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The bidirectional relationship between loneliness and common mental disorders in adults: findings from a longitudinal population-based cohort study

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Abstract

Purpose Limited longitudinal population-based research exists on the bidirectional association between loneliness and common mental disorders (CMDs). Using 3-year follow-up data, this study examined whether loneliness among adults increases the risk for onset and persistence of mild–moderate or severe CMD; and whether mild–moderate or severe CMD is a risk factor for onset and persistence of loneliness.

Methods Data were used from the second ('baseline') and third (3-year follow-up) waves of the Netherlands Mental Health Survey and Incidence Study-2, a prospective study of a representative cohort of adults aged 18–64 years. Twelve-month CMDs and their severity were assessed with the Composite International Diagnostic Interview 3.0, and current loneliness using the De Jong Gierveld Loneliness Scale. Multivariate analyses were controlled for several potential confounders.

Results Loneliness predicted onset of severe CMD at follow-up in adults without CMDs at baseline, and increased risk for persistent severe CMD at follow-up in those with CMD at baseline. Conversely, severe CMD predicted onset of loneliness at follow-up in non-lonely adults at baseline, but was not associated with persistent loneliness at follow-up in lonely adults at baseline. Observed associations remained significant after controlling for perceived social support at baseline, except for the relationship between loneliness and persistent severe CMD. No longitudinal relationships were observed between loneliness and mild–moderate CMD.

Conclusions Attention should be paid to loneliness, both in adults with and without CMD. Further research is needed to better understand the mechanisms underlying the observed associations between loneliness and CMDs to develop successful interventions.

Keywords Loneliness · Common mental disorder · Adult general population · Prospective cohort study

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Introduction

Loneliness can be defined as a situation experienced by an individual as one where there is an unpleasant or inadmissible lack of (quality of) certain relationships [1]. Large-scale studies of young, middle-aged and older adults in the general population report rates of loneliness ranging from 14 to 47% [2–6]. The public health importance of loneliness is further demonstrated by its association with developing coronary heart disease and dementia [7–10], and premature death [11, 12]. Furthermore, several cross-sectional, population-based studies found loneliness to be strongly related to mood and anxiety disorders in adults (including elderly) [13–16], and recent studies also suggest a cross-sectional link with substance-use disorders,

like alcohol and cannabis dependence [15, 17]. However, these findings give no insight into whether loneliness is a risk factor for onset or poor prognosis of these common mental disorders (CMDs; i.e., mood, anxiety, and substance-use disorders [18]), or vice versa. Longitudinal studies are needed to better understand these possible bidirectional relationships, which may provide useful information for strategies to prevent onset and persistence of loneliness and CMD. Yet, prospective studies are scarce.

Some evidence from population-based longitudinal research exists suggesting that loneliness increases risk for onset of anxiety and depressive disorders. Among adults aged 30–31 years at baseline, loneliness was found to increase the risk of first-time hospital admission for anxiety disorder during a 13-year follow-up period, also after adjusting for age, income and number of physical diseases [19]. An earlier study among older adults showed that baseline loneliness predicted incident depression at 3-year follow-up [20]. Other prospective population-based studies focused on the relationship between loneliness and onset of depressive symptoms and showed mixed evidence [21–23]. Another line of research, using data from clinical cohorts, found some evidence that loneliness predicts an unfavorable course of depressive disorder. Among older depressed patients recruited from general practices and mental health organizations, those who were very severely lonely at baseline had a lower chance to achieve remission at 2-year follow-up, while adjusting for baseline severity of depressive symptomatology, social network size, and various other potential predictors of depression course [24]. In a follow-up study covering 6 years, more severe baseline loneliness increased the risk of recurrent or chronic course of depression, and partial remission as compared to full remission [25]. A limitation was that, due to lack of power, only univariate analyses were performed, making it unknown whether other potential predictors of depression course influenced the observed relationships. Another clinical study showed that, among adults with depressive disorder at baseline, more severe loneliness lowered the chance of remission at 2-year follow-up, also after adjustment for demographics, chronic physical disorders, baseline severity of depressive symptomatology, and comorbid dysthymic or anxiety disorder [26]. However, when social network and social support characteristics at baseline were also included in the analysis, this relationship disappeared. The researchers explained this by the fact that the predictive values of loneliness, social network, and social support on depression course overlapped considerably. Noteworthy, research on the influence of loneliness on the course of anxiety and substance-use disorders is lacking, apart from a study that found baseline loneliness among patients with anxiety disorders to

be associated with more severe anxiety symptomatology at 1-year follow-up [27].

The existing research has a number of limitations. First, studies focused primarily on the impact of loneliness on onset and course of depressive disorder (the most common mood disorder). Taking a broad perspective of CMDs is relevant given the evidence that loneliness is not only associated with mood disorders, but also with anxiety and substance-use disorders [13, 15–17]. Also, the high level of comorbidity between mood, anxiety, and substance-use disorders [28, 29] points to the value of taking a broad approach of CMD rather than focusing on individual disorders. Second, findings are not generalizable to the adult population of 18–64 years, because most studies examined cohorts of older populations. The relevance of examining the nonelderly adult population is indicated by the high prevalence of both loneliness [4–6] and CMDs [28, 30, 31] among adults. Third, evidence for loneliness as a predictor of an unfavorable course of depressive disorder is derived from clinical studies. Prognostic factors are best studied using a general population sample without clear selection bias [32]. Fourth, previous studies did not consider severity in operationalizing onset and course of mental illness. The relevance of severity classification of CMDs is demonstrated by its associations with role impairment, perceived need for treatment and actually receiving treatment [33–35]. Possibly, loneliness contributes primarily to the onset and persistence of CMD at a certain level of severity.

