Long-term disability in major depressive disorder: a 6-year follow-up study

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Abstract

Background. Major depressive disorder (MDD) represents a leading cause of disability. This study examines the course of disability in patients with chronic, recurrent and remitting MDD compared to healthy controls and identifies predictors of disability in remitting MDD.
Methods. We included 914 participants from the Netherlands Study of Depression and Anxiety (NESDA). DSM-IV MDD and WHO DAS II disability were assessed at baseline and at 2, 4 and 6 years. Six-year total and domain-specific disability were analysed and compared in participants with chronic ($n = 57$), recurrent ($n = 120$), remitting ($n = 127$) MDD and in healthy controls ($n = 430$). Predictors of residual disability were identified using linear regression analysis.
Results. At baseline, most disability was found in chronic MDD, followed by recurrent MDD, remitting MDD and healthy controls. Across diagnostic groups, most disability was found in household activities, interpersonal functioning, participation in society and cognition. A chronic course was associated with chronic disability. Symptom remission was associated with a decrease in disability, but some disability remained. In remitting MDD, higher residual disability was predicted by older age, more severe avoidance symptoms, higher disability at baseline and late symptom remission. Severity of residual disability correlated with the severity of residual depressive symptoms.
Conclusions. Symptomatic remission is a prerequisite for improvements in disability. However, disability persists despite symptom remission. Therefore, treatment of MDD should include an explicit focus on disability, especially on the more complex domains. To this end, treatments should promote behavioural activation and address subthreshold depressive symptoms in patients with remitted MDD.

Introduction

Major depressive disorder (MDD) represents a leading cause of disability burden globally (Ferrari *et al.*, 2013; GBD 2015 Mortality and Causes of Death Collaborators, 2016), with high economic costs for society (Katon, 2009; Sobocki *et al.*, 2006; Gelenberg, 2010). MDD is associated with substantial disability across many domains of life (Coryell *et al.*, 1993; Ormel *et al.*, 1993; Judd *et al.*, 2000; Greer *et al.*, 2010; Kamenov *et al.*, 2016), affecting patients' ability to fulfil family roles, to work and to participate in the society at levels similar to or worse than those reported in chronic somatic diseases (Hays *et al.*, 1995; Buist-Bouwman *et al.*, 2006).

Numerous studies have found that a more severe depression is associated with more disability (Ormel *et al.*, 1993; Judd *et al.*, 2000; *Kruijshaar et al., 2003*; Spijker *et al.*, 2004*a*) and that a decrease in MDD severity is accompanied by a decrease in disability (Coryell *et al.*, 1993; Ormel *et al.*, 1993; Judd *et al.*, 2000; Hirschfeld *et al.*, 2002; Buist-Bouwman *et al.*, 2004). However, the longitudinal relationship between disability and symptomatic course of MDD is not fully understood. For example, two studies that followed primary care patients for 1 (Judd *et al.*, 2000) and 3.5 years (Ormel *et al.*, 1993), as well as one 10-year study conducted in tertiary care centres (Von Korff *et al.*, 1992) reported that disability disappears when patients become asymptomatic. However, later community-based studies with a 3-year follow-up (Buist-Bouwman *et al.*, 2004; Rhebergen *et al.*, 2010) and an outpatient study of 5 years (Coryell *et al.*, 1993) found residual disability after symptom remission. Similarly, the assumption that a chronic or recurrent course of depression leads to chronic disability was supported by some (Ormel *et al.*, 1993; Judd *et al.*, 2000) but not all (Kruijshaar *et al.*, 2003; Spijker *et al.*, 2004*b*) studies.

Comparison across these studies might be limited by differences in methodologies. As Buist-Bouwman *et al.* (2004) pointed out, samples were recruited from different settings (community, primary and specialized mental care) and thus probably reflect different severities of MDD symptoms. Similarly, studies used different criteria to define MDD remission. For

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example, Von Korf *et al.* (1992) defined MDD remission as a drop in MDD severity to the mean population level, whereas Buist-Bouwman *et al.* (2004) used dichotomous criteria for MDD diagnosis. Comparison across studies might further be complicated by the different ways in which disability was conceptualized. Most studies assessed work and social disability, which are known to be high in MDD (McKnight and Kashdan, 2009). However, various instruments were used, ranging from well-established to research-specific questionnaires, making the direct comparison of results difficult (McKnight and Kashdan, 2009). Furthermore, although most questionnaires also assessed other aspects of living with MDD, such as physical impairment, pain, impaired vitality or sexual activity, this was not done uniformly across the studies. Finally, since all but two studies have a duration of <3.5 years, insights into the long-term disability remain limited.

To overcome these limitations, the present study examines the 6-year disability in participants recruited from different settings, using a multiple-domain disability assessment scale consistent with the International Classification of Functioning, Disability and Health (ICF). We first examine whether MDD course influences disability by comparing the 6-year disability in participants with chronic, recurrent and remitting MDD and in healthy controls. Since sum-scores might obscure potential differences in disability across various domains (Kamenov *et al.*, 2016), we examine both total and domain-specific disability. Second, we examine whether disability persists after recovery from MDD, by comparing levels of disability in people with remitted MDD and healthy controls. The current practice assumes that patients who reach remission can also resume normal functioning. The study of residual disability and its predictors could help the timely identification of patients with increased risk for long-term disability and thus help alleviate the burden on individuals and society. According to the ICF, disability stems not only from illness, but also from its interaction with contextual factors (WHO, 2001). Therefore, our third aim is to identify socio-demographic, clinical and personality variables that predict residual disability in persons with remitting MDD. To our knowledge, such studies are still lacking.

Methods

Design

Data were drawn from the Netherlands Study of Depression and Anxiety (NESDA), a longitudinal cohort study examining the long-term course and consequences of depressive and anxiety disorders. Between September 2004 and February 2007, 2981 adults (18–65 years) with a current or remitted depressive and/or anxiety disorder (78%) and healthy controls (22%) were recruited from community (19%), primary (54%) and specialized (27%) mental health care. Exclusion criteria were: (1) a primary diagnosis of psychotic, obsessive-compulsive, bipolar or severe addiction disorder and (2) not being fluent in Dutch (Penninx *et al.*, 2008). Baseline assessments (T0) were conducted at three study sites (Amsterdam, Groningen, Leiden), by trained research staff. The face-to-face interviews explored a wide range of domains, including socio-demographics, psychopathology, risk factors and consequences of mental disorders. Follow-up assessments took place at 2 years (T1; $N = 2596$, 87.1%), at 4 years (T2; $N = 2402$, 80.6%) and at 6 years (T3, until April 2013; $N = 2256$, 75.7%). The Ethical Review Boards of all participating centres approved the study. All participants provided written informed consent after the procedures were fully explained.

