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Research report

Recurrence of major depressive disorder across different treatment settings: Results from the NESDA study

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ABSTRACT

Objective: Examine time to recurrence of major depressive disorder (MDD) across different treatment settings and assess predictors of time to recurrence of MDD.**Methods:** Data were from 375 subjects with a MDD diagnosis from the Netherlands Study of Depression and Anxiety (NESDA). The study sample was restricted to subjects with a remission of at least three months. These subjects were followed until recurrence or the end of the two year follow-up. DSM-IV based diagnostic interviews and Life Chart Interviews were used to assess time to recurrence of MDD across treatment settings. Predictors of time to recurrence were determined using Cox's proportional hazards analyses.**Results:** Although trends indicated a slightly higher rate of and shorter time to recurrence in specialized mental health care, no significant difference in recurrence rate (26.8% versus 33.5%, $p=0.23$) or in time to recurrence (controlled for covariates) of MDD was found between respondents in specialized mental health care and respondents treated in primary care (average 6.6 versus 5.5 months, $p=0.09$). In multivariable analyses, a family history of MDD and previous major depressive episodes were associated with a shorter time to recurrence. Predictors did not differ across treatment settings.**Limitations:** The study sample may not be representative of the entire population treated for MDD in specialized mental health care.**Conclusions:** Health care professionals in both settings should be aware of the same risk factors since the recurrence risk and its predictors appeared to be similar across settings.

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1. Introduction

Major depressive disorder (MDD) is among the leading causes of disability worldwide. This is largely due to its highly chronic and recurrent nature (Murray and Lopez, 1997; Vos et al., 2004). The risk of recurrence after a first major depressive episode is 50% and increases with subsequent episodes (Post, 1992; Kupfer et al., 1996; American Psychiatric Association, 2000). Efforts to reduce the disabling effects of depression should be expanded with recurrence prevention strategies, especially in patients at high risk of recurrence (Bockting et al., 2011). Strategies to prevent recurrence of a major depressive episode can be highly effective. A meta-analysis found a number needed to treat (NNT) of five

(Hansen et al., 2008). In comparison, the number needed to treat to prevent one major cerebrovascular event with aspirin over a mean follow-up of 6.9 years is 253 (Berger et al., 2011). However, knowledge of recurrence risk of MDD is incomplete (Hardeveld et al., 2010). It is still difficult to identify high risk groups, and data on MDD recurrence risk is mainly based on studies performed in specialized mental health care. It is important to understand the extent to which this information can be generalized to patients in primary care settings, where the majority of people with MDD are treated. If the risk of recurrence in MDD patients treated in primary care differs from those in specialized mental health care, different recommendations for prevention of recurrence are needed. This knowledge might facilitate further improvements in the quality and cost-effectiveness of depression management.

We expect the risk of recurrence of MDD to be higher in specialized mental health care than that in primary care since those with the most severe, complex, recurrent and long-lasting disorders are more often treated in specialized mental health care

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(Cooper-Patrick et al., 1994; Suh and Gallo, 1997). However, this hypothesis is not well documented, mainly because data on the risk of recurrence among MDD patients in primary care settings are scarce (Gilchrist and Gunn, 2007; Hardeveld et al., 2010) and, in particular, prospective longitudinal studies are lacking.

Furthermore, it is important to be aware of the predictors of recurrence of MDD. This knowledge would make it possible to identify patients with a high risk for recurrence. Predictors of recurrence of MDD might be different across treatment settings. The studies available to date, which have aimed to identify risk factors for recurrence, have largely been carried out in specialized mental health care. The results suggest that subclinical residual symptoms and the number of previous episodes are the most important predictors for recurrence of MDD, whereas demographic factors are not related to recurrence of MDD (Hardeveld et al., 2010). To our knowledge, a study on risk factors for (time to) recurrence among patients treated in the specialized mental health care as well as those in primary care—also allowing a direct comparison—has not been done.

The aim of this study was therefore to examine the time to recurrence of MDD and its predictors among subjects who recovered from their last episode of MDD, and compare the findings between primary care and specialized mental health care.

