Epidemiology of Major Depressive Disorder

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Epidemiology of Major Depressive Disorder

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Chapter 0

Introduction

"Every little evil is magnified by the scaring spectres of his anxiety. He looks on himself as a man whom the gods hate and pursue with their anger. Awake, he makes no use of his reason; and asleep, he enjoys no respite from his alarms. His reason always slumbers; his fears are always awake. Nowhere can he find escape from his imaginary terrors."

- Plutarch, 46-120 AD

The great cultures of old, such as those of Mesopotamia, thought of diseases as a supernatural or naturalistic phenomenon. The Greek developed this approach, but great advances were made by the likes of Empedocles, Hippocrates and Plato. Aretaeus of Cappadocia, who was allegedly born shortly after Jesus Christ, initiated the idea that a mental disorder could originate from anywhere in the body or mind. Later on, Persians and Muslims created ideas about melancholia, which were largely influenced by Greek and Roman texts. In the 17th to 19th centuries, the humoral theory of melancholia was refined and the term depression made its first appearance. To depress, which meant to press down, was derived from the Latin verb deprimere. Kraepelin, Maudsley and Freud all added to our knowledge on depression today. The term Major Depressive Disorder (MDD) was introduced in the mid 1970s and was incorporated into the Diagnostic and Statistical Manual of Mental Disorders (DSM). In the latest version of this manual, DSM-IV-TR, MDD is characterized by one or more major depressive episodes (MDE) without a history of manic, mixed, or hypomanic episodes.[1] The essential feature of a MDE is presence of at least one of the two core symptoms which have to be present most of the day for a period of at least two weeks: 1) depressed mood; 2) loss of interest or pleasure. In addition, four or more of the following symptoms have to be present for most of the time during the same period of at least two weeks in order to meet criteria for a MDE according to diagnostic criteria formalised in the DSM: fatigue or loss of energy, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, concentration problems, feelings of worthlessness or guilt, or recurrent suicidal ideation or thoughts of death.

Epidemiology

MDD is a serious health problem and will be the second leading cause of burden of disease worldwide by 2030.[2] The annual incidence rate of MDD is about 1 to 8%, as shown by population and primary care based surveys such as the National Comorbidity Survey (NCS), the Epidemiologic Catchment Area Study (ECA), the Stirling County Study, the Lundby Study, the Netherlands Mental Health Survey and Incidence Study (NEMESIS) and the PredictD study.[3-12] The 6 or 12 month prevalence of mood disorders is about 2 to 12%, while the lifetime prevalence is about 4 to 17%.[13] MDD is a debilitating illness and has major personal and public consequences. To be able to prevent MDD, insight into risk factors for the onset of MDD is of clear importance.

It has been suggested that some people may be more vulnerable than others to develop MDD if stress occurs, which may be in accordance with the vulnerability-stress model.[14-17] In general, this model suggests that the combination of vulnerability and stress factors may lead to the disorder. Therefore, it is likely that the strength of risk factors is different across groups of people, such as sex or age groups. Furthermore, the course and outcome of MDD over a period of greater

than 12 months is less well studied.[18] One may argue that different course patterns of MDD can be identified and that it is essential to examine their relationship to symptoms and function over time. Insight into these course patterns could assist in preventive strategies and management of MDD.

Main aims of this thesis

The first aim is to examine the differential impact of risk factors for the onset of MDD across groups at risk and to investigate to what extent our findings accord with the vulnerability-stress model for MDD. The second aim is to examine the natural course and outcome of MDD.

Study population

For this thesis data were used from a multicenter prospective cohort study of 10045 general practice attendees from which a multifactor algorithm was developed to predict risk of onset of MDD (PredictD).[8, 12, 19-26] The study was conducted in seven countries: United Kingdom, Spain, Portugal, Slovenia, Estonia, Chile and the Netherlands. Consecutive general practice attendees were recruited in Europe between April 2003 and September 2004 and in Chile between October 2003 and February 2005. Participants were followed up after 6 and 12 months in all countries, after 24 months in the United Kingdom, Spain, Portugal and Slovenia, and after 39 months in the Netherlands.

Outline of this thesis

The thesis is divided into two main topics. The first topic includes the influence of risk factors on the onset of MDD, which is described in chapter 1. The second topic includes the course and outcome of MDD, which is described in chapter 2.

In chapter 1.1 we examine whether risk factors for multiple or long episodes of MDD differ from those for single and short episodes of MDD. In chapter 1.2 we compare the impact of risk factors in women and men on the risk of onset of MDD. We also address whether the impact on recurrent MDD is different from the impact on a first onset of MDD, i.e. in the presence or absence of a lifetime history of MDD. In chapter 1.3 we set out to determine whether the effect of life events on MDD is different for different age groups.

In chapter 2.1 our goal is to examine whether different courses of MDD are associated with different levels of depressive and somatic symptoms, and mental and physical functioning over time. In chapter 2.2 we examine the bidirectional relationship of MDD, anxiety, and coexisting MDD and anxiety with physical function over time. Our aim is to estimate the strength of the associations and to explore the direction of causality. In chapter 2.3 we examine whether underrecognition of MDD in primary care affects the course and outcome.

In chapter 3 the main findings described in this thesis are discussed. Finally, chapter 4 provides a summary of the topics researched in this thesis (in English and Dutch), an acknowledgment section and curriculum vitae of the author.

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Chapter 1

Onset of major depressive disorder

Chapter 1.1

Risk factors for onset of multiple or long major depressive episodes versus single and short episodes

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It would be possible to describe everything scientifically, but it would make no sense;
it would be without meaning, as if you described a Beethoven symphony
as a variation of wave pressure.

Albert Einstein
German born American physicist, 1879-1955

Abstract

Introduction

Episodes of major depressive disorder (MDE) may vary according to number of episodes and duration of episode. It is unclear whether risk factors for onset of multiple or long MDE differ from risk factors for onset of single and short MDE.

Methods

Data were used from a international prospective cohort study of 5256 consecutive general practice attendees without major depressive disorder at baseline, who were followed up 3 times (predictD). We counted the number of MDE and took episode duration into account. MDE were categorized into no episodes, single and short (≤3 months) episodes, and multiple or long (>3 months) episodes at follow-up. Log-binomial regression models were used to calculate relative risks between the groups for 18 risk factors examined at baseline.

Results

165 persons (3%) had a single and short MDE and 328 persons (6%) had multiple or long MDE at follow-up. Lower levels of education (RR 1.15; 95% CI 1.01 to 1.32), generalized anxiety or panic syndrome (RR 1.22; 95% CI 1.08 to 1.38), problems at work (RR 1.20; 95% CI 1.06 to 1.36) and financial strain (RR 1.16; 95% CI 1.02 to 1.32) significantly increased the risk of multiple or long MDE when compared to single and short MDE. Those at younger age were at significantly reduced risk of multiple or long MDE than single and short MDE (RR 0.77; 95% CI 0.65 to 0.91).

Conclusion

The findings from this study suggest that several risk factors can be identified that may help to predict onset of different types of MDE. These factors are relatively easily assessable and may assist in preventive strategies.

Introduction

Major depressive disorder (MDD) is a serious health problem and will be the second leading cause of burden of disease worldwide by 2030.[1] MDD is a recurrent disorder and persons who have multiple major depressive episodes (MDE) have a higher intensity of MDD and lower response to treatment than those with a first MDE.[2] Moreover, the risk of recurrence increases with each additional episode and a dysphoric mood is a stronger predictor of recurrence than of a first onset of MDD.[3, 4] The level of depressive and somatic symptoms has been found to be higher among those with recurrent MDD compared to those with a first onset of MDD.[5] About 30 to 50% of patients diagnosed with MDD has a recurrent course of disease, while about 20% develops a chronic course.[6-13] Also, MDE may vary according to number of episodes and duration of episode. For example, recent population based studies showed that the median duration of incident MDE was about 3 months, although the risk of duration of MDE of more than 2 years was substantial.[6, 7, 14] The duration of episodes may not increase with each additional episode[15], although other studies showed that a longer duration of previous MDE may increase the duration of new MDE.[7, 16] One may thus argue that different types of MDE according to the risk factor profile can be identified. Identifying such differences in MDE types is important, because a short and single MDE seem to differ from multiple or long MDE in terms of clinical characteristics as well as consequences (e.g. health service utilisation and level of disability).[5] Consequently, the risk factors may also differ between those with a single and short MDE versus those with multiple or long MDE but to our knowledge, to date no study examined this. For example, severity of depressive symptoms, comorbid psychiatric disorders, lower levels of social support and a longstanding physical illness have been found to increase the duration of MDE[7, 16], but it is unclear whether these factors are also risk factors for shorter and less severe MDE.

The aim of this study is to explore whether risk factors differ in their association with onset of multiple or long MDE compared to onset of single and short MDE in a large cohort of general practice attendees without MDD at baseline.

Material and methods

Study setting and design

PredictD is a multicenter prospective cohort study from which a multifactor algorithm was developed to predict risk of onset of MDD in 6 European countries and Chile, and has been described in greater detail elsewhere.[12, 17-20] The study was approved by local ethical committees. The current analysis used data from 5 countries where 3 follow-up assessments were conducted: 1) 25 general practices in the Medical Research Council's General Practice Research Framework, United Kingdom (UK); 2) 9 large primary care centres in Andalucía, Spain; 3) 74 general practices nationwide in Slovenia; 4) 2 large primary care centres, one in the Lisbon area (urban) and the other in Alentejo (rural), Portugal; and 5) 7 large general practice centres near Utrecht, the Netherlands.

Study participants

Consecutive attendees aged 18 to 75 years were recruited (N=6102) and interviewed between April 2003 and September 2004, and re-interviewed after 6 and 12 months. A third follow-up interview was conducted in the UK, Spain, Slovenia and Portugal 24 months after entry into the study, and in the Netherlands 39 months after entry into the study. Exclusion criteria were an inability to understand one of the main languages involved, psychosis, dementia and incapacitating physical illness. Recruitment differed slightly in each country because of local service preferences. In the UK and the Netherlands, researchers approached patients waiting for consultations, whereas in the other countries doctors first introduced the study before contact with the research team. All participants gave written informed consent.

Outcome measure

A diagnosis of MDD in the preceding 6 months was assessed at baseline, 6, 12 and 24 months according to DSM-IV criteria using the depression section of the Composite International Diagnostic Interview (CIDI).[21, 22] At 39 months, a diagnosis of MDD was assessed covering the period between the 12-month and 39-month follow-up.

Risk factors

We selected risk factors for MDD which cover important areas identified in a systematic review of the literature performed for the predictD study.[23] The risk factors, which were also used in our previous work, were assessed at baseline using risk factor questionnaires, unless otherwise stated below.[18, 20] The following risk factors were included in this analysis:

Socio-demographic or personal

Age [1], sex [2], education level [3], marital status [4] and employment [5].

Social and environmental

Controls, demands and rewards for work in the preceding 6 months were estimated by an adapted version of the job content instrument.[24] Participants were categorised as having problems at work if they experienced lack of control, difficulties without support or distress without feeling respect for their paid or unpaid work [6]. Financial strain which was a single question commonly used in government and other UK social surveys [7].[25] The risk factor problems with neighbourhood or with living condition was defined as whether dissatisfaction with their living conditions or neighbourhood was present, or whether they perceived unsafety inside/outside of the home [8]. These risk factors were assessed using questions from the Health Surveys for England.[26] We also assessed whether the participant had adequate social support from family and friends [9].[27]

Psychiatric characteristics and functioning

A history of depressive symptoms was ruled out if the two core symptoms of the lifetime CIDI depression section were absent. If one or two of the core symptoms were present, participants were considered to have a history of depressive symptoms [10].[28] Family psychiatric history: serious psychological problems in first-degree family members requiring pharmacological or psychological treatment in primary or secondary care, or suicide in first-degree relatives [11].[29] Generalized anxiety or panic symptoms in the previous 6 months using relevant sections of the Patient Health Questionnaire (PHQ) [12].[30] Mental functioning was assessed by the Short Form 12 [13].[31]

Adverse experiences in childhood

Physical and/or emotional abuse [14] and sexual abuse [15] experienced during childhood.[32]

Recent negative life events

Major life events in the preceding 6 months were assessed using the List of Threatening Life Experiences Questionnaire [16].[33]

Physical illness and functioning

Presence of a long standing physical illness was assessed based on self-report [17] and physical functioning was assessed by the Short Form 12 [18].[31]

Data analysis

Of the 6102 participants aged 18 to 75 years in the 5 countries at baseline, 118 persons were dropped from the analysis because they had missing data on baseline CIDI diagnosis. For the present analyses, we included participants who had no MDD in the 6 months prior to baseline (N=5256). Most risk factors were binary; where they were not, they were converted into binary variables for the analysis. Variables that were originally continuous were categorised as being below or above the median score (with the exception of age which we analysed both as a continuous variable and categorized into tertiles). Where a variable had more than two categories, it was recoded so that the category with the highest prevalence of MDD was compared with the remaining categories combined (with the exception of number of life events which was categorized into 0, 1, and 2 or more events).

First, we defined four time points: T0 (baseline), T1 (6 months of follow-up), T2 (12 months of follow-up), and T3 (24 or 39 months of follow-up). We counted the number of times a person had a diagnosis of MDD at follow-up, self-evidently with a maximum of 3 times. We defined an outcome variable with three levels: 1) No MDD at T1, T2 and T3 (no MDE); 2) One time MDD at T1, T2 or T3 (single and short MDE); and 3) Two or three times MDD at T1, T2 or T3 (multiple or long MDE). For those who had one time MDD at T1, T2 or T3, we checked whether these persons had more than one episode within that time interval. We also checked whether the duration of MDE extended beyond 3 months as this has been reported to be the median duration of MDE in several studies.[6, 7, 14, 34] Persons who had multiple MDE within one

time interval or had MDE that lasted more than 3 months were categorized into the group with multiple or long MDE (see also Figure 1).

Second, we calculated the percentage of single and short MDE, and multiple or long MDE for each country. Next, we calculated the distribution of the episode categories for each of the 18 risk factors. Associations between the risk factors (independent variables) and the outcome variable (dependent variable) were calculated using log-binomial regression (binomial errors and log link function) where single and short MDE, and multiple or long MDE were first compared with no MDE (the reference category) to determine whether they were risk factors for onset of MDE, irrespective of number and duration of episodes. We then compared the risk of multiple or long MDE with the risk of single and short MDE (the reference category). We estimated relative risks (RR) and accompanying confidence intervals (CI)[35, 36] rather than odd ratios which may overestimate the relative risk in cohort studies, particularly for outcomes that are common (>10%).[37, 38] Age, sex, level of education and country were added to the models as a priori confounders. If the log-binomial model did not converge, the model was fitted using Poisson regression which also directly estimates relative risks.[38, 39] In a subsequent analysis, all risk factors that were (borderline) significantly different in risk of multiple or long MDE compared to risk of a single and short MDE ($p<0.10$) were entered in the model that also contained age, sex, level of education, country and unemployment. Analyses were performed using PASW version 17 (IBM SPSS Statistics).

Results

In the 5 countries, 6102 people took part. Response to recruitment was high in Spain (87%), Portugal (76%) and Slovenia (80%) but lower in the UK (44%) and the Netherlands (45%). Ethical constraints prevented the collection of data on non-responders at baseline. Of the 5256 participants without MDD at baseline, 91% had no MDE at follow-up; 165 persons (3%) had a single and short MDE at follow-up, varying from 2% in Slovenia to 4% in Spain and Portugal, and 328 persons (6%) had multiple or long MDE at follow-up, with the highest percentage found in Spain (10%) and the lowest in Slovenia (3%) (Table 1, Figure 1). About 85% of the 5256 participants without MDD at baseline completed at least two follow-up assessments, varying from 73% in Spain to 90% in the Netherlands (see also Table 1). Persons who completed two or more follow-up assessments were somewhat older than those who completed fewer follow-up assessments (age 51 years versus 47 years) but were not different in the sex distribution (65% female versus 64% female). The sample was predominantly female (65%) and middle aged (mean age 50 years with standard deviation 15) (Table 2).

Table 1 – Percentages of those with and without episodes of major depressive disorder (MDD) at follow-up in participants without MDD in the 6 months prior to baseline for each country

	Total	No episode	Single and short episode	Multiple or long episodes	≥ 2 follow-up assessments
	N	N (%)	N (%)	N (%)	N (%)
United Kingdom	1125	1007 (90)	38 (3)	80 (7)	960 (85)
Spain	1004	874 (87)	35 (4)	95 (10)	737 (73)
Slovenia	1047	998 (95)	19 (2)	30 (3)	926 (88)
Netherlands	1077	978 (91)	32 (3)	67 (6)	967 (90)
Portugal	1003	906 (90)	41 (4)	56 (6)	860 (86)
Total	5256	4763 (91)	165 (3)	328 (6)	4450 (85)

Table 3 presents the relative risks (RRs) of the association of the 18 risk factors with a single and short MDE, and multiple or long MDE compared with no MDE (first two columns). As can be seen, the majority of risk factors (83%) significantly increased the risk of a single and short MDE at follow-up, independent of age, sex, level of education and country. Furthermore, nearly all risk factors (89%) significantly increased the risk of multiple or long MDE at follow-up.

When we compared the risk of multiple or long MDE with the risk of single and short MDE at follow-up (Table 3, last column), we found that the following risk factors significantly increased the risk of multiple or long MDE when compared to a single and short MDE: lower levels of education (RR 1.15; 95% CI 1.01 to 1.32), problems at work (RR 1.20; 95% CI 1.06 to 1.36), financial strain (RR 1.16; 95% CI 1.02 to 1.32) and generalized anxiety or panic syndrome (RR 1.22; 95% CI 1.08 to 1.38). The risk factors lower levels of social support (RR 1.13; 95% CI 0.99 to 1.28), a history of depressive symptoms (RR 1.17; 95% CI 0.99 to 1.39), a longstanding physical illness (RR 1.13; 95% CI 0.98 to 1.31) and lower levels of physical function (RR 1.13; 95% CI 0.99 to 1.30) were borderline significant. The only factor that significantly reduced the risk of multiple or long MDE compared to a single and short MDE was age. Persons age 18 to 43 years had a reduced risk of multiple or long MDE compared to those aged 59 to 75 years (RR 0.77; 95% CI 0.65 to 0.91).

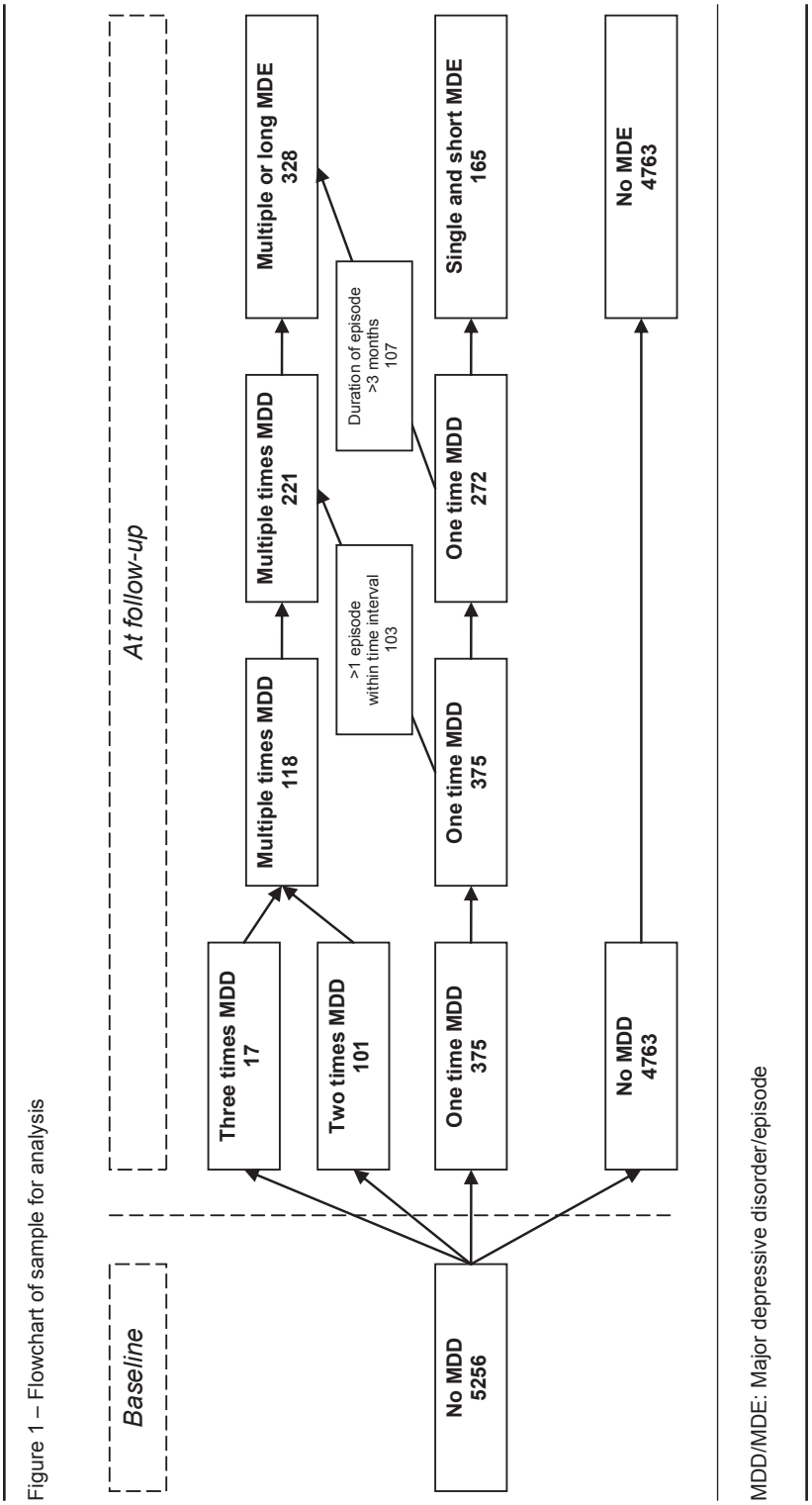

Figure 1 – Flowchart of sample for analysis

MDD/MDE: Major depressive disorder/episode

Table 2 – Baseline characteristics for those with and without episodes of major depressive disorder (MDD) at follow-up in participants without MDD in the 6 months prior to baseline

	Total (N=5256) %	No MDE (N=4763) %	Single and short MDE (N=165) %	Multiple or long MDE (N=328) %
Socio-demographic or personal				
Age in years, mean (SD)	50 (15)	50 (15)	47 (14)	51 (13)
Age in years, tertiles				
- 18 to 43	34	34	42	28
- 44 to 58	32	31	36	39
- 59 to 75	34	35	21	33
Female	65	64	77	74
Lower levels of education	41	40	42	49
Not married and not living with partner	27	27	36	29
Unemployed	51	50	52	59
Social and environmental				
Problems at work	37	35	42	53
Financial strain	18	17	29	32
Problems with living condition	20	19	29	31
Social support below median	47	46	49	56
Psychiatric characteristics				
A history of depressive symptoms	56	53	72	81
Family psychiatric history/suicide	33	32	46	50
Generalized anxiety or panic syndrome	9	7	19	33
SF-12 Mental function below median	45	41	71	76
Adverse experiences in childhood				
Physical or emotional abuse	13	12	24	25
Sexual abuse	4	3	9	9
Recent negative life events				
- No	42	44	28	30
- One	31	31	32	32
- Two or more	27	26	41	38
Physical illness and functioning				
Longstanding physical illness	40	40	42	49
SF-12 Physical function below median	47	46	51	63

MDE = Major depressive episode. All variables have less than 5% missing data.

In a subsequent analysis age, sex, level of education, country, unemployment, problems at work, financial strain, social support, a history of depressive symptoms, generalized anxiety or panic syndrome, a longstanding physical illness and level of physical function were entered in a model together. The results showed that the risk factors problems at work (RR 1.15; 95% CI 1.00 to 1.32) and generalized anxiety or panic syndrome (RR 1.15; 95% CI 1.01 to 1.31) remained significantly associated with an increased risk for multiple or long MDE compared to single and short MDE, and younger age (RR 0.75; 95% CI 0.62 to 0.91) remained significantly associated with a decreased risk for multiple or long MDE, while the other risk factors lost significance in the full model (data available on request).

Discussion

In this large scale cross-national prospective cohort study in general practice attendees we observed that lower levels of education, problems at work, financial strain and generalized anxiety or panic syndrome significantly increased the risk of multiple or long MDE when compared to single and short MDE, while lower levels of social support, a history of depressive symptoms, a longstanding physical illness and lower levels of physical function also increased the risk but were borderline significant, after adjusting for age, sex, level of education and country. In contrast, persons at younger age had a significantly greater risk of single and short MDE than multiple or long MDE.

Strengths of our study are that we used data from a large prospective cohort study which included participants from 5 European countries. We diagnosed MDD using DSM-IV criteria and response to follow-up was high in all countries. We assessed a wide range of psychosocial risk factors for MDD which reflect the current state of knowledge.[20]

Our study was limited by the lower response to recruitment in the UK and the Netherlands, which possibly occurred because the study was not so obviously endorsed by family doctors compared with the other countries in the study.[18] Unfortunately, ethical constraints prevented the collection of data on non-responders at baseline. However, loss to follow-up was low. Another potential limitation is that persons who were lost to follow-up throughout the study were also used to count the number of MDE at follow-up. As a result, these persons were more likely to be categorized into the group with no MDE at follow-up, which may have diluted the associations. Also, MDD was assessed retrospectively for the 6 months prior to each interview, with the exception of at 39 months. Thus, the participants who were followed up at 24 months may have had MDE in the 12 to 18 months period as the CIDI only enquired about MDD in the 6 months preceding that follow-up point. Therefore we possibly underestimated the total number of MDE. Still, most participants had at least two valid MDD diagnoses at follow-up and the incidence rate is in line with other studies. Further, despite the large sample size the relatively low number of single and short MDE did not allow stratification for a history of depressive symptoms. We were therefore unable to examine the risk factor profiles for those with a possible first onset of MDE. Finally, data on medication use and biologic factors were not available so we were unable to analyse the potential effects of these variables on the onset of MDE.