Another research gap is that, to our knowledge, no longitudinal population-based research exists on the reverse association, i.e., whether existing CMDs and their severity contribute to the onset and persistence of loneliness. Available research only focused on the impact of depressive symptomatology on loneliness. A population-based study of older adults without baseline loneliness found increased feelings of low mood to be associated with developing loneliness during the 28-year follow-up period [36]. However, a major study limitation was that both mood as well as loneliness were measured with a single-item question. Other population-based prospective research found evidence for a link between (higher levels of) depressive symptoms and subsequent (higher levels of) loneliness at follow-up in older adults [38–42], with one exception [37]. However, since these studies used baseline populations consisting of older persons with and without loneliness, findings cannot be used to ascertain whether depressive symptomatology increases the risk of developing loneliness (requiring examination of a 'non-lonely' baseline population), or poor prognosis of loneliness (requiring examination of a 'lonely' baseline population).

The present study elaborates on previous research by examining the bidirectional longitudinal relationship between loneliness and severity level of CMD. Data were

used from a longitudinal study of a nationally representative cohort of adults aged 18–64 years, The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). Specifically, using a 3-year follow-up period, we aimed to determine whether loneliness at baseline is a risk factor for onset and persistence of mild–moderate or severe 12-month CMD at follow-up, and conversely, whether a mild–moderate or severe 12-month CMD at baseline increases the onset and persistence of loneliness at follow-up.

Methods

Study design

NEMESIS-2 is a psychiatric epidemiological cohort study of the Dutch general population aged 18–64. It is based on a multistage, stratified random sampling of households, with one respondent randomly selected in each household. The face-to-face interviews were laptop computer-assisted. In the first wave (T_0; November 2007–July 2009), 6646 persons were interviewed (response rate 65.1%; average duration: 95 min). This sample was nationally representative, although younger subjects were somewhat underrepresented. A more comprehensive description of the design can be found elsewhere [43].

All T_0 respondents were approached for follow-up (T_1), 3 years after T_0. Of these, 5303 persons could be interviewed again (80.4% of T_0 respondents, excluding deceased individuals; duration: 84 min). All T_1 respondents were approached for second follow-up (T_2), 3 years after T_1; 4618 persons were re-interviewed (70.5% of T_0 respondents; duration: 83 min). At third follow-up (T_3), 3 years after T_2, 4007 persons were re-interviewed (61.6% of T_0 respondents; duration: 101 min). The present study used data from second (T_2) and third (T_3) follow-up ($N = 4007$), as loneliness was assessed at these measurement points. Neither loneliness at T_2 nor any mood, anxiety, or substance-use disorder in the 12 months prior to T_2 was significantly associated with attrition at T_3 after controlling for sociodemographics.

Measures

Loneliness

Current loneliness was assessed at T_2 and T_3 with the 11-item De Jong Gierveld Loneliness Scale [44], a commonly used and psychometrically sound measure of loneliness [45]. Based on the total score a severity classification can be made consisting of four categories: 'not lonely' (0–2), 'moderately lonely' (3–8), 'severely lonely' (9–10), and 'very severely lonely' (11) [46]. In this study, a distinction was made between 'non-lonely' and 'lonely' respondents, using the conventional cut-off score of 3 [46]. Onset of loneliness at T_3 was determined in the sub-cohort of respondents without loneliness at T_2. Among the sub-cohort of lonely respondents at T_2, those who reported loneliness again at T_3 were regarded as cases of persistent loneliness.

CMDs and their severity

DSM-IV diagnoses were made using the Composite International Diagnostic Interview (CIDI) version 3.0—a fully structured lay-administered diagnostic interview. This instrument was developed for use in the World Mental Health Survey Initiative [47]. The CIDI 3.0 version used in NEMESIS-2 was an improvement of the Dutch one used in this initiative.

The present study considered the following CMDs in the 12 months before T_2 and T_3 [18]: mood disorders (major depression, dysthymia, and bipolar disorder), anxiety disorders (panic disorder, agoraphobia without panic disorder, social phobia, specific phobia, and generalized anxiety disorder), and substance-use disorders (alcohol/drug abuse and dependence). Clinical calibration studies in various countries [48] found that the CIDI 3.0 assesses CMDs with generally good validity in comparison to blinded clinical reappraisal interviews.

Consistent with previous research [33, 49], a 12-month CMD was rated as severe if at least one of the following criteria was fulfilled: bipolar I disorder, substance dependence with a physiological dependence syndrome, a suicide attempt in the past 12 months, or severe self-reported impairment in at least two areas of role functioning, as assessed with the Sheehan Disability Scales (SDS) [50]. The SDS is a widely used self-report measure of condition-specific disability and is incorporated in all diagnostic CIDI sections. It consists of four questions, each asking the respondent to rate on a 0–10 scale, the extent to which a particular disorder 'interfered with' activities in one of four role domains (home, work, social, and close relationships) during the month in the past year when the disorder was most severe. The response options were visualized with the labels none (0), mild (1–3), moderate (4–6), severe (7–9), and very severe (10). Cases not classified as having a severe 12-month CMD were classified as moderate (i.e., the individual had substance dependence without a physiological dependence syndrome, or at least moderate-role impairment in any domain of the SDS) or mild (i.e., all other instances).

For this study, a distinction was made between severe and mild or moderate CMD. Onset of mild–moderate

and severe 12-month CMD at T_3 was determined in the sub-cohort of respondents without 12-month CMD at T_2. Among the sub-cohort of respondents with a 12-month CMD at T_2, those who had a mild–moderate 12-month CMD at T_3 were regarded as cases of persistent mild–moderate CMD, and those with a severe 12-month CMD at T_3 as cases of severe persistent CMD.

