Psychological Medicine (2014), **44**, 1369–1379. © Cambridge University Press 2011
doi:10.1017/S0033291711002303

ORIGINAL ARTICLE

Five-year outcome of major depressive disorder in primary health care

K. A. Riihimäki[1,2], M. S. Vuorilehto[1,3], T. K. Melartin[1,4] and E. T. Isometsä[1,5]*

[1] *National Institute for Health and Welfare, Mood, Depression and Suicidal Behaviour Research Unit, Helsinki, Finland*
[2] *Primary Health Care Organization of the City of Vantaa, Vantaa, Finland*
[3] *Ministry of Social Affairs and Health, Helsinki, Finland*
[4] *Department of Psychiatry, HUCH, Jorvi Hospital, Espoo, Finland*
[5] *Department of Psychiatry, University of Helsinki, Helsinki, Finland*

Background. Primary health care provides treatment for most patients with depression. Despite their importance for organizing services, long-term course of depression and risk factors for poor outcome in primary care are not well known.

Method. In the Vantaa Primary Care Depression Study, a stratified random sample of 1119 patients representing primary care patients in a Finnish city was screened for depression with the Primary Care Evaluation of Mental Disorders. SCID-I/P and SCID-II interviews were used to diagnose Axis I and II disorders. The 137 patients with DSM-IV depressive disorder were prospectively followed up at 3, 6, 18 and 60 months. Altogether, 82% of patients completed the 5-year follow-up, including 102 patients with a research diagnosis of major depressive disorder (MDD) at baseline. Duration of the index episode, recurrences, time spent in major depressive episodes (MDEs) and partial or full remission were examined with a life-chart.

Results. Of the MDD patients, 70% reached full remission, in a median time of 20 months. One-third had at least one recurrence. The patients spent 34% of the follow-up time in MDEs, 24% in partial remission and 42% in full remission. Baseline severity of depression and substance use co-morbidity predicted time spent in MDEs.

Conclusions. This prospective, naturalistic, long-term study of a representative cohort of primary care patients with depression indicated slow or incomplete recovery and a commonly recurrent course, which need to be taken into account when developing primary care services. Severity of depressive symptoms and substance use co-morbidity should be systematically evaluated in planning treatment.

Received 17 March 2011; Revised 13 September 2011; Accepted 21 September 2011; First published online 16 November 2011

Key words: Co-morbidity, course, depression, follow-up, outcome, primary care, recovery, recurrence.

Introduction

Primary health care provides treatment for most patients with major depression, one of the most common conditions encountered there (Sartorius *et al*. 1993; Hämäläinen *et al*. 2004; Rost, 2009). Adequate recognition of depression and knowledge of factors predicting its outcome are therefore necessary. Numerous medium- and long-term outcome studies have documented high rates of recurrence and residual symptoms of major depression, both in the general population (Ormel *et al*. 1993; Pirkola *et al*. 2005; Eaton *et al*. 2008; Rhebergen *et al*. 2009) and in psychiatric care settings (Kiloh *et al*. 1988; Lee & Murray, 1988; Keller *et al*. 1992; Angst & Preisig, 1995; Kennedy *et al*. 2003, 2004; Melartin *et al*. 2004; Furukawa *et al*. 2008; Holma *et al*. 2008; Solomon *et al*. 2008). However, long-term (i.e. $\geqslant$5 years) course of depression in primary care has remained little investigated. In the available primary care outcome studies, estimates of recurrence have varied between 35% and 77% and of full recovery between 25% and 50%, while chronic course has been seen in up to one-third of patients (van Weel-Baumgarten *et al*. 1998; Oldehinkel *et al*. 2000, Wilson *et al*. 2003; Yiend *et al*. 2009).

Factors influencing the long-term outcome of depression have remained mostly unknown in primary care. In both general population (Spijker *et al*. 2002; Stegenga *et al*. 2010) and psychiatric care (Keller *et al*. 1992; Melartin *et al*. 2004; Holma *et al*. 2008) studies, longer time to remission and non-recovery are associated with higher severity of depression. Moreover, in the general population, four-fifths of patients appear

* Address for correspondence: Professor E. T. Isometsä, MD, PhD, Department of Psychiatry, Institute of Clinical Medicine, P.O. Box 22, 00014 University of Helsinki, Finland.
(Email: erkki.isometsa@hus.fi)

to have a co-morbid Axis I disorder (Kessler *et al*. 2003) and up to one-half an Axis II disorder (Zimmerman & Coryell, 1989; Casey *et al*. 2004) and poor outcome is predicted by anxiety disorders, alcohol disorders (Hasin *et al*. 1996; Mattisson *et al*. 2009) and personality disorder type C (Johnson *et al*. 2005). In psychiatric care settings, poor outcome is also associated with co-morbid disorders, which seem to increase the risk of relapse or recurrence (Alnaes & Torgersen, 1997; Melartin *et al*. 2004; Holma *et al*. 2008), chronicity (Keller *et al*. 1984; Mueller *et al*. 1994) and residual symptoms (Paykel *et al*. 1995). The most important co-morbidities appear to be anxiety and cluster C personality disorders (Coryell *et al*. 1992; Viinamäki *et al*. 2002; Farabaugh *et al*. 2005; Holma *et al*. 2008).

However, whether the same risk factors are important predictors of outcome also in primary care remains unknown due to the lack of studies with life-chart methodology. The existing studies focus almost exclusively on the cross-sectional pictures of outcome, thus ignoring recurrences, chronicity and duration of illness states. Moreover, the available primary care studies vary greatly in their methods and definitions for diagnostic criteria (Widmer & Cadoret, 1978; Ormel *et al*. 1993; van Weel-Baumgarten *et al*. 1998; Oldehinkel *et al*. 2000; Simon, 2000; Wilson *et al*. 2003; Jackson *et al*. 2007; Poutanen *et al*. 2007; Wells *et al*. 2008; Yiend *et al*. 2009) and have seldom used structured or semi-structured interviews. Assessment of depression has often been based exclusively on self-reported scales, which may render the clinical significance uncertain. Drop-out rates are commonly high. Overall, an obvious need exists for comprehensive long-term follow-up of representative samples of primary care patients with major depressive disorder (MDD).