Table 3 – Relative risks for those with no episodes, a single and short episode, and multiple or long episodes of major depressive disorder (MDD) at follow-up in participants without MDD at baseline

	No MDE (ref)		**Single and short MDE (ref)**
	Single and short MDE†	**Multiple or long MDE†**	**Multiple or long MDE†**
Socio-demographic or personal			
Age in years	0.99 (0.98 to 1.00)*	1.00 (1.00 to 1.01)	1.01 (1.00 to 1.01)*
Age in years, tertiles¤			
- 18 to 43	1.98 (1.30 to 3.03)*	0.96 (0.73 to 1.26)	0.77 (0.65 to 0.91)*
- 44 to 58	1.95 (1.29 to 2.94)*	1.36 (1.06 to 1.74)*	0.91 (0.79 to 1.04)
Female	1.76 (1.23 to 2.53)*	1.62 (1.27 to 2.07)*	0.99 (0.87 to 1.14)
Lower levels of education	1.19 (0.82 to 1.72)	1.57 (1.22 to 2.01)*	1.15 (1.01 to 1.32)*
Not married and not living with partner	1.39 (1.01 to 1.92)*	1.13 (0.89 to 1.43)	0.92 (0.80 to 1.05)
Unemployed	1.44 (1.01 to 2.05)*	1.25 (0.96 to 1.62)	0.99 (0.87 to 1.13)
Social and environmental			
Problems at work	1.16 (0.85 to 1.58)	2.04 (1.64 to 2.54)*	1.20 (1.06 to 1.36)*
Financial strain	1.74 (1.23 to 2.47)*	2.11 (1.66 to 2.68)*	1.16 (1.02 to 1.32)*
Problems with neigbourhood or living condition	1.68 (1.18 to 2.40)*	1.82 (1.43 to 2.32)*	1.08 (0.95 to 1.22)
Social support below median	1.26 (0.93 to 1.71)	1.70 (1.37 to 2.11)*	1.13 (0.99 to 1.28)**
Psychiatric characteristics and functioning			
A history of depressive symptoms	2.09 (1.47 to 2.98)*	3.17 (2.40 to 4.20)*	1.17 (0.99 to 1.39)**
Family history of psychiatric disorder or suicide	1.58 (1.16 to 2.17)*	1.94 (1.57 to 2.40)*	1.07 (0.95 to 1.21)
Generalized anxiety or panic syndrome	2.59 (1.75 to 3.82)*	4.51 (3.58 to 5.68)*	1.22 (1.08 to 1.38)*
SF-12 Mental function below median	2.89 (2.04 to 4.02)*	3.88 (3.00 to 5.02)*	1.13 (0.97 to 1.30)
Adverse experiences in childhood			
Physical or emotional abuse	2.22 (1.56 to 3.14)*	2.18 (1.72 to 2.75)*	1.00 (0.87 to 1.15)
Sexual abuse	2.68 (1.60 to 4.49)*	2.47 (1.73 to 3.53)*	0.99 (0.79 to 1.23)
Recent negative life events			
- One	1.51 (1.02 to 2.25)*	1.35 (1.03 to 1.77)*	0.95 (0.82 to 1.09)
- Two or more	2.17 (1.49 to 3.18)*	1.83 (1.41 to 2.36)*	0.95 (0.83 to 1.07)
Physical illness and functioning			
Longstanding physical illness	1.60 (1.16 to 2.20)*	2.17 (1.71 to 2.73)*	1.13 (0.98 to 1.31)**
SF-12 Physical function below median	1.38 (1.01 to 1.89)*	1.92 (1.53 to 2.42)*	1.13 (0.99 to 1.30)**

MDE = Major depressive episode. ¤ Reference category is persons aged 59 to 75.
† All models are adjusted for age, sex, level of education and country. * $p < 0.05$, ** $0.05 < p < 0.10$

We are not aware of studies that directly compare risk factors for multiple or long MDE with risk factors for single and short MDE in persons without MDD at baseline, which makes it difficult to compare our findings with others. However, a number of the risk factors we identified for multiple or long MDE have also been reported as risk factors for persistence of MDD in persons with MDD at baseline. For instance, a lifetime history of MDE is a well-known risk factor for persistence of MDD.[40-46] Also, lower levels of education is a commonly observed risk factor for MDD.[43] Although recent studies do not concur about whether lower levels of education is a risk factor for persistence of MDD[16, 43], our findings suggest that lower levels of education are more likely to lead to multiple or long MDE than to single and short MDE.

When we entered the risk factors that were significant or borderline significant in one model, two factors remained stronger associated with multiple or long MDE compared to single and short MDE: generalized anxiety or panic syndrome, and problems at work, while younger age was stronger associated with a single and short MDE. Previous studies showed that comorbid psychiatric disorders and lower levels of social support are associated with a longer duration of MDE or recurrence of MDE.[7, 13, 16] Our findings accord with previous work in showing that presence of generalized anxiety or panic syndrome, and to lesser extent lower levels of social support, had a stronger association with the risk of multiple or long MDE compared to the risk of single and short MDE. However, our results add to the current knowledge in showing that problems at work are more likely to lead to multiple or long MDE than to single and short MDE, even independent of employment status. The work related problems included questions about lack of control, lack of support, and lack of respect, suggesting that these stress factors are particularly important in predicting onset of severe or more chronic types of MDE, whereas employment status itself was not.[47] Given that these problems at work were frequently reported in the study sample, this may be a risk factor of important public health consequences.

Interestingly, persons at younger age had a greater risk of a single and short MDE than of multiple or long MDE. As time is an important factor in developing multiple MDE, one may argue that younger persons were too young to have developed multiple MDE. However, we only enquired about onset of MDE in the period from T1 to T3, which was the same time period for all participants, and the results were independent of a history of depressive symptoms. It could be that persons at younger age may be more resilient when onset of MDE occurs and thus may be more likely to recover in a shorter period of time than those who are older. Another explanation could be that MDD treatment was lower among older persons compared to younger persons.[48, 49]

A number of risk factors did not differ in risk of multiple or long MDE compared to single and short MDE. For instance, recent negative life events increased the risk of onset of MDD, irrespective of number and duration of episodes, but the risk was not different for multiple or long MDE compared to single and short MDE. It could be that such recent life events trigger onset of MDD whereas other factors, including comorbidity factors and chronic problems that may cause ongoing stress, determine the duration and number of MDE.

In conclusion, the findings from this study suggest that several risk factors can be identified that may help to predict onset of different types of MDE. These factors are relatively easily assessable and may assist in preventive strategies.

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Chapter 1.2

Differential impact of risk factors for women and men on the risk of major depressive disorder

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It's a recession when your neighbour loses his job; it's a depression when you lose yours.

Harry S. Truman
American 33rd President of the United States, 1884-1972

Abstract

Background

Women have higher incidence rates of major depressive disorder (MDD) than men. One explanation may be that risk factors have a different impact across sex. Our aim is to examine which risk factors have a greater impact in women than in men on the risk of MDD and whether factors differ between recurrent MDD and a first onset of MDD.

Methods

Prospective cohort study of general practice attendees in six European countries and Chile, interviewed between April 2003 and February 2005 and followed up at 6 and 12 months (predictD). Absolute risk differences (interaction contrast) across sex for onset of DSM-IV MDD after 6 or 12 months of follow-up were estimated for 35 risk factors from 7101 participants without MDD in the 6 months prior to baseline.

Results

599 participants (80% female) had an onset of MDD at 6 or 12 months of follow-up. The majority of risk factors had a greater impact in women than in men on the risk of onset of MDD and were not restricted to a specific class of risk factors. After stratifying for a possible lifetime history of MDD, the impact of risk factors across sex was generally stronger on recurrent MDD than on a first onset of MDD.

Conclusions

Our findings may partly account for the observed difference in incidence of MDD between men and women. Future studies should discriminate a first onset of MDD from recurrent MDD.

Introduction

Major depressive disorder (MDD) is a serious health problem and will be the second leading cause of burden of disease worldwide by 2030.[1] The annual incidence rate of MDD is about 1 to 8%, as shown by population and primary care based surveys such as the Stirling County Study, the Lundby Study, the Epidemiologic Catchment Area Study (ECA) and the Netherlands Mental Health Survey and Incidence Study (NEMESIS).[2-9] Epidemiologic research, including ours, has consistently shown that women have higher incidence rates of MDD than men.[4, 6, 10-12] However, the cause of this sex difference remains unclear. Several hypotheses have been put forward trying to explain this difference.[11, 13-15] Some argue that biological factors such as genetic differences may account for the sex difference.[11, 16] Others hypothesize that the difference may be ascribed to artefacts involved in the measurement methods used.[15, 17] For example, women may report depressive symptoms more often than men, resulting in higher rates of MDD in women.[18, 19] Another hypothesis states that psychosocial factors may have a different impact in women than in men.[13, 20, 21]

In the light of the latter hypothesis several psychosocial factors have been studied. Factors like relational problems, lack of social support, adverse experiences in childhood and life events may have a greater impact in women than men in increasing their risk for MDD.[11, 13, 20, 22] However, most studies that examined risk factors for onset of MDD did not discriminate a first onset of MDD from recurrent MDD.[20] In addition, often studies did not have sufficient power to examine the differential impact of risk factors on a first onset of MDD in men and women.

Our first aim is to examine which risk factors have a greater impact in women compared to men on the risk of onset of major depressive disorder in a large cohort of primary care attendees. Our second aim is to examine whether these factors are different for those with recurrent MDD compared to those with a first onset of MDD.

Subjects and methods

Study setting and design

PredictD is a multicenter prospective cohort study from which a multifactor algorithm was developed to predict risk of onset of major depressive disorder in primary care attendees in 6 European countries and Chile. This has been described in greater detail elsewhere.[7, 12, 23-25] The study was approved by local ethical committees and conducted in seven countries: 1) 25 general practices in the Medical Research Council's General Practice Research Framework, in the United Kingdom; 2) nine large primary care centres in Andalucía, Spain; 3) 74 general practices nationwide in Slovenia; 4) 23 general practices nationwide in Estonia; 5) seven large general practice centres near Utrecht, The Netherlands; 6) two large primary care centres, one in the Lisbon area (urban) and the other in Alentejo (rural), Portugal; and 7) 78 general practices in Concepción and Talcahuano in the Eighth region of Chile.

Study participants

Consecutive attendees were recruited (N=10045) and interviewed between April 2003 and February 2005, and re-interviewed after 6 and 12 months. Exclusion criteria

were an inability to understand one of the main languages involved, psychosis, dementia and incapacitating physical illness. Recruitment differed slightly in each country because of local service preferences. In the UK and the Netherlands, researchers approached patients waiting for consultations, whereas in the other countries doctors first introduced the study before contact with the research team. All patients gave written informed consent and undertook a research evaluation within two weeks. For the present analyses, we included participants who had no MDD in the 6 months prior to baseline (N=8517).

Outcome measure

A diagnosis of major depressive disorder (MDD) in the preceding 6 months was assessed in all patients at baseline, and after 6 and 12 months according to DSM-IV criteria using the depression section of the Composite International Diagnostic Interview (CIDI).[26, 27]

Risk factors

We selected risk factors for MDD which cover all important areas identified in a systematic review of the literature performed for the predictD study.[28] The risk factors, which were also used in our previous work, were assessed at baseline using risk factor questionnaires, unless otherwise stated below.[7, 12] Most risk factors were binary; where they were not, they were converted into binary variables as this was needed for the analysis. Variables that were originally continuous were categorised as being below or above the median score. Where a variable had more than two categories, it was recoded so that the category with the highest prevalence of MDD was compared with the remaining categories combined. The following risk factors were included in this study:

Socio-demographic or personal

Age [1], education level [2], marital status [3], employment [4], ethnicity [5], born in the country of residence or abroad [6], religious or spiritual beliefs [7], and presence of long standing physical illness [8].

Psychiatric comorbidity and function

Hazardous alcohol use [9] using the WHO's AUDIT questionnaire (score cut off below 8 or equal and above), plus questions on whether or not the respondent had ever had an alcohol problem or treatment for same [10].[29] Ever use of recreational drugs [11], adapted from the relevant sections of the CIDI. Anxiety [12] and panic [13] symptoms in the previous 6 months using relevant sections of the Patient Health Questionnaire (PHQ).[30] Physical [14] and mental [15] function were assessed by the Short Form 12.[31]

Adverse experiences in childhood and life events

Physical and/or emotional abuse [16] and sexual abuse [17] experienced during childhood.[32] Major life events [18] in the preceding 6 months using the List of Threatening Life Experiences Questionnaire.[33]

Work, living and environment

Whether or not their occupation required specialized knowledge [19]. Controls, demands and rewards for paid and unpaid work in the preceding 6 months were estimated by an adapted version of the job content instrument.[34] Participants were categorised as feeling in control in paid [20] or unpaid work [21]; as experiencing difficulties without support in paid or unpaid work [22]; and experiencing distress without feeling respect for their paid or unpaid work [23]. Financial strain [24] which was a single question commonly used in government and other UK social surveys.[35] Living alone or with others [25], owner-occupier accommodation [26], and whether satisfaction with their living conditions was present [27]. Satisfaction with neighbourhood [28] and perception of safety inside/outside of the home [29] were assessed using questions from the Health Surveys for England.[36] Experiences of discrimination [30] on the grounds of sex, age, ethnicity, appearance, disability or sexual orientation using questions from a recent European study.[37]

Family and friends

Brief questions on the quality of sexual [31] and emotional relationships [32] with a partner were adapted from a standardized questionnaire.[38] Presence of serious physical, psychological or substance misuse problems, or any serious disability, in people who were in close relationship to participants [33]. Difficulties in getting on with people and maintaining close relationships were assessed using questions from a social functioning scale [34].[39] Family psychiatric history: serious psychological problems in first-degree family members requiring pharmacological or psychological treatment in primary or secondary care [35], and suicide in first-degree relatives [36].[40] And finally the adequacy of social support from family and friends [37].[41]

Data analysis

First, we calculated characteristics for men and women without MDD in the 6 months prior baseline. Variables with >20% missing data were dropped from further analysis. Next, for each risk factor we calculated which percentage of men and women had an onset of MDD at 6 or 12 months of follow-up. Onset was defined as a diagnosis of MDD between baseline and 6 months or between 6 and 12 months of follow-up. In women and men, we calculated the absolute risk difference between those with the risk factor compared to those without the risk factor. We calculated absolute risks rather than relative risks as we were interested in the impact of risk factors across sex. To estimate whether the impact of a risk factor was different in women than in men, we calculated the interaction contrast (IC).[42-44] The interaction contrast compares the risk difference (RD) between men and women given the risk factor. Consider the risk factor education. Suppose there are 100 women with lower levels of education and 100 women with higher levels of education. If 10 of the 100 women with lower levels of education become depressed and 5 of the 100 women with higher levels of education become depressed, then the risk difference among women is 10/100-5/100=5%. Suppose we obtain a risk difference of 3% in men. The difference in risk differences between women and men (i.e. the interaction contrast) is then 5%-3%=2%. In this example the impact of lower levels of education on the risk of becoming depressed is 2% higher for women than for men. We calculated an

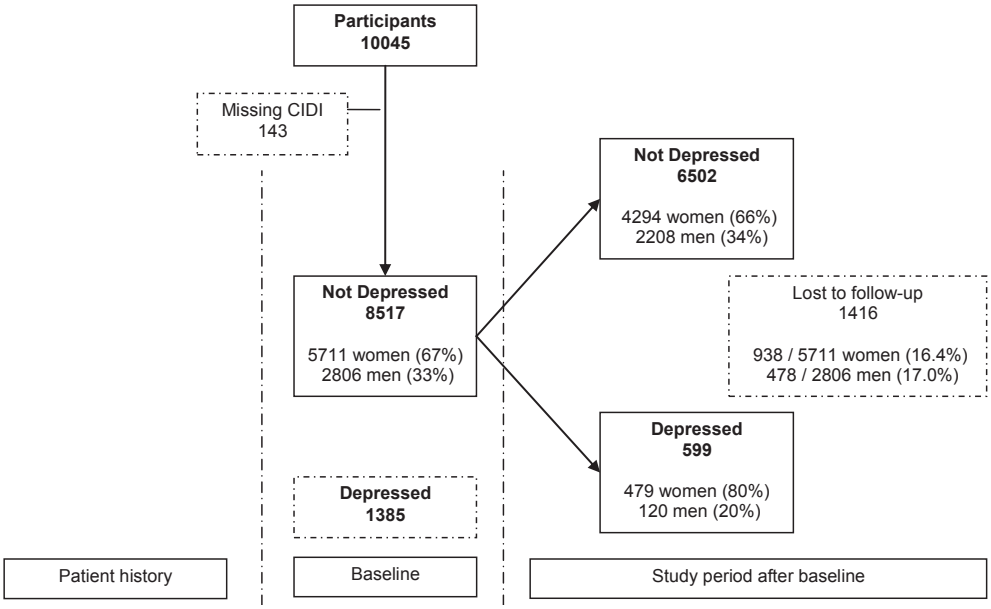
accompanying 95% confidence interval (CI) for the interaction contrast.[45] Note that 1/RD=NNH or number needed to harm, i.e. how many patients need to be exposed to a risk factor to cause harm in one patient that would not otherwise have been harmed. In an additional step, age, level of education and country were added to the models to control for potential confounding. To examine whether the impact of risk factors across sex on recurrent MDD was different than on a first onset of MDD at 6 or 12 months of follow-up, we repeated all analyses in strata of a possible lifetime history of MDD prior to baseline. A lifetime history of MDD was ruled out if the two core symptoms of the lifetime CIDI depression section were absent. If one or two of the core symptoms were present, participants were considered to have a lifetime history of MDD prior to baseline. All analyses were complete-case analysis, because missing data were few. Analyses were performed using PASW version 17 (IBM SPSS Statistics).

Results

The characteristics of the 8517 participants without MDD in the 6 months prior to baseline (5711 women and 2806 men, mean age 48 years with standard deviation 16) are presented in Table 1. Most risk factors were more common among women. Of the 8517 participants without MDD in the 6 months prior to baseline, 7101 (83.3%) had full data throughout the study (Figure 1). Attrition rates were similar for men (17.0%) and women (16.4%). Eight percent (N=599) had an onset of MDD at 6 or 12 months of follow-up, of whom 479 (80%) were female and 120 male.

Twenty-seven risk factors (77.1%) had a greater impact in women than in men on the risk of onset of MDD at 6 or 12 months of follow-up (Table 2). The risk factors lack of control in paid work and dissatisfied with partner were dropped from further analysis as they had more than 20% missing data. The following risk factors had a significantly greater impact in women: lower levels of education, non-European ethnicity, religious or spiritual, lifetime alcohol problem, anxiety syndrome, recent life events, financial strain, a neighbourhood perceived as not being safe, and problems with someone close. In men, the following risk factors had a significantly greater impact on the risk of onset of MDD at 6 or 12 months of follow-up: a non-professional occupation and living alone. The results were similar when the models were adjusted for age, level of education and country (data available on request).

Figure 1: Flowchart of participants without major depressive disorder (MDD) in the 6 months prior to baseline who have an onset of MDD at 6 or 12 months of follow-up



Of the participants who had no MDD in the 6 months prior to baseline, 3979 had no lifetime history of MDD and 4528 had a possible lifetime history of MDD (Figure 2). Of those with no lifetime history of MDD, 3357 participants had full data throughout the study of whom 142 (4.2%) had a first onset of MDD at 6 or 12 months of follow-up (107 women and 35 men). Of those with a lifetime history of MDD, 3737 participants had full data throughout the study of whom 455 (12.2%) had a recurrent MDD at 6 or 12 months of follow-up (372 women and 83 men). The distribution of women and men with or without a lifetime history of MDD was fairly similar across all countries (Table 3). The age and sex distribution were similar in those with a recurrent MDD at 6 or 12 months of follow-up and those with a first onset of MDD at 6 or 12 months of follow-up: mean age was 49 years and more than two-third was female. The impact of risk factors on recurrent MDD at 6 or 12 months of follow-up was generally comparable to the impact of risk factors on MDD before stratification for a lifetime history of MDD prior to baseline, although the impact of some risk factors became greater than in the whole population (e.g. lower levels of education) and some risk factors lost statistical significance (e.g. a lifetime alcohol problem) (see also Table 2).

Table 1: Baseline characteristics in percentages for those with no major depressive disorder in the 6 months prior to baseline (N=8517)

	Women (N=5711)	Men (N=2806)
Socio-demographic or personal		
Age: under 50§*	54	42
Lower education*	42	44
Not married / living with partner*	36	26
Unemployed*	54	46
Ethnicity: non-European§*	30	26
Immigrant¤	6	6
Religious or spiritual§*	78	69
Longstanding physical illness*	43	47
Psychiatric comorbidity and function		
Hazardous alcohol use*	3	14
Lifetime alcohol problem*	3	13
Ever used recreational drugs	7	8
Other anxiety syndrome*	5	2
Panic syndrome*	6	3
SF-12 Physical function below median*	49	45
SF-12 Mental function below median*	47	36
Adverse experiences and life events		
Physical or emotional abused*	20	16
Sexual child abused*	6	2
Life events	60	61
Work, living and environment		
Occupation: non-professional+*	13	18
Lack of control in paid work†	42	41
Lack of control in unpaid work§	20	20
Difficulties at work without support	11	10
Distress at work without respect§*	12	8
Financial strain*	32	28
Living alone*	10	8
Accommodation: not owned*	24	22
Dissatisfied with living condition‡*	15	13
Dissatisfied with neighbourhood*	17	15
Neighbourhood perceived not safe*	8	5
Discrimination*	10	8
Family and friends		
Dissatisfied with overall sex life§	14	15
Dissatisfied with partner∆*	12	10
Problems with someone close*	38	31
Difficulties in getting along with people§	7	6
Family history of psychiatric disorder*	32	26
Suicide in first-degree relatives	3	3
Social support below median*	42	48

All covariates have ≤ 1% missing data, except: § missing data = 2-3%,
‡ missing data = 7%, ¤ missing data = 11%, + missing data = 12%,
∆ missing data = 23%, † missing data = 49%
* P < 0.05 (Chi-Square tests)

Table 2: Differential impact of risk factors among women compared to men on the risk of onset of major depressive disorder at 6 or 12 months of follow-up

	N	Risk for MDD in women with the risk factor	Risk difference in women with and without RF	Risk for MDD in men with the risk factor	Risk difference in men with and without RF	Onset of MDD at follow-up IC_{crude}		Recurrent MDD at follow-up N=3737 IC_{crude}		First onset of MDD at follow-up N=3357 IC_{crude}	
		%	%	%	%	%	95% CI	%	95% CI	%	95% (CI)
Socio-demographic or personal											
Age: under 50	6934	9.8	-0.5	5.0	-0.5	0.0	-2.8 to 2.8	-0.2	-5.1 to 4.7	0.6	-2.3 to 3.4
Lower education	7052	14.1	6.8	5.9	1.5	5.3*	2.5 to 8.1	7.2*	2.4 to 12.0	2.5	-0.3 to 5.4
Not married / living with partner	7079	10.9	1.3	6.8	2.2	-0.8	-3.9 to 2.3	-2.2	-7.5 to 3.1	-0.4	-3.6 to 2.7
Unemployed	7063	11.7	3.5	6.3	2.1	1.5	-1.3 to 4.2	1.7	-3.0 to 6.5	1.0	-1.9 to 3.7
Ethnicity: non-European	7039	13.5	4.8	5.4	0.3	4.5*	1.4 to 7.6	10.3*	4.6 to 16.0	-0.4	-3.3 to 2.7
Immigrant	6239	11.2	0.7	7.1	2.1	-1.4	-7.7 to 4.9	-6.2	-16.6 to 4.3	4.9	-1.8 to 11.5
Religious or spiritual	6981	11.1	4.8	5.1	0.2	4.7*	1.6 to 7.8	7.2*	1.8 to 12.5	2.1	-1.1 to 5.1
Longstanding physical illness	7066	12.5	4.2	7.5	4.4	-0.2	-3.0 to 2.5	-2.1	-6.9 to 2.6	-0.1	-3.0 to 2.7
Psychiatric comorbidity / function											
Hazardous alcohol use	7064	11.5	1.5	4.0	-1.3	2.8	-3.1 to 8.7	4.3	-4.8 to 13.4	-0.6	-7.4 to 6.3
Lifetime alcohol problem	7075	20.8	11.1	9.6	5.2	6.0*	0.4 to 11.6	5.4	-2.8 to 13.7	2.7	-4.7 to 9.9
Ever used recreational drugs	7030	13.5	3.7	6.2	1.1	2.5	-3.1 to 8.2	2.5	-6.3 to 11.2	2.8	-3.6 to 9.1
Other anxiety syndrome	7022	33.9	25.0	21.2	16.5	8.6*	0.2 to 16.9	8.1	-3.3 to 19.6	9.0	-3.5 to 21.6
Panic syndrome	7069	28.0	19.0	21.1	16.5	2.5	-4.8 to 9.9	-0.5	-10.5 to 9.5	9.0	-2.2 to 20.3
SF-12 Physical function below median	7101	12.9	5.6	7.8	4.7	1.0	-1.7 to 3.8	0.0	-4.7 to 4.7	0.8	-2.1 to 3.6
SF-12 Mental function below median	7101	15.0	9.3	9.5	6.7	2.6	-0.2 to 5.4	3.0	-1.7 to 7.7	0.0	-3.1 to 3.0
Adverse experiences / life events											
Physical or emotional abused	7073	16.6	8.3	10.2	6.0	2.2	-1.4 to 5.9	5.0	-0.7 to 10.7	-2.1	-6.2 to 0.2
Sexual child abused	7060	19.3	9.9	17.9	13.0	-3.2	-12.5 to 6.2	0.2	-14.4 to 14.7	-5.8	-16.8 to 5.0
Life events	7082	12.3	5.5	6.0	2.1	3.3*	0.5 to 6.1	4.3	-0.5 to 9.2	0.3	-2.5 to 3.1

RF = Risk factor, MDD = Major depressive disorder, CI = Confidence interval
Risk difference = Risk difference between those with the risk factor compared to those without the risk factor
IC_{crude} = Risk difference of the interaction contrast between women and men (crude)
Note that a positive IC indicates a greater impact in women, while a negative IC indicates a greater impact in men
* Significant interaction on an additive scale

Table 2 (continued): Differential impact of risk factors among women compared to men on the risk of onset of major depressive disorder at 6 or 12 months of follow-up

