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Kirsi Riihimäki

Long-term outcome of depressive disorders in primary health care

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Kirsi Riihimäki

LONG-TERM OUTCOME OF DEPRESSIVE DISORDERS IN PRIMARY HEALTH CARE

Academic dissertation

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”Syksyinen sade puutarhan yllä
on tahtomme turtuminen masennuksen hetkellä.”

Sylvi Kekkonen

Dedicated to the patients and their dear ones

Abstract

Kirsi Riihimäki. Long-term Outcome of Depressive Disorders in Primary Health Care. [Long-term Follow-up Study Focusing on Outcome, Suicide Attempts, Disability and Current Borderline Personality Disorder among Primary Care Patients with Depressive Disorders] Research 126. 160 sidor. Helsinki, Finland 2014.
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The Vantaa Primary Care Depression Study (PC-VDS) is a naturalistic prospective cohort study of 137 primary care patients with depressive disorders followed up for five years. It covers the full range of depressive disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), fulfilling at least the diagnostic criteria for minor depression (MinD) (DSM-IV, Appendix B). The study forms a collaborative depression research project between the Mood, Depression and Suicidal Behaviour Research Unit of the National Institute for Health and Welfare, Primary Health Care Organization of the City of Vantaa, and the Department of Psychiatry of Helsinki University. The aim was to obtain a comprehensive view on the course and outcome of depressive disorders in primary health care. The additional aims were to investigate suicidality and functional and work disability of patients with depressive disorders, and the influence of concurrent borderline personality disorder (BPD).

A stratified random sample of 1119 general practitioners' patients aged 20-69 representing primary care patients of Vantaa, the fourth biggest Finnish city, was screened for depression with the Primary Care Evaluation of Mental Disorders (PRIME-MD) between January and December 2002. Altogether 402 patients had a positive screen. The exclusion criteria were psychosis other than depressive disorder, bipolar or organic mood disorders, alcohol use problems severe enough to prevent two weeks' abstinence, and those currently receiving treatment in psychiatric care. Altogether 175 potentially eligible patients completed the face-to-face interview with the Structured Clinical Interview for DSM-IV Axis I Disorders with psychotic screen (SCID-I/P). The final study cohort comprised 137 patients with DSM-IV depressive disorders, with at least diagnosis of MinD according to DSM-IV, Appendix B. SCID-I/P and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) interviews were used to diagnose axis I and II psychiatric disorders, respectively.

The 137 patients with DSM-IV depressive disorders were prospectively followed up at 3, 6 and 18 months and 5 years. Altogether 112 (82%) patients completed the 5-year follow-up investigation from March 2007 to August 2008, and of 134 (98%) patients some follow-up information was gathered. Of them, 102 patients fulfilled the diagnostic criteria for major depressive disorder (MDD) at baseline. Duration of the index episode of DSM-IV depressive disorder at baseline and information on timing of subsequent recurrences, major depressive episodes (MDEs) and partial or

full remission of MDD, and periods of substance abuse, suicide attempts, and sick leaves and disability pension were examined with a life-chart.

Patients with lifetime MDD (123/137) spent 34% of follow-up time of the five years in MDEs, 24% in partial remission and only 42% in full remission. Nine in ten achieved at least partial remission and two-thirds reached full remission. Baseline severity of depression and substance use comorbidity predicted time spent in MDEs: a rise in Hamilton Rating Scale for Depression (HAMD) score of ten at baseline predicted 14 months and comorbid substance use disorder 25 months more time in MDEs. One-half of those who achieved partial remission and one-third of those who reached full remission were having at least one recurrence. The recurrences were predicted by baseline personality disorders. The time from remission to recurrence was predicted by baseline generalized anxiety disorder and somatoform disorder.

One-tenth of all patients attempted suicide one to three times during five years. The incidence rate varied robustly depending on the level of depression, being 0 per 1000 patient-years during full remission, 5.8 per 1000 patient-years during partial remission and 107 per 1000 patient-years during MDEs. Although a history of suicide attempts and substance use disorder also indicated the risk, duration of MDEs was the central factor determining overall long-term risk.

In the whole cohort, level of functioning and work ability were strongly associated with time spent depressed and current severity of depression. Patients who belonged to the labour force at baseline spent one-third of the follow-up off work due to depression; two-thirds were granted sick leave, and one-tenth a disability pension due to depression. Longer duration of depression, comorbid disorders and having received social assistance predicted dropping out from work.

A quarter of all patients suffered from concurrent borderline personality disorder (BPD) at the study entry. This proportion diminished to one-fifth in five years. Comorbid anxiety and substance use disorders were common among them. Concurrent BPD increased the severity and duration of depression, suicidal behaviour, unemployment and economic difficulties. These patients comprised a particularly comorbid, chronic and disabled group.

This naturalistic prospective cohort study of primary care patients with depressive disorders revealed often slow and incomplete recovery and a common recurrent course, which needs to be taken into account when developing services. While the severity of depression predicts poor outcome, the use of measurement scales is warranted when planning and monitoring treatment. Comorbidity, concurrent substance use disorder, anxiety disorders, somatoform disorder and BPD all need to be taken into account in clinical practice guidelines. Duration of depression appears most decisive for suicide attempts among primary care patients with depression. Efforts should focus on the continuity of care.

Keywords: primary care, depression, follow-up, outcome, comorbidity, suicide attempts, disability, employment, borderline personality disorder

Tiivistelmä

Kirsi Riihimäki. Long-term Outcome of Depressive Disorders in Primary Health Care. [Pitkäaikaistutkimus perusterveydenhuollon masennuspotilaiden ennusteesta, itsemurhayrityksistä, toiminta- ja työkyvystä sekä samanaikaisesta epävakaasta persoonallisuushäiriöstä] Tutkimus 126. 160 sidor. Helsinki, Suomi 2014.
ISBN 978-952-302-152-5 (painettu); ISBN 978-952-302-153-2 (verkkojulkaisu)

Vantaan terveyskeskuksen masennustutkimus (PC-VDS) on naturalistinen etenevä 137 masennuspotilaan viiden vuoden seurantatutkimus. Tutkimukseen osallistui seulomalla valittuja DSM-IV-tautiluokituksen (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) mukaisesti diagnosoituja masennuspotilaita, jotka täyttivät vähintään Minor Depression -kriteerit (DSM-IV, Appendix B). Tutkimus on toteutettu Terveyden ja hyvinvoinnin laitoksen, Vantaan kaupungin sosiaali- ja terveystoimen ja Helsingin Yliopiston yhteistyönä. Tutkimuksen tavoitteena on luoda kattava käsitys kliinisesti merkittävän masennuksen kulusta ja ennusteesta sekä siihen liittyvästä itsetuhoisuudesta, toiminta- ja työkyvystä ja samanaikaisesta epävakaasta persoonallisuushäiriöstä. Koska valtaosa masennuspotilaista, myös monihäiriöisistä, hoidetaan perusterveydenhuollossa, on tämän tutkimuksen löydöksillä kansanterveydellistä merkitystä.

Kolmella vantaalaisella terveysasemalla terveyskeskuslääkärin vastaanotolle tulleet 1119 satunnaisesti valittua 20-69 -vuotiasta potilasta täyttivät PRIME-MD (Primary Care Evaluation of Mental Disorders) seulontakyselyn 1.1.2002 ja 31.12.2002 välisenä aikana. Masennuksen suhteen seulavastaus oli positiivinen 402 potilaalla. Poissulkukriteerit olivat muu kuin masennuksesta johtuva psykoosi, kaksisuuntainen tai orgaaninen masennus, päihdeongelma ilman kahden viikon raittiutta ja ajankohtainen hoito psykiatrisessa erikoissairaanhoidossa tai yksityispsykiatrilla. Valikoituneet 175 potilasta haastateltiin strukturoidulla kliinisellä SCID-I/P -menetelmällä (Structured Clinical Interview for DSM-IV Axis I Disorders / Psychotic Screen, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition). Tutkimukseen värvättiin ne 137 potilasta, joilla todettiin vähintään DSM-IV-tautiluokituksen mukainen Minor Depression (DSM-IV, Appendix B). Heidät haastateltiin SCID-I/P ja -II -menetelmillä (Structured Clinical Interview for DSM-IV Axis II Disorders) kaikkien akseli I ja II häiriöiden toteamiseksi.

Tutkimuspotilaita seurattiin 3, 6 ja 18 kuukauden sekä 5 vuoden kohdalla. 5-vuotisseuranta toteutettiin 15.3.2007 ja 31.8.2008 välisenä aikana. Seurantatietoa saatiin yhteensä 134 potilaasta (98%) ja 5-vuotishaastatteluun osallistui peräti 112 potilasta (82%), joista 102 kärsi tutkimuksen alussa ja 123 jo aiemmin masennustilasta. Elämänjanamenetelmällä mitattiin indeksimasennusjakson keston lisäksi masennustilan sekä osittaisen ja täydellisen toipumisen jaksojen kestot sekä ajoitettiin masennusjaksojen uudelleenpuhkeamiset, päihteiden haitallinen käyttö ja riippuvuus, itsemurhayritykset sekä masennuksesta johtuvat sairauslomat ja työkyvyttömyyseläkkeet.

Potilaat, joilla oli diagnosoitu masennustila, kärsivät siitä 34 % seuranta-ajasta ja olivat vain 42 % täysin toipuneina ja loput 24 % osittain toipuneina. Kaiken kaikkiaan 90 % potilaista toipui ainakin osittain ja 70 % täysin viiden vuoden seurannan aikana. Masennuksen vaikeusaste ja päihdehäiriö huononsivat ennustetta. Lähtötilanteen 10 pistettä korkeampi Hamiltonin depressioasteikon pistemäärä (HAMD) pidensi masennustilassa vietettyä aikaa 14 kk ja päihdehäiriö 25 kk. Osittain toipuneilla potilailla masennustila uusiutui joka toisella ja täysin toipuneilla joka kolmannella vähintään kerran. Uudelleen sairastumista ennusti persoonallisuushäiriö ja sitä nopeuttivat yleistynyt ahdistuneisuus ja somatoforminen häiriö.

Kaikista tutkimuspotilaista joka kymmenes yritti itsemurhaa yhdestä kolmeen kertaa kukin. Itsemurhayritysten ilmaantuvuus vaihteli suuresti riippuen masennuksen vaikeusasteesta. Se oli osittain toipuneena 5,8 ja masennustilassa 107 1000 potilasvuotta kohden. Kukaan ei yrittänyt itsemurhaa täysin toipuneena. Vaikka aiemmat itsemurhayritykset ja päihdehäiriö viittasivat lisääntyneeseen itsemurhayritysvaaraan, ainoastaan masennusjakson pituus lisäsi sitä merkitsevästi.

Toiminta- ja työkyky olivat vahvasti yhteydessä masennusjaksojen pituuteen sekä masennuksen vaikeusasteeseen. Ne potilaat, jotka kuuluivat työvoimaan tutkimuksen alussa, olivat kolmanneksen seuranta-ajasta poissa työstä masennuksen takia: kahdelle kolmasosalle oli määrätty sairauslomaa ja joka kymmenes oli päätynyt työkyvyttömyyseläkkeelle. Masennusjaksojen kesto, monihäiriöisyys ja toimeentulotuen saaminen olivat yhteydessä työelämästä poistumiseen.

Samanaikaisesta epävakaasta persoonallisuushäiriöstä kärsi kaikista tutkimuspotilaista joka neljäs tutkimuksen alussa ja viiden vuoden kuluttua joka viides. Nämä potilaat olivat erityisen monihäiriöisiä ja huonoennusteisia. Heillä oli usein myös ahdistuneisuus- ja päihdehäiriöitä. Epävakaa persoonallisuushäiriö masentuneilla perusterveydenhuollon potilailla lisäsi masennuksen vaikeutta ja kestoa, itsetuhoisia ajatuksia ja itsemurhayrityksiä sekä työttömyyttä ja taloudellisia vaikeuksia.

Viisivuotisseurannan aikana perusterveydenhuollon masennuspotilaat toipuivat hitaasti ja epätäydellisesti ja masennusjaksot uusiutuivat usein. Tieto ennusteesta on tärkeää palveluita kehitettäessä. Masennuksen syvyys ennusti vahvasti sekä huonoa toipumista että alentunutta toiminta- ja työkykyä, joten oiremittareiden systemaattinen käyttö on suositeltavaa masennuksen vaikeusasteen kartoittamisessa. Samanaikaiset muut psykiatriset häiriöt, etenkin päihdehäiriö, mutta myös ahdistuneisuushäiriöt, somatoforminen häiriö ja epävakaa persoonallisuushäiriö, vaikuttavat masennuksen kulkuun ja ne on syytä huomioida hoitosuosituksia laadittaessa. Masennusjaksojen pituus osoittautui merkittävimmäksi itsemurhayrityksien riskitekijäksi, joten jatko- ja ylläpitohoitoihin on kiinnitettävä huomiota.

Avainsanat: perusterveydenhuolto, terveyskeskus, masennus, depressio, seuranta, ennuste, monihäiriöisyys, itsemurhayritykset, toimintakyky, työkyky, epävakaa persoonallisuushäiriö

Sammandrag

Kirsi Riihimäki, Long-term Outcome of Depressive Disorders in Primary Health Care. Institutet för hälsa och välfärd. [Långsiktig undersökning om prognoser, självmordsförsök, funktions- och arbetsförmåga bland patienter med depression och samtidig instabil personlighetsstörning inom primärvården]. Forskning 126. 160 sidor. Helsingfors, Finland 2014.
ISBN 978-952-302-152-5 (tryckt); ISBN 978-952-302-153-2 (nätpublikation)

Vanda hälsocentrals undersökning om depression (PC-VDS) är en naturalistiskt framskridande femårig uppföljningsundersökning som omfattar 137 patienter som lider av depression. Till undersökningen valdes genom screening ett antal patienter med depression enligt sjukdomsklassificeringen DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) som åtminstone uppfyllde kriterierna för Minor Depression (DSM-IV, Appendix B). Undersökningen var ett samarbetsprojekt mellan Institutet för hälsa och välfärd, Vanda stads social- och hälsovårdsväsende samt Helsingfors universitet. Syftet med undersökningen var att skapa en heltäckande bild av hur kliniskt relevant depression framskrider och dess prognoser samt relaterade symptom på självdestruktivitet, funktions- och arbetsförmåga och samtidig instabil personlighetsstörning. Eftersom största delen av de patienter som lider av depression, även de med multipel personlighetsstörning, får vård inom primärvården har resultaten av denna undersökning betydelse för folkhälsan.

De slumpmässigt valda 1 119 patienter i åldern 20–69 som besökte läkare på tre hälsocentraler i Vanda uppfyllde kriterierna för PRIME-MD (Primary Care Evaluation of Mental Disorders) i screeningen mellan 1.1.2002 och 31.12.2002. Enligt screeningen led 402 patienter av depression. Uteslutningskriterierna var psykos som inte berodde på depression, bipolär eller organisk depression, missbruksproblem utan två veckors nykterhet och pågående vård inom psykiatrisk specialsjukvård eller hos privat psykiater. De utvalda 175 patienterna intervjuades med hjälp av den strukturerade kliniska SCID-I/P-metoden (Structured Clinical Interview for DSM-IV Axis I Disorders / Psychotic Screen, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition). De 137 patienter som värvades till undersökningen konstaterades lida åtminstone av Minor Depression enligt sjukdomsklassificeringen DSM-IV (DSM-IV, Appendix B). De intervjuades med hjälp av metoderna SCID-I/P och II (Structured Clinical Interview for DSM-IV Axis II Disorders) för att konstatera alla axis I och II störningar.

Patienternas situation följdes upp efter 3, 6 och 18 månader samt efter 5 år. 5-årsuppföljningen genomfördes mellan 15.3.2007 och 31.8.2008. I den deltog rentav 82 procent av de ursprungliga patienterna, av vilka 102 ursprungligen konstaterats lida av depression. Med hjälp av tidsaxelmetoden mättes utöver den indexerade depressionsperiodens längd dessutom längden på depressionstillståndet samt de partiella och fullständiga återhämtningsperiodernas längd och dessutom tidsbestämdes

utbrotten av nya depressionsperioder, skadlig användning och beroende av rusmedel, självmordsförsök samt sjukledighet och sjukpension på grund av depression.

Patienter med diagnosen depression led av sjukdomen 34 procent av uppföljningstiden och var helt tillfrisknade endast 42 procent av tiden medan resten var delvis tillfrisknade 24 procent av tiden. Totalt tillfrisknade 90 procent av patienterna delvis och 70 procent helt under den fem år långa uppföljningsperioden. Depressionens svårighetsgrad och missbruksproblem försämrade prognosen. Om poängantalet enligt Hamiltons depressionsskala (HAMD) i utgångsläget var 10 poäng högre förlängdes depressionsperioden med 14 månader och missbruksstörningen med 25 månader. Hos varannan person som delvis tillfrisknat förnyades depressionstillståndet och hos var tredje helt tillfrisknad person minst en gång. Återfallet föregicks av personlighetsstörning och det snabbades upp av mer allmän ångest och somatoformisk störning.

Av alla undersökta patienter försökte var tionde begå självmord från en till tre gånger. Förekomsten av självmordsförsök varierade i hög grad beroende på depressionens svårighetsgrad. Den var 5,8 hos delvis tillfrisknade och 107 hos personer med allvarlig depression per 1 000 patientår. Ingen helt tillfrisknad försökte begå självmord. Även om tidigare självmordsförsök och missbruksstörningar medförde en ökad risk för självmordsförsök var det endast längden på depressionsperioden som ökade den märkbart.

Funktions- och arbetsförmågan hade stark korrelation med depressionsperiodens längd och depressionens svårighetsgrad. De patienter som ingick i arbetskraften i början av undersökningen var borta från arbetet en tredjedel av uppföljningstiden på grund av depression: två tredjedelar hade ordinerats sjukledighet, och var tionde hade beviljats sjukpension. Depressionsperiodernas längd, multipel personlighetsstörning och erhållande av utkomststöd hade samband med lämnandet av arbetslivet.

Var fjärde patient led i början av undersökningen av samtidig instabil personlighetsstörning och var femte fem år senare. Dessa patienter hade särskilt allvarliga multipla personlighetsstörningar och en dålig prognos. De hade ofta också ångest- och missbruksstörningar. En instabil personlighetsstörning hos deprimerade patienter inom primärvården ökade depressionens svårighetsgrad och längd, självdestruktiva tankar och självmordsförsök samt arbetslöshet och ekonomiska problem.

Under den fem år långa uppföljningsperioden tillfrisknade deprimerade patienter inom primärvården långsamt och ofullständigt, och depressionsperioderna förnyades ofta. Information om prognosen är viktig när tjänsterna utvecklas. Djupa depressioner tenderade att leda till både bristfälligt tillfrisknande och nedsatt funktions- och arbetsförmåga, och därför rekommenderas en systematisk användning av symptomindikatorerna vid kartläggningen av depressionens svårighetsgrad. Samtidiga andra psykiatriska störningar, i synnerhet missbruksstörningar men också ångeststörningar, somatoformiska störningar och instabila personlighetsstörningar påverkar depressionens utveckling, och det gäller att beakta dem när vårdrekommendationer planeras. Depressionsperiodernas längd

visade sig vara den största riskfaktorn bakom självmordsförsök, och således bör uppmärksamhet fästas vid fortsatt vård och underhållsvård.

Nyckelord: primärvård, hälsocentral, depression, uppföljning, prognos, multipel personlighetsstörning, självmordsförsök, funktionsförmåga, arbetsförmåga, instabil personlighetsstörning

Contents

List of original papers

This thesis is based on the following original articles referred to in the text by their Roman numerals I–IV.

I Riihimäki K, Vuorilehto M, Melartin T, Isometsä E. Five-year outcome of major depressive disorder in primary health care. Psychological Medicine 2011;16:1-11.

II Riihimäki K, Vuorilehto M, Melartin T, Haukka J, Isometsä E. Incidence and predictors of suicide attempts among primary-care patients with depressive disorders: a 5-year prospective study. Psychological Medicine 2014;44:291-302.

III Riihimäki K, Vuorilehto M, Isometsä E. A 5-year prospective study of predictors for functional and work disability among primary care patients with depressive disorders. European Psychiatry 2014.

IV Riihimäki K, Vuorilehto M, Isometsä E. Borderline personality disorder among primary care depressive patients: A five-year study. Journal of Affective Disorders 2014;155:303-6.

Abbreviations

APA	American Psychiatric Association
AUDIT	Alcohol Use Disorders Identification Test
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BPD	Borderline Personality Disorder
BL	Baseline
CDC-NCHS	Centers for Disease Control and Prevention - National Center for Health Statistics
CDS	Collaborative Depression Study
CID	Clinical Interview for Depression
CIDI	Composite International Diagnostic Interview
CIDI-PHC	Composite International Diagnostic Interview–Primary Health Care Version
CIDI-SF	Composite International Diagnostic Interview-Short Form
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
DIS	Diagnostic Interview Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3th Edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3th Edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECA	Epidemiological Catchment Area Study
ECT	Electroconvulsive Therapy
ESEMeD	European Study of the Epidemiology of Mental Disorders
GAD	Generalized Anxiety Disorder
GAF	Global Assessment of Functioning
GP	General Practitioner
GWAS	Genome-Wide Association Studies
HAMD	Hamilton Rating Scale for Depression
HR	Hazard Ratio
HS	Beck Hopelessness Scale
ICD	International Statistical Classification of Diseases
ICD-10	International Statistical Classification of Diseases, 10th Edition
LCI	Life Chart Interview
LIFE	Longitudinal Interval Follow-up Evaluation
MDD	Major Depressive Disorder

MDE	Major Depressive Episode
MinD	Minor Depression
MLR	Robust Maximum Likelihood
NCCMH	National Collaborating Centre for Mental Health
NCS	National Comorbidity Survey
NCS-R	National Comorbidity Survey Replication
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NICE	National Institute for Health and Clinical Excellence
NIMH	National Institute of Mental Health
NS	Non-significant
ODIN	Outcomes of Depression International Network
OR	Odds Ratio
PC	Primary (Health) Care
PC-VDS	Vantaa Primary Care Depression Study
PPGHC	Psychological Problems in General Health Care
PRIME-MD	Primary Care Evaluation of Mental Disorders
PSSS-R	Perceived Social Support Scale - Revised
RCT	Randomized Controlled Trial
rTMS	Repetitive Transcranial Magnetic Stimulation
SCAN-2	Schedules for Clinical Assessment in Neuropsychiatry
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SCID-I/P	Structured Clinical Interview for DSM-IV Axis I Disorders / Psychotic Screen
SCID-II	Structured Clinical Interview for DSM-IV Axis II Disorders
SD	Standard Deviation
SDS	Sheehan Disability Scale
SOFAS	Social and Occupational Functioning Assessment Scale for DSM-IV
SPSS	Statistical Package for the Social Sciences
SSI	Scale for Suicidal Ideation
SubMDD	Subsyndromal Depression
VDS	Vantaa Depression Study
WHO	World Health Organization

1 Introduction

Depressive disorders are common in the general population and among the most common conditions encountered in primary care (Sartorius et al., 1993; Hämäläinen et al., 2004; Rost, 2009). Major depressive disorder (MDD) is considered to be the third leading illness in terms of global disease burden, and by the year 2030 the leading cause of functional disability among non-inflammatory diseases (Murray et al., 2012). MDD is the fourth leading illness worldwide causing functional disability and days lost from work (Wells et al., 1989; Hays et al., 1995; Salminen et al., 1997; Wells and Sherbourne, 1999; Thomas and Morris, 2003; Wittchen et al., 2011; Murray et al., 2012) resulting in considerable costs often exceeding those for chronic medical conditions (Moussavi et al., 2007; Alonso et al., 2011; Kessler, 2012). Although excess mortality may be somewhat higher in MDD than in subthreshold depression, no significant difference was found in a recent meta-analysis (Cuijpers et al., 2013). The risk of suicide in MDD is estimated 6.7% for men and 3.8% for women after their first contact with secondary mental health services with median follow-up 18 years (Nordentoft et al., 2011). Depressive disorders are also associated with a substantial loss of quality of life. Dysthymia and chronic anxiety disorders were associated with the largest loss of health-related quality of life on the individual level before and after adjusting for somatic and psychiatric comorbidity, and on the population level, depressive disorders accounted 55% of quality-adjusted life-year loss (Saarni et al., 2007). Depression is perceived to comprise a key challenge in primary care because its prevalence, type of presenting complaints and time constraints of the primary care doctors (Wittchen and Pittrow, 2002). Therefore, knowledge of outcome of depressive disorders and of factors predicting it and knowledge of suicide attempts among patients with depressive disorders is necessary in planning health services and treatment guidelines in primary care.

The Vantaa Primary Care Depression Study (PC-VDS) is a prospective naturalistic cohort study of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) depressive disorders followed up 5 years. This study covers the full range of DSM-IV depressive disorders, diagnosed at least for minor depression (MinD) according to DSM-IV, Appendix B. It comprises major depressive disorder (MDD), subsyndromal depression (SubMDD) and minor depression (MinD). SubMDD is defined as at least two current symptoms, present every day for most of the time, for at least two weeks, in persons not meeting the criteria for MDD, MinD or dysthymic disorder (Judd et al., 1994). SubMDD includes both recovering and prodromal cases of previous MDD. In this study, dysthymia and adjustment disorder with depressed mood are categorised as MinD or as SubMDD. This study investigated long-term outcome, suicide attempts, and functional and work disability, their risk factors, and the influence of concurrent borderline personality disorder (BPD) in a sample of 137 patients representing primary care patients in

Vantaa, the fourth biggest Finnish city with 179 856 inhabitants in 2002. Semi-structured interviews were used to diagnose all axis I and II disorders. The life-chart methodology was used to determine duration and timing of major depressive episodes (MDEs) and partial and full remissions, and substance abuse periods, and employment, unemployment, sick leaves, and granted pensions due to depression. In addition, targets of investigation were timing of suicide attempts, the relationship between suicidal ideation and the severity of depression, and treatment received before and after suicide attempts. Moreover, this study also gathered information on medical comorbidity and psychosocial and socio-economic factors.

2 Review of the literature

2.1 Diagnosis of depressive disorders

2.1.1 Classification of depressive disorders

The use of the term depression extends from temporal feelings of sadness up to life-threatening illness and also a large range of clinical depressive syndromes. Approaches to classify mental disorders have been multifarious and extended over two thousand years. In Finland, the classification officially in use is the International Statistical Classification of Diseases, 10th Edition (ICD-10) (World Health Organization, 2007, Tautiluokitus ICD-10, 2011). The process for developing an 11th Edition of ICD (ICD-11) is in progress and it is to be published in 2015.

In research practice, the Diagnostic and Statistical Manual of Mental Disorders (DSM) is more often used as DSM was first published in 1952. The American Psychiatric Association (APA) has worked closely with staff from the World Health Organization (WHO), Centers for Medicare and Medicaid Services (CMS), and Centers for Disease Control and Prevention - National Center for Health Statistics (CDC-NCHS) to ensure that the two systems are maximally compatible (American Psychiatric Association, 2013).

Diagnostic criteria of MDD in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and in ICD-10 are slightly different. In ICD-10, the two core symptoms are added with loss of energy and two of the three core symptoms have to be present. In addition, feelings of worthlessness and unreasonable guilt are defined as separate criteria. Also, ICD-I0 requires one symptom less for diagnosis of MDD. However, diagnostic criteria of MDD in DSM-IV and in ICD-10 are well comparable (American Psychiatric Association, 2000, World Health Organization, 2007). The concordance for MDD for ICD-10 and for DSM-IV has been found to be 83%, the diagnostic threshold for ICD-10 being lower (Andrews et al., 1999).

In DSM-IV, unipolar forms of primary mood disorders are divided into three groups: major depressive disorder (MDD), dysthymic disorder, and depression not otherwise specified (American Psychiatric Association, 2000). The DSM-IV Appendix B defines research diagnostic criteria for minor depression (MinD) (American Psychiatric Association, 2000). The essential features of MinD are identical to MDD in duration, but involve fewer symptoms and less impairment. In DSM-IV, adjustment disorder with depressed mood is not classified in mood disorders, but is included in MinD according to DSM-IV, Appendix B.

The DSM edition currently in use is the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), which was released in May 2013 (American Psychiatric Association, 2013). In this thesis, the previous Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) was used

(American Psychiatric Association, 2000). Regarding depressive disorders, there are changes from DSM-IV to DSM-5. Neither the core criteria symptoms applied to the diagnosis of major depressive episode (MDE) nor the requisite duration of at least 2 weeks have changed. Thus, although a new edition of DSM, the results of this study remain relevant concerning MDD patients.