2. Methods

2.1. Study sample

Data were from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study, which began in 2004, and examines the long-term course of depressive and anxiety disorders in different health care settings. The study protocol was approved centrally by the Ethical Review Board of the VU University Medical Centre, and subsequently by local review boards of each participating centre. All respondents provided informed consent. For the present study, data from the first two years of follow-up were used. The rationale, objectives, and methods of NESDA have been described in detail elsewhere (Penninx et al., 2008). In brief, the NESDA cohort ($N=2981$) consists of respondents (18–65 years) with (i) a current anxiety and/or depressive disorder, (ii) a prior history of a depressive and/or anxiety disorder and (iii) healthy controls. All respondents were administered a baseline assessment, which included evaluation of psychopathology, demographic and personal characteristics, psychosocial functioning, and biomarkers. Respondents were recruited in primary care through a screening procedure, in specialized mental health care when newly enrolled, and in the community. Respondents with a primary diagnosis of a psychotic disorder, obsessive-compulsive disorder, bipolar disorder, a severe addiction disorder, or who were not fluent in Dutch were excluded.

For our study sample, the classification of treatment settings (primary care versus specialized mental health care) was based on the recruitment setting but this was also confirmed with data from the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TIC-P) (Hakkaart-van Roijen, 2002). The TIC-P is a fully structured interview that assesses loss of productivity, health care utilization, and costs. Respondents were asked whether they had sought help for mental problems within the past six months. Those who had not sought help were not included because we wanted to compare respondents treated in specialized mental health care with those treated in primary care. Respondents were considered to be under treatment in specialized mental health care or primary care if they had at least two contacts in the six months prior to the baseline interview. The sources of care included primary care (general practitioner, first line psychologist, social worker, social psychiatric nurse) and specialized mental health care (ambulatory mental

health care including a psychiatrist/psychotherapist working in private practice and residential mental health care).

Diagnoses of MDD were based on the Composite International Diagnostic Interview (CIDI), Lifetime Version 2.1 (WHO Lifetime Version 2.1). The CIDI is a structured interview developed by the World Health Organization (1997) and has been found to have high inter-rater reliability (Wittchen, 1994), high test-retest reliability (Wacker et al., 2006), and satisfactory validity for depressive and anxiety disorders (Wittchen et al., 1989; Wittchen, 1994).

The study sample was restricted to subjects with a MDD diagnosis in the six months prior to baseline assessment, who were symptomatic in the month prior to baseline, and achieved remission during the two-year follow-up. In this way we tried to select a large sample of respondents who also had a MDD at baseline. Accordingly, the sample was limited to 706 subjects with a MDD diagnosis who confirmed symptoms in the month prior to baseline either through the CIDI recency questions or the Life Chart Interview (LCI) (Lyketsov et al., 1994) and who sought help for their MDD. Of these subjects, 566 (80.2%) participated in the two-year follow-up, of which a further six respondents were excluded because they did not have a (complete) LCI during follow-up. Drop-out was associated with lower educational attainment ($p=0.01$), but not with gender, age, severity of the last major depressive episode (MDE) or number of previous episodes of MDD. A further 142 respondents were excluded because they did not achieve remission from MDD within the two-year follow-up. Remission was defined as a reduction of symptoms to no or minimal severity for at least three consecutive months using the LCI. This three-month criterion is in line with previous research (Spijker et al., 2002). During follow-up the percentage of respondents achieving remission was not statistically significant (19.0% in primary care versus 24.0% in specialized mental health care, chi-square=1.33, $df=1$, $p=0.25$). Finally, 43 respondents were excluded because the diagnosis was changed to bipolar disorder during follow-up. So, the sample 'at risk' for a recurrence of MDD consisted of 375 respondents. Of those recruited from the community, 21 respondents were treated in specialized mental health care and twelve in primary care after checking data from the TIC-P. Furthermore, 29 respondents which were recruited in primary care were treated in specialized mental health care. As a consequence, 97 were treated in primary care (25.9%) and 278 (74.1%) were treated in specialized mental health care. A flow-chart is displayed in Fig. 1.

2.2. Time to recurrence

Time to recurrence was assessed prospectively during the two-year follow-up using the LCI. For each month with reported symptoms, severity was assessed (no or minimal severity, mild, moderate, severe, or very severe). Recurrence was operationalized as a return of symptoms after remission to at least mild severity level persisting for at least one month with the additional criterion that a CIDI-confirmed MDD diagnosis was present during follow-up.

2.3. Determinants of time to recurrence

The following variables that we considered relevant as determinant of time to recurrence or as covariate and were assessed at baseline with several semi-structured questionnaires.

2.3.1. Socio-demographic factors

Gender, age, and level of educational attainment (in years of education).