In this naturalistic study, we prospectively assessed the 5-year outcome of DSM-IV MDD in a sample of 137 patients, effectively representing primary care patients in the fourth biggest Finnish city. We overcame some major limitations of previous studies by using semi-structured interviews to obtain diagnoses of all Axis I and II disorders and a life-chart methodology to assess outcome of depression. Moreover, we also gathered information on medical co-morbidity and psychosocial risk factors. The medium-term 18-month follow-up findings have been reported earlier (Vuorilehto *et al*. 2009). In the present, long-term 5-year follow-up study, we investigated long-term outcome and its predictors. We hypothesized that both features of MDD itself (severity, duration and recurrences before entry) and co-morbidity (Axis I, II and III disorders) would effectively predict chronicity and recurrence of depression.

Materials and methods

The Vantaa Primary Care Depression Study (PC-VDS) is a naturalistic and prospective cohort study on depressive disorders. The pertinent ethics committee approved the baseline study protocol in December 2001 and the 5-year follow-up study protocol in February 2007. The PC-VDS is a collaborative research project between the National Institute of Health and Welfare, the University of Helsinki and the City of Vantaa, Finland. Screening for depression was based on stratified sampling within two representative catchment areas of the city, with a total population of 63 400 inhabitants, served by 30 general practitioners with a population-based responsibility. The baseline methodology (Vuorilehto *et al*. 2005) and the 18-month follow-up (Vuorilehto *et al*. 2009) have been described in detail elsewhere.

Screening and baseline evaluation

In the first stage, a total of 1119 patients aged 20–69 years were screened with the screening questionnaire of the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer *et al*. 1994) in general practitioners' waiting rooms. Altogether 373 patients had positive screen results. The presence of at least one core symptom of MDD according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I/P) (First *et al*. 2001) was then confirmed by telephone. We excluded patients with psychoses other than depressive disorder, patients with bipolar or organic mood disorder and patients currently receiving treatment in psychiatric care. In the second stage, after receiving written informed consent, we interviewed all 175 potentially eligible patients face to face using the SCID I/P with psychotic screen. Inclusion criteria were current: (1) MDD; (2) dysthymia; (3) subsyndromal MDD with two to four depression symptoms (minimum one core symptom) and lifetime MDD; (4) minor depression (MinD) otherwise similar to subsyndromal MDD, but without MDD history. Distress or functional impairment was required for all. Dysthymia was regarded as subsyndromal MDD or MinD according to a positive or negative history of MDD. The joint diagnostic reliability for current depressive disorders was 100% ($\kappa = 1.0$ for depression diagnoses). Patients who refused to participate (15%) did not differ significantly in age or gender from those who consented (Vuorilehto *et al*. 2005). The median time from the beginning of MDE to the study entry was 182 days (25 percentiles 52, 75 percentiles 748), and after study entry to remission (full or partial) 209 days (25 percentiles 88, 75 percentiles 773). The former did not differ

https://doi.org/10.1017/S0033291711002303 Published online by Cambridge University Press

Table 1. *Baseline characteristics of patients with major depressive disorder followed up for 5 years in the Vantaa Primary Care Depression Study* ($n = 102$)

Variable	*n*	%
Sociodemographic characteristics		
Male gender	21	21
Married or co-habiting	55	54
Unemployed	15	15[a]
Disability pension	16	16
Lifetime anxiety disorder (any)	53	52
Current co-morbid Axis I diagnosis	60	59
Anxiety disorder (any)	43	42
Generalized anxiety disorder	14	14
Panic disorder	7	7
Social phobia	17	17
Somatoform disorder	14	14
Substance use disorder (any)	16	16
Alcohol dependence	7	7
Any current Axis II diagnosis	53	52
Cluster A personality disorder	5	5
Cluster B personality disorder	30	29
Cluster C personality disorder	34	33
Current Axis III diagnosis		
Chronic medical illness	54	53
	Mean	S.D.
Age (years)	45.2	13.6
Beck Depression Inventory	19.6	10.2
Hamilton Depression Rating Scale	16.6	5.6
Beck Anxiety Inventory	17.5	12.5
Beck Hopelessness Scale	8.7	5.3
Perceived Social Support Scale – Revised	43.6	12.4
SOFAS[b]	56.7	11.2

[a] 16% from the subjects under 65 years ($n = 96$).

[b] Social and Occupational Functioning Assessment Scale for DSM-IV.

significantly between the patients who were interviewed at 5 years and the drop-outs.

Current and lifetime psychiatric disorders were assessed with SCID-I/P and SCID-II (First *et al*. 1997). Observed and self-report scales included the 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), the Scale for Suicide Ideation (SSI) (Beck *et al*. 1979) and the Social and Occupational Functioning Assessment Scale for DSM-IV (SOFAS) (Goldman *et al*. 1992). Self-report scales included the 21-item Beck Depression Inventory (BDI) (Beck *et al*. 1961), the Beck Anxiety Inventory (BAI) (Beck *et al*. 1988), the Beck Hopelessness Scale (BHS) (Beck *et al*. 1974) and the Perceived Social Support Scale – Revised (PSSS-R) (Blumenthal *et al*. 1987). A self-report questionnaire, medical records and an interview were used for chronic medical illnesses. Lifetime course of depression was reconstructed from the interview and medical and psychiatric records.

Follow-up at 3, 6 and 18 months

After baseline, patients were investigated at 3, 6 and 18 months with a life-chart methodology and the above-mentioned scales. Of the 137 patients included in the study, 127 (93%) participated in the 18-month follow-up. The median time for this follow-up was 18.7 months. The results have been presented earlier (Vuorilehto *et al*. 2009).