In the DSM-IV and DSM-5, there are some differences between depressive disorders especially concerning chronic depressive symptoms. DSM-5 no longer includes dysthymia and chronic depression but has persistent depressive disorder, which includes both chronic major depressive disorder and the previous dysthymic disorder. MDD can occur at the same time with persistent depressive disorder. Premenstrual dysphoric disorder has been moved from DSM-IV Appendix B to the main body of DSM-5. In DSM-IV, there was a bereavement exlusion criterion for MDE that is omitted in DSM-5. It was applied to depressive symptoms lasting less than two months following the death of a loved one. In DSM-5, the previous subtypes melancholic and atypical remained.

DSM-5 does not any longer include the multiaxial system. Regarding personality disorders, they are no longer called axis II disorders. The criteria for personality disorders in DSM-5 have not changed from those in DSM-IV. DSM-5 retains the DSM-IV categorical approach with the same 10 personality disorders. Personality disorders were divided into cluster A, B and C, cluster B including borderline personality disorder (BPD).

Thus, more than one classification exists with modified editions. Terminology has varied over time. For example, in previous literature, the term neurotic depression was used. Clinical depression is one common term, which is not always consistently defined. Furthermore, patients with MDD, dysthymic disorder, recurrent brief depression, MinD and SubMDD have been found to show little stability over time and to occur in combination (Angst et al., 2000; Forsell, 2007). In addition, depression research has used numerous diagnostic methods. Consequently, comparison of studies is a complex task. Nevertheless, approaches have emerged to diminish the heterogeneity of depression diagnosis and to more validly distinguish diagnostic thresholds (Klein, 2008; Wakefield and Schmitz, 2013; Snyder et al., 2013; Alexopoulos and Arean, 2014).

2.1.2 Diagnosis of major depressive disorder (MDD)

In DSM-IV, MDD consists of one or more major depressive episodes (MDEs) lasting at least two weeks (American Psychiatric Association, 2000). Diagnosis of MDD requires a total of five or more symptoms, including one of the two core symptoms, during most of the day or nearly every day. The two core symptoms are persistent depressive mood or significant loss of interest or pleasure. Moreover, by at least four associated symptoms are required: significant weight or appetite change, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy,

feelings of worthlessness or excessive or inappropriate guilt, a diminished or ability to think or to concentrate or indecisiveness, and recurrent thoughts of death or suicidal ideation, or a suicide attempt or a specific plan for committing suicide. In addition, these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning; they should not be caused by the direct physiological effects of a substance or a general medical condition; they should not be better accounted for by bereavement. DSM-IV divides MDE into three levels according to severity. MDD is classified as mild, moderate or severe (with or without psychotic features). The classification of severity is based on the number and severity of diagnostic criteria symptoms and the degree of functional disability and distress (American Psychiatric Association, 2000).

2.1.3 Diagnosis of dysthymic disorder

In DSM-IV, dysthymic disorder consists of depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, not been without the criteria for more than 2 months at a time, for at least 2 years. Depressed mood is required to be accompanied by at least two associated symptoms: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions and feelings of hopelessness. In addition, no MDE has been present during the first 2 years of the disturbance; i.e., the disturbance is not better accounted for by chronic MDD, or MDD in partial remission; there has never been a Manic Episode, a Mixed Episode or a Hypomanic Episode, and criteria have never been met for Cyclothymic Disorder, and the disturbance does not occur exclusively during the course of a chronic Psychotic Disorder. In addition, these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not due to the direct physiological effects of a substance or a general medical condition.

2.2 Prevalence of depressive disorders

Depressive symptoms are common, and there is much epidemiological research on depressive disorders. The prevalence of depressive disorders varies depending on diagnostic criteria, target populations, methods, time frames etc. The WHO World Mental Health Survey Initiative is an approach to shed light on this issue (Kessler et al., 2010). It comprises a series of community epidemiological surveys carried out in ten developed (N=51 771) and eight developing (N=37 265) countries. Record-based studies tend to underestimate mental disorders, especially as patients in primary

care tend to complain of somatic symptoms (Kirmayer et al., 1993; Goldberg et al., 1993; Kirmayer and Robbins, 1996; Koike et al., 2002; Katon, 2003; Keeley et al., 2004; Yamamoto et al., 2013). Primary care policy is based on patients' subjective complaints and, in addition, the time for each visit is limited compared to secondary and tertiary care.

Primary care patients and outpatients in specialty care with DSM-IV MDD had identical levels of moderately severe depression, identical distributions of depressive severity scores, and equal core depressive symptoms (Gaynes et al., 2007). Cross-sectional study design does not reveal if subsyndromal and minor depressions are in fact prodromal or residual phases of MDEs (Vuorilehto et al., 2005). Although excess mortality may be somewhat higher in major than in subthreshold depression, the difference is small and the overall impact on excess mortality is comparable (Cuijpers et al., 2013).

2.2.1 Prevalence of depressive disorders in the general population

The World Mental Health Survey Initiative presents results from 18 high and low to middle income countries (Bromet et al., 2011). The lifetime prevalence of DSM-IV MDE was 14.6% vs. 11.1%, and 12-month prevalence was 5.5% vs. 5.9% in the ten high vs. in the eight low to middle income countries. The 12-month prevalence of MDD is estimated 6.9%, and it has not increased in the community during the previous five years, varying between 4-9% (Kessler et al., 2003; Kessler et al., 2005; Hasin et al., 2005; Wittchen et al., 2011). The lifetime prevalence of MDD is found to be about 20% in the population studies (Kessler et al., 2003; Hasin et al., 2005; Kessler et al., 2005) .

In Finland, the Health 2011 Study reported a 12-month prevalence of DSM-IV depressive disorders (MDE or dysthymia) of 7% in females and of 4% in males (Suvisaari, 2012). The previous Health 2000 Study reported a 12-month prevalence of 4.9% and lifetime prevalence of 17.7% (Pirkola et al., 2005). In these studies, the prevalence of depressive disorders did not vary from the year 2000 to the year 2011. In these projects, depressive disorders were assessed with Composite International Diagnostic Interview (CIDI). The Finnish Health Care Survey (FINHCS) reported 12-month prevalence of MDE of 9.3% (Lindeman et al., 2000). The age-adjusted 6-month prevalence for MDE was found to be 4.1% for MDE and 1.7% for current dysthymia (Isometsä et al., 1997). These two studies assessed MDE with the short form of the University of Michigan version of the Composite International Diagnostic Interview. The Mini Finland Health Survey reported the 1-month prevalence of 4.6% of neurotic depression according to clinical assessment (Lehtinen et al., 1990). Incidence rate has also been estimated in Finland, based on the Finnish subsample of the European Outcomes of Depression International Network (ODIN) study and interviewed with Schedules for Clinical Assessment in Neuropsychiatry (SCAN-2)

to assign ICD-10 criteria. The estimated annual incidence rate was 2.1% for first-time episodes and 2.9% for all depressive disorders, including both first-time and recurrent episodes (Lehtinen et al., 2005).

The differences in the prevalence of diverse studies may be due to methodological choices such as diagnostic instruments and exclusion criteria. One reason of the differences in the prevalences of retrospective vs. cross-sectional/prospective studies may be the recall bias.

The median age of onset of MDD is in the range 20 to 25 (Andrade et al., 2003), over half have reported onset of MDD by age 25 (Sorenson et al., 1991). According to the recent WHO World Mental Health Survey Initiative of MDE, the average age of onset was 25.7 in high income and 24.0 in low to middle income countries (Bromet et al., 2011). Female gender and marital status (not being married or cohabiting) are consistent socio-demographic correlates (Andrade et al., 2003; Bromet et al., 2011).

2.2.2 Prevalence of depressive disorders in primary care and in psychiatric care

Depressive disorders are one of the most common illness among patients in primary care (Sartorius et al., 1993; Hämäläinen et al., 2004; Rost, 2009). The severity is usually mild to moderate (Simon, 2000; Thompson et al., 2001; Vuorilehto et al., 2005). However, there are also studies which have identified the majority of MDD cases in primary care for moderate or severe (Wittchen and Pittrow, 2002).

In primary care, prevalence estimates of depressive disorders range from 5% to 20% in adults (Sartorius et al., 1993; Thompson et al., 2001; Wittchen and Pittrow, 2002; Kessler et al., 2005). The WHO collaborative study Psychological Problems in General Health Care (PPGHC), an exceptionally large epidemiological study of depressive disorders in primary care, comprised 14 countries and 26 000 patients (Sartorius et al., 1993; Sartorius et al., 1996). The diagnostic assessment consisted of the Composite International Diagnostic Interview–Primary Health Care Version (CIDI-PHC). There, the prevalence of depressive disorders was estimated at 10%, but variations were found from 1.6% in Japan to 26.3% in Chile. In a large primary care organization from USA, prevalence of MDD was found to be 7.7% (Olfson et al., 1997). In Finland, in the cross-sectional Tampere Depression Project (TADEP), 10% of primary care patients vs. 50% of psychiatric outpatients suffered from clinical depression, and the 1-year prevalence rates were 20% vs. almost 60% (Salokangas et al., 1996). Prevalence rates of subthreshold depressive symptoms also vary considerably: on average nearly one-tenth of patients appear to suffer from subthreshold symptoms in primary care (Sartorius et al., 1996; Olfson et al., 1996; Pincus et al., 1999).

The prevalence of depressive disorders varies according to diagnostic classification. In the Depression 2000 study, among a large sample of unselected primary care attenders, 4.2% according to DSM-IV and 11.3% according to ICD-10 fulfilled criteria for MDE (Wittchen and Pittrow, 2002).

2.2.3 Psychiatric comorbidity of depressive disorders

Comorbidity is found to have impact on the course, outcome, suicidality and functional disability among depressed patients in the general population and in psychiatric care. General population studies have found 12-month prevalence of axis I comorbidity in DSM-IV MDD and in other DSM-IV depressive disorders up to 80% (Kessler et al., 2003; Hasin et al., 2005; Pirkola et al., 2005) and psychiatric care studies among outpatients with MDD up to 70% (Melartin et al., 2002; Rush et al., 2005), the most common concurrent comorbid conditions being anxiety disorders. The assessment of personality disorders during MDEs in cross-sectional studies has to be weighted with caution in order to distinguish personality traits from depressive symptoms. The few available general population studies have estimated prevalence of comorbid personality disorders in DSM-IV MDD, in DSM-IV depressive disorders, and in ICD-10 depressive disorders of about 20-40% (Casey et al., 2004; Pirkola et al., 2005; Hasin et al., 2005). Psychiatric care studies have reported estimates of comorbid personality disorders in DSM-III MDD and DSM-IV MDD of about 20-90%, on average about 50% (Zimmerman et al., 1991; Melartin et al., 2002). However, psychiatric comorbidity of depressive disorders in primary care and especially its long-term clinical significance there is not well known.

Psychiatric comorbidity among depressed patients in primary care is seldom studied with diagnostic instruments. The estimates are often based only on symptom rating scales or questionnaires (Simon, 2000; Thompson et al., 2001). Comorbidity has been estimated almost universally in a small sample of depressed patients (MDD and mixed anxiety and depressive disorder), reporting prevalence of concurrent anxiety 57%, concurrent alcohol abuse 14%, and concurrent somatoform disorder 4% (Lotfi et al., 2010).

Studies evaluating personality disorders among depressive patients from primary care are scarce. In addition to earlier reported lower rates (Patience et al., 1995), personality disorders have been found in up to two-thirds (Ekselius and von Knorring, 1998) and borderline personality disorder (BPD) in 20% of patients (Ekselius and von Knorring, 1998).

Half of DSM-IV MDD patients both in primary care and in outpatient specialty care had an anxiety disorder, 48.6% in primary care vs. 51.6% in specialty care (Gaynes et al., 2007). The baseline investigation of PC-VDS among DSM-IV depressive disorders found the current prevalence of anxiety disorder 43%, somatoform disorder 12%, substance use disorder 12%, axis I disorder 59%, personality disorder 52% including cluster B 28% (BPD 25%) and cluster C 32%, chronic somatic illness 47%, only 12% without any comorbidity, and lifetime prevalence of anxiety disorder 56%, substance use disorder 33%, and axis I disorder 70% (Vuorilehto et al., 2005).

2.2.4 Recognition of depressive disorders in primary care

The recognition of depressive disorders is essential for a proper diagnosis, which is the basis of optimal treatment. The Finnish Depression Current Care Guideline (Depressio, 2009 (updated 11.10.2013)) suggests targeted screening of risk groups in primary care, where most depressed patients are treated. The updated editions of the National Institute for Health and Clinical Excellence (NICE) Depression Guidelines in UK, the Treatment and Management of Depression in Adults guideline (NCCMH, 2010b) and the guideline on Depression in Adults with a Chronic Physical Health Problem (NCCMH, 2010a), recommend that health care professionals should be alert to possible depression particularly in people with a past history or somatic symptoms of depression or a chronic physical health problem with associated functional impairment.

In a prospective naturalistic cohort of primary care patients with physical symptoms, 8.4% had MDD and 10.4% MinD. Over 5 years, 56% of MDD and 20% of MinD patients were recognized. Recognition was associated with severity, persistence, comorbidity, and disability (Jackson et al., 2007).

There are many kinds of difficulties in the recognition of depressive disorders. In fact, general practitioners recognize about one-half of patients with MDD (Simon et al., 1999; Wittchen and Pittrow, 2002; Piek et al., 2012). Recognition is associated with patient-related factors such as prior treatment and more symptoms of depression, psychomotor retardation, comorbid anxiety disorder(s) and older age, and with physician-related factors such as practice experience of more than five years. It appears that the practitioners more often recognize severe and disabling depression and ignore mild cases. There is a curvilinear relationship between the severity of depression and practitioners' ratings of it (Thompson et al., 2001). General practitioners are estimated to recognize clinical depression in 25-40% of cases during one visit. Recognition improves with frequent visits and during visits of at least 15 minutes. In a major epidemiological study among unselected primary care attenders, Depression 2000, 75% of MDEs according to DSM-IV and 59% of depressive episodes according to ICD-10 were recognized (Wittchen et al., 2001). However, general practitioners also assigned diagnoses of depressive disorders in an additional 11.7% of patients, who did not meet either DSM-IV or ICD-10 criteria (Wittchen et al., 2001). Taken together, about half of the patients with depressive disorders were correctly diagnosed in primary care (Wittchen and Pittrow, 2002).

The recognition of depressive disorders may vary depending on different reasons, i.e., due to setting, era or treatment options. Overall, the primary care patients who most need the treatment are best detected (Karlsson et al., 2000). In a domestic survey from occupational health care, 6.2% of employees reported depressive symptoms and only a fourth of them were receiving appropriate treatment (Taimela et al., 2007).

Most patients with depressive disorders come to primary care with somatic complaints. Substantial medical comorbidity and physical complaints interfere and complicate recognition of depressive disorders (Lotfi et al., 2010). Depressed patients in primary care have significantly more medical comorbidity compared to patients who are not depressed (Kirmayer and Robbins, 1996; Katon, 2003). Comorbid chronic somatic illnesses are present up to 80% and two-thirds present exclusively with physical problems (Kirmayer et al., 1993; Goldberg et al., 1993; Koike et al., 2002; Keeley et al., 2004). Only a fifth of patients with current MDD on diagnostic interview presented psychosocial symptoms to their general practitioner, the others made only somatic presentations (Kirmayer and Robbins, 1996). Among patients with MDD assessed with Diagnostic Interview Schedule (DIS), somatization reduced recognition of MDD in primary care from 77%, for psychosocial presenters, to 22%, for true somatizers (Kirmayer et al., 1993).

The associations of recognition and treatment of depressive disorders can vary in many ways. In a 4-year follow-up in primary care, patients not initially in treatment for their psychiatric disorders were more likely to have enduring symptoms and use emergency psychiatric care compared to patients who were in treatment for their psychiatric disorders (Weissman et al., 2010). In a study examining the relationship between recognition and outcome among patients with depression in primary care, assessment of major depression based on CIDI, 42% of patients were appropriately recognized and diagnosed by their physician. Recognized patients were more severely ill and disabled compared to non-recognized patients. Recognized patients showed a significantly greater improvement at 3-month assessment but not at 12-months compared to non-recognized patients, suggesting that recognition of MDD in primary care does not automatically lead to better treatment or outcome. Overall, the recognition of depressive disorders is a complex task, and should be followed up by available mental health services (Simon et al., 1999).

2.3 Public health impact of depressive disorders

Depressive disorders cause great suffering for patients and their family and friends, as well as considerable health care costs. MDD is one of the leading illnesses causing suicidal behaviour (Beautrais, 2001). Worldwide, depressive disorders were the second leading cause of years lived with disability in 2010 (Ferrari et al., 2013). MDD was the fourth leading illness causing functional impairment, disability and days lost from work (Murray et al., 2012). Depression is the most prevalent disorder causing sickness absence from work (Druss et al., 2000). Primary care patients with depressive symptoms, with or without depressive disorder, have poorer mental, role-emotional and social functioning than patients with common medical conditions (Wells et al., 1989; Wells and Sherbourne, 1999). In Finland, a great number of

disability pensions granted for MDD is a major concern (Salminen et al., 1997). The annual cost of depression has been estimated to exceed 10 billion euros in England, with more than 100 million working days lost and over 2 500 deaths due to depression in 2000 (Thomas and Morris, 2003; McMahon et al., 2012). The total costs of depression are estimated to exceed 250 euros per capita per year in EU (Sobocki et al., 2006). Employees treated for depression incurred annual per capita health and disability costs of over 4000 euros, significantly more than the cost for hypertension and comparable to the cost for heart disease, diabetes and back problems (Druss et al., 2000). In Finland, the annual costs incurred due to sick leaves for depression are estimated at 6 760 euros, considerably more than costs of treatment (Kaila et al., 2012). With regard to primary care, the total cost per patient with depression was estimated at 5 500 euros over six months, direct costs causing a third (35%) and antidepressants 4% (Sobocki et al., 2007). Furthermore, depression effects on morbidity and mortality in diabetes, heart disease, stroke, and cancer (Sullivan et al., 2012; Voinov et al., 2013). Overall, there is a particular need for therapies with potential to improve functional ability in depressed patients.

2.4 Aetiology and pathogenesis of depressive disorders

Depressive disorders are a clinically complex group with multiple symptoms and behavioural changes, diagnosed on descriptive basis and considered to be multifactorial (Sullivan et al., 2012, Smoller, 2013). Many factors have been associated with the aetiology and pathogenesis of MDD. Genetic factors, temperament, early traumatic experiences and current life stress act as predisposing factors (Kendler and Myers, 2010; Kendler et al., 2011; Kendler et al., 2013). Furthermore, circadian rhythms, inflammatory and metabolic dysregulation, hyphothalamic-pituitary-adrenal axis dysfunction, hormonal factors and neuronal network plasticity are of importance (Castren, 2013; McClung, 2013; Valkanova et al., 2013; Stetler and Miller, 2011; Lamers et al., 2013). Risk factors from multiple domains are interrelated and interact with each other (Kendler and Gardner, 2010; Kendler et al., 2011).

Twin, adoption and family studies have revealed moderate hereditability estimated as 37%, showing evidence for multiple genetic factors for MDD (Sullivan et al., 2000; Kendler et al., 2013). MDD seems not to reflect a single dimension of genetic liability. Rather, these criteria reflect three underlying dimensions that index genetic risk for cognitive/psychomotor, mood and neurovegetative symptoms (Kendler et al., 2013). A current mega-analysis has revealed no findings of genome-wide significance in MDD (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium et al., 2013).

Although genetic studies have yielded variants that confer markedly increased risk for psychiatric disorders, these tend to be non-specific and increase risk for multiple conditions (Sullivan et al., 2012). Specific genome-wide singlenucleotide polymorphism is associated with a range of psychiatric disorders of childhood or adult onset, i.e., autism spectrum disorder, attention deficit hyperactivity disorder, bipolar disorder, MDD and schizophrenia, suggesting that genetic contributions to psychiatric disorders do not in all cases map to present diagnostic categories (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013).

The genes modulate neural activity, behaviour and ultimately clinical symptoms. Genes related to serotonin impact emotion-related neural activity. The role of gene x environment and brain x environment interactions seems to be central as genetic and neural predispositions of MDD (Northoff, 2013). At the moment, results that risk for MDD may be influenced by a gene–environment interaction with genetic variation near the serotonin transporter remains controversial (Caspi et al., 2010; Fergusson et al., 2011; Karg et al., 2011; Sullivan et al., 2012). In addition, genetic differences likely modulate the ability to use environmental support (Jokela et al., 2007), the influence of stressful life events (Elovainio et al., 2007, Chen et al., 2012) and drug response (Porcelli et al., 2012). The identification of genomic biomarkers may help to identify traumatized individuals susceptible to depression and those getting a preventive effect from the immediate treatment plus developing of novel pharmacological approaches (Saveanu and Nemeroff, 2012).

Personality and life events are essential. Of personality dimensions, neuroticism is most strongly found to associate with depressive symptoms (Jylhä and Isometsä, 2006; Kendler and Myers, 2010). Epidemiological, clinical and twin studies have found strong associations between early life stress and MDD (Edwards et al., 2003; Kendler and Gardner, 2010). Among patients with depressive disorders, childhood maltreatment is found to increase clinical and neurobiological pathology such as reduced hippocampal volume and amygdala hyperreactivity (Teicher and Samson, 2013). Childhood physical and emotional neglect, physical and sexual abuse, and losing a parent are proposed to be of special importance (Korkeila et al., 2005; Kendler et al., 2011). In the general population, adverse life events during childhood together with those in adulthood were found to associate with depressiveness in an additive manner, suggesting a pathway from childhood adversities to depressiveness through adult risk factors (Korkeila et al., 2005). In another domestic study from psychiatric care, the majority of MDD patients attributed the onset of MDE to some adverse event, although no clustering of them was seen to associate with the time of onset (Leskelä et al., 2004). Different kinds of recent adverse situations may evoke different patterns of depressive symptoms: guilt, rumination, fatigue and pessimism were found to be prominent following failed efforts, and crying, sadness and desire for social support prominent following social losses (Keller and Nesse, 2006). Fatigue, appetite gain and thoughts of self-harm were found to be prominent in those with depressive symptoms who did not report any adverse life events (Keller et al., 2007). Some genes seem to operate in multiple environments to induce risk

for depression after early life stress and to enhance the beneficial effects of a positive early environment. Sensitive periods may function as links for adverse effects of early life stress on depression (Heim and Binder, 2012). In addition, lack of social support is found to associate with the risk of recurrent MDE (Kendler and Gardner, 2010). On the contrary, major depression may effect on the social support (Coryell et al., 1993; Leskelä et al., 2008). Early and recent life events, social support and depression comprise a complex phenomenon, where different aspects are apparently in turn influencing each other and being influenced by additional factors, even across generations (Keller et al., 2007; Leskelä et al., 2008; Kendler and Gardner, 2010; Korkeila and Törmä, 2010; Heim and Binder, 2012; Danese and McEwen, 2012).

MDD has been associated with several structural and functional alterations in various brain regions, varying during MDEs and remission, and distinct from those seen in bipolar disorder (Kempton et al., 2011; Hamilton et al., 2012). Current meta-analytic results support a model of the salience of negative information in MDD (Hamilton et al., 2012). In addition, disconnection, inflammatory and hypoperfusion hypotheses are proposed, concepts which link underlying vascular processes with adverse effects on brain function that influence the development of depression (Taylor et al., 2013). Biochemically, serotonin and other substances like GABA, glutamate, adrenaline/noradrenaline and dopamine play an essential role in the pathogenesis of MDD (Northoff, 2013). For the time being, genetic polymorphisms are assumed to modulate brain structure and function. These changes are supposed to serve as intermediate phenotypes in determining the risk for depression. Environmental incidents can further exacerbate the neurobiological alterations in at-risk individuals and amplify the risk. In equal ways, enriched and supportive environments may improve the risk in genetically vulnerable individuals (Weir et al., 2012).

During the last years, there has emerged an approach to integrate psychological and biological theories of depression and the underlying neural mechanisms. One of the most promising seems to be the approach to integrate the cognitive model of depression (Beck, 1979) and the underlying neural mechanisms (Clark and Beck, 2010; Disner et al., 2011). Although the mechanisms underlying each element of the model differ, in general the negative cognitive biases in depression are facilitated by increased influence from subcortical emotion processing regions combined with attenuated top-down cognitive control (Disner et al., 2011).

There are clear advances in the genetic, biological, developmental and environmental risk factors, molecular mechanisms and their complex interactions (Kupfer et al., 2012). A specification of probably partly similar and partly distinctive neural mechanisms of cognitive therapy and antidepressants might in future be used to guide treatment selection (DeRubeis et al., 2008). At the moment, no clinical biomarkers, precise subgroups, nor fully satisfactory treatments are available. In addition, it has to be remembered that aetiological risk factors for depressive disorders are not necessarily similar to factors affecting the course and outcome of these disorders.

2.5 Course and outcome of depressive disorders

2.5.1 Course and outcome of depressive disorders in the general population

In long-term population studies (5 years or more), up to 90% of subjects with depressive disorders recovered at least once, but 35-55% experienced at least one recurrence, and chronic course emerged in 15% (Mattisson et al., 2007; Eaton et al., 2008; Rhebergen et al., 2009; Colman et al., 2011; Dowrick et al., 2011) (Table 1). Almost a half of subjects experienced a stable recovery (Steinert et al., 2013). Assessments of time spent in MDEs or recovered are missing.

Population studies with shorter follow-up have reported approximately the same estimates of chronic course, but lower rates of recurrence have emerged (Skodol et al., 2011). Based on a prospective cohort followed up 3 years after 6 months in remission, the cumulative recurrence rate of MDD was estimated 13.2% at 5 years and 42.0% at 20 years (Hardeveld et al., 2013). A 3-year survey estimating MDD, dysthymic disorder, MinD and SubMDD found severe prognosis in one-half of subjects in all diagnostic categories; depression seemed a dimensional illness where subjects move in and out of diagnostic subtypes (Forsell, 2007).

In the general population, diverse predictors are found in different studies, depending on study premises and hypothesis. Factors related to depression itself are among the most common. Longer time to remission and non-recovery are predicted by higher severity of depression and longer duration of previous episodes, shorter time to recurrence was predicted by younger age of onset, more previous MDEs, and a severe last MDE (Spijker et al., 2004; Eaton et al., 2008; Colman et al., 2011; Hardeveld et al., 2013).

Comorbidity is found to play an important role as a determinant of depressive disorders. Poor outcome is associated with anxiety disorders, alcohol disorders (Hasin et al., 1996; Mattisson et al., 2009), personality disorders (Johnson et al., 2005; Skodol et al., 2011) and chronic physical illness (Spijker et al., 2004).

Knowledge of other than illness-related predictors is scarce. Adverse life events are found to relate to different symptom profiles (Keller et al., 2007). Younger age, negative youth experiences and ongoing difficulties have predicted shorter time to recurrence (Hardeveld et al., 2013) as has neuroticism and poor functioning (Rhebergen et al., 2009) and lack of social support (Spijker et al., 2004; Dowrick et al., 2011).

Based on the Finnish subsample of the European Outcomes of Depression International Network study (ODIN), significant predictors for experiencing a depressive episode were suffering from self-perceived long-term illness or handicap, experiencing little or no concern from friends, low sense of coherence, low self-confidence, uncertainty about one's future, and reporting two or more threatening life events during the preceding 6 months (Lehtinen et al., 2005).

Table 1. Long-term studies (i.e. 5 years or more) of depressive disorders in general population.

