domains of psychosocial wellbeing (continued)

Correlations		PedsQL, total score	PedsQL, subscale physical funct.	PedsQL, subscale emotional funct.	PedsQL, subscale social funct.	PedsQL, subscale school funct.	RCADS, depression score	RCADS, total anxiety score	Cantril ladder, life satisfaction	Self-rated health	HBSC-SCL, Psychosomatic health
RCADS, total anxiety score	Spearman's rho	-.50	-.30	-.68	-.39	-.41	.68	1			
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001				
	n	755	755	755	755	755	932	932			
Cantril ladder, life satisfaction	Spearman's rho	.59	.47	.54	.48	.48	-.62	-.39	1		
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001			
	n	802	802	802	802	802	938	938	1009		
Self-rated health	Spearman's rho	-.67	-.65	-.43	-.50	-.54	.57	.27	-.55	1	
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		
	n	802	802	802	802	802	938	938	1009	1009	
HBSC-SCL, Psychosomatic health	Spearman's rho	.72	.59	.68	.46	.63	-.79	-.48	.56	-.56	1
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
	n	802	802	802	802	802	938	938	1009	1009	1009

Funct.=functioning; PedsQL = Pediatric Quality of Life Inventory; Sig.=significance; RCADS = Revised Child Anxiety and Depression Scale; HBSC-SCL = Health Behaviour in School-aged Children Symptom Checklist.

SUPPLEMENT 2:

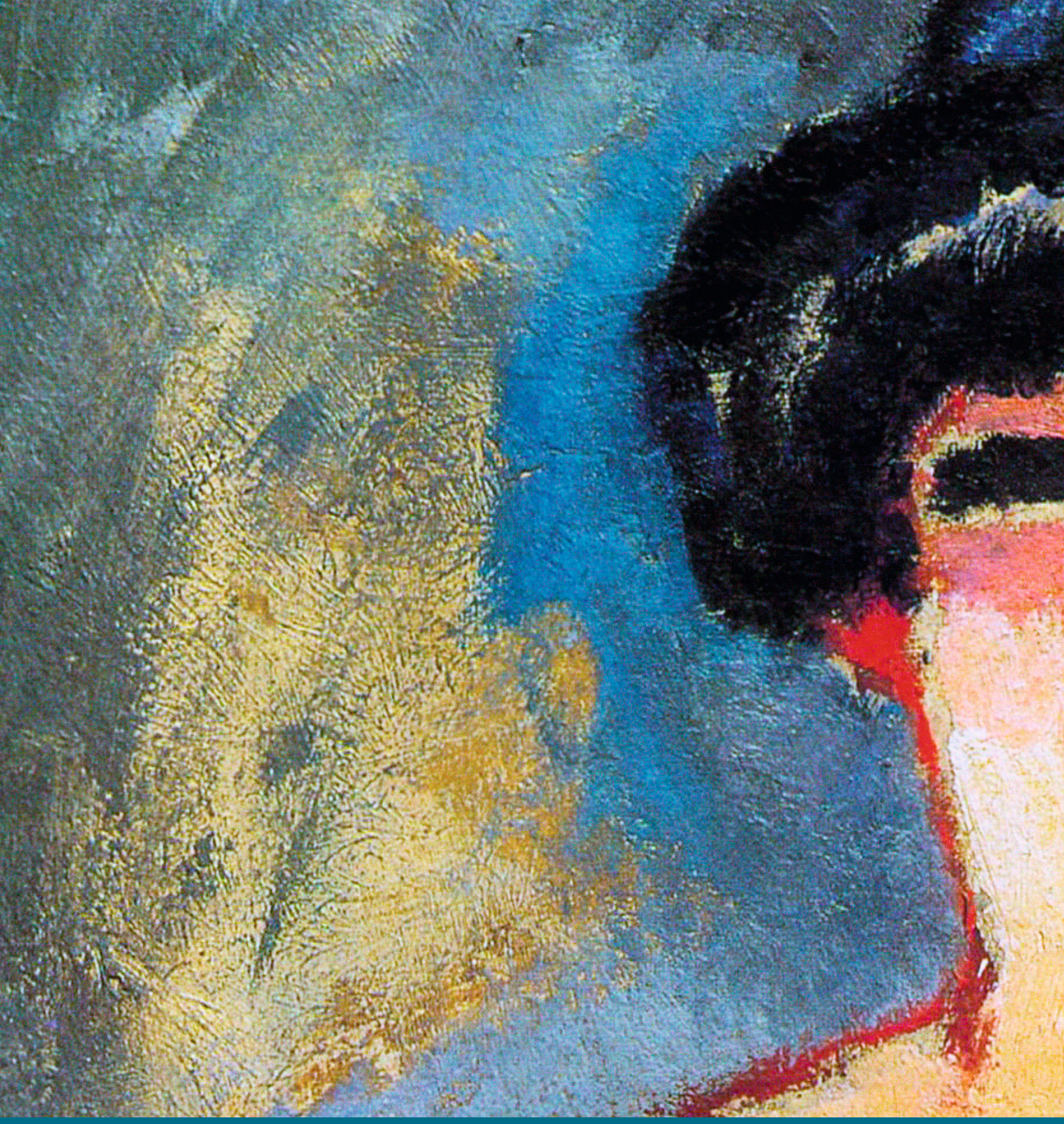
Psychosocial functioning per disease group, stratified by identification status

Auto-immune disease	**Total**		**Reporters**		**Non-reporters**		***p***
	***n*=266**		***n*=72**		***n*=194**		
Life satisfaction [range 1-10]	7.3	±1.6	7.0	±1.7	7.5	±1.5	0.02
Self-rated health [range 1-4]	2.5	±0.8	2.8	±0.8	2.4	±0.8	<0.001
Psychosomatic health [range 1-5]	3.7	±0.9	3.4	±1.0	3.9	±0.8	<0.001
Health-related QoL, total [range 1-100]	76.6	±15.6	71.2	±17.4	78.4	±14.6	0.002
Physical	76.3	±20.4	71.1	±20.4	78.1	±20.2	0.01
Emotional	75.8	±20.0	69.2	±23.0	78.0	±18.5	0.01
Social	84.9	±16.2	80.0	±19.5	86.5	±14.7	0.03
School	69.6	±18.9	64.6	±20.8	71.2	±18.0	0.02
Internalizing symptoms [t-score] [1]							
Anxiety symptoms	38.9	±10.3	43.2	±13.8	37.3	±8.0	0.004
Depressive symptoms	45.0	±12.3	50.4	±16.1	42.8	±9.7	0.001
Cystic Fibrosis	**Total**		**Reporters**		**Non-reporters**		***p***
	***n*=51**		***n*=14**		***n*=37**		
Life satisfaction [range 1-10]	7.4	±1.6	7.5	±1.3	7.4	±1.7	0.81
Self-rated health [range 1-4]	2.5	±0.8	2.3	±0.8	2.5	±0.8	0.54
Psychosomatic health [range 1-5]	3.9	±0.7	3.6	±0.7	4.0	±0.7	0.12
Health-related QoL, total [range 1-100]	77.0	±15.3	76.8	±15.6	77.1	±15.4	0.96
Physical	78.6	±19.4	80.1	±18.7	78.1	±19.8	0.78
Emotional	74.8	±20.5	72.7	±21.4	75.6	±20.4	0.59
Social	86.7	±14.2	89.2	±15.9	85.8	±13.7	0.25
School	67.0	±17.0	63.5	±17.6	68.8	±16.8	0.38
Internalizing symptoms [t-score] [1]							
Anxiety symptoms	38.2	±9.2	41.2	±9.9	36.9	±8.7	0.18
Depressive symptoms	44.9	±10.7	47.1	±9.4	44.0	±11.2	0.27
Congenital heart disease	**Total**		**Reporters**		**Non-reporters** ***n*=70**		***p***
	***n*=91**		***n*=21**				
Life satisfaction [range 1-10]	7.4	±1.4	7.1	±1.0	7.5	±1.4	0.34
Self-rated health [range 1-4]	2.2	±0.7	2.4	±0.6	2.1	±0.7	0.17
Psychosomatic health [range 1-5]	3.8	±0.8	3.6	±0.9	3.9	±0.7	0.14
Health-related QoL, total [range 1-100]	77.0	±12.7	70.4	±15.1	78.7	±11.5	0.03
Physical	77.8	±19.8	67.3	±24.6	80.5	±17.7	0.06
Emotional	74.9	±17.4	72.7	±16.8	75.5	±17.6	0.58

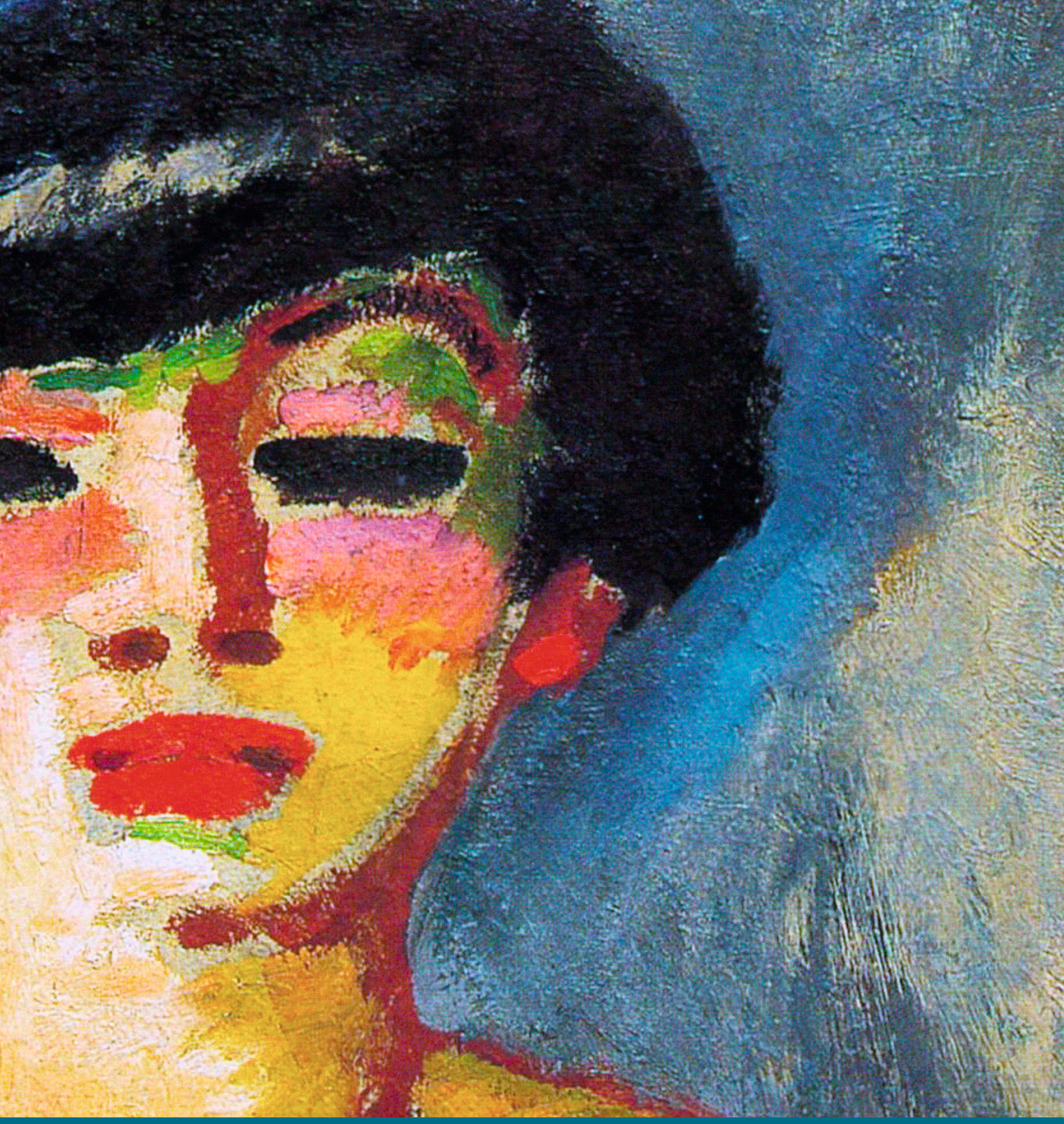
Psychosocial functioning per disease group, stratified by identification status (continued)

Social	82.5	±16.0	75.4	±18.7	84.3	±14.9	0.11
School	72.3	±16.4	68.1	±12.2	73.4	±17.5	0.30
Internalizing symptoms [t-score] [1]							
Anxiety symptoms	40.0	±9.0	40.8	±8.9	39.8	±9.1	0.63
Depressive symptoms	44.2	±11.1	45.4	±10.6	43.8	±11.3	0.39
Nephrological conditions	**Total**		**Reporters**		**Non-reporters**		***p***
	***n*=27**		***n*=12**		***n*=15**		
Life satisfaction [range 1-10]	7.8	±1.4	7.3	±1.6	8.3	±1.0	0.05
Self-rated health [range 1-4]	2.3	±0.7	2.4	±0.8	2.2	±0.7	0.45
Psychosomatic health [range 1-5]	3.9	±0.9	3.8	±1.0	4.1	±0.8	0.43
Health-related QoL, total [range 1-100]	82.8	±15.7	80.0	±16.2	85.3	±15.5	0.43
Physical	86.1	±17.6	85.8	±14.0	86.5	±21.0	0.49
Emotional	79.6	±18.3	76.4	±19.3	82.5	±17.8	0.38
Social	87.0	±17.0	81.4	±19.8	92.1	±12.9	0.12
School	76.5	±20.8	73.2	±22.5	79.6	±19.6	0.47
Internalizing symptoms [t-score] [1]							
Anxiety symptoms	37.2	±9.5	39.1	±9.4	35.7	±9.7	0.13
Depressive symptoms	39.7	±9.5	42.8	±11.9	37.2	±6.5	0.14
General pediatric conditions	**Total**		**Reporters**		**Non-reporters**		***p***
	***n*=574**		***n*=151**		***n*=423**		
Life satisfaction [range 1-10]	6.3	±1.8	5.7	±1.9	6.6	±1.7	<0.001
Self-rated health [range 1-4]	3.2	±0.7	3.5	±0.6	3.1	±0.7	<0.001
Psychosomatic health [range 1-5]	2.9	±0.7	2.7	±0.7	2.9	±0.7	0.003
Health-related QoL, total [range 1-100]	61.3	±15.4	54.3	±15.1	63.6	±14.7	<0.001
Physical	57.4	±22.3	47.2	±23.9	60.9	±20.6	<0.001
Emotional	62.9	±20.6	59.2	±19.4	64.2	±20.9	0.24
Social	75.4	±16.7	68.6	±18.3	77.8	±15.5	<0.001
School	51.5	±19.2	46.4	±18.7	53.3	±19.1	0.001
Internalizing symptoms [t-score] [1]							
Anxiety symptoms	42.1	±10.8	42.9	±11.5	41.8	±10.5	0.38
Depressive symptoms	55.6	±12.5	58.6	±12.0	54.5	±12.6	<0.001

Data are presented as *n* or mean ± standard deviation. [1] Raw scores were converted to normative T-scores based on sex and age, where <65 = normal, 65-70 = borderline, >70 = clinical.



PART II



RESILIENCE IN THE FACE OF THE CORONAVIRUS DISEASE 2019 (COVID-19) PANDEMIC

CHAPTER 7

GENDER-SPECIFIC CHANGES IN LIFE SATISFACTION AFTER THE COVID-19–RELATED LOCKDOWN IN DUTCH ADOLESCENTS:

A LONGITUDINAL STUDY

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ABSTRACT

Purpose

The purposes of this study were to assess whether mental wellbeing has changed after introduction of the lockdown measures compared with that before, whether this change differs between boys and girls, and whether this change is associated with COVID-19–related concerns.

Methods

This is a two-wave prospective study among Dutch adolescents using data collected up to one year before the COVID-19 pandemic (n = 224) and 5–8 weeks after the first introduction of lockdown measures (n = 158). Mental wellbeing was assessed by three indicators: life satisfaction, internalizing symptoms, and psychosomatic health. General linear model repeated-measures analysis of variance was used to assess whether mental wellbeing has changed and if this differed by sex. Univariate linear regressions were used to assess associations between COVID-19–related concerns and a change in mental wellbeing.

Results

Life satisfaction decreased (η^2_p = 0.079, p<0.001), but no change in internalizing symptoms was observed (η^2_p = 0.014, p=0.14), and psychosomatic health increased (η^2_p = 0.194, p<0.001) after the introduction of lockdown measures. Boys scored significantly better on all mental health indicators compared to girls at baseline and follow-up. However, boys' life satisfaction significantly decreased at follow-up (η^2_p = 0.038, p=0.015), whereas girls' life satisfaction did not change. Concerns about COVID-19 were significantly associated with a lower life satisfaction and more internalizing symptoms.

Conclusions

Adolescents', especially boys', life satisfaction decreased during the lockdown. They reported no change in internalizing symptoms and an improved psychosomatic health. Adolescents' mental wellbeing is expected to vary during the COVID-19 pandemic and should continue to be monitored.

INTRODUCTION

The coronavirus disease (COVID-19) outbreak rapidly progressed to a pandemic, affecting most countries globally [1]. Governments are implementing strict measures to control the spread of the virus that is responsible for this pandemic. Due to lockdown measures, such as school closures, quarantine and social distancing, millions of people worldwide face unprecedented periods of social isolation and stress [1]. Many families and children in particular are affected in multiple ways; school closures disrupt daily life structure and social interaction of all affected children and adolescents, and may lead to parents having to combine home schooling and work at the same time [2]. Recent narrative reviews and reports highlight the need for empirical research focusing on the effect of the pandemic on mental wellbeing in youth [3–6].

Adolescence is a key developmental time period marked by rapid neurocognitive and social developmental changes, as well as the first emergence of numerous mental health disorders [7–10]. During the adolescent years, young people spend increasingly more time with their peers, friendships grow stronger, and young people are more influenced by peers than adults [9,11,12]. Over these years, friendships are instrumental aspects of adolescent mental health and wellbeing [13]. Therefore, adolescents may be particularly susceptible to the social effects of lockdown measures. Indeed, scholars have warned that the pandemic could lead to a lower life satisfaction, increased stress, and mental health disorders in adolescents [14,15]. So far, several empirical articles have been published on various indicators of mental wellbeing in adolescents.

Studies, conducted in China and the Netherlands, reported a high prevalence of anxiety and depressive symptoms among children and adolescents (age range 8-18 years), especially girls, during the pandemic [16–18]. However, the above studies used cross-sectional designs and as such cannot disentangle whether the high prevalence of these symptoms is the effect of the pandemic. Longitudinal data with baseline measures assessed prior to COVID-19 are required to better understand the isolated, potentially causal, effects of lockdown measures on mental wellbeing in young people [3–6,19]. Several longitudinal studies reported on adolescent mental wellbeing in response to COVID-19 lockdown measures and found that anxiety and depressive symptoms increased in youth living in The Netherlands, Australia and North-America [20–23], and life satisfaction deteriorated during the first full lockdown in youth (8-18 years) living in Australia and North-America [20–22]. These negative changes in mental wellbeing were more pronounced in girls compared to boys [21]. A large international collaborative effort using data of twelve longitudinal studies (ten performed in the USA, one in the Netherlands, and one in Peru) identified an increase in depressive symptoms in adolescents (mean age 15.4 years) [24]. Although most countries have been affected by this COVID-19 pandemic, all national governments have implemented their own set of restriction measures to stop the spread of the virus. It is yet unknown whether

the above findings are generalizable to other populations and, whether Dutch adolescents show a similar change in mental wellbeing after introduction of the lockdown measures.

Therefore, this two-wave prospective study among Dutch adolescents aimed to assess whether mental wellbeing changed after the introduction of lockdown measures by comparing mental wellbeing assessed up to one year prior to COVID-19 (baseline; *n*=224) with that measured between 5-8 weeks after the first introduction of lockdown measures (follow-up; *n*=158); whether changes differed between boys and girls; and whether changes were associated with adolescents' concerns about COVID-19 and lockdown measures. Based on the current literature we expected that adolescent mental wellbeing would decrease after introduction of lockdown measures compared to before the pandemic.

METHODS

Study design and study population

Baseline; up to a year before the COVID-19 pandemic

Data were obtained from an ongoing population-based birth cohort study in the Netherlands, named WHISTLER. The original aim of WHISTLER was to investigate determinants for wheezing illnesses [25]. Between 2001 and 2012 newborns were recruited from the general population (n=2,456 at baseline) in a fairly affluent, and newly built suburb of Utrecht, the Netherlands. The participants have been followed at age of 3, 5 and 8 years, and over the years not only determinants of wheezing illnesses were researched but also many other topics. In March 2019, we invited the 12-16 year old WHISTLER participants to complete a questionnaire and undergo a health assessment. One of the primary aims was to assess their mental wellbeing during adolescence. Due to the start of the COVID-19 pandemic, we had to stop this follow-up round, but up to then 224 adolescents completed the questionnaires (52.7% girls, mean age (SD) 14.82 (1.24) years). Ethical approval for WHISTLER (file number: NL66918.041.18) was obtained from the Medical Ethics Review Committee of the University Medical Center Utrecht. Participants and their parents or legal guardians provided active written informed consent.

Follow-up: 5-8 weeks after introduction of lockdown measures

In the Netherlands, the first COVID-19 confirmed patient was diagnosed February 27, 2020, and starting on March 15 a partial lockdown was enforced, meaning closure of school and child care facilities (except for children of parent(s) with a profession classified as essential), as well as sport clubs, bars and restaurants. In contrast to many other Western countries, Dutch citizens were allowed to receive up to three visitors, to go outside (without proof of the essentiality to go outdoors), and children were allowed to play outside without social distancing. On May 11, primary schools partially reopened and on June 2 secondary schools followed [26].

To indicate the stringency of the Dutch lockdown measures in comparison with other lockdowns, we used the Oxford COVID-19 Government Response Tracker (OxCGRT) to establish a lockdown stringency index of the Dutch lockdowns based on composite measure of nine different lockdown measures. The index has values ranging from 0 to 100 (100 = strictest) [27]. This stringency index has been available from 1 January 2020, and identified that the stringency of the Dutch lockdown was 78.70 around April 2020.The 224 adolescents were invited to complete a follow-up questionnaire, regarding mental wellbeing and adolescents' concerns about COVID-19 and lockdown measures. We sent the questionnaires on April 18 (5 weeks after introduction of lockdown measures) and the participants were able to complete the questionnaire until May 8.

The vast majority of adolescents completed the baseline questionnaire well ahead of the start of the pandemic: the mean time between baseline and follow-up assessment was 227 days (range 46-405 days). A few adolescents completed the questionnaire 1.5 months before the start of the pandemic and at that point of time COVID-19 did not have a major impact on daily life in the Netherlands as the first Dutch case of COVID-19 was identified on February 27, 2020 (17 days before the start of the pandemic).

Mental wellbeing, measured at baseline and follow-up

In the WHISTLER cohort, mental wellbeing was assessed using three indicators: life satisfaction, internalizing symptoms, and psychosomatic health using the Cantril ladder [28,29], the Revised Child Anxiety and Depression Scale (RCADS) [30], and Health Behavior in School-aged Children Symptom Checklist (HBSC-SCL) 2017 [31], respectively. To investigate whether mental wellbeing changed from baseline to follow-up, we assessed the same instruments at follow-up. The specifics of these measures are described in short below; refer to Supplement 1 for full details about the instruments' content, subscales, items, values and Cronbach's alpha.

Life satisfaction was assessed with the Cantril ladder, a validated and reliable instrument to measure life satisfaction in adolescence [32–37]. The Cantril ladder includes one question "Looking at the past 3 months, how do you feel about your life?" and adolescents answered this question on a scale from 0 to 10 (10 = best possible life) [32–37]. The Cantril ladder is shown to be valid and reliable in adolescents [36,37].

The RCADS is used to assess the severity of self-reported anxiety and depressive symptoms based on selected Diagnostic and Statistical Manual of Mental Disorders-IV anxiety disorders and depression, using multiple subdomains [30]. As in our study the correlation between the subdomains 'anxiety' and 'major depressive disorder' was r>0.7, we choose to analyze these subdomains together as internalizing symptoms. Raw scores were converted into gender and age-normed T-scores and evaluated as a continuous score.

Psychosomatic health complaints are symptoms that are often related to psychosocial factors, such as stress [38]. Psychosomatic health was measured with the Health Behavior in School-aged Children Symptom Checklist (HBSC-SCL) 2017 [31]. Psychosomatic health is expressed in the mean score of all 10 symptoms, such as having a headache, being nervous, or feeling dizzy. The higher the mean score, the better psychosomatic health one is experiencing meaning that one is feeling little stress. The HBSC-SCL has good psychometric properties and has also been validated in Dutch [39–41].

Although some questions/symptoms seem to overlap between psychosomatic health and internalizing symptoms, we are measuring two different constructs. Internalizing symptoms were measured by the RCADS, a validated scale based on the DSM criteria of anxiety and depressive symptoms. Stress, indicated as a low psychosomatic health, could be associated with (and might lead to) anxiety and depressive symptoms, however, it could also stand on itself. Moreover, sometimes adolescents experience stress not on a mental level but only on a physical level (being dizzy, having a stomachache, or having a headache). Therefore, it is of relevance to measure both internalizing symptoms and psychosomatic health.

Concerns about COVID-19 and lockdown measures, measured at follow-up.
At follow-up, we assessed adolescents' concerns about COVID-19 and lockdown measures using a Dutch translation of the COVID-19 Adolescent Symptom & Psychological Experience (CASPE) Questionnaire developed by Ladouceur (2020) (concept version April 1, 2020, see Supplement 2) [42].

The CASPE Questionnaire included 16 items about COVID-19 and lockdown measures-related concerns, such as: "I might get sick", "people might die if they get sick", "parents might lose their job", and "not going to school". A 5-point Likert scale was used to measure the extent of concern: 1) 'very little or not at all', 2) 'a little', 3) 'some', 4) 'a lot' or 5) 'a great deal'. As these 16-items are not yet validated, we used factor analysis to explore whether there were underlying factors that explained variance across sets of items. To do so, we used exploratory factor analyses using orthogonal rotation (varimax). Based on Kaiser's criterion of >1 and the scree plot, we retained four factors. Factor 1 explained 14.9% of variance across 4 items that represented 'concerns about health'. Factor 2 explained 12.6% of variance across 6 items representing 'concerns about social consequences of lockdown measures'. Factor 3 explained 6.7% of variance across 3 items that represented 'concerns about financial matters'. Finally, factor 4 explained 5.8% of variance across 3 items representing 'concerns about family relations'. The factor loadings are shown in Supplement 3. The Pearson correlation between the four factors ranged between the 0.012-0.200, indicating that all factors measure a different construct.

Statistical analyses

We used descriptive statistics to summarize the characteristics of the study population at baseline (N=224) and follow-up (N=158).

To assess whether mental wellbeing changed after the introduction of the lockdown measures and whether this change differed between boys and girls, we used a general linear model (GLM) repeated measures analysis of variance (RMANOVA) for each mental wellbeing indicator separately. We specified wellbeing at baseline and follow-up as a repeated measure, and gender as predictor. We further specified a gender*time interaction term. We used partial eta squared (η^2_p) as measure of effect size. Additionally, McNemar's Chi-squared tests were used to analyze whether the frequency of occurrence of psychosomatic symptoms differed between baseline and follow-up.

To assess whether a change in mental wellbeing was associated with adolescents' concerns about COVID-19 and lockdown measures, we conducted linear regressions with each mental wellbeing indicator assessed after the introduction of the lockdown measures as a dependent variable and one of the four factors, derived from the factor analysis, as an independent variable. We performed these univariate linear regressions on all four factors. Associations were expressed as differences (βs), and adjusted for the mental wellbeing indicator score as assessed before the pandemic and gender.

A p-value <0.05 was considered statistically significant. All analyses were done with SPSS 25.0.

RESULTS

Study population

In total, 158 adolescents (n_{girls}=94, mean age (SD) 15.53 (1.25) years), representing 70.5% of the 224 baseline participants, also completed the questionnaire at follow-up (see Table 1 and Figure 1). Adolescents that were willing to complete the follow-up questionnaire were not different from those that were not with respect to the distribution of age (p=0.354), ethnicity (p=0.421) and educational level (p=0.566). However, more girls were willing to complete the follow-up questionnaire. Of these 158 adolescents, 96.2% has a Western ethnicity, and 93.04% of the adolescents has a parent with a high or intermediate level of education.

Table 1: Demographics of the study population completing questionnaire before the COVID-19 pandemic and after introduction of lockdown measures

Demographics	*Before*	*(n=224)*	*After*	*(n=158)*
Age in years, mean (SD)	14.82	(1.24)	15.53*	(1.25)
Gender (%)				
· Girl	118	(52.68)	94	(59.49)
*Educational level of the adolescent** (%)*				
· Primary school	3	(1.34)	2	(1.26)
· Low	52	(23.21)	34	(21.52)
· Intermediate	63	(28.13)	39	(24.68)
· High	101	(45.09)	79	(50.00)
· Special education	8	(3.57)	4	(2.53)

*calculated based on completion date of follow-up questionnaire
**low: pre-vocational secondary education; intermediate: higher general secondary education or intermediate vocational education; high: pre-university education, higher vocational education and university

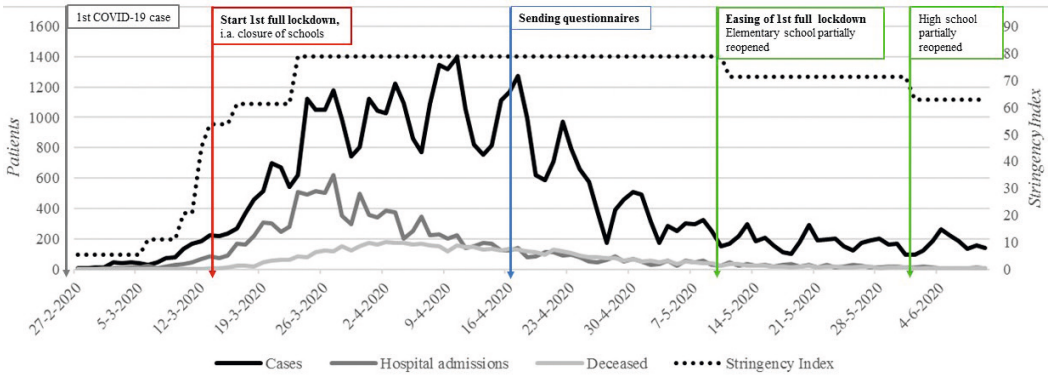

Figure 1: Prevalence of COVID-19 confirmed cases, hospital admissions, and deaths, stringency index, and specific time points of the current study.

Life satisfaction

At follow-up, life satisfaction decreased ($F(1,153)=13.195$, $p<0.001$, $\eta^2_p=0.079$) after the introduction of lockdown measures when compared to baseline assessments (Table 2). There was a significant main effect of gender on life satisfaction ($F(1,153)=22.187$, $p<0.001$, $\eta^2_p=0.127$), such that boys had a significantly higher life satisfaction both at baseline and follow-up compared to girls. Moreover, there was a significant interaction between gender and time since lockdown onset on life satisfaction $F(1,153)=6.034$, $p=0.015$, $\eta^2_p=0.038$), meaning that boys' life satisfaction decreased at follow up compared to their baseline life satisfaction, while the girls' life satisfaction did not significantly change over time (Figure 2).

The factor 'concerned about social consequences of lockdown measures' was significantly associated with a lower life satisfaction (adjusted β:-0.25, 95% CI: -0.43;-0.06, p=0.01) (Table 3). The factors 'concerns about health' (adjusted β:-0.04, 95% CI: -0.23;0.14, p=0.64), 'concerns about financial matters (adjusted β: -0.02, 95% CI: -0.23;0.19, p=0.86) and 'concerns about family relations' (adjusted β:-0.15, 95% CI: -0.37;0.08, p=0.21) were not significantly associated with a lower life satisfaction.

Internalizing symptoms

At follow-up, the adolescents did not report more internalizing symptoms (F(1,151)=2.152, p=0.144, η^2_p=0.014) after the introduction of lockdown measures when compared to baseline assessments (Table 2). There was a significant main effect of gender on internalizing symptoms (F(1,153)=12.486, p=0.001, η^2_p=0.127), meaning that boys had significantly less internalizing symptoms when compared to girls, both at baseline and follow-up. No significant interaction between gender and time of assessment on internalizing symptoms F(1,153)=0.018, p=0.573, η^2_p=0.002) was observed (Figure 2).

The factors 'concerns about health' (adjusted β:1.93, 95% CI: 0.53;3.33, p=0.01), 'concerns about social consequences of lockdown measures' (adjusted β: 2.39, 95% CI: 0.96;3.81, p=0.001), and 'concerns about family relations' (adjusted β:2.41, 95% CI: 0.73;4.08, p=0.01) were associated with more internalizing symptoms. The factor 'financial matters' was not associated with more internalizing symptoms (adjusted β:-0.74, 95% CI: -2.47;0.99, p=0.40) (Table 3).

Psychosomatic health

At follow-up, our sample reported significantly better psychosomatic health (F(1,152) =36.544, p<0.001, η^2_p=0.194) after the introduction of lockdown measures when compared to baseline assessments (Table 2). There was a significant main effect of gender on psychosomatic health (F(1,152)=16.405, p<0.001, η^2_p=0.097), with boys displaying significantly better psychosomatic health than girls, both at baseline and follow-up. There was no significant interaction between gender and time of assessment F(1,152)=0.100, p=0.752, η^2_p=0.001) on psychosomatic health (Figure 2).

Contrary to our expectations, psychosomatic health improved over time, and therefore, in an exploratory analysis, we assessed changes in specific psychosomatic symptoms (Supplement 4). Adolescents were able to fall asleep more easily (41.52% vs 20.25%,p<0.01) during the lockdown compared to before the pandemic. .

None of the factors were associated with a worse psychosomatic health ('concerns about health' (adjusted β:-0.04, 95% CI: -0.12;0.04, p=0.30), 'concerns about social consequences of lockdown (adjusted β:-0.08, 95% CI: -0.17;0.00, p=0.06), 'concerns about financial matters (adjusted β: 0.08, 95% CI: -0.01;0.17, p=0.09), 'concerns about family relations' (adjusted β:0.01, 95% CI: -0.09;0.11, p=0.88)) (Table 3).

Table 2: Change in mental wellbeing after introduction of lockdown measures compared with before the pandemic and differences between boys and girls in change of mental wellbeing

Mental wellbeing	**Before the pandemic n=224**		**After introduction lockdown measures n=158**		**Main effect of time**		**Main effect of gender**		**Main effect of interaction gender*time**	
					F	**η^2_p**	**F**	**η^2_p**	**F**	**η^2_p**
Life satisfaction[+] mean (SD), range 0-10	7.62	(1.19)	7.15	(1.08)	13.195	0.079***	22.187	0.127***	6.034	0.038*
Internalizing symptoms[++] mean (SD), range 0-141	40.28	(9.72)	41.77	(10.29)	2.152	0.014	12.486	0.076***	0.018	0.002
Psychosomatic health [+++] mean (SD), range 0-5	3.91	(0.67)	4.14	(0.66)	36.544	0.194***	16.405	0.097***	0.100	0.001

*$p<0.05$; **$p\leq0.01$: ***$p\leq0.001$.
+ a higher score indicates a higher life satisfaction; [++]a higher score more severe self-reported internalizing symptoms; [+++]a higher score indicates experiencing psychosomatic complaints less frequently.

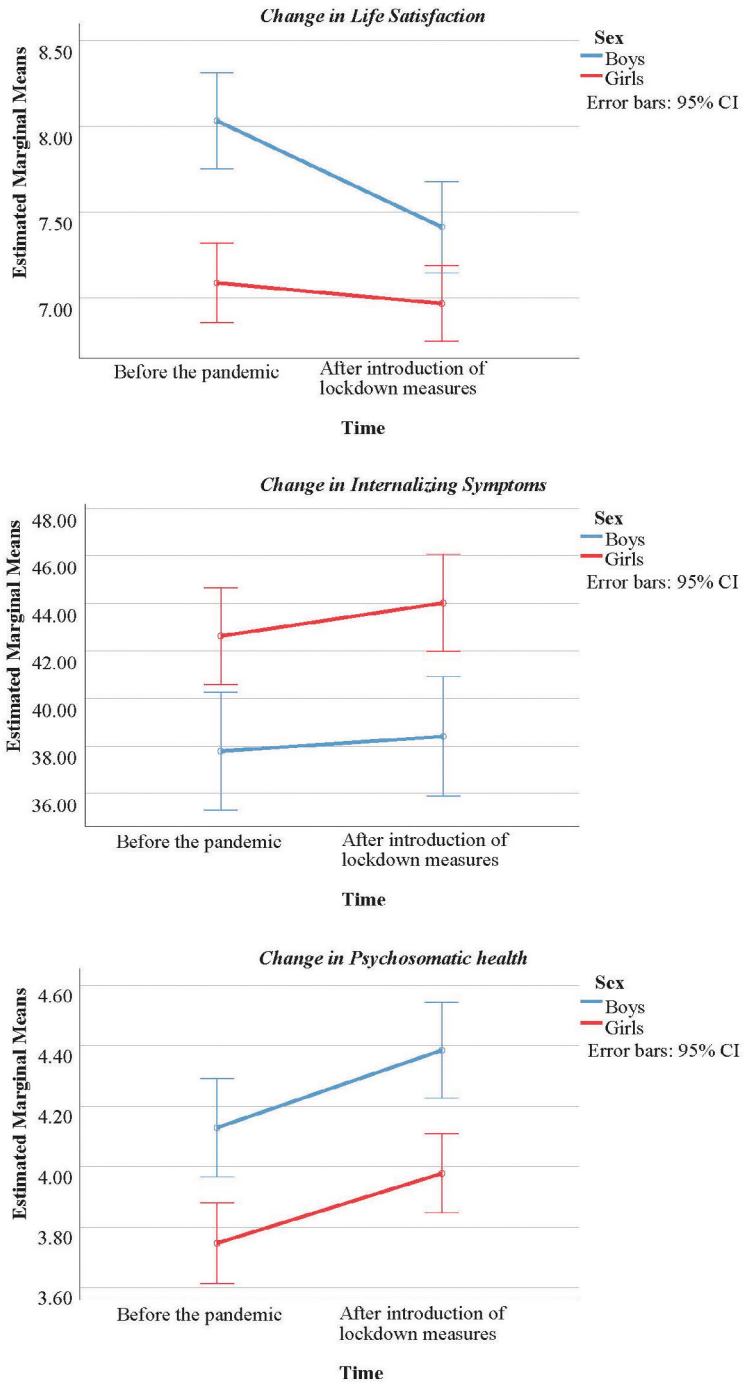

Figure 2: Changes in mental wellbeing after introduction of the lockdown measures compared to before the pandemic.