5-year follow-up

The median time for the 5-year interviews was 62.9 months (mean = 63.3). Of the 137 patients initially included in the study, only 25 (18%) dropped out at 5 years. The drop-outs did not differ from the patients who were followed up in age, gender or baseline depression severity. The diagnosis of six patients (4%) switched to bipolar disorder during the follow-up time. They were censored in the survival analysis at the time-point in the life-chart where the switch occurred. The final follow-up group in the survival analysis consisted of 110 patients, 89 of whom had baseline MDD. Baseline characteristics of the 102 lifetime MDD patients who completed the 5-year follow-up are shown in Table 1.

Outcome measures

The patients were prospectively followed up with a life-chart (Melartin *et al*. 2004; Vuorilehto *et al*. 2009) to determine the duration of the index episode after baseline and the timing of possible relapses and recurrences. At the 5-year follow-up assessments, depression was diagnosed in a face-to-face interview with the SCID-I. In addition to the interview, observer scales were used and all available data were gathered from medical and psychiatric records, which were integrated into a graphic life-chart, based on DSM-IV criteria and definitions.

The time after the baseline interview was divided into three categories: (1) state of major depressive episode (MDE) (five or more of the nine MDE criteria symptoms); (2) state of partial remission (one to four symptoms); or (3) state of full remission (no symptoms). We then calculated the following from the first baseline interview: (1) time to the first onset of state of full remission lasting at least two consecutive months (time to full remission); (2) probability of experiencing a recurrence; (3) time from remission to the first onset of recurrence; (4) time spent in MDE state, partial remission and full remission. Moreover, in patients with baseline MDD, we calculated from the first baseline

https://doi.org/10.1017/S0033291711002303 Published online by Cambridge University Press

interview; (5) the uninterrupted duration of the episode in the state of MDE (duration of MDE with full criteria). Remission and recurrence were defined as in the DSM-IV. In accordance with the DSM-IV definition for '296.3× MDD, Recurrent', recurrence referred to the return of MDE after at least two consecutive months of partial or full remission (First *et al*. 2001).

Statistical methods

We used Kaplan–Meier survival curves to estimate the probability of remaining ill during the 5-year follow-up. The results were reported in probabilities of achieving a symptom state below the MDE criteria and achieving full remission. Cox proportional hazards models were used in the multivariate analyses for predicting time: (1) from baseline MDD to symptom state below MDE criteria; (2) from baseline MDD to full remission; (3) from symptom state below MDE criteria to a recurrent MDE. In these analyses, censored data included patients who had not achieved the focused symptom state by the end of the follow-up period or by the time they left the study and patients whose diagnosis switched to bipolar disorder. In analyses of recurrences, only those who completed the whole 5-year follow-up were included.

In our final multivariate Cox models, we included variables on the basis of our primary hypothesis. The predetermined independent variables at baseline comprised HAMD (alternatively BDI), history of former MDE, BAI, psychiatric co-morbidity (substance use disorder, cluster A, B and C personality disorders, anxiety and somatoform disorders) and education and employment status. In the final models, we omitted the non-significant variables.

We used a structural equation model to determine the predictors for the total times spent in full remission and in MDEs. Because the dependent variables are censored (they cannot exceed 100% or be <0%), the robust maximum likelihood (MLR) estimator (Muthén & Muthén, 2007) was used, with both dependent time variables as censored (truncated) variables. The MLR estimator takes into account the censoring and produces unbiased estimates of the model parameters. For instance, many patients with substance use co-morbidity never achieved full remission during the observation period and, further, would likely not reach full remission, even if the observation period were extended. The MLR estimator takes this into account and accordingly adjusts the parameter estimate of the effect of substance use disorders to time in full remission. An ordinary estimate that does not incorporate such truncation would in this particular case mitigate the true effect of substance abuse on time in full remission. Mplus 5.21 (Muthén & Muthén, 2007) software was used to estimate the model.

All models were adjusted for age and gender. Regression analyses were also controlled for the time at risk and the structural equation model and the MLR estimator for the follow-up time. PASW, version 18.0 (SPSS Inc., USA), was used.

Results

Cross-sectional outcome at 5 years

At 5 years, nearly one-half [46% (46/102)] of the follow-up patients were in full remission (median HAMD 5 and BDI 7), one-third [32%, (33/102)] were in partial remission (1–4 residual depressive symptoms) (median HAMD 13 and BDI 16) and one-fourth [23% (23/102)] were in the midst of a MDE (median HAMD 23 and BDI 32).

Of all the patients, one-third [30% (31/102)] were currently using antidepressants. On antidepressant medication were one-fifth [22% (10/46)] of the patients with current full remission, nearly half [42% (14/33)] of those with partial remission and one-third [30% (7/23)] of those currently in a MDE.

Time to full remission

During the 5-year follow-up, up to 70% of the patients (71/102) reached a full remission lasting at least 2 months. The median time from entry to full remission was 20 months (Fig. 1*a*). In univariate analyses, several individual factors at baseline were associated with time to full remission: BDI, HAMD, BAI, BHS, SOFAS, PSSS-R, SSI and substance use disorder (co-morbid alcohol and prescription drug abuse or dependence) (Table 2). In multivariate Cox proportional hazards analyses, longer time to full remission was predicted by more severe symptoms of depression in HAMD (Fig. 1*b*) or BDI and a co-morbid substance use disorder (Fig. 1*c*) (Table 3).

Recurrences and time to first recurrence

Most patients [90% (92/102)] achieved a symptom state below full MDE criteria. One-half of them [51% (47/92)] had a recurrence during the follow-up (return of MDE after at least two consecutive months of partial or full remission). Of those with recurrences, 50% experienced only one recurrence, 25% experienced two recurrences and 25% experienced three or more recurrences during the follow-up. Recurrence was associated in univariate analyses with several baseline factors: younger age; co-morbid psychiatric disorder such as cluster C personality disorder; any lifetime

https://doi.org/10.1017/S0033291711002303 Published online by Cambridge University Press