2.3.2. Clinical factors

Using the CIDI, the following information was obtained: age of onset of MDD, severity of the MDE in the month preceding

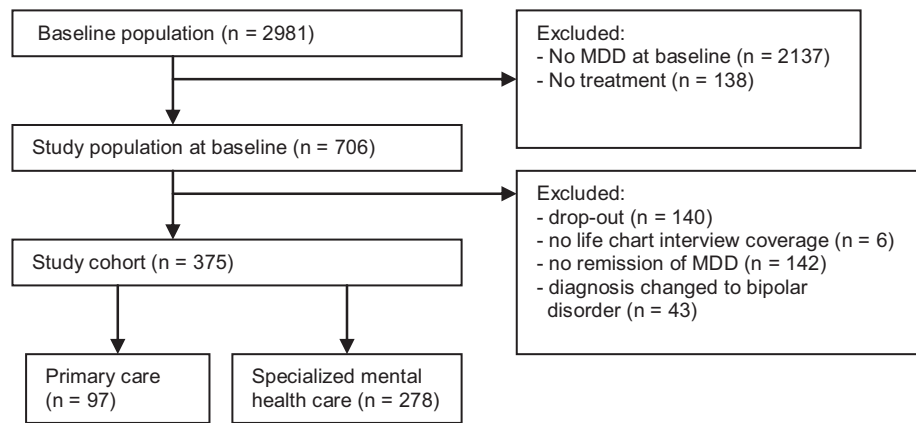


Fig. 1. Flow chart of selection process for study population.

baseline assessment (based on number of DSM-criteria and categorized into mild, moderate and severe), and lifetime number of MDEs categorized into single or recurrent. Information on the duration of symptoms prior to baseline was derived from the baseline LCI that assessed the percentage of time the respondent spent with depressive symptoms in the previous year. History of depression in first-degree family members was assessed using a family tree inventory (Fyer and Weissman, 1999), categorized into yes or no. The comorbid disorders that we deemed relevant were lifetime alcohol abuse/dependence or any anxiety disorder (panic disorder, social phobia, generalized anxiety disorder, agoraphobia) within the six months before baseline. Comorbidity with somatic illnesses was assessed by means of a questionnaire listing 20 mostly chronic disorders for which the respondent was treated.

2.3.3. Psychosocial factors

Neuroticism was measured with the twelve-item subscale of the NEO Five-Factor Inventory (NEO-FFI) Questionnaire ranging from 0 (low neuroticism) to 48 (high neuroticism) (Costa and McCrae, 1995). Negative life events in the last year were determined with the Brugha questionnaire ranging from 0 to 5 (Brugha et al., 1985) and included 12 specific events and one 'other' category asking about other serious negative life events. In order to examine the role of childhood trauma, a cumulative childhood index using the NEMESIS childhood trauma interview was constructed (De Graaf et al., 2002; Wiersma et al., 2009; Hovens et al., 2010). Participants were asked four questions regarding childhood experiences of emotional neglect, or emotional, physical, or sexual abuse. The cumulative index was calculated for each participant as the sum of the number and frequency of the four types of abuse (range, 0–8).

2.3.4. Treatment

Respondents were asked about the type of treatment they had received for their MDD, subdivided into pharmacological treatment and psychological treatment. Pharmacological treatment was assessed based on inspection of the medication boxes used in the past month and coded using the WHO Anatomical Therapeutic Chemical (ATC) classification (REF to URL). Use of antidepressants was taken into account when the medication was taken at least 50% of the time and included selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (N06AA) or other antidepressants (N06AF/N06AX). The receipt of psychological treatment (psychotherapy, counselling, and skills training) was based on self-report.

2.4. Statistical methods

For the analyses, SPSS for Windows Version 17.0 (SPSS Inc., USA) was used. Descriptives across treatment setting

(primary care, specialized mental health care) were compared using independent t-tests for continuous variables and chi-square tests for categorical variables. A two-tailed $p \leq 0.05$ was considered statistically significant. We used Kaplan–Meier survival curves to estimate the time to recurrence of MDD during follow-up across treatment settings. Subjects who—at the end of the follow-up period—did not meet the criteria for the endpoint event (recurrence) were censored. Subsequently, we studied possible predictors of recurrence of MDD (including treatment setting) using Cox's proportional hazards analyses. Predictors that had a p -value ≤ 0.20 in the univariable analyses were included in multivariable analyses in which the forced entry method was used. Time to recurrence of MDD (yes/no) during the two-year follow-up was the main outcome measure. Because the number of subjects treated in primary care was relatively small ($n=97$) we could not make a separate comparison of the predictors of recurrence between settings. Instead, we added a setting by predictor interaction term to check whether possible differences in recurrence risk between treatment settings were explained by differences in predictors.