	N	Risk for MDD in women with the risk factor %	Risk difference in women with and without RF %	Risk for MDD in men with the risk factor %	Risk difference in men with and without RF %	Onset of MDD at follow-up IC_{crude} %	Onset of MDD at follow-up IC_{crude} 95% CI	Recurrent MDD at follow-up N=3737 IC_{crude} %	Recurrent MDD at follow-up N=3737 IC_{crude} 95% CI	First onset of MDD at follow-up N=3357 IC_{crude} %	First onset of MDD at follow-up N=3357 IC_{crude} 95% (CI)
Work, living and environment											
Occupation: non-professional	6191	6.8	-4.4	5.9	0.8	-5.2*	-9.3 to -1.2	-5.8	-12.7 to 1.0	-3.9	-8.0 to 0.3
Lack of control in unpaid work	6962	11.6	1.9	6.4	1.6	0.2	-3.2 to 3.7	-2.2	-7.9 to 3.5	2.4	-1.2 to 6.1
Difficulties at work without support	7026	17.8	8.6	10.0	5.4	3.2	-1.3 to 7.8	3.4	-3.9 to 10.6	1.2	-3.9 to 6.3
Distress at work without respect	6989	18.3	9.3	11.9	7.3	2.0	-3.0 to 7.0	2.9	-4.8 to 10.6	-1.0	-6.9 to 4.8
Financial strain	7082	15.9	8.5	7.8	3.5	5.0*	2.0 to 8.1	6.8*	1.7 to 11.9	0.8	-2.4 to 4.0
Living alone	7101	8.6	-1.6	11.8	7.2	-8.8*	-13.7 to -3.8	-11.0*	-18.9 to -3.0	-7.7*	-13.1 to -2.3
Accommodation: not owned	7062	11.8	2.3	6.3	1.4	0.9	-2.4 to 4.3	1.1	-4.6 to 6.8	0.4	-3.0 to 3.8
Dissatisfied with living condition	6648	13.5	4.9	6.5	1.9	3.0	-1.1 to 7.0	7.3*	0.6 to 14.1	-5.0*	-9.3 to -0.8
Dissatisfied with neighbourhood	7095	14.0	4.8	7.8	3.1	1.7	-2.1 to 5.5	5.5	-0.7 to 11.7	-3.2	-7.3 to 0.9
Neighbourhood perceived not safe	7095	20.2	11.0	5.3	0.1	10.8*	4.8 to 16.8	11.0*	1.4 to 20.7	10.3*	3.8 to 16.8
Discrimination	7073	18.7	9.6	9.9	5.4	4.1	-0.7 to 9.0	3.9	-3.6 to 11.3	2.6	-3.0 to 8.2
Family and friends											
Dissatisfied with overall sex life	6890	12.7	3.0	8.3	3.7	-0.7	-4.6 to 3.2	-3.4	-9.6 to 2.8	2.2	-2.2 to 6.6
Problems with someone close	7066	13.5	5.6	6.4	2.0	3.6*	0.7 to 6.5	4.1	-0.8 to 9.1	2.5	-0.6 to 5.5
Difficulties in getting along with people	6976	14.8	5.0	8.7	3.7	1.3	-4.6 to 7.2	-2.2	-11.1 to 6.6	4.1	-2.9 to 11.1
Family history of psychiatric disorder	7027	13.4	4.9	8.2	4.1	0.7	-2.4 to 3.8	0.1	-5.0 to 5.1	1.1	-2.2 to 4.5
Suicide in first-degree relatives	7036	12.5	2.5	5.6	0.5	2.1	-6.8 to 11.0	-1.8	-16.0 to 12.5	5.0	-5.0 to 14.9
Social support below median	7035	11.1	1.8	5.5	0.7	1.2	-1.6 to 3.9	1.1	-3.7 to 5.9	0.8	-2.0 to 3.6

RF = Risk factor, MDD = Major depressive disorder, CI = Confidence interval
Risk difference = Risk difference between those with the risk factor compared to those without the risk factor
IC_{crude} = Risk difference of the interaction contrast between women and men (crude)
Note that a positive IC indicates a greater impact in women, while a negative IC indicates a greater impact in men
* Significant interaction on an additive scale

Table 3: The distribution of women and men with or without a lifetime history of major depressive disorder for all countries, in those with no major depressive disorder in the 6 months prior to baseline

	N	Women without a history of MDD %	Women with a history of MDD %	Men without a history of MDD %	Men with a history of MDD %
United Kingdom	1131	25	41	14	20
Spain	1011	20	49	14	17
Slovenia	1050	29	34	22	16
Estonia	923	29	43	16	12
Netherlands	1077	30	33	23	15
Portugal	1008	26	39	19	16
Chile	2317	34	37	19	11
Total	8517	28	39	18	15

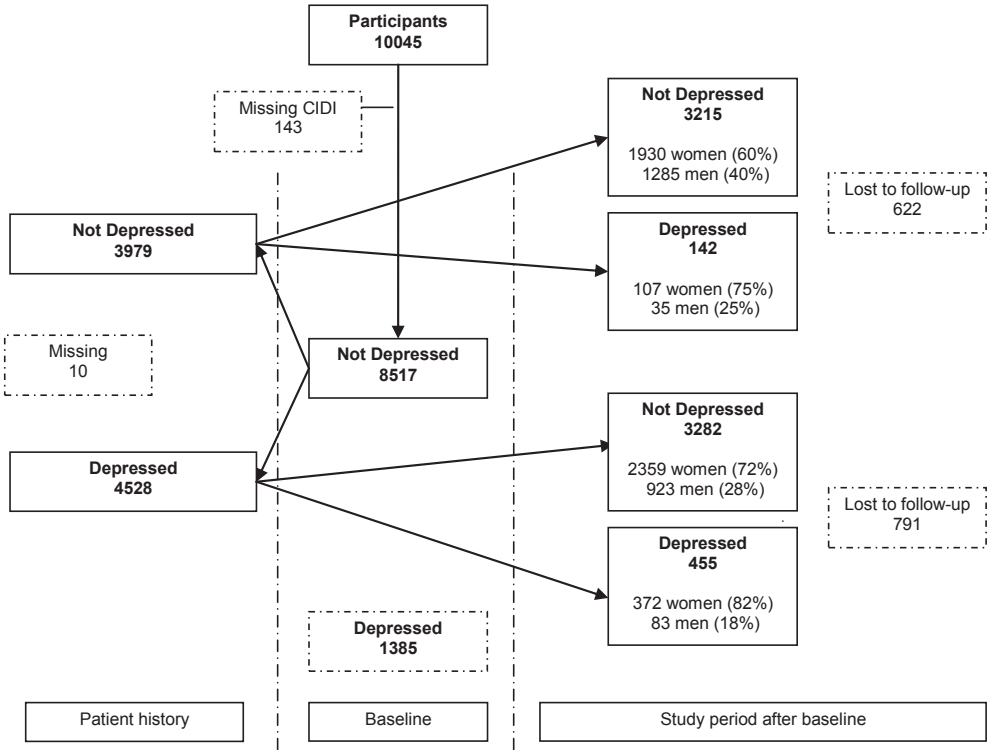
MDD = Major depressive disorder
Percentages may not add up to 100% due to rounding

When we considered those with a first onset of MDD at 6 or 12 months of follow-up, most risk factors had a greater impact in women than in men, although the impact of risk factors was generally weaker than on recurrent MDD at 6 or 12 months of follow-up. For example, lower levels of education had a greater impact in women than in men on recurrent MDD but not on a first onset of MDD. A neighbourhood that was perceived as not being safe had a greater impact in women than in men on both recurrent MDD and on a first onset of MDD. In contrast, living alone had a greater impact in men than in women on recurrent MDD as well as on a first onset of MDD. Dissatisfied with living condition had a greater impact on recurrent MDD in women but a greater impact on a first onset of MDD in men. The results were similar when the models were adjusted for age, level of education and country (data available on request).

Discussion

In this large scale cross-national study three main observations emerged: 1) most risk factors studied had a greater impact in women than in men on the risk of onset of MDD at 6 or 12 months of follow-up, independent of age, level of education and country; 2) risk factors that had greater impact in women were not restricted to a specific class of risk factors but varied across different groups of risk factors; and 3) the impact of risk factors across sex was generally stronger on recurrent MDD at 6 or 12 months of follow-up than on a first onset of MDD at 6 or 12 months of follow-up.

Figure 2: Flowchart of participants without major depressive disorder (MDD) in the 6 months prior to baseline who have a *first* onset of MDD or recurrent MDD at 6 or 12 months of follow-up



A body of research has examined sex differences in risk factors for onset of MDD.[11, 13, 20] However, most studies did not discriminate a first onset of MDD from recurrent MDD, which makes it difficult to make direct comparisons.[20] The finding that most risk factors studied had a greater impact in women than in men suggests that women are at greater risk of becoming depressed when a risk factor is present. It has been suggested that women may have greater biologic vulnerability to onset of MDD.[11] Although most risk factors in the present study were more common among women, our findings suggest that women may also be more likely to get affected by presence of risk factors than men.

The risk factors that had greater impact in women than in men were not restricted to a specific class of risk factors, such as socio-demographic or personal factors. However, two risk factors that had the strongest impact had a greater impact on recurrent MDD at 6 or 12 months of follow-up as well as on a first onset of MDD at 6 or 12 months of follow-up: a neighbourhood that was perceived as not being safe in women and living alone in men. In addition, being dissatisfied with living condition was the third factor that had the strongest impact on recurrent as well as on a first onset of MDD, although it had a greater impact in women on recurrent MDD and in men on a first onset of MDD. The relationship between poor neighbourhood

conditions and depressive symptoms has been well established.[46, 47] For example, poverty status may be associated with first onset of MDD in a 1 year period.[48] Our study is the first to show that a neighbourhood that was perceived as not being safe had a stronger impact in women than in men to become depressed, irrespective of whether a lifetime history of MDD prior to baseline was considered. Living alone had a significantly greater impact in men than in women on recurrent MDD as well as on a first onset of MDD. Studies among aged populations found that living alone was associated with MDD.[49] The few adult population based studies reported that living alone may have a stronger impact on mental health in men than in women.[50, 51] It could be that men who are living alone become more easily isolated than women as the latter may maintain more active social ties to family and friends.[52] Isolation may in turn lead to onset of depressive symptoms. The observation that being dissatisfied with living condition had a greater impact in women on recurrent MDD but in men on a first onset of MDD may suggest that in men it could be a real risk factor for a first onset of MDD, while in women dissatisfaction with living condition may have been caused by their lifetime history of MDD prior to baseline. It could be that a previous episode of MDD has sensitized women for perceiving and reporting risk factors.[53]

We observed that the impact of risk factors across sex was generally stronger on recurrent MDD at 6 or 12 months of follow-up than on a first onset of MDD at 6 or 12 months of follow-up. This suggests that the strength of impact of risk factors in men and women may be different on recurrent MDD than on a first onset of MDD, which may be in accordance with the kindling hypothesis.[53-55] This hypothesis suggests that susceptibility to a subsequent MDD may alter after onset of MDD as occurrence of a first onset of MDD may largely depend on the level of stress, while recurrent MDD may occur independent of stress. Risk factors that had a greater impact across sex on recurrent MDD were comparable to those before stratification for a lifetime history of MDD prior to baseline. Studies that examined onset of MDD did not always take a lifetime history of MDD into account. It could be that these studies examined recurrent MDD rather than a first onset of MDD. Our findings suggest that it is important to take a lifetime history of MDD into account when examining risk factors for onset of MDD, and to note the difference between recurrent MDD (i.e. new episode of depressive illness following recovery in those without MDD at baseline and with a lifetime history of MDD prior to baseline) and recurrence of MDD (i.e. new episode of depressive illness following recovery in those with MDD at baseline).[56]

Strengths of our study are that our cohort was large and included participants from 6 European countries and Chile. We diagnosed MDD using DSM-IV criteria and response to follow-up was high in all countries. As we included lifetime history of MDD data, not only were we able to examine recurrent MDD but also a first onset of MDD from a lifetime perspective. We assessed a wide range of risk factors for MDD which reflect the current state of knowledge.[12] Our study was limited by the lower response to recruitment in the UK and the Netherlands, which possibly occurred because the study was not so obviously endorsed by family doctors compared with the other countries in the study.[7] Yet, attrition was low and was not related to sex. Another limitation is that biologic factors were not available, which could have distorted the impact of risk factors on MDD across sex. For example, increased sensitivity to hormonal changes during the menopausal transition may increase vulnerability

to onset of MDD for women and not for men.[57] Another potential limitation is that presence of a lifetime history of MDD prior to baseline was based on an affirmative answer to either of the two core questions of the CIDI rather than assessment of a full CIDI depression interview. Although we excluded those who had dementia, we cannot rule out the possibility that cognitive impairment may have influenced the recalling of previous episodes of MDD in those who were older. Also, it is possible that general practice effects were present, however we were unable to analyse this as a result of the sample size.

In conclusion, most risk factors studied had a greater impact in women than in men on the risk of onset of major depressive disorder and were not restricted to a specific class of risk factors. These findings may account for the observed difference in incidence between men and women. Future studies should discriminate a first onset of MDD from recurrent MDD.

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Chapter 1.3

Recent life events pose greatest risk for onset of major depressive disorder during mid-life

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Concern should drive us into action, not into a depression.

Pythagoras
Greek philosopher and mathematician, BC 580-500

Abstract

The authors examined the association of life events and age with onset of major depressive disorder (MDD) and whether the combination of life events and age posed greater risk than the sum of their independent effects. Data were used from a prospective cohort study of 10045 general practice attendees (PredictD). We included those without MDD at baseline (N=8293). Participants were divided into tertiles according to age. Life events were assessed at baseline using the List of Threatening Life Experiences Questionnaire and categorized according to type. Main outcome measure was onset of DSM-IV MDD at 6 or 12 months of follow-up. The authors calculated Relative Excess Risks due to Interaction (RERI). 6910 persons (83.3%) had a complete follow-up, of whom 589 (8.5%) had an onset of MDD (166 younger, 254 middle aged and 169 older). Life events had the largest effect in mid-life. The combined effect of personal problems (RERI=1.30; 95%CI 0.29 to 2.32), events in family or friends (RERI=1.23; 95%CI 0.28 to 2.19), or problems with law (RERI=1.57; 95%CI 0.33 to 2.82) and middle age was larger than the sum of individual effects. Recent life events carry the largest risk of onset of MDD in mid-life. Understanding the different vulnerability to life events according to age may help to indicate groups at a particular risk and assist in preventive strategies.

Introduction

Major depressive disorder (MDD) is a serious health problem and will be the second leading cause of burden of disease worldwide by 2030.[1] MDD has severe personal and public health consequences. To be able to prevent MDD, insight in risk factors for the onset of MDD is of clear importance. A body of research has shown that major life events may lead to onset of MDD.[2] It has also been suggested that the interaction between vulnerability factors and life events plays a role in the onset of MDD. For example, one study showed that vulnerability factors such as lack of employment and early loss of mother largely influenced whether or not a life event resulted in depression.[3] Another study reported that women were approximately three times more likely to become depressed than men when a life event occurred.[4] These findings suggest that some people may be more vulnerable to onset of MDD than others, which is in accordance with the vulnerability-stress model.[5-8] In general, this model suggests that vulnerability and stress factors interact to cause the disorder. For instance, with higher a priori vulnerability, lower levels of stress may be needed to become depressed. Few studies have examined whether there is interaction of life events with age in the onset of MDD, although the frequency of life events and vulnerability to depression may differ throughout life.[9-13] Studies that have examined interaction between life events and age found inconsistent results. One study reported that maternal loss had a greater impact on the risk of onset of depression in those who were younger compared to those who were older, while another study showed that recent life events may have the strongest effect on depression in mid-life.[14, 15] Two other studies did not find an interaction between age and life events on the risk of depression.[10, 16] These studies were limited by a small number of patients, a cross-sectional or retrospective design, or a narrow age range.[10, 14-16] To examine the interaction between age and life events on the risk of onset of depression, large prospective studies with a reliable registration of life events and a wide age range are needed.[10] Our aim was to examine the association of recent life events and age with onset of major depressive disorder and whether the combination of life events and age posed greater risk than the independent effects of life events and age.

Material and methods

Study setting and design

PredictD is a multicenter prospective cohort study from which a multifactor algorithm was developed to predict risk of onset of major depressive disorder in 6 European countries and Chile, and has been described in greater detail elsewhere.[11, 17-20] The study was approved by local ethical committees and conducted in seven countries: 1) 25 general practices in the Medical Research Council's General Practice Research Framework, in the United Kingdom; 2) nine large primary care centres in Andalucía, Spain; 3) 74 general practices nationwide in Slovenia; 4) 23 general practices nationwide in Estonia; 5) seven large general practice centres near Utrecht, the Netherlands; 6) two large primary care centres, one in the Lisbon area (urban) and the other in Alentejo (rural), Portugal; and 7) 78 general practices in Concepción and Talcahuano in the Eighth region of Chile.

Study participants

Consecutive attendees aged 18 to 75 years were recruited (N=10045) and interviewed between April 2003 and September 2004 in Europe and between October 2003 and February 2005 in Chile, and re-interviewed after 6 and 12 months. Exclusion criteria were an inability to understand one of the main languages involved, psychosis, dementia and incapacitating physical illness. Recruitment differed slightly in each country because of local service preferences. In the UK and the Netherlands, researchers approached patients waiting for consultations, whereas in the other countries doctors first introduced the study before contact with the research team. All patients gave written informed consent.

Outcome measure

A diagnosis of major depressive disorder (MDD) in the preceding 6 months was assessed at baseline, 6 and 12 months in all patients according to DSM-IV criteria using the depression section of the Composite International Diagnostic Interview (CIDI).[21, 22]

Life events

Major life events in the preceding 6 months were assessed at baseline using the self-report List of Threatening Life Experiences Questionnaire.[23] First, we examined the number of life events and categorized them into 0, 1 and 2 or more life events. Second, we extended previous work by categorizing the 12 life events into 5 groups according to type of life event. Each life event group was then dichotomized into presence or absence of the life event:

1. Personal problems (suffered a serious illness, assault or injury);
2. Relational problems (separated due to marital difficulties, broke off a steady relationship, or a serious problem with a close friend, neighbour or relative);
3. Work related and financial problems (unemployed or seeking work unsuccessfully for more than one month, sacked from your job, or a major financial crisis);
4. Severe events in family or friends (a serious illness, assault, injury to or death of a parent, child, partner, close family friend or another relative);
5. Problems with law (problems with the police or court appearance, or something valuable was lost or stolen).

Other variables

Age, sex, level of education and country were assessed using self-report questionnaires at baseline. Higher education was defined as secondary school or higher, while lower education included primary school, trade or no education.

Data analysis

Of 10045 participants at baseline, 395 persons were dropped from the analysis because they were younger than 18 years or older than 75 years or had missing data on age or CIDI diagnosis. We included participants who had no MDD in the

6 months prior to baseline (N=8293). Onset was defined as a diagnosis of MDD between baseline and 6 months or between 6 and 12 months of follow-up.

Baseline characteristics for the sample with no MDD at baseline were calculated as means with standard deviations (SD) for continuous variables and numbers with percentages for categorical variables. We divided age in tertiles: younger, middle aged or older and calculated baseline characteristics according to these age groups. Characteristics were also calculated for those with and without onset of MDD at 6 or 12 months of follow-up. In addition, we used logistic regression models in which onset of MDD was the dependent variable to calculate Odds Ratio's (OR) with accompanying confidence intervals (CI) for the following variables at baseline: age, sex, level of education, country, number of life events and categories of life events.

In the present analyses we were interested in examining whether the effect of life events on the risk of onset of MDD was different for different age groups, i.e. whether there was an interaction between age (vulnerability factor) and life events (stressor). Most often, interaction is assessed by the addition of a product term in a statistical model. In logistic regression analysis the coefficient associated with this product term quantifies the departure from multiplicativity.[24] We were interested in identifying interactions on an additive rather than multiplicative scale as it has been argued that biological interactions can best be estimated by departure from additivity and this better reflects the vulnerability-stress model.[25-27] To measure the amount of interaction on an additive scale we calculated the Relative Excess Risk due to Interaction (RERI) and accompanying confidence intervals (CI) using the delta method.[25, 26, 28] If the CI does not include 0, the RERI is statistically significant and thus departure from additivity is present, i.e. the combined effect of age and life events is larger than the sum of age and life events separately.

We used logistic regression models to obtain both crude and adjusted estimates of the RERI. In these models onset of MDD at 6 or 12 months of follow-up was the dependent variable, and the following indicators (dummy variables) were included as independent variables: 1) no life event and young age (reference) [A-B-]; 2) no life event and middle age [A-B+]; 3) presence of a life event and young age [A+B-]; and 4) presence of a life event and middle age [A+B+]. We calculated RERIs using the following formula:

$$\mathrm{RERI} = OR_{A+B+} - OR_{A+B-} - OR_{A-B+} + 1$$

where OR_{A+B+}, OR_{A+B-}, OR_{A-B+} are odds ratios obtained from the logistic regression comparing groups A+B+, A+B- and A-B+ with the reference group. We also calculated the RERI for the combination of life event and older age, where a dummy variable was created in a similar way as described above with the same reference group of absence of life events and young age. Adjusted estimates of RERI were obtained by including a priori confounders sex, level of education and country in the models and using the resulting adjusted odds ratios in the formula given above. Confidence intervals for RERI were obtained using the delta method [28]. We repeated the analyses in those without a lifetime history of MDD to measure the amount of interaction on the risk of a first onset of MDD at 6 or 12 months of follow-up. A lifetime history of MDD was ruled out if the two core symptoms of the lifetime CIDI depression section were absent. If one or two of the core symptoms were present, participants

were considered to have a possible history of MDD. We used the same methods as mentioned above to calculate the crude and adjusted RERIs. All analyses were complete-case analysis, because missing data on covariates were few. Analyses were performed using PASW version 17 (IBM SPSS Statistics).

Results

Baseline characteristics for the study population (N=8293) according to age group are presented in Table 1. Compared to the young age group (aged 18 to 40 years), persons in the middle age (aged 41 to 57 years) and older age (aged 58 to 75 years) groups were less likely to have experienced two or more life events. They were more likely to have experienced personal problems, but less likely to have experienced work related or financial problems, severe events in family or friends, or problems with law.

Figure 1 shows that 6910 persons (83.3%) had a complete follow-up, of whom 589 (8.5%) had an onset of MDD at 6 or 12 months of follow-up. In the younger age group 166 persons (28%) had an onset of MDD at 6 or 12 months of follow-up, in the middle aged group 254 (43%) and in older age group 169 persons (29%) (Table 2). Attrition rates were similar for those who were middle aged (16.0%) or older (15.7%) but those who were younger were slightly more likely to be lost to follow-up (18.2%). Other risk factors for onset of MDD at 6 or 12 months of follow-up were being female and having lower levels of education. Compared to the UK, persons from Spain and Chile were more likely to have an onset of MDD at 6 or 12 months of follow-up, while persons from Slovenia, Estonia and the Netherlands were less likely to have an onset of MDD at 6 or 12 months of follow-up. The risk of onset of MDD at 6 or 12 months of follow-up increased with increasing number of life events, and was increased for all types of life event. Figure 2 shows that 137 out of 3243 persons (4.2%) with no MDD in the 6 months prior to baseline had a first onset of MDD at 6 or 12 months of follow-up in the absence of a lifetime history of MDD.

Figure 1: Flowchart of participants without major depressive disorder (MDD) in the 6 months prior to baseline who have an onset of MDD at 6 or 12 months of follow-up

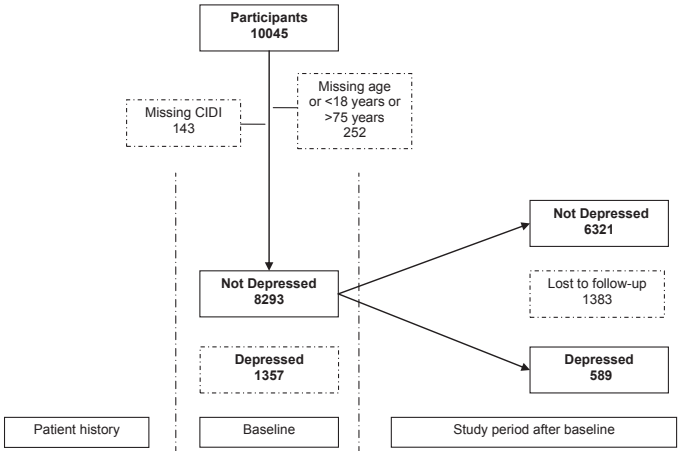

Table 1: Characteristics for 8293 participants with no major depressive disorder in the 6 months prior to baseline

	Total (N=8293) %	**Age 18 to 40 years (N=2797) %**	**Age 41 to 57 years (N=2780) %**	**Age 58 to 75 years (N=2716) %**
Socio-demographic				
Age in years, mean (SD)	49 (16)	30 (6)	49 (5)	66 (5)
Female	67	73	69	60
Education (lower)	43	28	45	53
Country				
- UK	14	10	13	18
- Spain	12	10	12	15
- Slovenia	13	11	15	12
- Estonia	11	18	8	7
- Netherlands	13	12	15	12
- Portugal	12	11	12	14
- Chile	26	29	25	23
Life events – number				
- No	40	36	40	44
- One	30	30	29	32
- Two or more	30	34	31	25
Life events – groups				
Personal problems	15	12	15	17
Relational problems	39	38	39	39
Work/financial problems	14	19	14	9
Events in family/friends	21	29	23	11
Problems with law	8	10	8	7

All covariates had ≤ 1% missing data, except for severe events in family or friends (13%)
Percentages may not add up to 100% due to rounding

Table 2: Characteristics for those with and without onset of major depressive disorder at 6 or 12 months of follow-up

	Total (N=6910) %	**No onset (N=6321) %**	**Onset (N=589) %**	**OR (95% CI)**
Socio-demographic				
Age in years, tertiles				
- 18 to 40	33	34	28	1 (ref)
- 41 to 57	34	33	43	1.56 (1.27 to 1.92)
- 58 to 75	33	34	29	1.02 (0.82 to 1.27)
Female	68	66	80	2.00 (1.62 to 2.46)
Education (lower)	41	39	55	1.89 (1.59 to 2.24)
Country				
- UK	14	14	14	1 (ref)
- Spain	10	10	18	1.83 (1.34 to 2.49)
- Slovenia	13	14	7	0.46 (0.31 to 0.68)
- Estonia	12	12	8	0.66 (0.46 to 0.96)
- Netherlands	14	14	8	0.57 (0.39 to 0.82)
- Portugal	12	12	12	0.95 (0.68 to 1.33)
- Chile	25	24	33	1.35 (1.03 to 1.78)
Life events – number				
- No	41	42	28	1 (ref)
- One	30	30	30	1.48 (1.18 to 1.84)
- Two or more	29	28	42	2.29 (1.87 to 2.82)
Life events – groups				
Personal problems	14	14	21	1.73 (1.40 to 2.13)
Relational problems	38	37	46	1.46 (1.23 to 1.73)
Work/financial problems	14	13	21	1.83 (1.48 to 2.26)
Events in family/friends	20	19	31	1.90 (1.56 to 2.31)
Problems with law	8	8	12	1.60 (1.22 to 2.09)

OR = Odds ratio, CI = Confidence intervals, Percentages may not add up to 100% due to rounding

Table 3 shows the results of the logistic regression analyses for the independent and combined effects of age group and life event on the risk of MDD, and the RERI with 95% CI. In the absence of a life event, persons in middle age (41 to 57 years) had the largest risk of MDD compared to those who were younger or older (e.g. OR 1.42; 95% CI 1.13 to 1.78 for no personal problems and middle age). If a life event was present, all types of life event showed the largest effect at age 41 to 57 years (e.g. OR 3.03; 95% CI 2.19 to 4.18 for personal problems and middle age). A statistically significant interaction between middle age and life event was found for personal problems (RERI=1.30; 95% CI 0.29 to 2.32), severe events in family or friends (RERI=1.23; 95% CI 0.28 to 2.19) and problems with law (RERI 1.57; 95% CI 0.33 to 2.82), indicating that the combined effect of middle age and life event on the risk of MDD was greater than the sum of the individual effects. No significant interaction between life events and older age was found for any of the life event categories. The results were similar when the models were adjusted for sex, level of education and country. When we repeated the analyses in those with a first onset of MDD at 6 or 12 months of follow-up, all types of life event still showed the largest effect at middle age, although none of the RERIs were statistically significant (data available on request).