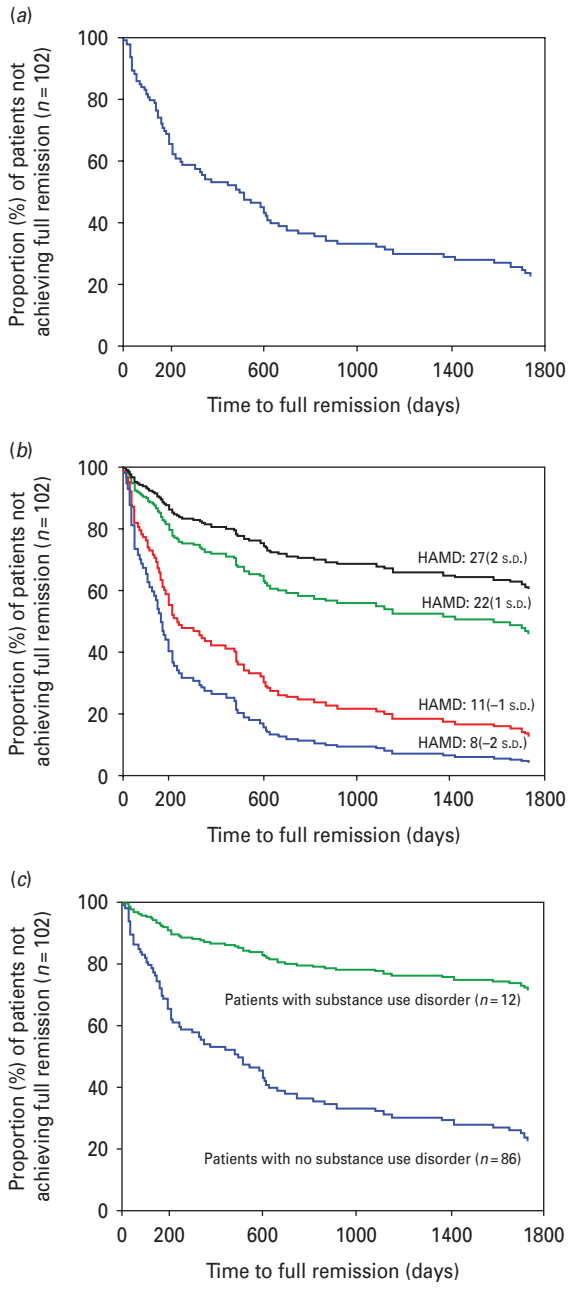

Fig. 1. Survival analysis to full remission of a major depressive episode or to 60 months (Kaplan–Meier survival curve). HAMD, Hamilton Depression Rating scale.

anxiety disorder; general anxiety disorder (GAD); or somatoform disorder and lifetime suicide attempts (Table 2). However, only personality disorders remained a significant predictor in multivariate logistic regression analyses.

Median time between remission and first recurrence was 8 months (S.D. = 25). The time from remission to recurrence was predicted in univariate analyses with several baseline factors: co-morbid psychiatric disorders such as cluster A and C personality disorder, any lifetime anxiety disorder; GAD or somatoform disorder and lifetime suicidal behaviour (Table 2). In multivariate analyses, GAD and somatoform disorder remained significant predictors (Table 3).

Time spent in MDEs, partial remission and full remission

Of the total follow-up time of 5 years, the patients spent, on average, less than one-half [42% (26.5 months, S.D. = 24.3)] in full remission, one-quarter [24% (15.3, S.D. = 18.0 months)] in partial remission and one-third [34% (21.7, S.D. = 22.4 months)] in MDEs (Fig. 2). The time spent in full remission and time spent in MDEs were associated in univariate analysis with several baseline factors: BDI; HAMD; BHS; BAI; SSI; SOFAS; PSSS-R; substance use disorder and alcohol abuse or dependence. In multivariate analyses of the baseline factors, more severe symptoms of depression in HAMD [0.028, 95% confidence intervals (CI) 0.016–0.040, $p < 0.001$] and co-morbid substance use disorder (0.415, 95% CI 0.245–0.596, $p < 0.001$) predicted longer time in MDEs significantly during the 5-year follow-up. High HAMD predicted time spent in MDEs; a rise in HAMD score of 10 at baseline predicted 14 months more time in MDEs. Substance use disorder predicted time spent in MDEs; substance use disorder predicted 25 months more time in MDEs ($B = 0.415$) and no substance use disorder 46 months more time in full remission ($B = -0.766$).

The patients who remained in the index MDE during the entire follow-up (10/102) suffered from more severe depression at baseline than the others [HAMD odds ratio (OR) 0.811, 95% CI 0.663–0.993, $p = 0.043$; BDI OR 0.882, 95% CI 0.803–0.969, $p = 0.009$]. They also had more psychiatric co-morbidity, especially substance use disorders (OR 16.087, 95% CI 2.675–91.972, $p = 0.002$).

Outcome of index MDE in baseline MDE patients

In separate analyses, the outcome in the subgroup of patients with a current MDE at baseline was found to be similar to the results presented above. These redundant results are therefore not presented here, but the data are available upon request.

Discussion

Our first-ever representative long-term, life-chart study of depression in primary care suggests a chronic episodic course, with often slow and incomplete recovery. Severity of MDEs in primary care is usually mild to moderate and two-thirds of the patients achieve full remission over time. However, one-half of them will have one or more recurrences in a 5-year

https://doi.org/10.1017/S0033291711002303 Published online by Cambridge University Press

Table 2. *Univariate analyses of predictors of recurrence, time from study entry to full remission, and time from remission to first recurrence among 102 patients with MDD followed up for 5 years in a Cox regression model*