Study sample

Since we were interested in the course of disability in MDD, we selected respondents with a 1-month diagnosis of MDD with or without dysthymia at baseline who participated in all subsequent assessments and who fulfilled diagnostic criteria for chronic, recurrent or remitting MDD (see below). To examine whether residual disability persists following remission, we additionally selected healthy controls, i.e. participants without (a history of) depressive or anxiety disorders at all assessments. Incident MDDs (i.e. healthy controls at baseline with an MDD diagnosis at T1, T2 or T3) were not included. The final sample consisted of 914 participants: 57 (6.3%) with chronic MDD, 210 (23.0%) with recurrent MDD, 217 (23.7%) with remitting MDD and 430 (47.0%) healthy controls. Factors associated with attrition were identified among baseline socio-demographic and clinical variables, using logistic regression. Attrition was significantly associated with education ($\beta = -0.3$, $p \leqslant 0.001$) and severity of anxiety ($\beta = 0.3$, $p = 0.007$) but not with age ($\beta = -0.1$, $p = 0.378$), gender ($\beta = 0.1$, $p = 0.396$), severity of MDD ($\beta = 0.2$, $p = 0.117$), severity of avoidance ($\beta = 0.1$, $p = 229$), alcohol consumption ($\beta = -0.1$, $p = 0.968$) or chronic somatic diseases ($\beta = -0.1$, $p = 0.834$).

Diagnosis

MDD was diagnosed with the Composite International Diagnostic Interview (CIDI), version 2.1, Dutch version (Smitten *et al.*, 1998), a structured interview with high reliability (Wittchen *et al.*, 1991; Wacker *et al.*, 2006) and high validity for depressive disorders (Wittchen, 1989, 1994). *Chronic MDD* (i.e. MDD during the entire study period) was defined as meeting 1-month DSM-IV-criteria for MDD at baseline and a diagnosis of MDD or dysthymia at all subsequent assessments. *Recurrent MDD* was defined as meeting 1-month criteria for MDD at baseline, followed by at least 1 month of remission (not fulfilling criteria of MDD nor dysthymia) and a subsequent recurrence of MDD or dysthymia at any of the later assessments. In this group, 111 participants (52.9%) reported remission at T1 and recurrence at T2, 61 participants (29.0%) reported remission at T1 and recurrence at T3 and 38 participants (18.1%) reported remission at T2 and recurrence at T3. *Remitting MDD* was defined as meeting the 1-month criteria for MDD at baseline, followed by remission of MDD and dysthymia at T1 (early remission, $n = 146$, 67.3%), at T2 (intermediate remission, $n = 48$, 22.1%) or at T3 (late remission, $n = 23$, 10.6%).

Disability

Disability was assessed at each wave using the World Health Organization Disability Assessment Schedule II (WHO DAS II) (Chwastiak and Von Korff, 2003). This self-report questionnaire assesses on a Likert scale how much difficulty participants experienced over the past 30 days in performing activities such as, for example, doing the most important work/school tasks well; maintaining friendships or joining community activities in the same way as everyone else. Seven domains were assessed: household activities, work/school activities, interpersonal functioning, participation in society, cognition, mobility and self-care. Domain-specific scores were added to calculate total disability. Higher scores indicate more disability. The WHO DAS II is highly sensitive to symptom change in MDD (Perini *et al.*, 2006) and has sufficient test–retest reliability (Chopra *et al.*,

2004). Since a large proportion of participants ($n = 266$, 29.1%) did not work nor go to school, we used the 32-item version of the questionnaire (excluding work disability). The internal consistency was high (Cronbach's $\alpha = 0.90$).

Putative predictors of disability in remitting MDD

We considered baseline socio-demographic, clinical and personality variables. *Socio-demographic variables* included: age, gender, education, presence of a partner and employment status. *Clinical variables.* Age of onset of depression was determined using the CIDI (Smitten *et al.*, 1998). Severity of MDD was assessed with the 30-item Inventory of Depressive Symptomatology (IDS) (Rush *et al.*, 1986). The presence of comorbid 1-month dysthymia and anxiety disorders (panic disorder with/without agoraphobia, social phobia, agoraphobia or generalized anxiety disorder) was assessed with the CIDI (Smitten *et al.*, 1998). Severity of anxiety and of avoidance symptoms was assessed using the 21-item Beck Anxiety Inventory (BAI) (Beck *et al.*, 1988) and the 15-item Fear Questionnaire (FQ) (Marks and Mathews, 1979), respectively. Alcohol consumption (number of drinks containing alcohol on a typical day) was assessed using the Alcohol Use Disorders Identification Test (AUDIT) (Saunders *et al.*, 1993). Consumption of 1–2 drinks was labelled as mild, 3–4 drinks as moderate; higher consumption was considered excessive drinking. The presence of somatic disease was operationalized as the number of chronic somatic diseases under medical treatment and was assessed using a comprehensive, self-reported inventory of 20 chronic conditions (Penninx *et al.*, 2008). Psychiatric treatment referred to use of antidepressant medication or psychological treatment. Current medication use was considered when taken at least 50% of the time and referred to use of antidepressants [serotonin reuptake inhibitors, Anatomical Therapeutic Chemical (ATC) code N06AB; tricyclic antidepressants, ATC N06AA; and other antidepressants, ATC N06AF/N06AX]. Psychological treatment included formal psychotherapy, counselling or skills training. Care setting referred to whether participants were recruited from specialized mental health outpatient clinics, from primary care or from the community. *Personality variables*, assessed with the 60-item Neuroticism–Extraversion–Openness (NEO) personality self-report questionnaire (Costa and McCrae, 1995), included neuroticism, extraversion, agreeableness, conscientiousness and openness to experience.