Study	Follow-up Sample size	Age	Female	Baseline: Diagnosis Instrument	Follow-up: Duration Number of assessments	Outcome	Chronic	Recovery: Stable At least once	Recurrence
	N	Years	%		Years	Instrument	%	%	%
Eaton et al. 2008 USA	92	≥18	76	MDD DSM-IV DIS	max 23 2	LCI	15%	50% 85%	35%
Mattison et al. 2007 Sweden	344	15-89	66	Depressive symptoms and GAF<60 Semi-structured interview by psychiatrists	max 49 median 20 3	Semi-structured interview by psychiatrists, registers, informants	-	60% -	40%
Dowrick et al. 2011 ODIN	182	18-64	68	Depressive disorders ICD-10 /DSM-IV SCAN II	9 1	BDI	-	cross-sectional at 9 years: 41%	-
Rhebergen et al. 2009 Netherlands	141	18-64	66	Depressive disorders DSM-III-R/DSM-IV CIDI	max 7 3	LCI	-	55% 89%	-
Colman et al. 2011 Canada	585	≥16	65	MDD DSM-IV CIDI	6 3	CIDI-SF	-	45% -	55%
Angst et al. 2009 Switzerland	55	young adults	47	MDD, Dysthymia, MinD, Recurrent Brief Depression DSM-III-R SPIKE (included comorbidity)	20 6	Interview at home with SPIKE	6% (23% when including also milder depressions)		21% (plus 16% milder episodes)

CID=Clinical Interview for Depression, CIDI=Composite International Diagnostic Interview, CIDI-SF=Composite International Diagnostic Interview-Short Form, DIS=Diagnostic Interview Schedule, GAF= Global Assessment of Functioning, LCI=Life Chart Interview, LIFE=Longitudinal Interval Follow-up Evaluation, SPIKE= Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology

Whether the risk factors found in population studies are important predictors, in primary care, where most patients with depressive disorders are encountered, it has also remained largely unknown for lack of naturalistic prospective studies in primary care.

2.5.2 Course and outcome of depressive disorders in primary care

The knowledge on course and outcome of depressive disorders in primary care is essential for organizing care and management. Previous studies have focused mainly on the cross-sectional findings, thus ignoring recurrences, chronicity and duration of illness states. None of the previous studies have used life-chart methodology to prospectively determine precise timing of MDEs and partial and full remission. The existing studies vary in methods and in definitions for diagnostic criteria and have seldom used structured or semi-structured interviews. Assessment of depression has often been based on self-reported scales or rating scales. In addition, the dropout rates have often been high. The most long-term follow-up time has been as long as 23 years, but the dropout rate was as high as 78% (Yiend et al., 2009). Research of risk factors is mainly based on registry-based, retrospective or short-term prospective studies. Diagnostic assessments of initial comorbid axis I and II disorders or somatic illnesses are not available. Some studies have evaluated concurrent psychopathology, mainly anxiety symptoms.

There are only two previous prospective long-term (5 years or more) studies of depressive disorders in primary care (Poutanen et al., 2007; Yiend et al., 2009; Steinert et al., 2013) (Table 2). One of them did assess time spent in MDEs and estimated it at 15% of 23 years (Yiend et al., 2009).

A few additional long-term studies from primary care are either retrospective, based on mental disorders in general or without proper diagnoses of depressive disorders (Widmer and Cadoret, 1978; van Weel-Baumgarten et al., 2000; Jackson et al., 2007; Wells et al., 2008). A couple of studies exist with follow-up time from 2 to 3 1/2 years (Ormel et al., 1993; Oldehinkel et al., 2000; Simon, 2000). A prospective 5-year study on natural history of mental disorders among patients with physical symptoms found that subthreshold disorders had a better prognosis, although 12% of MinD progressed to MDD (Jackson et al., 2007).

Studies among primary care patients with MDD have reported full recover between 25% and 50% and recurrence between 35% and 77%. Chronic course has been reported in up to one-third of patients with MDD and with experienced depression (van Weel-Baumgarten et al., 2000; Oldehinkel et al., 2000; Wilson et al., 2003; Yiend et al., 2009; Stegenga et al., 2012). Persistence of subthreshreshold symptoms is estimated to comprise one of the major risk factors associated with relapse (Lin et al., 1998). Of patients with severe depression, 42.4% had depression during a 7-year follow-up and 21.2% had

Table 2. Long-term (≥ 5 years) prospective studies in primary care.

Study	No. of patients at BL Drop-out	Age Female	Screening	DG Method	Follow-up time	Severity of MDD at BL	Duration of MDD	Recurrence of MDD	Comorbidity	Outcome measure
	N %	Years %	Method		Years	Instrument	At BL At F-up	At BL At F-up	At BL At F-up	Instrument
Poutanen et al. 2007 Finland	430 42	18-64 70	DEPS	Depressive disorders ICD-8 PSE	7	HAMD	not assessed not assessed	not assessed not assessed	not assessed Questionnaire	CIDI-SF, PSE, DEPS Interview
Yiend et al. 2009 UK	165 78	18-64 81	GPs: to need treatment, GHQ	MDD GPs, PSE	23	HAMD	assessed assessed	assessed assessed	Axis III Axis I	SCID-I, RDC, LIFE, CID, PSR, HAMD, OPCS Interview, Records

BL=Baseline, CID=Clinical Interview for Depression, CIDI-SF=Composite International Diagnostic Interview-Short Form, DEPS=Depression Scale, F-up=follow-up, GPs=assessment by general practitioners, LIFE=Longitudinal Interval Follow-up Evaluation, OPCS=Social Life Questions, PSE=present state examination, PSR=Psychiatric Status Rating, RDC=Research Diagnostic Criteria

depression at final assessment; outcome results were nearly the same for mild depression (Poutanen et al., 2007). Of prevalent patients of untreated MDD, a fourth has been estimated to remit within 3 months, a third within 6 months, and half within 12 months (Whiteford et al., 2013).

The medium-term 18-month follow-up study of PC-VDS reported 38% of patients with MDD achieved full remission, 25% remained in MDE, and 30% had a recurrence. Longer time to remission was predicted by older age and more severe depression, and shorter time to relapse or recurrence by more severe depression and cluster C personality disorders (Vuorilehto et al., 2009). In a domestic study of primary care patients with clinical depression, 61.5% achieved remission in 6 months (Luutonen et al., 2011). This better outcome may be due to differences in screening process, definition of remission and the relatively short duration of follow-up. In a study of MDD assessed with CIDI and comprising six countries, predictors of complete remission in nine months were higher education and quality of life and fewer negative life events, (De Almeida Fleck et al., 2005). Overall, depressive disorders in primary care tend to be recurrent, residual symptoms are common, and psychopathology is found even after a long time after MDEs.

2.5.3 Course and outcome of depressive disorders in psychiatric care

The available long-term psychiatric care studies are mainly difficult to generalize into primary care. Among the most remarkable reasons are that most of them have studied solely or mainly inpatients and that they are often relative old, i.e., from an era with rather different biological and psychological treatment options (Angst et al., 1978; Keller et al., 1982; Kiloh et al., 1988; Lee and Murray, 1988; Maj et al., 1992; Sartorius et al., 1993; Surtees and Barkley, 1994; Paykel et al., 1995; Ilardi et al., 1997).

Psychiatric care studies have reported high rates of recurrence and residual symptoms (Kiloh et al., 1988; Lee and Murray, 1988; Keller et al., 1992; Surtees and Barkley, 1994; Angst and Preisig, 1995; Kennedy et al., 2003; Melartin et al., 2004; Holma et al., 2008; Furukawa et al., 2008). Of patients with severe depression, 61.0% had depression during a 7-year follow-up and 26.2% had depression at final assessment; outcome results were nearly the same for mild depression (Poutanen et al., 2007). In a 5-year study, 88% of patients with MDD achieved full remission and 71% experienced recurrences; during five years, they spent 49% in full remission, 31% in partial remission and 20% in MDEs (Holma et al., 2008). Longer time to remission and non-recovery are predicted by higher initial severity of depression (Keller et al., 1992; Melartin et al., 2004; Holma et al., 2008).

Comorbid disorders increase the risk of relapse or recurrence of MDD (Melartin et al., 2004; Holma et al., 2008), chronicity (Keller et al., 1992; Mueller et al., 1999) and residual symptoms (Paykel et al., 1995). Important comorbid disorders appear to be anxiety and cluster C personality disorders (Farabaugh et al., 2005; Viinamäki

et al., 2006; Holma et al., 2008; Coryell et al., 2012). A study among academic care in- and outpatients with a mean follow-up time of 16.7 years found association of anxiety to time spent in MDEs to be stable over time (Coryell et al., 2012). BPD and substance use disorder increased the risk of relapse or recurrence of major depression in a 6-year follow-up (Alnaes and Torgersen, 1997). Comorbid personality disorder was found to associate with a two-fold risk of a poor outcome of depressive disorders in a meta-analysis of 34 studies (Newton-Howes et al., 2006).

Residual symptoms are estimated to comprise an important risk of relapse of MDD, particularly in the first year (Paykel, 2008). Among MDD patients in both primary care and outpatients in psychiatric care, the risk factors for chronic and recurrent depressive illness were frequently present, highlighting a clear risk for treatment resistance and need for aggressive management strategies in both settings (Gaynes et al., 2007). Overall, it remained uncertain whether outcome results from psychiatric care are applicable to primary care.

2.6 Suicidal behaviour in depressive disorders

Throughout the world, suicide is among the three most common causes of death in people aged 10-44 years (Morriss et al., 2013). In Finland suicide mortality was at its peak in the year 1990, when 1520 people committed suicide (Official Statistics of Finland). Since then, the suicide rate has declined and was 912 in the year 2011 and 873 in the year 2012. Still, the number of suicides is 1.4-fold greater than the average in the EU (Official Statistics of Finland). One in two completed suicides is preceded by at least one attempt (Isometsä and Lönnqvist, 1998), and every fifth attempt will eventually lead to death (Suominen et al., 2004). Approximately 43% of primary care patients with MDD have reported some degree of suicidal ideation within the previous week (Gaynes et al., 2007).

Nine of ten of persons committing suicide had mental disorder. Most common single disorders were affective disorders and substance use disorders (mostly depressive disorders and alcohol problems); comorbidity was common. Severe mood disorder was present in half of completed suicides, and, when including mild cases, the proportion was two-thirds (Cavanagh et al., 2003; Arsenault-Lapierre et al., 2004). The absolute risk of suicide, up to 36 years after the first psychiatric contac, was estimated at 6.7% for men and 3.8% for women suffering from unipolar affective disorder (Nordentoft et al., 2011). The lifetime prevalence of suicide has been estimated at 8.6% in those ever hospitalized for suicidality, 4.0% in those ever hospitalized for affective disorders without specification of suicidality, 2.2% in all psychiatric patients and less than 0.5% in non-affective psychiatric patients (Bostwick and Pankratz, 2000).

Completed suicides and serious suicide attempts have common risk factors such as current mood disorder, previous suicide attempts, prior psychiatric treatment, low income or education level and recent stressful life events. Those committing suicides were more likely men, older, and had current non-affective psychosis compared to suicide attempters; attempters had more likely a current anxiety disorder and were socially isolated compared to those committing suicide. Those who commit or attempt suicide appear to overlap and share common psychiatric and socio-economic features (Beautrais, 2001).

Among MDD patients in psychiatric care settings, medium- and long-term studies have documented risk factors related to depression itself as the severity of symptoms (Oquendo et al., 2004; Sokero et al., 2005, Holma et al., 2010) and the length of the time spent in depression (Melartin et al., 2004; Sokero et al., 2005; Holma et al., 2010). In a 5-year follow-up study, the incidence of suicide attempts was 21-fold during MDEs compared with full remission (Holma et al., 2010). Other than depression-related risk factors are psychiatric comorbidity including personality disorders and alcohol abuse, and sosio-demographic characteristics such as younger age, living alone and low perceived social support (Duggan et al., 1991; Malone et al., 1995; Sokero et al., 2003; Oquendo et al., 2004; Mann et al., 2005; Holma et al., 2010).

In old age, comorbid physical illnesses are found to play a more important role, especially in men (Szanto et al., 2002; Koponen et al., 2007). Among the elderly, poor detection of depression may often lead to unnoticed suicidal intentions by health care services (Pitkälä et al., 2000; Timonen et al., 2002). Also, younger adult patients rarely communicate their intentions (Isometsä et al., 1995).

According to a review on prospective studies of suicidal behaviour in MDD, previous suicide attempts, refractory and recurrent depression and comorbid alcohol use increase the risk of suicidal behaviour (Oquendo et al., 2006). Prospective data was estimated to be limited. No single risk factor was sufficient to predict future suicidal behaviour, and risk factors may be different in short- and long-term.

The role of life events in the timing of suicide attempts was carefully assessed in a two-year follow-up of depressed patients, where MDE was present in 33% and life events in 73% of person-months (Oquendo et al., 2013). MDE increased the risk of suicidal behaviour, but not life events even during MDEs. Taken into account the possibility of comorbid BPD, the role of life events was more complex.

For suicide prevention, improved detection and management of depressive disorders in primary health care are central (Mann et al., 2005; NICE, 2010). Treatment such as antidepressant use is found to result in fewer suicides (Angst et al., 2005). Still, most depressed patients at the time of suicide attempt are untreated or on inadequate antidepressant treatment (Oquendo et al., 2002). In primary care, programs to improve screening for suicidality need to occur within a well integrated treatment system in order to lower suicide rates (Bostwick and Rackley, 2012).

In primary care with intervention treatment guidelines with care management tailored for tdepressed elderly patients, suicidal ideation declined faster in intervention patients compared with usual care patients in a 12-month follow-up (Bruce et al., 2004). In an educational depression management program for general practitioners and their nurses, the suicide rate was decreased after 5 years (Szanto et al., 2007). In multimodal intervention, expanded to population level, a reduction of male suicides was observed after 5 years (Hübner-Liebermann et al., 2010). Overall, MDE is a strong predictor for suicidality and also a treatable risk factor, causing hope for future (Oquendo et al., 2013). Still, more has to be known about factors associated with suicidality and their interactions in order to improve treatment and prevention.

2.7 Disability in depressive disorders

Assessment of disability is important not only because of human suffering but also economically. Of disability pensions due to mental disorders, the most remarkable group is depressive disorders. According to Finnish Centre for Pensions, 36 358 Finns were on a disability pension on 31.12.2012, and 3 549 Finns (15.7% of all disability pensions) were granted a new disability pension due to depressive disorders in 2012. In the previous decade, the amount of disability pensions due to depressive disorders increased, but from 2011 to 2012 the amount decreased 5%. According to the Social Insurance Institution in Finland, due to depressive disorders, 20 000 new sickness allowance spells were begun in the year 2012. The average age of onset of disability pension due to depression was 49 years, three years earlier than due to any other illness. The annual costs of disability pensions due to depression were 500 million euros, and that of sickness allowances 110 million euros.

2.7.1 Functional disability in depressive disorders

In the general population, reductions in functioning for depressed patients equal or exceed those of patients with chronic general medical illness (Hays et al., 1995, Thomas and Morris, 2003). The relationship between psychosocial functioning and the severity of depression appeared curvilinear in a 10-year follow-up of tertiary care MDD patients (Judd et al., 2000). In psychiatric settings, functional disability in MDD was associated with severity and recurrence of depression, older age and current axis I and II comorbidity (Rytsälä et al., 2005). In an 18-months follow-up of MDD patients, determinants of functional and social disability were severity of depression, recurrence before baseline and during follow-up, lack of full remission and time spent depressed (Rytsälä et al., 2006). Primary care patients with depression were characterized by high levels of functional impairment and worse

social functioning than patients with common chronic medical conditions (Wells and Sherbourne, 1999; McMahon et al., 2012). In patients essentially disability free at baseline, after 12 months, depressive illness resulted in a 1.8-fold increase in risk of onset of physical disability, after controlling for physical disease severity, and in a 23-fold increase in risk of onset of social disability, after controlling for physical disease severity, physical disability and onset of physical disability (Ormel et al., 1999). An earlier cross-sectional and retrospective study of MDD patients compared primary care patients, psychiatric outpatients, and psychiatric inpatients with the other two groups, and found that inpatients had a lower level of functioning in the Social and Occupational Functioning Assessment Scale for DSM-IV (SOFAS) (54.9 v. 53.9 v. 41.7, $p<0.001$) (Vuorilehto et al., 2007).

2.7.2 Work disability and unemployment in depressive disorders

In general population studies, unemployment is associated with higher risk of depressive disorders than employment. Approximately half of the MDD patients were in the labour force, and compared with non-working depressed persons they were more often younger, male, better educated, had a higher income and lived alone or with a non-relative in an urban or suburban location (Elinson et al., 2004). In the domestic population-based Health 2000 Study, the risk of depressive disorders was generally higher among the unemployed and the economically inactive than among the employed (Honkonen et al., 2007). In the general population, psychiatric comorbidity, medical illness, workload, age over 45 years, low education and sick leave over 2 weeks predicted disability pension among patients with depressive disorders (Ahola et al., 2011). Of patients with depressive disorders, 29% had at least one period of sickness absence from work, predicted by age, employer, continuity of employment, somatic comorbidity and subjective vision to one's own ability to work (Ahola et al., 2009). MDD five-folded the risk for disability in one year and even MinD had a 1.5-fold risk (Broadhead et al., 1990). Higher depression severity was associated with more disability but not recurrent MDD compared to single episode MDD (Kruijshaar et al., 2003). A high depression score predicted disability attributable to any cause, and depressed people retired on average 1.5 years younger than those without depression (Karpansalo et al., 2005).

Of psychiatric outpatients with 2-12 months sick leave due to depression, only 29% were working full-time after 5 years (Raitasalo et al., 2010). In psychiatric settings, work disability in MDD was associated with severity and recurrence of depression, older age and current axis I and II comorbidity (Rytsälä et al., 2005). In psychiatric settings, most subjects granted a disability pension for MDD have comorbid mental or physical disorders contributing to their disability (Isometsä et al., 2000). In a retrospective 30-month study with MDD patients among psychiatric outpatients, sick leaves were granted to 61% and sick leave certificates were associated

with living with someone else, being employed and early recognition of illness; factors associated with being granted a pension were greater age, comorbidity, and lower self-esteem (Sorvaniemi et al., 2003). Approximately half of the employed MDD patients were on sick leave, which strongly associated with severity and duration of depression (Rytsälä et al., 2005). Disability pension was granted to 21.6% of MDD patients during a 30-month follow-up, strongly associated with older age, more hopelessness, worse social and occupational functioning, longer time spent in MDEs, comorbidity and lowered self-esteem (Sorvaniemi et al., 2003). In an 18-month follow-up, disability pension was granted to 11.3% of MDD patients, and being on sick leave at baseline remained a significant predictor (Rytsälä et al., 2007). In a long-term follow-up study with life-chart and diagnostic interviews among MDD patients in psychiatric care, risk factors for disability pension due to MDD were age more than 50, time spent depressed during follow-up, number of comorbid somatic disorders and lack of vocational education (Holma et al., 2012). In a study by questionnaire of MDD patients with a 2- to 12-month history of receiving sickness benefits, only 29% were employed after five years. Employment was associated with less severe depression, younger age, and higher socio-economic status and cognitive capacity (Raitasalo et al., 2010).

Employees with MDD missed more work compared to non-depressed (Birnbaum et al., 2010). Work participation was associated most strongly with MDE duration and also with depression severity, comorbidity, older age and previous sick leave (Bültmann et al., 2008; Lagerveld et al., 2010). In a 6-month follow-up, employees with dysthymia had 14% new unemployment, with MDD 12%, and with both disorders 15%, compared with 2% in controls and 3% in rheumatoid arthritis (Lerner et al., 2004). In employees, depressive disorders were associated with a mean of 9.86 annual sick days, significantly more than in heart disease, diabetes, hypertension and back problems (Druss et al., 2000), and between 1.5 and 3.2 more short-term work disability days in a thirty-day period than other workers (Kessler et al., 1999).

Among primary care patients with major depression beginning antidepressant treatment, those who recovered were more often employed than the non-recovered (Simon et al., 2000). In a cross-sectional and retrospective study of MDD patients, the primary care patients, the psychiatric outpatients and the psychiatric inpatients were equally unemployed (18% v. 22% v. 17%, NS) and on disability pension for mental health reasons (5% v. 3% v. 9%, NS) (Vuorilehto et al., 2007).

2.8 Borderline personality disorder comorbidity in depressive disorders in primary care

Borderline personality disorder (BPD) is a severe and chronic psychiatric disorder often present in primary care (Gross et al., 2002). It is characterized by comorbidity, suicidal behaviour and functional impairment (Zanarini et al., 1998, Zanarini et al., 1998, Zimmerman and Mattia, 1999, Skodol et al., 2002, Yen et al., 2004, Ansell et al., 2007, Leichsenring et al., 2011). Concurrent BPD complicates treatment and outcome of patients with depressive disorders. In primary care it is mostly unrecognized and untreated (Gross et al., 2002).

Lifetime prevalence of BPD is reported at 6.4% and BPD-like symptoms up to 26% among primary care patients (Hueston et al., 1999, Gross et al., 2002, Sansone et al., 2011). In primary care, lifetime prevalence of BPD is about 4-fold higher than in the general population, resembling the prevalence reported from psychiatric outpatient settings (Gross et al., 2002). High prevalence rates have provoked discussion about possible overdiagnosis (Gross et al., 2002). On the other hand general practitioners probably do not systematically diagnose BPD whereas structured interviews find missed BPD patients (Zimmerman and Mattia, 1999; Paris, 2007).

There are only a few studies on BPD comorbidity among depressed patients from primary care. The prevalence rate of concurrent BPD is estimated 20-25% (Ekselius and von Knorring, 1998). In Finland, the PC-VDS found more concurrent BPD in primary care patients with MDD than in psychiatric outpatients with MDD (Vuorilehto et al., 2005).

Of psychiatric care patients with MDD, 9.3-12% suffered from BPD (Melartin et al., 2002; Perugi et al., 2013). Personality disorder (mostly BPD, histrionic and avoidant) was found in 60% of dysthymic and in 18% of MDD patients, indicating that early-onset dysthymia is associated with significantly greater personality disorder comorbidity than episodic MDD (Pepper et al., 1995). Of BPD patients, up to 75% meet criteria for lifetime mood disorder (Zimmerman and Mattia, 1999). Dimensional representations of BPD were independently and significantly associated with increased risk for MDD (Reichborn-Kjennerud et al., 2010). BPD has also been associated with earlier age of onset of depression in primary care (Sullivan et al., 1994; Hueston et al., 1999; Ramklint and Ekselius, 2003; Joyce et al., 2003; Perugi et al., 2013). Although early age of onset of depression associates with BPD, BPD is not a universal feature of early-onset MDD (Rothschild and Zimmerman, 2002). BPD is found to associate with depressive symptoms (Hueston et al., 1999), more chronic depressions (Joyce et al., 2003) and more prior mood episodes (Perugi et al., 2013). Among in- and outpatients with MDE, 14.5% met criteria for BPD. They were significantly younger in age, for age at onset of first psychiatric symptoms and for age at first diagnosis of depression. They also reported significantly more comorbid alcohol and substance abuse, anxiety disorders, eating disorders, and ADHD, history of suicide attempts and resistance to antidepressant treatments (Perugi et

al., 2013; Perugi et al., 2013). Depressed patients with BPD or BPD alone showed more psychiatric (Skodol et al., 2002; Perugi et al., 2013) plus alcohol and cannabis comorbidity than depressed patients without BPD (Joyce et al., 2003).

The rate of MDD remissions was found to be reduced and time to remission longer by co-occurring BPD in psychiatric and general population settings (Joyce et al., 2003; Gunderson et al., 2004; Grilo et al., 2010; Skodol et al., 2011). BPD predicted a greater risk for recurrence of MDD than other personality disorders in a 6-year follow-up (Gunderson et al., 2008). Significant reduction in the frequency of BPD was seen among MDD patients in primary care following antidepressant treatment (Ekselius and von Knorring, 1998).

The suicide rate in BPD is about 8-10% (Gunderson et al., 2011). Patients with depression and BPD were more likely to have attempted suicide than patients with MDD only (Kelly et al., 2000; Joyce et al., 2003; Yen et al., 2004; Perugi et al., 2013). A high prevalence of current suicidal ideation (21.4%) was detected in primary care patients with BPD (Gross et al., 2002).

BPD accounts for more functional impairment than MDD alone (Hueston et al., 1999, Skodol et al., 2002, Skodol et al., 2011), and more severe and persistent impairment in social functioning (Gunderson et al., 2011). Even after remission of BPD, most patients have severe functional impairment, with only about 25% employed full time, and about 40% receiving disability payments after 10 years (Gunderson et al., 2011). In primary care, BPD is associated with high degrees of functional impairment and risk for depression and alcohol use (Hueston et al., 1996; Gross et al., 2002). Forty percent of BPD patients on Social Security Disability Insurance were able to get off disability, but 43% of them went back on such payment within ten years, and 39% of BPD patients who were not on disability payment at baseline started to receive federal benefits for the first time (Zanarini et al., 2009). Personality disorders increase the risk of early retirement at least to an equal extent as depression (Korkeila et al., 2011).

Only about half of BPD patients were recognized by their primary care physicians or had received mental health treatment during the past year (Gross et al., 2002). Patients with BPD symptomatology appear to see a greater number of primary care physicians than patients without these symptoms (Sansone and Sansone, 2004). MDD patients with comorbid BPD utilize services at higher rates than MDD patients without BPD (Hueston et al., 1999).

2.9 Treatment of depressive disorders in primary care

2.9.1 Guidelines for depression in primary care

According to Finnish Depression Current Care Guidelines (Depressio, 2009 (updated 11.10.2013)), depression is a central issue both in primary and in secondary care. In acute phase of depression care, central specific treatments are antidepressant medication and efficient psychotherapies. These are equally effective in mild and moderate MDD, where they may be used alternatively or simultaneously. The more severe MDD is, the more important the role of medication becomes. In addition to specific treatment methods, central objectives are evaluation of life situation and offering psychosocial support. After recovering, treatment and monitoring should continue for six months in order to prevent recurrences. Long-term maintenance antidepressant treatment is recommended to patients who experience their third MDE, to prevent recurrences. Furthermore, more developed psychiatric consultation and psychiatric nurses are needed in primary care, in order to educate, monitor and give psychosocial support.

NICE Depression Guidelines recommend that primary care doctors should not normally combine antidepressants without consulting a consultant psychiatrist, and should be aware that venlafaxine is associated with a greater risk of death from overdose (NICE, 2010). NICE Depression Guidelines lists: 1) factors that favour more active treatment in primary care: five or more symptoms with associated disability, persistent or long-standing symptoms, personal or family history of depression, low social support, and occasional suicidal thoughts, 2) factors that favour referral to mental health professionals: inadequate or incomplete response to two or more interventions, recurrent episode within 1 year of last one, history suggestive of bipolar disorder, the person with depression or relatives request referral, more persistent suicidal thoughts, and self-neglect, and 3) factors that favour urgent referral to specialist mental health services: actively suicidal ideas or plans, psychotic symptoms, severe agitation accompanying severe symptoms, and severe self-neglect.

Depression treatment guidelines may have limitations in their relevance to primary care. According to a review of seven national depression guidelines, management strategies (antidepressants and psychological strategies) are supported by all of them, with several listing drugs before psychological therapies. However, limited attention has been paid to the different types of psychological therapies (Hegarty et al., 2009). The majority of guidelines do not address associated risk factors sufficiently. Generally, they fail to acknowledge individual patient circumstances, in particular the influence of social issues such as adverse life events or social support. The research on long-term treatment strategies of depressive disorders in primary care is scarce. There are no randomized controlled trial (RCT) addressing the efficacy of maintenance treatment with antidepressants (Piek et al., 2010). Concerning chronic MDD, there is a lack of evidence, but the best treatment seems to be a combination of psychotherapy and antidepressants (Spijker et al., 2013).

The principles and the results of antidepressant treatment are similar in primary care and in psychiatric care (Wells et al., 2000; Casacalenda et al., 2002). Antidepressants are also found to be effective in primary care (Arroll et al., 2005; Arroll et al., 2009; Kendrick et al., 2009) and in physically ill patients (Rayner et al., 2010). Primary care doctors should be aware of special treatments available in psychiatric care for severe, psychotic or treatment resistant depressions, such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS).

There is a range of psychological approaches that can be offered as frontline treatments. Psychological treatments appear effective especially when general practitioners have referred patients to them (Cuijpers et al., 2009). In a meta-analysis of RCTs of brief psychological therapies in primary care, cognitive behaviour therapy, counselling and problem solving therapy were all effective, but effect sizes were low compared to longer treatments (Cape et al., 2010). Mindfulness-based cognitive therapy has prevented relapse of depression in primary care patients with a high risk of relapses (Mynors-Wallis et al., 2000; Kuyken et al., 2008). Computerized cognitive-behavioural therapy can be offered before a face-to-face one (Proudfoot et al., 2003).

2.9.2 Epidemiology of treatment of depressive disorders in primary care

Only a part of people with depressive disorders receives appropriate treatment (Whiteford, 2008). Only about half of people even with severe MDD appear to use health services (Kessler et al., 2005). General practitioners managed approximately one third to one half of all patients who received treatment for MDD. The severity of depressive symptoms in patients who received treatment in primary care was found to be equivalent to that of patients treated in psychiatric care (Gaynes et al., 2007).