	Time to full remission			Recurrence			Time to first recurrence		
Predictor at entry	HR	95% CI	*p*	OR	95% CI	*p*	HR	95% CI	*p*
Age (years)	0.99	0.98–1.01		1.03	1.00–1.07	0.033	0.98	0.96–1.01	
Gender (male)	1.55	0.84–2.84		1.56	0.57–4.24		0.72	0.32–1.65	
HAMD	0.92	0.88–0.96	<0.001	1.04	0.95–1.15		0.99	0.93–1.06	
Beck Depression Inventory	0.95	0.92–0.97	<0.001	1.02	0.97–1.07		0.99	0.95–1.03	
Beck Anxiety Inventory	0.96	0.94–0.97	0.002	1.02	0.98–1.07		0.98	0.95–1.01	
Beck Hopelessness Scale	0.93	0.89–0.98	0.003	1.03	0.94–1.13		0.98	0.92–1.05	
PSSS-R	1.02	1.00–1.04	0.045	1.00	0.96–1.04		0.99	0.96–0.02	
SOFAS	1.02	1.00–1.05	0.028	1.00	0.95–1.04		1.00	0.97–1.03	
Co-morbid psychiatric disorder	0.75	0.45–1.24		0.25	0.08–0.74	0.012	3.33	1.36–8.14	0.008
Axis I co-morbidity	0.68	0.43–1.09		0.52	0.20–1.35		2.02	0.98–4.16	(0.058)
Lifetime anxiety disorder (any)	0.74	0.46–1.18		0.38	0.15–0.98	0.045	1.97	0.98–3.94	(0.057)
Anxiety disorder (any)	0.84	0.52–1.35		0.51	0.19–1.37		1.61	0.76–3.42	
Panic disorder	0.75	0.27–2.07		1.86	0.22–16.31		0.66	0.15–2.97	
Social phobia	1.26	0.70–2.27		0.35	0.08–1.47		1.87	0.85–4.13	
GAD	0.67	0.32–1.41		0.18	0.03–0.98	0.047	3.85	1.63–9.13	0.002
Somatoform disorder	0.92	0.45–1.88		0.07	0.01–0.69	0.023	2.57	1.11–5.92	0.027
Substance use disorder (any)	0.13	0.03–0.51	0.004	1.13	0.21–6.23		1.15	0.34–3.90	
Alcohol abuse or dependence	0.26	0.06–1.07	(0.061)	1.02	0.13–8.07		1.16	0.25–5.47	
Axis II co-morbidity (any)	1.02	0.64–1.62		0.24	0.09–0.64	0.004	2.28	1.12–4.64	0.023
Cluster A personality disorder	0.36	0.09–1.47		−0.01	−0.01 to +0.99		6.23	1.71–22.7	0.006
Cluster B personality disorder	0.66	0.38–1.15		0.44	0.14–1.38		1.22	0.54–2.75	
Cluster C personality disorder	1.17	0.72–1.90		0.26	0.09–0.79	0.018	2.40	1.25–4.63	0.009
Antidepressive medication	0.95	0.59–1.52		0.53	0.21–1.38		1.73	0.91–3.29	(0.093)
Chronic physical illness perceived by doctor	0.81	0.50–1.30		0.72	0.27–1.91		1.17	0.61–2.23	

MDD, Major depressive disorder; HR, hazard ratio; CI, confidence intervals; OR, odds ratio; HAMD, Hamilton Rating Scale for Depression; PSSS-R, Perceived Social Support Scale – Revised; SOFAS, Social and Occupational Functioning Assessment Scale; GAD, generalized anxiety disorder.

Table 3. *Predictors of outcome among 102 patients with major depressive episode (MDE) in the Vantaa Primary Care Depression Study in a Cox multivariate regression model*

Baseline characteristic	HR	95% CI	*p* value
Time to full remission			
Age, years	0.99	0.97–1.0	
Gender, male	0.64	0.35–1.12	
Hamilton Depression Rating Scale score	1.10	1.04–1.15	0.000
Co-morbid substance use disorder	6.8	1.6–28.6	0.009
Interval from remission to first recurrence			
Age, years	0.99	0.97–1.02	
Gender, male	1.16	0.55–2.45	
Generalized Anxiety Disorder	0.35	0.16–0.78	0.010
Somatoform disorder	0.34	0.17–0.84	0.017
Personality disorder Cluster A	0.18	0.53–0.64	0.008

HR, Hazard ratio; CI, confidence intervals.

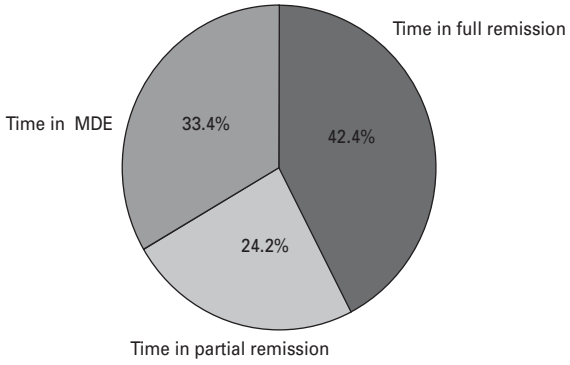

Fig. 2. Time spent in a major depressive episode (MDE) in partial and full remission in 102 primary care patients with major depressive disorder during a 5-year period.

period and as many as one-tenth of MDD patients remain chronically in MDEs. Overall, the patients spend more than half of the 5 years with at least some depressive symptoms. The prognosis appears poorest in those with initially abundant depressive symptoms and in the significant minority of patients with co-morbid substance use disorder.

The major strengths of this study include a medium-sized cohort of patients with depression, effectively representing primary health care patients in the fourth biggest Finnish city, derived from a screened stratified sample of 1119 patients. The patients were followed up with a life-chart, which offered an opportunity to assess the temporal course of the illness, with predictors for remission and recurrences as well as frequency of recurrences. As 82% of the patients could be assessed face to face at 5 years and the drop-outs did not differ from them in terms of age and gender or baseline severity of depression, attrition is unlikely to have biased our findings. Furthermore, we had information on multiple domains of risk factors, including severity and preceding course of depression, all co-morbid Axis I and II mental disorders, medical illnesses and numerous psychosocial factors.