3. Results

3.1. Characteristics

The mean age of the study sample was 40.3 years, and 66.9% were female. The socio-demographic, clinical and treatment variables are shown by setting in Table 1. Respondents treated in specialized mental health care were younger, had a younger age of onset, had a higher neuroticism score and a higher percentage had psychological treatment and/or medication ($p < 0.05$). Table 2 describes the course characteristics of MDD during follow-up. Percentage of recurrence, mean and average time to recurrence and average duration of follow-up did not differ significantly between treatment settings.

3.2. Recurrence risk

During the two-year follow-up, 26.8% ($n=26$) of respondents in primary care and 33.5% ($n=93$) treated in specialized mental health care experienced a recurrence of MDD after having achieved remission for at least three months (chi-square=1.47, $df=1$, $p=0.23$) (see inclusion criteria). Fig. 2 shows the survival curve of MDD recurrence across different settings. The slope of the survival curve suggests that the risk of recurrence is highest in the first months after recovery, regardless of treatment setting. There was no significant difference in time to recurrence of MDD between respondents in specialized mental health care in

Table 1
Characteristics of 375 subjects at risk for a recurrence of MDD from the NESDA study by treatment setting.

	Primary care (n=97)	Specialized mental health care (n=278)	p [*]
<i>Socio-demographic factors</i>			
Gender (% female)	70.1	65.8	0.44
Age (mean yrs, sd)	43.9 (12.1)	39.1 (11.7)	< 0.01
Educational attainment (mean yrs, sd)	11.5 (3.1)	11.4 (3.0)	0.75
<i>Clinical factors</i>			
Age of onset (mean yrs, sd)	30.4 (14.0)	27.1 (12.5)	0.03
Family history of depression (%)	87.6	85.6	0.62
Severity of the last MDE (CID)			0.13
	Mild	27.3	
	Moderate	31.7	
	Severe	41.0	
Recurrent MDD (%)	53.8	51.1	0.66
Percentage months with symptoms of MDD in past year (mean, sd)	0.6 (0.4)	0.7 (0.3)	0.08
Anxiety disorder (any, 6 months)	59.8	68.0	0.14
Alcohol abuse/dependence (lifetime)	37.1	29.5	0.16
Number chronic somatic illness (mean number, sd)	0.8 (1.2)	0.6 (0.9)	0.12
<i>Psychosocial factors</i>			
Trauma before age 16 (mean score, sd)	1.0 (1.2)	1.3 (1.2)	0.07
Negative life events (mean, sd)	1.2 (1.36)	0.9 (1.09)	0.06
Neuroticism (mean score, sd)	29.0 (6.6)	31.1 (6.5)	< 0.01
<i>Treatment</i>			
Pharmacological treatment (% yes)	49.5	65.1	< 0.01
Psychological treatment (% yes)	45.4	63.3	< 0.01

* p-value based on chi-square statistics for categorical variables and independent t-test for continuous variables. In bold: statistically significant.

Table 2
Course characteristics of 375 respondents at risk for a recurrence of MDD from NESDA by setting.

	Primary care	Specialized mental health care	p [*]
Percentage of recurrence (%)	26.8	33.5	0.23
Average time to recurrence (months)	6.6	5.6	0.30
Median time to recurrence (months)	5.5	5.0	0.30
Average duration of follow-up (months)	15.3	14.1	0.21

* Pearson Chi-square and Mann–Whitney U test used, uncontrolled for covariates.

comparison with respondents treated in primary care (HR=1.32, CI=0.86–2.05, $p=0.21$). When controlled for socio-demographic, clinical, psychosocial and treatment factors, time to recurrence did not differ significantly, but a trend was found towards a shorter time to recurrence in specialized mental health care (HR=1.52, 95% CI=0.93–2.48, $p=0.09$). Table 3 shows the potential risk factors of time to recurrence of MDD using both univariable and multivariable Cox proportional regression analyses. Analyses showed that the presence of a family history of depression and having a previous MDE were associated with a shorter time to recurrence of MDD. In multivariable analyses, the presence of a family history of depression (HR=2.12, 95%CI=1.07–4.22, $p=0.03$) and having a previous MDE (HR=1.59, 95% CI=1.08–2.35, $p=0.02$) remained significant predictors of time to recurrence. Finally, no significant interaction terms were found for treatment setting by predictor, implying that predictors of time to recurrence did not differ across treatment settings.