Data analysis

Baseline characteristics across groups were compared using two-tailed χ^2 tests for categorical variables, one-way analysis of variance statistics (ANOVA) for continuous variables, and non-parametric Kruskal–Wallis test for skewed variables. The course of total and domain-specific disability over time was examined using Linear Mixed Models (LMM). To correct for correlation in data due to the repeated measure design, 'participant' was introduced as a random factor. Group, time and group × time interaction were entered as fixed factors. The group × time interaction term compared changes in disability over time across groups. LMM analyses were adjusted for all socio-demographics, entered as fixed factors.

In remitting MDD ($n = 217$), residual disability was analysed using descriptive statistics (mean, S.D., minimum and maximum values). Predictors of residual disability in the remitting group were identified through regression analyses. Strength of association between putative predictors and disability was assessed through bivariate analysis (p value set at 0.1). Multicollinearity was suspected if Pearson's correlation coefficients were larger than 0.80 and if the variance inflation factor (VIF) was larger than 10 (Field, 2009). Independent predictors of disability were identified through four multivariate models (significance value set at 0.05). Models 1, 2 and 3 included socio-demographic, clinical and personality variables, respectively, that were significant in bivariate analyses. Significant factors obtained from Models 1, 2 and 3 were introduced in Model 4. We finally conducted a post-hoc analysis using the Spearman correlation coefficient and the coefficient of determination to examine the relationship between residual disability and residual depressive symptoms and to estimate their shared variance. Data were analysed using SPSS version 24.0 (IBM SPSS Statistics for Windows, 2016).

Results

Study sample

Baseline characteristics of the study sample ($n = 914$) are summarized in Table 1. Mean age was 41.8 years (S.D. 13.4). The majority of participants were female (62.0%), had followed 12.4 years of education (S.D. 3.2) and had a partner (69.3%). Compared to controls, MDD groups were significantly less educated, were less likely to have a partner or to be employed, were more likely to report abstinence from alcohol use, had more somatic diseases and reported higher neuroticism and lower extraversion, agreeableness and conscientiousness. Depressive symptoms were most severe in chronic MDD, followed by recurrent MDD, remitting MDD and healthy controls. Comorbid dysthymia was significantly less common in remitting MDD, compared to chronic and recurrent MDD.

Total disability

Total disability is presented Fig. 1 and in online Supplementary Table S1. At baseline, all diagnostic groups reported significantly more disability compared to healthy controls. Most disability was found in chronic MDD [β (S.E.) = 39.0 (1.8), $p \leqslant 0.001$], followed by recurrent MDD [β (S.E.) = 31.5 (1.1), $p \leqslant 0.001$] and remitting MDD [β (S.E.) = 27.2 (1.1), $p \leqslant 0.001$] (reference: healthy controls). Furthermore, we found a significant gradient in disability across diagnostic groups: chronic MDD functioned significantly worse than recurrent MDD [β (S.E.) = 6.0 (2.5), $p \leqslant 0.05$], which functioned significantly worse than remitting MDD [β (S.E.) = 3.8 (1.6), $p \leqslant 0.05$]. These differences remained statistically significant at T2 and T3.

Interaction with time between baseline and T3 was not significant for chronic MDD (see also Fig. 1), suggesting stable levels of disability during follow-up. By contrast, we found a significant negative interaction with time between baseline and T3 for recurrent MDD [β (S.E.) = −7.5 (1.1), $p \leqslant 0.001$] and for remitting MDD [β (S.E.) = −14.5 (1.0), $p \leqslant 0.001$] (reference: healthy controls), thus disability decreased over time in these groups. The significant decrease in disability occurred exclusively during the first 2 years of follow-up, when the majority of participants (81.9% for the recurrent group and 67.3% for the remitting group) achieved remission.

At T3, all MDD groups were significantly more disabled than healthy controls. Thus, significant residual disability persisted

Table 1. Baseline characteristics of participants with chronic, recurrent or remitting depressive disorder and of healthy controls (n = 914)