Potential confounders

Based on previous research [24–27, 37, 40, 41], a selection was made of variables related to loneliness and CMDs, all of which were assessed at T_2, except for education (assessed at T_0, and at T_3 in respondents younger than 40 years).

Sociodemographics were gender, age, education, living situation, job status, and household income situation.
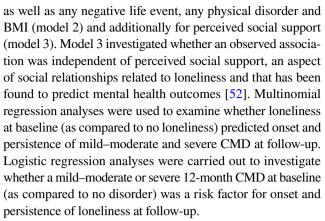
Any negative life event presence of ≥ 1 of 9 negative life events in the previous 12 months, such as death of a relative or friend, divorce, and financial difficulties, based on [51].

Physical health variables were any chronic physical disorder, i.e., presence of ≥ 1 of 17 chronic physical disorders treated or monitored by a medical doctor in the previous 12 months, assessed with a standard checklist; and body mass index (BMI).

Perceived social support assessed with 12 questions measuring two examples of emotional and instrumental support from each of three resources in the close network (partner, family or friends, and neighbors) as well as the respondent's evaluation of these types of support from all three resources. Any social support was calculated as the mean score on the support perceived from at least two resources, because not all respondents had a partner at the time of interview.

Statistical analysis

Based on the presence/absence of a 12-month CMD and loneliness at T_2 (herein after referred to as 'baseline'), the above-mentioned four sub-cohorts were established: (a) respondents without 12-month CMD ($n = 3535$); (b) respondents with a 12-month CMD ($n = 472$); (c) respondents without loneliness ($n = 3191$); and (d) respondents with loneliness ($n = 800$). Subsequently, after 3 years at T_3 (herein after referred to as 'follow-up'), the occurrence of the outcome variables of interest was calculated in each sub-cohort, being respectively: (a) onset and (b) persistence of mild–moderate and severe 12-month CMD; and (c) onset and (d) persistence of loneliness. Next, separately for each sub-cohort, univariate analyses were performed to examine the associations of the predictor and potentially confounding variables with the outcome variable, followed by testing three multivariate models in which the effect of the predictor variable was adjusted for gender and age (model 1), additionally for the other sociodemographics

as well as any negative life event, any physical disorder and BMI (model 2) and additionally for perceived social support (model 3). Model 3 investigated whether an observed association was independent of perceived social support, an aspect of social relationships related to loneliness and that has been found to predict mental health outcomes [52]. Multinomial regression analyses were used to examine whether loneliness at baseline (as compared to no loneliness) predicted onset and persistence of mild–moderate and severe CMD at follow-up. Logistic regression analyses were carried out to investigate whether a mild–moderate or severe 12-month CMD at baseline (as compared to no disorder) was a risk factor for onset and persistence of loneliness at follow-up.

Finally, the robustness of the observed associations in the latter analyses was examined by additionally controlling for change in severity level of 12-month CMD between baseline and follow-up. Change in severity was calculated based on four categories (i.e. no CMD [0], mild CMD [1], moderate CMD [2], and severe CMD [3]), resulting in a change score that could potentially range from -3 to 3. We have not explored the effect of change in severity of loneliness in the 3-year follow-up period on the observed associations of loneliness at baseline with onset and persistence of mild–moderate and severe 12-month CMD at follow-up. This was because the measurement of 12-month CMD severity at follow-up (the dependent variable) covered a period that largely preceded the time at which the degree of loneliness was assessed at follow-up.

Analyses were performed with STATA version 12.1. To ensure representativeness, data were weighted to correct for differences in the response rates in several sociodemographic groups at the waves and differences in the probability of selection of respondents within households at baseline. Robust standard errors were calculated to obtain correct 95% confidence intervals and p values. Two-tailed testing procedures were used with 0.05 alpha levels.

Results

Baseline loneliness as a predictor of onset of mild–moderate or severe CMD at follow-up

Of the sub-cohort of respondents without 12-month CMD at baseline, 16.8% were lonely. At follow-up, 5.8% of this sub-cohort developed a mild–moderate 12-month CMD, and 2.8% a severe 12-month CMD. Univariate multinomial logistic regression analyses showed that baseline loneliness increased the risk of developing severe CMD at follow-up, but not mild–moderate CMD (see right side of Table 1). In all three multivariate models, baseline loneliness remained a predictor of subsequent onset of severe CMD; thus also after adjustment for perceived social support at baseline (model 3).

Table 1 Left part: characteristics of respondents without 12-month common mental disorder (CMD) at baseline, in total and across categories of 12-month CMD status at follow-up 3 years later, in weighted column percentages or means (M) and standard errors (S.E.). Right part: results of univariate and multivariate multinomial logistic regression analyses predicting onset of mild–moderate or severe 12-month CMD at follow-up (reference group is no CMD at follow-up), in weighted adjusted relative risk ratios (aRRR) with 95% confidence intervals (95% CI)