Table 3: Changes in mental wellbeing indicators associated with concerns related to COVID-19 and lockdown measures

Life satisfaction+	***Factors, concerns about:***	**Crude β**	**(95% CI)**	**p**	**Adj. β***	**(95% CI)**	**p**
	Health	-0.02	(-0.21;0.18)	0.88	-0.04	(-0.23;0.14)	0.64
	Social consequences of lockdown measures	**-0.25**	**(-0.45;-0.05)**	**0.02**	**-0.25**	**(-0.43;-0.06)**	**0.01**
	Financial matters	-0.12	(-0.35;0.10)	0.29	-0.02	(-0.23;0.19)	0.86
	Family relations	-0.21	(-0.45;0.03)	0.09	-0.15	(-0.37;0.08)	0.21
Internalizing symptoms++	***Factors, concerns about:***	**Crude β**	**(95% CI)**	**p**	**Adj. β***	**(95% CI)**	**p**
	Health	**2.54**	**(0.67;4.41)**	**0.01**	**1.93**	**(0.53;3.33)**	**0.01**
	Social consequences of lockdown measures	**4.41**	**(2.32;5.93)**	**<0.001**	**2.39**	**(0.96;3.81)**	**0.001**
	Financial matters	-0.26	(-2.57;2.05)	0.82	-0.74	(-2.47;0.99)	0.40
	Family relations	**2.36**	**(0.08;4.63)**	**0.04**	**2.41**	**(0.73;4.08)**	**0.01**
Psychosomatic health+++	***Factors, concerns about:***	**Crude β**	**(95% CI)**	**p**	**Adj. β***	**(95% CI)**	**p**
	Health	-0.05	(-0.17;0.07)	0.39	-0.04	(-0.12;0.04)	0.30
	Social consequences of lockdown measures	**-0.17**	**(-0.29;-0.06)**	**0.01**	-0.08	(-0.17;0.00)	0.06
	Financial matters	0.02	(-0.11;0.16)	0.73	0.08	(-0.01;0.17)	0.09
	Family relations	-0.05	(-020;0.10)	0.52	0.01	(-0.09;0.11)	0.88

*adjusted for life satisfaction before the pandemic, gender, age, and level of education of the adolescent
+ a higher score indicates a higher life satisfaction; ++a higher score more severe self-reported internalizing symptoms; +++ a higher score indicates experiencing psychosomatic complaints less frequently.
Significant associations in **bold**.

DISCUSSION

Main results

In this two-wave prospective study among adolescents, we investigated whether adolescent mental wellbeing changed after the introduction of lockdown measures, whether changes differed between boys and girls, and whether changes were associated with adolescents' concerns about the COVID-19 and lockdown measures. At 5-8 weeks following the introduction of the lockdown measures in the Netherlands, life satisfaction decreased compared to baseline (up to one year before the COVID-19 pandemic), but internalizing symptoms did not change. Contrary to expectations, our study sample reported an improved psychosomatic health at follow-up, when compared to baseline. Boys scored better on all three mental health indicators compared to girls both at baseline and follow-up. However, boys' life satisfaction significantly decreased over time, whereas girls' life satisfaction did not change. Adolescents' concerns about COVID-19 and the lockdown measures were significantly associated with lower life satisfaction and more internalizing symptoms.

Results in the context of previous literature

Life satisfaction during COVID-19-related lockdown restrictions decreased (stringency index: 78.80), which is in line with two longitudinal studies reporting that life satisfaction of Australian adolescents decreased during the pandemic compared to before (stringency index: 65.74 - 69.44) [20,21]. It should be noted that the findings could be specific for adolescents, as a decline in life satisfaction was not observed in younger children (aged 8-10 years, stringency index: 50.46-65-74) living in South Korea nor in Chinese youth (aged 6-17 years) (stringency index: 79.17-81.02) [43,44]. In contrast to life satisfaction, there was no change in internalizing symptoms observed in our sample. However, a high prevalence of anxiety and depressive symptoms was observed among Chinese adolescents (12-18 years old) [16,17] during the pandemic (stringency index: 56.94-81.02). Similarly, a Dutch sample (aged 8-18 years) reported more anxiety and depressive symptoms during the pandemic (stringency index:78.80) than a similar sample of children and adolescents in 2017-2018 [18]. Dutch adolescents and young adults (10-25 years old) experienced higher depression levels during the pandemic (stringency index: 78.70-65.74) compared to younger adolescents [23]. Moreover, Australian youth (8-18 years old) (stringency index: 65.74 - 69.44) and adolescents (aged 14-17) living in the USA (stringency index: 67.13-72.69) reported more anxiety and depressive symptoms in the initial phase of the pandemic than before [21,22,45]. Additionally, Barendse et al. (2021) found an increase in depressive symptoms in an international sample of adolescents (mean age 15.4 years) during the pandemic compared to before, especially for biracial/multiracial adolescents [24]. There might be several explanations for the differences in observations. First, the some of the above described studies used cross-sectional designs [16–18] or did not have any pre-pandemic measures [23], and as such these studies cannot speak to potentially causal, effects

of lockdown measures: the high prevalence of anxiety and depressive symptoms could be pre-existing. Second, although all children and adolescents were encouraged to stay at home, the social distancing rules have been differently applied to youth between countries. For instance, Dutch youth younger than 18 years old, and youth younger than 16 years old living in the United Kingdom did not have to comply to social distancing rules [46,47]. This is in contrast to e.g. Australia and China, where social distancing rules were applied to all children [48,49]. Third, there might be a difference in experienced loneliness between the different study populations in the above mentioned studies. Luchetti et al. examined COVID-19-related effects on loneliness in the USA and reported that, although people were physically isolated as a consequence of the social distancing measures, there was no increase in loneliness in the first 4-8 weeks after implementation of lockdown measures [50]. Feeling socially supported might have acted as a protective factor against internalizing symptoms, because friendship quality aids resilient functioning in adolescence and could therefore be a protective factor [13,50,51]. Due to the lack of sufficient data, we were not able to test this suggestion in our sample. Therefore, future research could examine whether friendship interactions and/or social support remained comparable at follow-up as before and whether this acted as protective factor on internalizing symptoms. Moreover, it is conceivable that loneliness increases as the pandemic continues. Therefore, future research might also focus on the role of loneliness on internalizing symptoms during this pandemic.

Interestingly, the COVID-19 pandemic might even have a positive effect on adolescents' mental wellbeing as our study found that adolescents had a better psychosomatic health during the COVID-19-related lockdown compared to before the pandemic. Specifically, on average, our sample was able to fall asleep more easily. During puberty, hormonal changes alter the homeostatic and circadian regulation of sleep with the result that adolescents tend to stay up and sleep in later [52]. This altered sleep rhythm often conflicts with early school start times. At the time of completing the questionnaires, schools in the Netherlands were closed and the majority of adolescents attended their classes online. It is conceivable that this allowed our sample of adolescents to stay up late and sleep in, resulting in a better alignment of their sleep-wake behavior with their circadian rhythm. Both Munasinghe et al. and Orgilés et al. also reported that youth more often slept eight hours or longer during the COVID-19-related lockdown when compared to their rhythms prior to the pandemic [20,53]. In pre-pandemic studies it is shown that particularly for adolescents, chronic sleep loss is a common phenomenon. Sleep deprivation might lead to a lower mental and physical health, and therewith represents an important health risk [54–57]. Studies showed that delaying school start times lead to better alignment of circadian system and therefore result in better sleep quantity and quality. Moreover, delaying school start times is associated with less mental health issues, better physical health, and higher academic performances [54,55,58–60]. As multiple studies, including this current study, showed that adolescents' sleep improved [20,53] during the pandemic probably due to

a better alignment of their sleep-wake behavior with their circadian rhythm, national governments may consider possibilities that could enhance this alignment, e.g. by delaying school start times.

Mental wellbeing change differed between boys and girls. Although boys scored better on all three mental wellbeing indicators compared to girls, their life satisfaction decreased whereas girls' life satisfaction did not significantly change. Our findings are in line with those that show that adolescent girls, on average, have lower mental wellbeing than boys [7]. However, Magson et al. reported that a decline of life satisfaction in adolescents (aged 13-16 years) during the pandemic was particularly pronounced in girls [21]. There might be multiple explanations why boys' life satisfaction decreased, about which we can only speculate. For instance, boys are more likely to hang out in groups, whereas girls tend to spend more time in friendship dyads [61,62]. The lockdown measures discouraged group gatherings which might affected boys' life satisfaction more than girls' life satisfaction. Moreover, adolescent girls might have more tools to cope with lockdown measures and the pandemic as girls are more likely to ask for help, have more positive connections to their parents, and communicate more than boys [63]. Future research could focus on why gender matters when it comes to changes in life satisfaction during this pandemic.

In summary, the findings of this study provide a nuanced picture of the mental health of adolescents. On the one hand, on average, adolescents were doing quite well during first lockdown during the pandemic suggesting that adolescents are coping resiliently with this crisis. The unexpected positive change in psychosomatic health could be a lead for national governments to create possibilities that could encourage this positive change also post-pandemic. On the other hand, we also observed a negative changes in life satisfaction among boys but not girls. Future studies might examine whether our results are also generalizable to adolescents with different ethnic backgrounds, other socioeconomic status, or chronically ill adolescents. Adolescents' mental wellbeing and concerns are expected to continue to vary during the COVID-19 pandemic and should continue to be monitored.

Strengths and limitations

An important strength of this study was that we benefitted from a prospective design where we were able to compare mental wellbeing up to one year before the onset of pandemic with mental wellbeing about 5-8 weeks after the introduction of lockdown measures within the same adolescents. Moreover, we assessed multiple indicators of mental wellbeing. There are also some limitations. The participants of the WHISTLER birth cohort were recruited from the general population [25] living in a fairly affluent, and newly build suburb of Utrecht, the Netherlands. As a result, this sample is not completely representative of the general Dutch adolescent population as adolescents with parents with a lower educational background and a non-Western migration background were

underrepresented. This implies that our results may not be generalizable to populations with different educational, ethnic and/or cultural backgrounds. Data on mental wellbeing before the lockdown was collected between March 2019 and March 2020, whereas all included participants were invited to complete the follow-up questionnaire on April 18th 2020. Consequently, not only the time between baseline and follow-up assessment, but also the timing (during summer holiday versus during a stressful school week) of the baseline assessment varied between the adolescents. This could have affected our results in such a way that although a change in mental wellbeing was reported, it might not have been the effect of COVID-19-related lockdown measures. In cohort studies, loss-to-follow-up is a common phenomenon which can lead to attrition bias. In this study, no difference with respect to the distribution of age, ethnicity, educational level, internalizing symptoms and psychosomatic health were observed between the participants that completed the follow-up questionnaire compared to adolescents that did not. However, girls were more willing to complete the follow-up questionnaire compared to boys. Additionally, girls who completed the follow-up questionnaire at baseline reported a lower life satisfaction compared to girls who did not. In this study, no significant change in life satisfaction in girls was observed. If all girls had completed the follow-up questionnaire, it is likely that the change in life satisfaction in girls would have become even smaller (and still not significant). Therefore, this attrition is unlikely to have biased our results.

CONCLUSION

This study yielded an interesting picture on changes in adolescent mental wellbeing. Adolescents' life satisfaction decreased after introduction of lockdown measures compared to before the pandemic, especially in boys. However, no change in internalizing symptoms was reported. Yet, adolescents experienced a better psychosomatic health, potentially driven by falling asleep more easily during the pandemic compared to before.

REFERENCES

1. World Health Organisation. Q&A on coronaviruses (COVID-19). World Health Organization. Published 2020. Accessed March 27, 2020. www.who.int
2. Fegert JM, Vitiello B, Plener PL, Clemens V. Challenges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: a narrative review to highlight clinical and research needs in the acute phase and the long return to normality. *Child and Adolescent Psychiatry and Mental Health*. 2020;14(1):1-11. doi:10.1186/s13034-020-00329-3
3. The Alliance For Child Protection In Humanitarian. *Technical Note : Protection of Children during the Corona Pandemic*.; 2020.
4. Liu JJ, Bao Y, Huang X, Shi J, Lu J. Mental health considerations for children quarantined because of COVID-19. *The Lancet*. 2020;4(20):347-349. doi:10.1016/S2352-4642(20)30096-1
5. Fegert JM, Vitiello B, Plener PL, Clemens V. Challenges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: a narrative review to highlight clinical and research needs in the acute phase and the long return to normality. *Child Adolesc Psychiatry Ment Health*. 2020;14(1):1-11. doi:10.1186/s13034-020-00329-3
6. Golberstein E, Gonzales G, Meara E. How do economic downturns affect the mental health of children? Evidence from the National Health Interview Survey. *Health Economics (United Kingdom)*. 2019;28(8):955-970. doi:10.1002/hec.3885
7. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet*. 2012;379:1056-1067. doi:10.1016/S0140-6736(11)60871-4.Depression
8. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of. *Arch Gen Psychiatry*. 2005;62(June):593-602. doi:10.1001/archpsyc.62.6.593
9. Blakemore SJ, Mills KL. Is Adolescence a Sensitive Period for Sociocultural Processing? *Annual Review of Psychology*. 2014;65(1):187-207. doi:10.1146/annurev-psych-010213-115202
10. Blakemore S jayne. The art of medicine Adolescence and mental health. *The Lancet*. 2019;393(10185):2030-2031. doi:10.1016/S0140-6736(19)31013-X
11. Knoll LJ, Magis-Weinberg L, Speekenbrink M, Blakemore SJ. Social Influence on Risk Perception During Adolescence. *Psychological Science*. 2015;26(5):583-592. doi:10.1177/0956797615569578
12. Burnett Heyes S, Jih YR, Block P, Hiu CF, Holmes EA, Lau JYF. Relationship Reciprocation Modulates Resource Allocation in Adolescent Social Networks: Developmental Effects. *Child Development*. 2015;86(5):1489-1506. doi:10.1111/cdev.12396
13. van Harmelen AL, Kievit RA, Ioannidis K, Al E. Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychological medicine*. 2017;47(13):2312-2322.
14. Orben A, Tomova L, Blakemore S jayne. The effects of social deprivation on adolescent development and mental health. *Lancet Child Adolesc Health*. 2020;4:634-640.
15. Golberstein E, Wen H, Pilgrim H. Coronavirus Disease 2019 (COVID-19) and Mental Health for Children and Adolescents. 2020;2019:2019-2020. doi:10.1002/hec.3885
16. Chen F, Zheng D, Gong JL, Guan Z, Lou D. Depression and anxiety among adolescents during COVID-19 : A cross-sectional study. *Brain , Behavior , and Immunity*. 2020;88(May):36-38. doi:10.1016/j.bbi.2020.05.061
17. Zhou SJ, Zhang LG, Wang LL, et al. Prevalence and socio demographic correlates of psychological health problems in Chinese adolescents during the outbreak of COVID 19. *European Child & Adolescent Psychiatry*. 2020;29(6):749-758. doi:10.1007/s00787-020-01541-4
18. Luijten MAJ, Muilekom MM Van, Teela L, et al. The impact of lockdown during the COVID-19 pandemic on mental and social health of children and adolescents. *preprint*. Published online 2020.
19. Wade M, Prime H, Browne D. Why we need longitudinal mental health research with children and youth during (and after) the COVID-19 pandemic. *Psychiatry Research*. 2020;(January):19-21.
20. Munasinghe S, Sperandei S, Ph D, et al. The Impact of Physical Distancing Policies During the COVID-19 Pandemic on Health and Well-Being Among Australian Adolescents. *Journal of Adolescent Health*. 2020;67(5):653-661. doi:10.1016/j.jadohealth.2020.08.008
21. Magson NR, Fardouly J, Freeman JYA, Rapee RM, Richardson CE, Oar EL. Risk and Protective Factors for Prospective Changes in Adolescent Mental Health during the COVID-19 Pandemic. *Journal of Youth and Adolescence*. Published online 2020. doi:10.1007/s10964-020-01332-9

22. Breaux R, Dvorsky MR, Marsh NP, et al. Prospective impact of COVID-19 on mental health functioning in adolescents with and without ADHD: protective role of emotion regulation abilities. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. Published online 2021. doi:10.1111/jcpp.13382
23. Green KH, van de Groep S, Sweijen SW, et al. Mood and emotional reactivity of adolescents during the COVID-19 pandemic: short-term and long-term effects and the impact of social and socioeconomic stressors. *Scientific reports*. 2021;11(1):11563. doi:10.1038/s41598-021-90851-x
24. Barendse M, Flannery J, Cavanagh C, Aristizabal M, et al. Longitudinal change in adolescent depression and anxiety symptoms from before to during the COVID-19 pandemic: An international collaborative of 12 samples. *preprint*. 2021;1(2):7-8.
25. Katier N, Uiterwaal CSPM, De Jong BM, et al. The Wheezing Illnesses Study Leidsche Rijn (WHISTLER): Rationale and design. *European Journal of Epidemiology*. 2004;19(9):895-903. doi:10.1023/B:EJEP.0000040530.98310.0c
26. Wesbite Government of the Netherlands.
27. Hale T, Angrist N, Goldszmidt R, et al. A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). *Nature Human Behaviour*. 2021;5(4):529-538. doi:10.1038/s41562-021-01079-8
28. Szkultecka-Dębek M, Dzielska A, Drozd M, Małkowska-Szkutnik A, Mazur J. What does the Cantril Ladder measure in adolescence? *Archives of Medical Science*. 2018;14(1):182-189. doi:10.5114/aoms.2016.60718
29. Cantril H. *The Pattern of Human Concern*. Rutgers University press; 1965.
30. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
31. Ravens-Sieberer U, Erhart M, Torsheim T, et al. An international scoring system for self-reported health complaints in adolescents. *European journal of public health*. 2008;18(3):294-299. doi:10.1093/eurpub/ckn001
32. World Health Organization. Inequalities in Young People's Health. *World Health*. 2006;(5):1-224.
33. Ravens-Sieberer U, Torsheim T, Hetland J, et al. Subjective health, symptom load and quality of life of children and adolescents in Europe. *International Journal of Public Health*. 2009;54. doi:10.1007/s00038-009-5406-8
34. Cavallo F, Dalmasso P, Ottová-Jordan V, et al. Trends in life satisfaction in European and North-American adolescents from 2002 to 2010 in over 30 countries. *European Journal of Public Health*. 2015;25:80-82. doi:10.1093/eurpub/ckv014
35. Health Behaviour in School-aged Children. About HBSC. http://www.hbsc.org/about/index.html. http://www.hbsc.org/about/index.html
36. Levin KA, Currie C. Reliability and Validity of an Adapted Version of the Cantril Ladder for Use with Adolescent Samples. *Soc Indic Res*. 2014;119(2):1047-1063. doi:10.1007/s11205-013-0507-4
37. Szkultecka-Dębek M, Dzielska A, Drozd M, Małkowska-Szkutnik A, Mazur J. What does the Cantril Ladder measure in adolescence? *Archives of Medical Science*. 2018;14(1):182-189. doi:10.5114/aoms.2016.60718
38. Greene JW, Walker LS. Psychosomatic problems and stress in adolescence. *Pediatric Clinics of North America*. 1997;44(6):1557-1572. doi:10.1016/S0031-3955(05)70574-5
39. Erhart M, Ottova V, Gaspar T, et al. Measuring mental health and well-being of school-children in 15 European countries using the KIDSCREEN-10 Index. *Int J Public Health*. 2009;54(SUPPL. 2):160-166. doi:10.1007/s00038-009-5407-7
40. Ravens-Sieberer U, Erhart M, Torsheim T, et al. An international scoring system for self-reported health complaints in adolescents. *Eur J Public Health*. 2008;18(3):294-299. doi:10.1093/eurpub/ckn001
41. Kösters MP, Chinapaw MJM, Zwaanswijk M, van der Wal MF, Koot HM. Structure, reliability, and validity of the revised child anxiety and depression scale (RCADS) in a multi-ethnic urban sample of Dutch children. *BMC Psychiatry*. 2015;15(1):1-8. doi:10.1186/s12888-015-0509-7
42. Ladouceur LD. COVID-19 Adolescent Symptom & Psychological Experience (CASPE). OSFHOME. Published 2020. Accessed April 2, 2020. https://osf.io/mzrjg/
43. Choi J, Park Y, Kim HE, et al. Daily life changes and life satisfaction among korean school-aged children in the covid-19 pandemic. *International Journal of Environmental Research and Public Health*. 2021;18(6). doi:10.3390/ijerph18063324
44. Tang S, Xiang M, Cheung T, Xiang YT. Mental health and its correlates among children and adolescents during COVID-19 school closure: The importance of parent-child discussion. *Journal of Affective Disorders*. 2021;279(October 2020):353-360. doi:10.1016/j.jad.2020.10.016

45. Rogers AA, Ha T, Ockey S. Adolescents' Perceived Socio-Emotional Impact of COVID-19 and Implications for Mental Health: Results From a U.S.-Based Mixed-Methods Study. *Journal of Adolescent Health*. 2021;68(1):43-52. doi:10.1016/j.jadohealth.2020.09.039
46. Rijksoverheid. Corona en regels voor afstand houden. rijksoverheid.nl. Published 2020. Accessed June 17, 2021. https://www.rijksoverheid.nl/onderwerpen/coronavirus-covid-19/algemene-coronaregels/regels-voor-afstand-houden
47. bbc. What are the social distancing rules and when could they end? bbc.com. Published 2021. Accessed June 17, 2021. https://www.bbc.com/news/uk-51506729
48. Jiang E. Chinese children must wear "one-metre hats" to keep social distancing in class as they return to school after a three-month coronavirus lockdown. *Mailonline*. Published online April 2020.
49. Health AGD of. Australian Health Protection Principal Committee (AHPPC) coronavirus (COVID-19) statement on 17 March 2020. health.gov.au. Published 2020. Accessed June 17, 2021. https://www.health.gov.au/news/australian-health-protection-principal-committee-ahppc-coronavirus-covid-19-statement-on-17-march-2020-0
50. Luchetti M, Lee JH, Aschwanden D, et al. The Trajectory of Loneliness in Response to COVID-19. 2020;75(7):897-908.
51. van Harmelen AL, Blakemore SJ, Goodyer IM, Kievit RA. The Interplay Between Adolescent Friendship Quality and Resilient Functioning Following Childhood and Adolescent Adversity. *Adversity and Resilience Science*. Published online 2020. doi:10.1007/s42844-020-00027-1
52. Hagenauer MH, Perryman JI, Lee TM, Carskadon MA. Adolescent Changes in the Homeostatic and Circadian Regulation of Sleep. *Developmental Neuroscience*. 2009;1043:276-284. doi:10.1159/000216538
53. Orgiles M, Morales A, Delveccio E, Mazzeschi C, Espada J. Immediate psychological effects of the COVID-19 quarantine in youth from Italy and Spain. *preprint DOI*. Published online 2020. doi:10.31234/osf.io/5bpfz
54. Dunster GP, de la Iglesia L, Ben-Hamo M, et al. Sleepmore in Seattle: Later school start times are associated with more sleep and better performance in high school students. *Science Advances*. 2018;4(12):0-7. doi:10.1126/sciadv.aau6200
55. Au R, Carskadon M, Millman R, et al. School start times for adolescents. *Pediatrics*. 2014;134(3):642-649. doi:10.1542/peds.2014-1697
56. Chen M, Wang E, Jeng Y. Adequate sleep among adolescents is positively associated with health status and health-related behaviors. 2*BMC Public Health*. 2006;6:59.
57. Eaton D, McKnight-Eily L, Lowry R, Perry G, Presley-Cantrell L, Croft J. Prevalence of insufficient, borderline, and optimal hours of sleep among high school students. *Journal of Adolescent Health*. 2010;46(4):399-401.
58. Epstein R, Chillag N, Lavie P. Starting times of school: effects on daytime functioning of fifth-grade children in Israel. *Sleep*. 1998;21(3):250-256.
59. Lufi D, Tzischinsky O, Hadar S. Delaying school starting time by one hour: some effects on attention levels in adolescents. *J Clin Sleep Med*. 2011;7(2):137-143.
60. Wolfson A, Spaulding N, Dandrow C, Baroni E. Middle school start times: the importance of a good night's sleep for young adolescents. *Behav Sleep Med*. 2007;5(3):194-209.
61. Rose A, Rudolph K. A review of sex differences in peer relationship processes: Potential trade-offs for the emotional and behavioral development of girls and boys. *Psychological Bulletin*. 2006;132(1):98-131. doi:https://doi.org/10.1037/0033-2909.132.1.98
62. Watkins D, Cheng C, Mpofu E, Olowu S, Singh-Sengupta S, Regmi M. Gender differences in self-construal: How generalizable are western findings? *Journal of Social Psychology*. 2003;143(4):501-519. doi:10.1080/00224540309598459
63. Sun J, Stewart D. Age and Gender Effects on Resilience in Children and Adolescents. *International Journal of Mental Health Promotion*. 2007;(4).

SUPPLEMENT 1:

Summary of used instruments

Instrument	Content/subscales	Items	Values	α
Cantril ladder[1,2] General life satisfaction	How do you feel about your life?	*1*	0 (worst possible life) to 10 (best possible life)	na
RCADS[3] Internalizing symptoms	Subscale separation anxiety disorder Subscale social phobia Subscale generalized anxiety disorder Subscale panic disorder Subscale obsessive compulsive disorder Subscale major depressive disorder	47	never, sometimes, often, always higher score = more severe symptoms	0.94
HSBC-SCL 2017[4] Psychosomatic health	How often have you suffered from the following in the last 6 months? · Headache · Stomach ache · Back ache · Feeling unhappy · Having a bad mood · Being nervous · Being dizzy · Being tired · Being exhausted · - Trouble with falling asleep	*10*	About every day; more than once a week; about every week; about every month; rarely or never	*1.0*
CASPE*[5] COVID-19 related symptoms and experiences	Factors, concerned about: · Health · Social consequences of lockdown measures · Financial matters · Relations at home	*4*	Factor score derived from factor analysis, continuous	*0.25*

*Adapted version; CASPE = COVID-19 Adolescent Symptom & Psychological Experience Questionnaire. See Supplement 3
α = Cronbach's alpha; HSBC-SCL 2017 = Health Behavior in School-aged Children Symptom Checklist; na = not applicable; RCADS = Revised Child Anxiety and Depression Scale

REFERENCES

1. Szkultecka-Dębek M, Dzielska A, Drozd M, Małkowska-Szkutnik A, Mazur J. What does the Cantril Ladder measure in adolescence? *Archives of Medical Science*. 2018;14(1):182-189. doi:10.5114/aoms.2016.60718
2. Cantril H. *The Pattern of Human Concern*. Rutgers University press; 1965.
3. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
4. Ravens-Sieberer U, Erhart M, Torsheim T, et al. An international scoring system for self-reported health complaints in adolescents. *Eur J Public Health*. 2008;18(3):294-299. doi:10.1093/eurpub/ckn001
5. Ladouceur LD. COVID-19 Adolescent Symptom & Psychological Experience (CASPE). OSFHOME. Published 2020. Accessed April 2, 2020. https://osf.io/mzrjg/

SUPPLEMENT 2:

The adapted version of the COVID-19 Adolescent Symptom & Psychological Experience Questionnaire (CASPE)

Adapted COVID-19 Adolescent Symptom & Psychological Experience Questionnaire (CASPE)

- Derived of COVID-19 Adolescent Symptom & Psychological Experience Questionnaire (CASPE) version 1/4/2020
- https://osf.io/7y3mk/

A. EXPERIENCE RELATED TO COVID-19 AND SYMPTOMS

1. Overall, how much has the COVID-19 outbreak, and the resulting changes to daily life, affected your life in a negative way?

- Not at all
- A little
- Somewhat
- A lot
- A great deal

1.a. What event or change has been the most negative? (check all that apply)

- You or someone you love has the virus
- Having to stay at home
- Not seeing friends in person
- Many people are dying because of the virus
- Not going to school
- Spend more time with family
- Other: _____

2. Overall, how much has the COVID-19 outbreak, and the resulting changes to daily life, affected your life in a positive way?

- Not at all
- A little
- Somewhat
- A lot
- A great deal

2.a. What event or change has been the most positive? (check all that apply)

- Reduced amount of schoolwork
- Get more sleep
- Spend more time with family
- Not having to deal with kids at school
- Get more time on the phone/computer (texting, social media)
- Other: _____

3. In past 4 weeks have you had any flu like symptoms (e.g., fever, dry cough, shortness of breath)?

- Yes
  - If yes, which symptoms have you had? (select all that apply)
    - Fever
    - Dry Cough
    - Fatigue
    - Sputum Production (thick mucus from lungs)
    - Sore Throat
    - Shortness of Breath
    - Headache
    - Muscle or Joint Pain
    - Diarrhea
    - Nausea or Vomiting
    - Chills
    - Nasal Congestion
    - ~~Red/itchy eye~~
- No

4. If, yes Have you been tested for COVID-19?

- Yes
  - Yes, I have been tested by a doctor and I'm waiting for the results
  - Yes, I have been tested by a doctor and the result was positive
  - Yes, I have been tested by a doctor and the result was negative
- No
  - No, I have not been tested by a doctor because they did not test me
  - No, I did not ask for a test

5. Have you been hospitalized due to COVID-19?

- Yes
- No

Extra question

Has anyone in your household or extended family (i.e., grandparent, uncle/aunt, cousin) had COVID-19 or was suspected of it?

- Yes
  - How many people in your household or extended family had COVID-19 or was suspected of it?
  - Who of your household or extended family had COVID-19 or was suspected of it?
- No

6. Has anyone in your household or extended family (i.e., grandparent, uncle/aunt, cousin) been hospitalized because they had COVID-19?
- Yes
  - How many people in your household or extended family were hospitalized due to COVID-19?
  - Who of your household or extended family was hospitalized due to COVID-19?
- No

7. Has anyone in your household or extended family (i.e., grandparent, uncle/aunt, cousin) died because they had COVID-19?
- Yes
  - How many people in your household or extended family died due to COVID-19?
  - Who of your household or extended family died due to COVID-19?
- No

8. Have any of your friends (or their family members) had COVID-19, or was suspected of it?
- Yes
  - How many friends (or their family members) had COVID-19 or was suspected of it?
  - Who of your friends (or their family members) had COVID-19 or was suspected of it?
- No

9. Have any of your friends (or their family members) been hospitalized because of COVID-19?
- Yes
  - How many friends (or their family members) were hospitalized due to COVID-19?
  - Who of your household or extended family was hospitalized due to COVID-19?
- No

10. Following school closures, how did you continue with schoolwork? (consider after Spring Break if schools closed during that time)
- School sent printed packets and/or recommendations
- School sent on-line assignments to complete without virtual classes
- School organized on-line classes
- Signed-up for a different on-line academic program
- There has been no school since then
- Already in cyber school
- Other (please describe): _____

B. EMOTIONAL EXPERIENCE

11. In the past 7 days, including today, what has been your level of concern about the impact of COVID-19 outbreak about the following:

	Very Little or Not at all	A Little	Some	A Lot	A Great Deal
Having to stay at home	1	2	3	4	5
Not seeing friends in person	1	2	3	4	5
I might get sick	1	2	3	4	5
Family might get sick	1	2	3	4	5
Friends might get sick	1	2	3	4	5
Falling behind with schoolwork	1	2	3	4	5
Having to spend more time with family	1	2	3	4	5
People might die if they get sick	1	2	3	4	5
Parent will lose their job	1	2	3	4	5
Having enough to eat	1	2	3	4	5
Conflict between parents	1	2	3	4	5
Conflict with parents	1	2	3	4	5
Sibling conflicts	1	2	3	4	5
Not getting into college	1	2	3	4	5
Not having enough money	1	2	3	4	5
Miss events that were important to me (e.g., graduation)	1	2	3	4	5
Other:			Free text		

Do you see your fiends or boyfriend/girlfriend in person last month?

- Yes, every day or almost everyday
- Yes, we see each other a few times per week
- Yes, we see each other each week
- Less than once a week
- Never

12. ~~Since your school has closed,~~ how often do you talk/chat with friends online (including on your cell phone, on social media, or through online gaming) last month?

- Yes, every day or almost everyday
- Yes, we see each other a few times per week
- Yes, we see each other each week
- Less than once a week
- Never

SUPPLEMENT 3:

Exploratory factor analyses

Table 1: Factor analysis with loadings of each item within the newly formed clustered factors

Factor analysis				
Factors: concerns about	**Health**	**Social consequences of lockdown measures**	**Financial matters**	**Family relations**
- I might get sick	0.711	-	-	-
- My family might get sick	0.805	-	-	-
- My friends might get sick	0.747	-	-	-
- People might die if they get sick	0.562	-	-	-
- Having to stay at home	-	0.692	-	-
- Not seeing my friends in person	-	0.663	-	-
- Falling behind with schoolwork	-	0.331	-	-
- Having to spend more time with family	-	0.464	-	-
- Not going to school	-	0.744	-	-
- Miss events that were important to me	-	0.203	-	-
- Parents might lose their job	-	-	0.481	-
- Not having enough to eat	-	-	0.680	-
- Not having enough money	-	-	0.387	-
- Conflict between parents	-	-	-	0.488
- Conflict with parents	-	-	-	0.447
- Sibling conflict	-	-	-	0.512

Extraction Method: Principal Axis Factoring. Rotation Method: Varimax with Kaiser Normalization. Cutting value: eigenvalue >1.00 in combination with scree plot.

SUPPLEMENT 4:

Changes in specific psychosomatic symptoms

Table 1: Changes in specific psychosomatic symptoms during the COVID-19 pandemic, compared to before the pandemic

Psychosomatic health, Complaints experienced once a week or more often	**Before the COVID-19 pandemic**		**After introduction of lockdown measures**		
	n=224	**(%)**	**n=158**	**(%)**	**p**
- Headache	19	(8.48)	14	(8.86)	0.30
- Stomach ache	9	(4.02)	7	(4.43)	0.80
- Backache	14	(6.25)	10	(6.33)	0.48
- Feeling unhappy	15	(6.70)	14	(8.86)	0.79
- Having a bad mood	39	(17.41)	23	(14.56)	0.01
- Being nervous	22	(9.82)	17	(10.76)	0.46
- Being dizzy	18	(8.04)	16	(10.13)	0.83
- Being tired	66	(29.46)	41	(25.94)	<0.00
- Being exhausted	33	(14.73)	18	(11.39)	0.01
- Trouble with falling asleep	93	(41.52)	32	(20.25)	<0.00

*tested with McNemar's Chi-squared test
Significant differences in **bold**.

CHAPTER 8

TRACKING MENTAL WELLBEING OF DUTCH ADOLESCENTS DURING THE FIRST YEAR OF THE COVID-19 LOCKDOWN:

A LONGITUDINAL STUDY

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ABSTRACT

Purpose

Adolescents might be susceptible to the effects of the coronavirus disease 2019 (COVID-19) lockdown. We assessed changes in mental wellbeing throughout the first year of the pandemic and compared these with pre-pandemic levels.

Methods

This five-wave prospective study among Dutch adolescents aged 12-17 years used data collected before the pandemic (n=224) (T0), in May (T1), July (T2), and October 2020 (T3), and in February 2021 (T4). Generalized estimating equations were used to assess the association between stringency of the lockdown with mental wellbeing.

Results

Adolescents had a lower life satisfaction during the first full lockdown (T1) (adj β: -0.36, 95% CI: -0.58 to -0.13), during the partial lockdown (T3) (adj β: -0.37, 95% CI: -0.63 to -0.12), and during the second full lockdown (T4) (adj β: -0.79, 95% CI: -1.07 to -0.52) compared to before the pandemic (T0). Adolescents reported more internalizing symptoms during only the second full lockdown (T4) (adj β: 2.58, 95% CI: 0.41 to 4.75). During the pandemic, [at T1 (adj β: 0.29, 95% CI: 0.20 to 0.38), T2 (adj β: 0.36, 95% CI: 0.26 to 0.46), T3 (adj β: 0.33, 95% CI: 0.22 to 0.45), and T4 (adj β: 0.20, 95% CI: 0.07 to 0.34)], adolescents reported a better psychosomatic health, partly attributable to less trouble falling asleep ($p<0.01$).

Conclusion

The COVID-19 lockdown measures have had both a negative and positive impact on mental wellbeing of Dutch adolescents. However, mental wellbeing was most impacted during the second full lockdown compared to before the pandemic.

INTRODUCTION

All around the world, school closures, quarantining, and social distancing have been key in governmental attempts to reduce the transmission of the SARS-CoV-2 virus, hospitalizations and death in the coronavirus disease 2019 (COVID-19) pandemic [1,2]. As a result of these restriction measures, billions of people worldwide face unprecedented periods of social isolation and stress [3,4]. Adolescents might be particularly susceptible to the social effects of these lockdown measures [4,5]. Adolescence is not only marked as a time period in which numerous mental health disorders emerge for the first time, but also as a formative period for neurocognitive and social developments [6–8]. For instance, young people spend increasingly more time with their peers and are more influenced by peers than by adults in their social decision making, feeling accepted and rejected, and getting approval [5,7,9]. Friendships are therefore instrumental aspects of adolescent mental wellbeing [10]. Social face-to-face contacts in particular are not only actively discouraged by the COVID-19 restriction measures [3], but also limited due to the transition to online education. These aspects of the COVID-19 pandemic, among many others, might jeopardize adolescent mental wellbeing.

