


An abstract artwork featuring a dark, textured central shape, possibly a silhouette of a person or a map, set against a background of vibrant blue and purple hues. Several bright yellow and pink circular spots are scattered across the composition, and there is some faint red text at the bottom of the artwork.

Ulla Leskelä

Life Events and Social Support among Patients with Major Depressive Disorder

Publications of the National Public Health Institute  25/2008

Department of Mental Health and Alcohol Research
National Public Health Institute

and

Department of Psychiatry
University of Helsinki

Helsinki, Finland 2008

National Public Health Institute,
Department of Mental Health and Alcohol Research,
Helsinki, Finland
and
University of Helsinki,
Department of Psychiatry,
Helsinki, Finland

Ulla Leskelä

**LIFE EVENTS AND SOCIAL SUPPORT AMONG
PATIENTS WITH MAJOR DEPRESSIVE DISORDER**

ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Medicine, Institute of Clinical Medicine,
Department of Psychiatry, University of Helsinki, for public examination
at the Christian Sibelius-auditorium,
Välskärinkatu 12, on December 5th, at 12 noon.

Helsinki 2008

**Publications of the National Public Health Institute
KTL A25/2008**

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Julkaisija-Utgivare-Publisher

Kansanterveyslaitos (KTL)
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Mannerheimintie 166
FIN-00300 Helsinki, Finland
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ISBN 978-951-740-867-7
ISSN 0359-3584
ISBN 978-951-740-868-4 (pdf)
ISSN 1458-6290 (pdf)

Kannen kuva - cover graphic: Esa Leskelä

Yliopistopaino
Helsinki 2008

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MARGARET FULLER SLACK

Ellei sallimus olisi ollut niin ynseä minua kohtaan,
minusta olisi voinut tulla yhtä suuri kuin George Eliot –
katsokaa vain Penniwitin minusta ottamaa valokuvaa:
leuka käteen nojaten, syvämietteiset silmät,
harmaat ja kauaskatsovat kuin hänellä.
Mutta minun oli ratkaistava tuo ikuinen, ikuinen kysymys:
yksinkö, naimisiin vaiko turvautua vapaisiin suhteisiin?
Ja silloin John Slack, rikas apteekkari, kosi minua,
luvaten minulle mahdollisuudet antautua kirjoittamaan;
ja minä menin naimisiin hänen kanssaan
ja synnytin kahdeksan lasta saamatta koskaan aikaa kirjoittamiseen.
Kohdaltani kaikki oli jollakin tavalla lopussa
jo silloin, kun neula pisti käteeni lasten pyykkiä pestessäni
ja kuollessani jäykkäkouristukseen. Mikä ironinen loppu!
Kuulkaa minua, kunnianhimoiset sielut:
sukupuolivietti on elämän kirous!

Edgar Lee Masters: Spoon River antologia, 1915
Suomentaja Arvo Turtiainen

To Pekka, Anna-Elina, Leealaura and Antti

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Ulla Leskelä, Elämäntapahtumat ja sosiaalinen tuki vakavasti masentuneilla psykiatrisilla potilailla.

Kansanterveyslaitoksen julkaisuja, A25/2008, 88 sivua

ISBN 978-951-740-867-7; 978-951-740-868-4 (pdf-versio)

ISSN 0359-3584; 1458-6290 (pdf-versio)

<http://www.ktl.fi/portal/4043>

TIIVISTELMÄ

Tämä tutkimus on osa Kansanterveyslaitoksen Mielenterveyden ja alkoholitutkimuksen osaston ja Helsingin ja Uudenmaan sairaanhoitopiirin Peijaksen sairaalan Psykiatrian tulosyksikön vakavan masennuksen prospektiivista, naturalistista kohorttitutkimusta (Vantaa Depression Study), jossa seurataan 269 ajankohtaisesta vakavasta masennustilasta kärsivää psykiatrisen erikoissairaanhoidon avohoito- ja sairaalapotilasta.