Baseline characteristics	Total (N=3535)		No CMD (N=3367; 91.3%)	Onset of mild–modeate CMD (N=177; 5.8%)	Onset of severe CMD (N=91; 2.8%)	Univariate model aRRR (95% CI) N=3530		Model 1 aRRR (95% CI) N=3530		Model 2 aRRR (95% CI) N=3509		Model 3 aRRR (95% CI) N=3479	
	N	%, M (S.E.)	%, M (S.E.)	%, M (S.E.)	%, M (S.E.)	Onset of mild–moderate vs. no CMD	Onset of severe vs. no CMD	Onset of mild–moderate vs. no CMD	Onset of severe vs. no CMD	Onset of mild–moderate vs. no CMD	Onset of severe vs. no CMD	Onset of mild–moderate vs. no CMD	Onset of severe vs. no CMD
Loneliness	621	16.8	15.8	17.8	45.6	1.15 (0.69–1.92)	4.47*** (2.50–7.99)	1.33 (0.78–2.27)	5.22*** (2.88–9.44)	1.23 (0.69–2.18)	4.31*** (2.28–8.15)	0.94 (0.50–1.77)	3.28** (1.54–7.02)
Female gender	1933	49.4	49.6	44.3	53.7	0.81 (0.54–1.20)	1.18 (0.68–2.05)	0.79 (0.52–1.21)	1.24 (0.73–2.12)	0.78 (0.50–1.20)	1.01 (0.55–1.83)	0.82 (0.53–1.26)	1.07 (0.60–1.91)
Age	3535	48.7 (0.43)	49.2 0.43	42.9 (1.40)	44.7 (2.12)	0.96*** (0.95–0.98)	0.97* (0.95–1.00)	0.96*** (0.94–0.98)	0.97** (0.94–0.99)	0.96*** (0.94–0.98)	0.94*** (0.91–0.97)	0.96*** (0.94–0.98)	0.94** (0.91–0.98)
Education													
Primary; lower secondary[a]	996	25.1	25.0	23.3	31.8	Reference	Reference			Reference	Reference	Reference	Reference
Higher secondary	1077	39.8	39.8	39.3	40.6	1.06 (0.58–1.94)	0.80 (0.40–1.61)			0.89 (0.51–1.58)	0.76 (0.36–1.60)	0.90 (0.51–1.61)	0.78 (0.37–1.61)
Higher professional, university	1462	35.1	35.2	37.3	27.6	1.14 (0.73–1.77)	0.62 (0.28–1.35)			0.99 (0.64–1.53)	0.74 (0.29–1.91)	0.95 (0.61–1.49)	0.70 (0.27–1.83)
Living without partner	874	24.4	23.4	34.6	35.5	1.74* (1.05–2.86)	1.81 (0.99–3.30)			1.43 (0.86–2.38)	1.25 (0.71–2.21)	1.24 (0.74–2.08)	1.05 (0.60–1.85)
No paid job	1103	27.3	27.7	16.1	36.6	0.50** (0.33–0.78)	1.51 (0.82–2.77)			0.65 (0.38–1.12)	1.41 (0.61–3.25)	0.62 (0.36–1.08)	1.37 (0.58–3.22)
Not enough household income to live on	200	5.7	5.2	9.9	14.7	2.02* (1.11–3.67)	3.15*** (1.63–6.11)			2.05* (1.05–3.99)	1.91 (0.91–4.01)	1.99 (0.98–4.01)	1.77 (0.86–3.64)
Any negative life event	1525	43.4	42.9	48.3	50.0	1.25 (0.80–1.94)	1.33 (0.75–2.38)			1.25 (0.82–1.93)	1.15 (0.64–2.07)	1.24 (0.80–1.93)	1.12 (0.61–2.07)
Body mass index	3530	25.9 (0.12)	25.9 (0.11)	25.9 (0.45)	27.3 (1.19)	1.00 (0.96–1.04)	1.07 (0.98–1.16)			1.01 (0.97–1.05)	1.06 (0.96–1.17)	1.01 (0.96–1.05)	1.06 (0.96–1.16)
Any chronic physical disorder	1514	40.6	39.7	45.1	59.3	1.25 (0.83–1.86)	2.21** (1.28–3.82)			1.89** (1.17–3.07)	2.61** (1.36–4.99)	1.86* (1.14–3.04)	2.60** (1.36–4.96)

Table 1 (continued)

Baseline characteristics	N	Total (N=3535)	12-month CMD status at follow-up			Univariate model aRRR (95% CI) N=3530		Multivariate models					
			No CMD (N=3367; 91.3%)	Onset of mild–modeate CMD (N=177; 5.8%)	Onset of severe CMD (N=91; 2.8%)			Model 1 aRRR (95% CI) N=3530		Model 2 aRRR (95% CI) N=3509		Model 3 aRRR (95% CI) N=3479	
		%, M (S.E.)	%, M (S.E.)	%, M (S.E.)	%, M (S.E.)	Onset of mild–moderate vs. no CMD	Onset of severe vs. no CMD	Onset of mild–moderate vs. no CMD	Onset of severe vs. no CMD	Onset of mild–moderate vs. no CMD	Onset of severe vs. no CMD	Onset of mild–moderate vs. no CMD	Onset of severe vs. no CMD
Perceived social support	3505	3.4 (0.02)	3.4 (0.02)	3.2 (0.06)	3.0 (0.10)	**0.57*** (0.41–0.77)**	**0.35*** (0.23–0.52)**					**0.59** (0.40–0.87)**	**0.58* (0.35–0.94)**

Bold type indicates a significant result at the 0.05 level (*), at the 0.01 level (**) or at the 0.001 level (***)

a Including basic vocational education

None of the multivariate models identified baseline loneliness as a predictor of onset of mild–moderate CMD.

Baseline loneliness as a predictor of persistent mild–moderate or severe CMD at follow-up

Thirty-eight percent of the sub-cohort of respondents with a 12-month CMD at baseline reported loneliness. At follow-up, 45.3% of this sub-cohort again had a 12-month CMD, with 24.1% being mild–moderate cases and 21.2% severe cases. Univariate multinomial logistic regression analyses identified baseline loneliness as a predictor of persistent severe CMD at follow-up, but not of persistent mild–moderate CMD (see right part of Table 2). Similar results were found in the multivariate analyses except for model 3: when perceived social support was also taken into account, the association between baseline loneliness and increased likelihood of persistent severe CMD at follow-up disappeared. Multivariate analyses showed no relationship between baseline loneliness and persistent mild–moderate CMD at follow-up.