In Finland, only 28% (31% of men and 25% of women) of people with MDE in the general population used any health services for their depression in 1996. Use of health services was predicted by longer duration and greater severity of depression and perceived disability, but not by socio-demographic factors. However, those factors did not predict whether treatment was sought from primary or psychiatric care (Hämäläinen et al., 2004). Of people with MDD without or with anxiety disorders in 2000/2001, 34% vs. 58% used health services, predicted by greater severity of depression, perceived disability, psychiatric comorbidity, and living alone (Hämäläinen et al., 2008). Of all health service use associated with MDD, psychiatric care alone accounted for 36% vs. primary care for 25%, and both for 24%. Patients in primary care and psychiatric care did not differ by severity or duration of depression, perceived disability, or psychiatric comorbidity other than anxiety. Of MDD patients, 24% used antidepressants and 17% had received psychological treatment; 31% received antidepressants or psychological treatment or both (Hämäläinen et al., 2009). In a domestic primary care cohort, 38.5% of patients with clinical depression received some form of treatment: 34.6% antidepressants and 19.2% counselling appointments (Luutonen et al., 2011).

An educational program for primary care practitioners based on a clinical practice guideline did not improve either recognition or recovery from depression (Thompson et al., 2000; Lin et al., 2001). Depression screening programs without substantial staff-assisted depression care support are unlikely to improve depression outcomes (O'Connor et al., 2009). Consultation practices improved general practitioners' ability to recognize depression and outcome of them (Gilbody et al., 2006). Patients who do not respond to antidepressants are found to be at risk of being demedicalised by their general practitioners (McPherson and Armstrong, 2009). Although active monitoring is an essential part of depression guidelines, patients with depression in primary care receive inconsistent follow-up (Lin et al., 2000, Wagner and Simon, 2001). Patients may have neither the energy nor the inclination to make a return visit, and general practitioners have no system to check if this happens or not (McKall, 2001). A strategy for the alert practitioner is to book the next appointment while the patient is present, and if they do not show up to contact them (Arroll and Moir, 2010).

Medical comorbidity and somatic complaints are more the rule than the exception among depressed patients in primary care (Goldberg et al., 1993, Kirmayer et al., 1993, Koike et al., 2002, Keeley et al., 2004). Depressed primary care patients with medical comorbidity received similar rates of treatment but had worse depression outcome than patients without medical comorbidity. Combined quality improvement programs resulted in greater use of antidepressants and psychotherapy and improved outcome (Koike et al., 2002). Further, primary care is an ideal setting to treat mentally and physically comorbid patients (Whiteford, 2008).

A review of collaborative care programs for depression in primary care found strong evidence for their effectiveness and cost-effectiveness (Simon et al., 2001). Systematic identification of patients, case management, professional background of staff and specialist supervision improved outcome in primary care (Gilbody et al., 2006; Bower et al., 2006). A depression tool kit contains screening, diagnostic, management planning and outcomes assessment questionnaires, treatment and counselling guidelines, and patient education materials; the authors state that the effectiveness of it may have as much to do with the ways to implement and to use it as with its components (Brody et al., 2000).

Considering the high prevalence of depressive disorders, there is a need for easy-delivery low-cost interventions. Even befriending was found to be significant, though with modest effect on depressive symptoms and also in the long-term (Mead et al., 2010). Core principles of stepped care are to deliver low-burden treatments first, followed by careful progress monitoring to step patients up to more intensive treatment such as longer-term face-to-face psychotherapy and antidepressants. Stepped care sits in organizational systems from primary to specialist care (Richards, 2012). According to a qualitative study, elements of the stepped-care model were positively accepted by personnel in primary care (Franx et al., 2012). Stepped care trials have enhanced treatment initiation and continuation, precipitated treatment response, but not improved outcome compared with treatment as usual (Lin et al., 2000; Patten et al., 2008; Seekles et al., 2011; Oosterbaan et al., 2013; Szymanski et al., 2013; Bohnert et al., 2013).

There is weak evidence for usefulness of guided and self-guided management among depressed primary care patients (Anderson et al., 2005; Seekles et al., 2011), although, in a meta-analysis, only guided self-help with trained workers remained effective (Gellatly et al., 2007). Both guided self-help concreteness training and relaxation training reduced depressive symptoms more than treatment as usual (Watkins et al., 2012). In a recent trial from primary care, guided self-help cognitive-behavioural therapy for depression was substantially more effective than treatment as usual (Williams et al., 2013). Future research is needed to evaluate supportive monitoring, strategies of self-help, internet-based guided managements etc. and their effective implementation to primary care practice.

More evidence is needed from naturalistic prospective long-term cohorts from primary care, to estimate the favourable and unfavourable courses of depressive disorders and their determinants, in order to gain information to choose appropriate treatments for diverse patients groups.

2.10 Prevention of depressive disorders in primary care

Prevention may be directed toward the whole population (universal prevention), high-risk groups (selective prevention), or those with subsyndromal symptoms (indicated prevention). More than 30 randomized trials have demonstrated that preventive interventions can reduce the incidence of new episodes of MDD by about 25%, and by as much as 50% when preventive interventions are offered in stepped-care format. Methods with proven effectiveness involve educational, psychotherapeutic, pharmacological, lifestyle and nutritional interventions, which may all be used in concert (Munoz et al., 2010). Although prevention research and practice have progressed in the last years, it still remains unknown what is the most effective strategy to reduce the burden of depression (Cuijpers, 2011; Cuijpers et al., 2012).

A meta-analysis found prevention of new cases of depressive disorders possible. Interventions reduced their incidence by 22%. The number needed to treat to prevent one case was moderate 22, but focusing on selective and indicated prevention it was rather favourable 16 vs. 17. According to outcome, no systematic differences appeared between target populations or types of prevention; interpersonal psychotherapy may be more effective than cognitive-behavioural (Cuijpers et al., 2008). Minimal contact psychotherapy may be cost-effective in the prevention of the onset of depressive disorders among primary care patients with subthreshold depression (Smit et al., 2006). Many general prevention strategies for depressive disorders may be suitable in primary care too, such as promotion of physical activity. According to current systematic review, physical activity was negatively associated with a risk of depression, even in low levels (Mammen and Faulkner, 2013). Furthermore, even succeeding to delay the onset of illness is valuable, and not only the prevention of new cases (Cuijpers et al., 2008).

3 Aims of the study

This study investigated the prospective 5-year outcome of a stratified sample of 137 primary health care patients with DSM-IV depressive disorders.
Specific aims of the study were:

I To investigate the long-term course and outcome of depressive disorders among primary care patients, and the influence of various clinical, psychosocial and socio-demographic factors. It was hypothesized that both features of MDD itself (severity, duration and recurrences before entry) and comorbidity (axis I and II disorders plus medical comorbidity) would effectively predict chronicity and recurrences.

II To investigate long-term variations in incidence for suicide attempts among primary care patients with depressive disorders, and whether risk and protective factors modify this risk. It was hypothesized that the rate of incidence would be high during MDEs and substance abuse and highest when both are present, and that previous suicide attempts, psychiatric comorbidity (especially personality disorders and substance use disorder) and adverse socio-economic factors would all independently predict suicidal behaviour.

III To investigate factors predicting long-term functional and work disability among primary care patients with depressive disorders. It was hypothesized that incidence of disability pensions and sick leaves due to depression and the functional impairment would be high among those with more severe depression, longer time spent in MDEs, psychiatric comorbidity, and adverse psychosocial or socio-economic circumstances.

IV To investigate long-term differences between primary care depressive patients with or without borderline personality disorder. It was hypothesized that comorbid BPD would deteriorate the outcome of MDD (and vice versa), and enhance the risk for suicide attempts, and that the functional level and work status of MDD patients would be lowest among those with BPD.

4 Materials and methods

4.1 General study design

The Vantaa Primary Care Depression Study (PC-VDS) is a naturalistic and prospective cohort study concerning depressive disorders in primary health care. Depressive disorders are diagnosed according to DSM-IV-TR. The study comprises depressive disorders from minor depression (MinD) and subsyndromal depression (SubMDD) to severe major depressive disorder (MDD). SubMDD includes both recovering and prodromal cases of previous MDD.

The study forms a collaborative depression research project between the Department of Mental Health and Substance Abuse Services, Mood, Depression and Suicidal Behaviour Unit of the National Institute for Health and Welfare, Helsinki, the Department of Psychiatry, Institute of Clinical Medicine of the University of Helsinki and the Primary Health Care Organization of the City of Vantaa, Finland. The city of Vantaa was a town of 179 856 inhabitants in 2002 (206 283 inhabitants in 2013). The Primary Health Care Organization of the City of Vantaa provides health services to all Vantaa citizens. The pertinent Ethics Committee approved the baseline study protocol in December 2001 and the 5-year follow-up study protocol in March 2007.

4.2 Screening

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. A detailed flow chart of the screening process is given in Figure 1.

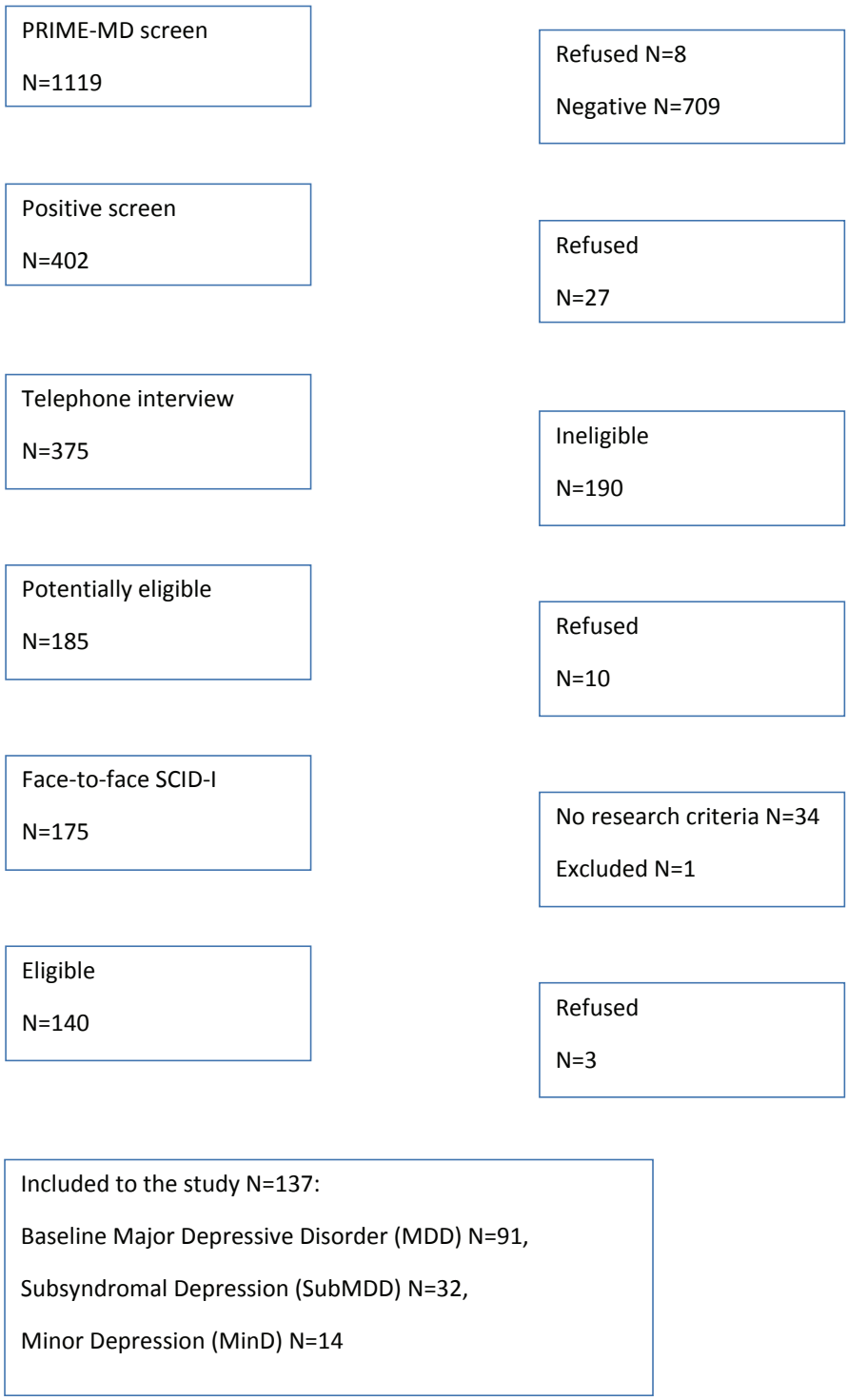


Figure 1. Flow chart of the screening process in the Vantaa Primary Care Depression Study.

In the first phase, 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 on randomly selected days between 2 January and 31 December 2002, stratified in terms of weekday, day of month and time of year. On these randomly selected days, PRIME-MD was offered to all consecutive patients except those not understanding Finnish (N=50), patients in medical emergency (N=14) or to handicapped patients unable to communicate (N=4). After answering "yes" to either question concerning depressed mood or anhedonia in PRIME-MD, the patients were fully informed about the study and were asked for their permission to accept a phone call within five days from the research psychiatrist. Of the 402 eligible patients, 27 (6.7%) refused to participate, but 375 (93.3%) agreed and gave written informed consent. 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., 2002) was then confirmed by telephone for 20-30 minutes.

4.3 Baseline evaluation

4.3.1 Diagnostic measures

In the second phase, after receiving written informed consent, all 175 potentially eligible patients were interviewed face-to-face using the SCID I/P with psychotic screen. Inclusion criteria were current 1) index MDD, 2) dysthymia, 3) subsyndromal depression (SubMDD) with two to four depression symptoms (minimum one core symptom) and lifetime MDD and 4) minor depression (MinD) otherwise similar to SubMDD, but without MDD history. The DSM-IV Appendix B defines research diagnostic criteria for subsyndromal depressive symptoms, though not an official clinical disorder (American Psychiatric Association, 2000). Subsyndromal depressive symptoms are defined as at least two current symptoms, present every day for most of the time, for at least two weeks, in persons not meeting the criteria for MDD, MinD or dysthymic disorder. SubMDD could refer to residual symptoms of a past MDE or a prodromal future MDE. The National Institute of Mental Health (NIMH) introduced SubMDD in Epidemiological Catchment Area Study (ECA) (Judd et al., 1994, Judd et al., 1997). Current distress or functional impairment was required for all. Dysthymia was regarded as subsyndromal MDD (four patients) or MinD (one patient) according to a positive or negative history of MDD.

All available medical records, including the results of a standardized set of laboratory tests, were used to exclude substance-induced depression or depression due to medical conditions. Patients currently abusing alcohol or other substances were interviewed after two to three weeks of abstinence, in order to exclude substance-induced depression. All current and lifetime psychiatric disorders were

assessed with Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First et al., 2002). DSM-IV axis II disorders comprises 10 personality disorders, divided into cluster A, B and C, cluster B including borderline personality disorder (BPD). They were all assessed with Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (First et al., 1997).

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).

4.3.2 Exclusion criteria

Patients with psychoses other than depressive (N=0), patients with bipolar or organic mood disorder (N=14), alcohol use problems severe enough to prevent two weeks abstinence (N=10) and patients currently receiving treatment in psychiatric care (N=32) were excluded.

4.3.3 Observer and self-report scales

Observer scales included the 17-item Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960) 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, 1979), the Beck Anxiety Inventory (BAI) (Beck et al., 1988), the Beck Hopelessness Scale (HS) (Beck et al., 1974), the Scale for Suicidal Ideation (SSI) (Beck et al., 1979), and the Perceived Social Support Scale - Revised (PSSS-R) (Blumenthal et al., 1987).

4.3.4 Additional characteristics

Age of onset, duration and recurrences of DSM-IV MDE during lifetime was assessed retrospectively with interview and medical and psychiatric records. Suicidal behaviour was investigated, with interview and records, in three time frames: a) current suicidal ideation, b) ideation and attempts within the ongoing depressive episode and c) lifetime ideation and attempts. Suicidal ideation refers to patients who scored more than 6 points on the SSI. By definition, a suicide attempt had to involve at least some degree of intent to die, by interview and medical and psychiatric records.

A self-report questionnaire, medical records, and the interview were used for diagnosing chronic medical illness, minimum duration three months and with functional impairment and/or constant suffering. Psychosocial and socio-economic

factors were assessed in the interviews and with self-report questionnaires. Professional education was divided into those with some professional education and those without. Subjective work ability was divided into categories: fully capable, decreased and incapable. Received social assistance was used as an indicator of economic situation. In Finland, it is a last resort for income security and effectively reflects severe economic difficulties. Patients were divided into those who had received social assistance at least once and those who had not.

4.4 Follow-up procedure

After baseline, patients were investigated at 3, 6 and 18 months (Vuorilehto et al., 2009) (Table 3). The 5-year interviews were accomplished from March 2007 to August 2008 by a psychiatrist (Riihimäki). BDI and other self-report scales were used at 3 months, and current state of depression was investigated by telephone at 6 months. Current state of depression was investigated face-to-face at 18 months by SCID-I/P, and all psychiatric disorders at 5 years with SCID-I/P and SCID-II; at both time-points, the above-mentioned scales and all medical and psychiatric records were used. The incidence of suicide attempts, their severity, methods, and treatment received was assessed with interviews and medical and psychiatric records.

In addition, at 5 years, the Alcohol Use Disorders Identification Test (AUDIT) and the Sheehan Disability Scale (SDS) were used. AUDIT was developed by the World Health Organization as a means of screening hazardous or harmful drinking and identifying persons at risk of developing alcohol problems, focusing on the last year (Saunders et al., 1993, Reinert and Allen, 2007). SDS is a self-reported outcome measure for assessing functional impairment in three domains: work/school activities, social activities and family life (Sheehan et al., 1996, Luciano et al., 2010). For each dimension, the patient rates the extent of impairment over the previous week due to their symptoms on a 10-point visual analogue scale. SOFAS was used at all interviews. It differs from the Global Assessment of Functioning (GAF) in measuring purely the level of social and occupational functioning, ignoring any symptoms. SOFAS scores of 40 to 50 represent the range from major to serious, 60 to 70 from moderate to some, and 80 to 90 from slight impairment to good functioning in social, occupational or school domains. Disability pension in Finland can be granted for a disability continuing after 300 sick leave days. The actual mean age for retirement was 60.5 years in 2012.

Table 3. Evaluation process in the Vantaa Primary Care Depression Study over a 5-years follow-up.

	Self-report scales	Observer-rated instruments	Other information
Baseline Face-to-face interview	BDI, BAI, HS, PSSS-R	SCID-I/P and SCID-II, HAMD, SSI, SOFAS, records	Interview, medical and psychiatric records
3 months By mail	BDI		Medical and psychiatric records
6 months Telephone interview and by mail	BDI	SCID-I	Interview, medical and psychiatric records
18 months Face-to-face interview	BDI, BAI, HS, PSSS-R	SCID-I, HAMD, SSI, SOFAS, Records	Interview, medical and psychiatric records
5 years Face-to-face interview	BDI, BAI, HS, PSSS-R, AUDIT, SDS	SCID-I/P and SCID-II, HAMD, SSI, SOFAS, records	Interview, medical and psychiatric records

4.4.1 Study participants

Baseline characteristics of the total sample of 137 patients with depressive disorders and of the subgroup of 123 patients with lifetime MDD, with and without concurrent BPD, are shown in Table 4. Of the 137 patients initially included in the study, 127 (93%) participated in the 18-month and 112 (82%) in the 5-year follow-up. The diagnosis of one patient, who participated in the 5-year interview, had switched to bipolar disorder after the 18-month interview, and this patient was censored in the survival analyses at the time-point where the switch occurred. A detailed flow chart of the follow-up process is given in Figure 2. Patients remained in the cohort until they were censored due to change of diagnosis to bipolar disorder (4%) or death (4%). The final follow-up group in the survival analysis consisted of 134 patients with any follow-up information, 110 of them with lifetime MDD (of them 91 with baseline MDE at the intake). At 5 years, there were 102 patients with lifetime MDD, 73 of them with baseline MDE. The median time for the 5-year interview was 62.9 (mean 63.3) months. The dropouts did not differ from the patients who were followed up at 5 years in age, gender, baseline depression severity, or the median time from the beginning of MDE to the study entry.

Table 4. Baseline characteristics of patients in the Vantaa Primary Care Depression Study.

	Total		Lifetime MDD		Total, followed up 5-years		Lifetime MDD, followed up 5-years		With BPD		Without BPD	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	137		123		111		102		35		102	
Socio-demographic features												
Female gender	104	76	95	77	87	78	81	79	30	86	74	72
Married or cohabiting	72	53	53	43	57	51	53	52	16	46	41	40
Any professional education	84	61	77	63	72	65	67	66	16	46	68	67
Employed	72	53	63	51	70	63	55	54	15	43	55	54
Unemployed	27	20	22	18	22	20	20	20	11	31	16	16
Disability pension due to depression	10	7	10	8	10	9	10	10	3	9	7	7
Social assistance within 6 months	49	36	44	36	40	36	37	36	21	60	28	28
Clinical features												
Psychiatric comorbidity	120	88	95	77	79	71	75	74				
Psychiatric comorbidity[a]									29	83	67	66
Current axis I comorbidity	82	60	76	62	64	58	60	59	27	77	55	54
Anxiety disorder (any)	59	43	54	44	47	42	43	42	22	63	37	36
GAD	22	16	20	14	15	14	14	14	7	20	15	15
Panic disorder	9	7	9	7	7	6	7	7	7	20	2	2
Social phobia	22	16	20	16	19	17	17	17	5	14	17	17
Somatoform disorder	17	12	17	14	14	13	14	14	3	9	14	14
Current axis II comorbidity	71	52	68	55	55	50	53	52				
Current axis II comorbidity[a]									15	43	36	35
Cluster B	39	29	38	31	31	28	30	30				
Cluster B[a]									0	0	4	4
Cluster A	7	5	7	6	5	5	5	5	5	11	3	3
Cluster C	44	32	42	34	35	32	34	34	33	37	31	30
Substance use disorder	20	15	19	15	14	13	14	14	10	29	10	10
Alcohol abuse or dependence	14	10	13	11	9	8	9	9	5	14	7	7
Treatment of alcohol abuse	12	9	12	10	9	8	9	9	8	23	4	4
Somatic comorbidity	73	53	66	54	56	51	54	53	18	51	55	54
Interfered everyday life	64	47	60	49	49	39	48	47	18	51	46	45
Suicide attempts before BL	23	17	23	19	19	17	19	19	14	40	9	9
Treatment history												
Psychiatric care before BL									24	69	49	39
Psychiatric hospital before BL									11	31	7	7
Treatment at BL												
Antidepressant medication	50	37	47	38	43	39	42	41	16	46	34	33
Socio-demographic features	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	45.3	13.7	45.6	13.7	44.8	13.7	45.2	13.6	37.3	13.7	48.0	12.7
Clinical features												
Age at onset of depression (years)	35.2	14.9	34.4	14.8	34.3	14.5	33.8	14.5	25.4	12.6	38.6	14.2
HAMD	16.1	5.3	16.7	5.3	16.2	5.5	16.6	5.6	17.2	5.7	15.8	5.1
BDI	19.3	10.0	20.1	10.0	18.9	10.2	19.6	10.2	24.3	11.9	17.5	8.6
No. of previous depressive episodes	2.7	3.9	3.1	4.0	2.9	4.0	3.1	4.1	4.37	6.1	2.19	2.6
BAI	17.0	12.6	17.8	12.8	17.2	12.4	17.7	12.5	24.1	16.6	14.2	9.8
HS	8.7	5.3	9.0	5.4	8.5	5.3	8.7	5.3	10.5	5.2	8.1	5.1
SOFAS	56.8	11.5	56.1	11.6	57.2	11.2	56.7	11.2	50.1	12.1	58.9	10.5
SSI	2.9	5.6	3.2	5.9	2.9	5.8	3.1	6.0	5.80	7.3	1.87	4.5
PSSS-R	43.0	12.6	42.7	12.7	43.6	12.5	43.6	12.4	41.5	12.9	43.5	12.6

[a]Other than BPD; BAI=Beck Anxiety Inventory, BDI=Beck Depression Inventory, BPD=Borderline Personality Disorder, BL =Baseline, GAD=Generalized anxiety disorder, HAMD=Hamilton Rating Scale for Depression, HS=Beck Hopelessness Scale, MDD=Major Depressive Disorder, PSSS-R=Perceived Social Support Scale - Revised, SD=Standard Deviation, SOFAS=Social and Occupational Functioning Assessment Scale, SSI=Scale for Suicidal Ideation. Between-group comparisons analysed using two-sample t-test or ANOVA, the Mann-Whitney and Kruskal-Wallis tests, and the chi-square tests.

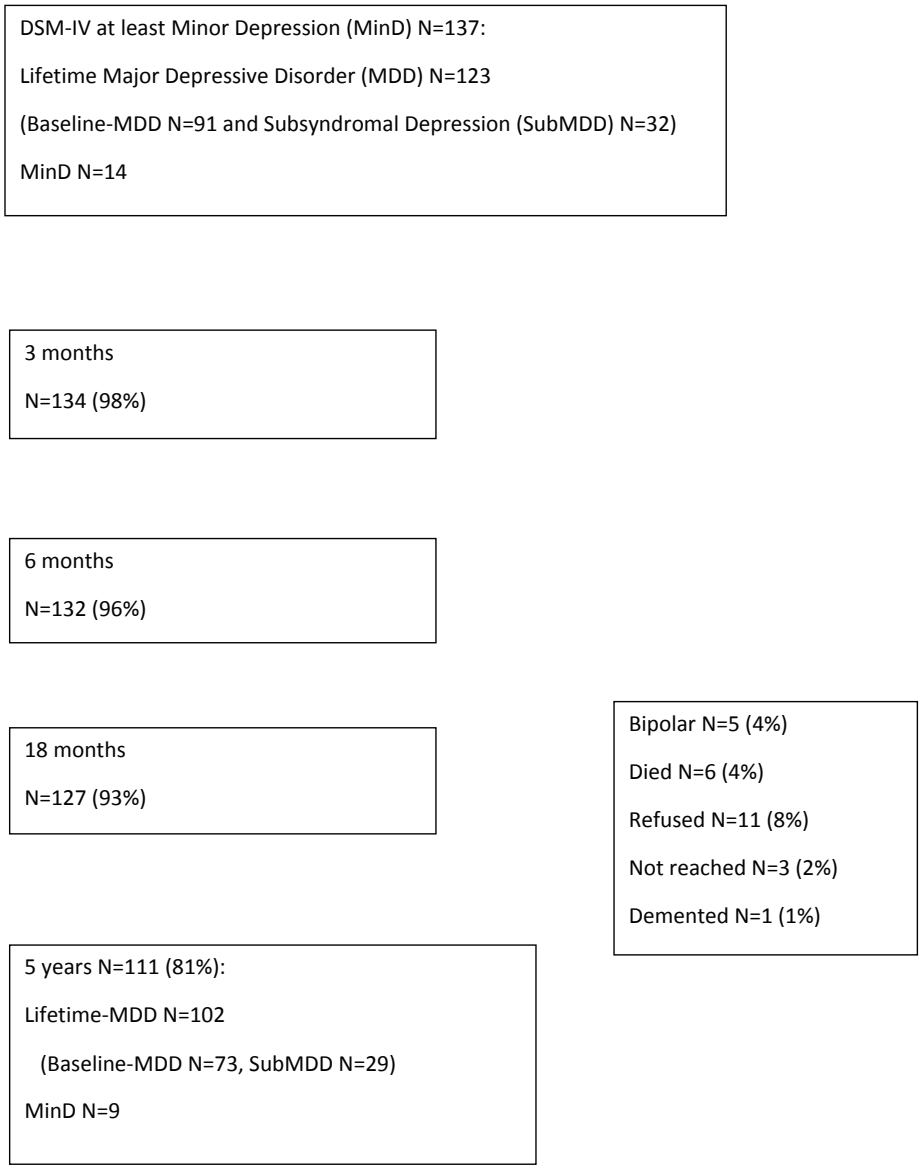


Figure 2. Flow chart of the follow-up process in the Vantaa Primary Care Depression Study.

4.4.2 Life-chart methodology

Patients were prospectively followed up with a life-chart. At 18 months and at 5 years, MDD and substance use disorders (dependence or abuse) were diagnosed in face-to-face interviews with the SCID-I/P to determine timing and duration of MDEs and episodes of substance abuse.