Longitudinal data are required to better understand the effects of lockdown measures on mental wellbeing, preferably including baseline measures assessed prior to COVID-19 [4,11]. Several longitudinal studies reported on adolescent mental wellbeing in response to COVID-19 lockdown measures and have shown that anxiety and depressive symptoms increased, and life satisfaction deteriorated during the first full lockdown in youth (8-18 years) living in The Netherlands, Australia and North-America [12–15]. A large international collaborative effort using data of twelve longitudinal studies (ten performed in the USA, one in the Netherlands, and one in Peru) identified an increase in depressive symptoms in adolescents (mean age 15.4 years) [16]. However, it is also known that although life satisfaction of Dutch adolescents (mean age 15.5 years) decreased, their internalizing symptoms did not change, and psychosomatic health even improved during the pandemic, compared to baseline [17]. To date, to our knowledge, no studies have taken multiple repeated assessments of adolescent mental wellbeing during the first year of the COVID-19 pandemic, and concomitantly the stringency of the lockdown, into account.

In this five-wave prospective longitudinal study among Dutch adolescents, we assessed changes in mental wellbeing throughout the first year of the COVID-19 pandemic and compared these with pre-pandemic levels (T0). The stringency of the lockdown was significantly different at the four follow-up assessments (T1-T4), due to diverse implemented restriction measures. Additionally, we explored whether there was a differential change in mental wellbeing between boys and girls, as girls have incidence of mental health problems during adolescence compared to boys [18].

METHODS

Study design and study population, baseline (T0)

Data were obtained from an ongoing population-based birth cohort study, named WHISTLER [17,19]. Between 2001 and 2012 newborns were recruited from the general population in a fairly affluent and newly built suburb of Utrecht, the Netherlands. The participants have been followed at age of 3, 5 and 8 years. In March 2019, we invited the 12-16 year old WHISTLER participants to complete a questionnaire and undergo a health assessment. One of the primary aims was to assess their mental wellbeing during adolescence. Due to the start of the COVID-19 pandemic, we had to stop this follow-up round. Up to then 224 adolescents completed the questionnaires (52.7% girls, mean age 14.82 years). This was indicated as T0. These adolescents were invited to complete the follow-up questionnaires (T1- T4) during the first year of the COVID-19 pandemic. Specifically, the questionnaires were sent in May (T1), in July (T2), in October 2020 (T3), and in February 2021 (T4). The participants were able to complete the questionnaire within one month. The analysis of adolescent mental wellbeing at T0 and T1 has been published elsewhere [17].

Ethical approval for WHISTLER (file number: NL66918.041.18) was obtained from the Medical Ethics Review Committee of the University Medical Center Utrecht. Participants and their parents or legal guardians provided active written informed consent.

Follow-up: assessments throughout the first year of the COVID-19 pandemic (T1-T4)

The Dutch restrictive measures varied considerable in the first year of the pandemic, and our follow-up assessments (T1-T4) captured four different phases of government policy. To more objectively rate the stringency of the restrictions and increase comparability with other countries, we used a national lockdown stringency index based on a composite measure of nine different lockdown measures: the Oxford COVID-19 Government Response Tracker (OxCGRT). The index has values from 0 to 100 (100 = strictest) [20]. This OxCGRT identified that the stringency of the Dutch lockdown was 78.70 around T1, during the first full lockdown; 39.81 around T2, during the period that this first full lockdown was eased; 62.04 around T3, a less restrictive 'partial' lockdown; and 78.70-82.41 around T4, a second full lockdown, respectively [20,21]. This indicates that T4 was the most stringent lockdown.

Figure 1 shows the timeline of COVID-19 cases, hospital admissions, deaths, and stringency index in the Netherlands, as well as the timing of sending the questionnaires and timing of introduction and easing of lockdown measures. For a full summary of when and which lockdown measures were introduced and eased, please refer to Supplement 1.

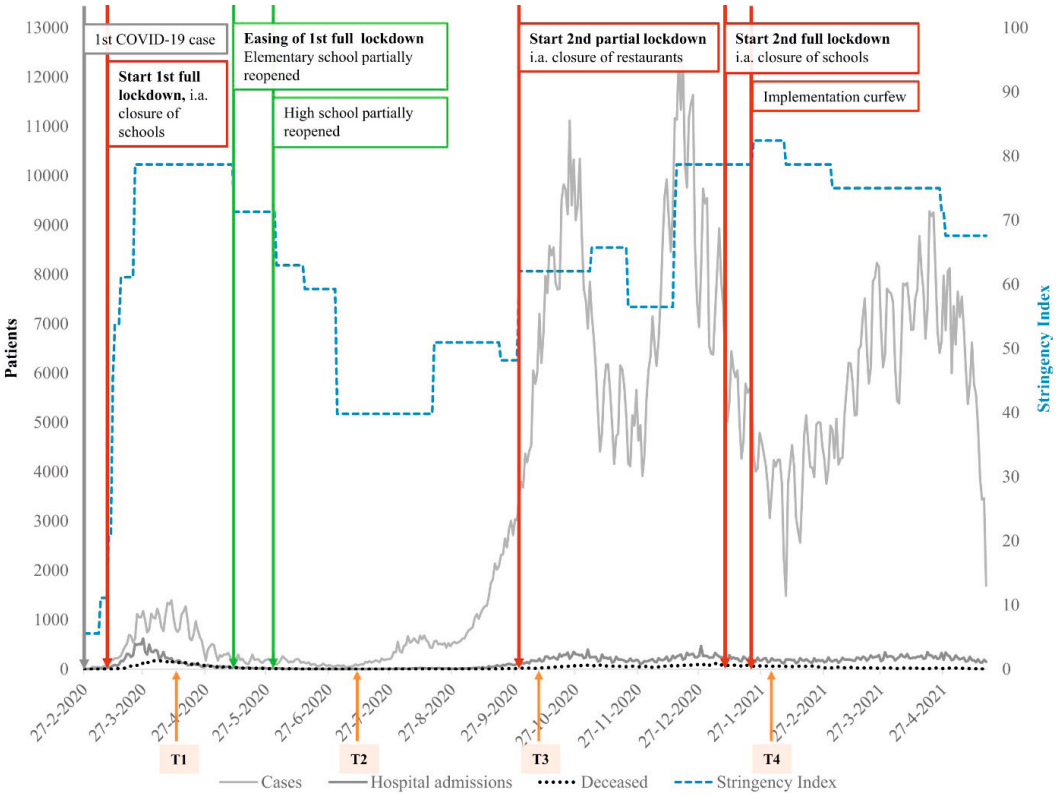

Figure 1: Timeline of COVID-19 cases, hospital admissions, deceased, and stringency index in the Netherlands. Introduction and easing of lockdown measures, and timing of sending the questionnaires. Orange arrows denote sending questionnaires at T1, T2, T3, and T4; brown arrows denote implementing restrictions; and green arrows denote easing of measures. T0 = before the COVID-19 lockdown; T1 = first full lockdown (assessment April 18, 2020); T2 = first full lockdown eased (assessment July 18, 2020); T3 = partial lockdown (assessment October 18, 2020); T4 = second full lockdown (assessment February 2, 2021).

Mental wellbeing assessments

Mental wellbeing was assessed using three indicators: life satisfaction, internalizing symptoms, and psychosomatic health using respectively the Cantril ladder [22,23], the Revised Child Anxiety and Depression Scale (RCADS) [24], and the Health Behavior in School-aged Children Symptom Checklist (HBSC-SCL) 2017 [25]. To investigate whether mental wellbeing changed from baseline to follow-up, we assessed the same instruments at each follow-up time period (T1-4). The specifics of these instruments are described in short below; please refer to Supplement 2 for full details.

Life satisfaction was assessed with the Cantril ladder, a valid and reliable instrument of life satisfaction in adolescence [22,23,26]. The Cantril ladder includes one question "Looking

at the past 3 months, how do you feel about your life?" and possible answers range from 0 to 10 (10 = best possible life) [22,23,26].

Internalizing symptoms, i.e., the severity of self-reported anxiety and depressive symptoms, was assessed using the RCADS. The RCADS is based on anxiety disorders and depression from the Diagnostic and Statistical Manual of Mental Disorders-IV [24]. The questionnaire contains 47 items, which are rated by respondents on a 4-point Likert scale ranging from 0 "never" to 3 "always". In our study the correlation between the subdomains 'anxiety' and 'major depressive disorder' was *r*(Pearson)>0.7 across waves, therefore we analyzed these subdomains together as internalizing symptoms. Raw scores were converted into gender and age-normed T-scores using the syntax from the RCADS-developer (based on USA population)[27] and evaluated as a continuous score.

Psychosomatic health complaints are symptoms that are often related to psychosocial factors, such as stress [28]. Psychosomatic health was measured with HBSC-SCL and expressed in a mean score of 10 symptoms, such as having a headache, being nervous, or feeling dizzy [25]. The higher the mean score, the better psychosomatic health one is experiencing, meaning that one is feeling little stress. The HBSC-SCL has good psychometric properties and has also been validated in Dutch [29,30].

Statistical analyses

We used descriptive statistics to summarize the characteristics of the study population. Due to correlations among repeated measures of outcomes in the same individual, regression models using generalized estimating equations (GEE) with an identity link function were used to assess the association between time of assessment (stringency of the lockdown) with repeated measures of mental wellbeing (life satisfaction/ internalizing symptoms/ psychosomatic health; each outcome measure analysed individually). While using the GEE, we choose for an independent correlation structure which enables the GEE to handle time dependent variables (such as age) to change over time [31]. Associations with the outcomes were expressed as differences (βs), with 'no lockdown measures' (T0) as the reference category. As a secondary analysis, we tested for interactions between gender and time of assessment to analyse whether boys' and girls' mental wellbeing changed differentially over time. Additionally, McNemar's Chi-squared tests were used to analyze whether the frequency of occurrence of psychosomatic symptoms differed between baseline and follow-up assessments.

We used multiple imputation, producing 25 sets of imputed data, with predictive mean matching to impute missing covariates and outcome measures, incorporating data on potential confounders (age and gender) and the outcomes [32]. We imputed the data for all participants that completed baseline (T0). Moreover, as auxiliary variables are considered to improve the quality of imputation and therefore might reduce bias, we included two

auxiliary variables: ethnicity and level of education of the adolescent [33,34]. Analysis on multiple imputation increases precision of the estimates and reduce the potential bias introduced by missing data [32]. Therefore, it was chosen as the primary analysis for the GEE. The results from the complete case analysis is shown in Supplement 3.

We adjusted the GEE for *a priori* selected potential confounders based on directed acyclic graphs: gender (male/female) and age. A p-value <0.05 was considered statistically significant. All analyses were done with SPSS 26.0.

RESULTS

Study population

Table 1 shows the characteristics of the study population at the five assessment waves (T0 to T4). Of the 224 participants who completed their questionnaire at baseline, 158 participants (70.5%) completed it at T1, 149 participants (66.5%) at T2, 152 participants (67.9%) at T3, and 128 participants (57.1%) at T4. Data on mental wellbeing were available for at least two out of five assessments for 186 (83%) participants, and for four of the five assessments for 132 (59%) participants. Of the 224 adolescents at T0, 95.1% had a Western ethnicity, and 93.3% had a parent with a high (university) or intermediate (vocational) level of education. Girls and adolescents with a higher level of education were more willing to complete the follow-up questionnaires (see Table 1). In general no differences with respect to the outcome measures were observed between the participants who completed the follow-up questionnaire and participants who did not. However, girls were more likely to complete the questionnaires at all follow-up rounds (T1 p=0.002, T2 p=0.004, T3 p=0.012, T4 p=0.000) compared to boys. In addition, adolescents with higher levels of education completed follow-up questionnaires more frequently at T2 (p=0.017) and T3 (p=0.005).

Table 1: Characteristics of the WHISTLER cohort study samples that completed the questionnaires before and throughout the COVID-19 pandemic

Demographics	***T0***	***(n=224)***	***T1***	***(n=158)***	***T2***	***(n=149)***	***T3***	***(n=152)***	***T4***	***(n=128)***
Age in years, mean (SD)*	14.82	(1.24)	15.53*	(1.25)	15.76	(1.28)	16.01	(1.28)	16.30	(1.28)
Gender (%)										
• Girl	118	(52.68)	94	(59.49)	88	(59.06)	87	(57.23)	82	(64.06)
*Educational level of the adolescent** (%)*										
• Primary school	3	(1.34)	2	(1.26)	2	(1.24)	3	(1.97)	2	(1.56)
• Low	52	(23.21)	34	(21.52)	27	(18.12)	32	(21.05)	24	(18.75)
• Intermediate	63	(28.13)	39	(24.68)	33	(22.15)	30	(19.74)	28	(17.72)
• High	101	(45.09)	79	(50.00)	75	(50.34)	75	(49.34)	64	(50.00)
• Special education	8	(3.57)	4	(2.53)	4	(2.68)	3	(1.97)	3	(2.34)
Stringency index of lockdown	na		78.70		39.81		62.04		78.80-82.41	

T0 = before the COVID-19 lockdown; T1 = first full lockdown (assessment April 18, 2020); T2 = first full lockdown eased (assessment July 18, 2020); T3 = partial lockdown (assessment October 18, 2020); T4 = second full lockdown (assessment February 2, 2021).
na = not applicable
*calculated based on completion date of follow-up questionnaire
**low: pre-vocational secondary education; intermediate: higher general secondary education or intermediate vocational education; high: pre-university education, higher vocational education and university

Figure 2 shows both the overall mean of the entire sample, as well as the mean stratified by gender for all three outcome measures per assessment (T0 - T4). This illustrates the trend over time. The exact values of the outcome measures are described in Supplement 4.

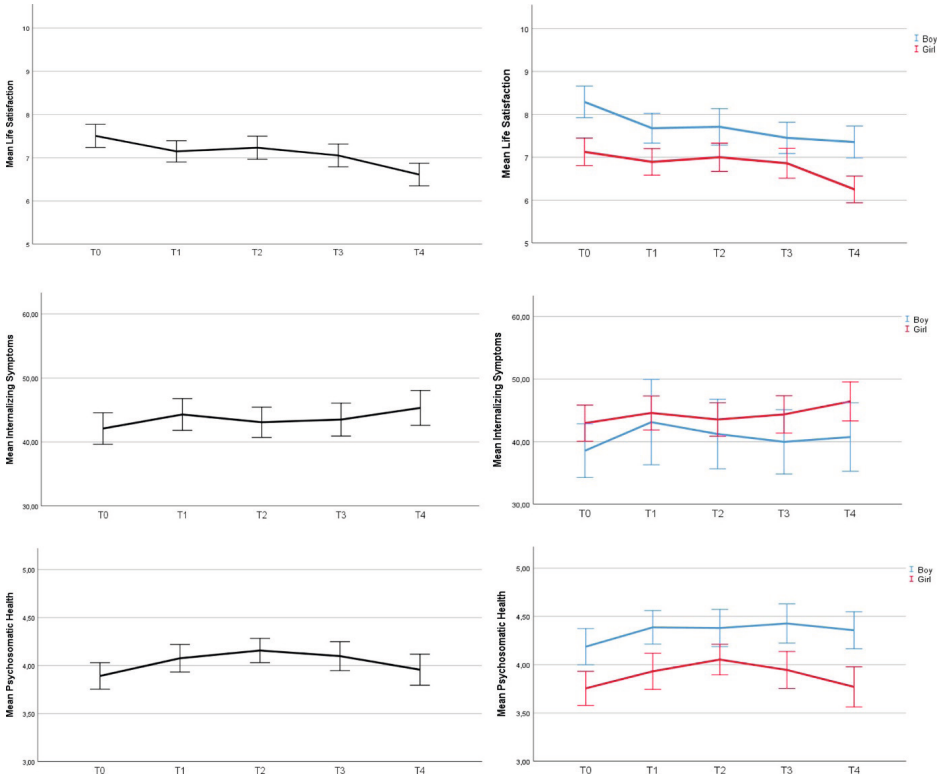

Figure 2: Life satisfaction, internalizing symptoms, and psychosomatic health before and throughout the first year of the COVID-19 pandemic for the entire sample and stratified by gender. T0 = before the COVID-19 lockdown; T1 = first full lockdown (assessment April 18, 2020); T2 = first full lockdown eased (assessment July 18, 2020); T3 = partial lockdown (assessment October 18, 2020); T4 = second full lockdown (assessment February 2, 2021).

Associations between time of assessment (lockdown stringency) and mental wellbeing

We used multiple imputation to impute missing covariate and outcome data. The effect estimates for results based on multiply imputed data were comparable to the complete case analysis. The precision was generally improved as the confidence intervals were slightly smaller. We considered the imputed results as the primary results and present the complete case results in the Supplement 3.

Adolescents had a significantly lower life satisfaction during the first full lockdown (T1) (adj β: -0.36**,** 95% CI: -0.58 to -0.13), during the partial lockdown (T3) (adj β: -0.37**,** 95%

CI: -0.63 to -0.12), and during the second full lockdown (T4) (adj β: -0.79**,** 95% CI: -1.07 to -0.52) compared to before the pandemic (*Table* 2). At the time that the first full lockdown was eased (T2), no significant change in life satisfaction was reported (adj β: -0.19**,** 95% CI: -0.42 to 0.05). There were differential changes in life satisfaction over time between boys and girls ($p_{interaction}$=0.015); boys' life satisfaction decreased at a faster rate over time than girls' life satisfaction.

Table 2: Life satisfaction, internalizing symptoms, and psychosomatic health: differences when measured before the start of the COVID-19 pandemic (reference), compared to assessments throughout the first year of the COVID-19 pandemic.

	Life satisfaction +			
Time of assessment	**Crude β**	**(95% CI)**	**Adj. β**	**(95% CI)**
To: before COVID-19 pandemic	ref	-	ref	-
T1: first full lockdown	-0.47	(-0.68;-0.26)	-0.36	(-0.58;-0.13)
T2: first full lockdown eased	-0.33	(-0.55;-0.12)	-0.19	(-0.42;0.05)
T3: partial lockdown	-0.56	(-0.78;-0.34)	-0.37	(-0.63;-0.12)
T4: second full lockdown	-1.02	(-1.25;-0.80)	-0.79	(-1.07;-0.52)
	Internalizing symptoms ++			
Time of assessment	**Crude β**	**(95% CI)**	**Adj. β**	**(95% CI)**
To: before COVID-19 pandemic	ref	-	ref	-
T1: first full lockdown	1.18	(-0.15;2.50)	0.96	(-0.58;2.50)
T2: first full lockdown eased	0.95	(-0.37;2.27)	0.66	(-1.00;2.31)
T3: partial lockdown	1.27	(-0.05;2.58)	0.90	(-0.90;2.69)
T4: second full lockdown	3.04	(1.50;4.58)	2.58	(0.41;4.75)
	Psychosomatic health +++			
Time of assessment	**Crude β**	**(95% CI)**	**Adj. β**	**(95% CI)**
To: before COVID-19 pandemic	ref	-	ref	-
T1: first full lockdown	0.25	(0.17;0.32)	0.29	(0.20;0.38)
T2: first full lockdown eased	0.30	(0.22;0.39)	0.36	(0.26;0.46)
T3: partial lockdown	0.26	(0.17;0.35)	0.33	(0.22;0.45)
T4: second full lockdown	0.12	(0.01;0.22)	0.20	(0.07;0.34)

Based on imputated data
Abbreviations: Adj.= adjusted. Adjusted for: gender and age. Ref = reference
T0 = before the COVID-19 lockdown; T1 = first full lockdown (assessment April 18, 2020); T2 = first full lockdown eased (assessment July 18, 2020); T3 = partial lockdown (assessment October 18, 2020); T4 = second full lockdown (assessment February 2, 2021).
+ a higher score indicates a higher life satisfaction; ++a higher score more severe self-reported internalizing symptoms; +++ a higher score indicates experiencing psychosomatic complaints less frequently.

Adolescents reported significantly more internalizing symptoms during the second full lockdown only (T4; adj β: 2.58**,** 95% CI: 0.41 to 4.75), compared to internalizing symptoms

assessed before the beginning of the pandemic (T0). During the first full lockdown (T1) (adj β: 0.96**,** 95% CI: -0.58 to 2.50), during the easing of the first full lockdown (T2) (adj β: 0.66**,** 95% CI: -1.00 to 2.31) and during the partial lockdown (T3) (adj β: 0.90, 95% CI: -0.90 to 2.69) no significant change in internalizing symptoms was reported (*Table 2*). Secondary analyses did not reveal a differential change in internalizing symptoms at the various assessments between boys and girls ($p_{interaction}$=0.46).

Throughout the first year of the COVID-19 pandemic, [at T1 (adj β: 0.29**,** 95% CI: 0.20 to 0.38), T2 (adj β: 0.36**,** 95% CI: 0.26 to 0.46), T3 (adj β: 0.33**,** 95% CI: 0.22 to 0.45), and T4 (adj β: 0.20**,** 95% CI: 0.07 to 0.34)], adolescents reported a significantly better psychosomatic health than before the start of the pandemic (T0) (Table 2). Secondary analyses did not reveal a differential change in psychosomatic health at the various assessments between boys and girls ($p_{interaction}$=0.29).

Contrary to our expectations, psychosomatic health was better throughout the first year of the pandemic than before. Therefore, in an exploratory *a posteriori* analysis, we assessed changes in specific psychosomatic symptoms which are presented in Supplement 5. We identified that adolescents were able to fall asleep more easily (p<0.01) throughout the first year of the pandemic at all follow-up rounds. In addition, adolescents also experienced other specific symptoms less frequently at some follow-up rounds (please see Supplement 5).

DISCUSSION

This is the first study that considered multiple repeated assessments of adolescent mental wellbeing, both pre-pandemic as well as during the first year of the COVID-19 pandemic (OxCGRT stringency index: T1: 78.80; T2: 39.81; T3: 62.04; and T4: 78.80-82.41). Our five-wave prospective cohort study among Dutch adolescents yielded an interesting picture of change on mental wellbeing throughout the first year of the COVID-19 pandemic. Life satisfaction decreased during the first and second full lockdowns as well as the partial lockdown, compared to before the pandemic. Notably, life satisfaction decreased most at the second full lockdown in February 2021. Moreover, boys' life satisfaction decreased at a faster rate than girls during the pandemic compared to the pre-pandemic baseline. Adolescents only reported more internalizing symptoms, reflecting anxiety and depression symptoms, during the second full lockdown. Interestingly, throughout the first year of the COVID-19 pandemic, adolescents reported significantly better perceived psychosomatic health. Exploratory analyses indicated that this improvement is partly attributable to being able to fall asleep more easily.

Previous longitudinal studies assessing mental wellbeing during and before the pandemic can be used to benchmark our findings, while keeping in mind that these studies did not assess mental wellbeing during the entire first year of the pandemic. Similar to our

study, a deterioration in life satisfaction during the pandemic was observed in Australian adolescents (aged 13-19 years, stringency index: 65.74 - 69.44) and in Dutch adolescents (aged 10-20 years, stringency index 78.80-65.74) [12,13,15,17]. In our study we observed that life satisfaction seems to be correlated with the stringency level of the lockdown: when the stringency index was high life satisfaction decreased, and vice versa. However, we did not observe this pattern when comparing the absolute values of the stringency index between countries, as Australian adolescents experienced a lower life satisfaction, but Chinese youth did not: the stringency index of the Australian lockdown was substantially lower compared to that of the Chinese lockdown. Therefore, focusing on a change in mental wellbeing over time within a specific context seems to be preferable over comparing adolescent mental wellbeing between countries while using the stringency index. However, future research could focus on disentangling which aspects of the different national lockdowns affects mental wellbeing.

Our sample only reported significantly more internalizing symptoms during the second full lockdown (stringency index: 78.80-82.41). Australian youth (8-18 years old) reported more anxiety and depressive symptoms in the initial phase of the pandemic [13] (stringency index: 65.74 - 69.44), as did adolescents (aged 14-17) living in the USA (stringency index: 67.13-72.69) [14,35]. Nonetheless, the average scores of the youth living in the USA did not reach the clinical threshold for anxiety disorders and depression [14,27]. Additionally, Barendse et al. (2021) showed, especially for bi- or multiracial adolescents, an increase in depressive symptoms in an international sample of adolescents (mean age 15.4 years) [16]. Therefore, it remains important to monitor internalizing symptoms and to evaluate potentially vulnerable subgroups, especially when the stringency level of the pandemic increases. Some studies identified vulnerable subgroups: Cohen et al. (2021) showed that healthy adolescents experienced more anxiety and depression during the pandemic compared to before, while adolescents with early life stress who were thought of being at particular risk did not [36]. Additionally, Zijlmans et al. (2021) showed that youth (aged 8-18 years) with a (chronic) somatic condition experienced a better mental wellbeing compared to their healthy peers [37]. However, youth with pre-existing mental problems had a lower mental wellbeing than youth with a somatic condition or healthy peers [37]. These studies suggested that some youth with adverse life events seemed to be more resilient than healthy adolescents. Therefore, future studies could examine which risk and resilience factors might be of influence on adolescent mental wellbeing changes during the COVID-19 pandemic.

Interestingly, reported psychosomatic health of adolescents increased during the pandemic. Although statistically significant, it is questionable whether this improvement was also clinically relevant. As psychosomatic health was expressed in a mean score of 10 symptoms, the direct impact on daily life, except for experiencing less stress in general, was difficult to determine. However by assessing changes in specific psychosomatic

symptoms, we identified that the improved psychosomatic health was partly attributable to falling asleep more easily during the pandemic compared to before. Other studies reported that youth more often slept eight hours or longer during the COVID-19-related lockdown compared to their sleep rhythms prior to the pandemic [12,38,39], and that bedtime and wake times shifted to later hours [39]. During puberty, hormonal changes alter the homeostatic and circadian regulation of sleep, with the result that adolescents tend to stay up and sleep in [40]. The altered sleep rhythm might conflict with early school start times. As a result, chronic sleep loss is a common phenomenon for adolescents [41]. Due to school closures, online education (T1, T3, and T4), and summer holidays (T2), it might be conceivable our sample of adolescents were able to shift their bedtime and wake times to later hours, resulting in better syncing of their sleep-wake behavior with their circadian rhythm. Multiple studies have shown that delaying school start times led to better alignment of circadian system and therefore resulted in better sleep quantity and quality. As a consequence, mental health issues decreased, and physical health and academic performances improved [42,43]. Therefore, it was previously recommended that national governments may consider possibilities that could enhance the alignment of adolescent sleep-wake behavior with their circadian rhythm, e.g. by delaying school start times [17].

It is well known that adolescent girls have lower mental wellbeing on average than boys [44]. Also in our study, boys scored better than girls on all three indicators of mental wellbeing. However, our results showed that boys' life satisfaction deteriorated during the pandemic, while Magson et al reported that a decline in life satisfaction among adolescents (13-16 years) during the pandemic was particularly pronounced among girls [13]. We can only speculate as to why only boys showed a deterioration in life satisfaction. Lockdown measures actively discouraged group gatherings. When focusing on social interactions, boys are more likely to hang out in groups, whereas girls tend to spend more time in friendship dyads [45,46]. Therefore the measures might have affected boys' life satisfaction more than girls'. Also, girls are more likely than boys to communicate with friends online [47]. Research showed that adolescents had higher anxiety and depression scores during the pandemic compared to before, when they experienced a poorer connection with friends and family [48]. Keeping in touch with friends online during the pandemic may reduce the impact of lockdown measures on girls' mental wellbeing. Finally, girls might have more communication tools to cope with changes due to the lockdown measures because they are, in general, more likely to ask for help, have more positive connections to their parents, and communicate more than boys [49]. Future research could focus on why gender matters when it comes to changes in life satisfaction during this pandemic.

Our study reported an interesting picture of change on mental wellbeing throughout the first year of the COVID-19 pandemic. By (partly) maintaining their mental wellbeing, our participants showed that they functioned resiliently during the pandemic. In the literature, it is described that supportive social environment like parent support, make adolescents

more able to respond resiliently to adversity [10,50]. In 2017, the Health Behavior in School-Aged Children (HBSC) study, conducted in 45 European countries plus Canada, found that Dutch adolescents were remarkably positive about their relationship with parents [47,51]. Of the Dutch 15-year-olds, 81 and 90 percent reported that they can easily talk to their father or mother about their worries, respectively. In other countries, the average was much lower: 65 percent (father) and 80 percent (mother) [47]. Although this data was collected in 2017, these results give an indication on how adolescent might experience being in lockdown at home with their parents. This gives them a good starting position regarding their mental wellbeing for the crisis. Future research may allow researchers to confirm these protective factors.

Nonetheless, adolescents' mental wellbeing changed the most during the longer lasting second full lockdown (T4) compared to pre-pandemic levels: life satisfaction was lowest and more internalizing symptoms were reported. During this lockdown, schools were closed for the second time during the pandemic. A recent systematic review showed that during the first wave of the COVID-19 pandemic, mental health issues among children and adolescents (mainly anxiety and depressive symptoms) and adverse health behaviors (such as decreased physical activity and increased screen time) were associated with school closures and the social lockdown [52]. Nonetheless, it was not possible to disentangle the effects of school closures from broader social lockdown measures [52].

A particular strength of this study is the longitudinal prospective design with five time waves of data collection, including a pre-pandemic baseline assessment. The follow up assessments included the initial but also the consecutive COVID-19 phases during the first year of the pandemic taking multiple lockdowns with a different stringency index into account. Multiple indicators of mental wellbeing were assessed, with internationally renowned instruments. Some limitations deserve mention. Despite the longitudinal design, we cannot determine a causal relation between the stringency of the lockdown and adolescent mental wellbeing. Mental wellbeing was most impacted during the second full lockdown. Moreover, also the stringency index was at its highest at that point of time: 78.70 to 82.41 [20,21]. However, the duration of the lockdown might be another driver of these negative outcomes, since participants had already been in a lockdown for over 3.5 months. The independent effect of the duration versus the stringency of the lockdown could not be disentangled. Additionally, factors unrelated to the pandemic, such as seasons and school breaks, might also have influenced the associations. For example, certain affective disorders are more present in particular seasons; adolescents especially suffer from seasonal affective disorder (SAD) in winter, resulting in feeling more irritable, fatigue, and sad [53]. SAD could also have had an effect on our outcome measures.

Moreover, the participants of the WHISTLER birth cohort were recruited from the general population living in a fairly affluent, and newly built suburb in the Netherlands [19]. As a

result, adolescents with parents with a lower educational background and a non-Western migration background were underrepresented. This limits the generalizability of our results to populations with different educational, ethnic, and/or cultural backgrounds.

In cohort studies, loss-to-follow-up is a common phenomenon which can lead to attrition bias. For all three outcome measures, there was no significant difference between responders and non-responders at baseline. However, girls and adolescents with higher levels of education were more likely to complete the questionnaires at follow-up rounds. Because girls scored lower on all three outcomes compared to boys, a lower mental wellbeing might have been observed than in a representative sample. Therefore, attrition bias might have been introduced by loss of boys completing the questionnaire in the follow-up rounds. Adolescent education level did not affect mental wellbeing and therefore, loss of follow up of adolescents with lower levels of education did not introduce attrition bias.

The COVID-19 pandemic is one of the most profound events for society and citizens in the last decades. Ongoing longitudinal research will grant researchers to appreciate its lasting impact with regard to mental wellbeing. Moreover, such research may allow researchers to identify why certain subgroups of youth were doing well or were doing poorly before, during, and in the aftermath of the pandemic. Due to co-occurrence of other factors that might have affected adolescent mental wellbeing, the independent effect of the lockdown severity on our outcome measures could not be established. To gain better insight in the impact of the COVID-19 pandemic on mental wellbeing, combining the results of various studies concerning this topic would be promising. Furthermore, our results suggest that further research is warranted on the relationship between sleep and mental wellbeing, and on interventions or policy (e.g., school starting time) changes that enhance better syncing of adolescent sleep-wake behavior with their circadian rhythm.

In conclusion, this prospective, longitudinal study among Dutch adolescents identified that the COVID-19 lockdown measures mainly have had a negative impact on adolescent life satisfaction, but have had a positive impact on psychosomatic health. Additionally, mental wellbeing changed most during the longer lasting second full lockdown when compared to pre-pandemic levels: life satisfaction was at its lowest, more internalizing symptoms were reported, and psychosomatic health increased the least at this period in time.

REFERENCES

1. Haug N, Geyrhofer L, Londei A, et al. Ranking the effectiveness of worldwide COVID-19 government interventions. *Nature Human Behaviour*. 2020;4(12):1303-1312. doi:10.1038/s41562-020-01009-0
2. World Health Organisation. Q&A on coronaviruses (COVID-19). World Health Organization. Published 2020. Accessed March 27, 2020. www.who.int
3. World Health Organisation. Q&A on coronaviruses (COVID-19). World Health Organization. Published 2020. Accessed March 27, 2020. www.who.int
4. Wade M, Prime H, Browne D. Why we need longitudinal mental health research with children and youth during (and after) the COVID-19 pandemic. *Psychiatry Research*. 2020;(January):19-21.
5. Orben A, Tomova L, Blakemore S jayne. The effects of social deprivation on adolescent development and mental health. *Lancet Child Adolesc Health*. 2020;4:634-640.
6. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of. *Arch Gen Psychiatry*. 2005;62:593-602. doi:10.1001/archpsyc.62.6.593
7. Blakemore SJ, Mills KL. Is Adolescence a Sensitive Period for Sociocultural Processing? *Annu Rev Psychol*. 2014;65:187-207. doi:10.1146/annurev-psych-010213-115202
8. Blakemore S jayne. The art of medicine Adolescence and mental health. *The Lancet*. 2019;393(10185):2030-2031. doi:10.1016/S0140-6736(19)31013-X
9. Knoll LJ, Magis-Weinberg L, Speekenbrink M, Blakemore SJ. Social Influence on Risk Perception During Adolescence. *Psychological Science*. 2015;26(5):583-592. doi:10.1177/0956797615569578
10. van Harmelen AL, Kievit RA, Ioannidis K, Al E. Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychological medicine*. 2017;47(13):2312-2322.
11. Liu JJ, Bao Y, Huang X, Shi J, Lu J. Mental health considerations for children quarantined because of COVID-19. *The Lancet*. 2020;4(20):347-349. doi:10.1016/S2352-4642(20)30096-1
12. Munasinghe S, Sperandei S, Ph D, et al. The Impact of Physical Distancing Policies During the COVID-19 Pandemic on Health and Well-Being Among Australian Adolescents. *Journal of Adolescent Health*. 2020;67(5):653-661. doi:10.1016/j.jadohealth.2020.08.008
13. Magson NR, Fardouly J, Freeman JYA, Rapee RM, Richardson CE, Oar EL. Risk and Protective Factors for Prospective Changes in Adolescent Mental Health during the COVID-19 Pandemic. *Journal of Youth and Adolescence*. Published online 2020. doi:10.1007/s10964-020-01332-9
14. Breaux R, Dvorsky MR, Marsh NP, et al. Prospective impact of COVID-19 on mental health functioning in adolescents with and without ADHD: protective role of emotion regulation abilities. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. Published online 2021. doi:10.1111/jcpp.13382
15. Green KH, van de Groep S, Sweijen SW, et al. Mood and emotional reactivity of adolescents during the COVID-19 pandemic: short-term and long-term effects and the impact of social and socioeconomic stressors. *Scientific reports*. 2021;11(1):11563. doi:10.1038/s41598-021-90851-x
16. Barendse M, Flannery J, Cavanagh C, Aristizabal M, et al. Longitudinal change in adolescent depression and anxiety symptoms from before to during the COVID-19 pandemic: An international collaborative of 12 samples. *preprint*. 2021;1(2):7-8.
17. van der Laan S, Finkenauer C, Lenters V, van Harmelen A, Van Der Ent C, Nijhof S. Gender-specific changes in life satisfaction after the COVID-19-related lockdown in Dutch adolescents: a longitudinal study. *Journal of Adolescent Health*. 2021;in press.
18. Van Droogenbroeck F, Spruyt B, Keppens G. Gender differences in mental health problems among adolescents and the role of social support: Results from the Belgian health interview surveys 2008 and 2013. *BMC Psychiatry*. 2018;18(1):1-9. doi:10.1186/s12888-018-1591-4
19. Katier N, Uiterwaal CSPM, De Jong BM, et al. The Wheezing Illnesses Study Leidsche Rijn (WHISTLER): Rationale and design. *European Journal of Epidemiology*. 2004;19(9):895-903. doi:10.1023/B:EJEP.0000040530.98310.0c
20. Hale T, Angrist N, Goldszmidt R, et al. A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). *Nature Human Behaviour*. 2021;5(4):529-538. doi:10.1038/s41562-021-01079-8
21. Blavatnik School of Government. COVID-19: Stringency Index. www.bsg.ox.ac.uk. Published 2020. Accessed May 26, 2021. https://www.bsg.ox.ac.uk/research/research-projects/covid-19-government-response-tracker#data

22. Szkultecka-Dębek M, Dzielska A, Drozd M, Małkowska-Szkutnik A, Mazur J. What does the Cantril Ladder measure in adolescence? *Archives of Medical Science*. 2018;14(1):182-189. doi:10.5114/aoms.2016.60718
23. Cantril H. *The Pattern of Human Concern*. Rutgers University press; 1965.
24. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
25. Ravens-Sieberer U, Erhart M, Torsheim T, et al. An international scoring system for self-reported health complaints in adolescents. *European journal of public health*. 2008;18(3):294-299. doi:10.1093/eurpub/ckn001
26. Levin KA, Currie C. Reliability and Validity of an Adapted Version of the Cantril Ladder for Use with Adolescent Samples. *Social Indicators Research*. 2014;119(2):1047-1063. doi:10.1007/s11205-013-0507-4
27. (CORC) CORC. Revised Children's Anxiety and Depression Scale (and subscales) (RCADS). Accessed April 19, 2021. https://www.corc.uk.net/outcome-experience-measures/revised-childrens-anxiety-and-depression-scale-and-subscales/
28. Greene JW, Walker LS. Psychosomatic problems and stress in adolescence. *Pediatric Clinics of North America*. 1997;44(6):1557-1572. doi:10.1016/S0031-3955(05)70574-5
29. Erhart M, Ottova V, Gaspar T, et al. Measuring mental health and well-being of school-children in 15 European countries using the KIDSCREEN-10 Index. *Int J Public Health*. 2009;54(SUPPL. 2):160-166. doi:10.1007/s00038-009-5407-7
30. Ravens-Sieberer U, Erhart M, Torsheim T, et al. An international scoring system for self-reported health complaints in adolescents. *Eur J Public Health*. 2008;18(3):294-299. doi:10.1093/eurpub/ckn001
31. Pardo MC, Alonso R. Working correlation structure selection in GEE analysis. *Statistical Papers*. 2019;60(5):1447-1467. doi:10.1007/s00362-017-0881-0
32. Moons KGM, Donders RART, Stijnen T, Harrell FE. Using the outcome for imputation of missing predictor values was preferred. *Journal of Clinical Epidemiology*. 2006;59(10):1092-1101. doi:10.1016/j.jclinepi.2006.01.009
33. Romaniuk H, Patton G, Carlin J. Multiple imputation in a longitudinal cohort study: a case study of sensitivity to imputation methods. *AM J Epidemiol*. 2014;180(9):920-932.
34. White I, Royston P, Wood A. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-399.
35. Rogers AA, Ha T, Ockey S. Adolescents' Perceived Socio-Emotional Impact of COVID-19 and Implications for Mental Health: Results From a U.S.-Based Mixed-Methods Study. *Journal of Adolescent Health*. 2021;68(1):43-52. doi:10.1016/j.jadohealth.2020.09.039
36. Cohen ZP, Cosgrove KT, Deville DC, et al. The Impact of COVID-19 on Adolescent Mental Health : Preliminary Findings From a Longitudinal Sample of Healthy and At-Risk Adolescents. 2021;9(June):1-8. doi:10.3389/fped.2021.622608
37. Zijlmans J, Teela L, Ewijk H Van, Klip H. Mental and Social Health of Children and Adolescents With Pre-existing Mental or Somatic Problems During the COVID-19 Pandemic Lockdown. 2021;12(July):1-11. doi:10.3389/fpsyt.2021.692853
38. Orgiles M, Morales A, Delveccio E, Mazzeschi C, Espada J. Immediate psychological effects of the COVID-19 quarantine in youth from Italy and Spain. *preprint DOI*. Published online 2020. doi:10.31234/osf.io/5bpfz
39. Kaditis A, Ohler A, Gileles A, et al. Effects of the COVID – 19 lockdown on sleep duration in children and adolescents : A survey across different continents. *Pediatric Pulmonology*. 2021;(February):1-9. doi:10.1002/ppul.25367
40. Hagenauer MH, Perryman JI, Lee TM, Carskadon MA. Adolescent Changes in the Homeostatic and Circadian Regulation of Sleep. *Developmental Neuroscience*. 2009;1043:276-284. doi:10.1159/000216538
41. Eaton D, McKnight-Eily L, Lowry R, Perry G, Presley-Cantrell L, Croft J. Prevalence of insufficient, borderline, and optimal hours of sleep among high school students. *Journal of Adolescent Health*. 2010;46(4):399-401.
42. Dunster GP, de la Iglesia L, Ben-Hamo M, et al. Sleepmore in Seattle: Later school start times are associated with more sleep and better performance in high school students. *Science Advances*. 2018;4(12):0-7. doi:10.1126/sciadv.aau6200
43. Au R, Carskadon M, Millman R, et al. School start times for adolescents. *Pediatrics*. 2014;134(3):642-649. doi:10.1542/peds.2014-1697

44. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet*. 2012;379:1056-1067. doi:10.1016/S0140-6736(11)60871-4.Depression

45. Rose A, Rudolph K. A review of sex differences in peer relationship processes: Potential trade-offs for the emotional and behavioral development of girls and boys. *Psychological Bulletin*. 2006;132(1):98-131. doi:https://doi.org/10.1037/0033-2909.132.1.98

46. Watkins D, Cheng C, Mpofu E, Olowu S, Singh-Sengupta S, Regmi M. Gender differences in self-construal: How generalizable are western findings? *Journal of Social Psychology*. 2003;143(4):501-519. doi:10.1080/00224540309598459

47. WHO. *Spotlight and Adolescent Health and Well-Being. Findings from the 2017/2018 Health-Behaviour in School-Aged Children (HBSC) Survey in Europe and Canada. International Report, Volume 1: Key Findings*.; 2020.