Baseline characteristics	Total N = 914 100%	Chronic N = 57 6.3%	Recurrent N = 210 23.0%	Remitting N = 217 23.7%	Controls N = 430 47.0%	p^a	Post-hoc analysis[b]
Socio-demographic variables							
Age, mean (s.d.), y	41.7(13.4)	43.2(10.3)	42.4(12.2)	41.4(12.7)	41.5(14.6)	0.701	–
Females, n (%)	567(62.0)	29(50.9)	144(68.6)	140(64.5)	254(59.1)	0.029	1 < 2, 2 > 4, 3 > 4
Education, mean (s.d.), y	12.4(3.2)	11.9(3.0)	11.9(3.2)	11.6(2.9)	13.1(3.2)	≤0.001	1 < 4, 2 < 4, 3 < 4
With partner, n (%)	630(69.3)	35(61.4)	138(65.7)	138(63.6)	327(76.0)	0.001	1 < 4, 2 < 4, 3 < 4
Employed[c], n (%)	643(70.7)	32(56.1)	122(58.7)	146(67.6)	343(80.1)	≤0.001	1 < 4, 2 < 4, 3 < 4
Clinical variables							
Age of onset MDD, mean (s.d.), y	29.1(10.9)	23.0(9.9)	25.4(11.8)	29.3(13.6)	–	≤0.001	1 < 3, 2 < 3
Severity of MDD (IDS), mean (s.d.)	21.3(16.4)	41.9(10.3)	34.6(10.6)	31.8(10.9)	6.7(5.9)	≤0.001	1 > 2, 1 > 3, 1 > 4, 2 > 3, 2 > 4, 3 > 4
Comorbid dysthymia, n (%)	200(41.3)	30(52.6)	98(46.7)	72(33.2)	–	0.018	1 > 3,2 > 3
Comorbid anxiety disorder, n (%)	287(59.3)	33(57.9)	134(63.8)	120(55.3)	–	0.196	–
Severity of anxiety symptoms (BAI), mean (s.d.)	11.0(10.7)	20.2(10.2)	18.5(9.7)	16.9(10.0)	3.1(3.9)	≤0.001	1 > 3, 1 > 4, 2 > 4, 3 > 4
Severity of avoidance symptoms (FQ), mean (s.d.)	22.3(19.7)	36.5(20.2)	34.7(20.2)	29.5(19.0)	10.7(11.2)	≤0.001	1 > 3, 1 > 4, 2 > 4, 3 > 4
Alcohol consumption[d], n (%)							
Abstainers	142(15.7)	19(33.3)	39(18.8)	36(16.7)	48(11.2)	≤0.001	1 > 2, 1 > 3, 1 > 4, 2 > 4, 3 > 4
Mild drinkers (1–2 units)	373(41.1)	21(36.8)	75(36.1)	95(44.2)	182(42.6)	0.276	–
Moderate drinkers (3–4 units)	258(28.4)	12(21.1)	57(27.4)	49(22.8)	140(32.8)	p ≤ 0.05	1 < 4, 3 < 4
Excessive drinkers (5 units or more)	134(14.8)	5(8.8)	37(17.8)	35(16.3)	57(13.3)	0.240	–
Number of somatic diseases n (%)	0.8(1.0)	1.1(1.3)	1.1(1.2)	1.0(1.0)	0.6(0.9)	≤0.001	1 > 4, 2 > 4, 3 > 4
Use of psychiatric treatment[e], n (%)	334(36.5)	45(78.9)	140(66.7)	130(59.9)	19(4.4)	≤0.001	1 > 2,1 > 3, 1 > 4,2 > 4,3 > 4
Use of specialized mental health care, n (%)	261(53.9)	42(73.7)	113(53.8)	106(48.8)	0(0.0)	≤0.001	1 > 2,1 > 3
Personality variables (NEO), mean (s.d.)							
Neuroticism	34.6(10.8)	44.4(4.7)	43.6(6.5)	41.2(6.9)	25.6(6.7)	≤0.001	1 > 3, 1 > 4, 2 > 3, 2 > 4, 3 > 4
Extraversion	37.3(8.2)	30.3(6.4)	31.5(6.4)	34.2(6.8)	42.7(6.1)	≤0.001	1 < 3, 1 < 4, 2 < 3,2 < 4, 3 < 4
Openness	38.3(5.9)	37.4(6.7)	38.9(6.0)	38.1(6.2)	38.2(5.6)	0.262	–
Agreeableness	44.3(5.2)	42.6(6.2)	42.7(5.5)	43.5(4.8)	45.6(4.8)	≤0.001	1 < 4, 2 < 4, 3 < 4
Conscientiousness	42.0(6.9)	37.0(7.6)	38.3(6.3)	39.9(7.0)	45.5(5.1)	≤0.001	1 < 3, 1 < 4, 2 < 3, 2 < 4, 3 < 4

BAI, Beck Anxiety Inventory; FQ, Fear Questionnaire; IDS, Inventory of Depressive Symptomatology; MDD, Major Depressive Disorder; NEO, Neuroticism–Extraversion–Openness personality self-report questionnaire.

[a]Overall group differences, based on χ^2 statistics for categorical variables, ANOVA for continuous variables and Kruskal–Wallis for skewed variables.

[b]Groups in post-hoc analysis noted as: 1 = chronic depressive disorder; 2 = recurrent depressive disorder; 3 = remitting depressive disorder; 4 = healthy controls. $p \leqslant 0.05$ is used as a level of significance.

[c]Analysis based on 909 cases (data on employment was missing for five out of 914 cases, 0.5%).

[d]Analysis based on 907 cases (data on alcohol consumption was missing for seven out of 914 cases, 0.8%).

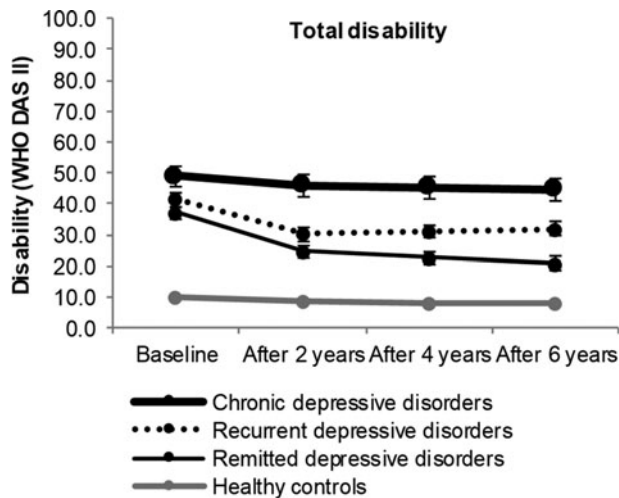[e]Antidepressant medication or psychological treatment.

Fig. 1. Six-year course of total disability in participants with chronic depressive disorder, recurrent depressive disorder, remitting depressive disorder and healthy controls. Analyses are adjusted for age, gender, education and partner status at baseline. Differences between depression groups and healthy controls are significant at all measurements ($p \leqslant 0.001$).

despite remission of MDD [β (S.E.) = 12.7 (1.1), $p \leqslant 0.001$]. Notably, residual disability showed significant heterogeneity in this group, with scores ranging between 0.0 and 81.1 (mean 19.2, S.D. 15.8). Furthermore, 18.0% of participants reported disability scores lower than the mean disability score of healthy controls, whereas 7.8% reported disability scores larger than the mean disability scores of chronic MDD.

Domain-specific disability

Domain-specific disability is presented in Fig. 2 and in online Supplementary Table S2. At baseline, all diagnostic groups reported significant disability in all domains. Regardless of the diagnostic group, most disability was found in household activities, followed by interpersonal functioning, participation in society and cognition, and least disability in mobility and self-care. Chronic MDD reported significantly more disability in household activities, interpersonal functioning, participation in society and cognition, but not in mobility and self-care, compared to recurrent and remitting MDD. In turn, recurrent MDD was significantly more disabled in interpersonal functioning, cognition and self-care, but not in household activities, participation in society and mobility, compared to remitting MDD.