However, some methodological choices need to be clarified and limitations noted. First, while the cohort probably represents the Finnish urban and suburban primary health care patient populations well, the generalizability to rural or foreign patient populations remains unknown. To the extent that other studies have investigated the same characteristics in primary care, no major differences are apparent. Moreover, epidemiology of depression and its treatment is unlikely to differ between Finland and other European Union countries (Hämäläinen *et al*. 2008, 2009; Pirkola *et al*. 2005). Second, in addition to municipal health centres, primary health care in Finland is also provided in occupational health care services, which are not included in our study. This alternative route to primary health care can be accessed by most Finns belonging to the workforce. Within our cohort, however, employment status at baseline did not predict outcome of depression. Thus, we are not aware of any obvious bias related to excluding occupational health services in our study. Third, we investigated the outcome of depression by using a graphic life-chart, which is similar, but not identical, to the Longitudinal Interval Follow-up Evaluation (LIFE) methodology used in NIMH-CDS (Keller *et al*. 1992; Melartin *et al*. 2004; Holma *et al*. 2008; Vuorilehto *et al*. 2009). Unlike in the LIFE, we classified patients' follow-up time into periods compatible with DSM-IV; MDEs, partial and full remissions. With use of rather stringent definitions, we found the cross-sectional full remission rate to be only 46%. It would have been only slightly higher (52%) if we had allowed one symptom instead

https://doi.org/10.1017/S0033291711002303 Published online by Cambridge University Press

of none in the definition of remission, but lower (38%) if we had defined remission as HAMD scores lower than eight. Fourth, chronicity could partly be explained by cross-sectional prevalence-based sampling. In any study involving screening for depression, probability of a positive screen is proportional to duration of depression. Fifth, because of the long interval between the follow-up interviews, some recall bias is likely to exist. This could be expected to be most pronounced in time periods most distant from the interviews. However, the shapes of e.g. the remission curve (Fig. 1*a*) or other similar time-related outcomes are regular, suggesting no significant bias. Finally, because of the naturalistic nature of our study, the treatment received was not controlled. The results in this study thus illustrate the outcome of patients who may have received treatment for depression only intermittently or, at worst, not at all during the follow-up.

This longitudinal study revealed the far-from-optimal prognosis of MDD in primary care. The process of recovery often appeared slow; only slightly more than one-half of the patients had achieved full remission by 2 years. Consequently, the patients spent less than half of the follow-up time in full remission. Slow recovery has been suggested in previous primary care studies (van Weel-Baumgarten *et al*. 1998; Oldehinkel *et al*. 2000; Wilson *et al*. 2003; Yiend *et al*. 2009) but the time to remission in primary care has not been reliably investigated earlier in a longer follow-up. Moreover, even one-half of those patients who achieved full or partial remission had one or more recurrences. High rates of recurrences have also been reported in psychiatric care studies (Kiloh *et al*. 1988; Lee & Murray, 1988; Keller *et al*. 1992; Angst & Preisig, 1995; Kennedy *et al*. 2003, 2004; Melartin *et al*. 2004; Furukawa *et al*. 2008; Holma *et al*. 2008; Solomon *et al*. 2008). Finally, large proportions of patients with only partial remission and chronic course emerged in our study, which is in accordance with earlier studies both in primary care and in the general population and secondary care (Kiloh *et al*. 1988; Lee & Murray, 1988; Keller *et al*. 1992; Ormel *et al*. 1993; Angst & Preisig, 1995; Kennedy *et al*. 2003, 2004; Melartin *et al*. 2004; Pirkola *et al*. 2005; Eaton *et al*. 2008; Furukawa *et al*. 2008; Holma *et al*. 2008; Solomon *et al*. 2008; Rhebergen *et al*. 2009). Considering the initially mild to moderate severity of depression in primary care, the chronicity is remarkable and needs to be taken into account when developing treatment and follow-up for patients with depression in primary health care.

The main predictor of poor outcome assessed by the time to remission was the initial severity of depression, despite variation in the phase of depression at study entry (Fig. 1*b*). Depression severity has also been a major predictor of outcome in general population and psychiatric care studies (Kiloh *et al*. 1988; Lee & Murray, 1988; Keller *et al*. 1992; Ormel *et al*. 1993; Angst & Preisig, 1995; Kennedy *et al*. 2003, 2004; Melartin *et al*. 2004; Pirkola *et al*. 2005; Eaton *et al*. 2008; Furukawa *et al*. 2008; Holma *et al*. 2008; Solomon *et al*. 2008; Rhebergen *et al*. 2009). For the purposes of predicting and following outcome, severity in our study could be assessed with BDI as well as with HAMD in patients with MDD. BDI or comparable questionnaires can easily be incorporated into routine clinical practice, even in primary care. While no substitute for clinical diagnosis, these symptom scales are necessary in primary care for the multiple purposes of improving recognition, evaluation of initial severity, follow-up of treatment response, plus evaluation of residual symptoms and prodromes of relapses and recurrences (NICE, 2010).

We also found co-morbidity to play a major role in predicting outcome. The small proportion of patients with co-morbid substance use disorder (one-sixth) especially had a chronic course of illness. Some general population (Johnson *et al*. 2005; Mattisson *et al*. 2009) and numerous psychiatric care studies have found co-morbidity to be associated with outcome (Keller *et al*. 1984; Coryell *et al*. 1992; Mueller *et al*. 1994; Paykel *et al*. 1995; Alnaes & Torgersen, 1997; Viinamäki *et al*. 2002; Melartin *et al*. 2004; Farabaugh *et al*. 2005; Holma *et al*. 2008). Also, recurrences were predicted by co-morbid psychiatric disorders, such as GAD, somatoform and personality disorders; however, not by the very heterogeneous group of chronic somatic illnesses. The role of somatoform disorders has not been recognized earlier, although two-thirds of patients with depression in primary care present exclusively with physical problems (Goldberg *et al*. 1993; Keeley *et al*. 2004; Vuorilehto *et al*. 2005). In this sense, patients in primary care may be different from the general population and from patients in secondary care. Our study included structured diagnostic evaluation of co-morbidity and life-chart methodology, thus providing a more accurate view of outcome than previous studies. Overall, as hypothesized, we found both the severity of depression and Axis I and II disorders to effectively predict outcome.

Conclusions

Mild to moderate depression in primary care appears to be a chronic episodic illness with often slow and incomplete recovery. Given that the poorest prognosis is related to the initial severity of depressive symptoms, the use of measurement scales is warranted. Co-morbid anxiety, somatoform and personality disorders had a marked impact on recurrence rates.

Special attention should be paid to substance use. This information is fundamental for improving management of depression in primary health care in everyday practice.