48. Widnall E, Winstone L, Mars B, Haworth C, Kidger J. Young people's mental health during the covid-19 pandemic: initial findings from a secondary school survey study in SouthWest England. https://sphr.nihr.ac.uk/wp- content/uploads/2020/08/Young-Peoples-Mental- Health-during-the-COVID-19-Pandemic-Report- Final.pdf.

49. Sun J, Stewart D. Age and Gender Effects on Resilience in Children and Adolescents. *International Journal of Mental Health Promotion*. 2007;9(4):16-25.

50. Ioannidis K, Askelund AD, Kievit RA, Van Harmelen AL. The complex neurobiology of resilient functioning after childhood maltreatment. *BMC Medicine*. 2020;18(1):1-16. doi:10.1186/s12916-020-1490-7

51. Health Behaviour in School-aged Children. About HBSC. http://www.hbsc.org/about/index.html. http://www.hbsc.org/about/index.html

52. Viner R, Russell S, Saulle R, et al. School Closures During Social Lockdown and Mental Health, Health Behaviors, and Well-being Among Children and Adolescents During the First COVID-19 Wave A Systematic Review. 2022;176(4):400-409. doi:10.1001/jamapediatrics.2021.5840

53. Rosenthal N, Carpenter C, James S, Parry B, Rogers S, Wehr T. Seasonal affective disorder in children and adolescents. *The American Journal of Psychiatry*. 1986;143(3):356-358.

SUPPLEMENT 1:

Summary of when and which lockdown measures were introduced and eased

In the Netherlands, the first COVID-19 confirmed patient was diagnosed February 27, 2020. Starting on March 15 a lockdown was enforced, meaning closure of school and child care facilities, as well as sport clubs, cafes and restaurants. The first follow-up questionnaire was sent on April 18, 2020 (T1). On May 11, primary schools partially reopened and on June 2 secondary schools followed [1]. On July 18, 2020, when the second follow-up questionnaire was sent (T2), the school summer holidays started. At that point in time, sport clubs, cafes and restaurants were open again. Face masks had to be worn only while taking public transportation [2]. From October 13, 2020, a partial lockdown was announced: cafes and restaurants closed and large social events were forbidden. Schools remained open, however, and face masks were obligatory inside the school buildings [3]. Just after this second lockdown was introduced, we sent our third follow-up questionnaire (T3, October 18, 2020). As the number of COVID-19 cases rose, more restrictions were incrementally implemented over time and in February 2021, a second full lockdown was implemented, including closure of schools, non-essential shops, sport clubs, and contact-based professions such as hairdressers [4]. Additionally, a curfew was implemented (from 9:00 p.m. – 04:30 a.m.) and citizens were only allowed to receive one visitor a day. Our fourth follow-up questionnaire was sent during this full lockdown (T4, February 2, 2021).

REFERENCES

1. Website Government of the Netherlands.
2. Rijksoverheid. Persconferentie coronavirus: nieuwe regels per 1 juli 2020 in eenvoudige taal. www.rijksoverheid.nl. Published 2020. Accessed April 1, 2021. https://www.rijksoverheid.nl/onderwerpen/coronavirus-covid-19/vraag-en-antwoord/persconferentie-coronavirus-nieuwe-regels-per-1-juli-2020-in-eenvoudige-taal
3. Rijksoverheid. Gedeeltelijke lockdown om besmettingen terug te dringen. www.rijksoverheid.nl. Published 2020. Accessed April 1, 2021. https://www.rijksoverheid.nl/actueel/nieuws/2020/10/13/gedeeltelijke-lockdown-om-besmettingen-terug-te-dringen
4. Rijksoverheid. *Routekaart Coronamaatregelen (Versie 2 Februari 2021)*.; 2020.

SUPPLEMENT 2:

Summary of used instruments

Instrument	Content/subscales	Items	Values	α
Cantril ladder[1,2] General life satisfaction	How do you feel about your life?	*1*	0 (worst possible life) to 10 (best possible life)	na
RCADS[3] Internalizing symptoms	Subscale separation anxiety disorder Subscale social phobia Subscale generalized anxiety disorder Subscale panic disorder Subscale obsessive compulsive disorder Subscale major depressive disorder	47	never, sometimes, often, always higher score = more severe symptoms	0.94
HSBC-SCL 2017[4] Psychosomatic health	How often have you suffered from the following in the last 6 months? · Headache · Stomach ache · Back ache · Feeling unhappy · Having a bad mood · Being nervous · Being dizzy · Being tired · Being exhausted · - Trouble with falling asleep	*10*	About every day; more than once a week; about every week; about every month; rarely or never	*0.995*

α = Cronbach's alpha; HSBC-SCL 2017 = Health Behavior in School-ages Children Symptom Checklist; na = applicable; RCADS = Revised Child Anxiety and Depression Scale

REFERENCES

1. Szkultecka-Dębek M, Dzielska A, Drozd M, Małkowska-Szkutnik A, Mazur J. What does the Cantril Ladder measure in adolescence? *Archives of Medical Science*. 2018;14(1):182-189. doi:10.5114/aoms.2016.60718
2. Cantril H. *The Pattern of Human Concern*. Rutgers University press; 1965.
3. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
4. Ravens-Sieberer U, Erhart M, Torsheim T, et al. An international scoring system for self-reported health complaints in adolescents. *Eur J Public Health*. 2008;18(3):294-299. doi:10.1093/eurpub/ckn001

SUPPLEMENT 3:

Original data and multiple imputation

	Life satisfaction +							
	Original data		*Multiple imputation*		*Original data*		*Multiple imputation*	
Time of assessment	**Crude**	**(95% CI)**	**Crude**	**(95% CI)**	**Adj.**	**(95% CI)**	**Adj.**	**(95% CI)**
To: before COVID-19 pandemic	ref	-	ref	-	ref	-	ref	-
T1: first full lockdown	-0.47	(-0.66;-0.28)	-0.47	(-0.68;-0.26)	-0.32	(-0.54;-0.11)	-0.36	(-0.58;-0.13)
T2: first full lockdown eased	-0.34	(-0.55;-0.13)	-0.33	(-0.55;-0.12)	-0.16	(-0.40;0.08)	-0.19	(-0.42;0.05)
T3: partial lockdown	-0.58	(-0.80;-0.36)	-0.56	(-0.78;-0.34)	-0.36	(-0.61;-0.10)	-0.37	(-0.63;-0.12)
T4: second full lockdown	-1.02	(-1.24;-0.81)	-1.02	(-1.25;-0.80)	-0.70	(-0.96;-0.44)	-0.79	(-1.07;-0.52)
	*Internalizing symptoms ++ **							
Time of assessment	**Crude**	**(95% CI)**	**Crude**	**(95% CI)**	**Adj.**	**(95% CI)**	**Adj.**	**(95% CI)**
To: before COVID-19 pandemic	ref	-	ref	-	ref	-	ref	-
T1: first full lockdown	1.49	(0.13;2.86)	1.18	(-0.15;2.50)	1.06	(-0.56;2.68)	0.96	(-0.58;2.50)
T2: first full lockdown eased	1.91	(0.34;3.49)	0.95	(-0.37;2.27)	0.68	(-1.11;2.47)	0.66	(-1.00;2.31)
T3: partial lockdown	2.33	(0.68;3.96)	1.27	(-0.05;2.58)	0.83	(-1.18;2.83)	0.90	(-0.90;2.69)
T4: second full lockdown	4.06	(2.31;5.82)	3.04	(1.50;4.58)	3.06	(0.68;5.44)	2.58	(0.41;4.75)
	Psychosomatic health +++							
Time of assessment	**Crude**	**(95% CI)**	**Crude**	**(95% CI)**	**Adj.**	**(95% CI)**	**Adj.**	**(95% CI)**
To: before COVID-19 pandemic	ref	-	ref	-	ref	-	ref	-
T1: first full lockdown	0.22	(0.14;0.31)	0.25	(0.17;0.32)	0.30	(0.20;0.39)	0.29	(0.20;0.38)
T2: first full lockdown eased	0.31	(0.22;0.41)	0.30	(0.22;0.39)	0.40	(0.29;0.50)	0.36	(0.26;0.46)
T3: partial lockdown	0.23	(0.13;0.33)	0.26	(0.17;0.35)	0.33	(0.20;0.46)	0.33	(0.22;0.45)
T4: second full lockdown	0.07	(-0.04;0.19)	0.12	(0.01;0.22)	0.21	(0.06;0.37)	0.20	(0.07;0.34)

Abbreviations: Adj.= adjusted. Adjusted for: gender and age. * as the RCADS score were already converted in gender and age-normed T-scores, we did not adjust for confounders. Ref= reference.
T0 = before the COVID-19 lockdown; T1 = first full lockdown (assessment April 18, 2020); T2 = first full lockdown eased (assessment July 18, 2020); T3 = partial lockdown (assessment October 18, 2020); T4 = second full lockdown (assessment February 2, 2021).
+ a higher score indicates a higher life satisfaction; ++a higher score more severe self-reported internalizing symptoms; +++ a higher score indicates experiencing psychosomatic complaints less frequently.

SUPPLEMENT 4:

Life satisfaction, internalizing symptoms, and psychosomatic health before and throughout the first year of the COVID-19 pandemic

Mental wellbeing	***T0***	***(n=224)***	***T1***	***(n=158)***	***T2***	***(n=149)***	***T3***	***(n=152)***	***T4***	***(n=128)***
Stringency index	na		78.70		39.81		62.04		78.80-82.41	
Life satisfaction[+] mean (SD), range 0-10	7.62	(1.19)	7.15	(1.08)	7.28	(1.19)	7.04	(1.30)	6.60	(1.53)
Internalizing symptoms[++] mean (SD), range 0-141	40.28	(9.72)	41.77	(10.29)	42.20	(10.33)	42.63	(10.49)	44.35	(11.37)
Psychosomatic health [+++] mean (SD), range 0-5	3.91	(0.67)	4.14	(0.66)	4.23	(0.59)	4.15	(0.69)	3.98	(0.77)

T0 = before the COVID-19 lockdown; T1 = first full lockdown (assessment April 18, 2020); T2 = first full lockdown eased (assessment July 18, 2020); T3 = partial lockdown (assessment October 18, 2020); T4 = second full lockdown (assessment February 2, 2021).
[+] a higher score indicates a higher life satisfaction; [++]a higher score more severe self-reported internalizing symptoms; [+++] a higher score indicates experiencing psychosomatic complaints less frequently.

SUPPLEMENT 5:

Changes in specific psychosomatic symptoms during the first year of the COVID-19 pandemic compared to before the pandemic.

Psychosomatic health, Mean (SD)	**T0 (n=224)**		**T1 (n=158)**		**p**	**T2 (n=149)**		**p**	**T3 (n=152)**		**p**	**T4 (n=128)**		**p**
- Headache	4.16	(1.06)	4.29	(1.05)	0.06	**4.47**	**(0.93)**	0.000	**4.43**	**(0.95)**	0.004	4.24	(1.07)	0.45
- Stomach ache	4.50	(0.83)	**4.67**	**(0.80)**	0.04	**4.73**	**(0.62)**	0.005	4.63	(0.66)	0.24	4.61	(0.71)	0.71
- Backache	4.44	(0.93)	4.42	(0.97)	0.73	4.48	(0.88)	0.50	4.32	(1.11)	0.24	4.25	(1.06)	0.046
- Feeling unhappy	4.32	(1.00)	4.36	(1.09)	0.09	**4.45**	**(1.02)**	0.04	4.31	(1.03)	0.84	**3.96**	**(1.21)**	0.001
- Having a bad mood+	3.51	(1.08)	3.67	(1.05)	0.16	3.67	(1.09)	0.23	**3.78**	**(1.11)**	0.027	3.60	(1.13)	0.63
- Being nervous	3.92	(1.04)	4.08	(1.14)	0.17	**4.23**	**(1.02)**	0.003	4.03	(1.10)	0.09	3.93	(1.18)	0.74
- Being dizzy	4.37	(1.03)	4.38	(1.06)	0.68	4.54	(0.93)	0.13	**4.53**	**(0.92)**	0.02	4.37	(1.08)	0.84
- Being tired +	3.15	(1.28)	**3.55**	**(1.33)**	0.001	**3.53**	**(1.24)**	0.003	**3.41**	**(1.23)**	0.03	3.27	(1.37)	0.46
- Being exhausted	4.04	(1.23)	**4.29**	**(1.15)**	0.005	**4.37**	**(1.05)**	0.007	4.10	(1.22)	0.57	4.06	(1.32)	0.99
- Trouble with falling asleep	2.72	(1.29)	**3.71**	**(1.34)**	0.000	**3.82**	**(1.34)**	0.000	**4.00**	**(1.25)**	0.000	**3.60**	**(1.40)**	0.000

All tested with Signed Wilcoxon rank test, compared with baseline, except when + is indicated. Then a dependent t test is used.
Significant differences in **bold**.

CHAPTER 9

THE IMPACT OF THE COVID-19 OUTBREAK ON MENTAL WELLBEING IN CHILDREN WITH A CHRONIC CONDITION COMPARED TO HEALTHY PEERS

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ABSTRACT

The aim of this study was to assess the impact of the COVID-19 pandemic on the mental wellbeing of children 8–18 years old with chronic conditions, by comparing pandemic data with pre-pandemic data and with healthy peers. Data were obtained from two ongoing longitudinal cohorts: the PROactive cohort study following children with a chronic condition, and the WHISTLER population cohort. Mental wellbeing was assessed by three indicators: life satisfaction, internalising symptoms, and psychosomatic health. The stringency of the COVID-19-related lockdown was considered a moderating factor. Data on chronic patients were recorded before (n = 934, 65% girls) and during (n = 503, 61% girls) the pandemic, and compared to healthy peers during the pandemic (n = 166, 61% girls). Children with a chronic condition reported lower life satisfaction, but no clinically relevant changes in internalising symptoms or psychosomatic health, during the pandemic compared to before. In comparison to healthy peers, children with a chronic condition experienced decreased life satisfaction and psychosomatic health, but internalising symptoms did not differ between groups during the COVID-19 pandemic. The lockdown stringency was negatively associated with all indicators of mental wellbeing—worse life satisfaction, more internalising symptoms, and more psychosomatic symptoms.

INTRODUCTION

At the end of 2019, a local outbreak of COVID-19 in Wuhan occurred, and rapidly progressed into a global pandemic [1,2]. Governments imposed strict measures to control the spread of the virus, which also impacted the daily routines of children and adolescents (hereafter referred to as children) [3]. The closing of schools and the reduction in social contact with peers are of particular concern from a psychosocial viewpoint [4,5]. Thus, the rapid spread of coronavirus and subsequent social restrictions have led to increased mental health problems [6,7]. The government restrictions differ from country to country. The Oxford Coronavirus Government Response Tracker (OxCGRT) calculates the stringency index, which indicates the strictness of COVID-19 restrictions by day and country [8,9].

COVID-19 literature regarding mental wellbeing has mostly focused on healthy children. The pandemic has often resulted in decreased life satisfaction [10], increased internalising symptoms (including anxiety and depression), and more mental health problems and psychosomatic complaints [11–14]. However, there is a paucity of knowledge about the effects of the pandemic on children with chronic conditions, who are a population at risk of decreased mental wellbeing [15,16]. In general, children with a chronic condition rate their psychosocial functioning, developmental milestones, and mental wellbeing lower than their healthy peers [15,17]. Pre-existing vulnerabilities—such as socioeconomic disadvantage, elevated levels of internalising and externalising problems, a higher amount of stressful events, or disabilities—are more common in this group, and may increase the risk of poor mental health outcomes during the COVID-19 pandemic [18,19,20,21]. At-risk individuals may experience new onset of mental health problems, while those with pre-existing mental health problems may experience symptomatic exacerbation—especially if access to mental health services is impeded due to COVID-19 regulations [21,22]. To date, empirical studies of the mental wellbeing burden of the pandemic are scarce in this vulnerable population—particularly longitudinal studies [23]. A better understanding is of clinical relevance, since this enables health professionals to incorporate pandemic-related effects into their care for their patients.

Before and during the pandemic, the Dutch Patient-Reported Outcomes active cohort study (PROactive) [24] and Wheezing Illnesses Study Leidsche Rijn population cohort study (WHISTLER) [25] collected data in children with chronic conditions and healthy peers. Importantly, measurements from both cohorts were harmonized, and participants were recruited from the same geographical area. This provides the unbiased and unique opportunity to study the impact of the pandemic on the wellbeing of children with a chronic condition compared to healthy children [24,26]. Therefore, the aims of this exploratory study were as follows: to compare the mental wellbeing of children with a chronic condition before and during the COVID-19 pandemic (*aim 1*), to compare the mental wellbeing of children with a chronic condition and healthy peers during the pandemic (*aim 2*), and to

explore the associations between government restrictions—as measured by the OxCGRT stringency index—and the mental wellbeing of children with a chronic condition and healthy children (*aim 3*).

2. METHODS

2.1. Research population and study design

We compared mental wellbeing in children with a chronic condition before and during the pandemic *(aim 1)*. For this comparison, children aged 8–18 years were selected from the ongoing PROactive cohort study [24,26]. Since 2016, this cohort has been collecting data on psychosocial wellbeing in children with various conditions—including cystic fibrosis, (auto)immune diseases, congenital heart diseases, kidney disease, and persistent physical complaints—visiting the outpatient clinic of the Wilhelmina Children's Hospital Utrecht, the Netherlands—hereafter referred to as "children with a chronic condition". Questionnaires completed before March 2020 were classified as "pre-COVID-19", as the first Dutch case was reported 27 February [27]. All data collected between July 2020 and July 2021 were classified as "during COVID-19".

Next, we compared children with a chronic condition with healthy peers, focused on effects during the pandemic (*aim 2*). We used data from the PROactive cohort [24] and the WHISTLER cohort [25]. The WHISTLER cohort's population included over 3000 newborns residing in the region of Utrecht, the Netherlands, born between 2002 and 2013 [25]. In March 2019, WHISTLER participants were routinely invited to the 12–16-year-old assessments, with a focus on their health and mental wellbeing during adolescence. Due to the onset of the pandemic, they had to pause this follow-up, but the 224 assessments already taken were considered the baseline for a five-wave prospective longitudinal study of changes in mental wellbeing during the Dutch pandemic [10]. For this study, a random sample was drawn from the subsequent 3 waves of data collection during the first year of the Dutch pandemic between 18 July 2020 and 9 March 2021.

Figure 1 visualises the timing of data collection, along with Dutch COVID-19 restrictions over the course of 15 months. For our 3rd aim, we investigated the effect of the lockdown stringency index on the different indicators of mental wellbeing in children with a chronic condition and their healthy peers [8,9].

Both cohorts were approved by the ethical committee of the University Medical Center Utrecht, the Netherlands.

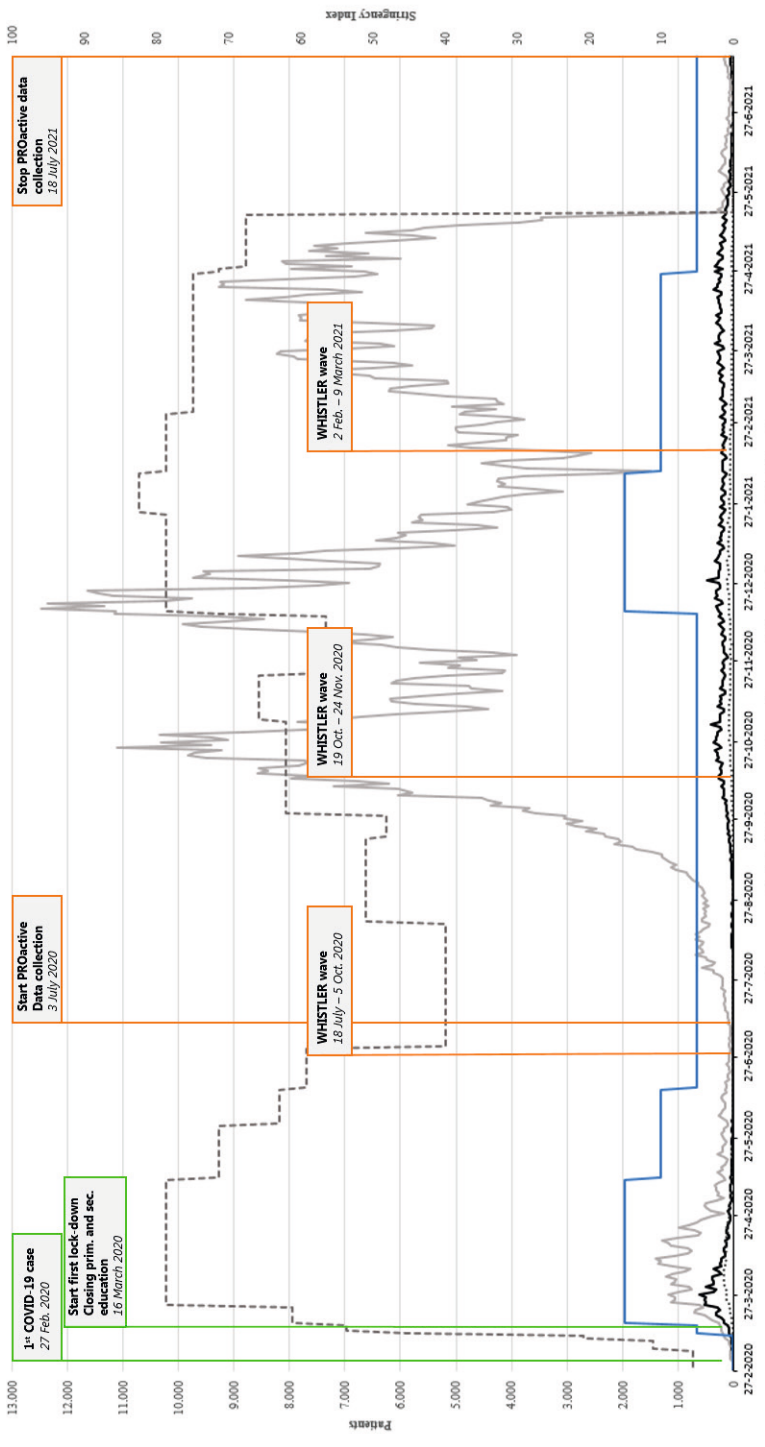

Figure 1: Prevalence of confirmed COVID-19 cases [28], hospital admissions [28], deaths [28], school closures [28], and stringency index scores [29], along with specific time points of the present study (data originating from the Dutch National Institute for Public Health and the Environment (RIVM)).

2.2. Measurements

Mental wellbeing was assessed using three indicators [10]: life satisfaction, internalising symptoms, and psychosomatic health. Questionnaires were aligned in both the PROactive and WHISTLER studies. Supplement 1 provides detailed information regarding the measurements.

Life satisfaction was measured using the Cantril ladder [30,31], which includes one question: "Looking at the past 3 months, how do you feel about your life?". Possible answers range from 0 to 10 (10 = best possible life).

Internalising symptoms were assessed using the Revised Child Anxiety and Depression Scale (RCADS) [32,33], which is based on anxiety disorders and depression from the DSM-IV [33]; it is a 47-item questionnaire with anxiety subscales such as social phobia, generalised anxiety disorder, depressive disorder, etc. The sum of all of the subscales (total score) is a global indication of internalising symptoms, with higher scores indicating more severe symptoms. As in our study the correlation between the subdomains "anxiety" and "depressive disorder" was $r > 0.7$, we choose to analyse these subdomains together as internalising symptoms. Based on age and sex, raw scores were converted to normative T-scores[34]. A score < 65 is considered normal, 65–70 is borderline, and > 70 is critical.

Psychosomatic health was assessed using the Dutch Health Behaviour in School-Aged Children Symptom Checklist (HBSC-SCL) 2017 [35,36], consisting of 10 questions evaluating the severity of symptoms, such as having a headache, being nervous, etc. These symptoms are often related to psychosocial factors, such as stress [10,37]. A high mean score reflects better psychosomatic health [15]. This instrument (Dutch 2017 version) has good psychometric properties, and has been validated as an unbiased measurement of subjective health complaints (Cronbach's alpha > 0.70) [15].

Stringency index was assessed with the OxCGRT [8,9], providing the stringency of COVID-19 restrictions per day and country. The index is based on 23 indicators, such as school closures and travel restrictions, resulting in a score of 0 to 100 (100 = strictest) [9]. We linked this stringency scores to the dates the patients' completed the questionnaires.

2.3. Statistical analyses

We compared the mental wellbeing of children with a chronic condition before and during the pandemic (aim 1), as well as mental wellbeing between children with a chronic condition and healthy peers during the pandemic (aim 2), using analysis of variance (ANOVA). Here, we considered two independent variables (main effects) and their interaction: time point (aim 1) or cohort (aim 2), and gender (girls or boys), as well as the interactions time point*gender (aim 1) and group*gender (aim 2). The interaction provides information on the extent to which potential gender differences are similar between time points (aim 1)

and groups (aim 2). In case of significant interactions, a stratified ANOVA was performed. In case of significant difference in time points (aim 1), the mean differences from aim 1 before and during the pandemic of the WHISTLER cohort [10] were compared (data not shown). We explored the association between local government restrictions (stringency index) and the mental wellbeing of children with a chronic condition and healthy children using a hierarchical linear regression (aim 3). In the hierarchical linear regression, we entered the stringency index, group (children with a chronic condition or healthy peers), and the interaction stringency index*group as independent variables in steps 1, 2, and 3, respectively. Separate models were run for each of the dependent variables (i.e., life satisfaction, internalising symptoms, and psychosomatic health). An observed p-value of < 0.05 was considered statistically significant.

3. RESULTS

3.1. First aim; mental wellbeing in children with a chronic condition before versus during the pandemic

Table 1 shows the characteristics of the two PROactive cohort samples of children with a chronic condition before (n = 944) and during the pandemic (n = 545). These are two different samples of children with a chronic condition. Life satisfaction was significantly lower during the pandemic compared to before the pandemic ($F(1, 1469) = 30.27$; $p < 0.001$). Girls had a significantly lower life satisfaction score compared to boys ($F(1, 1469) = 42.70$; $p < 0.001$) (Supplement 2). The interaction time point*gender was not significant ($F(1, 1469) = 2.25$; $p = 0.13$), indicating that COVID-19 had no difference in impact on girls than on boys. Figure 2 visualizes the findings.

We found non-significant findings for the two remaining dependent variables. First, internalising symptoms were similar during the pandemic compared to before the pandemic ($F(1, 1151) = 0.00$; p 0.96). Girls experienced internalising symptoms significantly more often compared to boys ($F(1, 1151) = 53.20$; $p \leq 0.001$), although in neither group was the change in mean score clinically relevant (mean < 60). The interaction time point*gender was not significant ($F(1, 1151) = 2.92$ p 0.09). Second, psychosomatic health did not significantly differ during the pandemic compared to before the pandemic ($F(1, 1245) = 0.72$; p 0.40). Girls experienced more psychosomatic symptoms ($F(1, 1245) = 80.44$; $p \leq 0.001$) (Supplement 2). The interaction time point*gender was not significant ($F(1, 1151) = 1.22$; p 0.27), indicating that similar differences between genders were observed for both time points; thus, stratified analyses were not necessary.

Table 1: Characteristics of the participants.

	1st Aim (Chronic Condition before vs. during)		**2nd and 3rd Aims (Chronic Condition vs. Healthy Peers during the Pandemic)**	
	PROactive (Chronic condition)		**PROactive** (Chronic condition) [a]	**WHISTLER** (Healthy peers)
Characteristics	*Pre-pandemic 8–18 yr N = 944*	*During pandemic 8–18 yr N = 545*	*During pandemic 12–18 yr N = 311*	*During pandemic 12–18 yr N = 166*
Age in years, mean ± SD	14.2 (2.8)	14.3 (2.9)	15.7 (1.8)	16.0 (1.3)
Girl, n (%)	601 (64.2)	332 (60.9)	200 (64.3)	94 (56.6)
Disease group				
Persistent physical complaints	481 (51.0)	269 (49.4)	67 (21.5)	n.a.
Paediatric (auto)immune diseases	305 (32.3)	106 (19.4)	163 (52.4)	n.a.
Paediatric cystic fibrosis	72 (7.6)	26 (4.8)	17 (5.5)	n.a.
Paediatric cardiology	63 (6.7)	111 (20.4)	46 (14.8)	n.a.
Paediatric nephrology	22 (2.3)	33 (6.1)	18 (5.8)	n.a.
Education level of the child [b], n (%)				
Primary school	219 (24.0)	105 (25.6)	14 (5.8)	(1.8)
Low	271 (29.7)	117 (28.5)	94 (39.0)	24.1)
Intermediate	208 (22.8)	86 (21)	69 (28.6)	22.3)
High	177 (19.4)	79 (19.3)	64 (26.6)	48.8)
Other (special education or working)	37 (4.1)	23 (5.6)	0 (0)	5 (3.0)

[a] For comparison with healthy peers (*aim 2 and 3*), the 12–18-year-old children from the PROactive cohort were selected. [b] Low: pre-vocational secondary education; intermediate: higher general secondary education or intermediate vocational education; high: pre-university education, higher vocational education, and university education. SD: standard deviation.

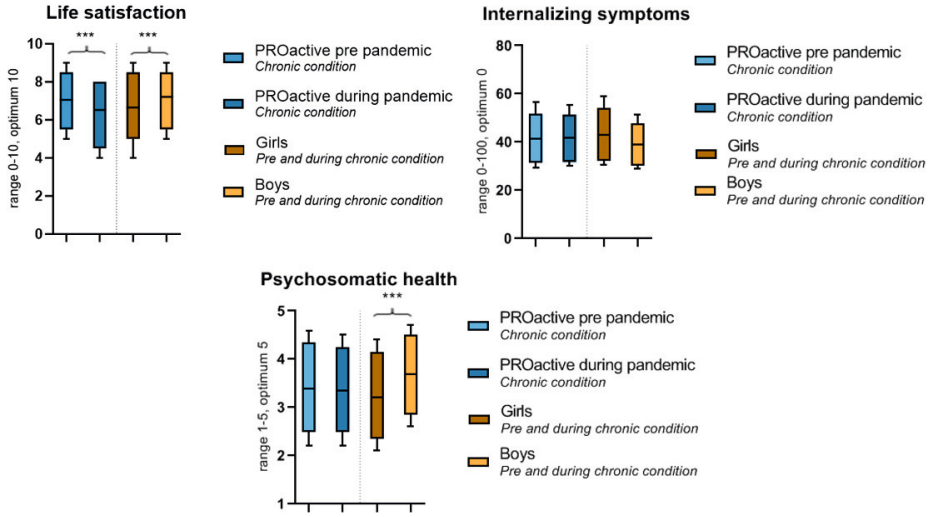

Figure 2: Group difference indicators of mental wellbeing in children with a chronic condition before and during the COVID-19 pandemic (aim 1).

3.2. Second aim: mental wellbeing in children with a chronic condition versus healthy peers during the pandemic

For the second aim, children with a chronic condition (n = 311) were compared to healthy peers (n = 166) during the pandemic. Table 1 provides the children's characteristics. Life satisfaction was significantly lower in children with a chronic condition compared to healthy peers ($F(1, 473) = 13.92$; $p < 0.001$). Girls reported lower life satisfaction than boys ($F(1, 473) = 13.41$; $p < 0.001$) (Supplement 3). The interaction group*gender was not significant ($F(1, 473) = 0.05$; $p = 0.83$), indicating that the reported difference is attributable to their chronic condition. Figure 3 visualises the findings.

Additional analysis with pre-pandemic WHISTLER data showed a difference in both cohorts (PROactive and WHISTLER) of 0.5 points in life satisfaction before and during the pandemic (data not shown), indicating that children with a chronic condition experienced a similar effect compared to healthy peers.

The internalising symptoms score was not significantly different in children with a chronic condition compared to healthy peers ($F(1, 359) = 0.03$; p 0.87) (Supplement 3). Girls had more internalising symptoms ($F(1, 359) = 26.40$; p <0.001) than boys. The interaction time group*gender was not significant ($F(1, 359) = 2.50$; p 0,12).

Psychosomatic health complaints were reported significantly more often in children with a chronic condition compared to healthy peers ($F(1, 345) = 91.77$; $p \leq 0.001$). Girls experienced more psychosomatic symptoms ($F(1, 345) = 48.48$; $p \leq 0.001$) than boys. The interaction group*gender was not significant ($F(1, 345) = 1.76$; $p \leq 0.19$) (Supplement 3).

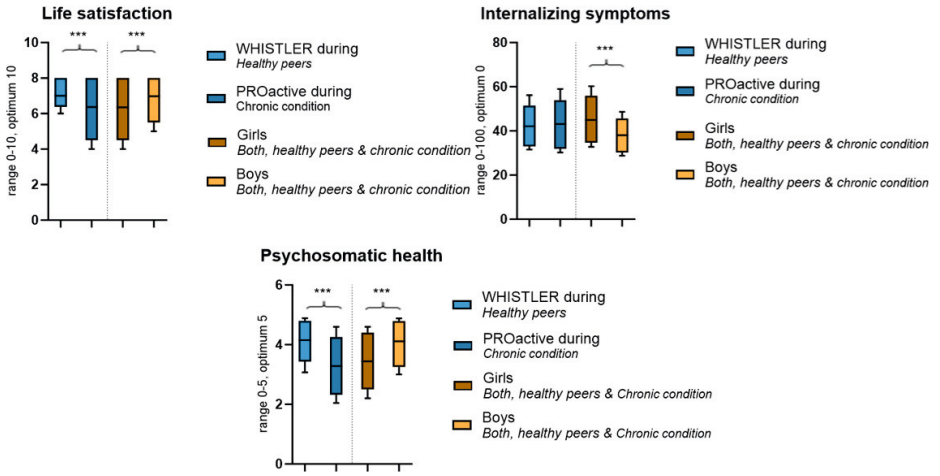

Figure 3: Group difference indicators of mental wellbeing in children with a chronic condition versus healthy peers during the pandemic (aim 2).