Similar to total disability, domain-specific disability in recurrent and remitted MDD decreased significantly over time across all domains, due to a significant decrease during the first 2 years. Notably, in remitted MDD, three domains (participation in society, interpersonal functioning and self-care) continued to improve even after the first 2 years of follow-up, suggesting that these domains need more time to improve. In chronic MDD, for which total disability did not change over time, disability was stable in all domains, except for cognition. Cognition improved significantly from baseline to T3 [β (S.E.) = −6.3 (2.2), $p \leqslant 0.05$, reference: healthy controls]. At T3, all domain-specific disability differed significantly across the groups, with worse disability reported by chronic MDD, followed by recurrent and remitting MDD and by healthy controls.

Predictors of residual disability

Predictors of disability in remitting MDD are shown in Table 2. In bivariate analysis, disability was associated with several predictors. Multicollinearity was not a problem (the largest Pearson's correlation coefficient was 0.5, the largest VIF was 1.6). Among socio-demographic variables (Model 1), age, education and employment status were predictive of residual disability. Among clinical variables (Model 2), residual disability was predicted by time-point of remission of MDD, severity of avoidance, number of somatic diseases and baseline disability. Among personality variables (Model 3), only neuroticism and extraversion remained significant. Our final model (Model 4) showed residual disability in remitting MDD was significantly predicted by older age, late remission of MDD (at T3), more severe avoidance symptoms and higher baseline disability. The total variance explained by the model was 43.9% ($F = 15.2$, df = 10, $p \leqslant 0.001$).

Discussion

Our primary aim was to examine the relationship between the course of depression and disability over a 6-year period. Results showed that MDD was associated with significantly more disability than no diagnosis and that most disability was reported by chronic MDD, followed by recurrent and remitting MDD. A chronic course of depression was associated with a chronic, stable course of disability. By contrast, remission of depressive symptoms was associated with a significant decrease in disability, which however did not reach the level of healthy controls. This synchrony of change between the symptomatic course of depression and the course of disability is in line with previous findings (Ormel, 2000).

MDD was associated with significant disability across all domains. Most disability was found in household activities, interpersonal functioning, participation in society and cognition, and least disability was found in mobility and self-care. Similar findings were reported in a recent study, in which domestic life and interpersonal activities, and to a lesser extent mobility and cognition (but not self-care) had a high impact on the quality of life in depressive disorder in nine countries (Kamenov *et al.*, 2016). This suggests that depression has a lower impact on mobility, compared to other domains of functioning. In line with Konecky *et al.* (2014), we conclude that the assessment of mobility might be less indicative of disability in MDD.

Across all disability domains, we found a synchrony of change, with significant changes within the first 2 years of follow-up. Chronic depression was associated with chronic domain-specific disability, except for cognition. This suggests that symptomatic remission might be a prerequisite for improvements in disability. In remitting MDD, interpersonal functioning and participation in society continued to improve even after the first 2 years of follow-up. This suggests that different domains improve at a different speed. It is possible that depressive symptoms remit at differential speeds, which in turn impacts on the domains of disability. This relationship was shown in a recent study, which found that early insomnia had strong effects on work disability, while self-blame impacted on close relationships, interest loss on social activities and fatigue on home management (Fried and Nesse, 2014).

Total and domain-specific disability persisted after symptomatic remission. This is remarkable, considering that at T3 the majority of participants with remitting MDD had been in remission for at least 2 years. Four scenarios are possible. First,
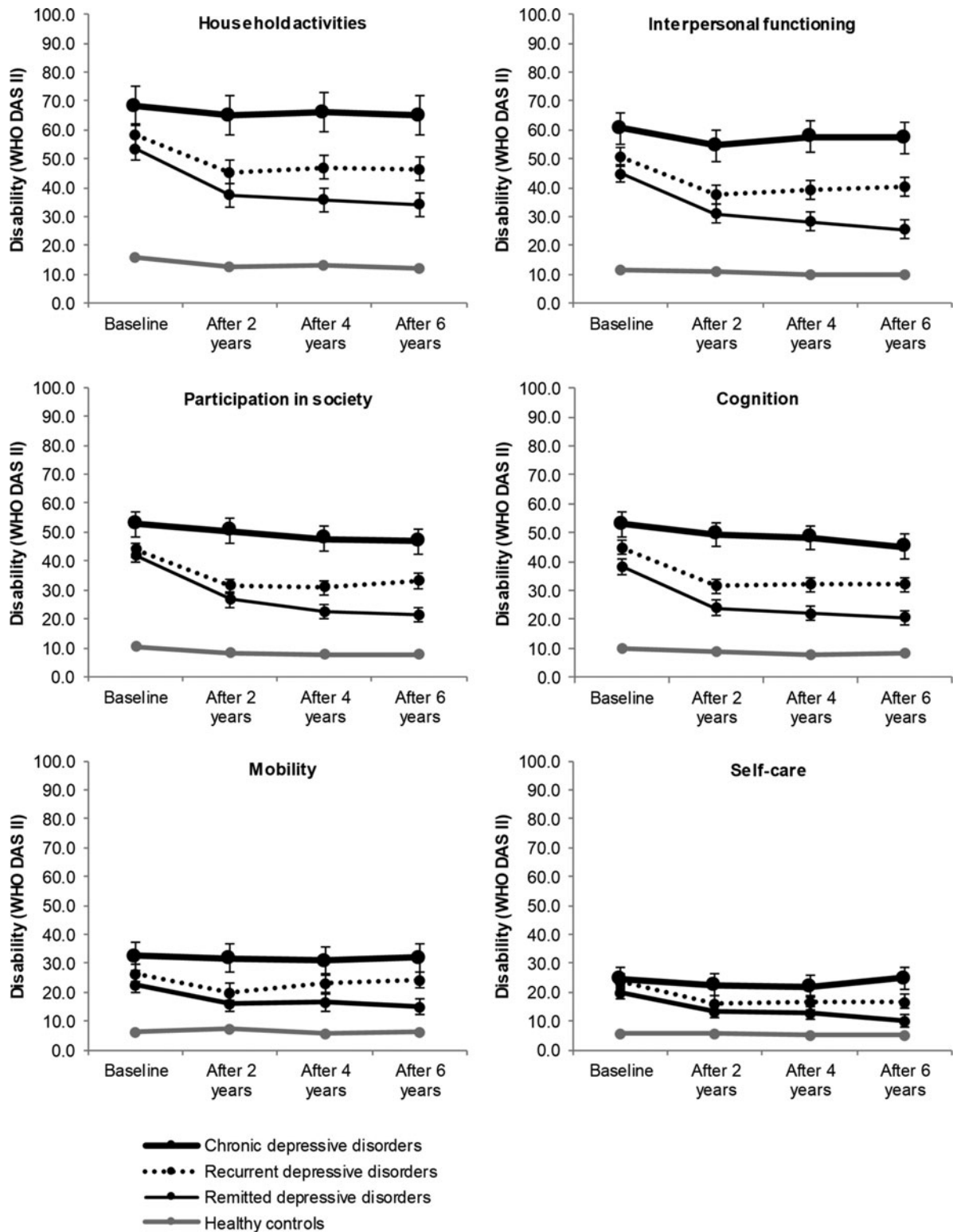
Fig. 2. Six-year course across domains of disability in participants with chronic depressive disorder, recurrent depressive disorder, remitting depressive disorder and healthy controls. Analyses are adjusted for age, gender, education and partner status at baseline. Differences between depression groups and healthy controls are significant at all measurements ($p \leqslant 0.001$).