Tutkimuksen tarkoituksena oli aluksi selvittää masennusepisodin alkuvaiheessa ilmeneviä eroavuuksia masennuspotilasryhmien välillä elämäntapahtumien esiintyvyydessä, lukumäärässä, negatiivisessa vaikutuksessa, attribuoinnissa ja tapahtumatyyppissä, sekä objektiivisessa ja subjektiivisessa sosiaalisessa tuessa. Elämäntapahtumien ajateltiin ryhmittyvän erityisesti aikaan ennen masennusta ja masennuksen prodromaalivaiheeseen. Seuraavaksi pyrittiin prospektiivisesti tutkimaan, ennustavatko elämäntapahtumien suurempi vakavuus ja vähäisempi objektiivinen ja subjektiivinen sosiaalinen tuki kaikkien, mutta erityisesti osittaisessa remissiossa olevien potilaiden heikompa toipumista. Kolmanneksi selvitettiin, heikkeneekö objektiivinen ja subjektiivinen sosiaalinen tuki vakavassa masennusepisodissa vietetyn ajan seurauksena, ja onko se sensitiivinen toipumiselle. Neljäntenä tavoitteena oli tutkia neuroottisuuden ja extraversion vaikutusta objektiiviseen ja subjektiiviseen sosiaaliseen tukeen vakavasta masennuksesta kärsivillä potilailla.

Seulonnan jälkeen 269, vakavan masennuksen oirekriteerit täyttävää, 20-59-vuotiasta potilasta (197 naista ja 72 miestä) tutkittiin puolistrukturoidulla haastattelumenetelmällä (the WHO Schedules for Clinical Assessment in Neuropsychiatry [SCAN], version 2.0). Vastaavasti selvitettiin kaikki muutkin psykiatriset diagnoosit. Elämäntapahtumia tutkittiin puolistrukturoidulla haastattelulla (Interview for Recent Life Events, IRLE; Paykel 1983) ja sosiaalista tukea edelleen puolistrukturoidulla haastattelumenetelmällä (the Interview Measure of Social Relationships, IMSR; Brugha et al. 1987). Subjektiivisesti havaittua sosiaalista tukea selvitettiin kyselykaavakkeella (the Perceived Social Support Scale-Revised, PSSS-R; Blumenthal et al. 1987) samoin kuin persoonallisuuden neurotisismia/ekstraversiota (the Eysenck Personality Inventory, EPI; Eysenck & Eysenck 1964). Kaikki tutkimukset toistettiin 6 ja 18 kuukauden kuluttua.

Depression alkuvaiheessa melkein kaikilla (91%) oli ollut elämäntapahtumia, keskimäärin 4.1±3.0 tapahtumaa edeltävän vuoden aikana. Sosiodemograafisten ja kliinisten ryhmien välillä ei ilmennyt suuria eroja; elämäntapahtumia oli jonkin verran enemmän nuoremmilla, kun taas ne masennuspotilaat, joilla oli myös komorbidi alkoholiongelmia tai persoonallisuushäiriö, kokivat vähemmän sosiaalista tukea. Vaikka tapahtumat jakautuivat tasaisesti aikaan ennen masennusta, prodromaalivaiheeseen ja vakavan masennuksen episodiin, kaksi kolmasosaa tutkituista arvioi elämäntapahtuman aiheuttaneen masennuksen, ja näistä tapahtumista vain yksi kolmasosa osui välittömästi prodromivaiheen alkuun.

Seurannassa ilmeni, että vastoinkäymiset ja/tai heikko havaittu sosiaalinen tuki vaikuttivat kaikkien vakavasti masentuneiden psykiatristen potilaiden toipumiseen heikentävästi. Voimakkaimmin ne vaikuttivat täyden remission alaryhmässä. Osittaisen remission ryhmässä vain vastoinkäymisillä, ja edelleen masennusepisodissa olevilla potilailla vain havaitulla sosiaalisella tuella oli merkitsevästi heikentävä vaikutus.