Acknowledgements

This study was supported by a grant from the Finnish Psychiatric Association.

Declaration of Interest

None.

References

Alnaes R, Torgersen S (1997). Personality and personality disorders predict development and relapses of major depression. *Acta Psychiatrica Scandinavica* **95**, 336–342.

Angst J, Preisig M (1995). Course of a clinical cohort of unipolar, bipolar and schizoaffective patients. Results of a prospective study from 1959 to 1985. *Schweizer Archiv fur Neurologie und Psychiatrie* **146**, 5–16.

Beck A, Ward C, Mendelson M, Mock J, Erbaugh J (1961). An inventory for measuring depression. *Archives of General Psychiatry* **4**, 561–571.

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

Beck AT, Kovacs M, Weissman A (1979). Assessment of suicidal intention: the Scale for Suicide Ideation. *Journal of Consulting and Clinical Psychology* **47**, 343–352.

Beck AT, Weissman A, Lester D, Trexler L (1974). The measurement of pessimism: the hopelessness scale. *Journal of Consulting and Clinical Psychology* **42**, 861–865.

Blumenthal JA, Burg MM, Barefoot J, Williams RB, Haney T, Zimet G (1987). Social support, type A behavior, and coronary artery disease. *Psychosomatic Medicine* **49**, 331–340.

Casey P, Birbeck G, McDonagh C, Horgan A, Dowrick C, Dalgard O, Lethinen V, Ayuso-Mateos JL, Dunn G, Page H, Wilkinson C, Wilkinson G, Vazquez-Barquero JL (2004). Personality disorder, depression and functioning: results from the ODIN study. *Journal of Affective Disorders* **82**, 277–283.

Coryell W, Endicott J, Keller M (1992). Major depression in a nonclinical sample. Demographic and clinical risk factors for first onset. *Archives of General Psychiatry* **49**, 117–125.

Eaton WW, Shao H, Nestadt G, Lee HB, Bienvenu OJ, Zandi P (2008). Population-based study of first onset and chronicity in major depressive disorder. *Archives of General Psychiatry* **65**, 513–520.

Farabaugh A, Fava M, Mischoulon D, Sklarsky K, Petersen T, Alpert J (2005). Relationships between major depressive disorder and comorbid anxiety and personality disorders. *Comprehensive Psychiatry* **46**, 266–271.

First M, Spitzer R, Gibbon M (1997). *Structured Clinical Interview for DSM-IV Personality Disorders* (*SCID-II*). American Psychiatric Press, Inc.: Washington, DC.

First M, Spitzer R, Gibbon M (2001). *Structural Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition with Psychotic Screen*. New York State Psychiatric Institute: New York.

Furukawa TA, Fujita A, Harai H, Yoshimura R, Kitamura T, Takahashi K (2008). Definitions of recovery and outcomes of major depression: results from a 10-year follow-up. *Acta Psychiatrica Scandinavica* **117**, 35–40.

Goldberg DP, Jenkins L, Millar T, Faragher EB (1993). The ability of trainee general practitioners to identify psychological distress among their patients. *Psychological Medicine* **23**, 185–193.

Goldman HH, Skodol AE, Lave TR (1992). Revising axis V for DSM-IV: a review of measures of social functioning. *American Journal of Psychiatry* **149**, 1148–1156.

Hamilton M (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* **23**, 56–62.

Hasin DS, Tsai WY, Endicott J, Mueller TI, Coryell W, Keller M (1996). Five-year course of major depression: effects of comorbid alcoholism. *Journal of Affective Disorders* **41**, 63–70.

Holma KM, Holma IA, Melartin TK, Rytsälä HJ, Isometsä ET (2008). Long-term outcome of major depressive disorder in psychiatric patients is variable. *Journal of Clinical Psychiatry* **69**, 196–205.

Hämäläinen J, Isometsä E, Laukkala T, Kaprio J, Poikolainen K, Heikkinen M, Lindeman S, Aro H (2004). Use of health services for major depressive episode in Finland. *Journal of Affective Disorders* **79**, 105–112.

Hämäläinen J, Isometsä E, Sihvo S, Kiviruusu O, Pirkola S, Lönnqvist J (2009). Treatment of major depressive disorder in the Finnish general population. *Depression and Anxiety* **26**, 1049–1059.

Hämäläinen J, Isometsä E, Sihvo S, Pirkola S, Kiviruusu O (2008). Use of health services for major depressive and anxiety disorders in Finland. *Depression and Anxiety* **25**, 27–37.

Jackson JL, Passamonti M, Kroenke K (2007). Outcome and impact of mental disorders in primary care at 5 years. *Psychosomatic Medicine* **69**, 270–276.

Johnson JG, Cohen P, Kasen S, Brook JS (2005). Personality disorder traits associated with risk for unipolar depression during middle adulthood. *Psychiatry Research* **136**, 113–121.

Keeley RD, Smith JL, Nutting PA, Miriam Dickinson L, Perry Dickinson W, Rost KM (2004). Does a depression intervention result in improved outcomes for patients presenting with physical symptoms? *Journal of General Internal Medicine* **19**, 615–623.

Keller MB (1992). The naturalistic course of anxiety and depressive disorders. *Clinical Neuropharmacology* **15** (Suppl. 1 Pt A), 171A–173A.

Keller MB, Klerman GL, Lavori PW, Coryell W, Endicott J, Taylor J (1984). Long-term outcome of episodes of major depression. Clinical and public health significance. *Journal of the American Medical Association* **252**, 788–792.

Keller MB, Lavori PW, Mueller TI, Endicott J, Coryell W, Hirschfeld RM, Shea T (1992). Time to recovery,

chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Archives of General Psychiatry* **49**, 809–816.

Kennedy N, Abbott R, Paykel ES (2003). Remission and recurrence of depression in the maintenance era: long-term outcome in a Cambridge cohort. *Psychological Medicine* **33**, 827–838.

Kennedy N, Abbott R, Paykel ES (2004). Longitudinal syndromal and sub-syndromal symptoms after severe depression: 10-year follow-up study. *British Journal of Psychiatry* **184**, 330–336.