Baseline mild–moderate or severe CMD as a predictor of onset of loneliness at follow-up

Of the sub-cohort of respondents without loneliness at baseline, 7.7% had a mild–moderate 12-month CMD and 3.3% a severe 12-month CMD. At 3-year follow-up, 9.6% of the sub-cohort reported loneliness. In univariate logistic regression analyses, severe CMD at baseline increased the risk of developing loneliness at follow-up, while mild–moderate CMD did not (see right side of Table 3). Severe CMD at baseline remained a predictor of onset of loneliness in multivariate analysis, also when adjusting for perceived social support at baseline (model 3). None of the three multivariate models found mild–moderate CMD to be at baseline associated with developing loneliness at follow-up. Similar results were found when adjusting additionally for change in severity level of 12-month CMD between baseline and follow-up (see Supplemental Table 1).

Baseline mild–moderate or severe CMD as a predictor of persistent loneliness at follow-up

Of the sub-cohort of respondents with loneliness at baseline, 12.1% had a mild–moderate 12-month CMD and 15.3% a severe 12-month CMD. At follow-up, 59.9% of the sub-cohort again reported loneliness. Univariate logistic regression analysis showed that severe CMD at baseline increased the likelihood of persistent loneliness at follow-up, while mild–moderate CMD exerted no influence (see right part of Table 4). In multivariate analysis, severe CMD at baseline remained a predictor of persistent loneliness at follow-up

after adjusting for gender and age (model 1). A trend towards statistical significance was found ($p = 0.076$) when testing model 2, while this 'borderline' significance disappeared when in addition controlling for perceived social support at baseline (model 3). Finally, the association between mild–moderate CMD at baseline and persistent loneliness at follow-up trended towards statistical significance in multivariate model 1 ($p = 0.094$) and model 3 ($p = 0.071$). Controlling additionally for change in severity level of 12-month CMD between baseline and follow-up resulted in stronger and significant effects for mild–moderate and severe 12-month CMD at baseline in all three multivariate models (see Supplemental Table 2).

Discussion

Using a representative sample of the Dutch adult general population, the current study expands existing knowledge on the bidirectional relationship between loneliness and CMDs in several ways. First, previous population-based longitudinal studies have shown that loneliness increases the risk of onset of anxiety and depressive disorders, but did not take into account disorder severity [19, 20]. Our study found that in adults without 12-month CMD at baseline, loneliness predicted onset of severe 12-month CMD at follow-up, but not of milder forms of CMD. It is unclear to us how to explain this finding. Biological, behavioral, psychological, and/or social mechanisms may be involved in this relationship, including suboptimal immune functioning, neuroendocrine dysregulation, poor health behaviors, passive coping strategies, low self-esteem, and stigma surrounding loneliness [12, 39, 53–57]. Possibly, these factors interplay, so that lonely adults are prone to developing a severe CMD. Second, this study identified among adults with a 12-month CMD at baseline that loneliness predicted persistent severe 12-month CMD at follow-up. So far, evidence of loneliness being an adverse prognostic factor for course of CMD was derived from studies that examined clinical cohorts of older patients with depressive disorder [24–26]. We observed that the association between baseline loneliness and persistent severe CMD at follow-up disappeared after controlling for perceived social support at baseline, implying overlapping adverse effects of loneliness and perceived low social support on course of CMD. This agrees with a previous finding that, among older patients with depressive disorder, the association between baseline loneliness and poor depression course became non-significant after adjusting for other aspects of social relationships, including subjective social support [26]. Third, our findings on the impact of CMD severity at baseline on the onset and persistence of loneliness at follow-up are new. To the best of our knowledge, prior longitudinal population-based research

examined older adults and focused on the predictive value of depressive symptomatology (as assessed using a single-item question or short questionnaire) for loneliness [36] [38–42] [37]. The current study found that non-lonely adults with a severe 12-month CMD at baseline had an increased risk of onset of loneliness at follow-up, while this was not true for mild–moderate CMD at baseline. The finding that only cases with severe 12-month CMD were at risk of developing loneliness persisted after controlling additionally for change in 12-month CMD severity between baseline and follow-up. Furthermore, severe 12-month CMD among lonely adults at baseline was found to predict persistent loneliness at follow-up in multivariate model 1 (adjusting for gender and age), while this effect tended toward statistical significance in model 2 (adjusting additionally for other sociodemographics, any negative life event, any physical disorder and BMI). The relationship between mild–moderate 12-month CMD at baseline and persistent loneliness at follow-up approached statistical significance in multivariate model 1 and model 3 (adjusting additionally for perceived social support). Possibly, remittance of CMDs during the 3-year follow-up period in a subset of adults may have lowered statistical power to detect effects, assuming that remission is related to a reduction in loneliness. In support of this explanation, a population-based study showed that feelings of loneliness decreased over time in older persons in whom depressive symptoms remitted [58]. Moreover, when change in 12-month CMD severity between baseline and follow-up was also taken into account in our analyses, the associations of both mild–moderate and severe 12-month CMD at baseline with persistent loneliness at follow-up became stronger and significant in all three multivariate models.

Strengths and limitations

Study strengths include the large population-based sample of adults, the prospective design covering 3 years, the use of a standardized diagnostic instrument (CIDI 3.0) to assess CMDs and their severity, the use of an established instrument (De Jong Gierveld Loneliness Scale) to assess loneliness, and the possibility to adjust for a range of potential confounders. Yet, some limitations need to be acknowledged.

First, although the sample was representative of the Dutch population on most parameters, people with an insufficient mastery of Dutch, those with no permanent residential address and the institutionalized, were underrepresented. Hence, our findings cannot be generalized to these groups.