remission of disability might lag behind symptomatic remission (Rhebergen *et al.*, 2010). A late remission (at T3) appeared to be the most important predictor of high levels of residual disability. It is thus possible that those who remitted at the end of the follow-up simply lack time for improvements in disability. Second, residual disability might be due to subthreshold symptoms (state effect) (Karsten *et al.*, 2010). In our study, residual disability showed substantial heterogeneity. Post-hoc analyses in

Table 2. Bivariate and multivariate predictors of disability at 6-year follow-up in participants with remitting depressive disorder ($n = 217$)

Baseline characteristics	Bivariate β (s.e.)	Bivariate p	Model 1 β (s.e.)	Model 1 p	Model 2 β (s.e.)	Model 2 p	Model 3 β (s.e.)	Model 3 p	Model 4 β (s.e.)	Model 4 p
Socio-demographic variables										
Age[a]	3.3(1.1)	0.003	2.7(1.1)	0.011					3.0(0.9)	0.001
Female (yes)	1.0(2.3)	0.671								
Education[a]	−3.2(1.1)	0.004	−2.8(1.1)	0.008					−1.5(0.9)	0.091
With partner (yes)	−2.6(2.3)	0.263								
Employed (yes)	−7.2(2.3)	0.002	−5.6(2.3)	0.016					−2.3(1.9)	0.225
Clinical variables										
Age of onset MDD	1.6(1.1)	0.143								
Severity of MDD (IDS[a])	6.1(1.0)	$p \leqslant 0.001$			−1.2(1.3)	0.366			–	–
Time-point of remission of MDD, v. early remission (at T1)										
Intermediate remission (at T2)	4.5(2.6)	0.084			1.5(2.2)	0.507			1.3(2.1)	0.528
Late remission (at T3)	14.2(3.5)	$p \leqslant 0.001$			11.0(3.0)	$p \leqslant 0.001$			10.6(2.9)	$p \leqslant 0.001$
Comorbid dysthymia (yes)	8.4(2.3)	$p \leqslant 0.001$			3.7(2.0)	0.071			–	–
Comorbid anxiety disorder (yes)	10.2(2.1)	$p \leqslant 0.001$			3.6(2.1)	0.084			–	–
Severity of anxiety symptoms (BAI[a])	6.1(1.0)	$p \leqslant 0.001$			0.7(1.3)	0.578			–	–
Severity of avoidance symptoms (FQ[a])	6.7(1.0)	$p \leqslant 0.001$			3.1(1.1)	0.006			2.7(1.0)	0.012
Alcohol consumption, v. abstainers										
Mild drinkers (1–2 units)	−5.4(3.1)	0.088			−0.7(2.6)	0.790			–	–
Moderate drinkers (3–4 units)	−3.7(3.5)	0.293			0.3(2.9)	0.930			–	–
Excessive drinkers (5 units or more)	−5.8(3.8)	0.129			−3.7(3.1)	0.600			–	–
Number of somatic diseases[a]	4.5(1.1)	$p \leqslant 0.001$			2.4(0.9)	0.014			1.7(0.9)	0.078
Use of psychiatric treatment[b] (yes)	4.2(2.2)	0.063			0.8(1.9)	0.669			–	–
Use of specialised mental health care (yes)	−1.6(2.2)	0.478								
Levels of disability[a]	7.9(1.0)	$p \leqslant 0.001$			5.5(1.2)	$p \leqslant 0.001$			5.3(1.0)	$p \leqslant 0.001$
Personality variables (NEO)										
Neuroticism[a]	4.9(1.1)	$p \leqslant 0.001$					3.3(1.2)	0.004	1.6(1.0)	0.138
Extraversion[a]	−4.8(1.1)	$p \leqslant 0.001$					−3.0(1.2)	0.013	−0.7(1.0)	0.442
Openness[a]	−0.8(1.1)	0.457								
Agreeableness[a]	−3.0(1.1)	0.007					−1.2(1.1)	0.296	–	–
Conscientiousness[a]	−1.9(1.1)	0.092								

BAI, Beck Anxiety Inventory; FQ, Fear Questionnaire; IDS, Inventory of Depressive Symptomatology; MDD, Major Depressive Disorder; NEO, Neuroticism–Extraversion–Openness personality self-report questionnaire.

Model 1: socio-demographic variables; Model 2: clinical variables; Model 3: personality variables; Model 4: final model.

[a]Per s.d. increase.

[b]Antidepressant medication or psychological treatment.

remitting MDD revealed a strong, positive correlation between the severity of residual disability and the severity of residual depressive symptoms (Spearman's $r = 0.7$, $p \leqslant 0.001$). Furthermore, we found that the severity of residual depressive symptoms explained nearly half of the variance in residual disability in this group (coefficient of determination = 48.6). This suggests that residual disability might be largely due to subthreshold depressive symptoms. Third, residual disability could be a continuation of pre-morbid disability (trait effect) (Ormel *et al.*, 2004; Bos *et al.*, 2018). In the absence of pre-morbid assessments, we cannot verify trait effects, but trait effects have been documented previously (Ormel *et al.*, 2004). Fourth, residual disability might represent persistent disability developed during MDD (scar effects) (Ormel *et al.*, 2004; Bos *et al.*, 2018). According to Ormel *et al.* (2004), scarring may occur in severe recurrent episodes. In our study, baseline severity of MDD did not predict residual disability.