The time after the baseline interview was divided into three categories: 1) state of MDE (5 or more of the 9 MDE criteria symptoms), 2) state of partial remission (1-4 symptoms) and 3) state of full remission (no symptoms). Remission and recurrence were defined as in the DSM-IV. In accordance with the DSM-IV definition for "296.3x MDD, Recurrent", recurrence referred to the return of MDE after at least two consecutive months of partial or full remission. Suicide attempts plus sick leaves and disability pensions granted for depression were also assessed from the interviews. In addition, all medical and psychiatric records were used. All this information was placed and integrated on the life-chart.

4.5 Principal outcomes

The principal outcomes of MDD were: 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 and 4) time spent in MDE state, partial remission and full remission. Factors predicting the different outcomes were investigated.

The incidence of suicide attempts, their medical severity and methods used, and treatment received for the attempts and referrals to any psychosocial care were investigated. The medical severity of the attempts was classified as mild (not necessitating treatment), moderate (necessitating emergency room) or severe (necessitating hospitalization). In addition, preceding communication of intent and later communication of attempts to health care personnel were recorded.

Information on employment and unemployment, disability pension and sick leaves plus their causes and durations, and retirement during the follow-up was collected in the interviews, with self-report questionnaires and from patient records. For functional and work disability at work, family and social activities, SOFAS and SDS were used. Only patients employed (54/111) were included in work/school and only patients married or cohabiting (57/111) in family life analyses.

Differences of depressive disorders with and without current borderline personality disorder (BPD) were investigated, focusing on the course and outcome of depressive disorders, other comorbidities, suicide attempts, functional ability and work status.

4.6 Statistical methods

Kaplan-Meier survival curves were used 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 and 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.

A structural equation model was used 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 below 0%), the robust maximum likelihood (MLR) estimator 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 comorbidity 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 adjusts the parameter estimate of the effect of substance use disorders to time in full remission accordingly. 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.

Univariate and multivariate logistic and linear regression models were used to analyse baseline predictors for recurrences of MDD, suicide attempts, social and occupational functioning, functional and work disability, employment status, and sick leaves and disability pensions due to depression.

In our final multivariate models, variables were included on the basis of our primary hypothesis. The predetermined independent variables at baseline comprised HAMD (alternatively BDI), history of former MDE, BAI, HS, psychiatric comorbidity (substance use, anxiety and somatoform disorders obtained by SCID-I/P, cluster A, B and C personality disorders obtained by SCID-II), medical comorbidity, perceived social support, subjective ability to work, marital, educational, occupational and economic status. A separate model that included proportion of time spent depressed during the follow-up was also created using multivariate logistic regression analyses. In the final models, the non-significant variables were omitted.

Between-group comparisons were computed using the paired-samples t-test or Wilcoxon or McNemar tests or the Chi-square test statistic with Yates' continuity correction or Fisher's exact test as appropriate. In comparisons of continuous variables, the two-sample t-test or ANOVA was used for variables with normal distribution, and the Mann-Whitney and Kruskal-Wallis tests for variables with non-normal distribution.

All models were adjusted for age and gender. Regression analyses were also controlled for the time at risk for MDE, and the structural equation model and the MLR estimator for the follow-up time (Study I). The logistic and linear models were also controlled for follow-up time (Study II-IV), and, when follow-up variables were included, also for SOFAS at baseline (Study III). Appropriate regression models were also adjusted for time spent depressed during the follow-up (Study IV).

Statistical Package for the Social Sciences, versions 18.0-21.0 (SPSS Inc., Chicago, IL, USA), was used. Mplus 5.21 (Munthén and Munthén, 2007) software was used to estimate the model. Cox and Poisson models were constructed with R language (1 R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: 2011. http://www.R-project.org/).

5 Results

The results presented in detail in the first section are those from lifetime MDD patients. In the three following sections, the results presented are those from all patients included in the study.

5.1 Long-term course and outcome of MDD (Study I)

The results presented in this section are those from lifetime MDD patients (at baseline 123/137 and at 5 years 102/111). The outcome in the subgroup of patients with a current MDE at baseline was found to be similar to these. Those patients who remained in the index MDE during the entire follow-up (10/102) suffered from more severe depression at baseline compared to other patients who reached at least partial remission in some point during the follow-up (HAMD mean 22.3 SD 4.5 vs. 16.0 SD 5.3, $p<0.001$; BDI mean 31.4 SD 10.8 vs. 18.3 SD 9.4, $p<0.001$) and had more psychiatric comorbidity, especially substance use disorders (comorbid alcohol and prescription drug abuse or dependence) (60.0% vs. 8.7%, $p<0.001$).

5.1.1 Time spent in MDEs, partial remission and full remission during the follow-up of 5 years

The MDD patients in this study (N=102) spent on average less than one-half (42% [26.5 months, SD±24.3]) in full remission, one-quarter (24% [15.3 months, SD±18.0]) in partial remission and one-third (34% [21.7 months, SD±22.4]) in MDEs (Fig. 3).

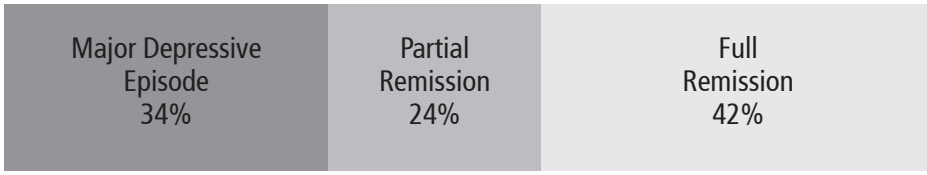


Figure 3. Time spent in MDE, in partial remission and in full remission among patients with lifetime MDD in the Vantaa Primary Care Depression Study over a 5-year follow-up (N=102).

In univariate analysis with several baseline factors, the time spent in full remission and the time spent in MDEs were associated with several baseline factors: BDI, HAMD, HS, 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 (HR 0.028, 95% CI 0.016-0.040, p<0.001) and comorbid substance use disorder (HR 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 ten at baseline predicted 14 months more time in MDEs. Substance use disorder predicted time spent in MDEs; substance use disorder at baseline predicted 25 months more time in MDEs and no substance use disorder 46 months more time in full remission.

5.1.2 Time to full remission and predictors of it

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.

In univariate analyses, several individual factors at baseline were associated with time to full remission: BDI, HAMD, BAI, HS, SOFAS, PSSS-R, SSI, and substance use disorder. In multivariate analyses, longer time to full remission was predicted by more severe symptoms of depression in HAMD (HR 1.10, 95% CI 1.04-1.15, p<0.001) or BDI (HR 1.06, 95% CI 0.916-1.92, p<0.001) and a comorbid substance use disorder (HR 6.80, 95% CI 1.60-28.6, p=0.009).

5.1.3 Recurrence and predictors of it

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 2 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.

In univariate analyses, recurrence was associated with several baseline factors: younger age, comorbid psychiatric disorder such as cluster C personality disorder, any lifetime anxiety disorder, general anxiety disorder (GAD), or somatoform disorder, and lifetime suicide attempts. However, in multivariate logistic regression analyses, only having a personality disorder remained a significant predictor (OR 2.398, 95% CI 1.034-5.560, p=0.041).

5.1.4 Time to first recurrence and predictors of it

Median time between remission and first recurrence was 8 months (SD±25).

In univariate analyses, the time from remission to recurrence was predicted by comorbid psychiatric disorders, i.e., cluster A and C personality disorder, any lifetime anxiety disorder, GAD or somatoform disorder, and lifetime suicidal behaviour. In multivariate analyses, GAD (HR 0.35, 95% CI 0.16-0.78, p=0.010), and somatoform disorder (HR 0.34, CI 95% 0.17-0.84, p=0.008) remained significant predictors.

5.1.5 Cross-sectional outcome at 5 years

At 5 years, nearly one-half (46%, 46/102) of the followed 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 an 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 an MDE.

5.2 Risk factors of suicide attempts during the prospective follow-up (Study II)

During the 5-year follow-up 10.4% (14/134) of the depressive primary care patients with any follow-up information attempted suicide, with altogether 22 discrete attempts. The degree of medical severity was mostly moderate (45%, 10/22). There were no completed suicides.

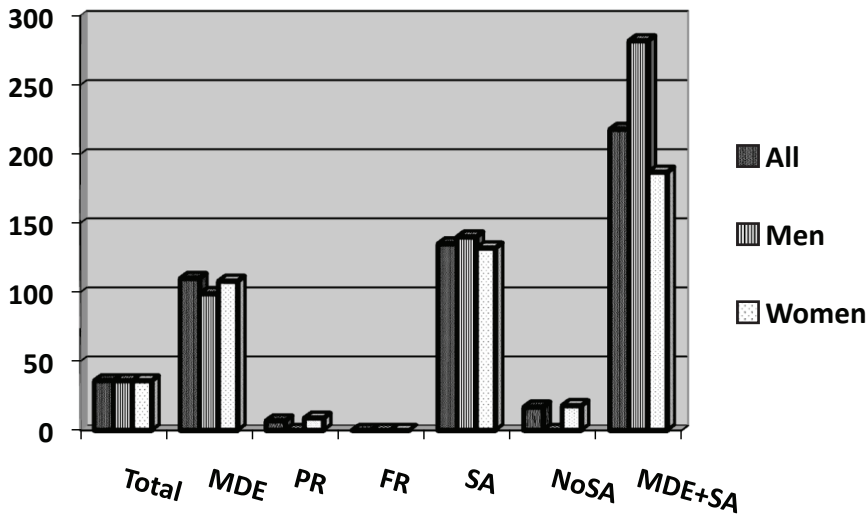
5.2.1 Predictors for attempting suicide during follow-up

In univariate analyses, suicide attempts were associated with several baseline factors: BDI, HS, SSI, BAI, PSSS-R, history of previous suicide attempts, Axis I comorbidity overall, and specifically comorbid substance use disorders and alcohol abuse or dependence, having received welfare benefits, and time spent in MDEs during follow-up. In multivariate logistic regression analyses, after removing the non-significant variables, suicide attempts were robustly predicted by previous suicide attempts (OR 4.386, 95% CI 1.095-17.558, p=0.037) and presence of a comorbid substance use disorder (OR 20.399, 95% CI 4.571-91.026, p<0.001), which increased the risk 20-fold.

5.2.2 Incidence and time-varying predictors for suicide attempts

Nearly all of the suicide attempts during follow-up (95%, 21/22) occurred during MDEs, and one (5%, 1/22) during partial remission. More specifically, almost half of the attempts (41%, 9/22) occurred during periods of concurrent MDE and substance abuse, over half (55%, 12/22) during MDEs but without substance abuse, and one (5%, 1/22) during partial remission and substance abuse (Figure 4). There occurred no suicide attempts during full remission or during partial remission in the absence of concurrent substance abuse.

The 5-year follow-up comprised 610 patient-years (N=134). Of this time, 196 patient-years were MDEs, 171 partial remission and 244 full remission. The overall estimate of incidence of suicide attempts was 36.0 per 1000 patient-years (95% CI 22.5-54.6), during MDEs 107 (95% CI 66.4-164), during partial remission 5.8 (95% CI 0.1-32.6), and during full remission 0 (95% CI 0-15.1) per 1000 patient-years. During the follow-up, time spent with substance abuse was 70 patient-years, and without substance abuse 540 patient-years. About half (45%) of all suicide attempts (10/22) occurred during periods of substance abuse. The incidence of suicide attempts during substance abuse was 142 (95% CI 68.4-262.7) and without substance abuse 22.2 (95% CI 11.4-38.8) per 1000 patient-years. In the Cox proportional hazards models, after removing the non-significant variables, hazard of suicide attempts was significantly higher (HR 33.5, 95% CI 3.6-309) during MDEs compared to full or partial remission. Substance abuse periods were not significant as independent predictors (HR 1.98, 95% CI 0.65-6.01).



MDE=during Major Depressive Episodes, PR=during partial remission, FR=during full remission, SA=during periods with substance abuse or dependence, NoSA=during periods without substance abuse or dependence

Figure 4. Incidence of suicide attempts/1000 patient-years in the Vantaa Primary Care Depression Study over a 5-year follow-up (N=134).

5.2.3 Treatment received and communication about suicide attempts to health care personnel

At the time of suicide attempts, in the minority of cases (31%, 9/22), the patients were receiving treatment for their depression. Of cases receiving treatment at the time of suicide attempts, a half (5) received it in primary care, and the other half (5) in psychiatric care, including 1 patient who was receiving intermittent hospital care in both primary and secondary care. According to the interviews and the primary care records, the patients did not communicate their suicidal thinking or intentions, or seek help before the attempt.

In two-thirds of the attempts (68%, 15/22), the patients received immediate medical care; in one-fourth of attempts (18%, 4/22) they were hospitalized in psychiatric care. In altogether 41% (9/22) of suicide attempts, the patients received psychiatric care (in- or outpatient), either immediately after the attempt or later for depression. However, only in one of the suicide attempts (5%, 1/22) did the patient talk about the attempt to their attending health care personnel in primary care.

5.2.4 Suicidal ideation and severity of depression

SSI scores correlated with both HAMD (at baseline rs= 0.395, p = <0.001, at 18 months rs= 0.449, p = <0.001, and at 5 years rs= 0.470, p = <0.001) and BDI scores (at baseline rs= 0.477, p = <0.001, at 18 months rs= 0.566, p = <0.001, and at 5 years rs= 0.502, p = <0.001), being essentially similar at different time-points. Like suicide attempts, suicidal ideation was very rare in the absence of clinically significant depression (at baseline HAMD < 8, SSI mean 0.11 median 0.00 SD 0.333, N=9; at 5-years HAMD < 8, SSI mean 0.222 median 0.000 SD 1.491, N=45) and was associated strongly (p < 0.001) with depression severity (Figure 5). However, the distribution of SSI scores was highly skewed at all levels, and even in the highest severity group (at baseline HAMD > 18, N=41) a significant minority had no suicidal ideation.

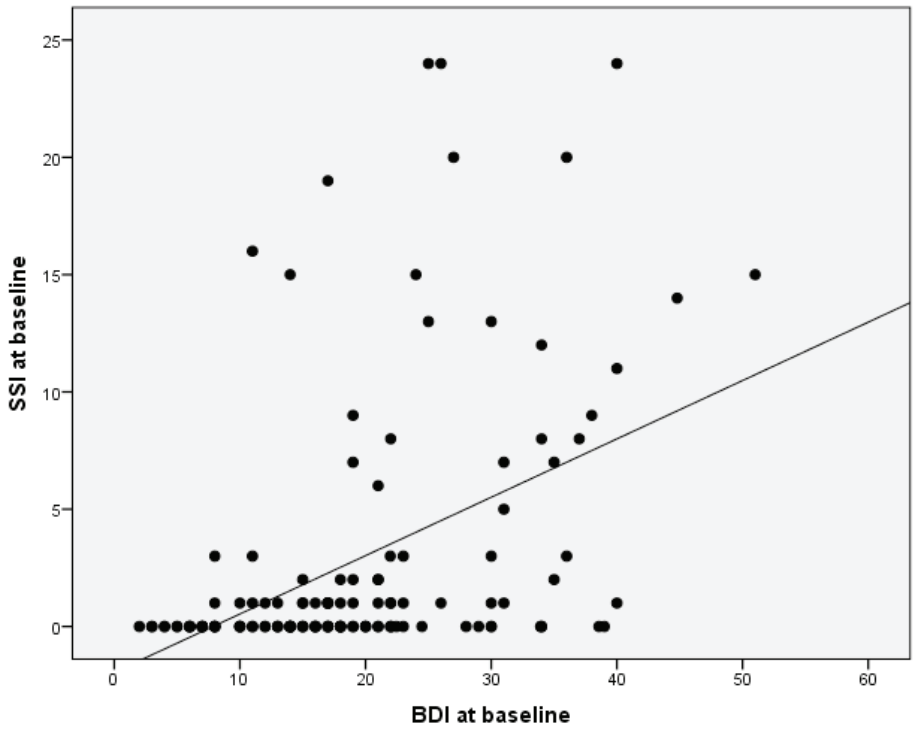


Figure 5. HAMD and SSI at study entry in the Vantaa Primary Care Depression Study (N=134).

5.3 Functional and work disability in a 5-year follow-up (Study III)

5.3.1 Functional capacity in Social, Occupational and Family Life Functioning (SOFAS, SDS) at five years

Initially, the patients followed up five years (111/137) suffered from clear functional impairment. The mean SOFAS scores were 57.2 at the study entry. The SOFAS scores improved in 68% (75/111), but declined in 28% (31/111) of patients from baseline to 5 years. In univariate regression analysis with the 5-year SOFAS score as the dependent variable, higher BDI and HS, and comorbid substance use disorders and personality disorder cluster B, and older age, less vocational education, unemployment, and having received welfare benefits, and time spent in MDEs during follow-up were associated with lower level of functioning. In multivariate regression analysis with the 5-year SOFAS score as the dependent variable, besides the baseline severity of depression (-0.384, 95% CI -0.643 – -0.126, p=0.004), also cumulative preceding time spent in MDEs when included (-0.278, 95% CI -0.380 –

-0.176, p<0.001) had an independent predictive effect on the level of functioning. In multivariate analyses, lower SDS dimensions were associated with several baseline factors. Work/school activities dimension was predicted by higher BDI (0.092, 95% CI 0.027-0.157, p=0.007), medical comorbidity (1.425, 95% CI 0.151-2.753, p=0.029), and less basic education (1.397, 95% CI 0.076-2.719, p=0.039) in patients who were employed (54/111). Social activities dimension was predicted by higher BDI (0.081, 95% CI 0.026-0.136, p=0.004), poor social support (-0.054, 95% CI -0.010 – -0.007, p=0.016), living alone (1.343, 95% CI 0.257-2.429, p=0.024) and unemployment (2.171, 95% CI 0.893-3.449, p=0.001), and most strongly by duration of depression during follow-up when included (0.054, 95% CI 0.022-0.085, p=0.001). Family life dimension was predicted by higher BDI (0.085, 95% CI 0.022-0.149, p=0.009), substance use (2.649, 95% CI 0.524-4.775, p=0.016), and unemployment (1.676, 95% CI 0.087-3.265, p=0.039) in patients married or cohabiting (57/111).

5.3.2 Employment and unemployment at five years

Depressed primary care patients at baseline and after five years (N=111), according to functional and work ability are presented in Table 5.

Table 5. Patient characteristics according to functional and work ability in the Vantaa Primary Care Depression Study over a 5-year follow-up (N=111).

	At baseline		At five years		p
	N	%	N	%	
Labour force	92	83	68	61	
Employed	70	63	54	49	0.002
On sick leave	21	19	0	0	<0.001
Unemployed	22	20	14	13	0.088
Retired	19	17	43	39	
Disability pension due to depression	10	9	21	19	0.001
Pension due to age or medical illness	9	8	22	20	0.001
Subjective work ability:					<0.001
Fully capable	20	18	58	52	<0.001
Decreased capacity	59	53	23	21	<0.001
Incapable	32	29	30	27	0.828
			Mean	SD	
Sheehan Disability Scale (SDS):					
Work/school dimension			4.0	3.3	
Social dimension			3.8	3.2	
Family life dimension			3.3	2.9	

In univariate regression analysis, younger age and female gender, lower BDI and BAI, higher SOFAS, fewer personality disorders particularly cluster B, less substance use disorders and medical comorbidity, more vocational education, and not being unemployed and not having received social assistance were associated with employment at 5 years. In multivariate logistic regression analyses, significant predictors for employment at 5 years were younger age (OR 0.887, 95% CI 0.844-0.933, p<0.001) and female gender (OR 0.235, 95% CI 0.057-0.971, p=0.045), no personality disorder (OR 3.165, 95% CI 1.069-9.373, p=0.037), and not received social assistance (OR 0.159, 95% CI 0.541-0.047, p=0.003). In addition, persons who were employed at 5-years spent less time depressed during follow-up when included in analysis (OR 0.959, 95% CI 0.932-0.986, p=0.004).

In univariate regression analysis, lower SOFAS, personality disorder cluster B, substance use disorder and received social assistance were associated with unemployment at 5 years. In multivariate logistic regression analyses, unemployment was associated with personality disorder cluster B (OR 0.084, 95% CI 0.010-0.717, p=0.024), social assistance (OR 0.100, 95% CI 0.016-0.632, p=0.014), and higher AUDIT at 5 years (OR 1.116, 95% CI 1.005-1.238, p=0.040). SOFAS and time spent depressed during follow-up did not differ between patients who were unemployed or on disability pension due to depression at five years.

5.3.3 Sickness absence and disability pension due to depression during follow-up

During follow-up, sick leave due to depression was granted to almost two-thirds (58%, 53/92) and disability pension to one-tenth (9%, 8/92) of patients belonging to the labour force at baseline. The mean number of days off work due to depression was 456 compared with 1119 days at work, comprising 29% and 71% of follow-up time, respectively. In multivariate linear analyses, the total time on sick leave was associated with medical comorbidity (0.935, 95% CI 0.197-1.674, p=0.014) and social assistance at baseline (1.111, 95%CI 0.334-1.888, p=0.006). In addition, duration of depression during follow-up was an independent predictor (0.025, 95% CI 0.007-0.042, p=0.006).

In univariate analysis, granted disability pension was associated with psychiatric comorbidity and subjective work disability. In multivariate analyses, granted disability pension was associated with subjective work disability (OR 8.439, 95% CI 1.669-42.662, p=0.010) and psychiatric comorbidity (OR 31.642, 95% CI 2.167-462.0, p=0.012). Time spent in MDEs during follow-up was not a significant predictor here, probably due to the small number of patients (8/111). However, the mean time spent in MDEs during follow-up by patients granted disability pension due to depression (before or after study entry, 21/111) was 36.6 months, whereas the corresponding figure was 16.0 months for other patients (p<0.001).

5.4 Concurrent Borderline Personality Disorder (BPD) (Study IV)

5.4.1 Prevalence of BPD among depressed primary care patients

The prevalence of concurrent BPD (26%, 35/137) decreased slightly to 19% (21/111) at five years. Of those 111 patients who participated in both baseline and 5-year interviews, 19% (20 patients) were assigned BPD diagnosis at both time-points, 8% (9 patients) only at baseline, and 1% (1) only at 5 years.

5.4.2 Differences at baseline between depressed patients with and without BPD

At baseline, depressed patients with BPD (35/137) had two-fold prevalence of co-occurring anxiety disorders (63% vs. 36%, p=0.006), previous depressive episodes (mean 4.37 SD 6.1 vs. mean 2.19 SD 2.6, p=0.006) and unemployment (31% vs. 16%, p=0.044); three-fold prevalence of co-occurring substance use disorders (29% vs. 10%, p=0.011), co-occurring suicidal ideation (mean 5.80 SD 7.3 vs. mean 1.87 SD 4.5, p=0.002) and severe economic difficulties (54% vs. 19%, p<0.001), and four-fold prevalence of preceding suicide attempts (40% vs. 9%, p<0.001) compared to depressed patients without BPD (102/137).

5.4.3 Differences in outcome between depressed patients with and without BPD

Differences in most clinical and socio-demographic features persisted from baseline to five years. At five years, depressed patients with and without BPD differed significantly according to, i.e., concurrent anxiety and substance use disorders, HAMD, BDI, BAI, SSI and SOFAS, employment and economic difficulties, and received treatment (Table 6).

Table 6. Differences between depressed primary care patients with and without BPD at five years follow-up in the Vantaa Primary Care Depression Study (N=111).

Variables	**With BPD**		**Without BPD**				
At five years	**N=29**		**N=82**				
	Mean	**SD**	**Mean**	**SD**	**OR**	**95% CI**	**p**
HAMD	15.8	9.1	9.6	6.8	8.072	4.66-11.5	<0.001
BDI	18.7	13.2	12.8	10.0	7.612	2.52-12.7	0.004
BAI	20.0	15.6	11.3	10.4	10.65	5.09-16.2	<0.001
HS	9.6	5.6	6.6	5.3	3.146	0.62-5.68	0.015
SSI	4.9	7.7	0.8	2.8	4.577	2.38-6.77	<0.001
SOFAS	57.6	16.2	66.4	15.7	-14.66	-21.5--7.84	<0.001
SOFAS[a]	57.6	16.2	66.4	15.7	-9.593	-15.8- -3.36	0.002
AUDIT	10.5	10.2	5.5	11.4	4.622	1.27-8.09	0.008
	N	**%**	**N**	**%**			
Employed[b]	12	41	42	51	18.615	3.74-92.5	0.001
Unemployed[b]	9	31	15	18	0.122	0.028-0.528	0.005
Social assistance	10	34	11	13	3.652	1.19-11.2	0.024
Social assistance[a]	10	34	11	13			0.233
MDE at 5years	12	41	11	13	0.098	0.027-0.356	<0.001
Axis I	23	79	35	43	0.174	0.058-0.525	0.002
Anxiety disorder	21	72	31	41	0.211	0.074-0.600	0.002
Substance use disorder	12	41	8	10	10.06	2.37-42.7	0.002
Treatment received during five years	**N**	**%**	**N**	**%**			
Psychosocial treatment (any)	17	59	36	44	0.32	0.108-0.915	0.034
Psychiatric care (any)	7	24	15	18			0.429
	Mean	**SD**	**Mean**	**SD**			
No of visits to PC physician	27.1	25.1	20.3	19.7	12.48	2.51-22.4	0.015
No of PC physician contacts for DD	14.6	20.1	7.4	8.3	9.41	3.61-15.2	0.002

All univariate logistic and linear regression analyses adjusted for age, gender and follow-up time.
[a] Adjusted for MDE duration.
[b] Only patients belonging to labour force at intake (N=26 with and N=66 without BPD).

In addition, during the follow-up, depressed patients with BPD spent more time depressed (mean 27.2 months SD 22.2 vs. mean 17.4 months SD 20.2; OR 15.011, 95% CI 4.78-25.2, p=0.004), achieving full remission took longer (mean 33.7 months SD 26.7 vs. mean 27.5 months SD 26.3; HR 1.829, 95% CI 1.04-3.21, p=0.035), and a higher proportion was chronically depressed throughout the whole follow-up (21% vs. 5%; OR 12.76, 95% CI 2.40-67.8, p=0.003) compared to patients without BPD. Among patients followed up at five years (N=111/137), time to full remission was 1011 days (±149) with concurrent BPD, and 826 days (±87) (p=0.050) without concurrent BPD. Outcome of depression during 5 years associated with having either concurrent BPD, other concurrent personality disorder or no personality disorder(s): duration of depression and sick leave due to depression was 27.2 and 14.2 months with BPD, 16.8 and 5.3 months with other personality disorder(s), and 17.8 and 8.1 months with no personality disorder(s) (p=0.045 and 0.007).

5.4.4 Outcome differences in BPD age groups

At the study entry, depressed primary care patients with concurrent BPD were younger (mean 37.3 SD 13.7 vs. mean 48.0 SD 12.7, p<0.001) and they experienced their first MDD younger than patients without BPD (mean 25.4 SD 12.6 vs. 38.6 SD 14.4, p <0.001). During follow-up, in subgroup analyses of depressed patients with concurrent BPD, differences emerged between older (35-69 years) and younger (20-35) patients. Older patients experienced longer duration of MDEs during follow-up (38 vs. 15 months, p=0.004), and those in the labour force at the study entry (N=92) experienced shorter time able to work during follow-up than younger patients (22.1 vs. 49.6 months, p=0.038).

6 Discussion

6.1 Methods

This is the first ever naturalistic prospective long-term study using life-chart to investigate outcome of DSM-IV MDD, suicide attempts, disability and concurrent BPD in a sample of primary care patients with DSM-IV depressive disorders. Major study strengths include a medium sized cohort of 137 patients covering the whole spectrum of depressive disorders. MDE, dysthymia, recurrent brief depression and MinD showed little stability among those who continued to manifest depression in a 15-year prospective community study: criteria for another subtype met 51% of those with MDE and 44% of those with recurrent brief depression, and in stable cases, the same subtype often occurred in combination with the development of another subtype (Angst et al., 2000). Patients presented in this study effectively represent primary care patients in the fourth biggest Finnish city, derived from a screened stratified sample of 1119 primary care patients (Vuorilehto et al., 2005). The use of Cox proportional hazards model enabled analyses of information on subjects remaining in the study for different lengths of time. In addition, logistic and linear regression models were adjusted for the duration of the follow-up time and in appropriate regression models for MDE duration, besides age and gender.