Figure 2: Flowchart of participants without major depressive disorder (MDD) in the 6 months prior to baseline and without a lifetime history of MDD, who have a first onset of MDD at 6 or 12 months of follow-up

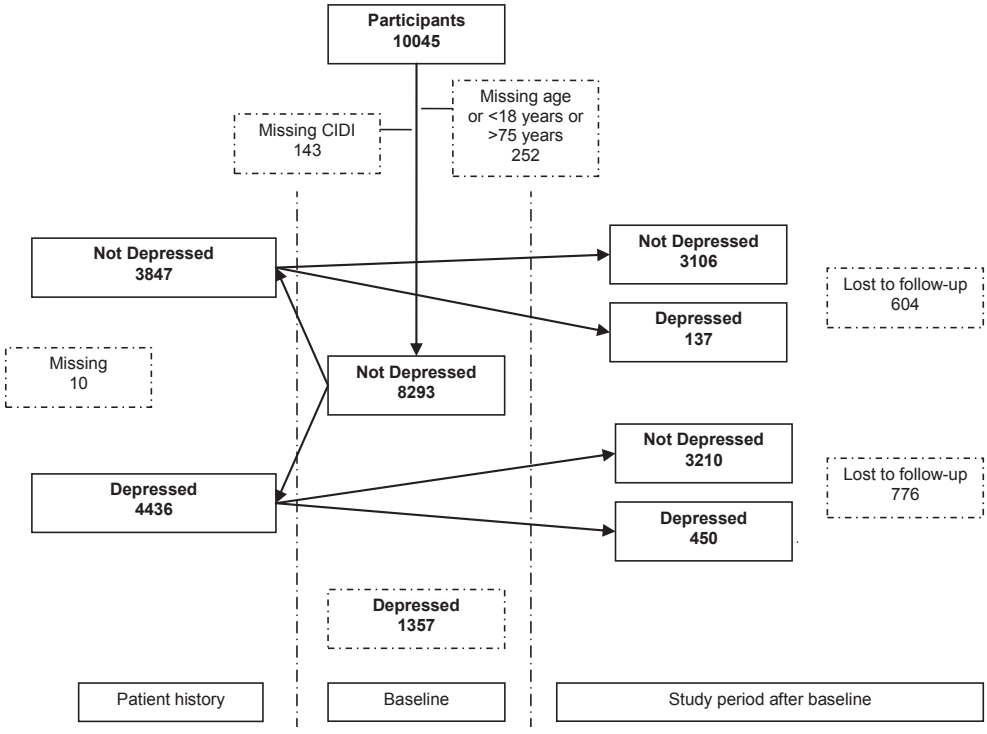

Table 3: Logistic regression models with onset of major depressive disorder at 6 or 12 months of follow-up as dependent variable, and the life event groups, age (tertiles) and their interaction as independent variables

	Onset of MDD at follow-up (N=6910)		
	Odds ratio (95% CI)	**$RERI_{crude}$ (95% CI)**	**‡$RERI_{adjusted}$ (95% CI)**
No personal problems and younger age	1 (reference)		
No personal problems and middle age	1.42 (1.13 to 1.78)		
No personal problems and older age	0.97 (0.76 to 1.25)		
Personal problems and younger age	1.31 (0.83 to 2.06)		
Personal problems and middle age	3.03 (2.19 to 4.18)	1.30 (0.29 to 2.32)*	1.35 (0.31 to 2.40)*
Personal problems and older age	1.52 (1.05 to 2.22)	0.24 (-0.54 to 1.02)	0.14 (-0.61 to 0.89)
No relational problems and younger age	1 (reference)		
No relational problems and middle age	1.66 (1.25 to 2.20)		
No relational problems and older age	1.18 (0.87 to 1.60)		
Relational problems and younger age	1.69 (1.23 to 2.32)		
Relational problems and middle age	2.43 (1.81 to 3.26)	0.09 (-0.62 to 0.79)	0.08 (-0.56 to 0.73)
Relational problems and older age	1.45 (1.04 to 2.01)	-0.42 (-1.07 to 0.24)	-0.37 (-0.96 to 0.22)
No work/financial problems and younger age	1 (reference)		
No work/financial problems and middle age	1.61 (1.27 to 2.03)		
No work/financial problems and older age	1.08 (0.84 to 1.39)		
Work/financial problems and younger age	1.74 (1.22 to 2.50)		
Work/financial problems and middle age	2.98 (2.11 to 4.21)	0.63 (-0.42 to 1.69)	0.65 (-0.45 to 1.75)
Work/financial problems and older age	2.21 (1.39 to 3.50)	0.38 (-0.71 to 1.48)	0.40 (-0.74 to 1.54)
No events in family/friends and younger age	1 (reference)		
No events in family/friends and middle age	1.46 (1.12 to 1.90)		
No events in family/friends and older age	1.16 (0.89 to 1.52)		
Events in family/friends and younger age	1.65 (1.18 to 2.31)		
Events in family/friends and middle age	3.34 (2.43 to 4.58)	1.23 (0.28 to 2.19)*	1.30 (0.35 to 2.25)*
Events in family/friends and older age	2.06 (1.30 to 3.26)	0.25 (-0.74 to 1.24)	0.19 (-0.73 to 1.12)
No problems with law and younger age	1 (reference)		
No problems with law and middle age	1.46 (1.18 to 1.82)		
No problems with law and older age	0.99 (0.78 to 1.26)		
Problems with law and younger age	0.99 (0.57 to 1.71)		
Problems with law and middle age	3.02 (2.02 to 4.53)	1.57 (0.33 to 2.82)*	1.31 (0.10 to 2.51)*
Problems with law and older age	1.75 (1.04 to 2.95)	0.77 (-0.25 to 1.79)	0.67 (-0.31 to 1.65)

MDD = Major depressive disorder, OR = Odds ratio, CI = Confidence interval, RERI = Relative excess risk due to interaction

RERI formula = OR_{A+B+} - OR_{A+B-} - OR_{A-B+} +1

RERI examples: Personal problems and middle age (3.03 – 1.31 – 1.42 + 1 = 1.30); personal problems and older age (1.52 –1.31 – 0.97 + 1 = 0.24)

* Significant departure from additivity; note that in the absence of interaction as departure from additivity, RERI = 0.

‡ Adjusted for sex, level of education and country

Discussion

In this large scale cross-national prospective cohort study in primary care attendees two main observations emerged: 1) life events, regardless type of life event, pose the largest risk on the onset of major depressive disorder in mid-life; 2) the combined effect of personal problems, severe events in family or friends, or problems with law and middle age is larger than the sum of the individual effects.

Strengths of our study are that we used data from a prospective cohort study and thus were able to examine life events before onset of MDD. Also, our cohort was large and had a wide age range and included participants from 7 countries. We diagnosed MDD according to DSM-IV criteria using the same structured interview in all countries and identified life events from a widely used schedule. Furthermore, loss to follow-up was low in all age groups. Our study was limited by the lower response to recruitment in the UK and the Netherlands, which possibly occurred because the study was not as strongly endorsed by family doctors as in the other countries in the study.[18] Ethical constraints prevented the collection of data on non-responders at baseline. Although we excluded those who had dementia, we cannot rule out the possibility that cognitive impairment may have influenced the recalling of life events in those who were older. This may have led to an underestimation of life events in the oldest group and possibly to a weaker effect on the onset of MDD.

To our knowledge, only four studies have examined whether life events have a different effect in different age groups on the risk of depression. In one large epidemiological study among 3491 individuals aged 48 to 79 years, maternal loss had a greater effect in those who were middle aged compared to those who were older, which is comparable to our results.[14] Another large study among 8580 participants aged 16 to 74 years showed that recent threats to health, recent interpersonal problems and lifetime stressors were associated with common mental disorders.[15] In particular, they found that the strength of association between recent life events and common mental disorders was the largest in those aged 45 to 54 years. Although the study had a cross-sectional design and included both depressive and anxious persons, the results were comparable to ours. Another study did not find an interaction between life events and age on the risk of onset of depression, but this study included only 64 patients with depression and 74 without depression and thus was likely to be limited in power.[16] The fourth study examined whether the impact of events (e.g. a recent divorce or suicide of a relative) on the risk of onset of depression varied with age in 13006 patients who were admitted to a psychiatric ward for the first time.[10] Although this study did not find an interaction between more remote life events and age, a significant interaction was observed between age and a recent divorce that occurred within the last year before admission, and between age and being unmarried in the two year period before admission on the risk of a first depression.

Findings from the present study suggest that life events have the largest effect in mid-life on the risk of onset of MDD. Especially the combined effect of personal problems and age, severe events in family or friends and age, or problems with law and age had a statistically significant RERI, which means that the combined effects were larger than the sum of the individual effects. This may suggest that those who are middle aged are more likely to become depressed if a recent personal problem occurs than younger or older people experiencing the same life event. These findings accord with the vulnerability-stress model of depression that states

that stressors in combination with vulnerability levels are needed in order to be sufficient to cause depression.[5-8] It could be that persons who are middle aged may be more vulnerable to the consequences of stressful life events like a recent serious illness, assault or injury than those who are younger or older.[15] One might argue that people in middle age have more responsibilities and social ties and thus life events at this stage of life have a larger impact in terms of onset of MDD, despite that they may also be the most resilient given they have had more life experience than the younger group and do not yet have the added vulnerability of poorer health and relative social isolation of older age. Management of MDD in middle age people in clinical practice may require dealing with the effects of major life events on the treatment and prognosis of the disorder.

Although the effect of life events may be different for different age groups on the risk of onset of MDD, our findings showed that none of the RERIs were statistically significant for a *first* onset of MDD, although all types of life event showed the largest effect at middle age. It is possible that even larger prospective studies are needed to detect whether or not life events have a different effect in different age groups on the risk of a first depression. Future research should take account of the possibility that the effect of life events may be different on a first onset of depression compared to recurrent depression.[29]

In conclusion, the results from the present study suggest that recent life events carry the largest risk of onset of major depressive disorder in mid-life. Understanding the different vulnerability to life events according to age may help to indicate groups at a particular risk and assist in preventive strategies.

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Chapter 2

Course and outcome of major depressive disorder

Chapter 2.1

The natural course and outcome of major depressive disorder in primary care: the PREDICT-NL study

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The greatest revolution in our generation is the discovery that human beings, by changing the inner attitudes of their minds, can change the outer aspects of their lives.

William James
American philosopher and psychologist, 1842-1910

Abstract

Purpose

To examine the natural course and outcome of major depressive disorder (MDD) in primary care over 39 months.

Methods

Prospective cohort study of 1338 consecutive attendees with follow-up after six, 12 and 39 months with DSM-IV MDD using the Composite International Diagnostic Interview (CIDI). We measured severity of depressive symptoms (Patient Health Questionnaire 9), somatic symptoms (Patient Health Questionnaire 15), and mental and physical function (Short Form 12, mental and physical component summary). Analysis of variance and random coefficient models were performed.

Results

At baseline, 174 people (13%) had MDD of which 17% had a chronic and 40% had a fluctuating course, while 43% remitted. Patients with chronic courses had more severe depressive symptoms (mean difference 6.54; 95% CI 4.38 to 8.70), somatic symptoms (mean difference 3.31; 95% CI 1.61 to 5.02) and greater mental dysfunction (mean difference -10.49; 95% CI -14.42 to -6.57) at baseline than those who remitted from baseline, independent of age, sex, level of education, presence of a chronic disease and a lifetime history of depression.

Conclusions

Although 43% of patients with MDD attending primary care recover, this leaves a majority of patients (57%) who have a chronic or intermittent course. Chronic courses are associated with higher levels of depressive symptoms and somatic symptoms and greater mental dysfunction at baseline.

Introduction

Major depressive disorder (MDD) is a serious health problem and will be the second leading cause of burden of disease worldwide by 2030.[1] In any given 12-month period, 10-20% of adults will visit their general practitioner (GP) for mental complaints, of which the majority are related to depression.[2] The prevalence of MDD in primary care is estimated to be between four and 18%.[3] People presenting with depressive symptoms are mainly seen in primary care, however treatment guidelines are mainly based upon data from hospital settings or the general population.[4] Few studies have examined the course and outcome of MDD in primary care over a greater period of time. In one study, 32% of the primary care patients who were depressed at baseline were not depressed after 12 months and 47% were not depressed after 3.5 years.[5] A recent study showed that of 79 primary care patients diagnosed with MDD at baseline, 25% persisted and 49% suffered from residual symptoms or recurrences after 18 months.[6] These data suggest that the majority of adult patients with depression in primary care do not recover in the medium-term, but also that some patients do recover.

Most of the observational cohort studies of depression in primary care included small sample sizes and had a short duration of follow-up.[4, 7] The nature of depression can be complex: symptoms can improve and deteriorate over time and patients can switch between depression categories.[4] However, this fluctuating course of depression can be missed in studies with a short duration of follow-up or few assessments.[8] A recent review showed that between 1985 and 2006 only two observational studies in primary care were performed with a follow-up longer than one year.[4] These studies included three assessments of depression at most.

The objective of this study was to examine the natural course of MDD in primary care attendees over a period of 39 months. We investigated the course of major depression and its relationship to the severity of depressive and somatic symptoms, and mental and physical function in a cohort of primary care attendees aged 18 years or older who were diagnosed with MDD at baseline.

Methods

Study setting and design

PredictD is a multicenter prospective cohort study from which a multifactor algorithm was developed to predict risk of onset of major depressive disorder in primary care patients in six European countries and Chile.[3, 9-11] In brief, in 2003, consecutive adult primary care patients were asked to participate, irrespective of their reasons for consulting their general practitioners. Patients were followed-up after six and 12 months. The current study used data from PREDICT-NL, the Dutch part of predictD, in which an additional follow-up after 39 months was conducted. The study was approved by the medical ethics committee of the University Medical Center Utrecht and was conducted in seven large general practice centres near Utrecht.

Study participants

Consecutive attendees aged 18 years or older were recruited and interviewed between April 2003 and September 2004. Patients willing to participate were asked to fill in risk factor questionnaires and sign informed consent within two weeks. After the risk factor questionnaires were returned, an appointment was made by the researchers to conduct a diagnostic depression interview at the general practice. If patients did not respond after two weeks, a first reminder was sent and, if necessary, a second reminder after four weeks. Participants who did not respond to the second reminder were considered to be non-responders. All participants gave written informed consent.

Diagnosis of major depressive disorder

The diagnosis of major depressive disorder (MDD) was assessed in all patients according to DSM-IV criteria using the depression section of the Composite International Diagnostic Interview (CIDI).[12, 13] The researchers contacted the participant by telephone and asked the two core questions of the depression section of the CIDI interview (depressed mood or a loss of interest). MDD was defined as absent if the participant responded negatively to both questions.[12] If the participant responded positively to either question, an appointment was made in the general practice to conduct the entire depression section of the CIDI interview. The interviewers were blinded to the answers on the risk factor questionnaires. At baseline, the six- and 12-month follow-up, diagnosis of MDD was assessed covering the preceding six months. At the 39-month follow-up, diagnosis of MDD was assessed covering the period between the 12-month and 39-month follow-up. If the participant was unable to schedule the interview at the general practice, the interview was done by telephone (23% of interviews at baseline, 17% at the six-month follow-up, and 19% at the 12-month follow-up). At the 39-month follow-up, all interviews were done by telephone. Several studies have shown that both methods are comparable with respect to validity and reliability.[14]

Outcome measures

Severity of depressive symptoms

The self report Patient Health Questionnaire 9 (PHQ-9) was included with the risk factor questionnaires.[15] It assesses the presence in the past two weeks of the nine DSM-IV criteria for major depressive disorder on a 4-point rating scale, ranging from 0 (“not at all”) to 3 (“nearly every day”). The scores on this questionnaire range from 0 to 27.

Severity of somatic symptoms

Severity of somatic symptoms was assessed by the PHQ-15, which inquires about 15 somatic symptoms in the preceding four weeks: 1) stomach pain, 2) back pain, 3) pain in your arms, legs or joints, 4) menstrual cramps or other problems with your periods (women only), 5) headaches, 6) chest pain, 7) dizziness, 8) fainting spells, 9) feeling your heart pound or race, 10) shortness of breath, 11) pain or problems during sexual intercourse, 12) constipation, loose bowels, or diarrhoea, 13) nausea,

gas, or indigestion, 14) feeling tired or having low energy, and 15) trouble sleeping.[16] It uses a 3-point rating scale, ranging from 0 ("not bothered at all") to 2 ("bothered a lot"). The scores on this questionnaire range from 0 to 30.

Mental and physical function

Mental function and physical function were assessed by the Short Form 12 (SF-12 MCS and PCS).[17] The SF-12 is derived from the SF-36, both of which have been widely used in primary care settings. The SF-12 yields a scale from 0 to 100, in which lower scores indicate greater dysfunction.

Other variables

Patient characteristics were obtained at baseline using self-report questionnaires and included age, sex, employment status (employed or unemployed), marital status (living with or without a partner), educational level (11-point ordinal scale ranging from 'no education' to 'PhD-level', categorized into lower, middle, and higher level of education), number of life events (no, one, or two or more events), and presence of one or more chronic diseases diagnosed by a physician.[18] Lifetime depression was based on affirmative answers to both of the first two questions of the CIDI depression section.[19]

Data analysis

Missing data rarely occurs completely at random and a complete case analysis may lead to loss of statistical power and to biased results.[20] We therefore used multiple imputation to address missing data which were imputed at baseline, at the six-month, 12-month and 39-month follow-up separately.[21] At each time-point 10 datasets were generated and all variables mentioned above were used as predictors. We compared results obtained by analysing with and without imputation to observe the extent of imputation used.

First, baseline characteristics before imputation for participants with and without MDD were presented as means with standard deviations (SD) for continuous variables and numbers with percentages for categorical variables, and tested with F-tests (ANOVA) and the Chi-squared tests respectively. Missing data for each covariate at baseline are presented.

Second, a flowchart was created to describe the course of participants with MDD at baseline. At each assessment, we calculated the number of lost to follow-up. The flowcharts categorized participants into different courses. We defined the following three courses: 1) patients who were in remission from baseline (remitted); 2) patients who had a fluctuating MDD course (intermittent); and 3) patients who had MDD at all four assessments (chronic).

Third, for each outcome variable (PHQ-9, PHQ-15, SF-12 MCS and PCS) separate Analysis of Variance (ANOVA) analyses were performed with the scores at each assessment as dependent and the course groups as independent variable. We used ANOVA analyses to test for differences in mean symptom or function score among each course group.

Fourth, SAS PROC MIXED was used in random coefficient analyses (RCA) with robust standard errors, to estimate the change in depressive symptoms, somatic

symptoms, mental function and physical function over time for each course group. We used random intercept and slope for best model fit. The courses and time, and the interaction between course group and time were entered as independent variables and the outcome measure was entered as the dependent variable. The coefficients of interaction between the course groups and time represent the change of symptom or function over time as a function of the course group. The time between the follow-up assessments was computed for each person individually. Age, sex, education level, presence of a chronic disease, and lifetime depression were added to the models to control for potential confounding. Analyses were performed using PASW version 17 (IBM SPSS Statistics) and SAS version 9.1 (SAS institute).

Results

In total, 3089 patients were asked to take part in the study, of which 83 did not meet inclusion criteria. Seventy-five were not fluent in Dutch, five had dementia, two had psychosis and one had severe learning disabilities. Of the remaining 3006 patients, 1338 (44.5%) consented and took part in the study, while 915 (30%) actively refused. Reasons for not participating were mostly lack of time (21%, N=192) and no interest (24%, N=224). Refusal without reason was present in 249 (8%) with and 504 (16%) without demographic information. Of the 1164 refusals on whom we had demographic information, we found no difference in the age (mean 51 years, SD 19) and sex (62% female) distribution when compared to our participants. The numbers lost to follow-up throughout the study period were similar amongst participants that were depressed at baseline (74/174, 43%) and those that were not depressed (504/1164, 43%). Participants who were lost to follow-up were similar in age and sex distribution, baseline PHQ-9, PHQ-15, SF-12 MCS and PCS scores to those who were retained in the study.

Table 1: Baseline characteristics for the participants with and without major depressive disorder

	Total (N=1318)*	MDD (N=174)	No MDD (N=1144)	Missing (N)
Age in years, mean (SD)	51 (17)	46 (14)	52 (17)	0
Female, N %	828 (63)	125 (72)	703 (62)	0
Employed, N (%)	728 (58)	97 (59)	631 (58)	64
Living with partner, N (%)	967 (75)	110 (64)	857 (76)	23
Education level§, N (%)				25
– Lower	298 (23)	50 (29)	248 (22)	
– Middle	600 (46)	73 (43)	527 (47)	
– Higher	395 (31)	48 (28)	347 (31)	
Life events, N (%)				16
– No	511 (39)	39 (23)	472 (42)	
– One	359 (28)	37 (22)	322 (28)	
– Two or more	432 (33)	96 (55)	336 (30)	
Presence of a chronic disease, N (%)	558 (44)	78 (46)	480 (43)	36
Lifetime depression, N (%)	425 (34)	108 (67)	317 (29)	57
PHQ-9 score, mean (SD)	4 (5)	10 (6)	3 (4)	42
PHQ-15 score, mean (SD)	6 (4)	10 (4)	6 (4)	37
SF-12 MCS, mean (SD)	48 (11)	32 (9)	50 (9)	195
SF-12 PCS, mean (SD)	47 (10)	47 (11)	47 (10)	195

* Missing values, N=20. § Lower = No education or primary school, Middle = Secondary school, Higher = Above secondary school. MDD = Major Depressive Disorder, SD = Standard Deviation, PHQ = Patient Health Questionnaire, SF = Short Form, MCS = Mental Component Summary, PCS = Physical Component Summary.

Of the 1338 participants, 1266 (95%) participated at the six-month follow-up, and 1206 (95% of 1266) at 12-months. At 39-months, 1133 were invited to take part, because 72 withdrew from the study and one had died. Of the 1133 invited, 759 consented to take part (67%). The mean durations of follow-up in months were 5.7 (SD 0.6) at the six months follow-up, 12.0 (SD 0.6) at 12 months and 39.2 (SD 2.3) at 39-months. The cohort was mainly female (63%) and middle-aged (mean 51 years, SD 17), and most were living with a partner (75%) (Table 1).

After imputation of missing values, at baseline the prevalence of MDD over the previous six-month was 13.0% (N=174), 9.0% (N=115) at six-months and 5.5% (N=67) at 12-months. At 39-months, 11.8% (N=90) had MDD in the period between 12-month and 39-month assessment. Of the 174 participants who were depressed at baseline, 100 were followed up at all three time points (Figure 1). Forty-three percent of the participants with MDD at baseline were in remission from baseline, 40% had a fluctuating course of depression, while 17% were chronically depressed over the 39 months of the study (Table 2).

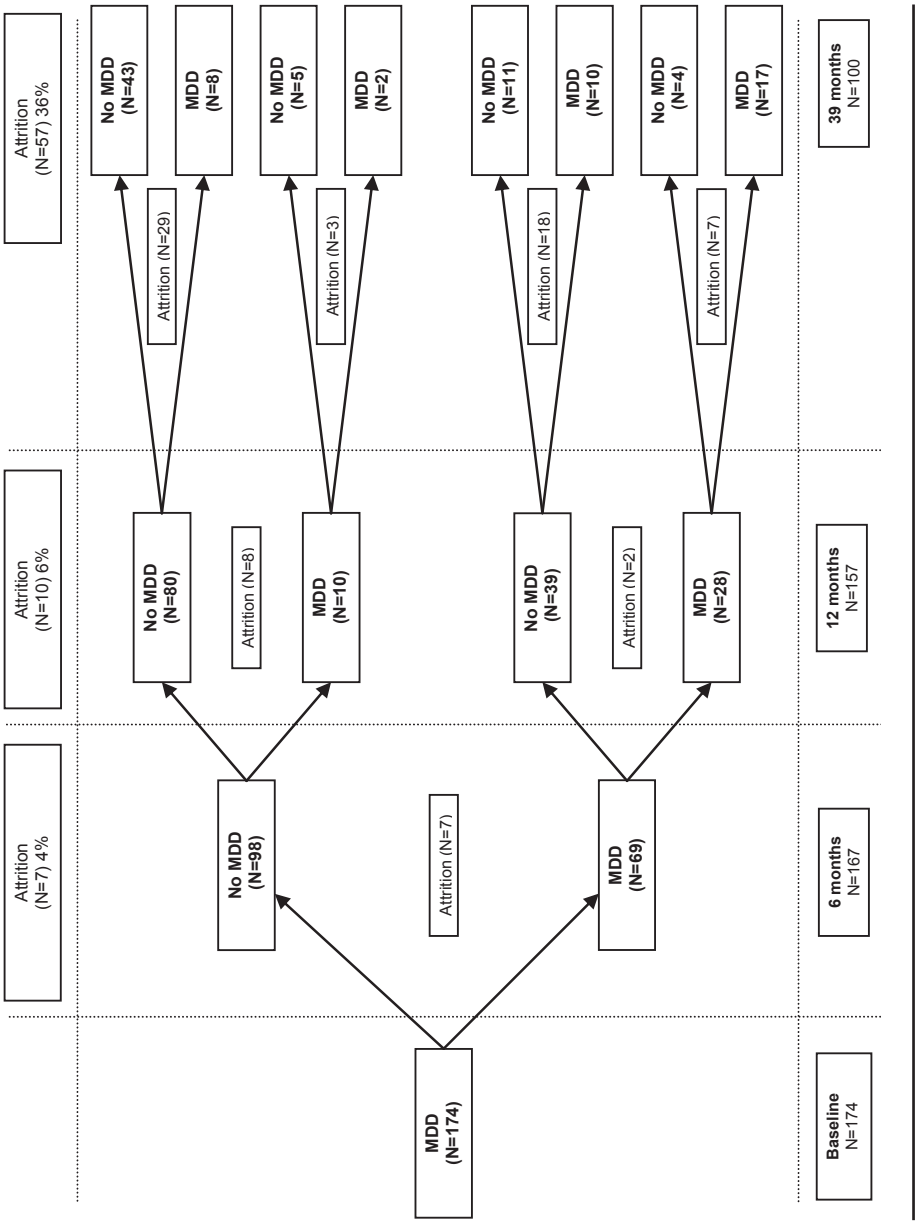


Figure 1: Flowchart with courses and attrition for participants with major depressive disorder at baseline (N=174)

Table 2: Numbers with major depressive disorder at baseline in each subgroup (N=174)

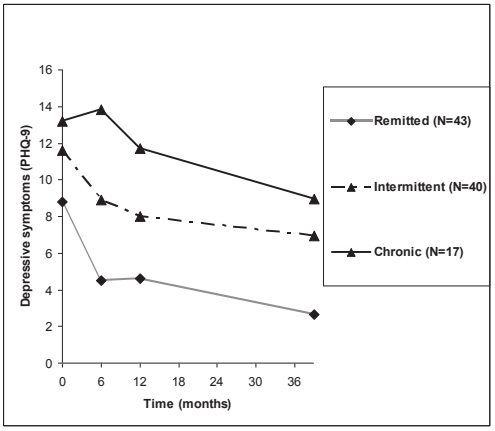
Course group	0	6	12	39	N	%
Remitted					43	43
Remitted from baseline	+	-	-	-		
Intermittent					40	40
No MDD at 39 months, intermittent course	+	-	+	-		
No MDD at 39 months, intermittent course	+	+	-	-		
No MDD at 39 months, intermittent course	+	+	+	-		
MDD at 39 months, intermittent course	+	-	-	+		
MDD at 39 months, intermittent course	+	+	-	+		
MDD at 39 months, intermittent course	+	-	+	+		
Chronic					17	17
MDD at all assessments	+	+	+	+		
Total					100	100
Lost to follow-up					74	

MDD = Major Depressive Disorder. 0, 6, 12 and 39 = Time point when assessment of MDD was made (in months). + = Presence of MDD, - = Absence of MDD.