4. Discussion

To our knowledge, this is the first prospective naturalistic cohort study to directly compare the recurrence risk and predictors of time to recurrence in subjects with a MDD diagnosis across different treatment settings. The results indicate that the

time to recurrence during the two-year follow-up did not differ between patients treated in primary care and in specialized mental health care. Given the presence of more severe, more treatment resistant, chronic and more complex patients in specialized mental health care, one might expect that the risk of recurrence would be higher in this care setting. However, our findings are in line with previous studies carried out in primary care (Lin et al., 1998; Gopinath et al., 2007; Vuorilehto et al., 2009; Suija et al., 2011). In a study performed in primary care among 386 respondents (Gopinath et al., 2007), 31.1% of patients had a recurrence after one year. Similar results were found in a study by Lin et al. (1998) (37.1% after one year), Vuorilehto et al. (2009) (27% after 15 months) and Suija et al. (2011) who observed a recurrence percentage of 28% after one year. In comparison, in specialized mental health care the percentage of MDD recurrence after one year ranges from 21% to 37% (Kanai et al., 2003; Maj et al., 1992; Hardeveld et al., 2010). Although remaining non-significant, a trend towards a shorter time to recurrence in specialized mental health care was noticeable (HR=1.52, 95% CI=0.93–2.48, $p=0.09$) and the hazard ratio increased from 1.32 to 1.52 when corrected for all covariates, suggesting that the risk of recurrence increases in secondary care in comparison with primary care and was confounded by these variables. A possible explanation for the similar recurrence risk found across treatment settings is that the distribution of risk factors for MDD recurrence does not differ much between treatment settings. Previous research, also performed with NESDA data (Piek et al., 2011), found that patients were more likely to be referred to secondary care if they were younger, reported suicidal symptoms, had chronic depression, or were referred for psychotherapy. It seems that factors related to referral to specialized mental health care, in general, differ from predictors of recurrence. It could be that the decision to refer to specialized mental health care is determined to a greater extent by the need for acute treatment of MDD or the preferences of the patient than by expectations of a protracted course. When we excluded those who did not recover from a MDE during follow-up, respondents who were younger, had an earlier age of onset and a higher neuroticism score were most likely to be referred and treated in specialized mental health care. Although these could be risk factors for recurrence, our study found that the

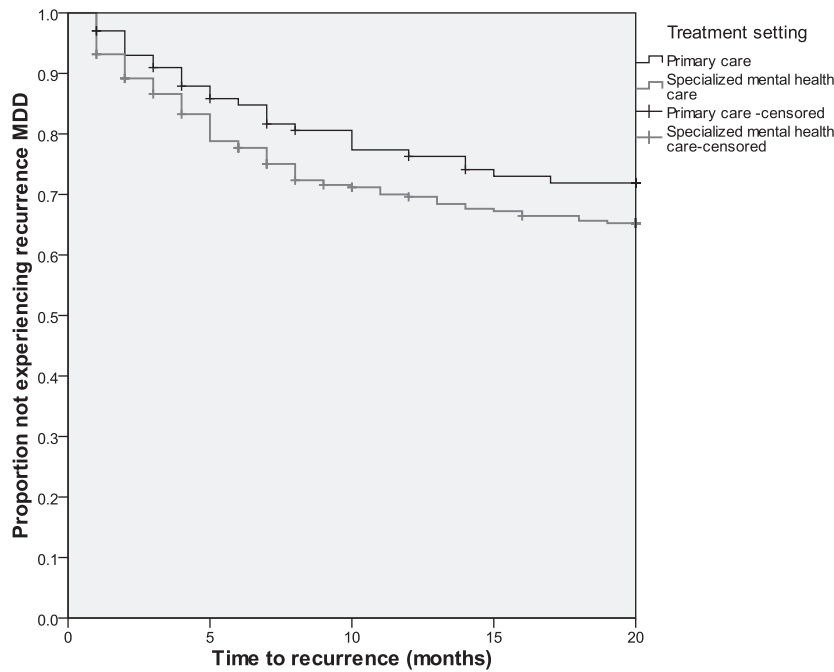


Fig. 2. Survival curve of time to recurrence of MDE across different settings in a cohort from NESDA.

Table 3

Univariable and multivariable analyses of potential predictors of time to recurrence of MDE in a cohort from NESDA (n=375).