Van Weel-Baumgarten and colleagues conclude in their systematic review that there are large gaps in the available knowledge about long-term outcome of depressive disorders in primary care. They cast four recommendations for future studies: 1) Prospective evaluation of the outcome of all types of depression at least 5 years, 2) Continuous longitudinal morbidity registration with fixed criteria, 3) Naturalistic follow-up relating treatment to follow-up and 4) Quality-of-life assessment (van Weel-Baumgarten et al., 2000). This particular study fills the first three of these requirements.

6.1.1 Representativeness of the sample

The cohort is socio-demographically representative of the city of Vantaa and probably represents the Finnish urban and suburban primary health care populations well. The findings are generalizable to countries with similar health services and social security systems. Patients who dropped out of the study unlikely biased the findings, while only 2% dropped out from all follow-ups and a large proportion (82%) underwent a face-to-face semi-structured interview at 5 years. Multivariate models were used to assess independent predictors and to control for confounding factors. The findings were robust, coherent, consistent, statistically highly significant, meaningful, and in accordance with literature in general. Naturalistic prevalence-

based sampling accurately reflects the actual workload in primary health care, while including all patients with depressive disorders despite recognition of depression by general practitioners or reason of the visit.

6.1.2 Instruments

The patients were interviewed with SCID-I/P and SCID-II, to assess all axis I and II DSM-IV disorders. The reliability for depressive disorders was excellent. Medical comorbidity was evaluated by semi-structured face-to-face interview, with self-report questionnaire and all available medical records. Psychiatrists accomplished all interviews and evaluations (at baseline Vuorilehto and at five years Riihimäki).

A broad range of potential risk and protective factors from several domains were investigated, including psychosocial and socio-economic factors. Multiple aspects of functioning, including a global estimate of level of functioning (SOFAS), information on occupational status, absence from work (sick leave or disability pension) due to illness or unemployment, and self-estimated functioning at work, family and other social activities (SDS subscales) were assessed.

6.1.3 Life-chart methodology

The outcome of depression was investigated by using a graphic life-chart, which offered an opportunity to assess temporal course of the illness, with predictors for remission and recurrences as well as frequency of recurrences. Life-chart was used to identify different levels of depression, variations in the incidence of suicide attempts during different levels of depression and substance use, durations of sickness absence, and timing of disability pensions during the 5-year follow-up.

Life-chart is similar but not identical to the Longitudinal Interval Follow-up Evaluation (LIFE) methodology used in Collaborative Depression Study by the National Institute of Mental Health (NIMH-CDS) (Keller et al., 1992; Melartin et al., 2004; Holma et al., 2008; Vuorilehto et al., 2009). Unlike the LIFE, it classifies patients´ follow-up time into periods compatible with DSM-IV: MDEs, partial and full remissions.

6.1.4 Study limitations

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 depressive disorders and their treatment is unlikely to differ between Finland and other European Union countries (Pirkola et al., 2005; Hämäläinen et al., 2008: Hämäläinen et al., 2009).

Second, besides municipal health centres, primary health care in Finland is also provided in occupational health care services, which are not included in this study. Most Finns belonging to the labour force can access this alternative route to primary health care. Within study cohort, however, employment status at baseline did not predict outcome of MDD.

Third, since prevalence is a product of incidence and duration of illness, cross-sectional sampling based on screening of current depressive symptoms always enriches chronicity, compared with sampling patients from the onset of illness. However, prevalence-based sampling accurately reflects actual patients in primary care and the workload of primary care physicians.

Fourth, although there was access to all patient records, the 3.5 years between the last two interviews likely caused some degree of retrospective recall bias. This could be expected to be most pronounced in time periods most distant from the interviews. However, the shapes of, for instance, the Kaplan-Meyer curves for attainment of remission, recurrence or other similar time-related outcomes were fairly regular, suggesting no significant bias. The exact timing and duration of sick leaves and disability pensions could be found from records. Similarly, there is no unexplained year-to-year variation in substance abuse during the follow-up, again consistent with, but not guaranteeing, an absence of significant bias. Nevertheless, timing of periods of substance abuse is unavoidably crude, and the findings must therefore be interpreted with caution.

Fifth, with using life-chart only the average risk for time spent in risk states (MDE, partial remission, full remission) could be investigated. The risk for suicide attempts likely varies markedly with variations in levels of hopelessness, depression, and possibly anxiety, none of which could be measured on a daily basis. Crudely categorizing depression into these three alternative states grossly underestimates the true variation. Despite this, the order of magnitude of variations in incidence of suicide attempts between the three states is remarkable.

Sixth, effort after meaning could affect the timing of suicide attempts as well as MDEs and substance abuse episodes, with patients attributing their attempts to these disorders and emphasizing their co-occurrence. This bias was attempted to be avoided by investigating the timings separately, but the success cannot be guaranteed. However, intensity of suicidal ideation had similar association with severity of depression at all the three cross-sectional time-points as that of suicide attempts. Thus, a very consistent association was found between severity of depression and presence of suicidal behaviour.

Seventh, the cohort size was moderate but the proportion of patients who attempted suicide was small and the number of discrete attempts was low. The proportion of granted disability pension was also small. Thus, in some of our analyses a risk for both type II errors and spurious findings exists. However, the

findings related to suicide attempts and suicidal ideation measured from all patients were quite consistent and in accordance with literature on suicidal behaviour in mood disorders in general (Malone et al., 1995; Sokero et al., 2003; Mann et al., 2005; Oquedo et al., 2006; Holma et al., 2010). Also the main findings concerning disability were quite consistent, statistically highly significant, and in accordance with the literature (Broadhead et al., 1990; Simon et al., 2000; Sorvaniemi et al., 2003; Sorvaniemi et al., 2003; Elinson et al., 2004; Rytsälä et al., 2005; Rytsälä et al., 2006; Rytsälä et al., 2007; Bültmann et al., 2008; Ahola et al., 2009; Lagerveld et al., 2010; Ahola et al., 2011; Holma et al., 2012).

Eighth, because of the naturalistic nature of this 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. However, the study represents realistic and generalizable risk estimates under usual treatment conditions.

Ninth, cognitive capacity, motivation, and occupational circumstances were not investigated, which could be of importance, particularly for work disability.

Tenth, despite excellent reliability of diagnosing depression (Vuorilehto et al., 2005), diagnostic reliability of BPD was not measured.

Finally, in this study the patients with concurrent BPD were about ten years older than patients in secondary and tertiary health care studies among BPD patients (Gunderson et al., 2011; Zanarini et al., 2009), which is important to notice when making comparisons.

6.2 Long-term outcome of MDD in primary care (Study I)

This longitudinal study revealed the far from optimal prognosis of MDD in primary care. The process of recovery appeared often slow. Only slightly more than one-half of the patients had achieved full remission by 5 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 (Oldehinkel et al., 2000; van Weel-Baumgarten 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 and Murray, 1988; Keller et al., 1992; Angst and Preisig, 1995; Kennedy et al., 2003; Kennedy et al., 2004; Melartin et al., 2004; Holma et al., 2008). Finally, large proportions of patients with only partial remission and chronic course emerged, which is in accordance with earlier studies both in primary care and in the general population

and secondary care (Kiloh et al., 1988; Lee and Murray, 1988; Keller et al., 1992; Ormel et al., 1993; Angst and Preisig, 1995; Kennedy et al., 2003; Kennedy et al., 2004; Melartin et al., 2004; Pirkola et al., 2005; Eaton et al., 2008; Furukawa et al., 2008; Holma et al., 2008; Rhebergen et al., 2009). Considering the initially mild to moderate severity of depression, the chronicity is remarkable, and needs to be taken into account when developing treatment and monitoring for patients in primary health care.

The main predictor of poor outcome assessed by the time to remission was the initial severity of depression. Depression severity has also been a major predictor of outcome in general population and psychiatric care studies (Kiloh et al., 1988; Lee and Murray, 1988; Keller et al., 1992; Ormel et al., 1993; Angst and Preisig, 1995; Kennedy et al., 2003; Kennedy et al., 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 monitoring outcome, severity of depression in this study could be assessed with BDI as well as with HAMD in patients with MDD. BDI or comparable self-report 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, evaluating initial severity, monitoring treatment response, plus evaluating residual symptoms and prodromes of relapses and recurrences (NICE, 2010).

Comorbidity was also found to play a major role in predicting outcome of MDD. The small proportion of patients with comorbid substance use disorder (1/6) had a particular chronic course of illness. Some general population (Johnson et al., 2005; Mattisson et al., 2009) and many psychiatric care studies have found comorbidity to be associated with outcome (Keller et al., 1983; Paykel et al., 1995; Alnaes and Torgersen, 1997; Mueller et al., 1999; Melartin et al., 2004; Farabaugh et al., 2005; Viinamäki et al., 2006; 8; Coryell et al., 2012). Recurrences were also predicted by comorbid psychiatric disorders, such as GAD and somatoform and personality disorders, however, not by the very heterogeneous group of chronic somatic illness. The role of somatoform disorders has not been recognized earlier, although it is as common as MDD at population level (Wittchen et al., 2011) and 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 psychiatric care. This study included structured diagnostic evaluation of comorbidity and life-chart methodology, thus providing a more accurate view of outcome than in previous studies.

Overall, both the severity of depression and axis I and II disorders were found to effectively predict outcome of MDD in primary care.

6.3 Long-term risk factors of suicide attempts during the prospective follow-up among primary care patients with depressive disorders (Study II)

Depressive disorders are known risk factors for suicide attempts (Beautrais, 2001). Nonetheless, the significance of depressive disorders has not been prospectively investigated earlier in primary care. In this study, suicide attempts emerged almost exclusively during MDEs, very seldom during partial remission, and never during full remission. This is concordant with psychiatric care studies (Sokero et al., 2005; Holma et al., 2010). In this study, the incidence of suicide attempts during MDEs was one-third of that in psychiatric care patients with MDD (Oquendo et al., 2004; Holma et al., 2010) or bipolar disorder (Valtonen et al., 2008). In addition, suicidal ideation was associated with clinically significant depression. Depressive mood has been found to be necessary for the occurrence of suicidal ideation (Hintikka et al., 2009). In psychiatric care, suicidal ideation tends to vanish when patients are no longer fulfilling the criteria of MDE (Sokero et al., 2006). Taken together, the risk of suicide attempts among patients with depressive disorders appears lower in primary care than in psychiatric care, and emerges almost exclusively during MDEs.

This study, as the first among patients with depressive disorders in primary care, investigated variations in the incidence of suicide attempts even during different levels of substance use. The incidence of suicide attempts was found to be over sevenfold during periods of substance abuse or dependence vs. abuse or dependence free periods. Though this risk was strongly associated with the presence of concurrent MDE. Patients did not attempt suicide during substance abuse or dependence periods without significant depression. Albeit baseline substance abuse strongly predicted suicide attempts, substance abuse did not reach significance in the Cox multivariate model accounting covariation with MDEs. This may represent a type II error, while the amount of patients with substance abuse and suicide attempts was scarce. In addition to alcohol dependence or abuse, substance abuse included mainly abuse of analgesics or benzodiazepines by medical prescription. These findings are in concordance with psychological autopsy studies regarding completed suicides (Cavanagh et al., 2003).

In multivariate logistic regression analyses, current substance abuse and previous suicide attempts were the only significant predictors of future suicide attempts. Nevertheless, concurrent MDEs in models accounting for time-varying risk factors remained as the only significant independent risk factor among many different risk factors evaluated in this study. There might be several reasons to that. Statistical power may be limited in some analysis. In addition, risk factors likely mediate the influence of each other. Factors like personality disorders and socio-demographic characteristics, which have been found to predict suicide attempts,

predispose to depression and substance abuse (Sokero et al., 2005; Vuorilehto et al., 2006; Holma et al., 2010). Many separate risk factors are associated with suicide attempts, but their effects unlikely exceed MDEs or substance abuse.

Patients seldom told about occurred suicide attempts to general practitioners, concordant with findings from primary care (Vuorilehto et al., 2006), and, regarding to bipolar patients, from psychiatric care (Valtonen et al., 2008). In addition, psychological autopsy studies have documented lack of communication of suicide intent to be more the rule than the exception particularly in primary care (Isometsä et al., 1995).

Overall, a significant minority of patients with depressive disorders in primary care will attempt suicide. Risk of suicide attempts seems almost exclusively to combine with MDEs, with or without concurrent substance abuse. General practitioners are seldom aware of the suicidal ideation or attempts of their patients.

6.4 Long-term risk factors of functional and work disability among primary care patients with depressive disorders (Study III)

Risk factors for sick leave and disability pension among patients with depressive disorders have been investigated mostly in psychiatric, general population and occupational settings. In primary health care, very few studies have investigated risk factors for disability among depressive patients (Nieuwenhuijsen et al., 2006; Vuorilehto et al., 2007; Lerner and Henke, 2008; Lagerveld et al., 2010).

In this follow-up study, primary care patients with depressive disorders suffered from variable, on average moderate, functional impairment still after 5 years. Even most of the recovered patients continued to have some minor impairment; thus, recovery does not necessarily fully normalize functional capacity (Lerner and Henke, 2008). Nevertheless, preceding duration and/or current severity of depression were the most powerful predictors of all aspects of functional status, as hypothesized. In addition, impairment at work was predicted by medical comorbidity and poor education, and impairment in family life by unemployment. Our findings confirm the presence of major functional impairment among primary care patients with depressive disorders (Ormel et al., 1999; Wells and Sherbourne, 1999; McMahon et al., 2012) also in the long term, but the scarcity of previous longitudinal studies renders comparison of predictors difficult. In the earlier cross-sectional report of this sample, the level of functioning in primary care patients did not differ from that in psychiatric outpatients (Vuorilehto et al., 2007), concordant with a study of different health care systems finding no significant differences in functioning (Stewart et al., 1993). Findings in this study, concerning the important role of severity and duration

of depression, are consistent with Finnish psychiatric care studies (Rytsälä et al., 2005; Holma et al., 2012). While socio-economic factors and comorbidity were of some importance, as hypothesized, the role of depression was crucial in all aspects of functioning.

The proportion of patients belonging to the labour force decreased by one-fifth during the follow-up of five years. Unemployment rate at study entry was 20%, twofold that of the city of Vantaa (9%). According to the occupational status at five years, the baseline characteristics of the patients also differed markedly. Employed patients functioned best already at study entry. Being employed at five years was predicted by less severe and shorter depression, less comorbidity, and less financial difficulties, concordant with previous findings in primary care (Simon et al., 2000) and occupational (Lagerveld et al., 2010) settings. In contrast, the unemployed had spent three times more time in MDEs during the follow-up, had more often cluster B personality disorders, and more often used social assistance already before study intake; they differed from patients on disability pension due to depression only by being younger and having more psychiatric but less somatic comorbidity. However, despite the statistical significance of the findings, they must be interpreted with caution due to the small number of unemployed patients. The important role of depression in unemployment is consistent with general population and employee studies (Elinson et al., 2004; Lerner et al., 2004; Honkonen et al., 2007). Overall, unemployed primary care patients with depressive disorders may suffer from multiple types of psychiatric and social problems, which may necessitate comprehensive rehabilitation efforts besides the usual treatments for depression.

Primary care patients with depressive disorders who belonged to the labour force at baseline spent one-third of the total follow-up off work due to depression. Sick leave was granted to two-thirds of patients, which is as much as in psychiatric care among patients with DSM-III-R MDD (Sorvaniemi et al., 2003) and twice the proportion granted to subjects with MDD or dysthymia in the Finnish general population (Ahola et al., 2009). Sick leave was associated with the duration of depression, chronic somatic illness and social assistance. The role of depression was concordant with findings from psychiatric care (Rytsälä et al., 2007). Before and after the study entry, disability pension was granted to altogether every fifth patient, which is almost as high a proportion as found in psychiatric care in Vantaa (Holma et al., 2012). In Finland, a specialist's certificate is needed for a disability pension; thus, a psychiatrist had evaluated all these patients. New disability pensions were associated with time spent depressed, psychiatric comorbidity, and subjective work disability. These findings are consistent with psychiatric care (Isometsä et al., 2000; Sorvaniemi et al., 2003; Holma et al., 2012) and occupational (Bültmann et al., 2008) and general population studies (Broadhead et al., 1990; Karpansalo et al., 2005; Ahola et al., 2009). Overall, risk of disability among patients with depressive disorders appears most strongly confined to MDEs.

This study highlights some important aspects of functional and work disability in primary health care patients with depressive disorders. While numerous factors influence functioning or disability to some extent, it is unlikely that their effect exceeds that of the presence of MDEs. This is consistent with a recent systematic review of factors associated with work functioning and participation by depressed workers, finding strong evidence only for a long duration of MDE (Lagerveld et al., 2010). MDD patients with greater clinical improvement are more likely to maintain paid employment and report fewer days missed from work due to illness (Simon et al., 2000), and productivity gains following effective depression treatment may far exceed treatment costs (Simon et al., 2001). Lack of evidence of an effect of interventions on sickness absence of depressed workers (Nieuwenhuijsen et al., 2008) may derive from underuse of optimal treatments (Isometsä et al., 2000; Vos et al., 2004; Honkonen et al., 2007; Beck et al., 2011; Ebrahim et al., 2012). Thus, improvement of treatment strategies is required (Katon, 2009; Rost, 2009).

Overall, primary care patients with depressive disorders suffer from multiple functional and work-related long-term impairments, for which duration of MDEs appears decisive. Patients spent one-third of the follow-up off work due to depression, and remaining outside the labour force was a common adverse outcome. Psychiatric and somatic comorbidities, education and socio-economic means influence the level of functioning and ability to work, but are not equally important for all areas of life.

6.5 Long-term associations between depressive disorders and borderline personality disorder (BPD) in primary care (Study IV)

In this long-term follow-up study on depressive disorders in primary care, one-fourth suffered from BPD at the beginning of the study compared to one-fifth of patients at the end. Although such prevalence rates has provoked discussion about possible overdiagnosis (Gross et al., 2002) and underdiagnosis (Zimmerman and Mattia, 1999; Paris, 2007), it is in concordance with previous scarce knowledge from primary care (Patience et al., 1995). The outcome of concurrent BPD was strongly related with the course of depression, concordant with previous findings in primary care (Newton-Howes et al., 2006). Similar prevalence of BPD is found among MDD patients in psychiatric care (Melartin et al., 2002), but reduction in the frequency of BPD there was smaller than seen in studies based basically on BPD patients (Grilo et al., 2000; Gunderson et al., 2011).

Concurrent BPD clearly influenced the course and outcome of depression among primary care patients with depressive disorders. Consistently throughout the five years, patients with concurrent BPD were more chronically and subjectively severely depressed. The rate of full remissions was reduced, and both time to full remission and time spent in MDE during follow-up were longer, concordant with studies from psychiatric care (Rytsälä et al., 2005; Holma et al., 2012).

Patients with concurrent BPD in this study were about ten years younger than patients without BPD, which needs to taken into account in comparisons. Among patients with concurrent BPD, depression had emerged at earlier age. Early onset of depressive disorders was an independent predictor for BPD (Ramklint and Ekselius, 2003). Although early age of onset of MDD is predictive of BPD, BPD is not a universal feature of early-onset MDD (Rothschild and Zimmerman, 2002). Comorbid BPD patients in this study were about ten years older than BPD patients studied in psychiatric health care (Gunderson et al., 2011). In a 27-year follow-up, patients with BPD continue to improve in later middle-age (Paris and Zweig-Frank, 2001). The outcome among older patients in this study was more adverse in terms of depression, anxiety and disability.

Depressed primary care patients with concurrent BPD suffered markedly more often from anxiety and substance use disorders, concordant with psychiatric care studies (Zanarini et al., 1998; Joyce et al., 2003; Skodol et al., 2005). Concurrent BPD was a strong predictor for suicide attempts and for adverse occupational and socio-economic outcomes. Those included lower level of social functioning, more unemployment, longer duration of sickness absence from work due to depression, and more severe economic difficulties in terms of more need of social assistance (Gross et al., 2002), compared to depressed patients without concurrent BPD or to depressed patients with other personality disorders (Zanarini et al., 2012).

Depressed patients with BPD had more hospitalizations, psychiatric contacts and visits to primary care than patients without BPD. Despite this, their outcome was worse. None of them had an official clinical diagnosis of BPD in primary care, nor targeted treatment for it. BPD has remained largely unrecognized and untreated in primary care (Gross et al., 2002) despite the greater number of visits there (Hueston et al., 1999).

Overall, concurrent BPD among primary care patients with depressive disorders is remarkably common, complicates the outcome of depressive disorders, strongly influences suicidal behaviour and ability to work, and is still mostly unrecognized and untreated.

7 Conclusions and future implications

7.1 Conclusions

The long-term outcome of major depressive disorder (MDD) among primary health care patients seems to be rather chronic and episodic, with often slow and incomplete recovery. Patients spent one-third of the 5-year follow-up time in MDEs and only 42% in full remission. Almost all patients reached partial remission. Nevertheless, one-half experienced at least one recurrence within five years, and one-tenth remained chronically in MDEs. Baseline severity of depression and substance use comorbidity predicted time spent in MDEs, personality disorders predicted recurrences. Generalized anxiety disorder and somatoform disorder predicted shorter time from remission to recurrence.

Among primary care patients with depressive disorders, there were no completed suicides in five years, but one-tenth attempted suicide one to three times. The incidence rate of suicide attempts varied robustly depending on the level of depression, emerging almost exclusively during MDEs, more often than not with concurrent active substance abuse. Duration of MDEs predicted most strongly the long-term risk for suicide attempts. A history of suicide attempts and substance use disorder also indicated the risk. The patients rarely told about their attempts to their primary care physicians.

Depressed primary care patients who belonged to the labour force at baseline spent one-third of the follow-up off work due to depression; two-thirds were granted sick leaves, and one-tenth a disability pension due to depression. Especially more time spent depressed, and also more severe depression at baseline, predicted functional impairment and work disability. In addition, comorbid disorders and having received social assistance predicted dropping out from work.

Among primary care patients with depressive disorders, the proportion of concurrent borderline personality disorder (BPD) decreased from one-fourth to one-fifth in five years. Comorbid anxiety and substance use disorders were common among patients with depressive disorders and BPD. Concurrent BPD increased the severity and duration of depression, suicidal behaviour, unemployment and economic difficulties.

7.2 Clinical and research implications

In primary care, depressive disorders tend to be chronic and recurrent, medical and psychiatric comorbidities are more a rule than an exception, and the first reason for a visit is often other than ongoing depression. In a primary care setting, the patients eventually decide the need for appointments and their frequency more

than physicians. In today's primary care praxis, the time available to use for one appointment and the frequency of appointments are often limited and far from optimal, although active monitoring is an essential part of depression guidelines. Applicable strategies to manage depressive disorders in primary care are needed.

For predicting outcome of depressive disorders among primary care patients, severity of depression could be assessed with BDI at least as well as with HAMD. BDI as a self-report questionnaire is easy to incorporate into routine clinical practice even in primary care to improve recognition, evaluation of initial severity, monitoring treatment response, plus evaluation of residual symptoms and prodromes of relapses and recurrences (NICE, 2010).

In addition to the features of depression, psychiatric and somatic comorbidity also predicts the outcome of depressive disorders. The role of somatoform disorders has not been recognized earlier, although presenting exclusively physical problems is common in primary care. Special attention should be paid to substance use, including non-medical use of prescription medication, which appears to have increased in the past 20 years (Compton and Volkow, 2006, Schepis and McCabe, 2012).

Because most patients with depressive disorders are encountered in primary care and because depression is present in up to two-thirds of suicides, identifying and treating depressive disorders is essential in suicide prevention. Among primary care patients with depressive disorders, the focus should be on a continuation and maintenance treatment of depression, treatment of comorbid substance use disorders, and improved recognition of suicidal behaviour. Health care personnel should ensure that the information about suicidal behaviour is passed to all treatment units taking care of the patient. In order to reduce suicide attempts and completed suicides, one focus should lay on a means to systematically evaluate suicidal thoughts, plans and acts in routine clinical practice in primary care, and to develop interventions and more continuous management with psychiatric care.

The duration of depression most effectively deteriorates functioning among primary care patients with depressive disorders. Disability assessment measures may be useful in routine screening and monitoring (Katon, 2009). Practical disability risk management in primary care includes both early recognition and continuation plus maintenance treatments of depression in order to prevent relapses and recurrences (NICE, 2010; Cuijpers et al., 2012). However, the overall complexity of factors influencing functioning must also be recognized. Comorbid psychiatric and medical disorders as well as socio-economic factors, all contributing to various aspects of disability, represent challenges for treatment and rehabilitation.

Comorbidity is common among depressive primary care patients. Concurrent BPD complicates the outcome of depression, including high rates of suicidal ideation and impaired functioning. Treatment guidelines made for separate disorders do not consider comorbidity enough, and depression of BPD patients is not always noticed in care. Treatment guidelines about psychiatric illness and future research should pay more attention to comorbidity and to circumstances in a primary care setting.

Structured appointments, use of self-report scales such as BDI and AUDIT, and active continuous and maintenance treatments could be useful in primary care, as well as flexible collaboration and consultation between primary care and psychiatric care. While most depressive patients with and without comorbidities are encountered in primary care, gains could easily exceed costs if future research could develop more effective treatment models.

Future research should take into account that MDD encountered in primary care is often recurrent or a chronic and comorbid disorder. Because the initial severity of depression appeared the most significant predictor of outcome of MDD, easy and reliable measurement instruments suitable even to general practice are warranted. Regarding future research, this study suggests focusing more on natural cohorts seen in real world praxis with all their comorbidities and circumstances as well as associated disability. Efforts to develop recognition of comorbid substance abuse are warranted. Life-chart methodology appears useful in follow-up studies even in a primary care setting. It reveals knowledge that otherwise may remain hidden. Attention should be paid to defining even more risk factors and their interactions. Concerning suicide prevention strategies, future research should concentrate even more on the duration of MDE and factors affecting it. It remains to future prospective studies to evaluate the significance of concurrent MDE and substance abuse to suicidal acts. Other comorbidities and factors other than illness related also need to be taken into account. In addition, efforts to develop recognition of suicidal ideation and suicide attempts are warranted. Depressive disorders in primary care comprise a heterogeneous group with multifarious treatment needs. More research should be conducted on received treatment from naturalistic follow-up studies, as well as on development and evaluation of interventions appropriate to primary care. The most apparent focus for future research is to develop the continuity of care. Besides treatment strategies and their separate components, implementation in the clinical primary care praxis and management of depression care through all levels of the treatment totality should also be evaluated.

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References

Ahola K, Virtanen M, Honkonen T, Isometsä E, Aromaa A, Lönnqvist J (2011). Common mental disorders and subsequent work disability: a population-based Health 2000 Study. Journal of Affective Disorders 134, 365-372.

Ahola K, Virtanen M, Honkonen T, Isometsä E, Aromaa A, Lönnqvist J (2009). Compensated sickness absence in relation to depressive disorders – Results from the Finnish Health 2000 Study (Sairauspoissaolot masennushäiriöiden yhteydessä: Terveys 2000 -väestötutkimuksen tuloksia). Finnish Medical Journal 64, 3081-3088.

Alexopoulos GS, Arean P (2014). A model for streamlining psychotherapy in the RDoC era: the example of 'Engage'. Molecular Psychiatry 19, 14-19.

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

Alonso J, Vilagut G, Chatterji S, Heeringa S, Schoenbaum M, Bedirhan Ustun T, Rojas-Farreras S, Angermeyer M, Bromet E, Bruffaerts R, de Girolamo G, Gureje O, Haro JM, Karam AN, Kovess V, Levinson D, Liu Z, Medina-Mora ME, Ormel J, Posada-Villa J, Uda H, Kessler RC (2011). Including information about comorbidity in estimates of disease burden: results from the World Health Organization World Mental Health Surveys. Psychological Medicine 41, 873-886.

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR. Text revision. 4th ed.

American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders DSM-5. 5th ed.

Anderson L, Lewis G, Araya R, Elgie R, Harrison G, Proudfoot J, Schmidt U, Sharp D, Weightman A, Williams C (2005). Self-help books for depression: how can practitioners and patients make the right choice? The British Journal of General Practice: The Journal of the Royal College of General Practitioners 55, 387-392.

Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl RV, De Graaf R, Vollebergh W, Dragomirecka E, Kohn R, Keller M, Kessler RC, Kawakami N, Kilic C, Offord D, Ustun TB, Wittchen HU (2003). The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. International Journal of Methods in Psychiatric Research 12, 3-21.

Andrews G, Slade T, Peters L (1999). Classification in psychiatry: ICD-10 versus DSM-IV. The British Journal of Psychiatry: The Journal of Mental Science 174, 3-5.