We present unadjusted mean depressive and somatic symptom levels at each assessment for the three course groups in Figure 2 and 3, and mean mental and physical function scores in Figure 4 and 5. Participants with a chronic course of disease had a higher level of depressive and somatic symptoms and greater mental and physical dysfunction over time compared to the other courses. However, the difference of physical function among all courses over time was little. Participants who remitted from baseline had a lower level of depressive and somatic symptoms and less mental dysfunction over time when compared to the other course groups. Complete case analysis before imputation for PHQ-9 (N=75), PHQ-15 (N=79), SF-12 MCS and PCS (both N=64) revealed similar results.

Severity of depressive and somatic symptoms decreased and mental function increased over time in participants with MDD at baseline (Table 3). When compared to participants who remitted from baseline, people with a chronic course had significantly higher levels of depressive and somatic symptoms and greater mental dysfunction at baseline, after adjustment for age, sex, education, presence of a chronic disease and lifetime depression. The severity of symptoms and function for those with a chronic course did not significantly change over time compared to those who were in remission from baseline. Physical function was similar in all course groups. Analysis before imputation (N=85) for PHQ-9, PHQ-15, SF-12 MCS and PCS did affect the estimates, but did not lead to other conclusions.

Figure 2 and 3: Unadjusted mean depressive (PHQ-9, left figure) and somatic (PHQ-15, right figure) symptom scores at each assessment for each of the three courses



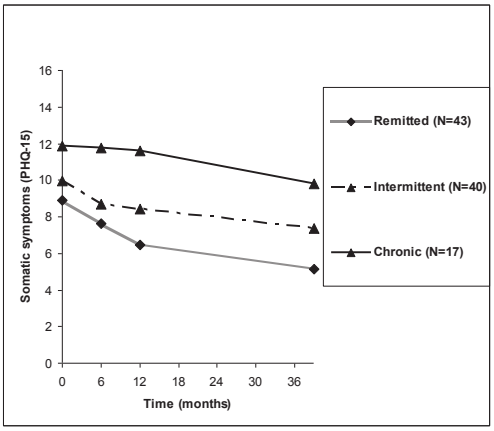
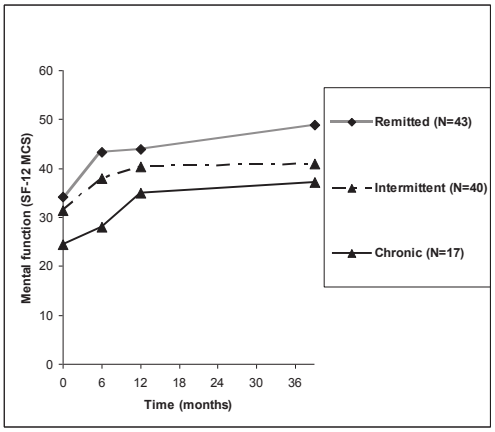
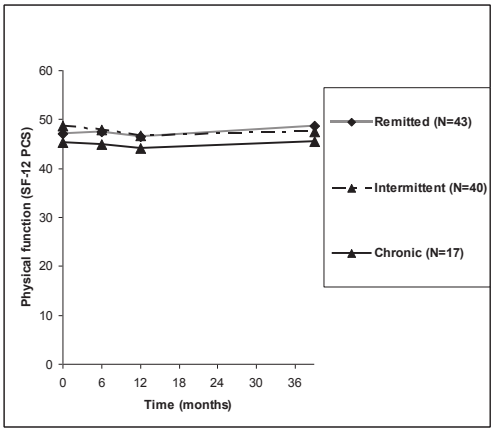


Figure 4 and 5: Unadjusted mean mental (SF-12 MCS, left figure) and physical (SF-12 PCS, right figure) function scores at each assessment for each of the three courses





Discussion

Our study examined the natural course and outcome of major depressive disorder in adult primary care attendees. We observed that 17% of participants with MDD at baseline continued to be depressed after 39 months, and another 40% had a fluctuating course of depression, while 43% were in remission from baseline. Participants with a chronic course of MDD had more depressive and somatic symptoms and greater mental dysfunction at baseline, independent of age, sex, level of education, presence of a chronic disease, and lifetime depression compared to those who remitted from baseline.

To our knowledge, this is one of the few observational studies on the natural course of MDD in primary care attendees with a medium-term follow-up and more than two assessments. Previous work is mainly restricted to specialty mental health care clinics or general population samples despite the fact that most people with depression and anxiety are managed in primary care.[22] Unlike previous research our study had a relatively long follow-up period during which we conducted several assessments. Furthermore, we had a medium-sized sample of 174 persons with MDD at baseline which we diagnosed using DSM-IV criteria rather than relying on cross-sectional questionnaires.

However, our study was limited by low response rates at baseline, although similar participation rates have been found in other observational studies in primary care.[10, 23] This could be partly explained by the fact that people were recruited to the study by researchers in the waiting room rather than by the consulting physicians. Given the relatively high prevalence of MDD at baseline, it is possible that persons with MDD were more willing to participate. Nevertheless, loss to follow-up was extremely low during the first 12 months, and during the entire follow-up period loss to follow-up in those depressed or not depressed at baseline was similar. Second, the time between 12 and 39 months was longer than in between the other assessments. Consequently, participants were asked about their symptoms retrospectively in the preceding two years and three months during the final follow-up, which might have been less reliable than for the other follow-up assessments. Third, since we did not have data on treatments received for depression we could not analyse the influences of these on the course of the illness. Nevertheless, these results still reflect the longitudinal history of MDD in people seen in general practice over time. Fourth, primary care is not uniformly organised in all countries so these findings might not be generalizable to all countries.

The majority of participants who were diagnosed with MDD at baseline had an intermittent or chronic course of disease. Our findings are concordant with several community-based studies with follow-up durations ranging from two to forty-nine years in adults diagnosed with MDD showing that about 20% developed a chronic course and about 30-50% had a recurrent course.[24-29] Our findings suggest that the natural history of depression in primary care resembles that of depression in the general adult population.

Table 3: Random coefficient analyses for all course groups and outcome variables‡ (N=100)

	PHQ-9		PHQ-15		SF-12 MCS		SF-12 PCS	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Intercept	2.90	-0.69 to 6.49	4.97	1.13 to 8.81	45.46	38.81 to 52.12	53.48	41.42 to 65.54
Time†	-0.12	-0.16 to -0.08	-0.09	-0.11 to -0.06	0.29	0.19 to 0.39	0.04	-0.05 to 0.14
Remitted (ref)	0		0		0		0	
Intermittent	3.23	1.49 to 4.98	0.83	-0.44 to 2.10	-2.97	-6.34 to 0.40	1.28	-2.51 to 5.10
Chronic	6.54	4.38 to 8.70	3.31	1.61 to 5.02	-10.49	-14.42 to -6.57	-0.87	-5.70 to 3.97
Time*Remitted (ref)	0		0		0		0	
Time*Intermittent	0.03	-0.03 to 0.09	0.03	-0.01 to 0.06	-0.11	-0.26 to 0.04	-0.06	-0.19 to 0.06
Time*Chronic	-0.01	-0.08 to 0.07	0.03	-0.04 to 0.09	0.01	-0.17 to 0.18	-0.02	-0.19 to 0.14
Female	1.62	0.44 to 2.79	2.31	1.06 to 3.55	-2.61	-4.70 to -0.52	-2.13	-5.83 to 1.58
Chronic disease present	2.51	1.38 to 3.65	2.77	1.69 to 3.84	-3.69	-5.83 to 1.54	-7.29	-10.54 to -4.03

‡ Models are adjusted for age, sex, education, presence of a chronic disease, and lifetime depression. Age, education and lifetime depression were not statistically significant and are therefore not presented. † Time is in months between individual assessments.
β = Estimates of the difference in mean symptom or function score for each course group compared to the remitted group.
CI = Confidence interval, PHQ = Patient Health Questionnaire, SF = Short Form, MCS = Mental Component Summary, PCS = Physical Component Summary.

Fifty-seven percents of patients diagnosed with MDD at baseline had not recovered after 39 months, which is consistent with findings from a study in primary care with three assessments, where 53% of the adult population diagnosed with MDD at baseline had not recovered after 3.5 years, in which partial remission rather than full recovery was the rule.[5, 30] Two methodological differences between their study and the present study are noteworthy. First, the latter study used a two-stage design in which consecutive primary care attendees were screened on psychiatric illness by their consulting physicians and by the researchers using the General Health Questionnaire (GHQ). Subsequently, a stratified random sample was selected for the baseline examination on basis of the outcome of this GP and GHQ screening. In our study, consecutive primary care attendees were included irrespective of their reasons for consulting the GP. Second, those who were included in the study by Ormel et al were diagnosed using the Present State Examination (PSE), while we diagnosed MDD using the CIDI. Disability was measured by the Groningen Social Disability Schedule (SDS) in their study compared to the SF-12 used in our study. We have built on their study by including a larger sample of primary care attendees, who were included irrespective of their reason for consultation. Although the methods employed in our study were somewhat different, the results were generally comparable and support the finding that the majority of those diagnosed with MDD have a poor course. Seventeen percent in our study had MDD at all assessments, which is lower than results from a primary care study of 160 patients diagnosed with MDD at baseline, of which 32% had not recovered at three years.[31] However, the latter study was performed in a sample of older people making direct comparisons difficult. Recent primary care based studies revealed that about 50% of depressed adolescents failed to recover after six months, while 74% of depressed adults had not recovered after 18 months.[6, 32] In addition, the recurrence rate of primary care depression may be up to 64% over a period of 23 years.[33]

Participants with a chronic course had more depressive and somatic symptoms and greater mental dysfunction at baseline than those remitted from baseline. Baseline severity of depression is a risk factor for persistence in the short-term, as shown by other studies, but our findings suggest that it is also a risk factor for persistence in the medium-term, even independent of a depression history.[34, 35] The latter has also recently been shown by a primary care study which followed recurrent depressive patients for three years, and our results underline these findings.[36] The study by Ormel et al reported that patients with depression who had higher levels of disability improved considerably over time, although residual disability was present in some cases.[5] A relationship between somatic symptoms and depression, and between mental dysfunction and depression severity has been found in cross-sectional studies in primary care, but our results add to the current knowledge that high levels of somatic symptoms and greater mental dysfunction at baseline are a risk factor for persistence of depression over 39 months.[37, 38] Within the chronic group, the level of depressive and somatic symptoms and mental functioning did not change over time compared to those who remitted from baseline, suggesting that those who are depressed and have higher symptom levels or lower levels of function at baseline are likely to persist in higher levels of symptoms and lower levels of function over the course of 39 months.

Findings from the current study suggest that for those attending primary care, a higher severity of depressive or somatic symptoms, or lower levels of mental function may be an indication of a poor course of MDD. The pattern of depressive and somatic symptoms over time for the course groups was similar to the pattern of mental function over time, which may suggest that depressive symptoms, somatic symptoms and mental function are related. Since we did not have premorbid functioning data available, we were unable to determine whether trait or scar effects were present.[39] Although we cannot confirm the presence of a state effect within the course groups, as all participants improved significantly over time, synchrony of change between severity of depressive symptoms and severity of mental function may be present.[39, 40] Moreover, it is possible that synchrony of change between the severity of somatic symptoms and severity of mental function also exists. Therefore, depressive and somatic symptoms and mental function have to be monitored closely in primary care patients diagnosed with MDD as such surveillance could assist in the management and possible prevention of chronic depression.

The results of this study suggest that although 43% of patients with MDD attending primary care recover, this leaves a majority of patients (57%) who have a chronic or intermittent course. Persistence or chronicity of MDD is associated with the severity of depressive and somatic symptoms and mental dysfunction at baseline.

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Chapter 2.2

Depression, anxiety and physical dysfunction: exploring the strength of causality

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Anxiety is the hand maiden of creativity.

T.S. Eliot
American born English editor and poet, 1888-1965

Abstract

Background

Depression, anxiety and physical function may be bi-directionally related. We aim to estimate the strength of the longitudinal associations between depression, anxiety, and physical function.

Methods

Prospective cohort study of general practice attendees across Europe (N=4757) assessed at baseline, 6, 12 and 24 months. Main outcome measures were DSM-IV major depression, Patient Health Questionnaire anxiety, and Short Form 12 physical function. Complete case analyses using random coefficient models and logistic regression models were performed.

Results

Those with depression (β=-1.90; 95% CI -3.42 to -0.39), anxiety (β=-4.12; 95% CI -5.39 to -2.86) or depression and anxiety (β=-5.74; 95% CI -7.38 to -4.10) had lower levels of physical function at baseline and over time compared to no diagnosis after adjustment for potential confounders. Physical function increased over time, but the rate of increase was not different between the groups. When compared to depression, those with anxiety (β=-2.22; 95% CI -4.08 to -0.36) or depression and anxiety (β=-3.83; 95% CI -5.95 to -1.71) had significantly lower levels of physical function at baseline. Lower levels of physical function at baseline were associated with onset of depression (OR 1.83; 95% CI 1.08 to 3.10), but even stronger with anxiety (OR 2.79; 95% CI 1.52 to 5.12) or depression and anxiety (OR 5.05; 95% CI 2.55 to 9.99) during 24 months compared to no dysfunction, after adjustment for potential confounders.

Conclusion

It is essential to prevent lower levels of physical function as this is likely to lead to onset of depression and anxiety over time.

Introduction

Depression, anxiety and lower levels of physical function may often occur together. Although a large number of studies examined the relation between depression and functioning, the relationship to anxiety and to coexisting depression and anxiety is less well researched.[1-12] In particular, few studies have examined the temporal relationship between lower levels of physical function and anxiety or coexisting depression and anxiety.

Lower levels of physical function refer to limitations in performing normal activities of daily living (ADL) such as personal hygiene and eating, or instrumental activities of daily living (IADL) which include more complex tasks such as preparing meals and doing housework. This type of function is characterized by an inability to perform physical activities and is different from lower levels of social or mental function.[13] Previous studies suggest that there is a relationship between depression and lower levels of physical function and, to a lesser extent, between anxiety and lower levels of physical function.[14, 15] A recent review proposed that the mechanisms by which depression may lead to lower levels of physical function can be placed in two groups.[13] One theory suggests that the depressed or anxious state itself leads to lower levels of function, while the other theory suggests that depression decreases the level of function from other medical conditions or disorders. On the other hand, it has been suggested that lower levels of physical function can affect perceptions of control and self-esteem leading to some loss of social support and isolation[16, 17], which in turn can lead to a higher level of depressive and anxiety symptoms. This may result in onset of depression and anxiety over time. Two recent adult population based studies showed an association between lower levels of physical function and both anxiety and depressive symptoms across the lifespan. As their design was cross-sectional the direction of causality was not determined.[10, 18]

We aimed to test for longitudinal associations between depression, anxiety and lower levels of physical function in both directions. As comorbidity is related to symptom severity and degree of impairment[19], it could be that persons with depression and anxiety together have lower levels of physical function at baseline and over time compared to persons with depression alone. On the other hand, lower levels of physical function may be more likely to lead to onset of both depression and anxiety compared to onset of depression alone, as it could be that persons may experience greater loss of social support and more isolation in the presence of lower levels of physical function.

First, we examined how depression and anxiety alone or together at baseline relate to physical function over 24 months, and if persons with both depression and anxiety at baseline have lower levels of physical function at baseline and over time than persons with depression alone at baseline. Second, we examined whether people with lower levels of physical function at baseline are more likely to develop depression, anxiety, or both depression and anxiety over 24 months.

Subjects and methods

Study setting and design

PredictD is a multicenter prospective cohort study from which a multifactor algorithm was developed to predict risk of onset of major depressive disorder in 6 European countries and Chile. The study is described in greater detail elsewhere and was approved by ethical committees in each participating country.[20-22] The current analysis used data from four countries: 1) 25 general practices in the Medical Research Council's General Practice Research Framework, in the United Kingdom; 2) nine large primary care centres in Andalucía, Spain; 3) two large primary care centres, one in the Lisbon area (urban) and the other in Alentejo (rural), Portugal; and 4) 74 general practices nationwide in Slovenia. The general practices taking part extend over urban and rural settings in each country and populations with considerable socio-economic and ethnic variation.

Study participants

Consecutive attendees aged 18 to 75 were recruited and interviewed between April 2003 and September 2004. Of the original predictD cohort that was followed up at 6 and 12 months, we only included the UK, Spain, Portugal and Slovenia, because in these countries further funding became available for a third follow-up interview between April and November 2005, 24 months after entry into the study. Exclusion criteria were an inability to understand one of the main languages involved or psychosis, dementia or other severe illness. Recruitment differed slightly in each country because of local service preferences. In the UK, researchers approached patients waiting for consultations, whereas in the other countries doctors first introduced the study before contact with the research team. All participants gave written informed consent and undertook a research evaluation within two weeks.

Measures

Physical function was assessed by the Short Form 12 (SF-12) at baseline, 6 and 24 months, which yields a physical component summary scale (PCS).[23] The self-report form includes 12 questions and is derived from the longer SF-36, both of which have been widely used.[24, 25] Lower scores indicate lower levels of physical function.

Psychiatric diagnoses and syndromes

Diagnosis of major depressive disorder (MDD) in the preceding 6 months at baseline, 6, 12 and 24 months was assessed in all patients according to DSM-IV criteria using the depression section of the Composite International Diagnostic Interview (CIDI).[26, 27] Anxiety and panic syndromes in the preceding 6 months were assessed at baseline, 6 and 24 months using the Patient Health Questionnaire (see also Appendix A).[28]

Other variables

Age, sex, marital status, education, country, employment status, financial strain, whether or not participants were born in the country of residence and ethnicity were assessed using self-report questionnaires at baseline. Marital status was defined as

(not) married or living with a partner. Higher education as secondary school or higher, while lower education included primary school, trade or no education. Ethnicity was defined as whether or not a person had an European ethnicity. Financial strain was a single question commonly used in government and other UK social surveys.[29] A lifetime history of depression was based on affirmative answers to both of the first two questions of the CIDI depression section.[30]

Data analysis

To examine the relationship between depression and/or anxiety at baseline and physical function over time as outcome we defined 4 groups at baseline: 1) No diagnosis, participants without either diagnoses; 2) Depression only, participants with a MDD diagnosis; 3) Anxiety only, participants with a panic syndrome and/or other anxiety syndrome; 4) Depression and anxiety, participants with a MDD diagnosis, and a panic syndrome or other anxiety syndrome. Baseline characteristics for the four groups were presented as means with standard deviations (SD) for continuous variables and numbers with percentages for categorical variables. Differences between the four groups were tested with F-tests (ANOVA) for continuous and with the Chi-squared tests for categorical variables. In model 1, we used SAS PROC MIXED random coefficient analyses (RCA), to estimate the change in physical function over time for each diagnostic group. We used a random intercept model to allow for dependence between measurements made on the same individual. The diagnostic groups variable and time, and the interaction between the diagnostic groups variable and time were entered as independent variables and physical function over time was entered as the dependent variable. The coefficients of interaction between the groups and time represent the difference in slopes of physical function over time between the reference group and the diagnostic groups at baseline. In model 2, we added age, sex, marital status, education, lifetime depression, employment status, financial strain, whether or not they were born in the country of residence and whether they had European ethnicity to the model to control for potential confounding. We also stratified our results by country.

To examine the relationship between physical function at baseline and the onset of depression and/or anxiety over time, we examined new diagnoses of depression at 6, 12 and 24 months and of anxiety at 6 and 24 months (no assessment for anxiety was made at 12 months). We restricted our analyses to participants without depression or anxiety at baseline. We fitted a multinomial logistic regression model with four outcome categories: 1) No onset of depression or anxiety during 24 months, the reference category; 2) Onset of depression only during 24 months follow-up; 3) Onset of anxiety only during 24 months follow-up; and 4) Onset of both depression and anxiety during 24 months follow-up. We categorized baseline PCS score into four categories for better interpretation: no dysfunction (>49), mild dysfunction (40-49), moderate dysfunction (30-39), and severe dysfunction (<30).[31] Age, sex, marital status, education and lifetime depression were added as a priori confounders. Also, employment status, financial strain, whether or not participants were born in the country of residence and ethnicity were added to the models. In a subsequent analysis, onset of depression only was used as the reference category. We also stratified our results by country. All analyses were complete-case analysis, because missing data were few. We report exponentiated coefficients from the

multinomial logistic regression models (often referred to as multinomial odds ratios or relative risk ratios). These parameter estimates approximate risk ratios since the reference category (no diagnosis) is considerably more common than the other categories. Analyses were performed using PASW version 17 (IBM SPSS Statistics) and SAS version 9.2 (SAS institute).

Results

Response

In the four countries 4905 people took part. Response to recruitment was high in Spain (87%), Portugal (76%) and Slovenia (80%) but lower in the UK (44%). Ethical constraints prevented the collection of data on non-responders at baseline. 148 people were excluded because they had missing data on MDD diagnosis or anxiety syndromes at baseline leaving a sample of 4757 participants. The majority, 3729 (78%), had no diagnosis, 291 (6%) had depression only, 422 (9%) had anxiety only, and 315 (7%) had depression and anxiety. Missing data for each covariate at baseline were less than 1%.

Characteristics of the diagnostic groups

Participants with any disorder or syndrome were more likely to be younger and to be women than those with no diagnosis (Table 1a). Moreover, depressed participants with or without anxiety were less likely to be married or living with a partner than those with no disorder. Lower education was most common in individuals with anxiety only (59% versus 48% for those with no diagnosis). PCS scores were lower for individuals with a disorder or syndrome, with the lowest scores occurring in those with anxiety and those with both depression and anxiety (mean PCS score 38 for both groups). When we stratified the results by country, we found that rates of depression and anxiety were the lowest in Slovenia and the highest in Spain, while persons in Slovenia generally had the lowest level of physical function in all diagnostic groups (Table 1b).

Response to follow-up

The follow-up at 6 and 12 months was 4200 (88%), and 4006 (84%) respectively. At 24 months valid SF-12 scores data were available on 3114 (65%) people. Similar proportions of people in each diagnostic group were lost to follow-up (Table 2), although some differences between the countries were present. For those lost to follow-up in each diagnostic group there were no significant differences on age, sex or baseline PCS scores from those that participated. The exception being those without a diagnosis of either depression or anxiety at baseline, who were younger than those who were retained in the study (48 versus 52 years, $p<0.001$).

Table 1a: Baseline characteristics of the diagnostic groups

	Total (N=4757)	No diagnosis (N=3729)	Depression only (N=291)	Anxiety only (N=422)	Depression and anxiety (N=315)	P-value	Missing (N)
Age in years, mean (SD)	50 (15)	51 (15)	47 (15)	50 (14)	47 (13)	<0.001	7
Sex, N (%)						<0.001	0
– Female	3186 (67)	2388 (64)	220 (76)	332 (79)	246 (78)		
– Male	1571 (33)	1341 (36)	71 (24)	90 (21)	69 (22)		
Marital status§, N (%)						0.005	6
– No	1348 (28)	1019 (27)	97 (33)	121 (29)	111 (35)		
– Yes	3403 (72)	2704 (73)	194 (67)	301 (71)	204 (65)		
Education level†, N (%)						<0.001	24
– Lower	2334 (49)	1775 (48)	153 (53)	248 (59)	158 (51)		
– Higher	2399 (51)	1936 (52)	137 (47)	172 (41)	154 (49)		
SF-12 Score‡, mean (SD)						<0.001	0
– PCS	43 (11)	44 (11)	42 (11)	38 (11)	38 (12)		
Unemployed, N (%)	2516 (53)	1941 (52)	148 (51)	250 (59)	177 (56)	0.02	9
Financial strain, N (%)	1121 (24)	696 (19)	114 (39)	163 (39)	148 (47)	<0.001	8
Not born in country of residence, N (%)	402 (9)	326 (9)	24 (8)	33 (8)	19 (6)	0.39	11
Non-European ethnicity, N (%)	69 (2)	57 (2)	4 (1)	5 (1)	3 (1)	0.83	50

§ Marital status = (not) Married or living with partner † Higher education = Secondary school or higher. Lower education = Primary school, trade, no education or other ‡ SF = Short Form. PCS = Physical Component Summary

Mental health related to physical health

Participants with depression only (β=-1.90; 95%CI -3.42 to -0.39), anxiety only (β=-4.12; 95%CI -5.39 to -2.86), or both (β=-5.74; 95%CI -7.38 to -4.10), all had lower levels of physical function at baseline than participants with no diagnosis, after adjustment for potential confounders (Table 3 & Figure 1). Physical function significantly increased over time for all diagnostic groups. However, the rate of increase of physical function for those with psychopathology at baseline was not significantly different from those who had no diagnosis at baseline. When compared to depression only, those with anxiety only (β=-2.22; 95%CI -4.08 to -0.36) or depression and anxiety (β=-3.83; 95%CI -5.95 to -1.71) had lower levels of physical function at baseline. After 24 months, those with depression and anxiety still had the lowest level of physical function. The results were similar when we stratified by country (data available on request).