Vakavalla masennuksella oli vaikutusta sosiaaliseen tukeen. Matalampaa objektiivista sosiaalista tukea ennustivat pitenevä aika vakavassa masennustilassa, objektiivisen tuen matalampi lähtötaso sekä sukupuoli (miehillä matalampi tuen ennuste), kun taas subjektiivisesti koettua sosiaalista tukea ennustivat pitenevä aika masennustilassa ja subjektiivisen tuen matalampi lähtötaso. Kliinisen toipumisen myötä subjektiivinen sosiaalinen tuki parani, mutta ei objektiivinen.

Neuroottisuus ja ekstaversio persoonallisuuden piirteinä seurannan aikana assosioituivat johdonmukaisesti sosiaalisen verkoston kokoon ja koettuun sosiaaliseen tukeen, ja ennustivat subjektiivisen, mutta eivät objektiivisen sosiaalisen tuen muutosta. Nämä persoonallisuudenpiirteet saattavat modifioida erityisesti havaitun sosiaalisen tuen tasoa ja muutosta ja siten mahdollisesti vaikuttaa epäsuorasti myöhempään masentumisalttiuteen.

Tästä tutkimuksesta ilmenee, että vakavat elämäntapahtumat olivat yleisiä kaikissa depression johtavissa vaiheissa. Elämäntapahtumien määrässä ja laadussa ei ilmennyt huomattavia eroja depression alaryhmien välillä. Vakavilla elämäntapahtumilla saattaa siis olla monenlaisia rooleja, kuten esimerkiksi altistava rooli ennen masennusta, oirehdintaa syventävä rooli prodromaalivaiheessa ja masennuksen puhjettua toipumista vaikeuttava rooli. Potilaat yleisesti katsoivat jonkin tapahtuman johtaneen masennukseen. Vastoinkäymiset ja koettu sosiaalinen tuki ennustivat toipumista masennuksesta, masennuksen pitkittyminen puolestaan objektiivisen tukiverkoston pienentymistä sekä vähäisempää koettua sosiaalista tukea. Persoonallisuuden piirteet, neuroottisuus ja ekstraversio, modifioivat erityisesti koetun sosiaalisen muutoksen tasoa ja muutosta vaikuttaen näin epäsuorasti tulevaan masennusalttiuteen.

Avainsanat: Elämäntapahtumat, sosiaalinen tuki, masennus, neuroottisuus, ekstraversio.

ABBREVIATIONS

ANOVA	Analysis of variance
APA	American Psychiatric Association
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CI	Confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3 rd edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th edition
E/PE/PA	Extraversion/Positive Emotionality/Positive Affectivity
EPI	Eysenck Personality Inventory
ESEMeD	European Study of the Epidemiology of Mental Disorders
FINHCS	Finnish Health Care Survey
HAM-D	Hamilton Rating Scale for Depression
HPA-axis	Hypothalamic-pituitary-adrenal-axis
HS	Hopelessness Scale
HTR2A	Serotonin (hydroxytryptamine) receptor 2A
5-HTT	Serotonin transporter
HUCH	Helsinki University Central Hospital
ICD-10	International Classification of Diseases, 10 th edition
IMSR	Interview Measure of Social Relationships
IRLE	Interview for Recent Life Events
LEDS	Bedford College Life Events and Difficulties Schedule
LIFE	Longitudinal Interval Follow-up Evaluation
M-CIDI	Munich-Composite International Diagnostic Interview
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
N/NE/NA	Neuroticism/Negative Emotionality /Negative Affectivity
NCS-R	National Comorbidity Survey Replication
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NIMH	National Institute of Mental Health

ODIN	European Outcome of Depression International Network
OR	Odds Ratio
PMCD	Peijas Medical Care District
PSSS-R	Perceived Social Support Scale-Revised
SCAN	Schedules for Clinical Assessment of Neuropsychiatry
SCID-II	Structured Clinical Interview for DSM-III-R personality disorders
SCL-25	Symptom Checklist
SPSS	Statistical Package for the Social Sciences for Windows
SRE	Shedule of Recent Experience
SSI	Scale for Suicidal Ideation
TPH 1	Tryptophan hydroxylase 1 gene
VDS	Vantaa Depression Study
WHO	World Health Organization