	Time to recurrence						
	Univariable analyses			Multivariable analyses*			
	HR	95% CI	p	HR	95% CI	p	
<i>Socio-demographic factors</i>							
Gender, female	1.43	0.95–2.16	0.09	1.42	0.92–2.20	0.11	
Age (yrs)	0.99	0.97–1.00	0.13	0.99	0.97–1.01	0.33	
Educational attainment (yrs)	1.03	0.97–1.10	0.29				
<i>Clinical factors</i>							
Age of onset (yrs)	0.99	0.98–1.0	0.11	1.00	0.98–1.02	0.80	
Family history of depression	Yes	2.16	1.09–4.26	0.03	2.12	1.07–4.22	0.03
Severity of the last MDE	Mild	1	–	–			
	Moderate	0.95	0.60–1.52	0.84			
	Severe	1.11	0.72–1.72	0.63			
Recurrent MDD (% recurrent)	1.61	1.10–2.35	0.01	1.59	1.08–2.35	0.02	
Percentage months with symptoms of MDD in past year	0.87	0.53–1.50	0.60				
Anxiety disorder (any)	Yes	0.90	0.62–1.31	0.60			
Alcohol abuse/dependence	Yes	0.88	0.59–1.30	0.51			
Number chronic somatic illnesses	High	1.05	0.88–1.24	0.61			
<i>Psychosocial</i>							
Trauma before age 16	High	1.10	0.95–1.26	0.22			
Life events	Low	1.02	0.87–1.19	0.81			
Neuroticism	High	1.00	0.97–1.03	0.93			
<i>Treatment</i>							
Pharmacological treatment	No	1.29	0.90–1.86	0.16	1.16	0.80–1.68	0.43
Psychological treatment	No	1.64	0.81–1.67	0.41			
<i>Setting</i>							
Specialized mental health care		1.32	0.86–2.05	0.21			

* Forced entry method used if in univariable analyses $p \leq 0.20$. In bold: statistically significant.

risk factors predicting a shorter time to recurrence were a history of recurrent MDEs and the presence of a family history of depression. These factors did not differ across treatment settings. An alternative explanation may be that those referred to specialized care receive more intensive treatment for recurrence prevention and that this reduced recurrence rate to a similar level as was found in primary care.

As mentioned earlier, our study found that a history of recurrent MDD and the presence of a family history of depression predicted a shorter time to recurrence. Previous research also found these predictors to be related to recurrence of MDD (Maj et al., 1992; Mueller et al., 1999; Solomon et al., 2000). Family history of MDD, which had the highest hazard ratio for recurrence, is of special interest, because this might indicate an important genetic

vulnerability for (the recurrence of) MDD. Further studies should examine this genetic basis, preferably prospectively, and should focus on predictors of recurrence early in the lifetime course. These studies should also take into account the interactions between genetic, biological, environmental, and clinical factors in concert, since causation of recurrence seems to be multifactorial with multiple putative causal factors that interact over time.

The strengths of our study are that we were able to examine a comprehensive set of predictors in a large representative sample and used standardized instruments to determine diagnosis and course. However, in interpreting the results of this study, one should also be aware of its limitations. First, the respondents treated in specialized mental health care were recently referred and, as a consequence, this sample is not representative of the entire population treated for MDD in specialized mental health care, since patients with more severe, chronic or frequent recurring MDD are probably underrepresented in the study. Consequently, the difference in recurrence risk between primary care and specialized mental health care could have been underestimated. On the other hand, the percentage of remission between respondents treated in primary care versus specialized mental health care was not statistically different in our study which suggests that the researched treatment cohorts are comparable in this way. Secondly, subclinical residual symptoms, which are a strong predictor of recurrence risk (Judd et al., 1998), could not be included in the analysis because the data did not allow for such precision. It is reasonable to assume that residual symptoms are more common in respondents treated in specialized mental health care than in respondents treated in primary care. Thirdly, the follow-up duration of two years was relatively short if one takes into account that respondents had to have been in remission first. Although the average duration of follow-up was modest at approximately 15 months, it is important to realise that the risk of relapse is greatest in the first year after recovery, and declines rapidly thereafter. Therefore, it is unlikely that the conclusions of the current paper would change if a longer follow-up period had been available. Finally, our results may have been influenced by the referral behaviour of general practitioners and may not be generalizable to health systems that are very different from the system in the Netherlands. However, the structure of the Dutch health care system is comparable to that of several other European countries in which the general practitioner serves as the gatekeeper and referrals are needed for access to specialized mental health care, and also the proportion of diagnosed persons receiving mental health treatment, as well as the quality of care received, is comparable to that in other high income countries (US, UK, Spain, Belgium) (Alonso et al., 2004; Wang et al., 2007).