Table 1b: Baseline characteristics of the diagnostic groups, stratified by country

	Total (N=4757)	**No diagnosis (N=3729)**	**Depression only (N=291)**	**Anxiety only (N=422)**	**Depression and anxiety (N=315)**
N, %					
UK	1273	991 (78)	73 (6)	112 (9)	97 (8)
Spain	1213	867 (72)	78 (6)	140 (12)	128 (11)
Slovenia	1099	969 (88)	42 (4)	66 (6)	22 (2)
Portugal	1172	902 (77)	98 (8)	104 (9)	68 (6)
Age in years, mean (SD)					
UK	51 (15)	52 (15)	48 (15)	50 (15)	48 (13)
Spain	50 (16)	51 (16)	45 (15)	51 (13)	47 (15)
Slovenia	49 (15)	49 (15)	48 (14)	52 (12)	47 (11)
Portugal	50 (15)	51 (16)	46 (16)	47 (13)	48 (13)
Female, %					
UK	67	66	64	73	69
Spain	70	66	80	85	90
Slovenia	63	62	69	70	77
Portugal	67	63	84	82	87
SF-12 PCS Score, mean (SD)					
UK	46 (12)	46 (11)	43 (12)	43 (12)	43 (14)
Spain	42 (12)	44 (11)	43 (11)	35 (11)	35 (11)
Slovenia	42 (11)	43 (11)	37 (10)	36 (10)	31 (11)
Portugal	43 (11)	44 (10)	42 (11)	40 (10)	38 (10)

Table 2: Baseline characteristics comparison of those who retained and those who were lost to follow-up within each group at baseline (N=4757)

	No diagnosis (N=3729)		**Depression only (N=291)**		**Anxiety only (N=422)**		**Depression and anxiety (N=315)**	
	Retained	Lost	Retained	Lost	Retained	Lost	Retained	Lost
Number, N (%)	2461 (66)	1268 (34)	175 (60)	116 (40)	285 (68)	137 (32)	193 (61)	122 (39)
Age in years, mean (SD)	52 (15)	48 (15)	47 (15)	46 (16)	51 (13)	48 (15)	47 (13)	47 (14)
Sex, N (%)								
– Female	1603 (65)	785 (62)	137 (78)	83 (72)	228 (80)	104 (76)	154 (80)	92 (75)
– Male	858 (35)	483 (38)	38 (22)	33 (28)	57 (20)	33 (24)	39 (20)	30 (25)
SF-12 Score, mean (SD)								
– PCS	44 (11)	44 (11)	41 (11)	42 (11)	39 (11)	38 (11)	38 (12)	38 (12)
Country								
– UK	710 (72)	281 (28)	40 (55)	33 (45)	79 (71)	33 (30)	63 (65)	34 (35)
– Spain	444 (51)	423 (49)	43 (55)	35 (45)	82 (59)	58 (41)	68 (53)	60 (47)
– Slovenia	660 (68)	309 (32)	30 (71)	12 (29)	49 (74)	17 (26)	13 (59)	9 (41)
– Portugal	647 (72)	255 (28)	62 (63)	36 (37)	75 (72)	29 (28)	49 (72)	19 (28)

Physical health related to onset of depression and anxiety

Of the 3729 participants without depression or anxiety at baseline, 2461 participants remained in the study at 24 months (Table 2). 2319 had complete data on all covariates of whom 144 (6%) had an onset of depression, 108 (5%) of anxiety and 86 (4%) of both. We observed that moderate levels of dysfunction were associated with onset of anxiety (OR 1.94; 95%CI 1.10 to 3.42) and both depression and anxiety (OR 2.77; 95%CI 1.44 to 5.33) during 24 months compared to no dysfunction, after adjustment for age, sex, marital status, education and a lifetime history of depression (Table 4). The results were similar when other confounding factors were added to the models (data available on request). Severe levels of physical dysfunction at baseline were associated with onset of depression (OR 1.83; 95%CI 1.08 to 3.10), anxiety (OR 2.79; 95%CI 1.52 to 5.12), and both depression and anxiety (OR 5.05; 95%CI 2.55 to 9.99). Those with severe levels of physical function were at greater risk of onset of both depression and anxiety compared to depression alone (OR 2.76; 95%CI 1.21 to 6.33). When we stratified by country, the results were similar (data available on request).

Discussion

To our knowledge, this is one of the few large scale studies to examine the temporal relationship between both depression and anxiety, and physical function. We observed that those with depression and anxiety together at baseline had lower levels of physical function at baseline as well as over time compared to those with depression alone, after adjustment for confounders. Although the level of physical function increased over time for all groups, the rate of increase was not different between the groups. On the other hand, lower levels of physical function at baseline were associated with onset of depression and anxiety alone but especially with onset of depression and anxiety together within the following 24 months.

The main strength of our study was our ability to examine both directions of association between depression and anxiety, and physical function. Our European cohort was large and our diagnosis of MDD adhered to DSM-IV criteria. Similarly, our definitions of anxiety and panic syndromes were based on DSM-IV criteria.

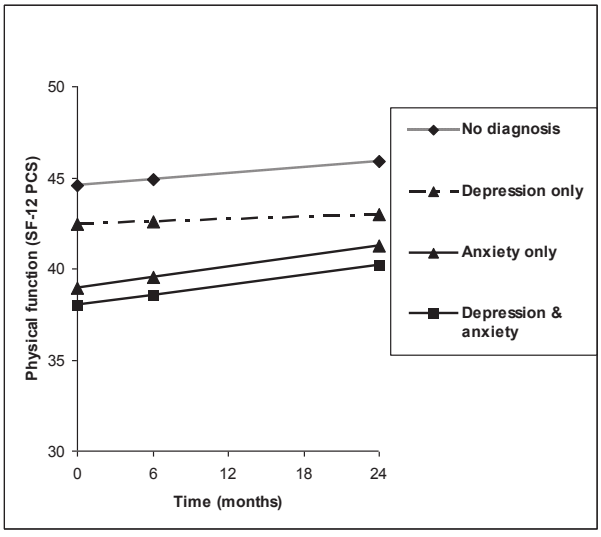
Our study was limited by the lower response to recruitment in the UK, which possibly occurred because the study was not endorsed by family doctors compared with the other countries. We cannot rule out the possibility that response affected measured prevalence within any one country. However, the lack of any clear association between prevalence of common mental disorders and response to the study seems to rule out the possibility that a low response might have led to a systematic bias.[21] Our study was based on general practice attendees and not on a probabilistic sample recruited in the community.[20] However, most people with depression and/or anxiety visit their GP, although many will not complain of depression or anxiety and nor will their disorder be recognized. Thus the epidemiology of these disorders in general practice closely mirrors that seen in the community, with the caveat that prevalence rates are usually higher in the former. There were also differences in the geographical distribution of participating general practices in each country. The general practices taking part extend over urban and rural settings in each country and populations with considerable socio-economic and ethnic variation.[20]

Table 3: Complete case analyses using random coefficient models with physical function score over time as dependent and the diagnostic categories at baseline as independent variable (N=3029)

	Physical function score over time as outcome			
	Model 1		Model 2§	
	β	95% CI	β	95% CI
Intercept	44.56	44.14 to 44.97	48.30	45.00 to 51.60
No diagnosis (ref)	0		0	
Depression only	-2.11	-3.81 to -0.42	-1.90	-3.42 to -0.39
Anxiety only	-5.58	-6.96 to -4.21	-4.12	-5.39 to -2.86
Depression & anxiety	-6.55	-8.31 to -4.78	-5.74	-7.38 to -4.10
Time	0.06	0.04 to 0.07	0.06	0.04 to 0.07
Time * Depression only	-0.04	-0.10 to 0.02	-0.04	-0.10 to 0.02
Time * Anxiety only	0.04	-0.02 to 0.09	0.04	-0.02 to 0.10
Time * Depression & Anxiety	0.03	-0.03 to 0.10	0.04	-0.03 to 0.10

β = Estimates of the mean physical function for each diagnostic group compared to the reference group (no diagnosis)
Beta is the regression coefficient associated with each variable. For the diagnostic groups this represents the difference in mean compared to no diagnosis at baseline. For time, the coefficient represent the slope in the no diagnosis group, and for the interaction terms it is the difference in slopes between the reference group and diagnostic group.
CI = Confidence Interval ‡ Higher education = secondary school or higher. Lower education = primary school, trade or no education
§ Adjusted for age, sex, marital status, level of education, a lifetime history of depression, employment status, financial strain, whether or not they were born in the country of residence and whether they had European ethnicity.

Figure 1: Physical function over time for the diagnostic categories at baseline (crude)



However, the structure and function of the primary care health service in each country is very similar in that all have a system of national healthcare provision whereby access to general practice care is free to all.[21] Also, we have adjusted our analyses for demographic factors that are associated with attendance behaviour, as well as prevalence of common mental disorders and similar patterns were seen in all countries. Another limitation was that depression and anxiety were assessed retrospectively for the 6 months prior to each interview. Thus, although participants were followed up at 6, 12 and 24 months, the CIDI only enquired about depression and the PHQ only about anxiety in the 6 months preceding that follow-up point. Moreover, at 12 months no assessment was made for anxiety. We were unable to capture the onset of depression in the 12 to 18 months period and anxiety in the 6 to 18 months after recruitment. This will have resulted in an underestimation of the incidence of these disorders. Unfortunately, since we did not have data on lifetime anxiety we could not analyse the influences on the relationship between depression, anxiety and physical function over time.

The temporal relationship between depression, anxiety and lower levels of physical function is in concordance with previous studies. Prospective community studies have shown a relationship between depression and lower levels of physical function, and to lesser extent, between anxiety and lower levels of physical function.[32-35] Few studies have simultaneously examined both depression and anxiety in relation to physical function. In two cross-sectional studies of adults, both depressive and anxiety symptoms were independently associated with lower levels of physical function.[10, 18] We are one of the first to show that adults with both depression and anxiety have lower levels of physical function at baseline as well as over time than adults with only depression. Physical function increased over time in all groups, but the rate of increase was not different between the diagnostic groups at baseline. This may suggest that the difference in physical function for all diagnostic groups remains fairly stable over time. It could also be that the study duration was too short to observe differences in the rate of change. It is likely that those with coexisting depression and anxiety have a higher level of symptoms than those with either diagnosis. This increased level of symptoms may lead to lower levels of physical function over time.[7] However, it could also be that depression and anxiety may have had an effect on physical function before entry into the study. Since we did not have premorbid functioning data available, we were unable to determine whether state, trait or scar effects were present.[1]

Lower levels of physical function at baseline may lead to onset of depression during follow-up, as shown by some studies.[15, 36, 37] However, the effects of lower levels of physical function on anxiety and coexisting depression and anxiety over time are less well researched. We found that lower levels of physical function were associated with anxiety alone over two years, but even stronger with both depression and anxiety. It has been suggested that lower levels of physical function can affect perceptions of control and self-esteem leading to some loss of social support and isolation.[16, 17] This in turn could result in a higher level of depressive and anxiety symptoms which may result in depression or anxiety over time.

Table 4: Complete case analyses using multinomial logistic regression models with onset of depression or anxiety at 6, 12 or 24 months as dependent and baseline PCS categories as independent variable in non-depressed or anxious participants at baseline (N=2319)

	Depression only (N=144)	Anxiety only (N=108)	Depression & anxiety (N=86)
	Odds ratio (CI)	Odds ratio (CI)	Odds ratio (CI)
No dysfunction (ref)*	1	1	1
Mild dysfunction*	1.11 (0.69 to 1.77)	1.72 (0.99 to 2.97)	2.02 (1.04 to 3.90)
Moderate dysfunction*	1.36 (0.85 to 2.18)	1.94 (1.10 to 3.42)	2.77 (1.44 to 5.33)
Severe dysfunction*	1.83 (1.08 to 3.10)	2.79 (1.52 to 5.12)	5.05 (2.55 to 9.99)
Age	0.99 (0.98 to 1.00)	1.00 (0.98 to 1.01)	0.99 (0.98 to 1.01)
Sex (female)	1.35 (0.92 to 2.00)	1.28 (0.82 to 2.00)	1.58 (0.93 to 2.69)
Married / living with a partner	0.91 (0.62 to 1.35)	0.92 (0.58 to 1.44)	1.20 (0.75 to 1.93)
Education (lower)‡	1.61 (1.13 to 2.30)	1.39 (0.92 to 2.08)	0.99 (0.63 to 1.55)
Lifetime history of depression	2.49 (1.76 to 3.52)	2.64 (1.78 to 3.93)	2.82 (1.80 to 4.40)

Note: the diagnostic categories are compared with no onset of depression or anxiety. All analyses are adjusted for age, sex, marital status, education level and a lifetime history of depression. CI = Confidence Interval

* Categories of dysfunction according to PCS score: No (>49), Mild (40-49), Moderate (30-39), Severe (<30)

‡ Higher education = secondary school or higher. Lower education = primary school, trade or no education

The current findings suggest that the difference in physical function between the baseline diagnostic groups may be due to an effect in the opposite direction. The level of physical function improved over time for all diagnostic groups at baseline but the rate of change was not different between the groups. This may suggest that the depressed or anxious state itself does not lead to lower levels of physical function over time, as suggested by previous work.[13] On the other hand, we found that lower levels of physical function are likely to lead to both depression and anxiety. Therefore, it is possible that persons who had depression and anxiety at baseline, already had lower levels of physical function before entry into the study resulting in the onset of depression and anxiety, which we measured at baseline.

The findings from the present study should be interpreted in the light of current debates in the literature regarding the co-morbidity between depression and anxiety.[38] Two main models have been proposed to describe the nature of the relationship between depression and anxiety. The first model by Clark and Watson depicts that depression and anxiety are separate constructs with shared factors.[38-40] The second model describes depression and anxiety as manifestations of the same underlying disease.[38, 41] On basis of the current data we cannot confirm either theory. However, one may argue that anxiety contributes the most in the relationship to lower levels of physical function when compared to depression. Moreover, our results suggest that those with the lowest levels of physical function carry the largest risk of onset of both depression and anxiety over time. This underlines the finding that synchrony of change between psychopathology and dysfunction may be present.[7, 11]

In conclusion, for those with lower levels of physical function a focus on the prevention of depression and anxiety in the long term is recommended. It is essential to prevent lower levels of physical function as this is likely to lead to onset of depression and anxiety over time.

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APPENDIX A

PHQ Anxiety section

Part 1

Possible answers: yes or no.

- In the last 4 weeks, have you had an anxiety attack / suddenly feeling fear or panic?
- Has this ever happened before?
- Do some of these attacks come suddenly out of the blue - that is, in situations where you don't expect to be nervous or uncomfortable?
- Do these attacks bother you a lot or are you worried about having another attack?

Part 2

Think about your last bad anxiety attack. Possible answers: yes or no.

- Were you short of breath?
- Did your heart race, pound, or skip?
- Did you have chest pain or pressure?
- Did you sweat?
- Did you feel as if you were choking?
- Did you have hot flashes or chills?
- Did you have nausea or an upset stomach, or the feeling that you were going
- to have diarrhoea?
- Did you feel dizzy, unsteady, or faint?
- Did you have tingling or numbness in parts of your body?
- Did you tremble or shake?
- Were you afraid you were dying?

If all questions in part 1 are answered positively and four or more in part 2, participants are considered to have a panic syndrome according to PHQ criteria.

Part 3

Over the last 4 weeks, how often have you been bothered by any of the following problems? Possible answers: not at all, several days, or more than half of the days.

- Feeling nervous, anxious, on edge, or worrying a lot about different things
- Feeling restless so that it is hard to sit still
- Getting tired very easily
- Muscle tension, aches, or soreness
- Trouble falling asleep or staying asleep
- Trouble concentrating on things, such as reading a book or watching TV
- Becoming easily annoyed or irritable

If the first question of this part is answered positively and three or more questions are answered "More than half the days", participants are considered to have an other anxiety syndrome as defined by the PHQ.

Chapter 2.3

Recognition of depression in primary care: does it affect outcome? The PREDICT-NL study

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A mind is like a parachute. It doesn't work if it is not open.

Frank Zappa
Composer and musician, 1940-1993

Abstract

Background

Detection rates of depression in primary care are below 50%. Studies showed similar outcome after 12 months for recognised- and unrecognised depression. Outcome beyond 12 months is less well studied.

Objective

We investigated recognition of depression in primary care and its relation to outcome after 6, 12 and 39 months.

Methods

Data were used from a prospective cohort study of 1293 consecutive general practice attendees (PREDICT-NL), who were followed up after 6 (n=1236), 12 (n=1179), and 39 (n=752) months. We measured the presence and severity of major depressive disorder (MDD) according to DSM-IV criteria and PHQ-9, and mental function with SF-12. Recognition of depression was assessed using ICPC codes (P03 and P76) and ATC (N06A) codes from the GP records (6 months before/after baseline).

Results

At baseline 170 (13%) of the participants had MDD, of whom 36% were recognised by their GP. The relative risk of being depressed after 39 months was 1.35 (95% CI 0.7 to 2.7) for participants with recognised depression compared to unrecognised depression. At baseline, participants with recognised depression had more depressive symptoms (mean difference PHQ-9 2.7, 95% CI 1.6 to 3.9) and worse mental function (mean difference MCS -3.8, 95% CI -7.8 to 0.2) than unrecognised depressed participants. After 12 and 39 months mean scores for both groups did not differ, but were worse than those without depression.

Conclusion

A minority of patients with MDD is recognised in primary care. Those who were unrecognised had comparable outcome after 12 and 39 months as participants with recognised depression.

Introduction

Unipolar major depressive disorder (MDD) is predicted to be the second cause of disability worldwide in 2030. This is due to the high prevalence of depression, ranging from 10-25% in women and 5-12% in men, and its impact on daily functioning and mortality.[1] Most patients suffering from depression are treated by their primary care physician.[2] A recent meta-analysis revealed that general practitioners (GP's) identified depression in 47% of the cases of which 34% was recorded in their notes.[3] Diagnostic sensitivity was larger in studies that used a longer time interval (53%) compared to cross-sectional data (34%).[3, 4]

Depressed patients who are not recognised in primary care may not receive the medical attention or treatment they need, which might worsen their prognosis. So far, few studies investigated the effect of recognition of depression in primary care in relation to outcome, and only one had a follow-up beyond 12 months. Patients recognised by their GP had more depressive symptoms at baseline than patients not recognised, while after 12 months both groups had the same outcome.[5-8] One study showed an increased risk of depression persistence after five years for depressed patients who were recognised compared to non-depressed patients, though the authors did not compare the outcome with unrecognised depressed patients.[9] None of these studies took baseline severity and a history of depression into account, while these are strong predictors of both recognition and a poor outcome.

We aimed to determine the proportion of patients with MDD in primary care that was recorded and/or treated by general practitioners. Second, we investigated to what extent recognition affected the outcome of MDD.

Methods

Study setting and design

We used data from the PREDICT-NL study, which is the Dutch part of the predictD study.[10-14] PredictD is a multicenter prospective cohort study from which a multifactor risk algorithm was developed to predict risk of onset of MDD in primary care patients in six European countries and Chile. PREDICT-NL is described in greater detail elsewhere.[10, 15] The PREDICT-NL study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and all participants gave written informed consent.

Study participants

Consecutive patients aged 18 years or older were recruited in the waiting room of six primary care practices in Utrecht and surroundings between April 2003 and September 2004. Patients willing to participate were asked to fill in risk factor questionnaires and sign informed consent within two weeks. In total, 3089 consecutive patients were asked to take part, of whom 83 did not meet inclusion criteria. Exclusion criteria were an inability to understand one of the main languages involved, psychosis, dementia and incapacitating physical illness. Of the remaining 3006 participants, 1338 (45%) consented and took part in the study. Reasons for not participating were mostly lack of time (21%) and no interest (24%). Of the 1164 refusals on which we had demographic information (70%), we found no significant difference in age (mean 51

years with standard deviation 19) and sex (62% female) distribution compared to our participants. Of the 1338 participants, 45 were excluded because no CIDI was taken (n=20) or no data from GP's was available (n=25). Of the remaining 1293 participants, 1236 (96%) participated at the 6-months, 1179 (95% of 1236) at 12 months and 752 (69% of 1106 invited) at 39 months. Mean follow-up durations were 5.7 (SD 0.6), 12.0 (SD 0.6) and 39.2 months (SD 2.3).

Diagnosis of major depressive disorder

The diagnosis of MDD was assessed in all participants according to DSM-IV criteria using the depression section of the Composite International Diagnostic Interview (CIDI).[16, 17] The researchers contacted the participant by telephone and asked the two core questions of the depression section of the CIDI interview (depressed mood or a loss of interest).[17] MDD was ruled out if the participant responded negatively to both questions. If the participant responded in the affirmative to one or both questions, an appointment was made in the general practice to conduct the entire CIDI depression interview. At baseline, the 6- and 12-month follow-up, diagnosis of MDD was assessed covering the preceding 6 months. At the 39-month follow-up, diagnosis of MDD was assessed covering the period between the 12-month and 39-month follow-up. If the participant was unable to schedule the interview at the general practice, the interview was done by telephone (23% of interviews at baseline, 17% at the 6-month follow-up, and 19% at the 12-month follow-up). At the 39-month follow-up, all interviews were done by telephone. Studies have shown that both methods are comparable with respect to reliability and validity.[18, 19]

Diagnosis and treatment of depression in primary care

Depression recording and treatment by the GP was retrieved from their electronic patient records. The GP's were trained to diagnose according to the international classification of primary care (ICPC).[20] They were blinded to the CIDI diagnosis. ICPC codes from the electronic patient records were retrieved in the period 6 months before and 6 months after CIDI assessment. The total number of GP consultations during this year was calculated for each participant. In addition, a medical researcher manually searched the electronic patient records of participants diagnosed with MDD according to the CIDI at baseline. A positive diagnosis of depression was defined as either an ICPC code of P03 (feeling depressed), P76 (depressive disorder), or a depression diagnosis retrieved by manual search. Treatment was defined as the prescription of anti-depressants (N06A) classified according to the Anatomical Therapeutic Chemical (ATC) classification system. In addition, ICPC codes of stress symptoms (P01, P02, P04, P05, P06), neuraesthenia/surmenage (P78), anxiety disorder (P74), other psychiatric disorders and prescription of sedatives (N05BA, N05CD, N05CF) were retrieved for baseline analyses.

Severity of depressive symptoms

The Patient Health Questionnaire 9 (PHQ-9) was included with the risk factor questionnaires.[21] It determines the presence of the nine DSM-IV criteria for MDD in the past two weeks on a 4-point rating scale, ranging from 0 ("not at all") to 3 ("nearly every day"). The scores on this questionnaire range from 0 to 27.

Mental function

Mental function was assessed by the Short Form 12 (SF-12), which yields a mental component summary scale (MCS).[22, 23] The SF-12 yields a scale from 0 to 100, in which lower scores indicate greater dysfunction.

Covariates

Patient characteristics at baseline included age, sex, marital status, presence of life events, level of education (11-point ordinal scale ranging from 'no education completed' to 'PhD-level'), presence of one or more chronic diseases diagnosed by a physician and number of complaints presented to the GP.[24] A history of depression was based on affirmative answers to both of the first 2 questions of the CIDI depression section.[24, 25]

Data analysis

Missing data rarely occurs completely at random and a complete case analysis may lead to loss of statistical power and biased results.[26] We used multiple imputation (10 datasets) to address missing values using the statistical programme R (version 2.8.1). Data were analyzed using PASW version 17.0 (IBM SPSS Statistics) by pooling the 10 imputed datasets.

First, we computed the frequency of MDD at baseline and the proportion recognised by their GP and/or receiving anti-depressants. We divided the participants into three groups using the CIDI diagnosis as golden standard: 1) MDD according to the CIDI and depression recorded and/or treated by the GP (referred to as recognised depression); 2) MDD according to the CIDI but depression not recorded and not treated by the GP (unrecognised depression); and 3) no MDD according to the CIDI (no depression) regardless of whether depression was recorded by the GP (this occurred in 1% of the cases). We compared the following diagnostic groups: 1) participants with recognised depression to unrecognised depression and 2) participants with unrecognised depression to no depression.

Second, relative risks (RR) were estimated with Poisson regression analyses with MDD according to a CIDI diagnosis after 39 months as the dependent variable.[27, 28] In the first model we adjusted for age (continuous), female gender (yes versus no), lower education (yes versus no), living together (yes versus no), and one or more life-events in the 6 months prior to baseline (yes versus no) as a priori confounders. In the second model, a history of depression (yes versus no) and baseline depression severity score (continuous) were added to the models.

Third, random coefficient analyses (RCA) with robust standard errors were performed to estimate marginal means for PHQ-9 and MCS at each assessment with the diagnostic group variable as independent variable. We used random intercept for best model fit. Diagnostic group, time, and the interaction between diagnostic group and time were entered as independent variables. Analyses were adjusted for a priori confounders as mentioned above. Also, change in PHQ-9 and MCS over time, represented by the coefficients of interaction between the diagnostic group and time, was compared between recognised- and unrecognised participants. We repeated the analyses in participants with no history of depression and who were thus likely to have their first episode of depression.

Results

At baseline, 170 out of 1293 patients had MDD in the 6 months prior to baseline (13.0%), of which 25% (n=42) were recorded by the GP and 27% (n=46) received anti-depressant medication in the period of 6 months before or after the CIDI interview was taken. Taking overlap into account, this resulted in 61 (36%) depressed participants who were recognised, 109 who were unrecognised and 1123 participants with no depression.

The mean age of the participants was 51 years and 63% were female (Table 1). Participants with recognised depression were more often male and more often had a history of depression than unrecognised participants. In addition, they had a higher consult frequency (52% versus 36%). Compared to non-depressed participants, unrecognised participants were younger and more often reported life events or had a history of depression. Also, they received sedative drugs more often (35% versus 17%) and presented more often with complaints (32% versus 19%).

Table 1: Baseline characteristics of participants for groups of diagnostic status

	Total	Recognised depression	Unrecognised depression	No depression
	(N=1293)	(N=61)	(N=109)	(N=1123)
Demographics				
Age in years, mean (SD)	51 (17)	47 (14)*	46 (14)	52 (17)
Female, N (%)	813 (63)	41 (67)	82 (75)	690 (61)
Living together, N (%)	947 (75)	40 (67)	67 (62)	840 (76)
Lower levels of education, N (%)	292 (23)	19 (31)	29 (27)	244 (22)
Presence of life events, N (%)	779 (61)	46 (75)	84 (79)	649 (59)
Chronic disease, N (%)	544 (42)	28 (49)	49 (43)	467 (42)
Lifetime history of depression, N (%)	414 (32)	42 (69)	63 (58)	309 (28)
Consult characteristics				
Disorders diagnosed by GP, N (%)				
- Depressive disorder/-symptoms	60 (5)	42 (69)	0	23 (2)
- Stress disorder/-symptoms	92 (7)	13 (21)	24 (22)	55 (5)
- Anxiety disorder	18 (1)	3(5)	3 (3)	12 (1)
- Other psychiatric diagnosis	46 (4)	6 (10)	7 (6)	33 (3)
- Weakness, fatigue	79 (6)	7 (11)	11 (10)	61 (5)
Two or more complaints, N (%)	252 (20)	18 (30)	32 (30)	202 (19)
High consult frequency, N (%)	474 (37)	32 (52)	39 (36)	403 (36)
Treatment, N (%)				
- Antidepressants	111 (9)	46 (75)	0	65 (6)
- Sedatives	255 (20)	28 (46)	38 (35)	189 (17)

Abbreviations: SD = Standard deviation

After 39 months participants with recognised depression had an increased risk of being depressed (RR 1.51, 95% CI 1.08-2.10). This risk diminished and became non-significant after additional adjustment for history of depression and baseline severity score (RR 1.35, 95% CI 0.68-2.68). Unrecognised participants had an increased risk of being depressed after 39 months compared to non-depressed participants (RR 2.68, 95% CI 1.54-4.66), which was mostly explained by a history of depression and baseline severity (RR 1.31, 95% CI 0.69-2.49) (Table 2).