Angst J, Angst F, Gerber-Werder R, Gamma A (2005). Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Archives of Suicide Research : Official Journal of the International Academy for Suicide Research 9, 279-300.

Angst J, Felder W, Frey R, Stassen HH (1978). The course of affective disorders. I. Change of diagnosis of monopolar, unipolar, and bipolar illness. Archiv Fur Psychiatrie Und Nervenkrankheiten 226, 57-64.

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 (Zurich, Switzerland: 1985) 146, 5-16.

Angst J, Sellaro R, Merikangas KR (2000). Depressive spectrum diagnoses. Comprehensive Psychiatry 41, 39-47.

Ansell EB, Sanislow CA, McGlashan TH, Grilo CM (2007). Psychosocial impairment and treatment utilization by patients with borderline personality disorder, other personality disorders, mood and anxiety disorders, and a healthy comparison group. Comprehensive Psychiatry 48, 329-336.

Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, Kerse N, Macgillivray S (2009). Antidepressants versus placebo for depression in primary care. The Cochrane Database of Systematic Reviews (3):CD007954. doi, CD007954.

Arroll B, Macgillivray S, Ogston S, Reid I, Sullivan F, Williams B, Crombie I (2005). Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. Annals of Family Medicine 3, 449-456.

Arroll B, Moir F (2010). Time for a rethink of treatment for patients with depression in primary care. The British Journal of General Practice: The Journal of the Royal

College of General Practitioners 60, 641-642.

Arsenault-Lapierre G, Kim C, Turecki G (2004). Psychiatric diagnoses in 3275 suicides: a meta-analysis. BMC Psychiatry 4, 37.

Beautrais AL (2001). Suicides and serious suicide attempts: two populations or one? Psychological Medicine 31, 837-845.

Beck A (1979). Cognitive Therapy of Depression.

Beck A, Crain AL, Solberg LI, Unutzer J, Glasgow RE, Maciosek MV, Whitebird R (2011). Severity of depression and magnitude of productivity loss. Annals of Family Medicine 9, 305-311.

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

Birnbaum HG, Kessler RC, Kelley D, Ben-Hamadi R, Joish VN, Greenberg PE (2010). Employer burden of mild, moderate, and severe major depressive disorder: mental health services utilization and costs, and work performance. Depression and Anxiety 27, 78-89.

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.

Bohnert KM, Pfeiffer PN, Szymanski BR, McCarthy JF (2013). Continuation of care following an initial primary care visit with a mental health diagnosis: differences by receipt of VHA Primary Care-Mental Health Integration services. General Hospital Psychiatry 35, 66-70.

Bostwick JM, Pankratz VS (2000). Affective disorders and suicide risk: a reexamination. The American Journal of Psychiatry 157, 1925-1932.

Bostwick JM, Rackley S (2012). Addressing suicidality in primary care settings. Current Psychiatry Reports 14, 353-359.

Bower P, Gilbody S, Richards D, Fletcher J, Sutton A (2006). Collaborative care for depression in primary care. Making sense of a complex intervention: systematic review and meta-regression. The British Journal of Psychiatry : The Journal of Mental Science 189, 484-493.

Broadhead WE, Blazer DG, George LK, Tse CK (1990). Depression, disability days, and days lost from work in a prospective epidemiologic survey. JAMA: The Journal of the American Medical Association 264, 2524-2528.

Brody DS, Dietrich AJ, deGruy F,3rd, Kroenke K (2000). The depression in primary care tool kit. International Journal of Psychiatry in Medicine 30, 99-110.

Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, de Graaf R, Demyttenaere K, Hu C, Iwata N, Karam AN, Kaur J, Kostyuchenko S, Lepine JP, Levinson D, Matschinger H, Mora ME, Browne MO, Posada-Villa J, Viana MC, Williams DR, Kessler RC (2011). Cross-national epidemiology of DSM-IV major depressive episode. BMC Medicine 9, 90-7015-9-90.

Bruce ML, Ten Have TR, Reynolds CF,3rd, Katz II, Schulberg HC, Mulsant BH, Brown GK, McAvay GJ, Pearson JL, Alexopoulos GS (2004). Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. JAMA: The Journal of the American Medical Association 291, 1081-1091.

Bültmann U, Christensen KB, Burr H, Lund T, Rugulies R (2008). Severe depressive symptoms as predictor of disability pension: a 10-year follow-up study in Denmark. European Journal of Public Health 18, 232-234.

Cape J, Whittington C, Buszewicz M, Wallace P, Underwood L (2010). Brief psychological therapies for anxiety and depression in primary care: meta-analysis and meta-regression. BMC Medicine 8, 38-7015-8-38.

Casacalenda N, Perry JC, Looper K (2002). Remission in major depressive disorder: a comparison of pharmacotherapy, psychotherapy, and control conditions. The American Journal of Psychiatry 159, 1354-1360.

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, ODIN Group (2004). Personality disorder, depression and functioning: results from the ODIN study. Journal of Affective Disorders 82, 277-283.

Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE (2010). Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. The

American Journal of Psychiatry 167, 509-527.

Castren E (2013). Neuronal network plasticity and recovery from depression. JAMA Psychiatry 70, 983-989.

Cavanagh JT, Carson AJ, Sharpe M, Lawrie SM (2003). Psychological autopsy studies of suicide: a systematic review. Psychological Medicine 33, 395-405.

Chen J, Li X, McGue M (2012). Interacting effect of BDNF Val66Met polymorphism and stressful life events on adolescent depression. Genes, Brain, and Behavior.

Clark DA, Beck AT (2010). Cognitive theory and therapy of anxiety and depression: convergence with neurobiological findings. Trends in Cognitive Sciences 14, 418-424.

Colman I, Naicker K, Zeng Y, Ataullahjan A, Senthilselvan A, Patten SB (2011). Predictors of long-term prognosis of depression. CMAJ : Canadian Medical Association Journal = Journal De L'Association Medicale Canadienne 183, 1969-1976.

Compton WM, Volkow ND (2006). Abuse of prescription drugs and the risk of addiction. Drug and Alcohol Dependence 83 Suppl 1, S4-7.

Coryell W, Fiedorowicz JG, Solomon D, Leon AC, Rice JP, Keller MB (2012). Effects of anxiety on the long-term course of depressive disorders. The British Journal of Psychiatry: The Journal of Mental Science 200, 210-215.

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

Cross-Disorder Group of the Psychiatric Genomics Consortium, Smoller JW, Craddock N, Kendler K, Lee PH, Neale BM, Nurnberger JI, Ripke S, Santangelo S, Sullivan PF (2013). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381, 1371-1379.

Cuijpers P (2011). Prevention of depressive disorders: towards a further reduction of the disease burden of mental disorders. Early Intervention in Psychiatry 5, 179-180.

Cuijpers P, Reynolds CF,3rd, Donker T, Li J, Andersson G, Beekman A (2012). Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. Depression and Anxiety 29, 855-864.

Cuijpers P, van Straten A, Smit F, Mihalopoulos C, Beekman A (2008). Preventing the onset of depressive disorders: a meta-analytic review of psychological interventions. The American Journal of Psychiatry 165, 1272-1280.

Cuijpers P, van Straten A, van Schaik A, Andersson G (2009). Psychological treatment of depression in primary care: a meta-analysis. The British Journal of General Practice: The Journal of the Royal College of General Practitioners 59, e51-60.

Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW (2013). Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. The British Journal of Psychiatry: The Journal of Mental Science 202, 22-27.

Danese A, McEwen BS (2012). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiology & Behavior 106, 29-39.

De Almeida Fleck MP, Simon G, Herrman H, Bushnell D, Martin M, Patrick D, Longitudinal Investigation of Depression Outcomes Group (2005). Major depression and its correlates in primary care settings in six countries. 9-month follow-up study. The British Journal of Psychiatry : The Journal of Mental Science 186, 41-47.

Depressio (2009, updated 11.10.2013). Finnish Depression Current Care Guidelines (Käypä hoito -suositus). Suomalaisen Lääkäriseuran Duodecimin ja Suomen Psykiatriyhdistys ry:n asettama työryhmä.

DeRubeis RJ, Siegle GJ, Hollon SD (2008). Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. Nature Reviews. Neuroscience 9, 788-796.

Disner SG, Beevers CG, Haigh EA, Beck AT (2011). Neural mechanisms of the cognitive model of depression. Nature Reviews.Neuroscience 12, 467-477.

Dowrick C, Shiels C, Page H, Ayuso-Mateos JL, Casey P, Dalgard OS, Dunn G, Lehtinen V, Salmon P, Whitehead M (2011). Predicting long-term recovery from depression in community settings in Western Europe: evidence from ODIN. Social Psychiatry and Psychiatric Epidemiology 46, 119-126.

Druss BG, Rosenheck RA, Sledge WH (2000). Health and disability costs of depressive illness in a major U.S. corporation. The American Journal of Psychiatry 157, 1274-1278.

Duggan CF, Sham P, Lee AS, Murray RM (1991). Can future suicidal behaviour in depressed patients be predicted? Journal of Affective Disorders 22, 111-118.

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.

Ebrahim S, Montoya L, Truong W, Hsu S, Kamal El Din M, Carrasco-Labra A, Busse JW, Walter SD, Heels-Ansdell D, Couban R, Patelis-Siotis I, Bellman M, de Graaf LE, Dozois DJ, Bieling PJ, Guyatt GH (2012). Effectiveness of cognitive behavioral therapy for depression in patients receiving disability benefits: a systematic review and individual patient data meta-analysis. PloS One 7, e50202.

Edwards VJ, Holden GW, Felitti VJ, Anda RF (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the adverse childhood experiences study. The American Journal of Psychiatry 160, 1453-1460.

Ekselius L, von Knorring L (1998). Personality disorder comorbidity with major depression and response to treatment with sertraline or citalopram. International Clinical Psychopharmacology 13, 205-211.

Elinson L, Houck P, Marcus SC, Pincus HA (2004). Depression and the ability to work. Psychiatric Services (Washington, D.C.) 55, 29-34.

Elovainio M, Jokela M, Kivimäki M, Pulkki-Raback L, Lehtimäki T, Airla N, Keltikangas-Järvinen L (2007). Genetic variants in the DRD2 gene moderate the relationship between stressful life events and depressive symptoms in adults: cardiovascular risk in young Finns study. Psychosomatic Medicine 69, 391-395.

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.

Fergusson DM, Horwood LJ, Miller AL, Kennedy MA (2011). Life stress, 5-HTTLPR and mental disorder: findings from a 30-year longitudinal study. The British Journal of Psychiatry : The Journal of Mental Science 198, 129-135.

Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, Vos T, 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.

First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS (1997). Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II).

First MB, Spitzer RL, Gibbon M, Williams JBW (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen.

Forsell Y (2007). A three-year follow-up of major depression, dysthymia, minor depression and subsyndromal depression: results from a population-based study. Depression and Anxiety 24, 62-65.

Franx G, Oud M, de Lange J, Wensing M, Grol R (2012). Implementing a stepped-care approach in primary care: results of a qualitative study. Implementation Science: IS 7, 8-5908-7-8.

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.

Gaynes BN, Rush AJ, Trivedi MH, Wisniewski SR, Balasubramani GK, Spencer DC, Petersen T, Klinkman M, Warden D, Nicholas L, Fava M (2007). Major depression symptoms in primary care and psychiatric care settings: a cross-sectional analysis. Annals of Family Medicine 5, 126-134.

Gellatly J, Bower P, Hennessy S, Richards D, Gilbody S, Lovell K (2007). What makes self-help interventions effective in the management of depressive symptoms? Meta-analysis and meta-regression. Psychological Medicine 37, 1217-1228.

Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ (2006). Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. Archives of Internal Medicine 166, 2314-2321.

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. The American Journal of Psychiatry 149, 1148-1156.

Grilo CM, McGlashan TH, Skodol AE (2000). Stability and course of personality disorders: the need to consider comorbidities and continuities between axis I psychiatric disorders and axis II personality disorders. The Psychiatric Quarterly 71, 291-307.

Grilo CM, Stout RL, Markowitz JC, Sanislow CA, Ansell EB, Skodol AE, Bender DS, Pinto A, Shea MT, Yen S, Gunderson JG, Morey LC, Hopwood CJ, McGlashan TH (2010). Personality disorders predict relapse after remission from an episode of major depressive disorder: a 6-year prospective study. The Journal of Clinical Psychiatry 71, 1629-1635.

Gross R, Olfson M, Gameroff M, Shea S, Feder A, Fuentes M, Lantigua R, Weissman MM (2002). Borderline personality disorder in primary care. Archives of Internal Medicine 162, 53-60.

Gunderson JG, Morey LC, Stout RL, Skodol AE, Shea MT, McGlashan TH, Zanarini MC, Grilo CM, Sanislow CA, Yen S, Daversa MT, Bender DS (2004). Major depressive disorder and borderline personality disorder revisited: longitudinal interactions. The Journal of Clinical Psychiatry 65, 1049-1056.

Gunderson JG, Stout RL, McGlashan TH, Shea MT, Morey LC, Grilo CM, Zanarini MC, Yen S, Markowitz JC, Sanislow C, Ansell E, Pinto A, Skodol AE (2011). Ten-year course of borderline personality disorder: psychopathology and function from the Collaborative Longitudinal Personality Disorders study. Archives of General Psychiatry 68, 827-837.

Gunderson JG, Stout RL, Sanislow CA, Shea MT, McGlashan TH, Zanarini MC, Daversa MT, Grilo CM, Yen S, Skodol AE (2008). New episodes and new onsets of major depression in borderline and other personality disorders. Journal of Affective Disorders 111, 40-45.

Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH (2012). Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. The American Journal of Psychiatry 169, 693-703.

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

Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman AT (2013). Recurrence of major depressive disorder and its predictors in the general population: results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Psychological Medicine 43, 39-48.

Hasin DS, Goodwin RD, Stinson FS, Grant BF (2005). Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Archives of General Psychiatry 62, 1097-1106.

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.

Hays RD, Wells KB, Sherbourne CD, Rogers W, 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.

Hegarty K, Gunn J, Blashki G, Griffiths F, Dowell T, Kendrick T (2009). How could depression guidelines be made more relevant and applicable to primary care? A quantitative and qualitative review of national guidelines. The British Journal of General Practice: The Journal of the Royal College of General Practitioners 59, e149-56.

Heim C, Binder EB (2012). Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. Experimental Neurology 233, 102-111.

Hintikka J, Koivumaa-Honkanen H, Lehto SM, Tolmunen T, Honkalampi K, Haatainen K, Viinamäki H (2009). Are factors associated with suicidal ideation true risk factors? A 3-year prospective follow-up study in a general population. Social Psychiatry and Psychiatric Epidemiology 44, 29-33.

Holma IA, Holma KM, Melartin TK, Rytsälä HJ, Isometsä ET (2012). A 5-year prospective study of predictors for disability pension among patients with major depressive disorder. Acta Psychiatrica Scandinavica 125, 325-334.

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

Holma KM, Melartin TK, Haukka J, Holma IA, Sokero TP, Isometsä ET (2010). Incidence and predictors of suicide attempts in DSM-IV major depressive disorder: a five-year

prospective study. The American Journal of Psychiatry 167, 801-808.

Honkonen T, Virtanen M, Ahola K, Kivimäki M, Pirkola S, Isometsä E, Aromaa A, Lönnqvist J (2007). Employment status, mental disorders and service use in the working age population. Scandinavian Journal of Work, Environment & Health 33, 29-36.

Hübner-Liebermann B, Neuner T, Hegerl U, Hajak G, Spiessl H (2010). Reducing suicides through an alliance against depression? General Hospital Psychiatry 32, 514-518.

Hueston WJ, Mainous AG,3rd, Schilling R (1996). Patients with personality disorders: functional status, health care utilization, and satisfaction with care. The Journal of Family Practice 42, 54-60.

Hueston WJ, Werth J, Mainous AG,3rd (1999). Personality disorder traits: prevalence and effects on health status in primary care patients. International Journal of Psychiatry in Medicine 29, 63-74.

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.

Ilardi SS, Craighead WE, Evans DD (1997). Modeling relapse in unipolar depression: the effects of dysfunctional cognitions and personality disorders. Journal of Consulting and Clinical Psychology 65, 381-391.

Isometsä E, Aro S, Aro H (1997). Depression in Finland: a computer assisted telephone interview study. Acta Psychiatrica Scandinavica 96, 122-128.

Isometsä ET, Heikkinen ME, Marttunen MJ, Henriksson MM, Aro HM, Lönnqvist JK (1995). The last appointment before suicide: is suicide intent communicated? The American Journal of Psychiatry 152, 919-922.

Isometsä ET, Katila H, Aro T (2000). Disability pension for major depression in Finland. The American Journal of Psychiatry 157, 1869-1872.

Isometsä ET, Lönnqvist JK (1998). Suicide attempts preceding completed suicide. The British Journal of Psychiatry : The Journal of Mental Science 173, 531-535.

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.

Jokela M, Keltikangas-Järvinen L, Kivimäki M, Puttonen S, Elovainio M, Rontu R, Lehtimäki T (2007). Serotonin receptor 2A gene and the influence of childhood maternal nurturance on adulthood depressive symptoms. Archives of General Psychiatry 64, 356-360.

Joyce PR, Mulder RT, Luty SE, McKenzie JM, Sullivan PF, Cloninger RC (2003). Borderline personality disorder in major depression: symptomatology, temperament, character, differential drug response, and 6-month outcome. Comprehensive Psychiatry 44, 35-43.

Judd LL, Akiskal HS, Paulus MP (1997). The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. Journal of Affective Disorders 45, 5-17; discussion 17-8.

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

Judd LL, Rapaport MH, Paulus MP, Brown JL (1994). Subsyndromal symptomatic depression: a new mood disorder? The Journal of Clinical Psychiatry 55 Suppl, 18-28.

Jylhä P, Isometsä E (2006). The relationship of neuroticism and extraversion to symptoms of anxiety and depression in the general population. Depression and Anxiety 23, 281-289.

Kaila E, Väisänen A, Leino T, Laamanen A, Vihtonen T, Hyvärinen H, Varjonen J (2012). ToMaHoK - Toimiva masennuksen hoitokäytäntö työterveyshuollossa, 128.

Karg K, Burmeister M, Shedden K, Sen S (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited:

evidence of genetic moderation. Archives of General Psychiatry 68, 444-454.

Karlsson H, Joukamaa M, Lehtinen V (2000). Differences between patients with identified and not identified psychiatric disorders in primary care. Acta Psychiatrica Scandinavica 102, 354-358.

Karpansalo M, Kauhanen J, Lakka TA, Manninen P, Kaplan GA, Salonen JT (2005). Depression and early retirement: prospective population based study in middle aged men. Journal of Epidemiology and Community Health 59, 70-74.

Katon W (2009). The impact of depression on workplace functioning and disability costs. The American Journal of Managed Care 15, S322-7.

Katon WJ (2003). Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biological Psychiatry 54, 216-226.

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, Lavori PW, Lewis CE, Klerman GL (1983). Predictors of relapse in major depressive disorder. JAMA: The Journal of the American Medical Association 250, 3299-3304.

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.

Keller MB, Shapiro RW, Lavori PW, Wolfe N (1982). Relapse in major depressive disorder: analysis with the life table. Archives of General Psychiatry 39, 911-915.

Keller MC, Neale MC, Kendler KS (2007). Association of different adverse life events with distinct patterns of depressive symptoms. The American Journal of Psychiatry 164, 1521-9; quiz 1622.

Keller MC, Nesse RM (2006). The evolutionary significance of depressive symptoms: different adverse situations lead to different depressive symptom patterns. Journal of Personality and Social Psychology 91, 316-330.

Kelly TM, Soloff PH, Lynch KG, Haas GL, Mann JJ (2000). Recent life events, social adjustment, and suicide attempts in patients with major depression and borderline personality disorder. Journal of Personality Disorders 14, 316-326.

Kempton MJ, Salvador Z, Munafo MR, Geddes JR, Simmons A, Frangou S, Williams SC (2011). Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Archives of General Psychiatry 68, 675-690.

Kendler KS, Aggen SH, Neale MC (2013). Evidence for multiple genetic factors underlying DSM-IV criteria for major depression. JAMA Psychiatry (Chicago, Ill.) 70, 599-607.

Kendler KS, Eaves LJ, Loken EK, Pedersen NL, Middeldorp CM, Reynolds C, Boomsma D, Lichtenstein P, Silberg J, Gardner CO (2011). The impact of environmental experiences on symptoms of anxiety and depression across the life span. Psychological Science 22, 1343-1352.

Kendler KS, Gardner CO (2010). Dependent stressful life events and prior depressive episodes in the prediction of major depression: the problem of causal inference in psychiatric epidemiology. Archives of General Psychiatry 67, 1120-1127.

Kendler KS, Myers J (2010). The genetic and environmental relationship between major depression and the five-factor model of personality. Psychological Medicine 40, 801-806.

Kendler KS, Myers J, Halberstadt LJ (2011). Do reasons for major depression act as causes? Molecular Psychiatry 16, 626-633.

Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, Peveler R, Leese M, McCrone P, Harris T, Moore M, Byng R, Brown G, Barthel S, Mander H, Ring A, Kelly V, Wallace V, Gabbay M, Craig T, Mann A (2009). Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study. Health Technology Assessment (Winchester, England) 13, iii-iv, ix-xi, 1-159.

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. The British Journal of Psychiatry: The Journal of Mental Science 184, 330-336.

Kessler RC (2012). The costs of depression. The Psychiatric Clinics of North America 35, 1-14.

Kessler RC, Barber C, Birnbaum HG, Frank RG, Greenberg PE, Rose RM, Simon GE, Wang P (1999). Depression in the workplace: effects on short-term disability. Health Affairs (Project Hope) 18, 163-171.

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

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry 62, 593-602.

Kessler RC, Birnbaum HG, Shahly V, Bromet E, Hwang I, McLaughlin KA, Sampson N, Andrade LH, de Girolamo G, Demyttenaere K, Haro JM, Karam AN, Kostyuchenko S, Kovess V, Lara C, Levinson D, Matschinger H, Nakane Y, Browne MO, Ormel J, Posada-Villa J, Sagar R, Stein DJ (2010). Age differences in the prevalence and comorbidity of DSM-IV major depressive episodes: results from the WHO World Mental Health Survey Initiative. Depression and Anxiety 27, 351-364.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry 62, 617-627.

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

Kirmayer LJ, Robbins JM (1996). Patients who somatize in primary care: a longitudinal study of cognitive and social characteristics. Psychological Medicine 26, 937-951.

Kirmayer LJ, Robbins JM, Dworkind M, Yaffe MJ (1993). Somatization and the recognition of depression and anxiety in primary care. The American Journal of Psychiatry 150, 734-741.

Klein DN (2008). Classification of depressive disorders in the DSM-V: proposal for a two-dimension system. Journal of Abnormal Psychology 117, 552-560.

Koike AK, Unutzer J, Wells KB (2002). Improving the care for depression in patients with comorbid medical illness. The American Journal of Psychiatry 159, 1738-1745.

Koponen HJ, Viilo K, Hakko H, Timonen M, Meyer-Rochow VB, Särkioja T, Räsänen P (2007). Rates and previous disease history in old age suicide. International Journal of Geriatric Psychiatry 22, 38-46.

Korkeila J, Oksanen T, Virtanen M, Salo P, Nabi H, Pentti J, Vahtera J, Kivimäki M (2011). Early retirement from work among employees with a diagnosis of personality disorder compared to anxiety and depressive disorders. European Psychiatry : The Journal of the Association of European Psychiatrists 26, 18-22.

Korkeila K, Korkeila J, Vahtera J, Kivimäki M, Kivelä SL, Sillanmäki L, Koskenvuo M (2005). Childhood adversities, adult risk factors and depressiveness: a population study. Social Psychiatry and Psychiatric Epidemiology 40, 700-706.

Korkeila K, Törmä M (2010). Psychologically traumatized patient on a general practitioner's consultation. Duodecim; Laaketieteellinen Aikakauskirja 126, 2645-2653.

Kruijshaar ME, Hoeymans N, Bijl RV, Spijker J, 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.

Kupfer DJ, Frank E, Phillips ML (2012). Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet 379, 1045-1055.

Kuyken W, Byford S, Taylor RS, Watkins E, Holden E, White K, Barrett B, Byng R, Evans A, Mullan E, Teasdale JD (2008). Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. Journal of Consulting and Clinical Psychology 76, 966-978.

Lagerveld SE, Bültmann U, Franche RL, van Dijk FJ, Vlasveld MC, van der Feltz-Cornelis CM, Bruinvels DJ, Huijs JJ, Blonk

RW, van der Klink JJ, Nieuwenhuijsen K (2010). Factors associated with work participation and work functioning in depressed workers: a systematic review. Journal of Occupational Rehabilitation 20, 275-292.

Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW (2013). Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Molecular Psychiatry 18, 692-699.

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

Lehtinen V, Joukamaa M, Lahtela K, Raitasalo R, Jyrkinen E, Maatela J, Aromaa A (1990). Prevalence of mental disorders among adults in Finland: basic results from the Mini Finland Health Survey. Acta Psychiatrica Scandinavica 81, 418-425.

Lehtinen V, Sohlman B, Nummelin T, Salomaa M, Ayuso-Mateos JL, Dowrick C (2005). The estimated incidence of depressive disorder and its determinants in the Finnish ODIN sample. Social Psychiatry and Psychiatric Epidemiology 40, 778-784.

Leichsenring F, Leibing E, Kruse J, New AS, Leweke F (2011). Borderline personality disorder. Lancet 377, 74-84.

Lerner D, Adler DA, Chang H, Lapitsky L, Hood MY, Perissinotto C, Reed J, McLaughlin TJ, Berndt ER, Rogers WH (2004). Unemployment, job retention, and productivity loss among employees with depression. Psychiatric Services (Washington, D.C.) 55, 1371-1378.

Lerner D, Henke RM (2008). What does research tell us about depression, job performance, and work productivity? Journal of Occupational and Environmental Medicine / American College of Occupational and Environmental Medicine 50, 401-410.

Leskelä U, Melartin T, Rytsälä H, Sokero P, Lestelä-Mielonen P, Isometsä E (2008). The influence of major depressive disorder on objective and subjective social support: a prospective study. The Journal of Nervous and Mental Disease 196, 876-883.

Leskelä US, Melartin TK, Lestelä-Mielonen PS, Rytsälä HJ, Sokero TP, Heikkinen ME, Isometsä ET (2004). Life events, social support, and onset of major depressive episode in Finnish patients. The Journal of Nervous and Mental Disease 192, 373-381.

Lin EH, Katon WJ, VonKorff M, Russo JE, Simon GE, Bush TM, Rutter CM, Walker EA, Ludman E (1998). Relapse of depression in primary care. Rate and clinical predictors. Archives of Family Medicine 7, 443-449.

Lin EH, Simon GE, Katzelnick DJ, Pearson SD (2001). Does physician education on depression management improve treatment in primary care? Journal of General Internal Medicine 16, 614-619.

Lin EH, VonKorff M, Russo J, Katon W, Simon GE, Unutzer J, Bush T, Walker E, Ludman E (2000). Can depression treatment in primary care reduce disability? A stepped care approach. Archives of Family Medicine 9, 1052-1058.

Lindeman S, Hämäläinen J, Isometsä E, Kaprio J, Poikolainen K, Heikkinen M, Aro H (2000). The 12-month prevalence and risk factors for major depressive episode in Finland: representative sample of 5993 adults. Acta Psychiatrica Scandinavica 102, 178-184.

Lotfi L, Flyckt L, Krakau I, Martensson B, Nilsson GH (2010). Undetected depression in primary healthcare: occurrence, severity and comorbidity in a two-stage procedure of opportunistic screening. Nordic Journal of Psychiatry 64, 421-427.

Luciano JV, Bertsch J, Salvador-Carulla L, Tomas JM, Fernandez A, Pinto-Meza A, Haro JM, Palao DJ, Serrano-Blanco A (2010). Factor structure, internal consistency and construct validity of the Sheehan Disability Scale in a Spanish primary care sample. Journal of Evaluation in Clinical Practice 16, 895-901.

Luutonen S, Karlsson H, Nieminen M, Salokangas RK (2011). Outcome of depression in primary care: better than expected. Public Health 125, 711-713.

Maj M, Veltro F, Pirozzi R, Lobrace S, Magliano L (1992). Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. The American Journal of Psychiatry 149, 795-800.

Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, et a (2013). A mega-analysis of genome-wide association studies for major depressive disorder. Molecular Psychiatry 18, 497-511.

Malone KM, Haas GL, Sweeney JA, Mann JJ (1995). Major depression and the risk of attempted suicide. Journal of Affective Disorders 34, 173-185.