Second, a time-frame difference existed between both main variables: assessment of loneliness concerned the current situation at baseline and follow-up, while measurement of CMD severity related to the 12 months preceding baseline and follow-up. Measurement of current loneliness rather than loneliness in the previous 12 months may have

Table 2 Left part: characteristics of respondents with a 12-month common mental disorder (CMD) at baseline, in total and across categories of 12-month CMD status at follow-up 3 years later, in weighted column percentages or means (M) and standard errors (S.E.). Right part: results of univariate and multivariate multinomial logistic regression analyses predicting persistent mild–moderate or severe 12-month CMD at follow-up (reference group is no CMD at follow-up), in weighted adjusted relative risk ratios (aRRR) with 95% confidence intervals (95% CI)

Baseline characteristics		12-month CMD status at follow-up				Univariate model		Multivariate models					
	Total (N=472)		No CMD (N=284; 54.7%)	Persistent mild–moderate CMD (N=103; 24.1%)	Persistent severe CMD (N=85; 21.2%)	aRRR (95% CI) N=470		Model 1 aRRR (95% CI) N=470		Model 2 aRRR (95% CI) N=468		Model 3 aRRR (95% CI) N=464	
	N	%, M (S.E.)	%, M (S.E.)	%, M (S.E.)	%, M (S.E.)	Persistent mild–moderate vs. no CMD	Persistent severe vs. no CMD	Persistent mild–moderate vs. no CMD	Persistent severe vs. no CMD	Persistent mild–moderate vs. no CMD	Persistent severe vs. no CMD	Persistent mild–moderate vs. no CMD	Persistent severe vs. no CMD
Loneliness	186	38.0	32.8	34.6	54.9	1.08 (0.52–2.26)	2.48* (1.21–5.11)	1.24 (0.59–2.60)	2.94** (1.38–6.24)	1.03 (0.51–2.08)	2.12* (1.03–4.36)	1.15 (0.54–2.47)	1.80 (0.83–3.91)
Female gender	292	56.7	56.2	64.4	49.4	1.41 (0.79–2.52)	0.76 (0.39–1.50)	1.46 (0.82–2.61)	0.76 (0.37–1.55)	1.39 (0.74–2.58)	0.60 (0.30–1.19)	1.36 (0.72–2.59)	0.56 (0.27–1.15)
Age	472	42.9 (0.95)	44.3 (1.04)	40.8 (1.60)	41.7 (2.37)	0.98 (0.96–1.00)	0.98 (0.95–1.01)	0.98* (0.95–1.00)	0.98 (0.94–1.01)	0.98 (0.95–1.01)	0.97* (0.94–0.99)	0.98 (0.95–1.00)	0.96** (0.94–0.99)
Education													
Primary; lower secondary[a]	137	27.5	25.1	26.8	34.7	Reference	Reference			Reference	Reference	Reference	Reference
Higher secondary	154	37.1	42.5	29.2	32.2	0.64 (0.28–1.46)	0.55 (0.24–1.27)			0.60 (0.28–1.28)	0.72 (0.30–1.70)	0.59 (0.27–1.29)	0.82 (0.35–1.90)
Higher professional, university	181	35.4	32.5	44.0	33.1	1.27 (0.57–2.78)	0.74 (0.30–1.80)			1.16 (0.53–2.54)	1.20 (0.56–2.59)	1.12 (0.51–2.43)	1.17 (0.54–2.52)
Living without partner	202	44.7	38.8	40.7	64.2	1.08 (0.63–1.86)	2.83*** (1.57–5.12)			0.84 (0.47–1.49)	1.57 (0.81–3.03)	0.85 (0.48–1.51)	1.57 (0.82–3.00)
No paid job	174	35.3	27.3	35.8	55.3	1.48 (0.73–3.01)	3.29*** (1.66–6.51)			1.84 (0.98–3.45)	2.31* (1.21–4.42)	1.95* (1.04–3.64)	2.75** (1.43–5.30)
Not enough household income to live on	65	15.4	9.9	12.3	33.2	1.28 (0.42–3.88)	4.52*** (2.19–9.37)			1.15 (0.40–3.30)	2.54* (1.15–5.60)	1.09 (0.39–3.05)	1.89 (0.86–4.17)
Any negative life event	281	56.2	54.1	59.9	57.2	1.27 (0.76–2.10)	1.13 (0.66–1.93)					1.52 (0.95–2.43)	0.87 (0.45–1.68)
Body mass index	471	25.5 (0.27)	25.8 (0.36)	25.0 (0.64)	25.5 (0.47)	0.96 (0.88–1.04)	0.99 (0.94–1.04)					0.97 (0.89–1.05)	0.96 (0.90–1.03)

Table 2 (continued)

Baseline characteristics	12-month CMD status at follow-up				Univariate model aRRR (95% CI) N=470		Multivariate models							
	Total (N=472)		No CMD (N=284; 54.7%)	Persistent mild-moderate CMD (N=103; 24.1%)	Persistent severe CMD (N=85; 21.2%)			Model 1 aRRR (95% CI) N=470		Model 2 aRRR (95% CI) N=468		Model 3 aRRR (95% CI) N=464		
	N	%, M (S.E.)	%, M (S.E.)	%, M (S.E.)	%, M (S.E.)	Persistent mild-moderate vs. no CMD	Persistent severe vs. no CMD	Persistent mild-moderate vs. no CMD	Persistent severe vs. no CMD	Persistent mild-moderate vs. no CMD	Persistent severe vs. no CMD	Persistent mild-moderate vs. no CMD	Persistent severe vs. no CMD
Any chronic physical disorder	245	46.0	45.0	34.1	61.8	0.63 (0.30–1.33)	1.97 (0.97–4.00)			0.66 (0.28–1.54)	**2.35* (1.06–5.19)**	0.61 (0.27–1.36)	2.13 (0.97–4.67)
Perceived social support	468	3.1 (0.05)	3.2 (0.05)	3.2 (0.10)	2.8 (0.13)	0.92 (0.59–1.43)	**0.44*** (0.31–0.64)**					0.99 (0.61–1.63)	**0.69* (0.48–0.99)**

Bold type indicates a significant result at the 0.05 level (*), at the 0.01 level (**) or at the 0.001 level (***)

[a]Including basic vocational education

resulted in some respondents being incorrectly classified as being non-lonely at baseline or follow-up in the various analyses. Such misclassification would likely have resulted in an underestimation of the observed associations.