At baseline, participants with recognised depression had more depressive symptoms (mean difference PHQ-9 2.7, 95% CI 1.6 to 3.9) and worse mental function than unrecognised participants (mean difference MCS -3.8, 95% -7.8 to 0.2) (Figure 1A+B). At 12 and 39 months the mean scores did not differ between these groups. Nevertheless, at 39 months unrecognised participants had more depressive symptoms (mean difference PHQ-9 1.6, 95% CI 0.7 to 2.4) and worse mental function (mean difference MCS -5.2, 95% CI -7.6 to -2.8) than non-depressed participants.

Table 2: Estimated relative risks of depression at 39 months for diagnostic groups

		Model 1	Model 2
	Cases/N	RR (95% CI)	RR (95% CI)
Unrecognised depression	19/ 63	1	1
Recognised depression	18/ 38	1.51 (1.08 to 2.10)	1.35 (0.68 to 2.68)
No depression	51/ 651	1	1
Unrecognised depression	19/ 63	2.68 (1.54 to 4.66)	1.31 (0.69 to 2.49)

Abbreviations: CI = Confidence interval, RR = Relative risk
Model 1: Adjusted for age (continuous), female (yes versus no), living alone (yes versus no), lower levels of education (yes versus no) and presence of life events (yes versus no)
Model 2: + Adjusted for a history of depression (yes versus no) and baseline depression severity score (continuous)

Participants with recognised depression had a greater, though non-significant, decline in severity of depressive symptoms over time and increase in mental function compared to unrecognised depression (Table 3). These estimates did not change when a history of depression was added to the models (model 2). In participants with no history of depression, there was a significant decline in depressive symptoms and a significant increase in mental functioning for participants with recognised compared to unrecognised depression. At 39 months recognised participants had a slightly, but not statistically significant, better outcome than unrecognised participants (mean difference PHQ-9 -1.1, 95% CI -3.5 to 1.3 and mean difference MCS 6.1, 95% CI -3.6 to 15.8) (Figure 2A+B).

Discussion

We studied recognition of MDD and its relation to outcome after 6, 12 and 39 months in primary care. We observed that the GP recorded a depression diagnosis or depressive complaints or prescribed anti-depressants in 36% of the depressed participants. After 12 and 39 months depression severity and mental functioning were similar between recognised and unrecognised patients but still worse than non-depressed participants.

To our knowledge, this is the first study with a relatively long follow-up period with several assessments. Previous studies either had a follow up of 12 months with several assessments[5-8] or a follow-up of five years but no assessments in between.[9] Another strength is that we were able to examine the natural course of recognition of depression, because GP's were blinded to the CIDI diagnosis. Third, we retrieved data on recognition and treatment of depression from the electronic patient records with use of ICPC and ATC codes as well as with manual search, which will have yielded more valid results than self-report.[9] Fourth, MDD was diagnosed in an interview using DSM-IV criteria rather than relying on self-report symptom questionnaires.

A limitation of our study is that we had a low response rate at baseline, although similar participation rates have been found in other observational studies in primary care.[29] Patients with depression may be more reluctant to participate in a study due to loss of interest or apathy. On the other hand they may have been more likely to participate in PREDICT-NL because the prognosis of depression is studied. The prevalence of 13% found in our study is higher than the 1-year prevalence of depression in the general population.[30] However, the prevalence of depression in primary care based on DSM-IV diagnosis is not known. Nevertheless, loss to follow-up was extremely low during the first 12 months of follow-up and after 39 months loss to follow up was comparable for participants with unrecognised depression (42%) and no depression (42%), but somewhat lower for recognised depression (37%). Another limitation is that we had no data on the dose of anti-depressants prescription. In some cases tricyclic antidepressants (TCA's) are described in low dose for pain management, which we could not distinguish from the high doses TCA's prescribed for depression. Third, we had no data on treatment in second line, which may underestimate the part of recognised depression.

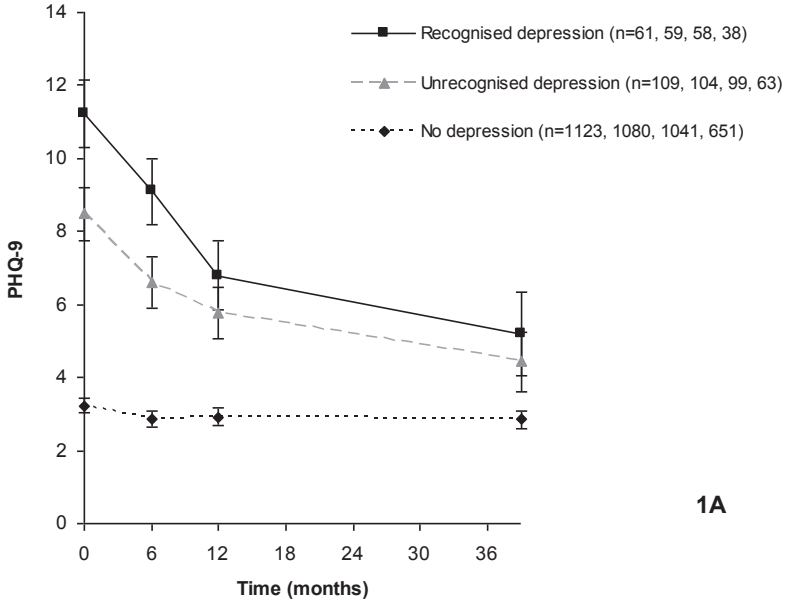
We found that only 25% of the depressed patients were recorded by the GP in the 6 months before or after they were diagnosed with MDD according to the CIDI. When we also included patients who were treated with antidepressants recognition was still low (36%). Although the recorded proportion of 25% is slightly lower compared to a pooled sensitivity of 37% found in studies that used case notes of primary care with a follow up from 3 to 12 months[3], these results are in accordance with recognition rates of two other Dutch studies (21% and 29%).[31, 32]

Table 3: Random coefficient analyses for recognised compared to unrecognised depressed patients

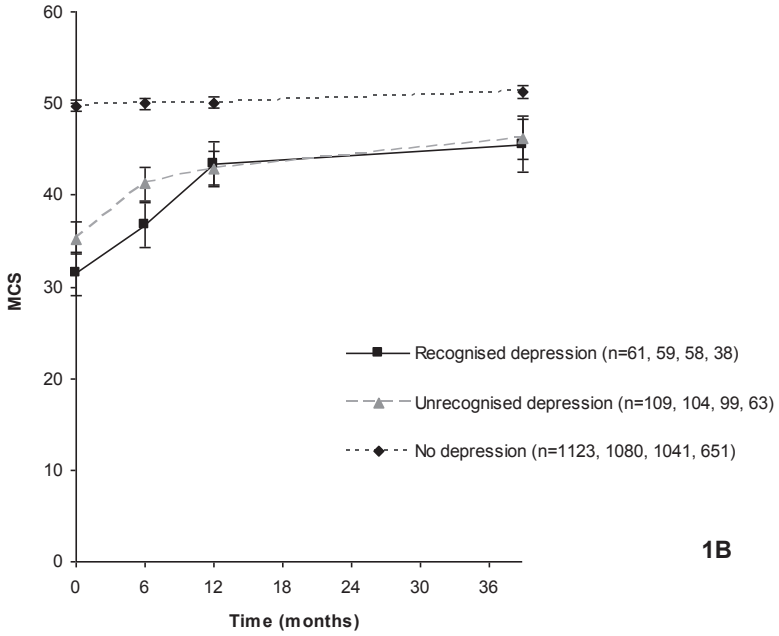
	PHQ-9 model 1		PHQ-9 model 2		SF-12 MCS model 1		SF-12 MCS model 2	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Total Group								
Intercept	5.61	1.76 to 9.45	5.57	1.75 to 9.38	40.71	33.50 to 47.83	40.12	33.73 to 47.84
Time†	-0.10	-0.12 to -0.06	-0.10	-0.13 to -0.06	0.25	0.17 to 0.34	0.25	0.17 to 0.32
Unrecognised (ref)	0		0		0		0	0
Recognised	2.71	1.24 to 4.18	2.52	1.05 to 4.00	-3.81	-6.61 to -0.92	-3.42	-6.24 to -0.68
Time*Unrecognised (ref)	0		0		0		0	
Time*Recognised	-0.05	-0.11 to 0.003	-0.05	-0.11 to 0.004	0.09	-0.03 to 0.22	0.09	-0.04 to 0.22
No history of depression								
Intercept	6.35	1.06 to 11.7			35.52	25.03 to 45.91		
Time†	-0.10	-0.14 to -0.05			0.23	0.11 to 0.35		
Unrecognised (ref)	0				0			
Recognised	2.59	0.21 to 4.96			-5.01	-10.10 to -0.12		
Time*Unrecognised (ref)	0				0			
Time*Recognised	-0.10	-0.18 to -0.01			0.29	0.08 to 0.50		

Abbreviations: CI = Confidence interval, MCS = mental component summary, PHQ =Patient Health Questionnaire
Model 1: Adjusted for age (continuous), female (yes versus no), living alone (yes versus no), lower levels of education (yes versus no) and presence of life events (yes versus no)
Model 2: + Adjusted for a history of depression (yes versus no)

Figure 1: Mean PHQ-9 (A) and MCS scores (B) for the 3 diagnostic groups (with number of participants at baseline, 6, 12, and 39 months), adjusted for confounders



1A



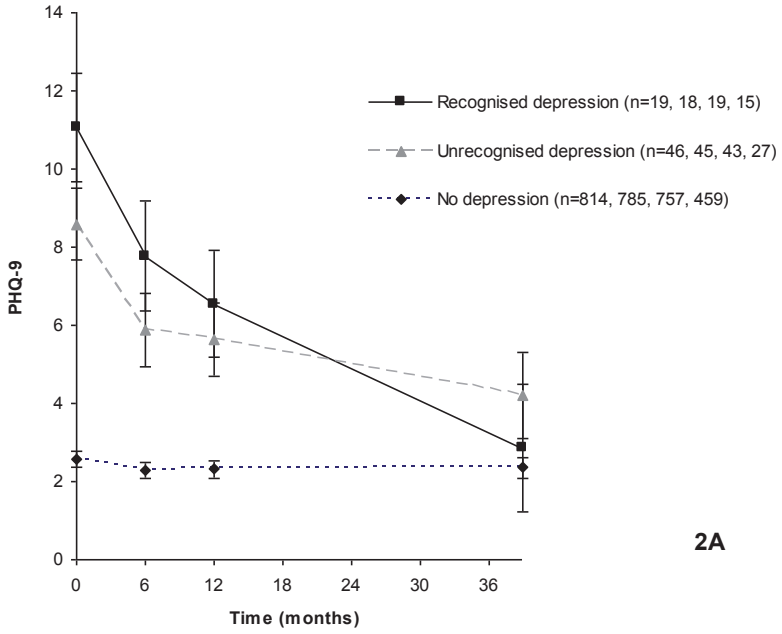
1B

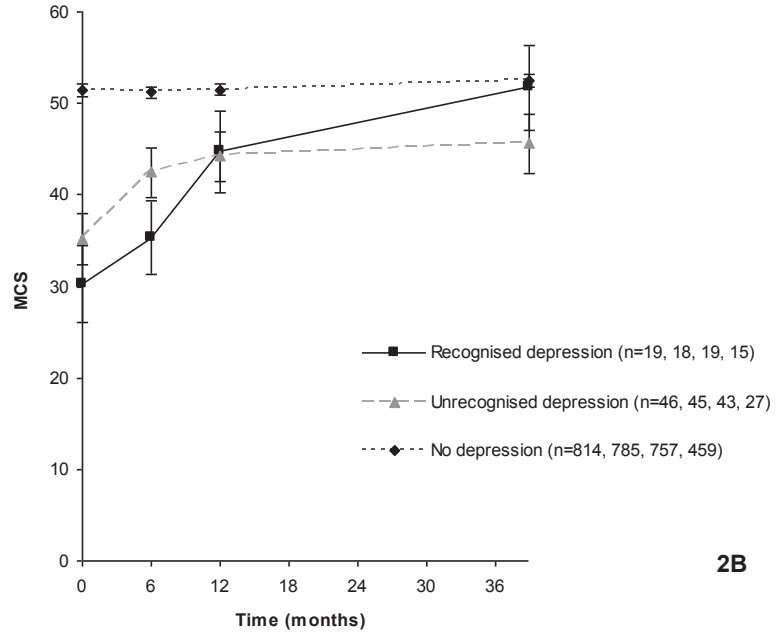
We observed that the risk of MDD after 39 months was higher for participants with recognised depression compared to unrecognised depression, which was mostly explained by presence of a history of depression and a greater baseline severity score. This may resemble patients with severe therapy resistant depression. Another study showed that patients with recognised depression also had a greater risk of being depressed after five years, but this was compared to patients with no depression and they did not account for baseline severity score.[9] In our study, participants with recognised depression had more depressive symptoms and worse mental function at baseline than those who were unrecognised, while after 12 months and 39 months outcomes did not differ anymore. This is in agreement with results from previous studies with 12 months of follow-up. However, those who were not recognised had a higher level of symptoms and greater dysfunction over time than those with no depression, although not significant.

Results of exploratory analyses in participants without history of depression suggest that participants with recognised depression had a significantly larger decrease in depressive symptoms and increase in mental function over time compared to unrecognised participants, suggesting that recognition or treatment of first episode MDD may lead to a more favourable course. However, the numbers of participants in our subgroups were very low and we could not calculate the risk of recurrence.

Major depressive disorder accounts for a considerable part of the burden of disease. This is due to increasing incidence, its chronic nature, and disability that causes absence from work and high health care costs.[1] Our results illustrate the chronic course of depression, since both recognised- and unrecognised depressed patients still had symptom levels above the threshold for mild depression and an increased risk of being depressed after 39 months compared to participants without depression at baseline. This course is not influenced by recognition or treatment by the GP, since the outcome between both groups did not differ. This does not necessarily implicate that there is no need for the GP's to detect or treat depression. While the outcome for both groups was comparable, the recognised patients had more symptoms at the outset of the research. A recent meta-analysis showed that treatment effect was only substantial in patients with severe depressive symptoms compared to patients with mild or moderate symptoms.[33] Apparently GP's already detect the more severe cases of depression, who may benefit most from antidepressant treatment. Moreover, in patients with a first episode of depression, recognition may improve outcome. Because a shorter interval between onset of depression and start of treatment is associated with a better prognosis, early recognition in these patients is warranted.[34] Clinical prediction rules might be used to detect high risk patients who need further attention.[15]

Figure 2: Mean PHQ-9 (A) and MCS scores (B) for the 3 diagnostic groups (with number of participants at baseline, 6, 12, and 39 months) in participants with no history of depression, adjusted for confounders





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Chapter 3

General discussion

The aim of this thesis was to examine the differential impact of risk factors for the onset of major depressive disorder (MDD) across groups at risk and to investigate to what extent our findings accord with the vulnerability-stress model for MDD. The second aim was to examine the natural course and outcome of MDD. The main findings are:

1. Women and those at middle age may not only have greater vulnerability to onset of major depressive disorder (MDD), they may also be more likely to get affected by risk factors than others (chapters 1.2 and 1.3). Risk factors may have a different effect on a first onset of MDD than on recurrent MDD (chapter 1.2) and on multiple or long episodes of MDD than on a short and single episode of MDD (chapter 1.1).

2. MDD generally has a poor course and is associated with a higher level of depressive and somatic symptoms and worse mental functioning at baseline (chapter 2.1). Coexisting MDD and anxiety are associated with substantial levels of physical dysfunction over time and severe levels of physical dysfunction are likely to lead to the combination of MDD and anxiety (chapter 2.2). A minority of people with MDD is recognised in primary care. Unrecognised people have a comparable outcome over time compared to people who are recognised, which is worse than people without MDD (chapter 2.3).

In the first part of this chapter, we will discuss which of the variants of the vulnerability-stress model (for explanation, see below) accords most with our findings. In a subsequent section, some methodological issues are discussed. In the second part of this chapter, we focus on our findings of chapter 2.2 and discuss the nature of the relationship between MDD, anxiety and function.

Onset of MDD

The vulnerability-stress model for MDD

The field of psychiatric epidemiology is evolving and several theories have been developed to get insight in the etiology of major depressive disorder (MDD). One of these theories states that onset of MDD can be conceptualized in a vulnerability-stress model.[1-5] This model suggests that the combination of vulnerability and stress factors may contribute to the onset of the disorder. Several variants of the model have been proposed and four of them will be shortly discussed (see also Table 1).

The first variant is the pure vulnerability model in which sufficient vulnerability is needed to cause MDD. This implies that onset of MDD will not occur in those with low vulnerability; even if high levels of stress are present. The second variant is the additive vulnerability model in which stress factors and vulnerability factors work in an additive way. This implies that with higher levels of stress, lower levels of vulnerability may be needed to cause the disorder and vice versa. The interactive vulnerability model is the third variant which is similar to the additive model, but with the extension that the level of vulnerability may intensify the effects of stressors on the risk of MDD. The fourth variant has components of the additive and interactive

vulnerability model, but is unique in its dynamic feature. This dynamic feature is expressed in a way that stressful events largely influence whether or not the level of vulnerability increases or decreases. In the next sections, we will discuss our main findings and their relationship to the vulnerability-stress model.

Table 1 – Variants of the vulnerability-stress model‡

		Vulnerability	Relation	Stress	MDD
1.	Pure	-	→	- / +	-
		-	→	++	-
		+	→	- / +	+
2.	Additive	+++	↔	+	+
		++	↔	++	+
		+	↔	+++	+
3.	Interactive	+++	↔ / →	++	+
		++	↔ / →	++	+
		+	↔ / →	+	+
4.	Dynamic	-	↔ / → / ←	-	-
		++	↔ / → / ←	+	+
		+	↔ / → / ←	++	+

+ = Presence, - = Absence, → = Vulnerability in relation to stress, ← = Stress in relation to vulnerability, ↔ = Bidirectional relationship between vulnerability and stress
MDD = Major depressive disorder
‡ Based on work from Holmes, Masuda, Krantz, de Jonghe and Ormel.[1-5]

Age and sex as vulnerability factors

In this thesis we studied the vulnerability factors sex and age. In chapter 1.2 we were interested in the differential impact of psychosocial risk factors for women compared to men on the risk of onset of MDD. Epidemiologic research has consistently shown that women have higher incidence rates of MDD than men.[6-9] This sex difference in the onset of MDD was also observed in the Predict data.[10] We examined the differential impact of risk factors such as socio-demographic factors, psychiatric comorbidity factors and functioning, adverse experiences and life events, work or environmental factors and relational factors across sex. We observed that most risk factors had a greater impact in women than in men on the risk of onset of MDD and that these risk factors were not restricted to a specific class of risk factors. In chapter 1.3 we examined whether the effect of recent life events on the risk of onset of MDD was different for different age groups. The frequency of life events and vulnerability to MDD may differ throughout life.[11-14] Our results suggest that life events, and in

particular personal problems, severe events in family or friends, and problems with law carry the largest risk of onset of MDD during mid-life.

Our findings denote that sex and age are examples of variables which may indicate groups with a greater vulnerability to onset of MDD. It has been suggested that women may have greater biologic vulnerability to onset of MDD[9] but our findings add to the current knowledge that women may also be more likely to get affected by risk factors than men. Understanding the combination of higher vulnerability to and the greater impact of risk factors on the onset of MDD in women compared to men is crucial to further elucidate the etiology of MDD and to possibly prevent onset of MDD. Also, we showed that those in mid-life are at greater risk of becoming depressed when a life event occurs compared to those who are younger or older experiencing the same life event. One might argue that people in middle age have more responsibilities and social ties and thus life events at this stage of life have a larger impact in terms of onset of MDD. However, those in mid-life may also be the most resilient given they have had more life experience than the younger group and do not yet have the added vulnerability of poorer health and relative social isolation of older age. Nevertheless, management of MDD in middle aged people in clinical practice may require dealing with the effects of major life events on the treatment and prognosis of the disorder. Our results indicate that women and those at middle age may not only have greater vulnerability to onset of MDD, but that they may also be more likely to get affected by risk factors than others.

The role of a lifetime history of MDD

One other noteworthy vulnerability factor is a lifetime history of MDD. It is known from the literature that MDD is recurrent and that presence of a lifetime history of MDD increases the risk of new episodes of MDD.[15, 16] Previous studies that examined risk factors for onset of MDD did not always discriminate a first onset of MDD from recurrent MDD.[17] In persons with no MDD at baseline and with onset of MDD at follow-up, one may discriminate those with and without a lifetime history of MDD prior to baseline. It is likely that persons who become depressed for the first time are different from those who have a recurrent episode of MDD. Therefore, it could be that risk factors have a different impact in those with a first onset of MDD compared to those with recurrent MDD. This is in accordance with the kindling hypothesis.[18-20] This hypothesis suggests that occurrence of a first onset of MDD largely depends on the level of stress, but recurrent MDD occurs independent of stress. Thus, susceptibility to a subsequent MDD may alter after a first onset of MDD. This is in line with the findings that are presented in chapter 1. We showed that risk factors may have a different impact on the risk of onset of MDD in those with a possible lifetime history of MDD compared to those without a lifetime history of MDD. Future research should take account of the possibility that the effect of risk factors may be different on a first onset of MDD compared to recurrent MDD.

The interactive vulnerability model: in accordance with our findings?

A good candidate for describing the psychosocial process which may contribute to the onset of MDD is the interactive vulnerability variant of the vulnerability-stress model. In the present thesis we showed that several vulnerability factors and stress

factors not only work in an additive way but also interact, which accords with the suggested variant.

Methodological issues: estimating interaction

In a typical setting, data are obtained from a prospective cohort study in which associations between a determinant and outcome are studied. By definition, etiologic studies are longitudinal as the goal is to relate a potentially causal determinant to future occurrence of a disease, in this case MDD.[21] A cohort study design allows to research a temporal relationship in which the determinant precedes the onset of MDD. In the present thesis, we examined interaction between several determinants on the risk of MDD. One of the issues that may arise during data analysis is which method to use to estimate interaction. In the analyses employed in this thesis we were interested in examining whether the strength of risk factors on the risk of onset of MDD was different for different groups of people (e.g. woman versus men, younger versus older); i.e. whether there was an interaction between a vulnerability factor and a risk factor. Most often, interaction is assessed by the addition of a product term in a statistical model. In logistic regression the coefficient associated with this product term quantifies the departure from multiplicativity.[22] However, we were interested in identifying interactions on an additive rather than multiplicative scale as it has been argued that biological interactions can best be estimated by departure from additivity.[23-26] Several methods have been proposed to estimate the level of interaction on an additive scale.[23-25] In chapter 1.2 we used the interaction contrast (IC), while in chapter 1.3 we used the relative excess risk due to interaction (RERI). With the IC, we were able to calculate the absolute risk differences between those with the risk factor and those without the risk factor. We calculated the absolute risk difference in women and men without MDD at baseline for those who had an onset of MDD at follow-up. The risk difference between these risk differences is referred to as the interaction contrast. This method may be suitable when absolute risks are of interest and the contrast variable has two categories (e.g. sex). When relative risks are warranted and the variable of interest has more than two levels, a RERI may be better applicable. To calculate the RERI in our study, a dummy variable with four levels was created for the combination of two risk factors. The first level was the reference category, in our case absence of a life event and young age [A-B-]. Subsequently, the following levels were defined: no life event and middle age [A-B+], presence of a life event and young age [A+B-], and presence of a life event and middle age [A+B+]. When we entered this dummy variable as independent variable into a logistic regression model in which onset of MDD was the dependent variable, we were able to calculate odds ratios (OR) for each level of the dummy variable. Then, we calculated the RERI using the following formula:

$$\mathrm{RERI} = OR_{A+B+} - OR_{A+B-} - OR_{A-B+} + 1$$

where OR_{A+B+}, OR_{A+B-}, OR_{A-B+} are odds ratios obtained from the logistic regression comparing groups A+B+, A+B- and A-B+ with the reference group. If the RERI is greater than 0 and 0 was not included in the confidence intervals (CI), positive interaction on an additive scale is present; the combined effect of life event and age is larger than the sum of the individual effects. Although these methods are somewhat different in that the RERI estimates departure from additivity on a relative scale and

the IC estimates departure from additivity on an absolute scale, both methods are suitable to quantify the interactive vulnerability-stress model for the etiology of MDD.