Ulla Leskelä, Life events and social support among patients with major depressive disorder
Publications of the National Public Health Institute, A25/2008, 88 Pages
ISBN 978-951-740-867-7; 978-951-740-868-4 (pdf-version)
ISSN 0359-3584; 1458-6290 (pdf-version)
<http://www.ktl.fi/portal/4043>

ABSTRACT

This study is part of a collaborative depression research project, Vantaa Depression Study (VDS), between the Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki and the Department of Psychiatry of Helsinki University Central Hospital (HUCH), Peijas Hospital (the Peijas Medical Care District, PMCD), Vantaa. The VDS is a prospective, naturalistic cohort study of 269 secondary-level care psychiatric out- and inpatients with a new episode of DSM-IV major depressive disorder (MDD).

The aim of this study was firstly to examine at the onset of major depressive episode the differences in the prevalence, number, negative impact, attribution and type of life events in addition to objective and subjective support among subgroups of patients. It was also expected that life events are clustering into time before depression and prodromal phase of depression. Secondly it was prospectively investigated whether greater severity of life events and less subjective and objective social support would predict poorer outcome in all patients, but most among those currently in partial remission. The third aim was to find out whether objective and subjective social support decline as a consequence of time spent in Major Depressive Episode, and is sensitive to improvement. Fourthly it is examined whether objective and subjective social support are influenced by neuroticism and extraversion.

After screening, 269 Patients (aged 20-59; 197 women and 72 men) were investigated with a semistructured interview (the WHO Schedules for Clinical Assessment in Neuropsychiatry [SCAN], version 2.0) for the presence of a new episode of DSM-IV MDE, and other psychiatric diagnoses. Life events were investigated using semistructured method, Interview for Recent Life Events (IRLE; Paykel 1983), social support also with semistructured method, the Interview Measure of Social Relationships (IMSR; Brugha et al. 1987) and subjective, perceived social support with a questionnaire, the Perceived Social Support Scale-Revised (PSSS-R; Blumenthal et al. 1987). Neuroticism/extraversion was measured using a questionnaire, the Eysenck Personality Inventory (EPI; Eysenck and Eysenck 1964). All measures were repeated at 6- and 18-month interviews.

At the onset of depression nearly all patients (91%) reported life events, on average 4.1 ± 3.0 per preceding year. No major differences between sociodemographic and clinical subgroups were found; the frequency of events was somewhat greater among younger subjects, whereas those with comorbid alcoholism and personality disorders perceived less social support. Although events were distributed evenly between the time preceding depression, the prodromal phase and the index major depressive episode, two thirds of the patients attributed their depression to some life event. Only one third of the attributed events occurred immediately at the onset of the prodrome.

Adverse life events and/or poor perceived social support influenced the medium-term outcome of all psychiatric patients with MDD. These factors appeared to have the strongest predictive value in the subgroup of full remission. In the partial remission group, only the impact of severe life events was pronounced. In the MDE group the level of perceived social support was a significant predictor.

When investigating the impact of depression on social support, low objective social support was predicted by longer time spent in MDEs, low baseline objective support and male gender, whereas low subjective social support, again by longer time spent in MDE and lower baseline subjective social support. Along with clinical improvement subjective, but not objective, social support improved.

In medium-term follow-up of MDD patients, the personality dimensions of neuroticism and extraversion were consistently associated with the size of social network and perceived support and predicted change of subjective, but not objective, social support over time.

In conclusion, adverse life events were common in all phases towards depression. Differences between subgroups of depression were relatively small. It is conceivable that life events have many roles, for instance, before depression they may well precipitate it, in the prodromal phase impair symptoms of depression and during the treatment of MDE influence negatively the outcome of depression, even among already fully remitted patients. Patients frequently attributed their depression to some life event. Furthermore, adversities and perceived social support are important predictors of the outcome of depression, and time spent in MDE in turn has a negative impact on objective and subjective social support. Finally, the personality dimensions of neuroticism and extraversion may modify the level and change particularly in perceived social support, thereby indirectly having effect on future vulnerability to depression.