Third, degree of loneliness could not be considered in analysis, because the numbers of adults with (very) severe loneliness were too low to perform meaningful analyses.

Fourth, measurement of outcomes was limited in some respects. Since history of CMD prior to baseline assessment was not considered, onset of a 12-month CMD at follow-up concerned both first-onset and recurrent disorder. The numbers were too small to take this aspect into account in the analysis. Hence, it is unclear whether the observed association between loneliness and subsequent onset of severe CMD exists among both incident and recurrent cases. Similarly, as information on loneliness before baseline assessment was lacking, onset of loneliness at follow-up involved both first-ever and recurrent periods of loneliness. Therefore, it is unknown whether our finding of severe CMD being a risk factor for developing loneliness relates to incident as well as recurrent loneliness. Consistent with previous studies [e.g., 59–61], persistent CMD was regarded to be present if respondents had a 12-month CMD both at baseline and follow-up. Consequently, persistent cases may also have included respondents who had a recurring CMD after recovery during the follow-up period. Our operationalization of persistent loneliness was similarly limited. As the De Jong Gierveld Loneliness Scale measures [44] current loneliness, the course of loneliness between baseline and follow-up was unknown. Hence, persistent cases might also have involved respondents who experienced one or more non-lonely periods during follow-up. The 'broad' definitions of persistent CMD and persistent loneliness would likely have attenuated the observed associations.

Fifth, despite a range of potential confounders was controlled for in multivariate analyses, it is possible that any observed relationship might have been the result of non-measured sources of confounding. The final multivariate models tested whether an association was independent of perceived social support, a concept related to loneliness [52]. However, more objectively measured aspects of social relationships, like social network size and frequency of social interactions, were not considered.

Implications

Given the limitations, further longitudinal research, including detailed measurement of course trajectories of CMD, loneliness, and related concepts in social relationships, is needed to better understand the mechanisms underlying the observed associations. This also requires considering potential mediating and moderating factors. Several factors have been suggested to explain a link between loneliness and

Table 3 Left part: characteristics of respondents without loneliness at baseline, in total and by loneliness status at follow-up 3 years later, in weighted column percentages or means (M) and standard errors (S.E.). Right part: results of univariate and multivariate logistic regression analyses predicting onset of loneliness at follow-up (reference group is no loneliness at follow-up), in weighted adjusted odds ratios (aOR) with 95% confidence intervals (95% CI)

| | Total (N=3191) | | Onset of loneliness at follow-up | | Univariate model | Multivariate models | | |
| | | | No (2893; 90.4%) | Yes (N=298; 9.6%) | aOR (95% CI) N=3191 | Model 1 aOR (95% CI) N=3191 | Model 2 aOR (95% CI) N=3174 | Model 3 aOR (95% CI) N=3153 |
Baseline characteristics	N	%, M (S.E.)	%, M (S.E.)	%, M (S.E.)	Onset of loneliness	Onset of loneliness	Onset of loneliness	Onset of loneliness
12-month CMD status[a]								
No	2907	89.0	89.4	85.8	Reference	Reference	Reference	Reference
Mild–moderate	200	7.7	7.9	5.9	0.78 (0.47–1.28)	0.92 (0.54–1.55)	0.76 (0.43–1.34)	0.75 (0.41–1.37)
Severe	84	3.3	2.7	8.3	**3.16** (1.42–7.05)	**3.73** (1.68–8.27)	**2.66** (1.44–4.88)	**2.67** (1.48–4.79)
Female gender	1792	50.7	51.2	45.3	0.79 (0.60–1.04)	0.79 (0.60–1.05)	**0.68** (0.51–0.90)	**0.70*** (0.52–0.93)
Age	3191	47.3 (0.50)	47.0 (0.52)	50.1 (1.20)	**1.02*** (1.00–1.03)	**1.02** (1.01–1.03)	1.01 (1.00–1.03)	1.02 (1.00–1.03)
Education								
Primary; lower secondary[b]	850	23.9	22.9	33.3	Reference		Reference	Reference
Higher secondary	978	39.5	40.1	33.0	**0.57*** (0.36–0.88)		0.69 (0.44–1.06)	0.69 (0.44–1.09)
Higher professional, university	1363	36.6	37.0	33.7	**0.63*** (0.42–0.93)		0.83 (0.57–1.22)	0.85 (0.57–1.28)
Living without partner	708	23.5	22.3	34.5	**1.83** (1.27–2.65)		**1.78** (1.26–2.50)	**1.64** (1.15–2.34)
No paid job	925	24.8	23.6	36.1	**1.83*** (1.33–2.52)		1.22 (0.85–1.75)	1.18 (0.81–1.72)
Not enough household income to live on	159	5.3	4.6	11.8	**2.79** (1.43–5.41)		**2.40*** (1.18–4.86)	**2.35*** (1.15–4.81)
Any negative life event	1374	43.1	42.9	45.9	1.13 (0.80–1.60)		0.97 (0.68–1.38)	0.95 (0.66–1.36)
Body mass index	3187	25.8 (0.13)	25.7 (0.12)	25.9 (0.41)	1.01 (0.97–1.05)		0.98 (0.94–1.02)	0.98 (0.94–1.02)
Any chronic physical disorder	1340	39.6	38.0	54.6	**1.96*** (1.36–2.84)		**1.69*** (1.11–2.57)	**1.69*** (1.11–2.58)
Perceived social support	3170	3.49 (0.02)	3.5 (0.02)	3.3 (0.04)	**0.49*** (0.34–0.70)			**0.57** (0.39–0.82)