Mammen G, Faulkner G (2013). Physical activity and the prevention of depression: a systematic review of prospective studies. American Journal of Preventive Medicine 45, 649-657.

Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, Hegerl U, Lönnqvist J, Malone K, Marusic A, Mehlum L, Patton G, Phillips M, Rutz W, Rihmer Z, Schmidtke A, Shaffer D, Silverman M, Takahashi Y, Varnik A, Wasserman D, Yip P, Hendin H (2005). Suicide prevention strategies: a systematic review. JAMA: The Journal of the American Medical Association 294, 2064-2074.

Mattisson C, Bogren M, Horstmann V, Munk-Jorgensen P, Nettelbladt P (2007). The long-term course of depressive disorders in the Lundby Study. Psychological Medicine 37, 883-891.

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.

McClung CA (2013). How might circadian rhythms control mood? Let me count the ways. Biological Psychiatry 74, 242-249.

McKall K (2001). An insider's guide to depression. British Medical Journal 323(7319), 1011.

McMahon EM, Buszewicz M, Griffin M, Beecham J, Bonin EM, Rost F, Walters K, King M (2012). Chronic and recurrent depression in primary care: socio-demographic features, morbidity, and costs. International Journal of Family Medicine 2012, 316409.

McPherson S, Armstrong D (2009). Negotiating 'depression' in primary care: a qualitative study. Social Science & Medicine (1982) 69, 1137-1143.

Mead N, Lester H, Chew-Graham C, Gask L, Bower P (2010). Effects of befriending on depressive symptoms and distress: systematic review and meta-analysis. The British Journal of Psychiatry: The Journal of Mental Science 196, 96-101.

Melartin T, Leskelä U, Rytsälä H, Sokero P, Lestelä-Mielonen P, Isometsä E (2004). Comorbidity and stability of melancholic features in DSM-IV major depressive disorder. Psychological Medicine 34, 1443-1452.

Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET (2002). Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. The Journal of Clinical Psychiatry 63, 126-134.

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. The Journal of Clinical Psychiatry 65, 810-819.

Morriss R, Kapur N, Byng R (2013). Assessing risk of suicide or self harm in adults. BMJ (Clinical Research Ed.) 347, f4572.

Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 370, 851-858.

Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, Maser JD (1999). Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. The American Journal of Psychiatry 156, 1000-1006.

Munoz RF, Cuijpers P, Smit F, Barrera AZ, Leykin Y (2010). Prevention of major depression. Annual Review of Clinical Psychology 6, 181-212.

Munthén LK, Munthén BO (2007). Mplus User's Guide. 5th ed. Munthen & Munthen. Los Angeles, CA: 1998-2007.

Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380, 2197-2223.

Mynors-Wallis LM, Gath DH, Day A, Baker F (2000). Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. BMJ (Clinical Research Ed.) 320, 26-30.

Newton-Howes G, Tyrer P, Johnson T (2006). Personality disorder and the outcome of depression: meta-analysis of published studies. The British Journal of Psychiatry : The Journal of Mental Science 188, 13-20.

NICE (2010). Depression: The NICE Guideline on the Treatment and Management of Depression in Adults (Updated edition).

Nieuwenhuijsen K, Bültmann U, Neumeyer-Gromen A, Verhoeven AC, Verbeek JH, van der Feltz-Cornelis CM (2008). Interventions to improve occupational health in depressed people. Cochrane Database of Systematic Reviews (Online) (2):CD006237. doi, CD006237.

Nieuwenhuijsen K, Verbeek JH, de Boer AG, Blonk RW, van Dijk FJ (2006). Predicting the duration of sickness absence for patients with common mental disorders in occupational health care. Scandinavian Journal of Work, Environment & Health 32, 67-74.

Nordentoft M, Mortensen PB, Pedersen CB (2011). Absolute risk of suicide after first hospital contact in mental disorder. Archives of General Psychiatry 68, 1058-1064.

Northoff G (2013). Gene, brains, and environment-genetic neuroimaging of depression. Current Opinion in Neurobiology 23, 133-142.

O'Connor EA, Whitlock EP, Beil TL, Gaynes BN (2009). Screening for depression in adult patients in primary care settings: a systematic evidence review. Annals of Internal Medicine 151, 793-803.

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.

Olfson M, Broadhead WE, Weissman MM, Leon AC, Farber L, Hoven C, Kathol R (1996). Subthreshold psychiatric symptoms in a primary care group practice. Archives of General Psychiatry 53, 880-886.

Olfson M, Fireman B, Weissman MM, Leon AC, Sheehan DV, Kathol RG, Hoven C, Farber L (1997). Mental disorders and disability among patients in a primary care group practice. The American Journal of Psychiatry 154, 1734-1740.

Oosterbaan DB, Verbraak MJ, Terluin B, Hoogendoorn AW, Peyrot WJ, Muntingh A, van Balkom AJ (2013). Collaborative stepped care v. care as usual for common mental disorders: 8-month, cluster randomised controlled trial. The British Journal of Psychiatry : The Journal of Mental Science 203, 132-139.

Oquendo MA, Currier D, Mann JJ (2006). Prospective studies of suicidal behavior in major depressive and bipolar disorders: what is the evidence for predictive risk factors? Acta Psychiatrica Scandinavica 114, 151-158.

Oquendo MA, Galfalvy H, Russo S, Ellis SP, Grunebaum MF, Burke A, Mann JJ (2004). Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. The American Journal of Psychiatry 161, 1433-1441.

Oquendo MA, Kamali M, Ellis SP, Grunebaum MF, Malone KM, Brodsky BS, Sackeim HA, Mann JJ (2002). Adequacy of antidepressant treatment after discharge and the occurrence of suicidal acts in major depression: a prospective study. The American Journal of Psychiatry 159, 1746-1751.

Oquendo MA, Perez-Rodriguez MM, Poh E, Sullivan G, Burke AK, Sublette ME, Mann JJ, Galfalvy H (2013). Life events: a complex role in the timing of suicidal behavior among depressed patients. Molecular Psychiatry.

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.

Ormel J, Vonkorff M, Oldehinkel AJ, Simon G, Tiemens BG, Ustun TB (1999). Onset of disability in depressed and non-depressed primary care patients. Psychological Medicine 29, 847-853.

Paris J (2007). Why Psychiatrists are Reluctant to Diagnose: Borderline Personality Disorder. Psychiatry (Edgmont (Pa.: Township)) 4, 35-39.

Paris J, Zweig-Frank H (2001). A 27-year follow-up of patients with borderline personality disorder. Comprehensive Psychiatry 42, 482-487.

Patience DA, McGuire RJ, Scott AI, Freeman CP (1995). The Edinburgh Primary Care Depression Study: personality disorder and outcome. The British Journal of Psychiatry : The Journal of Mental Science 167, 324-330.

Patten SB, Bilsker D, Goldner E (2008). The evolving understanding of major depression epidemiology: implications for practice and policy. Canadian Journal of Psychiatry.Revue Canadienne De Psychiatrie 53, 689-695.

Paykel ES (2008). Partial remission, residual symptoms, and relapse in depression. Dialogues in Clinical Neuroscience 10, 431-437.

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.

Pepper CM, Klein DN, Anderson RL, Riso LP, Ouimette PC, Lizardi H (1995). DSM-III-R axis II comorbidity in dysthymia and

major depression. The American Journal of Psychiatry 152, 239-247.

Perugi G, Angst J, Azorin JM, Bowden C, Vieta E, Young AH (2013). The bipolar-borderline personality disorders connection in major depressive patients. Acta Psychiatrica Scandinavica.

Perugi G, Angst J, Azorin JM, Bowden C, Vieta E, Young AH, BRIDGE Study Group (2013). Is comorbid borderline personality disorder in patients with major depressive episode and bipolarity a developmental subtype? Findings from the international BRIDGE study. Journal of Affective Disorders 144, 72-78.

Piek E, Nolen WA, van der Meer K, Joling KJ, Kollen BJ, Penninx BW, van Marwijk HW, van Hout HP (2012). Determinants of (non-)recognition of depression by general practitioners: results of the Netherlands Study of Depression and Anxiety. Journal of Affective Disorders 138, 397-404.

Piek E, van der Meer K, Nolen WA (2010). Guideline recommendations for long-term treatment of depression with antidepressants in primary care-a critical review. The European Journal of General Practice 16, 106-112.

Pincus HA, Davis WW, McQueen LE (1999). 'Subthreshold' mental disorders. A review and synthesis of studies on minor depression and other 'brand names'. The British Journal of Psychiatry: The Journal of Mental Science 174, 288-296.

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.

Pitkälä K, Isometsä ET, Henriksson MM, Lönnqvist JK (2000). Elderly suicide in Finland. International Psychogeriatrics / IPA 12, 209-220.

Porcelli S, Fabbri C, Serretti A (2012). Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology 22, 239-258.

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.

Proudfoot J, Goldberg D, Mann A, Everitt B, Marks I, Gray JA (2003). Computerized, interactive, multimedia cognitive-behavioural program for anxiety and depression in general practice. Psychological Medicine 33, 217-227.

Raitasalo R,T, Saarijärvi S, Salminen J (2010). Masennus ja työssäkäynti: Viiden vuoden seurantatutkimus. People on sick leave due to depression: A follow-up at 5 years. 65 6, 481-484.

Ramklint M, Ekselius L (2003). Personality traits and personality disorders in early onset versus late onset major depression. Journal of Affective Disorders 75, 35-42.

Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M (2010). Antidepressants for depression in physically ill people. The Cochrane Database of Systematic Reviews (3):CD007503. doi, CD007503.

Reichborn-Kjennerud T, Czajkowski N, Roysamb E, Orstavik RE, Neale MC, Torgersen S, Kendler KS (2010). Major depression and dimensional representations of DSM-IV personality disorders: a population-based twin study. Psychological Medicine 40, 1475-1484.

Reinert DF, Allen JP (2007). The alcohol use disorders identification test: an update of research findings. Alcoholism, Clinical and Experimental Research 31, 185-199.

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.

Richards DA (2012). Stepped care: a method to deliver increased access to psychological therapies. Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie 57, 210-215.

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

Rothschild L, Zimmerman M (2002). Borderline personality disorder and age of onset in major depression. Journal of Personality Disorders 16, 189-199.

Rush AJ, Zimmerman M, Wisniewski SR, Fava M, Hollon SD, Warden D, Biggs MM, Shores-Wilson K, Shelton RC, Luther JF, Thomas B, Trivedi MH (2005). Comorbid psychiatric disorders in depressed outpatients: demographic and clinical features. Journal of Affective Disorders 87, 43-55.

Rytsälä HJ, Melartin TK, Leskelä US, Lestelä-Mielonen PS, Sokero TP, Isometsä ET (2006). Determinants of functional disability and social adjustment in major depressive disorder: a prospective study. The Journal of Nervous and Mental Disease 194, 570-576.

Rytsälä HJ, Melartin TK, Leskelä US, Sokero TP, Lestelä-Mielonen PS, Isometsä ET (2005). Functional and work disability in major depressive disorder. The Journal of Nervous and Mental Disease 193, 189-195.

Rytsälä HJ, Melartin TK, Leskelä US, Sokero TP, Lestelä-Mielonen PS, Isometsä ET (2007). Predictors of long-term work disability in Major Depressive Disorder: a prospective study. Acta Psychiatrica Scandinavica 115, 206-213.

Saarni SI, Suvisaari J, Sintonen H, Pirkola S, Koskinen S, Aromaa A, Lönnqvist J (2007). Impact of psychiatric disorders on health-related quality of life: general population survey. The British Journal of Psychiatry: The Journal of Mental Science 190, 326-332.

Salminen JK, Saarijarvi S, Raitasalo R (1997). Depression and disability pension in Finland. Acta Psychiatrica Scandinavica 95, 242-243.

Salokangas RK, Poutanen O, Stengård E, Jähi R, Palo-oja T (1996). Prevalence of depression among patients seen in community health centres and community mental health centres. Acta Psychiatrica Scandinavica 93, 427-433.

Sansone RA, Farukhi S, Wiederman MW (2011). Utilization of primary care physicians in borderline personality. General Hospital Psychiatry 33, 343-346.

Sansone RA, Sansone LA (2004). Borderline personality: a primary care context. Psychiatry (Edgmont (Pa.: Township)) 1, 19-27.

Sartorius N, Ustun TB, Costa e 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.

Sartorius N, Ustun TB, Lecrubier Y, Wittchen HU (1996). Depression comorbid with anxiety: results from the WHO study on psychological disorders in primary health care. The British Journal of Psychiatry. Supplement (30), 38-43.

Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction (Abingdon, England) 88, 791-804.

Saveanu RV, Nemeroff CB (2012). Etiology of depression: genetic and environmental factors. The Psychiatric Clinics of North America 35, 51-71.

Schepis TS, McCabe SE (2012). Exploring age of onset as a causal link between major depression and nonmedical use of prescription medications. Drug and Alcohol Dependence 120, 99-104.

Seekles W, van Straten A, Beekman A, van Marwijk H, Cuijpers P (2011). Effectiveness of guided self-help for depression and anxiety disorders in primary care: a pragmatic randomized controlled trial. Psychiatry Research 187, 113-120.

Seekles W, van Straten A, Beekman A, van Marwijk H, Cuijpers P (2011). Stepped care treatment for depression and anxiety in primary care. a randomized controlled trial. Trials 12, 171-6215-12-171.

Sheehan DV, Harnett-Sheehan K, Raj BA (1996). The measurement of disability. International Clinical Psychopharmacology 11 Suppl 3, 89-95.

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

Simon GE, Barber C, Birnbaum HG, Frank RG, Greenberg PE, Rose RM, Wang PS, Kessler RC (2001). Depression and work productivity: the comparative costs of treatment versus nontreatment. Journal of Occupational and Environmental Medicine / American College of Occupational and Environmental Medicine 43, 2-9.

Simon GE, Goldberg D, Tiemens BG, Ustun TB (1999). Outcomes of recognized and unrecognized depression in an international primary care study. General Hospital Psychiatry 21, 97-105.

Simon GE, Katon WJ, VonKorff M, Unutzer J, Lin EH, Walker EA, Bush T, Rutter C, Ludman E (2001). Cost-effectiveness of a collaborative care program for primary care patients with persistent depression. The American Journal of Psychiatry 158, 1638-1644.

Simon GE, Revicki D, Heiligenstein J, Grothaus L, VonKorff M, Katon WJ, Hylan TR (2000). Recovery from depression, work productivity, and health care costs among primary care patients. General Hospital Psychiatry 22, 153-162.

Skodol AE, Grilo CM, Keyes KM, Geier T, Grant BF, Hasin DS (2011). Relationship of personality disorders to the course of major depressive disorder in a nationally representative sample. The American Journal of Psychiatry 168, 257-264.

Skodol AE, Grilo CM, Pagano ME, Bender DS, Gunderson JG, Shea MT, Yen S, Zanarini MC, McGlashan TH (2005). Effects of personality disorders on functioning and well-being in major depressive disorder. Journal of Psychiatric Practice 11, 363-368.

Skodol AE, Gunderson JG, McGlashan TH, Dyck IR, Stout RL, Bender DS, Grilo CM, Shea MT, Zanarini MC, Morey LC, Sanislow CA, Oldham JM (2002). Functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder. The American Journal of Psychiatry 159, 276-283.

Smit F, Willemse G, Koopmanschap M, Onrust S, Cuijpers P, Beekman A (2006). Cost-effectiveness of preventing depression in primary care patients: randomised trial. The British Journal of Psychiatry : The Journal of Mental Science 188, 330-336.

Smoller JW (2013). Disorders and borders: Psychiatric genetics and nosology. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics 162, 559-578.

Snyder R, Liebman LS, Simon AB, Kellner CH (2013). Does heterogeneity of depression diagnosis harm those with severe mood disorders? Medical Hypotheses 81, 316-318.

Sobocki P, Ekman M, Agren H, Krakau I, Runeson B, Martensson B, Jonsson B (2007). Resource use and costs associated with patients treated for depression in primary care. The European Journal of Health Economics: HEPAC : Health Economics in Prevention and Care 8, 67-76.

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

Sokero P, Eerola M, Rytsälä H, Melartin T, Leskelä U, Lestelä-Mielonen P, Isometsä E (2006). Decline in suicidal ideation among patients with MDD is preceded by decline in depression and hopelessness. Journal of Affective Disorders 95, 95-102.

Sokero TP, Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Isometsä ET (2003). Suicidal ideation and attempts among psychiatric patients with major depressive disorder. The Journal of Clinical Psychiatry 64, 1094-1100.

Sokero TP, Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Isometsä ET (2005). Prospective study of risk factors for attempted suicide among patients with DSM-IV major depressive disorder. The British Journal of Psychiatry: The Journal of Mental Science 186, 314-318.

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.

Sorenson SB, Rutter CM, Aneshensel CS (1991). Depression in the community: an investigation into age of onset. Journal of Consulting and Clinical Psychology 59, 541-546.

Sorvaniemi M, Helenius H, Salokangas RK (2003). Factors associated with being granted a pension among psychiatric outpatients with major depression. Journal of Affective Disorders 75, 43-48.

Sorvaniemi M, Helenius H, Salokangas RK (2003). Sick-leave certificates granted to psychiatric outpatients with major depression. Depression and Anxiety 17, 220-223.

Spijker J, de Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA (2004). 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, van Straten A, Bockting CL, Meeuwissen JA, van Balkom AJ (2013). Psychotherapy, antidepressants, and their combination for chronic major depressive disorder: a systematic review. Canadian Journal of Psychiatry.Revue Canadienne De Psychiatrie 58, 386-392.

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

Stegenga BT, Kamphuis MH, King M, Nazareth I, Geerlings MI (2012). The natural course and outcome of major depressive disorder in primary care: the PREDICT-NL

study. Social Psychiatry and Psychiatric Epidemiology 47, 87-95.

Steinert C, Hofmann M, Kruse J, Leichsenring F (2013). The prospective long-term course of adult depression in general practice and the community. A systematic literature review. Journal of Affective Disorders.

Stetler C, Miller GE (2011). Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosomatic Medicine 73, 114-126.

Stewart AL, Sherbourne CD, Wells KB, Burnam MA, Rogers WH, Hays RD, Ware JE,Jr (1993). Do depressed patients in different treatment settings have different levels of well-being and functioning? Journal of Consulting and Clinical Psychology 61, 849-857.

Sullivan MD, O'Connor P, Feeney P, Hire D, Simmons DL, Raisch DW, Fine LJ, Narayan KM, Ali MK, Katon WJ (2012). Depression predicts all-cause mortality: epidemiological evaluation from the ACCORD HRQL substudy. Diabetes Care 35, 1708-1715.

Sullivan PF, Daly MJ, O'Donovan M (2012). Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nature Reviews.Genetics 13, 537-551.

Sullivan PF, Joyce PR, Mulder RT (1994). Borderline personality disorder in major depression. The Journal of Nervous and Mental Disease 182, 508-516.

Sullivan PF, Neale MC, Kendler KS (2000). Genetic epidemiology of major depression: review and meta-analysis. The American Journal of Psychiatry 157, 1552-1562.

Suominen K, Isometsä E, Suokas J, Haukka J, Achte K, Lönnqvist J (2004). Completed suicide after a suicide attempt: a 37-year follow-up study. The American Journal of Psychiatry 161, 562-563.

Surtees PG, Barkley C (1994). Future imperfect: the long-term outcome of depression. The British Journal of Psychiatry : The Journal of Mental Science 164, 327-341.

Suvisaari J (2012). Psyykkiset oireet ja mielenterveyden häiriöt. In Terveys, toimintakyky ja hyvinvointi Suomessa 2011 (eds. S. Koskinen, A. Lundqvist, N. Ristiluoma), pp. 96. THL.

Szanto K, Gildengers A, Mulsant BH, Brown G, Alexopoulos GS, Reynolds CF,3rd (2002). Identification of suicidal ideation and prevention of suicidal behaviour in the elderly. Drugs & Aging 19, 11-24.

Szanto K, Kalmar S, Hendin H, Rihmer Z, Mann JJ (2007). A suicide prevention program in a region with a very high suicide rate. Archives of General Psychiatry 64, 914-920.

Szymanski BR, Bohnert KM, Zivin K, McCarthy JF (2013). Integrated care: treatment initiation following positive depression screens. Journal of General Internal Medicine 28, 346-352.

Taimela S, Mäkelä K, Justen S, Schugk J (2007). Screening for depressive symptoms in occupational health care and referral of symptomatic employees for treatment (Masennusoireiden seulonta ja oireisten työntekijöiden hoitoonohjaus työterveyshuolloss). Finnish Medical Journal 45, 4203-4207.

Tautiluokitus ICD-10 (2011). Third edition of the Finnish version of the International Statistical Classification of Diseases and Related Health Problems.

Taylor WD, Aizenstein HJ, Alexopoulos GS (2013). The vascular depression hypothesis: mechanisms linking vascular disease with depression. Molecular Psychiatry 18, 963-974.

Teicher MH, Samson JA (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. The American Journal of Psychiatry 170, 1114-1133.

Thomas CM, Morris S (2003). Cost of depression among adults in England in 2000. The British Journal of Psychiatry : The Journal of Mental Science 183, 514-519.

Thompson C, Kinmonth AL, Stevens L, Peveler RC, Stevens A, Ostler KJ, Pickering RM, Baker NG, Henson A, Preece J, Cooper D, Campbell MJ (2000). Effects of a clinical-practice guideline and practice-based education on detection and outcome of depression in primary care: Hampshire Depression Project randomised controlled trial. Lancet 355, 185-191.

Thompson C, Ostler K, Peveler RC, Baker N, Kinmonth AL (2001). Dimensional perspective on the recognition of depressive symptoms in primary care: The Hampshire Depression Project 3. The British Journal of Psychiatry: The Journal of Mental Science 179, 317-323.

Timonen M, Viilo K, Väisänen E, Räsänen P, Hakko H, Särkioja T (2002). Burden of illness and suicide in elderly people. Physical disease and depression are prevalent in elderly Finnish suicide victims. BMJ (Clinical Research Ed.) 325, 441.

Valkanova V, Ebmeier KP, Allan CL (2013). CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. Journal of Affective Disorders 150, 736-744.

Valtonen HM, Suominen K, Haukka J, Mantere O, Leppämäki S, Arvilommi P, Isometsä ET (2008). Differences in incidence of suicide attempts during phases of bipolar I and II disorders. Bipolar Disorders 10, 588-596.

van Weel-Baumgarten EM, Schers HJ, van den Bosch WJ, van den Hoogen HJ, Zitman FG (2000). Long-term follow-up of depression among patients in the community and in family practice settings. A systematic review. The Journal of Family Practice 49, 1113-1120.

Viinamäki H, Haatainen K, Honkalampi K, Tanskanen A, Koivumaa-Honkanen H, Antikainen R, Valkonen-Korhonen M, Hintikka J (2006). Which factors are important predictors of non-recovery from major depression? A 2-year prospective observational study. Nordic Journal of Psychiatry 60, 410-416.

Voinov B, Richie WD, Bailey RK (2013). Depression and chronic diseases: it is time for a synergistic mental health and primary care approach. The Primary Care Companion to CNS Disorders 15, 10.4088/PCC.12r01468. Epub 2013 Apr 4.

Vos T, Haby MM, Barendregt JJ, Kruijshaar M, Corry J, Andrews G (2004). The burden of major depression avoidable by longer-term treatment strategies. Archives of General Psychiatry 61, 1097-1103.

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

Vuorilehto MS, Melartin TK, Isometsä ET (2006). Suicidal behaviour among primary-care patients with depressive disorders. Psychological Medicine 36, 203-210.

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

Vuorilehto MS, Melartin TK, Rytsälä HJ, Isometsä ET (2007). Do characteristics of patients with major depressive disorder differ between primary and psychiatric care? Psychological Medicine 37, 893-904.

Wagner EH, Simon GE (2001). Managing depression in primary care. BMJ (Clinical Research Ed.) 322, 746-747.

Wakefield JC, Schmitz MF (2013). When does depression become a disorder? Using recurrence rates to evaluate the validity of proposed changes in major depression diagnostic thresholds. World Psychiatry: Official Journal of the World Psychiatric Association (WPA) 12, 44-52.

Watkins ER, Taylor RS, Byng R, Baeyens C, Read R, Pearson K, Watson L (2012). Guided self-help concreteness training as an intervention for major depression in primary care: a Phase II randomized controlled trial. Psychological Medicine 42, 1359-1371.

Weir JM, Zakama A, Rao U (2012). Developmental risk I: depression and the developing brain. Child and Adolescent Psychiatric Clinics of North America 21, 237-59, vii.

Weissman MM, Neria Y, Gameroff MJ, Pilowsky DJ, Wickramaratne P, Lantigua R, Shea S, Olfson M (2010). Positive screens for psychiatric disorders in primary care: a long-term follow-up of patients who were not in treatment. Psychiatric Services (Washington, D.C.) 61, 151-159.

Wells KB, Sherbourne C, Schoenbaum M, Duan N, Meredith L, Unutzer J, Miranda J, Carney MF, Rubenstein LV (2000). Impact of disseminating quality improvement programs for depression in managed primary care: a randomized controlled trial. JAMA: The Journal of the American Medical Association 283, 212-220.

Wells KB, Sherbourne CD (1999). Functioning and utility for current health of patients with depression or chronic medical conditions in managed, primary care practices. Archives of General Psychiatry 56, 897-904.

Wells KB, Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, Berry S, Greenfield S, Ware J (1989). The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. JAMA: The Journal of the American Medical Association 262, 914-919.

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.

Whiteford HA (2008). Depression in primary care: expanding the evidence base for diagnosis and treatment. The Medical Journal of Australia 188, S101-2.

Whiteford HA, Harris MG, McKeon G, Baxter A, Pennell C, Barendregt JJ, Wang J (2013).

Estimating remission from untreated major depression: a systematic review and meta-analysis. Psychological Medicine 43, 1569-1585.

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

Williams C, Wilson P, Morrison J, McMahon A, Andrew W, Allan L, McConnachie A, McNeill Y, Tansey L (2013). Guided self-help cognitive behavioural therapy for depression in primary care: a randomised controlled trial. PloS One 8, e52735.

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

Wittchen HU, Hofler M, Meister W (2001). Prevalence and recognition of depressive syndromes in German primary care settings: poorly recognized and treated? International Clinical Psychopharmacology 16, 121-135.

Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen HC (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology 21, 655-679.

Wittchen HU, Pittrow D (2002). Prevalence, recognition and management of depression in primary care in Germany: the Depression 2000 study. Human Psychopharmacology 17 Suppl 1, S1-11.

World Health Organization (2007). International Statistical Classification of Diseases and Related Health Problems. 10th Revision 2nd ed.

Yamamoto K, Shiota S, Ohno S, Kuroda A, Yoshiiwa A, Abe K, Murakami K, Fujioka T (2013). A diagnosis of depression should be considered in patients with multiple physical symptoms in primary care clinics. The Tohoku Journal of Experimental Medicine 229, 279-285.

Yen S, Shea MT, Sanislow CA, Grilo CM, Skodol AE, Gunderson JG, McGlashan TH, Zanarini MC, Morey LC (2004). Borderline personality disorder criteria associated with prospectively observed suicidal behavior. The American Journal of Psychiatry 161, 1296-1298.

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.

Zanarini MC, Frankenburg FR, Dubo ED, Sickel AE, Trikha A, Levin A, Reynolds V (1998). Axis I comorbidity of borderline personality disorder. The American Journal of Psychiatry 155, 1733-1739.

Zanarini MC, Frankenburg FR, Dubo ED, Sickel AE, Trikha A, Levin A, Reynolds V (1998). Axis II comorbidity of borderline personality disorder. Comprehensive Psychiatry 39, 296-302.

Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G (2012). Attainment and stability of sustained symptomatic remission and recovery among patients with borderline personality disorder and axis II comparison subjects: a 16-year prospective follow-up study. The American Journal of Psychiatry 169, 476-483.

Zanarini MC, Jacoby RJ, Frankenburg FR, Reich DB, Fitzmaurice G (2009). The 10-year course of social security disability income reported by patients with borderline personality disorder and axis II comparison subjects. Journal of Personality Disorders 23, 346-356.

Zimmerman M, Mattia JI (1999). Axis I diagnostic comorbidity and borderline personality disorder. Comprehensive Psychiatry 40, 245-252.

Zimmerman M, Pfohl B, Coryell WH, Corenthal C, Stangl D (1991). Major depression and personality disorder. Journal of Affective Disorders 22, 199-210.