5. Conclusion

In conclusion, the recurrence risk of MDD appeared to be similar in specialized mental health care and primary care meaning that the risk of recurrence in primary care is also considerable. Respondents with a history of recurrent MDD and a family history of MDD in first-degree relatives had a shorter time to recurrence. Patients with these risk factors should be closely monitored and treatment strategies to prevent recurrence should be considered. Our results also imply that prevention of recurrence of MDD is advised for high-risk groups, not only in specialized mental health care, but also in primary care. However, aside from pharmacological treatment (Kaymaz et al., 2008), other programmes to prevent recurrence, e.g. mindfulness-based cognitive therapy (Piet and Hougaard, 2011) and cognitive therapy (Beshai et al., 2011) are mainly carried out in specialized mental health care. Therefore, general practitioners should refer patients, not only for

specialized treatment of depression, but also for prevention of recurrence. Another possibility is to expand these programmes beyond specialized mental health care. To improve the management of recurrence prevention of MDD, collaborative care models (Katon and Guico-Pabia, 2011), in which long term management and communication between primary- and specialized mental health care professionals are optimized across psychiatric services, may be helpful.

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Conflict of interest

Dr. Nolen has received speaking fees from Astra Zeneca, Eli Lilly, Pfizer, Servier, Wyeth; unrestricted grants from The Netherlands Organization for Health Research and Development, European Union, Stanley Medical Research Institute, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Wyeth; and served on advisory boards for Astra Zeneca, Cyberonics, Pfizer, and Servier. Dr. Spijker has received speaking fees from Astra Zeneca, Wyeth, Servier, Eli Lilly and GlaxoSmithKline.

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References

- American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, Washington DC, Text Revision—Fourth.
- Alonso, J., Angermeyer, M.C., Bernert, S., et al., 2004. Use of mental health services in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica Supplement*, 47–54.
- Berger, J.S., Lala, A., Krantz, M.J., et al., 2011. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. *American Heart Journal* 162, 115–124.
- Beshai, S., Dobson, K.S., Bockting, C.L., et al., 2011. Relapse and recurrence prevention in depression: current research and future prospects. *Clinical Psychological Review* 31, 1349–1360.
- Bockting, C.L., Kok, G.D., van der Kamp, L., et al., 2011. Disrupting the rhythm of depression using Mobile Cognitive Therapy for recurrent depression: randomized controlled trial design and protocol. *BMC Psychiatry* 11, 12.
- Brugha, T., Bebbington, P., Tennant, C., et al., 1985. The list of threatening experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychological Medicine* 15, 189–194.
- Cooper-Patrick, L., Crum, R.M., Ford, D.E., 1994. Characteristics of patients with major depression who received care in general medical and specialty mental health settings. *Medical Care* 32, 15–24.
- Costa Jr., P.T., McCrae, R.R., 1995. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. *Journal of Personality Assessment* 64, 21–50.
- De Graaf, R., Bijl, R.V., Smit, F., et al., 2002. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *American Journal of Psychiatry* 159, 620–629.
- Fyer, A.J., Weissman, M.M., 1999. Genetic linkage study of panic: clinical methodology and description of pedigrees. *American Journal of Medical Genetics* 88, 173–181.
- Gilchrist, G., Gunn, J., 2007. Observational studies of depression in primary care: what do we know? *BMC Family Practice* 8, 28.
- Gopinath, S., Katon, W.J., Russo, J.E., et al., 2007. Clinical factors associated with relapse in primary care patients with chronic or recurrent depression. *Journal of Affective Disorders* 101, 57–63.
- Hakkaart-van Roijen, L., 2002. Handleiding Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TIC-P), July 2002 ed. Institute for Medical Technology Assessment & Erasmus Universitair Medisch Centrum Rotterdam, Rotterdam.
- Hardeveld, F., Spijker, J., De Graaf, R., et al., 2010. Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatrica Scandinavica* 122, 184–191.