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *Journal of the American Medical Association* **289**, 3095–3105.

Kiloh LG, Andrews G, Neilson M (1988). The long-term outcome of depressive illness. *British Journal of Psychiatry* **153**, 752–757.

Lee AS, Murray RM (1988). The long-term outcome of Maudsley depressives. *British Journal of Psychiatry* **153**, 741–751.

Mattisson C, Bogren M, Horstmann V, Tambs K, Munk-Jorgensen P, Nettelbladt P (2009). Risk factors for depressive disorders in the Lundby cohort – a 50 year prospective clinical follow-up. *Journal of Affective Disorders* **113**, 203–215.

Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET (2004). Severity and comorbidity predict episode duration and recurrence of DSM-IV major depressive disorder. *Journal of Clinical Psychiatry* **65**, 810–819.

Mueller TI, Lavori PW, Keller MB, Swartz A, Warshaw M, Hasin D, Coryell W, Endicott J, Rice J, Akiskal H (1994). Prognostic effect of the variable course of alcoholism on the 10-year course of depression. *American Journal of Psychiatry* **151**, 701–706.

Muthén LK, Muthén BO (2007). *Mplus User's Guide*. Muthén & Muthén: Los Angeles.

NICE (2010). *The Treatment and Management of Depression in Adults with Chronic Physical Health Problems*. (NICE Clinical Guideline 91). National Institute for Health and Clinical Excellence: London.

Oldehinkel AJ, Ormel J, Neeleman J (2000). Predictors of time to remission from depression in primary care patients: do some people benefit more from positive life change than others? *Journal of Abnormal Psychology* **109**, 299–307.

Ormel J, Oldehinkel T, Brilman E, vanden Brink W (1993). Outcome of depression and anxiety in primary care. A three-wave 3 1/2-year study of psychopathology and disability. *Archives of General Psychiatry* **50**, 759–766.

Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A (1995). Residual symptoms after partial remission: an important outcome in depression. *Psychological Medicine* **25**, 1171–1180.

Pirkola SP, Isometsä E, Suvisaari J, Aro H, Joukamaa M, Poikolainen K, Koskinen S, Aromaa A, Lönnqvist JK (2005). DSM-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population – results from the Health 2000 Study. *Social Psychiatry and Psychiatric Epidemiology* **40**, 1–10.

Poutanen O, Mattila A, Seppälä NH, Groth L, Koivisto AM, Salokangas RK (2007). Seven-year outcome of depression in primary and psychiatric outpatient care: results of the TADEP (Tampere Depression) II Study. *Nordic Journal of Psychiatry* **61**, 62–70.

Rhebergen D, Beekman AT, Graaf R, Nolen WA, Spijker J, Hoogendijk WJ, Penninx BW (2009). The three-year naturalistic course of major depressive disorder, dysthymic disorder and double depression. *Journal of Affective Disorders* **115**, 450–459.

Rost K (2009). Disability from depression: the public health challenge to primary care. *Nordic Journal of Psychiatry* **63**, 17–21.

Sartorius N, Ustun TB, Costae Silva JA, Goldberg D, Lecrubier Y, Ormel J, von Korff M, Wittchen HU (1993). An international study of psychological problems in primary care. Preliminary report from the World Health Organization Collaborative Project on 'Psychological Problems in General Health Care'. *Archives of General Psychiatry* **50**, 819–824.

Simon GE (2000). Long-term prognosis of depression in primary care. *Bulletin of the World Health Organization* **78**, 439–445.

Solomon DA, Leon AC, Coryell W, Mueller TI, Posternak M, Endicott J, Keller MB (2008). Predicting recovery from episodes of major depression. *Journal of Affective Disorders* **107**, 285–291.

Spijker J, de Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA (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.

Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy 3rd FV, Hahn SR, Brody D, Johnson JG (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *Journal of the American Medical Association* **272**, 1749–1756.

Stegenga BT, Kamphuis MH, King M, Nazareth I, Geerlings MI (2010). The natural course and outcome of major depressive disorder in primary care: the PREDICT-NL study. *Social Psychiatry and Psychiatric Epidemiology*, doi: 10.1007/s00127-010-0317-9, published online 6 November 2010.

van Weel-Baumgarten E, van den Bosch W, van den Hoogen H, Zitman FG (1998). Ten year follow-up of depression after diagnosis in general practice. *British Journal of General Practice* **48**, 1643–1646.

Wells KB, Tang L, Miranda J, Benjamin B, Duan N, Sherbourne CD (2008). The effects of quality improvement for depression in primary care at nine years: results from a randomized, controlled group-level trial. *Health Services Research* **43**, 1952–1974.

Widmer RB, Cadoret RJ (1978). Depression in primary care: changes in pattern of patient visits and complaints during a developing depression. *Journal of Family Practice* **7**, 293–302.

Viinamäki H, Hintikka J, Honkalampi K, Koivumaa-Honkanen H, Kuisma S, Antikainen R, Tanskanen A, Lehtonen J (2002). Cluster C personality disorder impedes alleviation of symptoms in major depression. *Journal of Affective Disorders* **71**, 35–41.

Wilson I, Duszynski K, Mant A (2003). A 5-year follow-up of general practice patients experiencing depression. *Family Practice* **20**, 685–689.

Vuorilehto M, Melartin T, Isometsä E (2005). Depressive disorders in primary care: recurrent, chronic, and co-morbid. *Psychological Medicine* **35**, 673–682.

Vuorilehto MS, Melartin TK, Isometsa ET (2009). Course and outcome of depressive disorders in primary care: a prospective 18-month study. *Psychological Medicine* **39**, 1697–1707.

Yiend J, Paykel E, Merritt R, Lester K, Doll H, Burns T (2009). Long term outcome of primary care depression. *Journal of Affective Disorders* **118**, 79–86.

Zimmerman M, Coryell W (1989). DSM-III personality disorder diagnoses in a nonpatient sample. Demographic correlates and comorbidity. *Archives of General Psychiatry* **46**, 682–689.