Keywords: Life events, social support, depression, neuroticism and extraversion.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals:

- I** 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.
Journal of Nervous and Mental Disease 192(5):373-381.
- II** Leskelä U, Rytsälä H, Komulainen E, Melartin T, Sokero P, Lestelä-Mielonen P, Isometsä E. 2006. The influence of adversity and perceived social support on the outcome of major depressive disorder in subjects with different levels of depressive symptoms.
Psychological Medicine 36(6):779-788.
- III** 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.
In press: Journal of Nervous and Mental Disease.
- IV** Leskelä U, Melartin T, Rytsälä H, Jylhä P, Sokero P, Lestelä-Mielonen P, Isometsä E. 2008. The Influence of personality on objective and subjective social support among patients with Major Depressive Disorder: a prospective study.
Submitted.

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1 INTRODUCTION

Painful experiences and severe losses have always aroused sadness. When facing adversities people have often been able "to work them through" or grieve them over. What happens, when this does not succeed? Normal affect of sorrow turns into the illness of severe depression, and according to DSM-IV MDD the patient has persistent depressed mood, loses the pleasure in his/her life, has sleeping difficulties, fatigue, feelings of worthlessness and excessive guilt, difficulties to concentrate, make definitions and has suicidal thoughts or attempts (American Psychiatric Association 1987; American Psychiatric Association (APA) 1993; American Psychiatric Association (APA) 2000). Major depressive disorder (MDD) is highly prevalent, more common among women, comorbid (Melartin et al. 2002), often recurrent and chronic illness leading to functional impairment and disability (Rytsälä et al. 2006).

Aetiologically major depressive disorder is multifactorial. Adverse life events together with genetic vulnerability and temperamental factors form the greatest, mutually interacting risk factors for major depression (Kendler et al. 1993a; Kendler et al. 2002; Kendler et al. 2006a). About one third of the association between adversities and onset of depression is also genetically influenced (Kendler and Baker 2007), mainly through neurotic temperament (Kendler et al. 1999a). The concept of social support is intertwined with that of life events, because the two concepts address different aspects of social interaction. Lack of social support, as broadly defined, seems also to be a risk factor for depression (Brown and Harris 1978; Cooper and Paykel 1994; Kendler et al. 2002; Paykel 1978). Genetic factors have again been found of aetiologic importance for social support in epidemiologic twin studies (Agrawal et al. 2002; Kendler and Karkowski-Shuman 1997; Kendler and Baker 2007). Whether psychosocial pathways to major depression may differ in demographically and clinically heterogeneous subgroups of major depression, is not well known. Another source of interest in this study was to find out whether the precipitating events would, logically, cluster in time before major depressive episode and whether patients attributed depression to some event. From the clinical point of view it is important to make clear whether adversities and social support are influencing the outcome of depression. It has been found earlier that fewer conflicts within the family and helpful friends outside it, predicted stable remission (Moos et al. 1998). Few close relationships have been associated to partial or non-remission (Cronkite et al. 1998). Adversities and social support, however, have been less important among those in severe depression (Andrew et al. 1993; Paykel et al. 1996; Sherrington et al. 2001). The aim of the second study was to investigate firstly whether psychosocial factors generally among all patients predict the outcome of depression, and secondly among patients with different levels of depressive symptoms, supposing that those with partial remission may have higher sensitivity to adversities and poor social support, compared with patients in full remission or in MDE. Depressive symptoms may create a burden for family, elicit criticism

(Moos et al. 1998) and provoke depression-dependent events (Hammen 1991), propagate negative feedback-seeking, excessive reassurance-seeking or avoiding interpersonal conflicts (Joiner 2000). Whether depressive episodes lead to long-term psychosocial consequences persisting after recovery has remained unclear. Only few studies comprise clinical samples and longitudinal designs. That is why it is important to study, whether objective and subjective social support decline as a consequence of time spent in MDE, and whether they are sensitive to improvement among patients with DSM-IV MDD. Relationships between major depression, psychosocial factors and premorbid vulnerability are complex and often reciprocal. Personality dimensions of neuroticism and extraversion have been found to associate with depression (Boyce et al. 1991; Fanous et al. 2007; Kendler et al. 2006b; Ormel et al. 2004), but they may also influence how people create and maintain their social world (Roberts and Gotlib 1997). Prospective, clinical investigations among patients with MDD, however, are not to be found. So it seemed worth of studying whether neuroticism and extraversion, by affecting social support, would modify and indirectly influence future vulnerability to depression.