- Hansen, R., Gaynes, B., Thieda, P., et al., 2008. Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. *Psychiatric Services* 59, 1121–1130.
- Hovens, J.G., Wiersma, J.E., Giltay, E.J., et al., 2010. Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs. controls. *Acta Psychiatrica Scandinavica* 122, 66–74.
- Judd, L.L., Akiskal, H.S., Maser, J.D., et al., 1998. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *Journal of Affective Disorders* 50, 97–108.
- Kanai, T., Takeuchi, H., Furukawa, T.A., et al., 2003. Time to recurrence after recovery from major depressive episodes and its predictors. *Psychological Medicine* 33, 839–845.
- Katon, W., Guico-Pabia, C.J., 2011. Improving quality of depression care using organized systems of care: a review of the literature. *Primary Care Companion CNS Disorders* 13 (1).
- Kaymaz, N., van Os, J., Loonen, A.J., et al., 2008. Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *Journal of Clinical Psychiatry* 69, 1423–1436.
- Kupfer, D.J., Frank, E., Wamhoff, J., 1996. Mood disorders: update on prevention of recurrence. In: Mundt, C., Goldstein, M.J. (Eds.), *Interpersonal Factors in the Origin and Course of Affective Disorders*. Gaskell/Royal College of Psychiatrists, London, England, pp. 289–302.
- Lin, E.H., Katon, W.J., VonKorff, M., et al., 1998. Relapse of depression in primary care. Rate and clinical predictors. *Archives of Family Medicine* 7, 443–449.
- Lyketsos, C.G., Nestadt, G., Cwi, J., et al., 1994. The life-chart method to describe the course of psychopathology. *International Journal of Methods in Psychiatric Research* 4, 143–155.
- Maj, M., Veltro, F., Pirozzi, R., et al., 1992. Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. *Am J Psychiatry* 149, 795–800.
- Mueller, T.I., Leon, A.C., Keller, M.B., et al., 1999. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *American Journal of Psychiatry* 156, 1000–1006.
- Murray, C.J., Lopez, A.D., 1997. Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet* 349, 1436–1442.
- Penninx, B.W., Beekman, A.T., Smit, J.H., et al., 2008. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International Journal of Methods in Psychiatric Research* 17, 121–140.
- Piek, E., van der Meer, K., Penninx, B.W., et al., 2011. Referral of patients with depression to mental health care by Dutch general practitioners: an observational study. *BMC Family Practice* 12, 41.
- Piet, J., Hougaard, E., 2011. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. *Clinical Psychological Review* 31, 1032–1040.
- Post, R.M., 1992. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry* 149, 999–1010.
- Solomon, D.A., Keller, M.B., Leon, A.C., Mueller, T.I., et al., 2000. Multiple recurrences of major depressive disorder. *American Journal of Psychiatry* 157, 229–233.
- Spijker, J., de Graaf, R., Bijl, R.V., 2002. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *British Journal of Psychiatry* 181, 208–213.
- Suh, T., Gallo, J.J., 1997. Symptom profiles of depression among general medical service users compared with specialty mental health service users. *Psychological Medicine* 27, 1051–1063.
- Suija, K., Aluoja, A., Kalda, R., et al., 2011. Factors associated with recurrent depression: a prospective study in family practice. *Family Practice* 28, 22–28.
- Vos, T., Haby, M.M., Barendregt, J.J., et al., 2004. The burden of major depression avoidable by longer-term treatment strategies. *Archives of General Psychiatry* 61, 1097–1103.
- Vuorilehto, M.S., Melartin, T.K., Isometsä, E.T., 2009. Course and outcome of depressive disorders in primary care: a prospective 18-month study. *Psychological Medicine* 39, 1697–1707.
- Wacker, H.R., Bategay, R., Mullejans, R., et al., 2006. Using the CIDI-C in the general population. In: Stefanis, C.N., Rabavilas, A.D., Soldatos, C.R. (Eds.), *Psychiatry: A World Perspective*. Elsevier Science Publishers, Amsterdam.
- Wang, P.S., Aguilar-Gaxiola, S., Alonso, J., et al., 2007. Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. *Lancet* 370, 841–850.
- Wiersma, J.E., Hovens, J.G., van Oppen, P., et al., 2009. The importance of childhood trauma and childhood life events for chronicity of depression in adults. *Journal of Clinical Psychiatry* 70, 983–989.
- Wittchen, H.U., Burke, J.D., Semler, G., et al., 1989. Recall and dating of psychiatric symptoms. Test–retest reliability of time-related symptom questions in a standardized psychiatric interview. *Archives of General Psychiatry* 46, 437–443.
- Wittchen, H.U., 1994. Reliability and validity studies of the WHO—Composite International Diagnostic Interview (CIDI): a critical review. *Journal of Psychiatric Research* 28, 57–84.
- World Health Organisation, 1997. *Composite International Diagnostic Interview, Core version 2.1: Interviewer's Manual*. World Health Organisation, Sydney, Australia.