3.3. Third aim: associations between government restrictions and the mental wellbeing of children with a chronic condition and healthy children

Here, a hierarchical linear regression analysis with separate models was conducted for each of the dependent variables (see Table 2). In step 1, higher scores on the stringency index were associated with worse life satisfaction (t = -3.67, $p < 0.001$), internalising symptoms (t = 3,303, $p \leq 0.001$), and psychosomatic health (t = -2.48, $p \leq 0.01$). Stringency index explained 2–3% of the variability in mental wellbeing; adjusted R^2 values were 0.03, (F(1, 475) = 13.47; $p < 0.001$) for life satisfaction, 0.03, (F(1, 360) = 6.42; $p < 0.002$) for internalising symptoms, and 0.02, (F(1, 347) = 6.16; p 0.01) for psychosomatic health. In step 2, disease state (i.e., chronic condition vs. healthy peers) additionally explained 3–6% of the remaining variability in general wellbeing; adjusted R^2 values were 0.06, (F(1, 474) = 20.44; $p < 0.001$) for life satisfaction, 0.04, (F(1, 360) = 4,59; p 0.04) for internalising symptoms, and 0.27, (F(1,346) = 121.39; p 0.00) for psychosomatic health. In step 3, stringency index, group (disease state), and the interaction stringency*group explained 28% of the variability in the dependent variable "psychosomatic health" (adjusted R^2 = 0.28; F(1, 345) = 7.78; p 0.01). The interaction stringency index*group was not significant for life satisfaction nor for internalising symptoms (p 0.68 and 0.34). Table 2 displays the findings.

Table 2: Regression indicators of mental wellbeing in children with a chronic condition versus healthy peers during the pandemic (aim 2 and 3).

	Life Satisfaction					*Internalising Symptoms*					*Psychosomatic Health*				
	B	**95% CI for B**		**β**	**Adj. R^2**	**B**	**95% CI for B**		**β**	**Adj. R^2**	**B**	**95% CI for B**		**β**	**Adj. R^2**
Step 1					0.026 ***					0.029 *					0.015 *
Stringency	−0.015	(−0.023;	−0.007)	−0.166 ***		0.107	(0.043;	0.171)	0.183 ***		−0.007	(−0.012;	−0.001)	−0.132 **	
Step 2					0.064 ***					0.034 **					0.268 ***
Stringency	−0.017	(−0.025;	−0.009)	−0.185 ***		0.114	(0.050;	0.178)	0.183 ***		−0.009	(−0.014;	−0.005)	−0.182 ***	
Group	−0.698	(−1.002;	−0.395)	−0.201 ***		1.683	(−0.718;	4.08)	0.072 ns		−0.912	(−1.075;	−0.749)	−0.508 ***	
Step 3					0.062 ns					0.037 **					0.282 **
Stringency	−0.010	(−0.042;	0.021)	−0.114 ns		0.000	(−0.241;	0.241)	0.001 ns		0.12	(−0.004;	−0.027)	0.238 ns	
Group	−0.693	(−0.998;	0.389)	−0.200 ***		1.529	(−0.892;	3.951)	0.066 ns		−0.900	(−1.061;	−0.738)	−0.501 ***	
Interaction	−0.004	(−0.021;	0.041)	−0.073 ns		0.068	(−0.071;	0.206)	0.188 ns		−0.013	(−0.022;	−0.004)	−0.438 **	

Adj. R^2: adjusted R^2 with significance levels of F-change; B: unstandardized regression coefficient; β: standardized regression; CI: Confidence intervals; ns: p not significant; *: $p < 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$.

4. DISCUSSION

This study of children's mental wellbeing compared pandemic data with pre-pandemic data between children with a chronic condition and healthy peers. The present study provides four key findings. First, the pandemic had a negative impact on the life satisfaction of children with a chronic condition, but our data showed no clinically relevant changes in internalising symptoms or psychosomatic health during the pandemic compared to before. Second, compared to healthy peers, children with a chronic condition experienced poorer life satisfaction and psychosomatic health during the pandemic, but internalising symptoms did not differ between groups. Third, compared to boys, girls robustly reported worse mental wellbeing, and this difference was apparent regardless of the pandemic or their disease state. Fourth, stricter governmental restrictions [9] were significantly associated with poorer life satisfaction, more internalising symptoms, and worse psychosomatic health in both children with a chronic condition and healthy peers, with the stringency index explaining up to 28% of variance in psychosomatic symptoms.

Adolescents with a chronic condition might be particularly susceptible to the effects of the pandemic on mental wellbeing. Our study found that, compared with healthy peers, children with a chronic condition experienced both decreased life satisfaction and decreased psychosomatic health during the pandemic; however, this difference was probably pre-existing. We performed an additional analysis with pre-pandemic WHISTLER data that showed a mean difference in life satisfaction in both cohorts of 0.5 points before and during the pandemic. This suggests that children with a chronic condition did not experience more distress than healthy peers due to the pandemic, but that the difference was there before, and remained without increasing.

Previous studies of mental wellbeing in children during and before the pandemic can be used to benchmark our findings, keeping in mind that these studies likely did not evaluate mental wellbeing throughout the first year of the pandemic, and that little literature is available on the impact of the pandemic on wellbeing in children with a chronic condition.

Zijlmans et al. [38] compared a clinical paediatric sample (aged 8–18 years, n = 90, including juvenile idiopathic arthritis, endocrinological diseases, and cystic fibrosis) with the general population (n = 844), and reported significantly better scores for anxiety, depressive symptoms, and anger in the clinical sample; however, they collected data in a relatively small group and small timeframe at the beginning of the Dutch pandemic (April–May 2020), making their data difficult to compare with our data. Nevertheless, children with pre-existing mental health problems had lower mental wellbeing than children with somatic disease or healthy peers. The findings suggest that it is possible that some children growing up in more challenging circumstances—such as those with a chronic illness—are more resilient than healthy children.. Therefore, follow-up research within our research

field should aim to identify what risk and resilience factors might influence changes in mental wellbeing during the pandemic—especially in subgroups at higher risk of mental health problems. As a result, we hope that when another pandemic occurs, we will have a better understanding of which children need additional observations and support. A recent study in children with genetic generalised epilepsy showed emotional and psychological resilience during the COVID-19 pandemic; we wonder whether this is also the case transdiagnostically (across disease groups) and in comparison to healthy peers [39]. A recent review of 116 articles that evaluated the impact of the pandemic on the mental health of children—including children with a chronic condition—concluded that children with neurodiversity and/or chronic physical conditions were more likely to have negative mental health outcomes such as fear, anxiety, and depression compared to healthy peers [40]. This is not consistent with our findings, as we found no changes in internalising symptoms in children with a chronic condition. This may be due to differences in outcome measures, as well as the relatively small numbers of children with a chronic condition in this review. Notably, less than 15% of the available studies in this review used validated instruments, which the authors rightly state leads to challenges in interpreting the clinical relevance of mental health impacts and differentiation between adaptive symptoms and mental illness. Neither study considered the relationship between mental health outcomes and the degree of governmental restrictions.

We showed that a stricter OxCGRT stringency index [9] was associated with worse life satisfaction, more internalising symptoms, and worse psychosomatic health in both children with a chronic condition and healthy peers. These data suggest that distress is associated with the degree of governmental restrictions. Our results are consistent with a recent systematic review [41] that reported on the association of school closures during the broader social lockdown of the first waves of the pandemic with mental health, health behaviours, and wellbeing in children aged 0–19 years. The authors found that school closures and social lockdown during the first wave of the pandemic were associated with adverse mental health symptoms (such as anxiety and distress) and health behaviours (such as reduced physical activity and more screen time) [41]; they could not distinguish between the effects of school closures and broader social lockdown measures.

Our and their findings support the idea that the potential epidemiological benefits of closing schools during broader social lockdown measures for infectious disease control must be weighed against the potential adverse effects on mental wellbeing and health behaviours in children. These findings are important for informing government and society about the adverse impacts of the pandemic on children's mental wellbeing with regard to closure measure choices, and also advocate the use of the stringency index in this type of study.

Some strengths and limitations deserve consideration. Our findings are novel and exploratory in nature; independent replication by other research teams would greatly strengthen the conclusions. Our data do not allow us to identify links between different lockdown measures—for example, between school closures/social distancing and mental wellbeing outcomes—nor was it possible to identify which children are most at risk of adverse mental health outcomes. Therefore, it is of interest for future research to consider the extent of governmental restrictions in studies that include mental wellbeing as an outcome measure for the impact of the pandemic, as well as to identify risk and resilience factors that may influence the impact of the pandemic on mental wellbeing in children. The inclusion of two cohorts from the same geographical area and with harmonised measurements is a strength of the present study. Additional strengths include the relatively large sample size and the inclusion of several indicators of mental wellbeing. An interesting future directive would be to substantiate the recorded subjective information with objective biomarkers (e.g., cortisol as a marker of stress), as this may provide a more comprehensive understanding of our findings.

5. CONCLUSIONS

To conclude, children with a chronic condition reported lower life satisfaction during the pandemic than before the pandemic. Compared to healthy peers, both life satisfaction and psychosomatic health were worse in children with a chronic condition. COVID-19 governmental restrictions were associated with all indicators of mental wellbeing, and explained up to 28% of the observed variation in both children with a chronic condition and healthy peers. Further research should focus on determining the clinical relevance of these findings, and explore strategies to identify those children most at risk of serious deterioration in mental wellbeing.

REFERENCES

1. Jiao WY, Wang LN, Liu J, et al. Behavioral and Emotional Disorders in Children during the COVID-19 Epidemic. *Journal of Pediatrics*. 2020;221:264-266.e1. doi:10.1016/j.jpeds.2020.03.013
2. Zhou SJ, Zhang LG, Wang LL, et al. Prevalence and socio-demographic correlates of psychological health problems in Chinese adolescents during the outbreak of COVID-19. *European Child and Adolescent Psychiatry*. 2020;29(6):749-758. doi:10.1007/s00787-020-01541-4
3. Moore SA, Faulkner G, Rhodes RE, et al. Impact of the COVID-19 virus outbreak on movement and play behaviours of Canadian children and youth: A national survey. *International Journal of Behavioral Nutrition and Physical Activity*. 2020;17(1). doi:10.1186/s12966-020-00987-8
4. Hofmann SG, Hayes SC. The Future of Intervention Science: Process-Based Therapy. *Clinical Psychological Science*. 2019;7(1):37-50. doi:10.1177/2167702618772296
5. Ghosh R, Dubey MJ, Chatterjee S, Dubey S. Impact of COVID-19 on children: Special focus on the psychosocial aspect. *Minerva Pediatrica*. 2020;72(3):226-235. doi:10.23736/S0026-4946.20.05887-9
6. Salari N, Hosseinian-Far A, Jalali R, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. *Globalization and Health*. 2020;16(1):57. doi:10.1186/s12992-020-00589-w
7. Almhizai RA, Almogren SH, Altwijery NA, et al. Impact of COVID-19 on Children's and Adolescent's Mental Health in Saudi Arabia. *Cureus*. 2021;13(December 2019):1-13. doi:10.7759/cureus.19786
8. annah Ritchie, Edouard Mathieu, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald DB and MR. Coronavirus Pandemic (COVID-19). OurWorldInData.org. Published 2020. Accessed August 31, 2020. https://ourworldindata.org/covid-stringency-index
9. Hale T, Angrist N, Goldszmidt R, et al. A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). *Nature Human Behaviour*. 2021;5(4):529-538. doi:10.1038/s41562-021-01079-8
10. van der Laan S, Finkenauer C, Lenters V, van Harmelen A, Van Der Ent C, Nijhof S. Gender-specific changes in life satisfaction after the COVID-19-related lockdown in Dutch adolescents: a longitudinal study. *Journal of Adolescent Health*. 2021;69(5):737-745. doi:https://doi.org/10.1016/j.jadohealth.2021.07.013
11. Marques de Miranda D, da Silva Athanasio B, Sena Oliveira AC, Simoes-e-Silva AC. How is COVID-19 pandemic impacting mental health of children and adolescents? *International Journal of Disaster Risk Reduction*. 2020;51:101845. doi:10.1016/j.ijdrr.2020.101845
12. Loades ME, Chatburn E, Higson-Sweeney N, et al. Rapid Systematic Review: The Impact of Social Isolation and Loneliness on the Mental Health of Children and Adolescents in the Context of COVID-19. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2020;59(11):1218-1239.e3. doi:10.1016/j.jaac.2020.05.009
13. Singh S, Roy D, Sinha K, Parveen S, Sharma G, Joshi G. Impact of COVID-19 and lockdown on mental health of children and adolescents: A narrative review with recommendations. *Psychiatry Research*. 2020;293:113429. doi:10.1016/j.psychres.2020.113429
14. Duan L, Shao X, Wang Y, et al. An investigation of mental health status of children and adolescents in china during the outbreak of COVID-19. *Journal of Affective Disorders*. 2020;275:112-118. doi:10.1016/j.jad.2020.06.029
15. Berkelbach van der Sprenkel EE, Nijhof SL, Dalmeijer GW, et al. Psychosocial functioning in adolescents growing up with chronic disease: The Dutch HBSC study. *European Journal of Pediatrics*. Published online 2021:1-11. doi:10.1007/s00431-021-04268-9
16. Varengue R, Brochard S, Bouvier S, et al. Perceived impact of lockdown on daily life in children with physical disabilities and their families during the COVID-19 pandemic. *Child: Care, Health and Development*. 2021;(December 2021):1-14. doi:10.1111/cch.12952
17. Maurice-Stam H, Nijhof SL, Monninkhof AS, Heymans HSA, Grootenhuis MA. Review about the impact of growing up with a chronic disease showed delays achieving psychosocial milestones. *Acta Paediatrica*. Published online August 2019:apa.14918. doi:10.1111/apa.14918
18. Liu JJ, Bao Y, Huang X, Shi J, Lin Lu. Mental health considerations for children quarantined because of COVID-19. *Lancet*. 2020;4(January):19-21. doi:10.1192/bjp.2019.244.2
19. J.R. H, S. T, D.B. H, et al. Reconsidering the juvenile idiopathic arthritis core SET: How patients and caregivers define disease activity. *Arthritis and Rheumatology*. 2016;68:4166-4167. doi:10.1002/art.39977
20. Joyce Lee. Mental health effects of school closures during COVID-19. *Lancet (London, England)*. 2020;4(jun 2020):421.

21. Fegert JM, Vitiello B, Plener PL, Clemens V. Challenges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: A narrative review to highlight clinical and research needs in the acute phase and the long return to normality. *Child and Adolescent Psychiatry and Mental Health*. 2020;14(1):1-11. doi:10.1186/s13034-020-00329-3
22. Moreno C, Wykes T, Galderisi S et al. How mental health care should change as a consequence of the COVID-19 pandemic. *Lancet Psychiatry*. 2020;7(January):813–24.
23. Borel M, Xie L, Kapera O, Mihalcea A, Kahn J, Messiah SE. PrePrint: Long-term physical, mental and social health effects of COVID-19 in the pediatric population: a scoping review. *World Journal of Pediatrics*. 2022;(2022):1-11. doi:10.1007/s12519-022-00515-7
24. Vlist MMN van Der, Hoefnagels JW, Dalmeijer GW, et al. Preprint: The PROactive Cohort Study : Rationale , Design , and Study Procedures. *Research square*. Published online 2021:17. doi:https://doi.org/10.21203/rs.3.rs-1008731/v1 License:
25. Katier N, Uiterwaal CSPM, De Jong BM, et al. The Wheezing Illnesses Study Leidsche Rijn (WHISTLER): Rationale and design. *European Journal of Epidemiology*. 2004;19(9):895-903. doi:10.1023/B:EJEP.0000040530.98310.0c
26. Nap-van der Vlist MM, Dalmeijer GW, Grootenhuis MA, et al. Fatigue in childhood chronic disease. *Archives of disease in childhood*. 2019;104:1090-1095. doi:10.1136/archdischild-2019-316782
27. Wiersinga WJ. SARS-CoV-2 in Nederland: de kliniek van een nieuw virus [Clinical Characteristics of Coronavirus Disease 2019 in the Netherlands]. *Nederlands tijdschrift voor geneeskunde*. 2020;164:20-22.
28. Rijksinstituut voor Volksgezondheid en Milieu. Webpage COVID data on confirmed cases, hospitalization, school closure and deceased. Published 2021. Accessed August 31, 2021. https://www.rivm.nl/coronavirus-covid-19/grafieken#vanaf-27-februari-2020-462441
29. Rijksinstituut voor Volksgezondheid en Milieu. Webpage COVID-19 Dutch Stringency Index. Published 2021. Accessed August 31, 2021. bron: COVID maatregelen https://www.rivm.nl/gedragsonderzoek/tijdlijn-maatregelen-covid
30. Mazur J, Szkultecka-dębek M, Dzielska A, Drozd M. What does the Cantril Ladder measure in adolescence ? 2018;1:182-189. doi:10.5114/aoms.2016.60718
31. Levin KA, Currie C. Reliability and Validity of an Adapted Version of the Cantril Ladder for Use with Adolescent Samples. *Social Indicators Research*. 2014;119(2):1047-1063. doi:10.1007/s11205-013-0507-4
32. Kösters MP, Chinapaw MJM, Zwaanswijk M, van der Wal MF, Koot HM. Structure, reliability, and validity of the revised child anxiety and depression scale (RCADS) in a multi-ethnic urban sample of Dutch children. *BMC Psychiatry*. 2015;15(1):2-8. doi:10.1186/s12888-015-0509-7
33. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
34. Revised Children's Anxiety and Depression Scale (and Subscales) (RCADS). Child outcomes and research consortium. Accessed December 20, 2021. https://www.corc.uk.net/outcome-experience-measures/revised-childrens-anxiety-and-depression-scale-rcads/
35. Ravens-Sieberer U, Erhart M, Torsheim T, et al. An international scoring system for self-reported health complaints in adolescents. *European journal of public health*. 2008;18(3):294-299. doi:10.1093/eurpub/ckn001
36. Erhart M, Ottova V, Gaspar T, et al. Measuring mental health and well-being of school-children in 15 European countries using the KIDSCREEN-10 Index. *International Journal of Public Health*. 2009;54(SUPPL. 2):160-166. doi:10.1007/s00038-009-5407-7
37. Greene JW, Walker LS. Psychosomatic problems and stress in adolescence. *Pediatr Clin North Am*. 1997;44(6):1557-1572. doi:10.1016/S0031-3955(05)70574-5
38. Zijlmans J, Teela L, van Ewijk H, et al. Mental and Social Health of Children and Adolescents With Pre-existing Mental or Somatic Problems During the COVID-19 Pandemic Lockdown. *Frontiers in Psychiatry*. 2021;12(July):1-11. doi:10.3389/fpsyt.2021.692853
39. Kwok S, Engle J, Datta AN. Resilience of adolescents and teenagers with self-limited and genetic-generalized epilepsy during the COVID-19 pandemic. *Epilepsy and Behavior Reports*. 2022;17(March 2020):100520. doi:10.1016/j.ebr.2021.100520
40. Hasina Samji; Judy Wu; Amilya Ladak; Caralyn Vossen; Evelyn Stewart; Naomi Dove; David Long; Gaelen Snell. Review: Mental health impacts of the COVID-19 pandemic on children and youth – a systematic review. *Child and Adolescent Mental Health*. Published online 2021:1-17.
41. Russell Viner, PhD; Simon Russell, PhD; Rosella Saulle, MD; Helen Croker, PhD; Claire Stansfield, PhD; Jessica Packer, MSc; Dasha Nicholls, MD(Res); Anne-Lise Goddings, PhD; Chris Bonell, PhD; Lee Hudson, PhD; Steven Hope, PhD; JosephWard, MBBS; Nina Schw M. School Closures During Social Lockdown and Mental Health, Health Behaviors, and Well-being Among Children and Adolescents During the First COVID-19 Wave A Systematic Review. *JAMA pediatrics*. 2022;18:1-10. doi:10.1001/jamapediatrics.2021.5840

SUPPLEMENT 1:

Summary of used instruments

Instrument	Content/subscales	Items	Values
Cantril ladder [31,32] Life satisfaction	How do you feel about your life?	*1*	0 (worst possible life) to 10 (best possible life)
RCADS [33,34] Internalizing symptoms	Total score [a]	*47*	never, sometimes, often, always higher score = more severe symptoms
HSBC-SCL 2017 [15,38] Psychosomatic health	How often have you suffered from the following in the last 6 months? · Headache · Stomach ache · Back ache · Unhappy · Moody · Nervous · Dizzy · Tired · Exhausted[b] · Difficulties getting to sleep[b]	*10*	About every day; more than once a week; about every week; about every month; rarely or never

a. The total score was used for the analysis. Domains correlate >0.07 with the total score
b. Since 2017, the HBSC added tired and exhausted to the Dutch HBSC questionnaire[15]

SUPPLEMENT 2:

Group difference indicators of mental wellbeing in children with a chronic condition before and during the COVID-19 pandemic (1st aim)

	PROactive before Chronic condition *(N=944)*	**PROactive during** Chronic condition *(N=545)*	**Main effect of group**		**Girls** *Both groups (N=933)*	**Boys** *Both groups (N=548)*	**Main effect of gender**	
			F	df (error)			F	df (error)
Life satisfaction [a] mean (SD), range 0-10	7.05 (1.72)	6.52 (1.73)	30.27***	1 (1469)	6.65 (1.77)	7.21 (1.65)	42.70***	1 (1469)
Internalizing symptoms [b.] mean (SD), range 0-100	41.76 (11.06)	41.98 (11.41)	0.00[ns]	1 (1151)	43.58 (11.85)	38.86 (9.00)	53.20***	1 (1151)
Psychosomatic health [c] mean (SD), range 1-5	3.40 (0.89)	3.35 (0.84)	0.72[ns]	1 (1245)	3.21 (0.87)	3.69 (0.81)	80.44***	1 (1245)

SD, standard deviation; * ns=not significant p<0.05; **p≤.01; *** p≤.001
a. A higher score indicates a higher life satisfaction.
b. A higher score (T-values) indicates more severe self-reported internalizing symptoms. Score <60 is normal, score 65-70 is borderline, >70 is critical
c. A higher score indicates a better psychosomatic health (= less psychosomatic symptoms)

SUPPLEMENT 3:

Group difference indicators of mental wellbeing in children with a chronic condition (12-18 year) versus healthy peers during the pandemic (2nd aim)

	PROactive Chronic condition (N=311)	**WHISTLER** Healthy peers (N=166)	**Main effect of group**		**Girls** *Both groups (N=294)*	**Boys** *Both groups (N=183)*	**Main effect of gender**	
			F	df (error)			F	df (error)
Life satisfaction [a] mean (SD), range 0-10	6.37 (1.75)	7.01 (1.38)	13.92***	1 (473)	6.35 (1.72)	6.98 (1.47)	13.41***	1 (473)
Internalizing symptoms [b.] mean (SD), range 0-100	43.13 (12.03)	42.13 (10.11)	0.03[ns]	1 (359)	44.95 (16.93)	38.06 (8.9)	26.40***	1 (359)
Psychosomatic health [c] mean (SD), range 1-5	3.28 (0.88)	4.15 (0.67)	91.77***	1 (345)	3.44 (0.90)	4.11 (0.722)	48.48***	1 (345)

SD, standard deviation; * ns=not significant p<0.05; **p≤.01; *** p≤.001
a. N=311 versus N=166; A higher score indicates a higher life satisfaction.
b. N=223 versus N=166; A higher score (T-values) indicates more severe self-reported internalizing symptoms. Score <60 is normal, score 65-70 is borderline, >70 is critical
c. N=183 versus N=166; A higher score indicates a better psychosomatic health (= less psychosomatic symptoms)

CHAPTER 10

RESILIENCE IS NOT A SUPERPOWER

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RESILIENCE IS NOT A SUPERPOWER*

**Translated into English from the original blog titled 'Veerkracht is geen superkracht'.*

For over two years, our lives have been dominated by the COVID-19 pandemic. Newspapers were filled with stories of young people struggling with burnout symptoms, depression, and loneliness. However, not everyone was equally affected by this crisis. Most young people demonstrated psychological resilience; they proved to be flexible and adaptive in dealing with the consequences of lockdowns, maintaining their mental wellbeing. This kind of resilience almost seems like a superpower: those who are resilient simply handle stress better. But is that really the case?

WHAT IS RESILIENCE?

Resilience is not a superpower. Resilience involves the process of maintaining mental health in response to a stressful event [1]. This can involve staying or becoming mentally healthy during a stressful experience, as well as regaining mental wellbeing some time after the stressor has occurred. What makes people resilient depends on a wide range of factors. These factors can be categorized into personal factors and factors in the (social) environment. Examples of personal factors include your genetic makeup or your body's hormonal response to stress. Factors from the (social) environment include support from parents or friends, as well as the culture and/or religion of a country and the era in which we live [2]. All these factors are referred to as resilience factors [1,3–6]. To illustrate, we will share the story of Sjors (a fictional name):

Sjors is 14 years old and lives with his mother in Utrecht. His mother is diagnosed with a mood disorder, which seems to be reasonably well controlled at the moment. However, Sjors finds himself concerned, particularly on days when his mother stays in bed and does not go to work.

Fortunately, Sjors has a robust social network. He often hangs out with his friends on the soccer field, and with a few guys, he discusses his feelings and the dynamics at home. The parents of his friends are aware of the situation and regularly invite Sjors to join them for meals. They offer support, ask about his needs, and actively engage in helping him navigate through this challenging home situation. This approach allows Sjors to handle his home life effectively.

In early 2020, the COVID-19 crisis unfolded, disrupting Sjors's life. He could no longer attend school, was restricted to being indoors, and lost invitations to his friends' homes. His mother became disoriented and experienced sudden, unprovoked fits of rage. Sjors felt scared, stress levels escalated, and he found himself with nowhere to turn, feeling increasingly isolated and miserable. The school arranged online classes, but Sjors struggled to keep up. Recognizing that some students were falling behind, the school implemented an online after-school buddy system.

This buddy system allowed Sjors to discuss his home situation with friends and teachers. The school involved social work to provide assistance to both Sjors and his mother. Additionally, his friends organized game nights, offering Sjors much-needed support. Gradually, he started to feel more at ease and mentally well again.

A COMBINATION OF RESILIENCE FACTORS

Sjors openly discussed his emotions, possessed an easygoing nature, and benefited from a supportive social network, enabling him to adapt positively to his home situation. However, these resilience factors diminished when the COVID-19 crisis began. He experienced stress due to the mental challenges of his mother. This chronic stress led to prolonged activation of the stress system, resulting in a high presence of stress-related hormones in Sjors's blood and brain. This has immediate and long-term consequences for the functioning and development of his brain [7]. Eventually, support from school, along with a different form of friendship, helped reduce Sjors's stress levels, ultimately restoring his mental wellbeing.

This example illustrates how different resilience factors, e.g., neurobiological factors, support from friends and school, and the contemporary era we live in, contribute to our ability to function resiliently—both now and in the future.

IS RESILIENCE MEASURABLE?

Considering resilience as a dynamic process dependent on personal and (social) environmental factors, it becomes clear that resilience cannot be measured with a single simple test. Just as fever is measured with a thermometer and heart rate with a stethoscope, resilience cannot be measured using an online questionnaire or a blood test. Such a measurement would provide too restricted a view of the resilience concept.

However, there are ways to assess resilience. Resilience comprises mental wellbeing during and after stress. To measure this, it is important to assess mental wellbeing both before and after the stressful event. This approach allows us to interpret how someone responds to a stressor, investigating whether their mental wellbeing remained the same or declined, and how long it took for their wellbeing to return to its usual state. By measuring multiple indicators of mental wellbeing, a more complete picture can be formed regarding resilience. For instance, focusing solely on depression might overlook symptoms of anxiety, or vice versa.

Finally, it is important to measure the (severity of the) stressor as well. By doing so, mental wellbeing can be compared to that of others who experienced the same stressor. For example, while all young people were at home during (parts of) the COVID-19 crisis, not all had a mentally ill mother like Sjors. When Sjors functions in terms of his mental

wellbeing just as effectively as a peer with a secure home situation, he demonstrates more resilience. He has a higher mental wellbeing than expected, given the severity of the stressor he has experienced.

CONCLUSION

Resilience is not a personal superpower, but a process of adaptation to maintain or regain mental wellbeing during or after a stressful event. Factors that support resilience exist both within the individual, but also in the environment in which the individual is situated. This implies that each of us can contribute to the resilience of those around us. So, talk, meet up, support, and laugh with friends and family: that is your true superpower!

REFERENCES

1. Kalisch R, Baker DG, Basten U, et al. The resilience framework as a strategy to combat stress-related disorders. *Nat Hum Behav*. 2017;1(11):784-790. doi:10.1038/s41562-017-0200-8
2. Ioannidis K, Dahl Askelund A, Kievit RA, al E. The complex neurobiology of resilient functioning after childhood maltreatment. *BMC Med*. 2020;18(32). doi:10.13140/RG.2.2.17380.48005
3. Van Breda A. A critical review of resilience theory and its relevance for social work. *Soc Work*. 2018;54(1). doi:10.15270/54-1-611
4. van Harmelen AL, Kievit RA, Ioannidis K, Al E. Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychol Med*. 2017;47(13):2312-2322. doi:10.1017/S0033291717000836
5. van Harmelen AL, Blakemore SJ, Goodyer IM, Kievit RA. The Interplay Between Adolescent Friendship Quality and Resilient Functioning Following Childhood and Adolescent Adversity. *Advers Resil Sci*. Published online 2020. doi:10.1007/s42844-020-00027-1
6. Fritz J, de Graaff AM, Caisley H, al E. A Systematic Review of Amenable Resilience Factors That Moderate and/or Mediate the Relationship Between Childhood Adversity and Mental Health in Young People. *Front Psychiatry*. 2018;9(June). doi:10.3389/fpsyt.2018.00230
7. Tamnes CK, Herting MM, Goddings A lise, et al. Development of the cerebral cortex across adolescence : A multisample study of interrelated longitudinal changes in cortical volume , surface area and thickness. *Journal of neuroscience*. 2017;37(12):3402-3412. doi:10.1523/JNEUROSCI.3302-16.2017

CHAPTER 11

GENERAL DISCUSSION

To better understand the various *colors* of resilience in adolescents, this thesis examined adolescent mental wellbeing before, during and after facing disease-related challenges. The investigated challenges were related to chronic health conditions and the COVID-19 pandemic.

In this general discussion, I will first present recommendations that may help future researchers when starting to study resilience in the pediatric healthcare field. Subsequently, I will delve into the implications of our findings and the novel research challenges they pose regarding resilience research in youth. Finally, I will explore the strategies how to integrate resilience research into pediatric healthcare.

A. RESEARCHING RESILIENCE IN PEDIATRIC HEALTHCARE; SOME LESSONS FROM LITERATURE

Over the last decennia, researchers studying resilience have portrayed resilience in various *colors*. As stated in the introduction, some have regarded resilience purely as a trait, others depicted resilience as a complex combination of multiple factors including various traits, skills, beliefs, and behaviors , as a dynamic process, or as an ultimate outcome [1–6]. Our scoping review in *Chapter 2* shows that multiple definitions of resilience are used in current pediatric healthcare literature considering youth with a chronic health condition. In the included articles of this review, resilience is both conceptualized as a dynamic concept that signals a positive adaptive response to stress or adversity, and as a personality trait [7]. These different conceptualizations of resilience lead to a variety in measurements, as also structurally reported in this scoping review. Resilience is measured, for instance, by assessing mental health following a stressor. It can be qualified as a trait or skill, or even quantified as a score obtained from a resilience questionnaire [7]. This variety in definitions and instruments makes it challenging to interpret the findings of resilience research [6–10].

Therefore, the recommendations on the definition and measurement of resilience might assist researchers in the pediatric healthcare field. By describing what experts in resilience research see as the primary *colors* of resilience research in general, I aim to provide fellow researchers with a basic *palette,* serving as a starting point for portraying resilience.

1. Standardizing the definition of resilience

Over the last two decades, leading experts agreed that resilience should be seen as a dynamic concept of a positive adaptive response following an adversity [5,11]. In this line of thought, Kalisch et al. proposed the following operational definition in 2017: *resilience is a dynamic process that involves adaptation to a stressor leading to the maintenance or the quick recovery of mental health* [6].

This operational and standardized definition of resilience empowers researchers from diverse theoretical backgrounds to establish a common foundation regarding the concept of resilience. The adoption of such a standardized definition has the potential to clarify the complex concept of resilience and mitigate the oversimplified use of the term 'resilience' [6]. Moreover, it enables the use of suited study designs and measurement tools, facilitating easier summarization and comparability of results. This might shed light on novel opportunities for interventions and identify gaps in current knowledge.

This definition avoids assuming a specific theory about the essential mechanisms leading to resilient outcomes. Therefore, it can be applied transdisciplinary across various scientific fields and tailored to specific adversities or study domains. In the context of youth with a chronic health condition, adaptation to a stressor may manifest as academic achievement, rather than in mental health in general [6]. The definition of adversity can also be adjusted to what is relevant for the population under study. Please see recommendation 2 for more information.

Adopting Kalisch et al.'s definition of resilience had significant implications for the study design and assessment of resilience. The following recommendations (2, 3, and 4) are therefore derived from and dependent on this definition.

2. Defining and assessing the adversity

In the field of pediatric healthcare, it is imperative to thoughtfully define adversity when considering resilience. There is a wide range of adversities and challenges one can endure, and even more relate to having a chronic health condition. To illustrate, individuals dealing with a chronic health condition already face diverse challenges related to the disease, including, but not limited to, the diagnosis, fluctuations in disease severity, exacerbations, intensive treatments, physical symptoms, perceived burden, social difficulties, and existential challenges [12,13]. The adversity, and its severity should be defined and quantified as clearly as possible. This will be valuable in statistical analyses and enhance comparability between resilience studies within the same population.

The adversity, and its severity, can be measured in various ways. Adversities can be quantified, by clear descriptives or cut-off points for diagnosis, or by using continuous variables such as serum HbA1c to diagnose diabetes, or a lung function test to establish the severity of asthma. *Chapter 6* shows that individuals with a chronic health condition who self-report as having a chronic health condition experience a lower wellbeing than their peers who do not self-report having a chronic health condition. The level of perceived burden, rather than the actual burden itself, is presumed to influence their subsequent adaptation responses [14,15]. Hence, incorporating self-assessed evaluations of how individuals perceive their chronic health condition broaden the comprehensiveness of the adversity assessment. Furthermore, adversities have the tendency to co-occur with

one another. Individuals exposed to a chronic health condition experience often multiple adversities [16]. A cumulative score of multiple disease-related challenges might be taken into account as well.

Lastly, some aspects of having a chronic health condition are time-related; for instance, the potential improvement or progressive nature of its course, and the frequency of relapses or exacerbations. These time-related aspects may exert an influence on the adaptation process. Therefore, researchers studying resilience should carefully consider when and over which timeframe the adversity is measured.

3. Longitudinal study designs

Considering resilience as a dynamic process, an ideal study design would be of a longitudinal nature, observing participants over an extended period [6,17]. Ideally, this design involves assessments of outcomes related to, for instance, mental health both before, during, and after the experience of an adversity.

Conducting longitudinal studies within pediatric healthcare is easier said than done, yet could in practice be less restrictive than it initially may sound. This preferred study design introduces specific challenges, especially in the face of disease-related challenges. Obtaining a baseline mental health measurement before the disease's onset is challenging, given that the onset of most diseases is seldom predictable. Moreover, especially in medical settings, patients often come under our care when they are potentially already experiencing or have experienced adversities that we aim to investigate, such as the disease itself. Furthermore, obtaining a mental health measurement after exposure may pose distinct challenges within the context of chronic health conditions, as the term "chronic" implies a sustained or ongoing condition, challenging the concept of a distinct 'after' period. The feasibility of longitudinal studies with assessments of mental health outcomes prior, during, and after experiencing the adversity might be dependent on the definition of adversity (please see *Recommendation 2*).

Following this guideline could, in practice, be less restrictive than it initially may sound. (Advanced) statistical methods can be employed to simulate causal inferences, or conditions can be formulated to articulate statements regarding resilient functioning in cross-sectional studies. I will discuss these statistical methods in the third section of this general discussion 'integrating resilience research in pediatric healthcare'.

4. Distinction between resilience as an outcome or as a factor

The proposed definition by Kalisch et al. not only implies that resilience is a dynamic process, but also that resilience leads to a certain outcome, guiding researchers on how to measure resilience [6,18]. The dynamic nature of resilience suggests that resilience is not restricted to a single stable or fixed aspect, such as a trait or a personality characteristic.

Instead, resilience appears to be an emergent phenomenon that arises from various mechanisms during or after exposure to a stressor [6,19]. Therefore, measuring the concept of resilience with solely a score on a resilience questionnaire test lacks meaningful coherence [6].

To this end, *Chapter 2* proposes a clear distinction between resilience as an outcome and resilience factors. When resilience is assessed as an outcome of positive adaptation to adversity, we seek to understand an individual's mental health after the adversity. When researchers seek to capture why individuals are able to positively adapt and maintain or regain positive outcomes, they should preferably focus on resilience factors, which facilitate positive adaptation to adversity [20,21]. Certain traits, alongside other fixed factors (e.g. a particular genetic makeup, or a particular brain structure) may reduce an individual's susceptibility to develop mental health issues following the adversity, and can therefore be considered as resilience factors [6,22,23].

Chapter 2 also outlined the considerations for determining which outcomes or factors to assess. We emphasized that choosing positive outcome measurements for resilience outcomes is more straightforward when assessing positive adaptation than using negative outcome measurements [7]. However, current literature in pediatric healthcare, often selects negative outcomes, such as anxiety and depressive symptoms [7,24,25]. Children and adolescents are identified as being resilient when they do not experience these symptoms. However, the absence of these negative outcomes does not necessarily imply the opposite; the presence of a sound mental health [26–29]. Furthermore, assessing continuous scores often offers a more comprehensive understanding of variables, in contrast to a binary classification [7].