Bold type indicates a significant result at the 0.05 level (*), at the 0.01 level (**) or at the 0.001 level (***)

[a]CMD: common mental disorder

[b]Including basic vocational education

*p<0.05; **p<0.01; ***p<0.001

mental health, including biological (e.g., defective immune functioning and neuroendocrine dysregulation), behavioral (e.g. physical inactivity, smoking, and poorer sleep), psychological (e.g., low self-esteem, limited use of active coping strategies, unwillingness, or inability to maintain social relationships), and social (e.g., stigma surrounding

Table 4 Left part: characteristics of respondents with loneliness at baseline, in total and by loneliness status at follow-up 3 years later, in weighted column percentages or means (M) and standard errors (S.E.). Right part: results of univariate and multivariate logistic regression analyses predicting persistent loneliness at follow-up (reference group is no loneliness at follow-up), in weighted adjusted odds ratios (aOR) with 95% confidence intervals (95% CI)

Baseline characteristics			Persistent loneliness at follow-up		Univariate model	Multivariate models		
		Total (N=801)	No (N=321; 40.1%)	Yes (N=480; 59.9%)	aOR (95% CI) N=801	Model 1 aOR (95% CI) N=801	Model 2 aOR (95% CI) N=795	Model 3 aOR (95% CI) N=783
	n	%, M (S.E.)	%, M (S.E.)	%, M (S.E.)	Persistent loneliness	Persistent loneliness	Persistent loneliness	Persistent loneliness
12-month CMD status[a]								
No	617	72.6	79.9	67.7	Reference	Reference	Reference	Reference
Mild–moderate	83	12.1	9.4	13.9	1.75 (0.86–3.56)	1.88 (0.90–3.94)	1.69 (0.83–3.44)	1.98 (0.94–4.18)
Severe	101	15.3	10.7	18.4	**2.02* (1.16–3.53)**	**2.09* (1.15–3.79)**	1.66 (0.95–2.91)	1.38 (0.75–2.54)
Female gender	429	50.3	46.6	52.7	1.28 (0.92–1.77)	1.19 (0.85–1.67)	1.16 (0.82–1.64)	1.06 (0.74–1.50)
Age	801	50.3 (0.68)	49.6 (1.01)	50.7 (0.91)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.00 (0.98–1.02)
Education								
Primary; lower secondary[b]	277	31.2	29.0	32.6	Reference		Reference	Reference
Higher secondary	249	39.5	44.0	36.4	0.74 (0.49–1.11)		0.83 (0.53–1.32)	0.86 (0.53–1.41)
Higher professional, university	275	29.4	27.0	30.9	1.02 (0.68–1.53)		1.29 (0.85–1.95)	1.24 (0.82–1.89)
Living without partner	365	42.5	37.0	46.2	1.46 (0.96–2.23)		1.28 (0.82–2.00)	1.15 (0.74–1.79)
No paid job	346	43.3	38.3	46.6	1.40 (0.93–2.10)		1.14 (0.73–1.77)	1.18 (0.79–1.77)
Not enough household income to live on	104	14.3	9.4	17.6	**2.06* (1.07–3.97)**		1.58 (0.78–3.17)	1.14 (0.55–2.34)
Any negative life event	422	53.0	51.4	54.0	1.11 (0.77–1.59)		0.98 (0.68–1.39)	0.93 (0.63–1.35)
Body mass index	799	26.2 (0.18)	25.9 (0.28)	26.5 (0.23)	1.03 (0.99–1.06)		1.02 (0.98–1.06)	1.01 (0.97–1.05)
Any chronic physical disorder	413	48.9	43.1	52.7	**1.47* (1.04–2.09)**		1.29 (0.90–1.84)	1.26 (0.88–1.80)
Perceived social support	789	2.85 (0.03)	3.1 (0.05)	2.7 (0.04)	**0.43*** (0.31–0.60)**			**0.46*** (0.34-0.61)**

Bold type indicates a significant result at the 0.05 level (*) or at the 0.001 level (***)

[a]CMD: common mental disorder

[b]Including basic vocational education

loneliness and mental illness) factors [12, 39, 53–57]. Future research could also examine the potential influence of categories of CMD (i.e., mood, anxiety, and substance-use disorders).

Furthermore, this study points to the importance to pay adequate attention to loneliness, both in adults with and without CMD. Professionals working in various settings, including local community, general practice, and mental health care, should be aware that lonely adults are at

increased risk of developing severe CMD, and that loneliness in adults with an existing CMD increases the risk of poor outcome, in terms of persistent severe CMD. Moreover, professionals should be alert to onset of loneliness among adults with severe CMDs as they are an at-risk group. Our findings suggest that interventions to reduce loneliness may help to prevent onset of severe CMD in adults, and may contribute to better outcomes in those with an existing CMD. However, despite the fact that various interventions are available to tackle loneliness, including some approaches for adults with mental health problems, there is as yet too little evidence to draw conclusions about their effectiveness [55, 62]. Further research is needed to test the effectiveness of promising interventions, and to better understand the mechanisms involved in the link between loneliness and CMD to develop successful interventions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval NEMESIS-2 was approved by the Medical Ethics Review Committee for Institutions on Mental Health Care. After having been informed about the study aims, respondents provided written informed consent at each wave.

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