The Vantaa Depression Study (VDS) is a prospective, naturalistic research and development study of 269 secondary-level care psychiatric out- and inpatients with a new episode of DSM-IV MDD. Life events and social support were firstly investigated at the onset of MDE and secondly as predictors for the outcome of depression. Thirdly, the consequences of time spent in MDD to social support was the main interest of the study and finally, the influence of personality dimensions of neuroticism and extraversion on social support.

2 REVIEW OF THE LITERATURE

2.1 Major Depressive Disorder (MDD)

2.1.1 Diagnosis of MDD

Painful experiences and severe losses have always aroused sadness. When facing adversities people have often been able "to work them through" or grieve them over. What happens, when this does not succeed? Normal affect of sorrow turns into the illness of severe depression.

Severe, clinical unipolar depression according to DSM-IV (American Psychiatric Association 1987; American Psychiatric Association (APA) 1993; American Psychiatric Association (APA) 2000) is characterized by one or more episodes of major depression lasting more than two weeks. During this time at least five symptoms are present, and out of these at least one of the symptoms must be either 1) persistent depressed mood or 2) loss of interest or pleasure. In addition at least 4 out of the following symptoms must be present: 3) significant weight change, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue or loss of energy, 7) feelings of worthlessness or excessive or inappropriate guilt, 8) diminished ability to think or concentrate or make decisions and 9) suicidal thinking, recurrent suicidal ideation with or without a specific plan to commit suicide. According to ICD-10 (World Health Organization 1992; World Health Organization 1993) the diagnosis of MDD requires one symptom less than DSM-IV, because fatigue and loss of energy is included in core symptoms of persistent depressed mood and loss of interest and pleasure. Feelings of worthlessness and inappropriate guilt are separated from each other. ICD-10 is in clinical use in Finland, while DSM-IV in research programmes.

2.1.2 Epidemiology of MDD

Despite variations in time references, age ranges, diagnostic criteria or methodology, studies about prevalence of depression in the general population have indicated that it is relatively common, recurrent, often with chronic course and comorbidity with Axis I and II and with somatic diseases. It is usually associated with substantial symptom severity and role impairment. About a fifth of the population, females more often than males, will experience major depressive episode at some point of their lives (Kessler et al. 1994; Kessler et al. 2003; Kessler et al. 2005). In USA study of the National Comorbidity Survey Replication (NCS-R) the lifetime prevalence of unipolar depression was 16.2% and the 12-month prevalence 6.6% (Kessler et al. 2003). In another large USA study, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Hasin et al. 2005), the

DSM-IV MDD prevalences were a little lower, 13.2% for lifetime, and 5.3% for 12 months. In Australia, the 12-month prevalences for major depression in adults aged 18 or more were very similar to NCS-R, namely 6.7(0.4)% in ICD-10 and 6.3(0.3)% in DSM-IV (Andrews et al. 2001).

The prevalence studies for MDD in Europe resemble those in USA and Australia. The Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Bijl et al. 1998) found that, in the general population of 7076 members, the lifetime MDD prevalence was 15.5%, and the 12-month prevalence 5.8%. In the European Study of the Epidemiology of Mental Disorders (ESEMED), the lifetime prevalence of MDD was 12.8%, and 12-month prevalence 3.9% estimated from a large population from Belgium, France, Germany, Italy, the Netherlands and Spain (Alonso et al. 2004). In the European Outcome of Depression International Network (ODIN) an overall prevalence of depressive disorders in randomly selected samples of the general population in United Kingdom, Ireland, Norway, Spain and Finland was 8.56% (10.05% for women and 6.61% for men) (Ayuso-Mateos et al. 2001).