When selecting appropriate resilience factors in youth, one must consider the variability of chronic diseases in predictability, treatment, side effects, life expectancy, and challenges. Resilience factors may contribute differently to positive adaptation in specific disease-related challenges. Self-esteem and self-efficacy in treatment management contribute to resilience, yet their impact may vary across diseases [7]. To illustrate: high levels of self-esteem are associated with demonstrating resilience, and pediatric cancer patients' self-esteem may be challenged due to changes in physical appearance. Trying to improve self-esteem might contribute to better adaptation. On the other hand, self-efficacy in treatment management might contribute less to resilience in pediatric cancer patients, given the typical hospital settings regarding treatment.

B. DISEASE-RELATED CHALLENGES IN ADOLESCENTS AND IMPLICATIONS FOR RESILIENCE RESEARCH

In this section, I will initially assess how the results of the empirical chapters of this thesis (i.e. *Chapter 4 through 9*) addressed the identified knowledge gaps. And while abstaining from drawing definitive conclusions about the resilience I will now explore whether the studied population demonstrated resilience in each empirical chapter. Additionally, I will discuss how my findings contribute to the implications for future resilience research in pediatric healthcare, addressing each chapter separately.

1. Cystic Fibrosis

Cystic fibrosis (CF) is an multiorgan disease caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR)-protein due to genetic defects [30]. The introduction of new medications (CFTR modulators), the triple combination elexacaftor/tezacaftor/ivacaftor (ETI) in particular, has marked a new era in the management of CF. These medications fundamentally altered the perception of CF from a life-threatening condition to a chronic disease characterized by improved disease manifestation and expected improved life expectancy [31,32].

ETI significantly improves lung function and reduces pulmonary exacerbations [32,33]. Gaining access to ETI therapy is, therefore, considered a positive and major life event [34]. Unexpectedly, several case series reported that a subset of individuals experienced a decline in their mental health following initiation of ETI therapy [35–37]. Long term longitudinal studies systematically investigating changes in mental health after initiation of ETI are not available yet. Therefore, we conducted a prospective, longitudinal study and identified that people with cystic fibrosis experienced a significant and clinically relevant improvement in their psychosocial health following the initiation of ETI. People using psychotropic medications at baseline reported structural lower psychosocial health scores, compared to their peers without using these medications. Yet, we did not find differential changes regarding psychosocial health after ETI between the analyzed subgroups. To gain a deeper understanding of those who may experience mental health issues after commencing ETI, future studies could shift their focus towards examining several potential predictors of changes in psychosocial health, instead of concentrating solely on a single factor as we did in our subgroup analyses [35–37]. People are more than a set of numbers such as age, sex, or lung function. Perhaps the combination of these biological factors could be distinctive in terms of changes in psychosocial health after the initiation of ETI. Furthermore, incorporating psychological factors, such as illness identity (defined as the degree to which a chronic health condition becomes integral to an individual's sense of self) or illness perception (defined as one's perception of their disease as threatening), could yield valuable insights [38–40]. Psychosocial health is influenced not solely by the physical aspects of a chronic health condition, but also by how individuals

perceive and engage with these aspects. Insight in the mechanisms of these psychological factors could potentially enhance patients' awareness of the impact of their condition on their daily lives and self-perception, making these factors viable targets for therapeutic interventions [41].

In the context of investigating resilience within the provided definition (*Recommendation 1*), this study sample demonstrated resilience as their psychosocial health was maintained and even increased on group level after commencing ETI. We applied a longitudinal, prospective study design with pre- and post-exposure assessments, (*Recommendation 3)* and measured the resilience outcome using positive and continuous outcomes measures regarding mental health (*Recommendation 4*). Considering that previous literature suggested that only a minority experienced reduced mental health after starting ETI, as opposed to the majority reporting positive changes, we sought to identify who might be at risk or what factors may or may not contribute to the risk (*Recommendation 4*). In light of *Recommendation 2*, one could argue that accessing to ETI is not an adversity, but rather a positive life event - as also stated in *Chapter 4*. This argument raises the question whether people with CF experience ETI therapy as an actual adversity. An individual's subjective perception of starting ETI, regarding their hopes and expectations of ETI, could have played a significant role. Hence, incorporating self-assessed evaluations might have revealed the extent to which this positive life event was perceived as a stressor rather than an opportunity. This information could have been valuable and at use. For example, conducting stratified analyses or employing mediation analyses based on the extent to which individuals perceive accessing ETI therapy as a stressor or an opportunity might offer insights into why some people experience a negative change in mental health following ETI therapy. In conclusion, I recommend incorporating subjective perceptions of initiating ETI into future research (*Recommendation 2*).

2. Asthma

Much of the current literature on the association between asthma and mental wellbeing relies on cross-sectional studies, which limits the ability to draw inferences about the impact of asthma on mental wellbeing during adolescence [42–45]. In our prospective, longitudinal cohort, we found that adolescents with asthma did not exhibit lower mental wellbeing when compared to their healthy peers, although they did report a lower level of perceived general health [46].

These findings indicated that despite growing up with asthma, affected adolescents can still experience a good mental wellbeing. This illustrates, that asthmatic adolescents demonstrate resilience, as interpreted by the definition in *Recommendation 1*. By following the recommendations presented above further investigation into the impact of asthma on mental wellbeing may be warranted. Although we used data from a prospective, longitudinal study (*Recommendation 3*), we might have missed the most critical

developmental years concerning disease onset, severity and consequently, adaptation to asthma-related challenges. According to the literature, asthma is most likely to develop during childhood and asthma remission occurs most commonly between the ages of 14 to 21 years [47,48]. No self-reported data regarding mental wellbeing was available of children younger than eleven years old, which made it impossible to check this assumption. However, not including this data might have resulted in underestimating the impact of asthma on mental wellbeing in *Chapter 5* [49].

Not only the timing of measuring the adversity is of importance, also adequately measuring the severity of the adversity (*Recommendation 2*). With regard to asthma, inadequate control yields a multitude of adverse consequences for affected children and adolescents, influencing not just their physical health but also their mental wellbeing and academic performance. Poor control can lead to severe symptoms, and in some cases, even life-threatening asthma attacks [50]. Asthma control is identified as the most important determinant of health-related quality of life [51]. Poor asthma control is associated with heightened rates of school absences, increased demands for educational support, and diminished academic achievements [52]. As we did not have data regarding asthma control, we used current medication use as a proxy. Unfortunately, we did not have any data regarding the level of asthma control when using these medications. Therefore, to obtain a comprehensive understanding of resilient functioning in adolescents with asthma, I propose, for future research, to use data collected from childhood up to adolescence (*Recommendation 3)*, incorporating disease severity by both subjective and objective measures of asthma control (*Recommendation 2*).

3. Self-reporting on having a chronic health condition

Both self-reporting a chronic health condition (regardless of diagnosis or further medical context) and having a chronic health condition (regardless of one's "willingness" to report it) are associated with lower psychosocial health [12,53–55]. However, it is still unknown whether self-report of a chronic health condition in adolescents with a physician diagnosed chronic health condition also is associated with a poorer psychosocial wellbeing. *Chapter 6* investigates differences in psychosocial wellbeing among adolescents with a physician diagnosed chronic health condition who self-report or do not self-report having a chronic health condition. Out of the 1009 included adolescents with a clinical diagnosis, 270 (26.7%) were reporters. Our findings revealed that reporters had significantly worse outcomes in all psychosocial domains assessed, a pattern that seems to hold across some, but not all, disease groups.

Unlike the previous chapters, this study had a cross-sectional design which precludes drawing firm conclusions about resilient functioning of the study group. Nevertheless, *Chapter 6* suggests that subjectively reporting on a chronic health condition also impacts psychosocial functioning. We hypothesize on underlying mechanisms about why reporting

or not reporting might affect adjustment to disease-related challenges. Associations may, for instance, exist between reporting status and experiencing more severe disease symptoms or, conversely, there may be an association with the perception of a higher burden, independent of disease severity [14,15]. Future research might find an opportunity in longitudinally (*Recommendation 3*) assessing the cumulative effect of subjective and objective aspects of disease-related adversities (*Recommendation 2*), attempting to better understand the association between psychosocial wellbeing and reporting status.

Moreover, future research might delve into understanding the factors influencing whether or not to report having a chronic health condition, by trying to identify resilience factors (*Recommendation 4*). Future research could, for instance, focus on the relation between illness identity, reporting status, and psychosocial health. For example, one could argue that whether someone reports having a chronic health condition depends on how the condition is integrated into their identity. Forming an identity is conceptualized as 1) the extent to which an individual successfully integrates various self-elements into a cohesive sense of self, and 2) how this cohesive sense of self manifests in daily activities, influencing decisions and values [56]. When facing a chronic health condition, individuals need to relate to their condition which can lead to constructing or reestablishing a new sense of self, wherein the condition becomes integrated in their identity. This phenomenon is recognized as the development of illness identity [38,57]. Illness identities characterized by acceptance of the condition or viewing the condition as an enrichment in life are positively linked to mental wellbeing, and could therefore function as resilience factors. Conversely, when an individual rejects the condition regarding their identity or perceives it as a total engulfment on their identity, then there is a negative association with mental wellbeing [58]. These identities could be risk factors for adaptation to disease-related challenges. The exploration of the relationship between illness identity, reporting status, and psychosocial functioning, may reveal new mechanisms for positive adaptation in the face of disease-related challenges, offering potential targets for therapeutic interventions.

4. The Coronavirus Disease 2019 (COVID-19) pandemic

The COVID-19 pandemic has been considered to be a major threat to mental health of youth, emphasizing the need to research adolescents' wellbeing during the pandemic [59–62]. Our studies showed that adolescents reported an interesting picture of mental wellbeing throughout the first year of the pandemic, as not all mental wellbeing outcomes exhibited similar patterns of change. Life satisfaction decreased, internalizing symptoms remained stable, and psychosomatic health showed improvement [63,64].

Since the onset of the COVID-19 pandemic, there has been a substantial growth of literature concerning the mental health of children and adolescents. Multiple systematic, scoping and umbrella reviews have been published in an attempt to consolidate the breadth of findings [65–73]. Among these reviews, numerous differences in e.g., study design, outcome

measures, and analyses were observed, which had an impact on the presented results and interpretations. For instance, some reviews included multiple measured outcomes and reported indictors of both positive and negative mental health [65,70–73]. Others solely focused on one or two topics, such as depression and anxiety, loneliness, or suicide, suicidal ideation and self-harm [67–69]. With regard to the study design, some reviews did make a distinction between cross-sectional and longitudinal studies of the original (included) studies into account when presenting the results, but others did not [65–73]. Considering this distinction did have implications for interpreting the results of the reviews. To illustrate, some reviews presented a high prevalence of mental health problems during the pandemic, such as depression, anxiety, loneliness, and sleep disorders, but did not elaborate on whether these problems were pre-existing [66,70]. No conclusions could be drawn about whether these symptoms had increased due to the pandemic. The majority of the reviews -only including the results of longitudinal studies- did find a decrease in indicators of good mental health (e.g., life satisfaction and positive affect) and an increase in indicators of mental health problems (e.g., internalizing symptoms and stress) [67–69]. However, some reviews identified that there were also studies that reported no changes in mental health, or reported an increase in indicators of good mental health and a decrease in indicators of mental health problems [65,71,73]. Focusing on multiple outcomes, using pre-post longitudinal studies, with a within-subjects design, might therefore yield more nuanced results [65]. With regard to resilience research, focusing on positive outcomes, rather than negative ones, might give a better representation of positive adaptation to a stressor (*Recommendation 4*).

Differences in timing and locations (e.g., country or region) of assessments across the studies examined could significantly have contributed to the discrepancy in results of our findings compared to (some) reviews. Varied stages of the pandemic and geographic locations are associated with fluctuations in infection rates and lockdown measures [65]. Hence, it may be beneficial to consider only Dutch studies when comparing and interpreting our results, rather than examining studies conducted worldwide. The Netherlands Youth Institute summarized the results of 40 studies, conducted in the Netherlands between March 2020 and April 2022 [74]. (Our results of *Chapter 7*, *8* and *9* were cited in this report [63,64,75].) In their report, the researchers concluded that not all children and adolescents responded similarly to the COVID-19 pandemic, explaining the differences in findings. However, it can be said in general that most children and adolescents reported a heightened degree of depressive symptoms and perceived a lower quality of life [74]. The results in the presented reviews and reports indicated that while some adolescents seemed to have adapted and therefore remained or maintained their mental wellbeing, others had not. This leads us to the question: which (sub)groups demonstrated resilience, and which (sub) groups reported lower mental health?

Youth with a chronic health condition are more likely to experience mental health issues compared to peers, and they often face physical and psychosocial challenges [9,76–81].

Therefore, they might be more vulnerable to developing mental health issues during the COVID-19 pandemic. We focused on the comparison between mental wellbeing of adolescents with and without a chronic health condition during the COVID-19 pandemic (*Chapter 9*). Data was collected at different moments in the pandemic, encompassing various stringencies. The results showed that although adolescents without a chronic health condition had a higher life satisfaction compared to adolescents with a chronic health condition during the COVID-19 pandemic, this difference seemed to exist before the pandemic and persisted during the pandemic. Keeping the limitations in mind regarding differences in local lockdowns, a longitudinal study (intra pandemic assessments in March 2020, December 2020, and March 2021) with Canadian children (mean age of 9.4 years) with rheumatological, respiratory and hematological conditions, showed similar results: having a chronic health condition was associated with higher levels of distress before the pandemic, but not with intra-pandemic distress, when compared to healthy peers [82]. A cross-sectional study conducted in Brazil (July-October 2020) showed that adolescents with preexisting chronic immunosuppressed and/or immune-mediated conditions (mean age of 14 years) did not report more mental health issues during the pandemic, compared to their healthy peers (mean age of 15 years) [83]. Moreover, Zijlmans et al. identified that a Dutch clinical sample of youth (mean age of 12.8 years) with chronic health conditions like juvenile idiopathic arthritis, endocrinological diseases, and cystic fibrosis exhibited significantly better scores in terms of anxiety and depressive symptoms during the pandemic (March-April 2020) compared to before [84]. Based on this sparse literature, we can tentatively assume for now that adolescents with chronic health conditions are not, on average, at higher risk for mental health problems during the COVID-19 pandemic compared to their healthy peers.

Reviews did identify other potential groups to be at risk for mental health problems during the pandemic. Adolescents (aged 12-18) seem to be more susceptible to adverse mental health changes compared to younger children (aged 6-12) [65]. Moreover, a more significant decline in mental health was identified among individuals who had pre-existing mental health issues before the COVID-19 pandemic, particularly in female adolescents [67,71,84]. Some research suggested that individuals with relatively higher income backgrounds were more at risk, while other studies indicated that the most significant declines in mental health occurred in families with low socioeconomic status, a migration background, and/or limited living space [65,67,71]. Participants from the WHISTLER birth cohort were recruited from the general population living in a relatively affluent and newly built suburb of Utrecht, the Netherlands [85]. As a result, adolescents with parents having a lower educational background and a non-Western migration background were underrepresented. Consequently, we did not have the statistical power to test whether adolescents with different educational, socioeconomic positions, ethnic, and/or cultural backgrounds were more at risk. Therefore, the results of *Chapter 7* and *8* regarding this factors may not be

generalizable to the general Dutch population and explain differences in findings between our studies and systematic reviews and reports.

Within the context of investigating resilience within the provided definition of *Recommendation 1*, the WHISTLER adolescents, our study population of *Chapter 7* and *8*, seemed to respond more resiliently than the Dutch population in general during the COVID-19 pandemic. Contrary to the findings of the Netherlands Youth Institute, our study population showed no increase in (clinical) depressive symptoms compared to the situation before the pandemic. However, as not all measured mental wellbeing outcomes exhibited similar patterns of change (i.e., life satisfaction decreased, internalizing symptoms remained stable, and psychosomatic health showed improvement), we cannot simply categorize our study population as either resilient or non-resilient. Instead, it exhibits *various shades of color.* Based on the results of *Chapter 8*, our study demonstrates that resilience was affected by the pandemic: based on life satisfaction, it appeared as though the adolescents did not function resiliently, but when we consider other aspects of mental wellbeing, we see that they were. It is important to note that although our longitudinal assessments of mental wellbeing were conducted before and during the pandemic (*Recommendation 3*), we do not have follow-up assessment after the pandemic was ended. Therefore, we do not know whether post-pandemic mental health levels returned to pre-pandemic levels. Notably, the provided definition of resilience implies that mental health outcomes should ideally be measured after experiencing the adversity, a task challenging to implement during chronic or enduring adverse events [6]. Fluctuations in the severity of adversity may serve as a proxy. Some follow-up rounds of *Chapter 8* occurred during more stringent lockdown periods, while other rounds were during more lenient phases. During the latter period, life satisfaction seemed to return to pre-pandemic levels.

Furthermore, despite the longitudinal design, it is difficult to determine causal relationship between the stringency of the lockdown and adolescent mental wellbeing. Although mental wellbeing was most impacted during the most stringent parts of the pandemic, other factors, such as the duration of the lockdown, might be another driver of these negative outcomes. *Chapter 7* identified that concerns about COVID-19 pandemic were associated with a lower life satisfaction and more internalizing symptoms in the first lockdown. But, as the pandemic progressed, other factors might have had a cumulative effect in terms of the adversity, such as the duration of the pandemic, increased loneliness over time, and financial problems that developed during the pandemic. Combining objective pandemic measures with subjective adolescent experiences at various points could offer additional insights (*Recommendation 2*).

C. INTEGRATING RESILIENCE RESEARCH IN PEDIATRIC HEALTHCARE

With the recommendations presented before, I aimed to describe what experts see as the primary *colors* of resilience research in general. When integrating resilience research into pediatric healthcare, there are additional *colors* to consider. In the following section, I will delve into the complexity of researching the underlying mechanisms of resilience, address methodological challenges and opportunities, discuss advanced statistics regarding resilience research, and consider how to optimally align outcomes for the benefit of all. Finally, I will conclude with a personal note based on *Chapter 10*.

1. Capturing complexity of resilience

Current resilience research in pediatric healthcare is quite descriptive, rather than explanatory. Unfortunately, resilience factors are generally accounting for only a small portion of the variability in long-term mental health within populations exposed to stressors or trauma [86]. Furthermore, numerous factors exhibit conceptual similarities and are interconnected, correlated, or influenced by each other [17,87]. It would therefore be of value to focus on the underlying mechanisms regarding positive adaptation to an adversity. Multiple mechanisms from neurobiological and socioecological levels explaining resilience in the face of childhood maltreatment have been described [10,19,20,88,89]. These mechanisms may not only apply to physical stress reactions in youth who have experienced childhood maltreatment, but potentially also to those who have faced other adverse events, such as disease-related challenges [19].

The neurobiological mechanisms include increased brain volumes in areas like the prefrontal cortex and hippocampus, improved connections between brain regions, favorable genetics, and the capacity to regulate stress-related hormones effectively through the hypothalamus-pituitary-adrenal system [10,19,23,90,91]. Additionally, Ioannidis et al. stated that the positive effects from socioecological levels, such as social support from friends and family, might also be mediated through the neurobiological mechanisms [19].

In pediatric healthcare, there is a role for future research to explore these mechanisms underlying adaptation to disease-related adversities and challenges. It is essential to explore whether there are variations in the underlying mechanisms among different diseases and between different ages. First, certain conditions may affect the previously described neurobiological mechanisms, such as those seen in neuro-oncology, autoimmune diseases, and endocrinological disorders. To illustrate, the craniopharyngioma, originating from pituitary gland tissue, is a clinically malignant brain tumor due to its location, despite its histologically benign nature [92]. Both the tumor and the surgery for its removal can impact the function of the pituitary gland, hypothalamus, and optic nerves, potentially leading to visual impairment, endocrine deficiencies, and obesity, respectively

[92]. Regarding childhood craniopharyngiomas, some neurobiological mechanisms underlying resilience, such as the capacity to regulate stress-related hormones effectively through the hypothalamus-pituitary-adrenal system, may be influenced by the tumor itself or treatment of the tumor. Therefore, gaining more knowledge regarding these mechanisms underlying resilience in specific diseases might lead us to target mechanisms for therapeutic interventions to increase resilience in specific disease-related challenges.

Regarding age, the neurobiological mechanisms might work differently in the transition from childhood to adolescence. The adolescent brain undergoes transformative changes; some regions in the brain mature later than others [93]. In particular, the prefrontal, parietal, and temporal cortices, which are involved in higher-level cognitive functions such as mentalizing, planning, and inhibiting inappropriate behavior, show later maturation [93]. Regarding social relations, adolescents spend increasingly more time with their peers and friendships become closer and are more influenced by peers than adults [15,93–96]. Adapting to adversities might be more challenging for adolescents, and underlying mechanisms or factors, such as cognitive skills, identity-forming, and social support from friends may become more important during adolescence for resilient functioning. To illustrate, van Harmelen et al. showed that friendship support, rather than family support, functions as an significant positive predictor (and is therefore seen as a resilience factor) of both immediate and future resilient psychosocial functioning in adolescence and early adulthood [15,97].

2. Conceptual and methodological challenges and opportunities

Recommendation 3 proposes to investigate resilience through a longitudinal study design, but also disclaimed that following this guideline is easier said than done, yet could in practice be less restrictive than it initially may sound. Therefore, in this section I will first introduce what kind of longitudinal data could be used for resilience research in pediatric healthcare, and subsequently discuss statistical methods to analyze both longitudinal data as well as cross-sectional data in the context of resilience research.

In general there are two main types of clinical data regarding longitudinal study designs: experimental data, from e.g. randomized clinical trials (RCT), and observational data, from e.g. cohort studies [98]. RCTs are not often used in resilience research in the pediatric healthcare field, yet there are examples known where a RCT is employed to assess if specific resilience factors can be enhanced through interventions, aiming to improve adaptation to stressors compared to alternative or no interventions [99,100]. Cohort studies would be the preferred choice for resilience research, encompassing non-interventional clinical research that systematically gathers data from a group of individuals with or without a chronic health condition [98]. In this thesis, data were used from the following cohort-studies: the RISE study (*Chapter 3* and *4*), the PIAMA cohort (*Chapter 5*), the PROactive

study (*Chapter 6* and *9*), the WHISTLER birth cohort study (*Chapter 7*, *8*, and *9)* [49,85,101–104]. Nonetheless, there are some limitations associated with cohort studies.

Observational cohorts can be time-consuming and resource-intensive, which can pose a particular challenge in the context of slowly progressive chronic health conditions. In such cases, collecting all the necessary information may require several years. Furthermore, most cohort studies often include a fixed framework regarding visits and set of clinical factors or outcomes for patient assessment, which might lead to missing relevant disease events that occur between these scheduled visits. Likewise, the choice of measurements taken is influenced by researchers' hypotheses and determined in advance, which may result in the exclusion of elements initially deemed less important [98]. Additionally, the study participants in cohort studies often do not represent the broader society. Non-participants tend to be older, unmarried, immigrants, with lower socioeconomic status, higher mortality rates, and increased risk of chronic, especially psychiatric, diseases [105–108]. Unfortunately, in the Netherlands, like many other European countries, there are ongoing health inequalities between individuals with higher and lower socioeconomic position. A lower socioeconomic position is associated with higher prevalence rates of various chronic physical and mental conditions, diminished self-assessed health, and numerous lifestyle-related risk factors, including tobacco use and obesity [109–111]. In the WHISTLER, PIAMA, and PROactive cohort studies, participants with parents having a lower educational background, a non-Western migration background, or with a lower socioeconomic position were underrepresented [46,63,64]. This underrepresentation limits the generalizability to the Dutch population and consequently reduces the clinical relevance of research findings.

Under specific circumstances, the use of real-world data might be an alternative for cohort studies. It has the potential to mitigate the limitations related to the time-consuming and resource-intensive aspects of cohort studies, as well as the absence of relevant disease events and the underrepresentation of certain individuals. Real-world data is defined as 'data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources' [112]. The increasing use of electronic health records and continuous data registration through digital technology in hospitals, such as vital parameter monitoring, has led to a substantial expansion in the accessibility of real-world data. This goes beyond biological parameters and includes the frequent and extensive use of questionnaires in healthcare. In the Netherlands, for instance, KLIK (in Dutch: 'Kwaliteit van Leven in Kaart') is widely used, currently being implemented across 192 patient groups in 47 healthcare-related centers, including in the Wilhelmina Children's Hospital [113]. These KLIK questionnaires are used not only to evaluate the psychosocial functioning and quality of life of patients but also to inquire about potential protective and risk factors. The results of these questionnaires can offer healthcare professionals valuable insights. If an individual's mental health crosses predefined thresholds or shows

a significant decline from their previous records, healthcare providers can give immediate feedback and consider whether further assessment or treatment is necessary for their patients. This approach has already been implemented at the Wilhelmina Children's Hospital, initiated by the PROactive study [101,102].

Ideally, this real-world data collected during clinical care could also be used for research purposes, as it includes sufficient aspects to perform resilience studies. A broad consent policy would enable researchers to use clinically obtained data. This policy entails asking patients' consent to anonymously store and re-use their medical data for research, as well as asking their willingness to share their data with external parties, commercial and/or non-commercial [114]. At the moment, the Wilhelmina Children's Hospital conducts a pilot to implement such broad consent policy. Incorporating clinical data on biological and mental health aspects under broad consent could potentially be the perfect breeding ground for exploring the underlying (biological) mechanisms behind resilience.

3. Advanced statistical methods

a. Longitudinal data

When analyzing the results of resilience research, researchers may encounter a number of challenges. For instance, researching how a specific adversity is associated with mental health outcomes, is challenged by the tendency of adversities to occur with one another [16]. To illustrate, an adolescent with cystic fibrosis facing an exacerbation due to pneumonia may encounter several disease-related challenges, for instance heightened symptoms such as shortness of breath, the necessity for intensive treatment, and a period away from home and school due to hospitalization. As a result, researchers are confronted with the question of how to best model the adversity and its associations with outcomes. Cecil and Schuurmans suggest several options. First, researchers can employ a *specificity model*, focusing their attention on a single adversity. By referring to the previous example, the severity of the exacerbation can be measured by lung function, or oxygen saturation in blood. This specificity-model could be used to conduct in-depth examinations of the adversity being studied, such as exploring its timing, severity, and chronicity. Furthermore, the outcomes can be more readily translated into recommendations for the field and aid in the identification of specific targets for customized early interventions related to that specific adversity [115]. Yet, the specificity model does not account for potential presence of multiple adversities at the same time, and therefore, researchers, using this model, might not fully grasp the etiology, as well as potential possibilities for devising personalized intervention approaches. Hence, *a cumulative model*, using a total adversity score formed from different adversities related to a stressor, would potentially depict a more encompassing perceived burden [115]. For instance, researchers could use both objective (lung function, and oxygen saturation) as well as subjective (shortness of breath, and impact of hospitalization) measures. However, this cumulative model, using a sum score of the experienced adversities, implicitly assumes that all adversities hold an equal weight

in determining the score, a scenario that may not align with real-life circumstances [115]. By considering the advantages and disadvantages of specificity and cumulative models in relation to integrating a disease-specific challenge, a more informed decision about statistical methods can potentially be made when conceptualizing new resilience studies.

When focusing on the association between the adversity and mental health outcomes, Cecil and Schuurmans discuss different statistical strategies: *variable-centered* and *person-centered approaches* [115]. In this thesis, *variable-centered approaches* were applied, by focusing how the dependent and independent variables relate to each other. This approach is likely to yield the greatest benefits at the population level, but its applicability at the individual level is less certain. The variable-centered approach assumes that the relationship between variables remains consistent for all individuals within a given population [116]. When using more data-driven methods, a *person-centered approach*, subgroups of individuals can be identified, clustered according to key variables of interest, (e.g., patterns of adversity) [117]. Latent class analyses or latent growth analyses are examples of such person-centered approaches [115,117,118]. Choosing the right approach might find new, relevant findings. For instance, with regard to *Chapter 4*, on group level an increase in psychosocial health after initiation of ETI therapy was observed. Yet, in previous case studies individuals were described with mental health symptoms after initiation of ETI [35–37]. Using a variable-centered approach, we did not find a differential change between subgroups. A person-centered approach, on the other hand, might identify subgroups of individuals based on unforeseen factors/patterns.

b. Cross-sectional data

Instead of solely relying on longitudinal data to explore resilience following disease-related challenges, alternative methods using cross-sectional data are also discussed in literature. The 'residual' method is performed to study resilience [119,120]. Using this method, resilience is investigated by assessing the extent to which an individual demonstrates better or worse outcomes than the average score expected given their experienced disease-related stressor or challenge. This approach uses residual scores from a (linear) regression, where the degree of psychosocial functioning as outcome (y-axis) is plotted against the severity of the adversity (x-axis). Residuals represent the differences between observed and predicted values in a statistical model, illustrating the unexplained variations between individuals [121]. To illustrate, Van Harmelen et al. examined resilience by the degree to which the child showed better psychosocial functioning than expected, given their experienced family experiences [15,122]. Those with positive residuals had a better psychosocial functioning than expected, given their experienced adversity. These scores were referred to as resilient functioning, where higher scores indicated higher resilient functioning. Consequently, Van Harmelen et al. were able to examine which factors predict resilient functioning [15,122]. Notably, in their studies, they also used the cumulative model, calculating the degree of family experiences from multiple questionnaires, as the 'adversity'. In conclusion, instead

of examining mental health outcomes over time, the residual approach focuses on how individuals adapt to mental health challenges based on the severity of the stressor. This approach might also be used when studying resilience in pediatric healthcare, when no longitudinal data is available.

4. Improving outcome measures

When working with real-world data, the harmonization of outcomes regarding mental health would be beneficial. In collaboration with key stakeholders, including the Dutch Ministry of Health, Welfare, and Sport, healthcare associations, patient advocacy groups, and professional medical organizations, the Outcomes-Oriented Care program in the Netherlands released a new report earlier this year on a standardized set of patient-reported outcomes (PROs) and relevant measures (PROMs) [123]. This report presents a limited core set of comprehensible generic PROMs for youth per age category, applicable across all disease groups, with the goal of facilitating data integration, result comparisons, and reducing redundancy in the questions presented to youth across various measurements [123].

Although generic PROMs hold the promise of making meaningful transdiagnostic comparisons across different groups, certain disease-specific PROMs might be more relevant for specific disease groups. As chronic diseases exhibit variations in terms of predictability, treatment regimens, side effects, life expectancy, disability, and their impact on daily functioning, it is conceivable that adversities, outcomes, and resilience factors differ in the context of distinct disease-related challenges. This recognition extends to the pediatric healthcare field, where specific PROMs tailored to particular disease groups within specialized medical domains are also being developed [124]. For instance, Van Kalsbeek et al. recommend both a set of generic PROs and a disease-specific set for various types of pediatric oncology [124]. They acknowledge that, for youths having (surgery for) craniopharyngiomas, disease-related challenges such as visual impairment, strokes, and temperature dysregulation might be relevant, while for those with Ewing sarcomas (a bone tumor) reduced joint mobility and disfigurements could be significant challenges [124]. When such generic but also relevant disease-specific PROMs are standardly being implemented in healthcare, they will empower future researchers studying resilience to concentrate on understanding the underlying mechanisms responsible for positive adaptation in the context of specific disease-related challenges and how these mechanisms interact with each other.

D. ADDING VARNISH, A PERSONAL NOTE

Also promoted in *Chapter 10*, I consider the message 'resilience is not a personal trait' essential [125]. Viewing resilience as a personal trait may lead to individuals facing adversity being held responsible for their inability to adapt. In my opinion, it is key to understand that one cannot truly take credit for their own successes, nor truly blame others for

their failures. Over the past two decades, mental wellbeing of adolescents, particularly adolescent girls, has significantly deteriorated in the Netherlands [126]. This decline is partly due to the contemporary challenges faced by many adolescents, such as increasing pressure on academic achievements [126]. As long as we continue to hold young people accountable for their own successes and failures, this pressure is likely to intensify.

Many believe that a tree with robust roots cannot topple, but the quality of the soil in which these roots are embedded, as well as the interconnection with the roots of other trees, might be equally, if not more, important [15,19,122,125].

E. Conclusion

The prevalence of chronic health conditions among youth is increasing. Youth with chronic health conditions face many disease-related challenges. Additionally, they experience more mental health issues compared to healthy peers. Adolescents, in particular, might be more susceptible to negative effects of these challenges. Resilience research offers valuable insights into preventing mental health deterioration in youths with chronic health conditions and identifying potential targets for treatment and interventions to enhance mental health. Initiated by the increasing prevalence of chronic health conditions, there has been a paradigm shift from disease-centered to health-centered care. Paralleling this shift, there has been an increasing focus in pediatric healthcare and research on the resilience of youth with chronic health conditions. Instead of painting a consistent pattern of resilience, researchers studying resilience have portrayed resilience in various *colors*.

This paradigm shift and a complex concept like resilience do not require oversimplification, but rather demand clarification. The studies presented in this thesis reflect studying these various *colors* of resilience in the face of disease-related challenges. This thesis provides insight into the state-of-the-art literature regarding definitions and measurements of resilience in pediatric healthcare research and into changes in adolescent mental wellbeing in the face of disease-related challenges. Lastly, this thesis discusses recommendations to integrate resilience research into pediatric healthcare research.