Higher residual disability was predicted by late symptom remission, as well as by older age, more severe avoidance symptoms and higher disability at baseline. Severity of avoidance symptoms predicts disability in anxiety disorders (Iancu *et al.*, 2014; Hendriks *et al.*, 2016), but to our knowledge, no studies examined this predictor in relation to disability in MDD. Use of psychiatric treatment did not reach statistical significance in predicting residual disability ($p = 0.063$). This may seem surprising, since both antidepressant medication and psychotherapy can reduce disability even in patients with severe MDD (Hirschfeld *et al.*, 2002). However, one should bear in mind that this study has a naturalistic design. Hence, this finding is likely due to the fact that treatment is used most often by the most severe patients, who also happen to have the worst outcomes (Cabello *et al.*, 2014).

Strengths and limitations

Strengths of this study include the large sample size, recruitment from different settings, use of structured diagnostic procedures, follow-up of 6 years and assessment of several domains of disability, in line with the ICF. One limitation resides in the assessment of disability. We rely on self-reported measures, which are important to assess the patient's perspectives but might be impacted by information-processing biases. Depressive symptoms are known to alter the interpretation of one's own functioning (Kempen *et al.*, 1996) and of socially relevant information (Weightman *et al.*, 2014). Since the NESDA study did not collect any information from other sources (such as family members, friends or healthcare providers), it is not possible to assess whether the disability scores of participants with MDD were erroneously increased. Further limitations are the lack of insights regarding the level of premorbid functioning and the fact that work disability could not be assessed because a large proportion of included participants did not work. Also, MDD course neglected symptom fluctuations between assessments. This study did not include data on income and therefore could not provide a complete assessment of the role played by the socio-economic status in predicting disability in people with remitted MDD. Finally, we do not know whether the predictors of residual disability are causal, and hence, we cannot be sure that targeting these predictors will improve functioning after symptomatic remission.

Clinical implications

Chronic MDD was associated with a chronic course of disability, whereas symptomatic remission was associated with a significant decrease in disability, suggesting that symptomatic remission is a prerequisite for improvements in disability. However, symptom remission does not imply full remission of disability. Therefore, treatment of MDD should explicitly focus on disability, especially on the more complex domains. Older age, high levels of disability and severe avoidance symptoms represent risk factors for residual disability. This underlines the importance of current treatment strategies that promote behavioural activation (i.e. diminishing avoidance). Furthermore, severity of residual disability correlated with the severity of residual depressive symptoms. Therefore, treating subthreshold depressive symptoms in patients with remitted MDD might prevent recurrence of MDD and thus reduce the burden of this disease.

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References

Beck AT, Epstein N, Brown G and Steer RA (1988) An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology* **56**, 893–897.

Bos EH, ten Have M, van Dorsselaer S, Jeronimus BF, de Graaf R and de Jonge P (2018) Functioning before and after a major depressive episode: pre-existing vulnerability or scar? A prospective three-wave population-based study. *Psychological Medicine* **48**, 2264–2272.

Buist-Bouwman MA, Ormel J, De Graaf R and Vollebergh WAM (2004) Functioning after a major depressive episode: complete or incomplete recovery? *Journal of Affective Disorders* **82**, 363–371.

Buist-Bouwman MA, De Graaf R, Vollebergh WAM, Alonso J, Bruffaerts R and Ormel J (2006) Functional disability of mental disorders and comparison with physical disorders: a study among the general population of six European countries. *Acta Psychiatrica Scandinavica* **113**, 492–500.

Cabello M, Caballero FF, Chatterji S, Cieza A and Ayuso-Mateos JL (2014) Risk factors for incidence and persistence of disability in chronic major depression and alcohol use disorders: longitudinal analyses of a population-based study. *Health and Quality of Life Outcomes* **12**, 186–198.

Chopra PK, Chopra PK, Couper JW and Herrman H (2004) The assessment of patients with long-term psychotic disorders: application of the WHO Disability Assessment Schedule II. *Australian & New Zealand Journal of Psychiatry* **38**, 753–759.

Chwastiak LA and Von Korff M (2003) Disability in depression and back pain: evaluation of the World Health Organization Disability Assessment Schedule (WHO DAS II) in a primary care setting. *Journal of Clinical Epidemiology* **56**, 507–514.

Coryell W, Scheftner W, Keller M, Endicott J, Maser J and Klerman GL (1993) The enduring psychosocial consequences of mania and depression. *American Journal of Psychiatry* **150**, 720–727.

Costa PT and McCrae RR (1995) Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. *Journal of Personality Assessment* **64**, 21–50.

Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, Vos T and Whiteford HA (2013) Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Medicine* **10**, e1001547.

Field A (2009) *Discovering Statistics Using SPSS*, 3rd Edn. London: Sage Publications.

Fried EI and Nesse RM (2014) The impact of individual depressive symptoms on impairment of psychosocial functioning. *PLoS ONE* **9**, e90311.

GBD 2015 Mortality and Causes of Death Collaborators (2016) Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet* **388**, 1459–1544.

Gelenberg AJ (2010) The prevalence and impact of depression. *The Journal of Clinical Psychiatry* **71**, e06.

Greer TL, Kurian BT and Trivedi MH (2010) Defining and measuring functional recovery from depression. CNS Drugs 24, 267–284.

Hays RD, Wells KB, Sherbourne CD, Rogers W and Spritzer K (1995) Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. Archives of General Psychiatry 52, 11–19.

Hendriks SM, Spijker J, Licht CMM, Hardeveld F, de Graaf R, Batelaan NM, Penninx BWJH and Beekman ATF (2016) Long-term disability in anxiety disorders. BMC Psychiatry 16, 248–255.

Hirschfeld RMA, Dunner DL, Keitner G, Klein DN, Koran LM, Kornstein SG, Markowitz JC, Miller I, Nemeroff CB, Ninan PT, Rush AJ, Schatzberg AF, Thase ME, Trivedi MH, Borian FE, Crits-Christoph P and Keller MB (2002) Does psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone, psychotherapy, and their combination. Biological Psychiatry 51, 123–133.