Methodological issues: role of a lifetime history of MDD

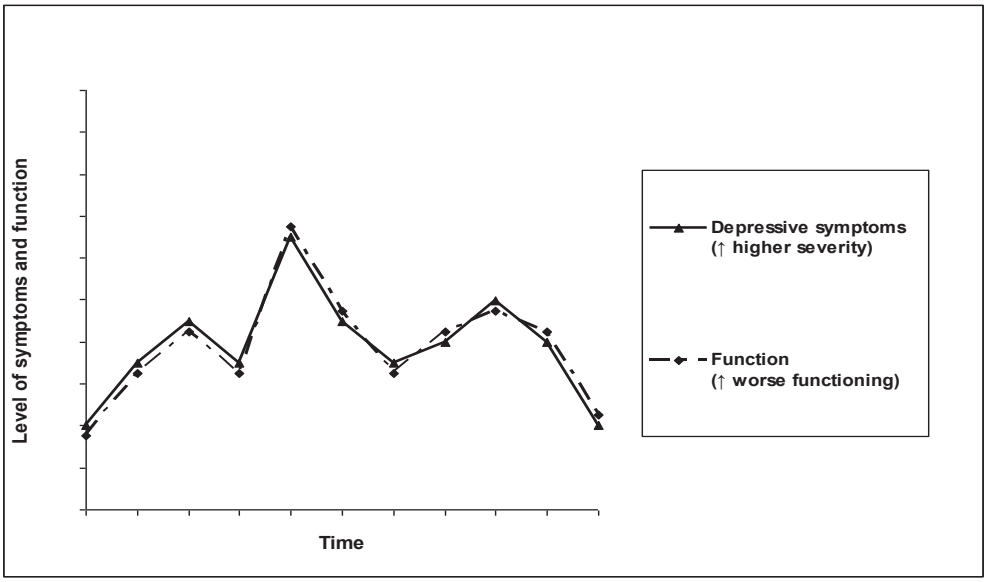
Another issue that may arise during data analysis in psychiatric epidemiologic research is the potential role a lifetime history of MDD may play in the relationship between the variable of interest and the outcome. One possibility to adjust for the effect of a lifetime history of MDD is to exclude those with or without a lifetime history of MDD in the design of the study. One may also stratify or adjust for a lifetime history of MDD in the analysis. If a lifetime history of MDD is added to the model, one can examine the effects of a variable on the outcome, independently of a lifetime history of MDD. If one stratifies for a lifetime history of MDD, one can examine the role of both presence and absence of a lifetime history of MDD simultaneously, in the relationship between a variable and the outcome. Although the methods mentioned above have their own advantages and drawbacks, it depends on the research question and sample size which method may be best suitable. When studying the etiology of MDD, however, it is important to take a lifetime history of MDD into account, and to note the difference between recurrent MDD (i.e. new episode of depressive illness following recovery in those without MDD at baseline and with a lifetime history of MDD prior to baseline) and recurrence of MDD (i.e. new episode of depressive illness following recovery in those with MDD at baseline).

Course and outcome of MDD

MDD, anxiety and the relationship to dysfunctioning

In chapter 2.1 we showed that the majority of patients with MDD have a chronic or intermittent course. Persistence or chronicity of MDD is associated with the severity of depressive and somatic symptoms, and worse mental functioning at baseline. When MDD is considered, one should be aware of potential coexistence of other psychiatric disorders or physical dysfunction. For instance, it is known from the literature that MDD and physical dysfunction are associated with each other[27-30] and synchrony of change may be present between the severity of depression and dysfunction (Figure 1).[31, 32]

Figure 1 – Synchrony of change between symptoms and function*



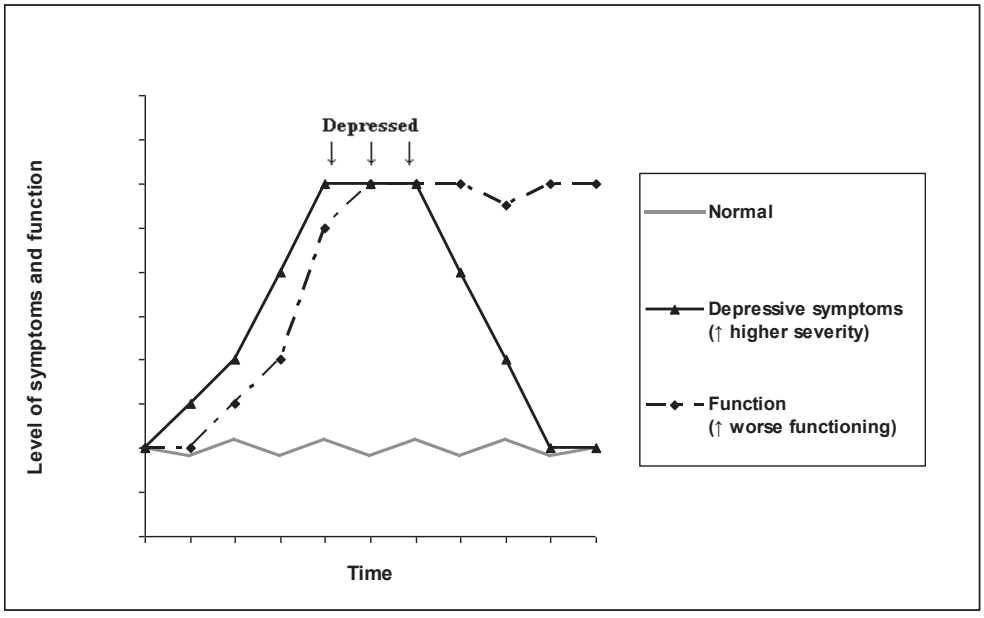
* Based on work from Hirschfeld, Akiskal, Reich, Rohde, Maier, Kendler, Shea, de Jonghe and Ormel.[5, 32, 40-46]

The strength of chapter 2.2 was our ability to examine the longitudinal bidirectional associations between MDD and anxiety, and physical function. A body of research has examined the relation between MDD, anxiety and quality of life, social dysfunction or role dysfunction.[28, 30-39] Although a large number of studies examined the relation between MDD and functioning, the relationship to anxiety and to coexisting MDD and anxiety has been less well studied. In particular, few studies have examined the temporal relationship between physical dysfunction and anxiety or coexisting MDD and anxiety. Our study showed that those with the combination of MDD and anxiety had greater physical dysfunction over time compared to those with MDD alone. On the other hand, severe levels of physical dysfunction are likely to lead to the combination of MDD and anxiety. This suggests that those with coexisting MDD and anxiety are likely to persist in higher levels of physical dysfunction and vice versa. However, it could also be that MDD and anxiety may have had an effect on physical function before entry into the study. Since we did not have premorbid functioning data available, we were unable to determine whether scar, trait or state effects were present.[5, 32, 40-46] A possible scar effect is present if an episode of MDD results in dysfunction and persists over time, without presence of dysfunction before the onset of an episode of MDD (Figure 2), while a trait effect is a continuation of premorbid dysfunction (Figure 3). A state effect, also known as residual symptom state effect, occurs when residual depressive symptoms are present after an

episode of MDD (Figure 4). We showed in chapter 2.1 that the level of depressive and somatic symptoms and mental function are related which underlines the finding that synchrony of change may be present.[31]

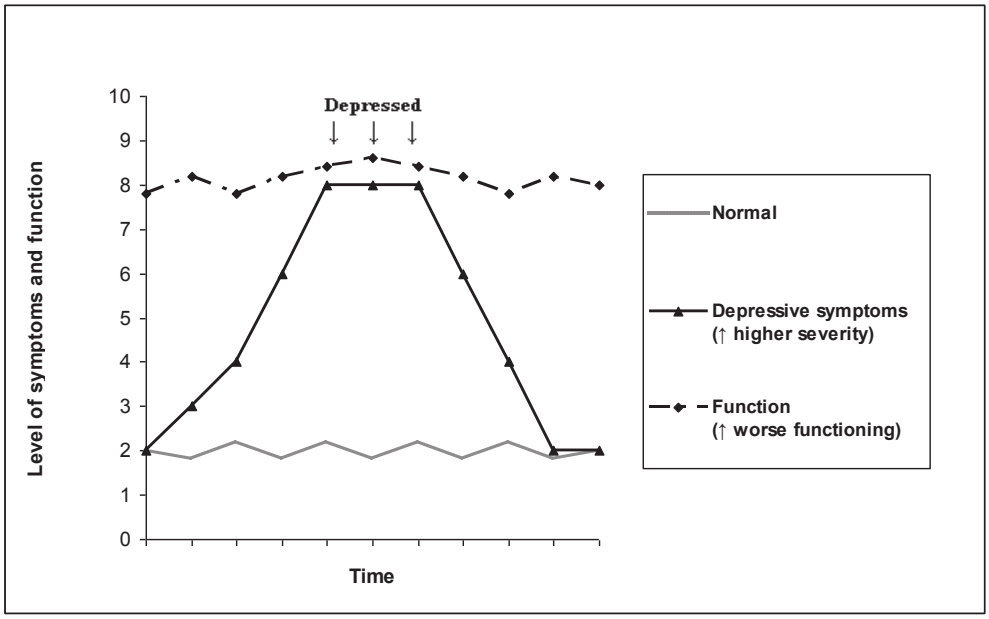
Although we examined MDD and anxiety as separate disorders, our findings in the present thesis should be interpreted in the light of current debates in the literature regarding the co-morbidity between MDD and anxiety.[47-52] Two main models have been proposed to describe the nature of the relationship between MDD and anxiety. The first model by Clark and Watson depicts that MDD and anxiety are separate constructs but have shared and unique factors such as low positive affectivity (depression), high physiological arousal (anxiety), and high negative affectivity (both).[47, 53] The second model describes MDD and anxiety as manifestations of the same underlying disease which may be situated in a continuum.[47, 54, 55] On basis of the present thesis we cannot confirm that MDD and anxiety are manifestations of the same underlying disease nor can we state that they fit the tripartite model suggested by Clark and Watson. However, we did show that persons with both MDD and anxiety have lower levels of physical function over time compared to MDD alone, and that anxiety contributed the most to physical dysfunction. This may suggest that if MDD and anxiety coexist, management of anxiety may be more important than management of MDD in order to prevent severe levels of physical dysfunction over time.

Figure 2 – Scar effect*



* Based on work from Hirschfeld, Akiskal, Reich, Rohde, Maier, Kendler, Shea, de Jonghe and Ormel.[5, 32, 40-46]

Figure 3 – Trait effect*

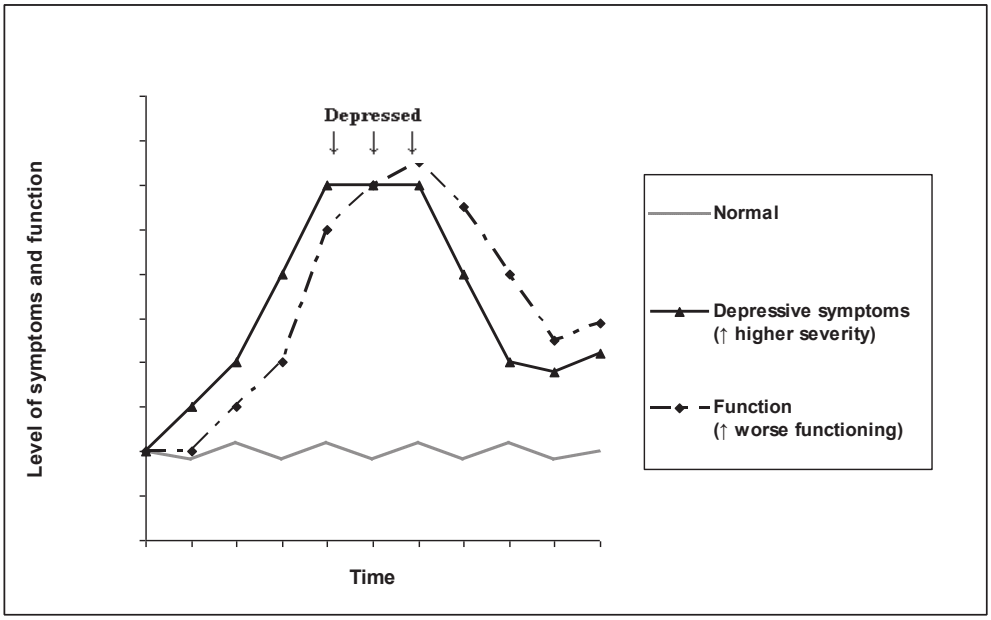


* Based on work from Hirschfeld, Akiskal, Reich, Rohde, Maier, Kendler, Shea, de Jonghe and Ormel.[5, 32, 40-46]

Future work

The study of psychosocial factors is essential in the etiology of MDD. However, one of the main limitations of this thesis is that genetic or biological factors were not collected in the PredictD study, with the exception of Spain.[56, 57] Previous studies have suggested that an integrated model of biological or genetic factors and psychosocial factors is warranted when studying risk factors for MDD.[58-60] Another limitation of this thesis is that we did not have data from all countries on treatments received for MDD and we therefore could not analyse the influences of these treatments on the course of the illness. In our successor study (PREDICT-MR), biological and genetic factors such as cortisol levels in the saliva and DNA will be collected. Patients will also undergo an ultrahigh high field Magnetic Resonance Imaging (MRI) scan to visualize small vessels and substructures in the brain. Including genetic and biological factors and the use of medication in future work will allow us to further unravel the etiology of MDD.

Figure 4 – State effect*



* Based on work from Hirschfeld, Akiskal, Reich, Rohde, Maier, Kendler, Shea, de Jonghe and Ormel.[5, 32, 40-46]

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Chapter 4

Summary and acknowledgment

Chapter 4.1

Summary

Introduction

Major depressive disorder (MDD) is a serious health problem and will be the second leading cause of burden of disease worldwide by 2030. To be able to prevent MDD, insight into risk factors for the onset of MDD is of clear importance. On the other hand, if onset of MDD has occurred, one may argue that different course patterns of MDD can be identified and that it is essential to examine their relationship to symptoms and function over time. Insight into these course patterns could assist in preventive strategies and management of MDD.

Aims

The first aim of this thesis was to examine the differential impact of risk factors for the onset of MDD across groups at risk and to investigate to what extent our findings accord with the vulnerability-stress model for MDD. The second aim was to examine the natural course and outcome of MDD.

Onset of major depressive disorder

The first main topic of this thesis includes the influence of risk factors on the onset of major depressive disorder (MDD), which is described in chapter 1. In chapter 1.1 we examined whether risk factors for multiple or long episodes of MDD (MDE) differed from those for single and short episodes MDE. We found that lower levels of education, generalized anxiety or panic syndrome, problems at work and financial strain significantly increased the risk of multiple or long MDE when compared to single and short MDE. Those at younger age were at significantly reduced risk of multiple or long MDE than single and short MDE. The findings suggest that several risk factors can be identified that may help to predict onset of different types of MDE. These factors are relatively easily assessable and may assist in preventive strategies.

In chapter 1.2 we compared the impact of risk factors in women and men on the risk of onset of MDD. Our results showed that the majority of risk factors had a greater impact in women than in men on the risk of onset of MDD and were not restricted to a specific class of risk factors. After stratifying for a possible lifetime history of MDD, the impact of risk factors across sex was generally stronger on recurrent MDD than on a first onset of MDD. Our findings may partly account for the observed difference in incidence of MDD between men and women. Future studies should discriminate a first onset of MDD from recurrent MDD.

In chapter 1.3 we set out to determine whether the effect of life events on MDD was different for different age groups. We found that life events had the largest effect in mid-life. The combined effect of personal problems, events in family or friends, or problems with law and middle age was larger than the sum of individual effects. Recent life events carry the largest risk of onset of MDD in mid-life. Understanding the different vulnerability to life events according to age may help to indicate groups at a particular risk and assist in preventive strategies.

Course and outcome of major depressive disorder

The second main topic of this thesis comprised the course and outcome of MDD, which is described in chapter 2. In chapter 2.1 our goal was to examine whether different courses of MDD were associated with different levels of depressive and somatic symptoms, and mental and physical functioning over time. We showed that although 43% of patients with MDD attending primary care recover, this leaves a majority of patients (57%) who have a chronic or intermittent course. Chronic courses are associated with higher levels of depressive symptoms and somatic symptoms and greater mental dysfunction at baseline.

In chapter 2.2 we examined the relationship between MDD, anxiety alone or together and physical function over time. Our aim was to estimate the strength of the associations and to explore the direction of causality. We found that depression and anxiety together or alone had a lower level of physical function at baseline than those with no diagnosis. Physical function may increase over time, but the rate of increase may not be different between the diagnostic groups. On the other hand, lower levels of physical function may lead to onset of depression and anxiety over time. Therefore, it is essential to prevent lower levels of physical function as this is likely to lead to onset of both depression and anxiety.

In chapter 2.3 we examined whether underrecognition of MDD in primary care affected the outcome. We observed that a minority of patients with MDD is recognised in primary care. Those who are unrecognised have comparable outcome after 12 and 39 months as participants with recognised depression, which is worse than those without MDD.

General discussion

In the first part of chapter 3, we have discussed which of the variants of the vulnerability-stress model accords most with our findings and have discussed some methodological issues. In the second part of this chapter, we focused on our findings of chapter 2.2 and discussed the nature of the relationship between MDD, anxiety and function.

Our findings denote that sex and age are examples of variables which may indicate groups with a greater vulnerability to onset of MDD. It has been suggested that women may have greater biologic vulnerability to onset of MDD but our findings add to the current knowledge that women may also be more likely to get affected by risk factors than men. Understanding the combination of higher vulnerability to and the greater impact of risk factors on the onset of MDD in women compared to men is crucial to further elucidate the etiology of MDD and to possibly prevent onset of MDD. Also, we showed that those in mid-life are at greater risk of becoming depressed when a life event occurs compared to those who are younger or older experiencing the same life event. In the present thesis we showed that several vulnerability factors and stress factors not only work in an additive way but also interact, which accords with the interactive vulnerability variant of the vulnerability-stress model.

In the second part of chapter 3 we showed that the majority of patients with MDD have a chronic or intermittent course. Persistence or chronicity of MDD was associated with the severity of depressive and somatic symptoms, and worse mental functioning at baseline. Our results also showed that those with the combination of

MDD and anxiety had greater physical dysfunction at baseline compared to those with MDD alone. On the other hand, severe levels of physical dysfunction are likely to lead to the combination of MDD and anxiety. On basis of the present thesis we cannot confirm that MDD and anxiety are manifestations of the same underlying disease nor can we state that they fit the tripartite model suggested by Clark and Watson. However, our results do suggest that anxiety has a stronger relationship to physical function than depression has to physical function.

The study of psychosocial factors is essential in the etiology of MDD. Including genetic and biological factors and the use of medication in future work will allow us to further unravel the etiology of MDD.

Chapter 4.2

Summary in Dutch (Nederlandse samenvatting)

Introductie

Depressie is een serieus gezondheidsprobleem en zal in 2030 wereldwijd tot de top 3 van aandoeningen met de grootste ziektelast behoren. Om depressie te kunnen voorkomen, is inzicht in risicofactoren voor het ontstaan van depressie belangrijk. Aan de andere kant, als depressie eenmaal is opgetreden, kan het zinvol zijn om verschillende beloopspatronen te identificeren en hun relatie tot symptomen en functioneren te onderzoeken. Inzicht in dit soort beloopspatronen kan bijdragen aan de preventie en management van depressie.

Doelen

Het eerste doel van dit proefschrift was het onderzoeken van de differentiële impact van risicofactoren op het ontstaan van depressie tussen verschillende risicogroepen. Verder onderzochten we in hoeverre onze bevindingen overeenkwamen met het kwetsbaarheid-stress model voor depressie. Het tweede doel was het onderzoeken van het natuurlijk beloop en de uitkomst van depressie.

Ontstaan van depressie

Het eerste onderwerp in dit proefschrift bevat de invloed van risicofactoren op het ontstaan van depressie, dat beschreven staat in hoofdstuk 1. In hoofdstuk 1.1 hebben we onderzocht of risicofactoren die ervoor zorgen dat iemand meerdere episoden van depressie dan wel een lange episode van depressie krijgt, verschillen van risicofactoren die ervoor zorgen dat een depressie kort of incidenteel is. We hebben geobserveerd dat een lager opleidingsniveau, algemeen angst of panieksyndroom, problemen op het werk en financiële moeilijkheden ervoor kunnen zorgen dat de kans op meerdere episoden of een lange episode van depressie groter is dan de kans op een enkele of korte episode. Jongere mensen hadden een verlaagd risico op meerdere episoden of een lange episode van depressie. Deze bevindingen suggereren dat verschillende risicofactoren geïdentificeerd kunnen worden die bij kunnen dragen aan het voorspellen van het type depressie dat op kan treden. Deze factoren zijn relatief eenvoudig vast te stellen en kunnen mogelijk helpen bij preventieve strategieën.

In hoofdstuk 1.2 hebben we de impact van risicofactoren vergeleken tussen mannen en vrouwen op het risico van het ontstaan van depressie. Onze resultaten lieten zien dat de meerderheid van risicofactoren een grotere impact heeft in vrouwen dan in mannen en dat deze risicofactoren niet binnen een bepaald type risicofactor valt. Nadat we de mensen met en zonder een mogelijke voorgeschiedenis van depressie hadden bekeken, bleek dat de impact van de risicofactoren over het algemeen sterker was op terugkerende depressies dan op een eerste depressie. Onze bevindingen kunnen deels het verschil in incidentie van depressie tussen mannen en vrouwen verklaren. Toekomstige studies moeten een onderscheid maken tussen een eerste depressie en een terugkerende depressie.

In hoofdstuk 1.3 was ons doel te bepalen of het effect van levensgebeurtenissen op depressie verschillend was voor verschillende leeftijdsgroepen. We observeerden dat levensgebeurtenissen het grootste effect hebben op middelbare leeftijd. Het gecombineerde effect van persoonlijke problemen, gebeurtenissen van familie of vrienden, problemen met de wet en middelbare leeftijd was groter dan de

som van de individuele effecten. Recente levensgebeurtenissen dragen het grootste risico op middelbare leeftijd op het ontstaan van depressie. Het begrijpen van de mate van kwetsbaarheid die elke leeftijdsgroep heeft bij het optreden van bepaalde levensgebeurtenissen kan helpen bij het vaststellen van risicogroepen en bijdragen aan de preventie van depressie.

Beloop en uitkomst van depressie

Het tweede onderwerp van dit proefschrift omvat het beloop en de uitkomst van depressie, dat beschreven staat in hoofdstuk 2. In hoofdstuk 2.1 hebben we onderzocht of verschillende beloopspatronen geassocieerd zijn met verschillende niveaus van depressieve en somatische symptomen, en mentaal en fysiek functioneren over de tijd. We hebben laten zien dat ondanks dat 43% van de mensen met een depressie opknapt, alsnog de meerderheid een chronisch of wisselend beloop kent. Een chronisch beloop wordt gekenmerkt door een hoog niveau van depressieve en somatische symptomen, en slecht mentaal functioneren op baseline.

In hoofdstuk 2.2 hebben we de relatie tussen depressie, angst en fysiek functioneren over de tijd onderzocht. Ons doel was een inschatting maken van de sterkte van de associaties en de richting van causaliteit te verkennen. We observeerden dat personen met depressie en angst samen of alleen, een lager niveau van fysiek functioneren kenden dat diegenen zonder diagnose op baseline. De mate van fysiek functioneren kan toenemen over de tijd, maar we zagen geen verschillen tussen de groepen in de mate van toename. Aan de andere kant kan een laag niveau van fysiek functioneren er toe leiden dat depressie en angst ontstaan. Daarom is het essentieel om slecht fysiek functioneren te voorkomen aangezien dit kan leiden tot het ontstaan van depressie en angst over de tijd.

In hoofdstuk 2.3 hebben we onderzocht of onderherkenning van depressie in de eerste lijn van invloed was op de uitkomst van depressie. We observeerden dat de minderheid van patiënten met depressie wordt herkend door de huisarts. Diegenen die niet herkend worden hebben een vergelijkbare uitkomst als diegenen die wel herkend worden door de huisarts, wat dus slechter is dan mensen zonder depressie.

Algemene discussie

In het eerste deel van hoofdstuk 3 hebben we besproken welke van de varianten van het kwetsbaarheid-stress model het meest overeenkomt met onze bevindingen. Daarnaast hebben we wat methodologische zaken besproken. In het tweede deel van dat hoofdstuk hebben we ons gericht op onze bevindingen in hoofdstuk 2.2 en daarbij besproken wat de aard van de relatie is tussen depressie, angst en functioneren.

Onze bevindingen laten zien dat geslacht en leeftijd voorbeelden zijn van variabelen die bij kunnen dragen aan het vaststellen van groepen die een verhoogde kwetsbaarheid hebben op het krijgen van een depressie. Het is bekend dat vrouwen een verhoogde biologische kwetsbaarheid hebben op het krijgen van een depressie, maar onze bevindingen voegen daar aan toe dat vrouwen ook een groter effect van risicofactoren ervaren. Het is belangrijk om de combinatie van een verhoogde kwetsbaarheid en de mate van impact van risicofactoren in kaart te brengen om zo

de etiologie van depressie verder te ontrafelen en mogelijk depressies te voorkomen. We hebben ook laten zien dat mensen op middelbare leeftijd een verhoogd risico hebben op het krijgen van een depressie als bepaalde levensgebeurtenissen optreden. De kans op een depressie is voor deze groep groter dan voor jongere of oudere mensen die eenzelfde gebeurtenis ervaren. In het huidige proefschrift hebben we aangetoond dat verschillende kwetsbaarheidfactoren and stressfactoren niet alleen additief werken maar ook interactie vertonen, wat sterk overeenkomt met de interactieve variant van het kwetsbaarheid-stress model.

In het tweede deel van hoofdstuk 3 hebben we laten zien dat de meerderheid van patiënten met depressie een chronisch of wisselend beloop kent. Persistentie of chroniciteit van depressie wordt gekenmerkt door de ernst van depressieve en somatische symptomen, en slecht mentaal functioneren op baseline. Onze bevindingen lieten ook zien dat personen met de combinatie van depressie en angst een lager niveau van fysiek functioneren hebben dan personen met alleen een depressie. Aan de andere kant kan slecht fysiek functioneren ertoe leiden iemand een depressie en angststoornis ontwikkelt. Op basis van het huidige proefschrift kunnen we niet concluderen dat depressie en angst manifestaties zijn van dezelfde aandoening, noch kunnen we concluderen dat ze overeenkomen met het tripartite model van Clark en Watson. Echter, onze resultaten suggereren wel dat angst een sterkere relatie kent met fysiek functioneren dan depressie dit heeft.

Onderzoek naar psychosociale risicofactoren is essentieel in het begrijpen van de etiologie van depressie. Genetische en biologische factoren, en het gebruik van medicatie kunnen in toekomstige studies een grote rol gaan spelen in het ontrafelen van de etiologie van depressie.

Chapter 4.3

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Chapter 4.4

Curriculum Vitae

Bauke Tiede Stegenga was born on June 2nd 1983 in Hilversum, The Netherlands. He attended secondary school at Sint Vitus College in Bussum and at Luzac College in Zwolle. From 2003 to 2008, he studied Medical Informatics at the University of Amsterdam and Biomedical Sciences – Epidemiology at Utrecht University. As part of the latter training, he was an intern at the Julius Center for Health Sciences and Primary Care. The 13-month internship was completed under supervision of Dr. Mirjam I. Geerlings and Dr. Marjolein H. Kamphuis, and involved data collection and analysis on 760 participants of the PREDICT study. This collaboration resulted in the PhD project described in this thesis. In September 2008, Bauke commenced the project under supervision of Prof. dr. Diederick E. Grobbee (University Medical Center Utrecht), Prof. dr. Michael King (University College London) and Dr. Mirjam I. Geerlings (University Medical Center Utrecht). As part of his PhD project, Bauke was trained at University College London from March 2009 to June 2009 under supervision of Prof. dr. Michael King and Prof. dr. Irwin Nazareth. During his PhD project, Bauke was awarded for the best scientific poster presentation at the annual conference of the Dutch Association of Psychiatry (Nederlandse Vereniging voor Psychiatrie) in April 2010.