REFERENCES

1. Block JH, Block J. The role of ego-control and ego-resiliency in the organization of behavior. In: *Development of Cognition, Affect, and Social Relations*. Erlbaum; 1980:39-101.
2. Kobasa SC. Stressful life events, personality, and health: An inquiry into hardiness. *J Pers Soc Psychol*. 1979;37(1):1-11. doi:10.1037/0022-3514.37.1.1
3. Masten AS, Garmezy N. Risk, vulnerability, and protective factors in developmental psychopathology. In: Lahey BB, Kazdin AE, eds. *Advances in Clinical Child Psychology*. Vol 8. Plenum Press; 1985:1-52.
4. Werner E, Smith R. *Vulnerable but Invincible: A Lonogitudinal Study of Resilient Children and Youth*. Adams, Bannister and Cox; 1982.
5. Luthar SS, Cicchetti D, Becker B. The Construct of Resilience: A Critical Evaluation and Guidelines for Future Work. *Child Dev*. 2000;71(3):543-562. doi:10.1111/1467-8624.00164
6. Kalisch R, Baker DG, Basten U, et al. The resilience framework as a strategy to combat stress-related disorders. *Nat Hum Behav*. 2017;1(11):784-790. doi:10.1038/s41562-017-0200-8
7. van der Laan SEI, Berkelbach van der Sprenkel EE, Lenters VC, Finkenauer C, van der Ent CK, Nijhof SL. Defining and Measuring Resilience in Children with a Chronic Disease: a Scoping Review. *Advers Resil Sci*. 2023;4:105-123. doi:10.1007/s42844-023-00092-2
8. Hilliard ME, McQuaid EL, Nabors L, et al. Resilience in Youth and Families Living With Pediatric Health and Developmental Conditions: Introduction to the Special Issue on Resilience. *J Pediatr Psychol*. 2015;40(9):835-839.
9. Perfect MM, Frye SS. Resiliency in pediatric chronic illness: Assisting youth at school and home. *Resilience interventions for youth in diverse populations*. Published online 2014:423-446.
10. Zhang L, Rakesh D, Cropley V, Whittle S. Neurobiological correlates of resilience during childhood and adolescence – A systematic review. *Clin Psychol Rev*. 2023;105:102333. doi:10.1016/j.cpr.2023.102333
11. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: Interdisciplinary perspectives. *Eur J Psychotraumatol*. 2014;5. doi:10.3402/ejpt.v5.25338
12. van Hal L, Tierolf B, van Rooijen M, van der Hoff M. *Een Actueel Perspectief Op Kinderen En Jongeren Met Een Chronische Aandoening in Nederland. Omvang , Samenstelling En Participatie*.; 2019.
13. Huber M, Van Vliet M, Giezenberg M, et al. Towards a "patient-centred" operationalisation of the new dynamic concept of health: A mixed methods study. *BMJ Open*. 2016;6(1):1-11. doi:10.1136/bmjopen-2015-010091
14. van Wingen GA, Geuze E, Vermetten E, Fernández G. Perceived threat predicts the neural sequelae of combat stress. *Mol Psychiatry*. 2011;16(6):664-671. doi:10.1038/mp.2010.132
15. van Harmelen AL, Kievit RA, Ioannidis K, Al E. Adolescent friendships predict later resilient functioning across psychosocial domains in a healthy community cohort. *Psychol Med*. 2017;47(13):2312-2322. doi:10.1017/S0033291717000836
16. Maurice-Stam H, Nijhof SL, Monninkhof AS, Heymans HSA, Grootenhuis MA. Review about the impact of growing up with a chronic disease showed delays achieving psychosocial milestones. *Acta Paediatr*. 2019;108(12):2157-2169.
17. Kalisch R, Müller MB, Tüscher O. Advancing empirical resilience research. *Behavioral and Brain Sciences*. 2015;38(e128).
18. Bonanno GA. Loss, Trauma, and Human Resilience: Have We Underestimated the Human Capacity to Thrive After Extremely Aversive Events? *American Psychologist*. 2004;59(1):20-28. doi:10.1037/0003-066X.59.1.20
19. Ioannidis K, Dahl Askelund A, Kievit RA, al E. The complex neurobiology of resilient functioning after childhood maltreatment. *BMC Med*. 2020;18(32). doi:10.13140/RG.2.2.17380.48005
20. Kalisch R, Baker DG, Basten U, et al. The resilience framework as a strategy to combat stress-related disorders. *Nat Hum Behav*. 2017;1(11):784-790. doi:10.1038/s41562-017-0200-8
21. Van Breda A. A critical review of resilience theory and its relevance for social work. *Soc Work*. 2018;54(1). doi:10.15270/54-1-611
22. Fritz J, de Graaff AM, Caisley H, al E. A Systematic Review of Amenable Resilience Factors That Moderate and/or Mediate the Relationship Between Childhood Adversity and Mental Health in Young People. *Front Psychiatry*. 2018;9(June). doi:10.3389/fpsyt.2018.00230
23. Amstadter AB, Myers JM, Kendler KS. Psychiatric resilience: longitudinal twin study. *British Journal of Psychiatry*. 2014;205(4):275-280. doi:10.1192/bjp.bp.113.130906

24. Rassart J, Luyckx K, Goossens E, Al E. A big five personality typology in adolescents with congenital heart disease: Prospective associations with psychosocial functioning and perceived health. *Int J Behav Med*. 2016;23(3):310-318.
25. Simon K, Barakat LP, Patterson CA, Al E. Symptoms of depression and anxiety in adolescents with sickle cell disease: The role of intrapersonal characteristics and stress processing variables. 2009;40(2):317-330.
26. Smith AJ, Moreno-López L, Davidson E, et al. REACT study protocol: resilience after the COVID-19 threat (REACT) in adolescents. *BMJ Open*. 2021;11(1):e042824. doi:10.1136/bmjopen-2020-042824
27. Diener E. Subjective Well-being. *Psychol Bull*. 1984;95(3):542-575.
28. Weich S, Brugha T, King M, et al. Mental well-being and mental illness: findings from the Adult Psychiatric Morbidity Survey for England 2007. *British Journal of Psychiatry*. 2011;199(1):23-28. doi:10.1192/bjp.bp.111.091496
29. Rao SK, Wallace LMK, Theou O, Rockwood K. Is it better to be happy or not depressed? Depression mediates the effect of psychological well-being on adverse health outcomes in older adults. *Int J Geriatr Psychiatry*. 2017;32(9):1000-1008. doi:10.1002/gps.4559
30. Férec C, Scotet V. Genetics of cystic fibrosis: Basics. *Archives de Pediatrie*. 2020;27:eS4-eS7. doi:10.1016/S0929-693X(20)30043-9
31. McBennett KA, Davis PB, Konstan MW. Increasing life expectancy in cystic fibrosis: Advances and challenges. *Pediatr Pulmonol*. 2022;57(S1). doi:10.1002/ppul.25733
32. Bierlaagh MC, Muilwijk D, Beekman JM, van der Ent CK. A new era for people with cystic fibrosis. *Eur J Pediatr*. 2021;180(9):2731-2739. doi:10.1007/s00431-021-04168-y
33. Goetz DM, Savant AP. Review of CFTR modulators 2020. *Pediatr Pulmonol*. 2021;56(12):3595-3606. doi:10.1002/ppul.25627
34. Kapouni N, Moustaki M, Douros K, Loukou I. Efficacy and Safety of Elexacaftor-Tezacaftor-Ivacaftor in the Treatment of Cystic Fibrosis: A Systematic Review. *Children*. 2023;10(3):554. doi:10.3390/children10030554
35. Spoletini G, Gillgrass L, Pollard K, et al. Dose adjustments of Elexacaftor/Tezacaftor/Ivacaftor in response to mental health side effects in adults with cystic fibrosis. *Journal of Cystic Fibrosis*. 2022;21:1061-1065. doi:10.1016/j.jcf.2022.05.001
36. Heo S, Young DC, Safirstein J, et al. Mental status changes during elexacaftor/tezacaftor / ivacaftor therapy. *Journal of Cystic Fibrosis*. 2022;21(2):339-343. doi:10.1016/j.jcf.2021.10.002
37. Tindell W, Su A, Oros SM, Rayapati AO, Rakesh G. Trikafta and Psychopathology in Cystic Fibrosis: A Case Report. *Psychosomatics*. 2020;61:735-738. www.psychosomaticsjournal.org
38. Charmaz K. The Body, Identity, and Self: Adapting To Impairment. *Sociol Q*. 1995;36(4):657-680. doi:10.1111/j.1533-8525.1995.tb00459.x
39. Oris L, Rassart J, Prikken S, et al. Illness identity in adolescents and emerging adults with type 1 diabetes: Introducing the illness identity questionnaire. *Diabetes Care*. 2016;39(5):757-763. doi:10.2337/dc15-2559
40. Broadbent E, Petrie KJ, Main J, Weinman J. The Brief Illness Perception Questionnaire. *J Psychosom Res*. 2006;60(6):631-637. doi:10.1016/j.jpsychores.2005.10.020
41. Oris L, Luyckx K, Rassart J, et al. Illness Identity in Adults with a Chronic Illness. *J Clin Psychol Med Settings*. 2018;25(4):429-440. doi:10.1007/s10880-018-9552-0
42. Määttä H, Hurtig T, Taanila A, et al. Childhood chronic physical condition, self-reported health, and life satisfaction in adolescence. *Eur J Pediatr*. 2013;172(9):1197-1206. doi:10.1007/s00431-013-2015-6
43. Cui W, Zack M, Zahran H. Health-Related Quality of Life and Asthma among United States Adolescents. *Physiol Behav*. 2016;176(1):139-148. doi:10.1016/j.physbeh.2017.03.040
44. Mohangoo AD, Sc M, Koning HJ De, et al. Health-Related Quality of Life in Adolescents with Wheezing Attacks. 2007;41:464-471. doi:10.1016/j.jadohealth.2007.06.002
45. Matterne U, Schmitt J, Diepgen TL, Apfelbacher C. Children and adolescents' health-related quality of life in relation to eczema, asthma and hay fever: results from a population-based cross-sectional study. *Qual Life Res*. 2011;20:1295-1305.
46. van der Laan SEI, de Hoog MLA, Nijhof SL, et al. Mental Well-being and General Health in Adolescents with Asthma: The Prevention and Incidence of Asthma and Mite Allergy Birth Cohort Study. *J Pediatr*. 2021;233:198-205.e2. doi:10.1016/j.jpeds.2021.01.074
47. Tai A, Tran H, Roberts M, et al. Outcomes of childhood asthma to the age of 50 years. *Journal of Allergy and Clinical Immunology*. 2014;133(6):1572-1578.e3. doi:10.1016/j.jaci.2013.12.1033
48. Ducharme FM, Dell SD, Radhakrishnan D, et al. Diagnosis and Management of Asthma in Preschoolers: A Canadian Thoracic Society and Canadian Paediatric Society Position Paper. *Can Respir J*. 2015;22(3):135-143. doi:10.1155/2015/101572

49. Universiteit Utrecht. Over PIAMA, opzet. https://piama.iras.uu.nl/opzet/. Published 2022. Accessed October 22, 2023. https://piama.iras.uu.nl/opzet/
50. FitzGerald JM, Barnes PJ, Chipps BE, et al. The burden of exacerbations in mild asthma: a systematic review. *ERJ Open Res*. 2020;6(3):00359-02019. doi:10.1183/23120541.00359-2019
51. Petsios KT, Priftis KN, Hatziagorou E, et al. Determinants of quality of life in children with asthma. *Pediatr Pulmonol*. 2013;48(12):1171-1180. doi:10.1002/ppul.22768
52. Fleming M, Fitton CA, Steiner MFC, et al. Educational and health outcomes of children treated for asthma: Scotland-wide record linkage study of 683716 children. *European Respiratory Journal*. 2019;54(3):1802309. doi:10.1183/13993003.02309-2018
53. Maurice-Stam H, Nijhof SL, Monninkhof AS, Heymans HSA, Grootenhuis MA. Review about the impact of growing up with a chronic disease showed delays achieving psychosocial milestones. *Acta Paediatrica, International Journal of Paediatrics*. 2019;108(12):2157-2169. doi:10.1111/apa.14918
54. Mokkink LB, Van Der Lee JH, Grootenhuis MA, Offringa M, Van Praag BMS, Heymans HSA. Omvang en gevolgen van chronische aandoeningen bij kinderen. *Tijdschr Kindergeneeskd*. 2007;75(4):138-142. doi:10.1007/bf03061684
55. Berkelbach van der Sprenkel EE, Nijhof SL, Dalmeijer GW, et al. Psychosocial functioning in adolescents growing up with chronic disease: The Dutch HBSC study. *Eur J Pediatr*. 2022;181(2):763-773. doi:10.1007/s00431-021-04268-9
56. Identity youth and crisis. *Erikson, Erik H*. Vol 7. WW Norton & company; 1968.
57. Leventhal H, Idler EL, Leventhal EA. The impact of chronic illness on the self system. In: *Self, Social Identity, and Physical Health*. Vol 2. Ocford University Press; 1999:185-208.
58. Van Bulck L, Luyckx K, Goossens E, Oris L, Moons P. Illness identity: Capturing the influence of illness on the person's sense of self. *European Journal of Cardiovascular Nursing*. 2019;18(1):4-6. doi:10.1177/1474515118811960
59. The Alliance For Child Protection In Humanitarian. *Technical Note : Protection of Children during the Corona Pandemic.*; 2020.
60. Liu JJ, Bao Y, Huang X, Shi J, Lu J. Mental health considerations for children quarantined because of COVID-19. *The Lancet*. 2020;4(20):347-349. doi:10.1016/S2352-4642(20)30096-1
61. Fegert JM, Vitiello B, Plener PL, Clemens V. Challenges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: a narrative review to highlight clinical and research needs in the acute phase and the long return to normality. *Child Adolesc Psychiatry Ment Health*. 2020;14(1):1-11. doi:10.1186/s13034-020-00329-3
62. Golberstein E, Gonzales G, Meara E. How do economic downturns affect the mental health of children? Evidence from the National Health Interview Survey. *Health Economics (United Kingdom)*. 2019;28(8):955-970. doi:10.1002/hec.3885
63. van der Laan S, Finkenauer C, Lenters V, van Harmelen A, Van Der Ent C, Nijhof S. Gender-specific changes in life satisfaction after the COVID-19-related lockdown in Dutch adolescents: a longitudinal study. *Journal of Adolescent Health*. 2021;69(5):737-745. doi:https://doi.org/10.1016/j.jadohealth.2021.07.013
64. van der Laan SEI, Lenters VC, Finkenauer C, van Harmelen AL, van der Ent CK, Nijhof SL. Tracking Mental Wellbeing of Dutch Adolescents During the First Year of the COVID-19 Lockdown: A Longitudinal Study. *Journal of Adolescent Health*. 2022;71(4):414-422. doi:10.1016/j.jadohealth.2022.06.006
65. Wolf K, Schmitz J. Scoping review: longitudinal effects of the COVID-19 pandemic on child and adolescent mental health. *Eur Child Adolesc Psychiatry*. Published online April 21, 2023. doi:10.1007/s00787-023-02206-8
66. Theberath M, Bauer D, Chen W, et al. Effects of COVID-19 pandemic on mental health of children and adolescents: A systematic review of survey studies. *SAGE Open Med*. 2022;10:205031212210867. doi:10.1177/20503121221086712
67. Madigan S, Racine N, Vaillancourt T, et al. Changes in Depression and Anxiety Among Children and Adolescents From Before to During the COVID-19 Pandemic. *JAMA Pediatr*. 2023;177(6):567. doi:10.1001/jamapediatrics.2023.0846
68. Madigan S, Korczak DJ, Vaillancourt T, et al. Comparison of paediatric emergency department visits for attempted suicide, self-harm, and suicidal ideation before and during the COVID-19 pandemic: a systematic review and meta-analysis. *Lancet Psychiatry*. 2023;10(5):342-351. doi:10.1016/S2215-0366(23)00036-6
69. Farrell AH, Vitoroulis I, Eriksson M, Vaillancourt T. Loneliness and Well-Being in Children and Adolescents during the COVID-19 Pandemic: A Systematic Review. *Children*. 2023;10(2):279. doi:10.3390/children10020279

70. Hossain MM, Nesa F, Das J, et al. Global burden of mental health problems among children and adolescents during COVID-19 pandemic: An umbrella review. *Psychiatry Res*. 2022;317:114814. doi:10.1016/j.psychres.2022.114814
71. Kauhanen L, Wan Mohd Yunus WMA, Lempinen L, et al. A systematic review of the mental health changes of children and young people before and during the COVID-19 pandemic. *Eur Child Adolesc Psychiatry*. 2023;32(6):995-1013. doi:10.1007/s00787-022-02060-0
72. Marchi J, Johansson N, Sarkadi A, Warner G. The Impact of the COVID-19 Pandemic and Societal Infection Control Measures on Children and Adolescents' Mental Health: A Scoping Review. *Front Psychiatry*. 2021;12. doi:10.3389/fpsyt.2021.711791
73. Samji H, Wu J, Ladak A, et al. Review: Mental health impacts of the COVID–19 pandemic on children and youth – a systematic review. *Child Adolesc Ment Health*. 2022;27(2):173-189. doi:10.1111/camh.12501
74. Van den Berg G, Donker A, van Hummel N, et al. *Mentaal Welbevinden van de Jeugd: De Lessen Uit de Coronacrisis. Een Nieuw Overzicht van de Onderzoeksliteratuur.*; 2023.
75. Hoefnagels JW, Schoen AB, Laan SEI Van Der, et al. The Impact of the COVID-19 Outbreak on Mental Wellbeing in Children with a Chronic Condition Compared to Healthy Peers. *Environmental Research and Public Health*. 2022;19(5). doi:https://doi.org/10.3390/ijerph19052953
76. Compas BE, Jaser SS, Dunn MJ, Rodriguez EM. Coping with Chronic Illness in Childhood and Adolescence. *Annu Rev Clin Psychol*. 2012;8(1):455-480. doi:10.1146/annurev-clinpsy-032511-143108
77. Michaud PA, Suris JC, Viner R. The adolescent with a chronic condition. Part II: Healthcare provision. *Arch Dis Child*. 2004;89(10):943-949. doi:10.1136/adc.2003.045377
78. Pinquart M. Achievement of developmental milestones in emerging and young adults with and without pediatric chronic illness--a meta-analysis. *J Pediatr Psychol*. 2014;39(6):577-587.
79. Pinquart M, Teubert D. Academic, physical, and social functioning of children and adolescents with chronic physical illness: A meta-analysis. *J Pediatr Psychol*. 2012;37(4):376-389. doi:10.1093/jpepsy/jsr106
80. Pinquart M, Shen Y. Depressive Symptoms in Children and Adolescents with Chronic Physical Illness: An Updated Meta-Analysis. *J Pediatr Psychol*. 2011;36(4):375-384. doi:10.1093/jpepsy/jsq104
81. Pinquart M, Shen Y. Behavior problems in children and adolescents with chronic physical illness: A meta-analysis. *J pediatr Psychol*. 2011;36(9):1003-1016.
82. Ferro MA, Toulany A. Longitudinal Association Between Youth Multimorbidity and Psychological Distress: Impact of the COVID-19 Pandemic. *Child Psychiatry Hum Dev*. Published online June 26, 2023. doi:10.1007/s10578-023-01564-3
83. Lindoso L, Astley C, Queiroz LB, et al. Physical and mental health impacts during COVID-19 quarantine in adolescents with preexisting chronic immunocompromised conditions. *J Pediatr (Rio J)*. 2022;98(4):350-361. doi:10.1016/j.jped.2021.09.002
84. Zijlmans J, Teela L, Ewijk H Van, Klip H. Mental and Social Health of Children and Adolescents With Pre-existing Mental or Somatic Problems During the COVID-19 Pandemic Lockdown. 2021;12(July):1-11. doi:10.3389/fpsyt.2021.692853
85. Katier N, Uiterwaal CSPM, De Jong BM, et al. The Wheezing Illnesses Study Leidsche Rijn (WHISTLER): Rationale and design. *Eur J Epidemiol*. 2004;19(9):895-903. doi:10.1023/B:EJEP.0000040530.98310.0c
86. Chmitorz A, Neumann RJ, Kollmann B, et al. Longitudinal determination of resilience in humans to identify mechanisms of resilience to modern-life stressors: the longitudinal resilience assessment (LORA) study. *Eur Arch Psychiatry Clin Neurosci*. 2021;271(6):1035-1051. doi:10.1007/s00406-020-01159-2
87. Stewart DE, Yuen T. A Systematic Review of Resilience in the Physically Ill. *Psychosomatics*. 2011;52(3):199-209.
88. Kalisch R, Cramer AOJ, Binder H, et al. Deconstructing and Reconstructing Resilience: A Dynamic Network Approach. *Perspectives on Psychological Science*. 2019;14(5):765-777. doi:10.1177/1745691619855637
89. Masten AS, Lucke CM, Nelson KM, Stallworthy IC. Resilience in Development and Psychopathology: Multisystem Perspectives. *Annu Rev Clin Psychol*. 2021;17(1):521-549. doi:10.1146/annurev-clinpsy-081219-120307
90. González-García N, Buimer EEL, Moreno-López L, et al. Resilient functioning is associated with altered structural brain network topology in adolescents exposed to childhood adversity. *Dev Psychopathol*. Published online July 26, 2023:1-11. doi:10.1017/S0954579423000901
91. McEwen BS. Protective and Damaging Effects of Stress Mediators. *New England Journal of Medicine*. 1998;338(3):171-179. doi:10.1056/NEJM199801153380307

92. Park SW, Jung HW, Lee YA, et al. Tumor origin and growth pattern at diagnosis and surgical hypothalamic damage predict obesity in pediatric craniopharyngioma. *J Neurooncol*. 2013;113(3):417-424. doi:10.1007/s11060-013-1128-0

93. Blakemore S jayne. The art of medicine Adolescence and mental health. *The Lancet*. 2019;393(10185):2030-2031. doi:10.1016/S0140-6736(19)31013-X

94. Blakemore SJ, Mills KL. Is Adolescence a Sensitive Period for Sociocultural Processing? *Annu Rev Psychol*. 2014;65(1):187-207. doi:10.1146/annurev-psych-010213-115202

95. Knoll LJ, Magis-Weinberg L, Speekenbrink M, Blakemore SJ. Social Influence on Risk Perception During Adolescence. *Psychol Sci*. 2015;26(5):583-592. doi:10.1177/0956797615569578

96. Burnett Heyes S, Jih YR, Block P, Hiu CF, Holmes EA, Lau JYF. Relationship Reciprocation Modulates Resource Allocation in Adolescent Social Networks: Developmental Effects. *Child Dev*. 2015;86(5):1489-1506. doi:10.1111/cdev.12396

97. van Harmelen AL, Blakemore SJ, Goodyer IM, Kievit RA. The Interplay Between Adolescent Friendship Quality and Resilient Functioning Following Childhood and Adolescent Adversity. *Advers Resil Sci*. 2021;2(1):37-50. doi:10.1007/s42844-020-00027-1

98. Knevel R, Liao KP. From real-world electronic health record data to real-world results using artificial intelligence. *Ann Rheum Dis*. 2023;82(3):306-311. doi:10.1136/ard-2022-222626

99. Whiteley L, Brown LK, Mena L, Craker L, Arnold T. Enhancing health among youth living with HIV using an iPhone game. *AIDS Care*. 2018;30(sup4):21-33. doi:10.1080/09540121.2018.1503224

100. Rosenberg AR, Bradford MC, McCauley E, et al. Promoting resilience in adolescents and young adults with cancer: Results from the PRISM randomized controlled trial. *Cancer*. 2018;124(19):3909-3917. doi:10.1002/cncr.31666

101. Nap-van Der Vlist MM, Hoefnagels JW, Dalmeijer GW, et al. The PROactive cohort study: rationale, design, and study procedures. *Eur J Epidemiol*. 2022;37:993-1002.

102. Nijhof SL, van de Putte EM, Hoefnagels JW. PROactive Cohort Study. DataverseNL. Published 2021. Accessed November 10, 2022. https://dataverse.nl/dataset.xhtml?persistentId=doi:10.34894/FXUGHW

103. van der Heijden E, van den Bor RM, van der Ent CK, Nijhof SL, van der Laan SEI. The RISE study protocol: resilience impacted by positive stressful events for people with cystic fibrosis. *ERJ Open Res*. 2023;9(3):00535-02022. doi:10.1183/23120541.00535-2022

104. Brunekreef B, Smit J, de Jongste J, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatric allergy and immunology*. 2002;13(15):55-60.

105. Knudsen AK, Hotopf M, Skogen JC, Overland S, Mykletun A. The Health Status of Nonparticipants in a Population-based Health Study: The Hordaland Health Study. *Am J Epidemiol*. 2010;172(11):1306-1314. doi:10.1093/aje/kwq257

106. Langhammer A, Krokstad S, Romundstad P, Heggland J, Holmen J. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC Med Res Methodol*. 2012;12(1):143. doi:10.1186/1471-2288-12-143

107. Klijs B, Scholtens S, Mandemakers JJ, Snieder H, Stolk RP, Smidt N. Representativeness of the LifeLines Cohort Study. *PLoS One*. 2015;10(9):e0137203. doi:10.1371/journal.pone.0137203

108. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: The Tromso Study. *Int J Epidemiol*. 2012;41(4):961-967. doi:10.1093/ije/dyr049

109. van der Lucht F, Polder JJ. *Van Gezond Naar Beter. Volksgezondheid Toekomst Verkenning* .; 2010.

110. de Hollander AEM, Hoeymans N, Melse JM, van Oers JAM, Polder JJ. *Zorg Voor Gezondheid. Volksgezondheid Toekomst Verkenning* .; 2006.

111. Mackenbach JP, Stirbu I, Roskam AJR, et al. Socioeconomic Inequalities in Health in 22 European Countries. *New England Journal of Medicine*. 2008;358(23):2468-2481. doi:10.1056/NEJMsa0707519

112. U.S. Food and Drug Administration. *Framework for FDA's: REAL-WORLD EVIDENCE PROGRAM*.; 2018.

113. hetklikt.nu. KLIK: kwaliteit van leven in kaart. www.hetklikt.nu. Accessed October 19, 2023. https://www.hetklikt.nu/

114. Maloy JW, Bass PF. Understanding Broad Consent. *Ochsner Journal*. 2020;20(1):81-86. doi:10.31486/toj.19.0088

115. Cecil CAM, Schuurmans IK. On Navigating Analytical Choices in Research on Early Life Adversity: A Commentary on Sisitsky et al. (2023). *Res Child Adolesc Psychopathol*. Published online August 3, 2023. doi:10.1007/s10802-023-01103-7

116. Jobe–Shields L, Andrews AR, Parra GR, Williams NA. Person–Centered Approaches to Understanding Early Family Risk. *J Fam Theory Rev*. 2015;7(4):432-451. doi:10.1111/jftr.12118

117. Spurk D, Hirschi A, Wang M, Valero D, Kauffeld S. Latent profile analysis: A review and "how to" guide of its application within vocational behavior research. *J Vocat Behav*. 2020;120:103445. doi:10.1016/j.jvb.2020.103445

118. Bollen K, Curran P. *Latent Curve Models: A Structural Equation Perspective*. John Wiley & Sons; 2006.

119. Höltge J, Ungar M. Quantifying Resilience as an Outcome: Advancing the Residual Approach with Influence Statistics to Derive More Adequate Thresholds of Resilience. *Advers Resil Sci*. 2022;3(4):381-390. doi:10.1007/s42844-022-00078-6

120. Cahill S, Hager R, Chandola T. The validity of the residuals approach to measuring resilience to adverse childhood experiences. *Child Adolesc Psychiatry Ment Health*. 2022;16(1):18. doi:10.1186/s13034-022-00449-y

121. Mitchell DJ, Beckmann C, Biro PA. Understanding the unexplained: The magnitude and correlates of individual differences in residual variance. *Ecol Evol*. 2021;11(12):7201-7210. doi:10.1002/ece3.7603

122. van Harmelen AL, Blakemore SJ, Goodyer IM, Kievit RA. The Interplay Between Adolescent Friendship Quality and Resilient Functioning Following Childhood and Adolescent Adversity. *Advers Resil Sci*. Published online 2020. doi:10.1007/s42844-020-00027-1

123. Programma Uitkomstgerichte Zorg. *Adviesrapport Set Generieke PRO(M)s Voor Kinderen*.; 2023. Accessed October 20, 2023. https://www.platformuitkomstgerichtezorg.nl/aan+de+slag/documenten/HandlerDownloadFiles.ashx?idnv=2471004

124. van Kalsbeek RJ, Hudson MM, Mulder RL, et al. A joint international consensus statement for measuring quality of survival for patients with childhood cancer. *Nat Med*. 2023;29(6):1340-1348. doi:10.1038/s41591-023-02339-y

125. van der Laan S, van Harmelen A. Veerkracht is geen superkracht. Sociaal web. Published September 16, 2022. Accessed November 26, 2023. https://sociaalweb.nl/nieuws/veerkracht-is-geen-superkracht/

126. Boer M, van Dorsselaer S, de Looze M, et al. *HBSC 2021: Gezondheid En Welzijn van Jongeren in Nederland*.; 2022. Accessed August 9, 2023.

A

APPENDICES

SUMMARY

The prevalence of chronic health conditions among youth is increasing. Nowadays, one in four individuals under the age of twenty-five is living with one or more chronic conditions. Youth living with a chronic condition often experience physical and psychosocial challenges, due to symptom distress, demanding therapeutic regimens, periods of hospitalization, uncertainty about the future, social exclusion, and/or the inability to fully participate in school or society. Moreover, youth with a chronic condition are more likely to experience depressive symptoms and behavioral problems, compared to their healthy peers. Adolescents, in particular, might be more susceptible to negative effects of these challenges. There are, however, large inter-individual differences and not all youth with similar chronic conditions experience (similar) difficulties: many children and adolescents manage to positively adapt to disease-related challenges. These children and adolescents are often described as being resilient. Resilience research has the potential to offer valuable insights into preventing mental health deterioration in youth with a chronic condition and identifying potential targets for treatment and interventions to enhance mental health.

Initiated by the increasing prevalence of chronic conditions, there has been a paradigm shift from disease-centered to health-centered care. Paralleling this shift, there has been an increasing focus on resilience of youth with chronic conditions in pediatric healthcare and research. Instead of painting a consistent picture of resilience, researchers studying resilience have portrayed resilience differently over the last decades. These different conceptualizations of resilience have led to a variety in definitions, study designs, and measures of resilience, making it challenging to compare the results of resilience research. Also, within the medical field, these different colors of resilience have impeded comprehensive analyses and implore us to delve deeper into the intricate concept of resilience.

This thesis aimed to better understand the various colors of resilience in adolescents facing disease-related challenges. It is divided into two parts. The first part of this thesis focused on resilience in the face of the increasing prevalence of chronic conditions in youth, the second part explored resilience in the face of the COVID-19 pandemic.

In this thesis, data from four prospective cohort studies were used: the WHISTLER study, PROactive study, RISE study, and PIAMA study. In short, the WHISTLER study is an ongoing population-based birth cohort study established in 2002, in which participants have been followed at ages 0, 3, 5, 8, and 12-16 years old, in which respiratory, cardiovascular, and mental health is monitored. The PROactive cohort study is an ongoing longitudinal study that commenced in 2016 focusing on fatigue, daily life participation, and psychosocial wellbeing of children and adolescents with chronic conditions. The RISE study is an

observational, longitudinal cohort study, newly established in 2021, that tracks the mental wellbeing of people with cystic fibrosis before and after the use of elexacaftor/tezacaftor/ivacaftor, a promising new drug. Lastly, the PIAMA study is a birth cohort that recruited pregnant women in 1996/1997 and has been following their children since, aiming to assess the incidence of asthma and mite allergy.

Part 1- Resilience in the face of increasing prevalence of chronic conditions in youth

Chapter 2 presented a scoping review regarding the used definitions and measures regarding resilience in the pediatric field. Over the 55 included articles, multiple definitions and measures of resilience in youth with a chronic condition were used. Resilience was often conceptualized as a dynamic concept that signals a positive adaptive response to stress or adversity but is, for instance, also conceptualized as a personality trait. Moreover, different assessments of resilience were used in the included articles. To interpret these different assessments, we made the distinction between assessments that measured resilience as an outcome and assessments that measured resilience as a resilience factor. When resilience was measured as an *outcome,* resilience was considered as the outcome of positive adaptation to an adversity. When resilience was assessed as a *factor*, resilience was considered as a factor facilitating positive adaptation to a stressor. Most studies assessed resilience both by measuring an outcome of positive adaptation and by measuring (a) resilience factor(s), and statistically tested whether certain resilience factors were significantly associated with the resilience outcome. As different types of resilience outcomes were assessed, we categorized the outcomes into three groups: personal traits, psychosocial functioning, and disease-related outcomes. Additionally, myriad resilience factors were identified, which we grouped into internal resilience factors (cognitive, social, and emotional competence factors), disease-related factors (such as disease-related distress or disease-related coping), and external factors (caregiver factors, social factors, and contextual factors). This review showed that, at this point, no unified approach is used to define and measure resilience in pediatric healthcare research. This finding indicated that one cannot simply compare "resilience" in one paper with "resilience" in other papers. We therefore provided some recommendations to enhance resilience research in pediatric healthcare research. An operational and standardized definition of resilience empowers researchers to establish a common foundation regarding the concept. Such common foundation might enable the use of suited study designs and measurement tools, facilitating easier summarization and comparison of results. Additionally, more knowledge is needed on which resilience factors are related to positive adaptation in specific disease-related challenges, the underlying mechanisms responsible for this positive adaptation, and how these underlying mechanisms interact with one another. These results might shed light on novel opportunities for interventions and identify gaps in current knowledge.

Chapter 3 described the study protocol of the Resilience Impacted by Positive Stressful Events (RISE) study. The primary objective of the RISE study was to investigate if and how

(various indicators of) mental wellbeing of people with cystic fibrosis (CF) changes after starting elexacaftor/ tezacaftor/ ivacaftor (ETI) therapy. By tracking mental wellbeing before and after the use of ETI therapy, the RISE study aims to identify individuals who demonstrate resilience and those who are at a higher risk of experiencing a deterioration in mental wellbeing after ETI therapy. We set up a single arm, observational, prospective longitudinal cohort with a timeframe of 60 weeks including pre- and post-treatment measurements.

Chapter 4 presented the key findings of the RISE study: people with CF reported a significantly and clinically relevant improvement in psychosocial health following ETI therapy. We evaluated whether specific subgroups were more susceptible to diminished psychosocial health after starting ETI by conducting subgroup analyses. Subgroups were based on age, sex, lung function, earlier use of a cystic fibrosis transmembrane conductance regulator (CFTR) modulator, and use of psychotropic medication at baseline. We did not identify subgroups that might be more vulnerable in terms of their psychosocial health. People using psychotropic medication at baseline, however, reported structurally lower psychosocial health scores than people who did not use psychotropic medication at baseline. Future studies are needed to investigate the underlying biological, pharmacological, and psychological mechanisms at the individual level to better understand why individuals respond differently to ETI therapy in terms of their psychosocial health.

Chapter 5 focused on differences in mental wellbeing and perceived general health between adolescents with asthma and adolescents without asthma. In 2019, asthma was the most common chronic disease among Dutch youth aged 0-25 years. The severity of asthma can vary greatly between individuals; for some people, asthma symptoms may be mild, while for others, asthma symptoms can be severe, having a significant impact on their daily life. Much of the current literature on the association between asthma and mental wellbeing is cross-sectional in design, limiting the ability to draw inferences about the effect of asthma on mental wellbeing over time. We therefore investigated whether adolescents with asthma experience a lower mental wellbeing and lower general health compared with their peers without asthma. We used data from de PIAMA study, collected at four timepoints during adolescence: at the ages of 11, 14, 17 and 20 years. We did not find significant differences in mental wellbeing between adolescents with asthma and their peers without asthma. However, adolescents with asthma were less likely to perceive their own health as good or excellent compared to adolescents without asthma. All examined associations between asthma (severity) and mental wellbeing/ perceived general health were similar for boys and girls and across different age groups. Our findings provide insight into adolescents' experiences with asthma and suggest that having asthma does not prevent them from feeling mentally well during adolescence.

Chapter 6 explored the impact of self-reporting as having a chronic condition on psychosocial wellbeing, within a sample of adolescents diagnosed with a chronic condition by a physician. Conditions included were auto-immune disease, cystic fibrosis, congenital heart disease, nephrological condition, or a general pediatric condition. Our findings revealed that only a minority of adolescents with a physician-diagnosed chronic condition self-report as having a chronic disease. Self-reporters had significantly worse outcomes in all psychosocial domains assessed; a pattern that seems to hold across some, but not all, disease groups. In general, no clear moderating effects of gender, age, or socioeconomic status on the relationship between reporting status and psychosocial wellbeing were identified. This study underlines the importance of adopting a multidimensional healthcare perspective emphasizing the transition from a biomedical disease-centered approach toward a more individual-centered approach.

Part 2 - Resilience in the face of the COVID-19 pandemic

During the second year of my PhD, we unfortunately needed to pause the WHISTLER study due to the COVID-19 pandemic. This pandemic, however, also raised opportunities to learn more about mental wellbeing of adolescents in the face of the COVID-19 pandemic. Data had already been collected on the mental wellbeing of 224 adolescents. We continued and expanded the assessment of their mental wellbeing by sending online questionnaires throughout the first year of the pandemic. These data resulted in **Chapters 7** and **8**. Through close collaboration between the WHISTLER study and the PROactive study, we were able to investigate whether adolescents, with or without a chronic condition, demonstrated greater resilience during the pandemic. These collaboration efforts resulted in **Chapter 9**.

In **Chapter 7**, we investigated whether adolescent mental wellbeing changed after the introduction of lockdown measures (May 2020) compared with pre-pandemic levels baseline (up to 1 year before the COVID-19 pandemic); whether changes in mental wellbeing differed between boys and girls; and whether changes were associated with adolescents' concerns about the COVID-19 and lockdown measures. At 5–8 weeks after the introduction of the lockdown measures in the Netherlands, life satisfaction decreased, but internalizing symptoms (anxiety and depressive symptoms) did not change, compared to pre-pandemic levels. Contrary to expectations, our study sample reported an improved psychosomatic health at follow-up, when compared with pre-pandemic psychosomatic health. Boys scored better on all three mental wellbeing indicators (higher life satisfaction, less internalizing symptoms, and better psychosomatic health) compared with girls both before as well as during the pandemic. However, boys' life satisfaction significantly decreased over time, whereas girls' life satisfaction did not change. Adolescents' concerns about the COVID-19 and the lockdown measures were significantly associated with lower life satisfaction and more internalizing symptoms.

Adolescents' mental wellbeing and concerns were expected to continue to vary during the COVID-19 pandemic. We therefore tracked mental wellbeing of adolescents during the first year of the COVID-19 pandemic (**Chapter 8**). We assessed mental wellbeing both before the pandemic and four times during lockdown periods with varying lockdown stringencies. We identified an interesting picture of change on mental wellbeing throughout the first year of the pandemic. Life satisfaction decreased during the first (May 2020) and second full lockdowns (February 2021) as well as during the partial lockdown (October 2020), compared to before the pandemic. Notably, life satisfaction decreased most at the second full lockdown in February 2021. Moreover, boys' life satisfaction decreased more than girls' during the pandemic, compared to pre-pandemic levels. Adolescents only reported more internalizing symptoms, reflecting anxiety and depression symptoms, during the second full lockdown (February 2021), yet did not reach a (sub)clinical threshold for therapy. Interestingly, throughout the first year of the COVID-19 pandemic, adolescents reported significantly better perceived psychosomatic health, which might be partly attributable to less trouble falling asleep. These findings indicated that the COVID-19 lockdown measures may have had both a negative and positive impact on mental wellbeing of our study sample.

Chapter 9 evaluated mental wellbeing of adolescents with and without a chronic condition during the COVID-19 pandemic. This study provided four key findings. First, the pandemic had a negative impact on the life satisfaction of adolescents with a chronic condition, but our data showed no clinically relevant changes in internalizing symptoms or psychosomatic health of adolescents with a chronic condition during the pandemic compared to before. Second, compared to healthy peers, adolescents with a chronic condition experienced poorer life satisfaction and psychosomatic health during the pandemic, but internalizing symptoms did not differ between groups. The difference in life satisfaction seemed to be pre-existing. These results suggested that adolescents with a chronic condition did not experience more distress than their healthy peers due to the pandemic, but that the difference was there before, and persisted without increasing. Third, compared to boys, girls reported worse mental wellbeing, and this difference was apparent regardless of the pandemic or their disease state. Fourth, stricter governmental restrictions were significantly associated with poorer life satisfaction, more internalizing symptoms, and worse psychosomatic health in both adolescents with a chronic condition and healthy peers, with the stringency index explaining up to nearly a third of variance in psychosomatic symptoms. Based on these findings, it seemed that adolescents with a chronic condition did not appear to be at a higher risk for mental health issues compared to their healthy peers in the COVID-19 pandemic.

Chapter 10 presented a non-academic blog about resilience written in layman's terms, aiming to translate academic findings for society. The main message of this blog is that resilience is not a personal superpower, but a process of adaptation to maintain or regain mental wellbeing during or after a stressful event. Factors that support resilience exist

both within the individual, but also in the environment in which the individual is situated. Examples of personal factors include a genetic makeup or a body's hormonal response to stress. Factors from the (social) environment include, among others, support from parents or friends. This implies that each of us can contribute to the resilience of those around us.

In the general discussion (**Chapter 11**) I have reflected upon the strengths and limitations of the research in this thesis.

First, I provided four recommendations regarding researching resilience in pediatric healthcare based on lessons from literature and **Chapter 2**. By describing what experts in resilience research see as the primary *colors* of resilience research in general, I aimed to provide fellow researchers with a basic *palette,* serving as a starting point for portraying resilience. Recommendation I included the introduction of a standardized definition of resilience. Recommendation II described that the adversity, and its severity should be defined and quantified as clearly as possible. Recommendation III entailed that an ideal study design for resilience research would be of a longitudinal nature. Lastly, Recommendation IV, suggested that the concept of resilience could be elucidated by distinguishing between resilience as an outcome and resilience as a factor.

Subsequently, I evaluated whether the researched study populations of the empirical chapters (i.e. **Chapter 4** through **9**) demonstrated resilience using the proposed definition of resilience (Recommendation 1). In short, people with CF demonstrated resilience as their psychosocial health was maintained and even increased on group level after commencing ETI (**Chapter 4**). Furthermore, asthmatic adolescents demonstrated resilience, as our findings indicated that despite growing up with asthma, affected adolescents can still experience a good mental wellbeing (**Chapter 5**). Unlike the previous chapters, **Chapter 6** had a cross-sectional design which precludes drawing firm conclusions about resilient functioning of the study group. We did, however, identified that only a minority of adolescents with a physician diagnosed chronic condition self-report as having a chronic disease and that these reporting adolescents had a lower psychosocial wellbeing. Not self-reporting as having a chronic condition could therefore be a resilience factor, yet future research might focus on underlying mechanisms regarding the association between psychosocial wellbeing and reporting status. Regarding **Chapters 7** and **8**, we could not simply categorize healthy adolescents aged 12-16 years as either resilient or non-resilient. This was because not all measured mental wellbeing outcomes exhibited similar patterns of change; life satisfaction decreased, internalizing symptoms remained stable, and psychosomatic health showed improvement. **Chapter 9** indicated that adolescents with a chronic condition appeared to be equally resilient as their healthy peers during the COVID-19 pandemic, as they did not, on average, exhibit a higher risk for mental health problems during this time period.