Iancu SC, Batelaan NM, Zweekhorst MBM, Bunders JFG, Veltman DJ, Penninx BWJH and Van Balkom AJLM (2014) Trajectories of functioning after remission from anxiety disorders: 2-year course and outcome predictors. Psychological Medicine 44, 593–605.

IBM Corp. (2016) IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

Judd LL, Akiskal HS, Zeller PJ, Paulus M, Leon AC, Maser JD, Endicott J, Coryell W, Kunovac JL, Mueller TI, Rice JP and Keller MB (2000) Psychosocial disability during the long-term course of unipolar major depressive disorder. Archives of General Psychiatry 57, 375–380.

Kamenov K, Caballero FF, Miret M, Leonardi M, Sainio P, Tobiasz-Adamczyk B, Haro JM, Chatterji S, Ayuso-Mateos JL and Cabello M (2016) Which are the most burdensome functioning areas in depression? A cross-national study. Frontiers in Psychology 7, 1–9.

Karsten J, Hartman CA, Ormel J, Nolen WA and Penninx BWJH (2010) Subthreshold depression based on functional impairment better defined by symptom severity than by number of DSM-IV symptoms. Journal of Affective Disorders 123, 230–237.

Katon W (2009) The impact of depression on workplace functioning and disability costs. The American Journal of Managed Care 15, S322–S327.

Kempen GIJM, van Heuvelen MJG, van den Brink RHS, Kooijman AC, Klein M, Houx PJ and Ormel J (1996) Factors affecting contrasting results between self-reported and performance-based levels of physical limitations. Age and Ageing 25, 458–464.

Konecky B, Meyer EC, Marx BP, Kimbrel NA and Sandra B (2014) Using the WHODAS 2.0 to assess functional disability associated with mental disorders. American Journal of Psychiatry 171, 818–820.

Kruijshaar ME, Hoeymans N, Bijl RV, Spijker J and Essink-Bot ML (2003) Levels of disability in major depression: findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Journal of Affective Disorders 77, 53–64.

Marks IM and Mathews AM (1979) Brief standard self-rating for phobic patients. Behaviour Research and Therapy 17, 263–267.

McKnight PE and Kashdan TB (2009) The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. Clinical Psychology Review 29, 243–259.

Ormel J (2000) Synchrony of change in depression and disability: what next? Archives of General Psychiatry 57, 381–382.

Ormel J, von Korff M, van den Brink W, Katon W, Brilman E and Oldehinkel T (1993) Depression, anxiety, and social disability show synchrony of change in primary care patients. American Journal of Public Health 83, 385–390.

Ormel J, Oldehinkel AJ, Nolen WA and Vollebergh W (2004) Psychosocial disability before, during, and after a major depressive episode: a 3-wave population-based study of state, scar, and trait effects. Archives of General Psychiatry 61, 387–392.

Penninx BWJH, Beekman ATF, Smit JH, Zitman FG, Nolen WA, Spinhoven P, Cuijpers P, De Jong PJ, Van Marwijk HWJ, Assendelft WJJ, van der Meer K, Verhaak P, Wensing M, de Graaf R, Hoogendijk WJ, Ormel J and van Dyck R (2008) The Netherlands Study of Depression and Anxiety (NESDA): Rationale, objectives and methods. International Journal of Methods in Psychiatric Research 17, 121–140.

Perini SJ, Slade T and Andrews G (2006) Generic effectiveness measures: sensitivity to symptom change in anxiety disorders. Journal of Affective Disorders 90, 123–130.

Rhebergen D, Beekman ATF, de Graaf R, Nolen WA, Spijker J, Hoogendijk WJ and Penninx BWJH (2010) Trajectories of recovery of social and physical functioning in major depression, dysthymic disorder and double depression: a 3-year follow-up. Journal of Affective Disorders 124, 148–156.

Rush AJ, Giles DE, Schlesser MA, Fulton CL, Weissenburger J and Burns C (1986) The inventory for depressive symptomatology (IDS): preliminary findings. Psychiatry Research 18, 65–87.

Saunders JB, Aasland OG, Babor TF, de la Fuente JR and Grant M (1993) Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption. Addiction 88, 791–804.

Smitten HM, Smeets RMW and Brink W (1998). Composite International Diagnostic Interview (CIDI), Version 2.1, 12-months (in Dutch). Amsterdam/Geneva: World Health Organization.

Sobocki P, Jönsson B, Angst J and Rehnberg C (2006) Cost of depression in Europe. The Journal of Mental Health Policy and Economics 9, 87–98.

Spijker J, De Graaf R, Bijl RV, Beekman ATF, Ormel J and Nolen WA (2004a) Determinants of persistence of major depressive episodes in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Journal of Affective Disorders 81, 231–240.

Spijker J, Graaf R, Bijl RV, Beekman ATF, Ormel J and Nolen WA (2004b) Functional disability and depression in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Acta Psychiatrica Scandinavica 110, 208–214.

Von Korff M, Ormel J, Katon W and Lin EHB (1992) Disability and depression among high utilizers of health care: a longitudinal analysis. Archives of General Psychiatry 49, 91–100.

Wacker H, Battegay R, Mullejans R and Schlosser C (2006) Using the CIDI-C in the general population. In Stefanis CN, Rabavilas AD and Soldatos CR (eds), Psychiatry: A World Perspective. Amsterdam: Elsevier Science Publishers, pp. 138–143.

Weightman MJ, Air TM and Baune BT (2014) A review of the role of social cognition in major depressive disorder. Frontiers in Psychiatry 5, 1–13.

WHO (2001) International Classification of Functioning, Disability and Health (ICF). Geneva: World Health Organization.

Wittchen H (1989) Recall and dating of psychiatric symptoms. Archives of General Psychiatry 46, 437–443.

Wittchen H (1994) Reliability and validity studies of the WHO – Composite International Diagnostic Interview (CIDI): a critical review. Journal of Psychiatric Research 28, 57–84.

Wittchen H, Robins LN, Cottler LB, Sartorius N, Burke JD and Regier D (1991) Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. British Journal of Psychiatry 159, 645–665.