To articulate novel research challenges for resilience research concerning adolescents facing disease-related challenges, I used Recommendation II, III, and IV.

Finally, I explored strategies how to integrate resilience research into pediatric healthcare. I started by discussing opportunities to capture the complexity of resilience, suggesting not to focus merely on resilience factors but mainly on the underlying mechanisms of positive adaptation to adversity. Concerning chronic conditions in youth, it is essential to explore whether there are variations in the underlying mechanisms among different diseases and between different age groups. Secondly, I discussed conceptual and methodological challenges, and opportunities regarding resilience research in pediatric healthcare. I addressed the advantages and disadvantages of cohort studies. Additionally, I explored the potential benefits of using real-world data. Subsequently, I discussed advanced statistical methods and different models for resilience research – both for longitudinal as well as cross-sectional data. Lastly, I focused on how we could improve outcome measures for resilience research in pediatric healthcare.

In this thesis I have explored various colors of resilience, by drawing insights from literature, by identifying new research avenues for disease-related challenges, and by examining strategies to integrate resilience research into pediatric healthcare. Through these efforts, I have endeavored to paint a more complete picture of resilience in the face of disease-related challenges.

NEDERLANDSE SAMENVATTING

In de afgelopen decennia is de prevalentie van chronische aandoeningen bij jongeren aanzienlijk toegenomen. Tegenwoordig heeft één op de vier personen onder de vijfentwintig jaar te maken met één of meer chronische aandoeningen. Jongeren met een chronische aandoening ervaren vaak fysieke en psychosociale uitdagingen, veroorzaakt door symptomen van hun aandoening, veeleisende behandelingen, ziekenhuisopnames, onzekerheid over de toekomst, en/of het onvermogen om volledig deel te nemen aan school of de samenleving. Bovendien vertonen jongeren met een chronische aandoening vaker depressieve klachten en gedragsproblemen vergeleken met hun gezonde leeftijdsgenoten. Adolescenten in het bijzonder kunnen gevoeliger zijn voor de negatieve effecten van deze ziekte-gerelateerde uitdagingen. Er zijn echter grote individuele verschillen, en niet alle jongeren met vergelijkbare chronische aandoeningen ervaren (vergelijkbare) moeilijkheden: veel kinderen en adolescenten slagen erin om zich aan te passen aan hun ziekte-gerelateerde uitdagingen. Zij worden vaak beschreven als veerkrachtig. Veerkrachtonderzoek kan waardevolle inzichten opleveren, bijvoorbeeld over het voorkomen van achteruitgang in mentaal welzijn van jongeren met een chronische aandoening, en tevens over potentiële behandeling doelen en interventies om dit welzijn te verbeteren.

De groeiende prevalentie van chronische aandoeningen leidt tot een paradigmashift binnen de gezondheidszorg: van een focus op ziekte naar een focus op gezondheid. Als gevolg van deze shift, wordt er meer tijd en aandacht besteed aan veerkracht van jongeren met een chronische aandoening, zowel in de gezondheidszorg als binnen onderzoek. Maar wat is veerkracht precies? In de afgelopen decennia hebben onderzoekers die veerkracht hebben bestudeerd, veerkracht op verschillende manieren geportretteerd. Dit heeft geresulteerd in diverse definities, onderzoeksopzetten en meetmethoden voor veerkracht, waardoor het moeilijk is om resultaten van veerkrachtonderzoek samen te vatten of te vergelijken.

Dit proefschrift had als doel de verschillende kleuren van veerkracht van adolescenten die te maken hebben met ziekte-gerelateerde uitdagingen beter te begrijpen. Dit proefschrift is verdeeld in twee delen. Het eerste deel van dit proefschrift richtte zich op veerkracht in het licht van de toenemende prevalentie van chronische aandoeningen bij jongeren. Het tweede deel van dit proefschrift ging over veerkracht in het licht van de COVID-19 pandemie.

In dit proefschrift werd data gebruikt van vier prospectieve cohortstudies: de WHISTLER-studie, de PROactive-studie, de RISE-studie en de PIAMA-studie. Kort gezegd is de WHISTLER-studie een doorlopend geboortecohort onderzoek dat in 2002 is gestart met deelnemers uit de algemene bevolking. Deelnemers worden gevolgd vanaf de geboorte

en op verschillende leeftijden gedurende hun jeugd gemonitord op hun ademhalings-, cardiovasculaire en mentale gezondheid. De PROactive-cohortstudie is een doorlopend longitudinaal onderzoek dat in 2016 is gestart en zich richt op vermoeidheid, participatie in het dagelijks leven en psychosociaal welzijn van kinderen en adolescenten met chronische aandoeningen. De RISE-studie is een observationele cohortstudie, opgericht in 2021. De RISE-studie volgt (indicatoren van) mentaal welzijn van mensen met cystische fibrose vóór en na het gebruik van een veelbelovend nieuw medicijn, genaamd elexacaftor/tezacaftor/ivacaftor. Ten slotte is de PIAMA-studie een geboortecohort dat zwangere vrouwen heeft gerekruteerd in 1996/1997 uit de algemene bevolking en hun kinderen sindsdien volgt, met als doel de incidentie van astma en mijtallergie te bepalen.

Deel 1 - Veerkracht in het licht van de toenemende prevalentie van chronische aandoeningen bij jongeren

Hoofdstuk 2 presenteerde een *scoping review* van definities en meetmethoden van veerkracht die gebruikt worden in wetenschappelijk onderzoek binnen kindergeneeskundig onderzoek. Deze review liet zien dat onderzoekers verschillende definities en meetmethoden voor veerkracht hebben gebruikt wanneer veerkracht wordt onderzocht bij jongeren met een chronische aandoening. Veerkracht werd vaak gedefinieerd als een dynamisch concept van positieve adaptatie aan stress, maar bijvoorbeeld ook als persoonlijkheidskenmerk. Om verschillende meetmethoden van veerkracht te interpreteren, maakten we onderscheid tussen methoden die veerkracht beoordeelden als een uitkomst of als een veerkrachtfactor. Als veerkracht als uitkomst werd gemeten, beschouwde men veerkracht als het resultaat van een positieve aanpassing aan een stressor. Als veerkracht als een veerkrachtfactor werd gemeten, werden factoren in beschouwing genomen die het aanpassingsproces aan de stressor faciliteerden. De meeste studies hebben veerkracht gemeten als uitkomst en als factor. Deze studies testten vervolgens op statistische wijze of bepaalde veerkrachtfactoren significant geassocieerd waren met veerkracht als uitkomst. Omdat verschillen tussen de diverse veerkracht uitkomsten werden waargenomen, categoriseerden we veerkracht uitkomsten in drie groepen: persoonseigenschappen, psychosociaal functioneren, en ziekte-gerelateerde uitkomsten. Ook werden talloze veerkrachtfactoren geïdentificeerd. Deze factoren hebben we gegroepeerd in interne veerkrachtfactoren (cognitieve, sociale en emotionele competentie factoren), ziekte-gerelateerde factoren (zoals ziekte-gerelateerde stress of ziekte-gerelateerde coping mechanismen), en externe factoren (factoren van de ouder/verzorger, sociale factoren en context factoren). Deze review toonde aan dat op dit moment geen uniforme aanpak wordt gebruikt om veerkracht te definiëren en te meten binnen de kindergeneeskunde. Hierdoor kan men "veerkracht" in het ene artikel niet zomaar vergelijken met "veerkracht" in een ander artikel. Daarom hebben we de volgende aanbevelingen gedaan om veerkrachtonderzoek in het kindergeneeskundige onderzoeksveld te verbeteren. We stelden voor een gestandaardiseerde definitie van veerkracht te introduceren. Dit stelt onderzoekers in staat om een gemeenschappelijke basis te leggen met betrekking tot het concept veerkracht. Een dergelijke basis kan het

gebruik van geschikte onderzoeksopzetten en meetinstrumenten faciliteren, waardoor het gemakkelijker wordt om resultaten samen te vatten en te vergelijken. Bovendien is er meer kennis nodig over welke veerkrachtfactoren gerelateerd zijn aan positieve aanpassing bij specifieke ziekte-gerelateerde uitdagingen, welke onderliggende mechanismen verantwoordelijk zijn voor deze positieve aanpassing, en hoe deze onderliggende mechanismen met elkaar samenhangen. Deze resultaten kunnen nieuwe mogelijkheden voor interventies aan het licht brengen en hiaten in de huidige kennis identificeren.

Hoofdstuk 3 beschreef het onderzoeksprotocol van de RISE-studie (*Resilience Impacted by Positive Stressful Events*). Het primaire doel van de RISE-studie was om te onderzoeken of en hoe (verschillende indicatoren van) het mentaal welzijn van mensen met cystische fibrose (CF) verandert na het starten van elexacaftor/tezacaftor/ivacaftor (ETI)- therapie. Door mentaal welzijn zowel vóór als na het gebruik van ETI te meten, beoogt de RISE-studie individuen te identificeren die veerkrachtig functioneren, maar ook diegenen te vinden die een hoger risico lopen op verslechtering van hun mentaal welzijn na ETI-therapie. Om dit te onderzoeken, hebben we een observationele, prospectieve, longitudinale cohortstudie opgezet met een totale duur van 60 weken.

Hoofdstuk 4 presenteerde de antwoorden op de primaire onderzoeksvraag van de RISE-studie: mensen met CF rapporteerden een significante en klinisch relevante verbetering van hun psychosociale gezondheid na ETI-therapie. Met subgroep analyses hebben we geprobeerd te voorspellen of specifieke groepen - gebaseerd op leeftijd, geslacht, longfunctie, eerdere gebruik van een cystische fibrose transmembraan conductantieregulator (CFTR) modulator, of (eerder) gebruik van psychotrope medicatie - een afname in psychosociale gezondheid zouden ervaren na het gebruik van ETI. We hebben geen subgroepen geïdentificeerd die mogelijk gevoeliger waren wat betreft hun psychosociale gezondheid. Mensen die al psychotrope medicatie gebruikten, rapporteerden echter structureel een lagere psychosociale gezondheid vergeleken met degenen die geen psychotrope medicatie gebruikten. Om beter te begrijpen waarom individuen verschillend reageren op ETI wat betreft hun psychosociale gezondheid, zouden toekomstige studies kunnen focussen op onderliggende biologische, farmacologische en psychologische mechanismen.

Hoofdstuk 5 richtte zich op verschillen in mentaal welzijn en algemene ervaren gezondheid tussen adolescenten met astma en adolescenten zonder astma. In 2019 was astma de meest voorkomende chronische ziekte onder Nederlandse jongeren van 0-25 jaar. De ernst van astma kan sterk variëren tussen individuen; voor sommige mensen kunnen astmasymptomen bijvoorbeeld mild zijn, terwijl voor anderen astmasymptomen ernstig van aard zijn en een aanzienlijke invloed hebben op het dagelijks leven. Een groot deel van de huidige literatuur dat de associatie tussen astma en mentaal welzijn heeft bestudeerd, is gebaseerd op cross-sectionele studies. Het is bij deze onderzoeksopzet niet mogelijk om conclusies te trekken over het effect van astma op het mentaal welzijn

over een langere periode, zoals tijdens de adolescentie. Daarom onderzochten wij, op een longitudinale manier, of adolescenten met astma een lager mentaal welzijn hadden en een lager algemene gezondheid ervaarden in vergelijking met hun leeftijdsgenoten zonder astma. We gebruikten gegevens uit de PIAMA-studie. De analyses zijn gebaseerd op vier momenten tijdens de adolescentie: op de leeftijden van 11, 14, 17 en 20 jaar. We vonden geen significante verschillen in mentaal welzijn tussen adolescenten met astma en zonder astma. Adolescenten met astma waren echter minder geneigd om hun eigen gezondheid als goed of uitstekend te beschouwen in vergelijking met adolescenten zonder astma. Alle onderzochte verbanden tussen astma (ernst) en mentaal welzijn/ algemene gezondheid waren vergelijkbaar voor jongens en meisjes en op verschillende leeftijden. Onze bevindingen lieten zien dat het hebben van astma adolescenten niet belemmert om zich mentaal goed te voelen.

Hoofdstuk 6 bekeek de impact van zelfrapportage van het hebben van een chronische aandoening op psychosociaal welzijn in adolescenten gediagnosticeerd met een chronische aandoening door een arts. Adolescenten hadden een auto-immuunziekte, cystische fibrose, aangeboren hartafwijking, nefrologische aandoening of een algemene pediatrische aandoening. Onze bevindingen onthulden dat slechts een minderheid van adolescenten met een door een arts gediagnosticeerde chronische aandoening rapporteerde een chronische aandoening te hebben. Zij die dit rapporteerden, hadden significant slechtere uitkomsten op alle psychosociale domeinen die werden onderzocht. Dit patroon leek zich te herhalen voor sommige, maar niet alle, specifieke ziektegroepen. Over het algemeen werden geen duidelijke modererende effecten van geslacht, leeftijd of sociaaleconomische status op de relatie tussen rapportagestatus en psychosociaal welzijn geïdentificeerd. Deze studie benadrukte het belang van het omarmen van een multidimensionaal gezondheidsperspectief. In dit gezondheidsperspectief wordt zowel de ziekte als de psychosociale impact geëvalueerd, waarbij de subjectieve ervaring van het hebben van een chronische ziekte wordt meegenomen.

Deel 2 - Veerkracht in het licht van de COVID-19-pandemie

Door de COVID-19 pandemie moesten we tijdelijk de inclusie van de WHISTLER-studie stoppen, waardoor we geen nieuwe data konden verzamelen. Er ontstond echter ook een kans om meer te leren over het mentaal welzijn van adolescenten tijdens deze periode. Voordat de pandemie begon, hadden we van 224 adolescenten medische gegevens en informatie over hun mentaal welzijn verzameld. We hebben ten tijde van de eerste lockdown besloten om deze adolescenten via online vragenlijsten te gaan volgen. De resultaten van dit onderzoek zijn beschreven in **Hoofdstuk 7** en **8**. Dankzij samenwerking tussen de WHISTLER-studie en de PROactive-studie konden we onderzoeken of adolescenten met of juist zonder een chronische aandoening tijdens de pandemie meer veerkrachtig functioneerde. Deze samenwerking resulteerde in **Hoofdstuk 9**.

In **Hoofdstuk 7** onderzochten we of het mentaal welzijn van adolescenten veranderde na de invoering van lockdownmaatregelen (mei 2020) vergeleken met het mentaal welzijn gemeten voor de pandemie (tot 1 jaar voor de COVID-19-pandemie); of deze veranderingen verschilden tussen jongens en meisjes; en of veranderingen verband hielden met de zorgen van adolescenten over COVID-19 en de lockdownmaatregelen. Ten opzichte van voor de pandemie nam de levenstevredenheid van adolescenten af, maar hun angst- en depressie klachten veranderden niet. In tegenstelling tot onze verwachting rapporteerde onze onderzoeksgroep een verbeterde psychosomatische gezondheid tijdens de pandemie, vergeleken met daarvoor. Jongens scoorden beter op alle drie de indicatoren mentaal welzijn (hogere levenstevredenheid, minder angst- en depressieklachten, en betere psychosomatische gezondheid) vergeleken met meisjes zowel voor als tijdens de pandemie. Echter, de levenstevredenheid van jongens nam significant af in de loop van de tijd, terwijl de levenstevredenheid van meisjes niet veranderde. Zorgen over COVID-19 en de lockdownmaatregelen waren geassocieerd met lagere levenstevredenheid en meer angst- en depressie klachten.

Experts verwachtten dat het mentaal welzijn van adolescenten verder kon afnemen tijdens de COVID-19 pandemie. Mede daarom hebben we het mentaal welzijn onze studiepopulatie gevolgd gedurende het eerste jaar van de COVID-19-pandemie (**Hoofdstuk 8**). We hebben hun mentaal welzijn één keer voor de pandemie en vier keer tijdens lockdownperioden gemeten. Tijdens deze lockdownperioden waren er verschillende lockdownmaatregelen van kracht, wisselend in ernst. We zagen een interessant patroon van veranderingen in het mentaal welzijn. De levenstevredenheid nam af tijdens de eerste (mei 2020) en tijdens de tweede volledige lockdown (februari 2021), evenals tijdens de gedeeltelijke lockdown (oktober 2020), vergeleken met vóór de pandemie. De levenstevredenheid was het laagst tijdens de tweede volledige lockdown in februari 2021. Bovendien nam de levenstevredenheid van jongens meer af dan die van meisjes tijdens de pandemie. Adolescenten meldden meer angst- en depressie klachten tijdens de tweede volledige lockdown (februari 2021). De ernst van deze klachten was echter laag. Interessant genoeg rapporteerden adolescenten gedurende het eerste jaar van de COVID-19 pandemie significant betere ervaren psychosomatische gezondheid. Dit kon mogelijk verklaard worden doordat jongeren minder moeite hadden om in slaap te vallen. De resultaten van **Hoofdstuk 8** suggereerden dat de lockdownmaatregelen tijdens de COVID-19-pandemie zowel negatieve als positieve effecten kunnen hebben gehad op het mentaal welzijn van onze onderzoeksgroep.

Hoofdstuk 9 evalueerde het mentaal welzijn tijdens de COVID-19-pandemie van adolescenten met en zonder een chronische aandoening. Deze studie resulteerde in vier bevindingen. Ten eerste had de pandemie een negatieve invloed op de levenstevredenheid van adolescenten met een chronische aandoening, maar er werden geen klinisch relevante veranderingen in angst- en depressie klachten of psychosomatische gezondheid

geïdentificeerd tijdens de pandemie vergeleken met daarvoor. Ten tweede, in vergelijking met gezonde leeftijdsgenoten, ervoeren adolescenten met een chronische aandoening een lagere levenstevredenheid en lagere psychosomatische gezondheid tijdens de pandemie dan hun gezonde leeftijdsgenoten. Het verschil in levenstevredenheid leek al te bestaan vóór de pandemie, wat suggereert dat adolescenten met een chronische aandoening niet meer stress ervoeren dan gezonde leeftijdsgenoten vanwege de pandemie, maar dat het verschil al aanwezig was en niet toenam. Angst- en depressieklachten verschilden niet tussen adolescenten met en zonder chronische aandoening. Daarnaast meldden meisjes een lager mentaal welzijn dan jongens, ongeacht de pandemie of hun ziektestatus. Verder waren strengere overheidsbeperkingen significant geassocieerd met een lagere levenstevredenheid, meer angst- en depressieklachten, en een slechtere psychosomatische gezondheid, zowel bij adolescenten met als zonder een chronische aandoening. Hierbij verklaarde de striktheid van de lockdown bijna een derde van de variantie in psychosomatische symptomen. Op basis van de bevindingen van dit hoofdstuk lijkt het erop dat adolescenten met een chronische aandoening tijdens de COVID-19-pandemie niet meer risico liepen op mentale problemen vergeleken met hun gezonde leeftijdsgenoten.

Hoofdstuk 10 presenteerde een niet-academische blog, geschreven in begrijpelijke taal, met als doel academische bevindingen over veerkracht te vertalen voor de samenleving. De belangrijkste boodschap van deze blog was dat veerkracht geen persoonlijke superkracht is, maar een proces van aanpassing tijdens of na een stressvolle gebeurtenis om mentaal welzijn te behouden of terug te krijgen. Factoren die veerkracht ondersteunen zijn zowel binnen het individu als in de omgeving waarin het individu zich bevindt aanwezig. Voorbeelden van persoonlijke factoren zijn genetische aanleg of het hormonale stressrespons van het lichaam. Factoren uit de (sociale) omgeving zijn onder meer steun van ouders of vrienden. Dit impliceert dat elk van ons kan bijdragen aan de veerkracht van de mensen om ons heen.

In de algemene discussie (**Hoofdstuk 11**) heb ik gereflecteerd op de sterke punten en beperkingen van het onderzoek in dit proefschrift. Allereerst heb ik vier aanbevelingen opgeschreven over veerkrachtonderzoek in de kindergeneeskunde, gebaseerd op lessen uit de literatuur en **Hoofdstuk 2**. Door te beschrijven wat experts in veerkrachtonderzoek zien als de primaire kleuren van veerkrachtonderzoek, heb ik geprobeerd medeonderzoekers een basispalet te bieden, dat dient als startpunt voor het portretteren van veerkracht. Aanbeveling I ging over het introduceren een gestandaardiseerde definitie van veerkracht. Aanbeveling II benadrukte het belang van een duidelijke definitie en beoordeling van de (ernst van de) stressor. Aanbeveling III beschreef dat het ideale onderzoeksdesign voor veerkrachtonderzoek longitudinaal van aard is. Ten slotte suggereerde Aanbeveling IV dat het concept van veerkracht verduidelijkt zou kunnen worden door onderscheid te maken tussen veerkracht als uitkomst en veerkracht als factor.

Vervolgens heb ik geëvalueerd met behulp van de voorgestelde definitie van veerkracht (Aanbeveling I) of de onderzochte onderzoekspopulaties van **Hoofdstuk 4** tot **9** veerkracht hebben getoond. Mensen met CF, uit **Hoofdstuk 4**, toonden veerkracht, aangezien hun psychosociale gezondheid behouden bleef en zelfs toenam na het start van ETI. De astmatische adolescenten uit **Hoofdstuk 5** toonden veerkracht, omdat astmatische adolescenten hetzelfde mentaal welzijn ervoeren als hun leeftijdsgenoten zonder astma. In tegenstelling tot de eerdere hoofdstukken had **Hoofdstuk 6** een cross-sectioneel onderzoeksdesign waardoor we niets over het veerkrachtig functioneren van de onderzoeksgroep konden zeggen. Het niet rapporteren van een chronische aandoening kan echter een veerkracht factor zijn, omdat dit geassocieerd is met een hogere psychosociale gezondheid. We kunnen de gezonde adolescenten van 12-16 jaar uit **Hoofdstuk 7** en **8** niet eenvoudig categoriseren als veerkrachtig of niet-veerkrachtig. Dit komt omdat niet alle gemeten indicatoren van mentaal welzijn vergelijkbare patronen van veranderingen vertoonden; de levenstevredenheid nam af, angst- en depressieklachten bleven stabiel, en psychosomatische gezondheid verbeterde. **Hoofdstuk 9** gaf aan dat adolescenten met een chronische aandoening tijdens de COVID-19-pandemie even veerkrachtig leken te zijn als hun gezonde leeftijdsgenoten, aangezien ze niet, gemiddeld genomen, een hoger risico op psychische problemen vertoonden tijdens deze periode.

Om nieuwe onderzoeksvraagstukken voor veerkrachtonderzoek bij adolescenten die geconfronteerd worden met ziekte-gerelateerde uitdagingen te identificeren, heb ik gebruik gemaakt van Aanbeveling II, III en IV.

Ten slotte heb ik strategieën onderzocht om veerkrachtonderzoek te integreren in de kindergeneeskunde. Ik besprak mogelijkheden om de complexiteit van veerkracht te grijpen, waarbij ik voorstelde niet alleen te focussen op veerkrachtfactoren maar vooral op de onderliggende mechanismen van positieve aanpassing aan stress. Met betrekking tot chronische aandoeningen in jongeren is het essentieel om te onderzoeken of er variaties zijn in de onderliggende mechanismen tussen verschillende ziekten en tussen verschillende leeftijdsgroepen. Ten tweede besprak ik conceptuele en methodologische uitdagingen, en kansen met betrekking tot veerkrachtonderzoek in kindergeneeskunde. Ik sprak over de voor- en nadelen van cohortstudies. Daarnaast heb ik de mogelijke voordelen van het gebruik van "real-world data" verkend. Vervolgens exploreerde ik de implicaties van geavanceerde statistische methoden en verschillende modellen voor veerkrachtonderzoek - zowel voor longitudinale als voor cross-sectionele data. Ten slotte richtte ik me op hoe we uitkomstmaten kunnen verbeteren binnen veerkrachtonderzoek in de kindergeneeskunde.

In dit proefschrift heb ik verschillende kleuren van veerkracht onderzocht, door inzichten uit de literatuur te halen, door nieuwe onderzoeksmogelijkheden te identificeren voor ziekte-gerelateerde uitdagingen, en door strategieën te onderzoeken om veerkrachtonderzoek te integreren in de kindergeneeskunde. Zo heb ik gepoogd veerkracht beter te portretteren in het licht van ziekte-gerelateerde uitdagingen.

LIST OF ABBREVIATIONS

ACT	Asthma Control Test
Adj	Adjusted
AFQ-Y	Avoidance and Fusion Questionnaire for Youth
ANOVA	Analysis of variance
ARC	Adolescent Resilience Questionnaire
ART	Antiretroviral treatment
ASRI	Adolescent Self-Regulatory Inventory
ATQ	Automatic Thoughts Questionnaire
BASC	Behavior Assessment System for Children
BASC-2 SRP	Behavior Assessment System for Children 2nd edition Self-Report of Personality
BBSC	Benefit Finding/Burden Scale for Children
BFSC	Benefit Finding Scale for Children
B-IPQ	Brief Illness Perception Questionnaire
BMI	Body mass index
BMLSS	Brief Multidimensional Life Satisfaction Scale
BMT	Bone marrow transplantation
Brief COPE	Coping orientation to problems experienced
BRS	Brief Resilience Scale
BSCI-Y	Chinese Beck Self-Concept Inventory
CASPE	COVID-19 Adolescent Symptom & Psychological Experience
CASQ-R	Children's Attributional Style Questionnaire-Revised
CATIS	Child Attitude Toward Illness Scale
CBCL	Child Behavior Checklist
CD-RISC (-10/-25)	Conner-Davidson Resiliency Questionnaire
CDRS	Contour Drawing Rating Scale
CEQ	Coping Efficacy Questionnaire
CESDS	Center for Epidemiologic Studies Depression Scale
CF	Cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFLD	Cystic Fibrosis related Liver Disease
CFQ-R	Cystic Fibrosis Questionnaire Revised
CFRD	Cystic Fibrosis Related Diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
CHD	Congenital heart disease
CHS	Children's Hope Scale

CI	Confidence Intervals
CICRS	Chronic Illness Children's Resilience Scale
CISS	Coping Inventory for Stressful Situations
CKD	Chronic kidney disease
COVID-19	Coronavirus disease 2019
CPAQ-A	Dutch Chronic Pain Acceptance Questionnaire — Adolescent Version
CSES	Child Self-Efficacy Scale
CSQ	Coping Strategies Questionnaire for Sickle Cell Disease
CYRM-28	Child and Youth Resilience Measures-28
DEPS-R	Diabetes Eating Problem Survey-Revised
DMD	Duchenne muscular dystrophy
DSMP	Diabetes Self-Management Profile
DSTAR-Teen	Diabetes strengths and resilience measure for adolescents
EAC	Emotional Approach & Coping Scale
EFI	Eco-cultural family interview
EMM	Estimated marginal means
ETI	Elexacaftor/ tezacaftor/ ivacaftor
FACES III	Family Adaptability and Cohesion Scale
FAMSS	Family Asthma Management System Scale
FEV1pp	Percentage predicted forced expiratory volume in 1 second
FRAS-C	Family Resilience Assessment Scale
GAD-7	Generalized Anxiety Disorder-7
GEE	Generalized estimating equations
GHQ	General Health Questionnaire
GLM	General linear model
GSE-10	General Self-efficacy Questionnaire
HARIS	Haase Adolescent Resilience in Illness Scale
HbA1c	Hemoglobin A1c
HBSC	Health Behaviour in School-aged Children
HBSC-SCL	Health Behavior in School-aged Children Symptom Checklist
HIV	Human deficiency virus
HMAC	Hemingway measure of adolescent connectedness
HSCT	Hematopoietic stem cell transplant
IBD	Inflammatory bowel diseases
ICQ	Illness Cognition Questionnaire
ICU	Intensive Care Unit
IIQ	Illness Identity Questionnaire
IQR	Interquartile range

K6	Kessler-6 Psychological Distress Scale
KBIT-2	Kaufman Brief Intelligence Test: Second Edition
LKQCHD	Leuven Knowledge Questionnaire for Congenital Heart Disease
LOT	Life Orientation Test
MCID	Minimal clinically important difference
MESH	Medical Subject Headings
METC	Medical Research Involving Human Subjects Act
MHI-5	Mental Health Index-5
MS	Multiple sclerosis
NA	Not applicable
OxCGRT	Oxford COVID-19 Government Response Tracker
PACE-Adolescent	Patient-based assessment and counseling for physical activity and nutrition-adolescent
PAID	Problem Areas in Diabetes Scale
PANAS-C	Positive and Negative Affect Scale for Children
PCCS	Pediatric Cancer Coping Scale
PedsQL	Pediatric Quality of Life Inventory
PEx	Frequency of pulmonary exacerbations
PHQ-9	Patient Health Questionnaire-9
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
PPVT-III	Peabody Picture Vocabulary Test — Third Edition
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta analyses
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
PSI-SF	Parenting Stress Index — Short Form
PSS	Perceived stress scale
PTSDI	University of California, Los Angeles Post-Traumatic Stress Disorder Reaction Index for Diagnostic and Statistical Manual of Mental Disorders
PWCF	People with cystic fibrosis
QoL	Quality of life
RCADS	Revised Child Anxiety and Depression Scale
RCT	Randomized controlled trial
RISE	Resilience lmpacted by positive Stressful Events
RMANOVA	Repeated measures analysis of variance
RS	The Wagnild and Young Resilience Scale
RSCA	Resilience Scale for Children and Adolescents
RSQ	Responses to Stress Questionnaire
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCC	Sweat chloride concentration

SCD	Sickle cell disease
SCL	Hopkins Symptom Checklist
SCS	School Connectedness Scale
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
SE	Standard error
SEARS	Social-Emotional Assets and Resilience Scales
SED	Self-efficacy for diabetes
SPSI-R:S	Social Problem-Solving Inventory-Revised short form
SRH	Self-rated Health
SSS	School Support Scale
SSSS	Scale of Satisfaction with Social Support
STARx	Self-Management and Transition to Adulthood with Rx = Treatment
T1D	Type 1 diabetes
TRAQ	Transition Readiness Assessment Questionnaire
UMCU	University medical center Utrecht
WHISTLER	WHeezing Illnesses STudy Leidsche Rijn
WHO	World Health organization
WKZ	Wilhelmina Children's Hospital
YSR	Youth Self-Report

LIST OF PUBLICATIONS

In this thesis

1. **van der Laan SEI***, Berkelbach van der Sprenkel EE*, Finkenauer C, Lenters VC, van de Putte EM, Bont LJ, van der Ent CK, Nijhof SL. Chronic conditions and adolescents' psychosocial wellbeing: The impact of self-reporting. 2024; submitted

2. van der Heijden E, van den Bor RM, Bierlaagh MC, Muilwijk D, de Graaf JM, Nijhof SL, Bronsveld I, van der Ent CK, **van der Laan SEI**. Psychosocial health changes in people with cystic fibrosis after initiation of elexacaftor/tezacaftor/ivacaftor therapy: insights from the RISE study. 2024; submitted

3. **van der Laan SEI**, Berkelbach van der Sprenkel EE, Lenters VC, Finkenauer C, van der Ent CK, Nijhof SL. Defining and Measuring Resilience in Children with a Chronic Disease: a Scoping Review. *Advers Resil Sci*. 2023;4:105-123. doi:10.1007/s42844-023-00092-2

4. van der Heijden E, van den Bor RM, van der Ent CK, Nijhof SL, **van der Laan SEI**. The RISE study protocol: resilience impacted by positive stressful events for people with cystic fibrosis. *ERJ Open Res*. 2023;9(3):00535-02022. doi:10.1183/23120541.00535-2022

5. **van der Laan SEI**, Lenters VC, Finkenauer C, van Harmelen AL, van der Ent CK, Nijhof SL. Tracking Mental Wellbeing of Dutch Adolescents During the First Year of the COVID-19 Lockdown: A Longitudinal Study. *Journal of Adolescent Health*. 2022;71(4):414-422. doi:10.1016/j.jadohealth.2022.06.006

6. Hoefnagels JW, Schoen AB, **van der Laan SEI**, Rodijk LH, van der Ent CK, van de Putte EM, Dalmeijer GW, Nijhof SL. The Impact of the COVID-19 Outbreak on Mental Wellbeing in Children with a Chronic Condition Compared to Healthy Peers. *Environmental Research and Public Health*. 2022;19(5). doi: 10.3390/ijerph19052953

7. **van der Laan SEI**, Finkenauer C, Lenters VC, van Harmelen A, Van Der Ent CK, Nijhof SL. Gender-specific changes in life satisfaction after the COVID-19-related lockdown in Dutch adolescents: a longitudinal study. *Journal of Adolescent Health*. 2021;69(5):737-745. doi: 10.1016/j.jadohealth.2021.07.013

8. **van der Laan SEI**, de Hoog MLA, Nijhof SL, et al. Mental Well-being and General Health in Adolescents with Asthma: The Prevention and Incidence of Asthma and Mite Allergy Birth Cohort Study. *J Pediatr*. 2021;233:198-205.e2. doi:10.1016/j.jpeds.2021.01.074

Other

9. van der Linden IA, Roodenburg R, Nijhof SL, van der Ent CK, Venekamp RP, **van der Laan SEI***, Schipper HS*. Early life determinants of carotid intima-media thickness and carotid stiffness in adolescence. 2024; submitted

10. de Jong-Witjes S, Kars MC, van Vliet M, Huber M, **van der Laan SEI**, Gelens E, Berkelbach van der Sprenkel EE, Nijhof SL, de Jonge MV, Rippen H, van de Putte EM. Development of the My Positive Health dialogue tool for children: a qualitative study on children's views of health. *BMJ Paediatr Open*. 2022;6(1):e001373. doi:10.1136/bmjpo-2021-001373

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vraagstukken, maar ook vele avonturen gedeeld: 180 km fietsend in één dag bij 32 graden, gin-tonics drinkend in de speeltuin, goed toeven in Herberg het Volle Leven, en talloze bezoeken aan uiteenlopende tentoonstellingen en musea. Ik ben je dankbaar voor deze rijke vriendschap. Lieve Marlou, "jou maak je niet gek". Ondanks dat jouw PhD aanzienlijk anders verloopt dan ooit verwacht (*hoezo is de levensduur van menig farmaceutische bedrijf zo kort?!*), houd je moed en blijf je rustig. Bovendien zet jij je altijd en voor iedereen in. Je hebt bijvoorbeeld zes weken, fulltime en belangeloos, het Kaftrio cohort incluis RISE studie gedraaid. Ik weet niet hoe ik je daar ooit genoeg voor kan bedanken. Samen kleurden we de dagen van onze PhD's in; geen dag begon zonder goede koffiestart, we pakten door met een uitgebreide lunch, of sloten af met kleine een thee-klaagzang over het één of ander. Het feit dat ik enorm van mijn PhD heb genoten, kwam voornamelijk omdat jíj degene bent geweest met wie ik de meeste tijd heb doorgebracht. Lieve Emma, waar zijn onze wegen niet gekruist? Beginnend als psychologie student (jij) en geneeskunde student (ik), daarna als geneeskunde student (jij) en PhD student (ik), en tenslotte als PhD student (wij). Ondanks dat onze favoriete werktijden ietwat uit elkaar liggen - ik in de ochtend, jij in de avond - maakten we samen vele meters. We motiveerden onszelf tijdens (voor mij) noodgedwongen avondwerk met sushi en vierden kleine en grote successen. Bovendien ben je de allerbeste bondgenoot om feedback op manuscripten mee te relativeren. Kortom, ik heb genoten van onze projecten samen.

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1 vrije vertaling van het woord *Ubuntu*, afkomstig van de Bantoetalen uit Zuidelijk Afrika.

ABOUT THE AUTHOR

Sabine thrives on learning new things and does not simply take new information for granted. She enjoys questioning, debating, and philosophizing until she understands the topic.

During her medical studies, Sabine developed her interests broadly by taking part in multiple (extra-curricular) programs. She started conducting research in her second year by participating in the medical school's honors programs. Additionally, she pursued an elective internship in pediatrics in Machame (Tanzania), studied in China through the Netherlands-Asia Honors Summer School (NAHSS), and participated in debating competitions at Cambridge and Harvard University with Utrecht University Model United Nations (UUMUN). Sabine combined her joy for acquiring knowledge and debating with her passion for medicine by co-founding Apollo Society, an international student association with an interest in Translational Medicine.

After her medical studies, Sabine worked in a pediatric ward as a medical doctor, where she noticed differences in the ways children cope with their chronic illnesses. Why are some children able to maintain or regain their mental wellbeing while having a chronic condition, whereas others with the same condition experience a deterioration in mental wellbeing? Her questions regarding resilience in the face of disease-related challenges formed the starting point of her PhD. To be able to answer these questions and try to conduct the right research in the right way, she pursued a post-graduate master in clinical epidemiology during her PhD.

In the midst of her PhD, the COVID-19 pandemic started and seemed to predominantly hit younger generations mentally instead of physically. This crisis raised opportunities to learn more about mental wellbeing of adolescents in the face of the COVID-19 pandemic. Sabine therefore extended her line of research, resulting in the second part of her thesis.

After her PhD defense, Sabine will continue her work as a post-doc, concentrating on resilience of people with cystic fibrosis. Her work involves tracking changes in mental wellbeing and identifying predictors for these changes following the use of elexacaftor/tezacaftor/ivacaftor, a promising novel drug. Furthermore, she will start working in the psychiatry ward to further develop her skills and knowledge as a medical doctor.

Sabine lives in Utrecht with her partner Daan, their daughter Sophie and dog Theo. They are expecting their second child in the summer of 2024.