In a Finnish Health Care Survey (FINHCS) the 12-month prevalence of 9.3% (females 10.9% and males 7.2%) was found (Lindeman et al. 2000), while more recently in the Health 2000 Study it was only 4.9% (females 6.3% and males 3.4%) (Pirkola et al. 2005b). The difference may be due to stringent exclusion criteria in diagnostic interview (M-CIDI) used in the Health 2000 Study. In the European Outcome of Depression International Network (ODIN) the overall weighted prevalences of depressive disorders' diagnostic groups (DSM-IV criteria and ICD-10 criteria) in Finland were 4.7% (females 6.6% and males 2.7%) for urban and rural populations 4.1% (females 3.8% and males 4.3%) (Ayuso-Mateos et al. 2001).

While up to 4% of men and 8% of women in epidemiological studies suffer from a clinically significant depressive disorder, symptoms of depression are much more common. Only one third of persons suffering from depression were being treated for the disorder in Finland (Lehtinen and Joukamaa 1994). Recognition of mental disorders is essential. According to the Symptom Checklist (SCL-25) used in primary care, one fourth of the sample had a mental disorder, but only two fifths of them were identified by the general practitioners (Joukamaa et al. 1994).

2.1.3 Comorbidity in MDD

2.1.3.1 Axis I comorbidity in MDD

Comorbidity, the occurrence of two or more disorders in a person in a defined period of time (Klerman 1990), among patients with major depressive disorder is very common. These patients generally suffer from at least one comorbid Axis I disorder (Hasin et al. 2005; Melartin et al. 2002; Melartin et al. 2004; Merikangas et al. 2003; Placidi et al. 2000; Vuorilehto et al. 2005). In the NCS-R, out of respondents with lifetime MDD, 72% met the criteria of at least one other comorbid disorder, including 59% with anxiety disorder, 24% with substance use disorder and 30% with impulse control disorder. Out of respondents with

12-month MDD, 64% had at least one other 12-month disorder, and again anxiety disorder (57.5%) was more common than substance use disorder (8.5%) or impulse control disorder (16.6%) (Kessler et al. 2003). In a clinical sample, 42% of patients with MDE had any anxiety disorder, 10% panic disorder, 20% generalized anxiety disorder, 15% social phobia and 8% alcohol use disorders (Sanderson et al. 1990). In Vantaa Depression Study 57% (N=152) had anxiety disorders, 25% (N=66) alcohol abuse/dependence and only 21% (N=56) out of patients had pure MDD (Melartin et al. 2002).

2.1.3.2 Axis II comorbidity in MDD

In epidemiologic investigations the overall personality disorder prevalence has been from 5% to 13% in the general population (Coid et al. 2006; Kantojärvi 2008), but 22% (Casey et al. 2004) and 38% (Hasin et al. 2005) in community samples with depressive disorders. Among patients with MDD in psychiatric care, the prevalences have been still greater, while about half of the patients have had also current personality disorder (Sanderson et al. 1990). In Vantaa Depression Study 44% out of patients with DSM-IV MDD had also current personality disorder (Melartin et al. 2002). The prevalence of different personality disorder clusters has varied in different sampling populations. In Oulu Study (Kantojärvi 2008), for instance, avoidant and obsessive-compulsive personality disorders in Cluster C were most common in the population sample, whereas borderline and antisocial personality disorders in cluster B were more common in the hospital-treated sample.

2.1.4 Aetiology of MDD

Aetiologically major depression is a multifactorial disorder with interacting developmental pathways reflecting internalizing symptoms, externalizing symptoms and psychosocial adversity (Kendler et al. 1993a; Kendler et al. 2002; Kendler et al. 2006a). Causal relationships between the individuals and their environment are seen as bidirectional, where the individuals actively create their internal and external worlds.

In intensive studies of the heritability (proportion of variability due to genetic factors) of depression (Kendler et al. 2006a; Korszun et al. 2004), the family history of even subsyndromal depression has been a risk factor for MDD (Lewinsohn et al. 2003), growing threefold among the first-degree relatives of MDD patients (Sullivan et al. 2000). Usually heritability, estimated somewhat higher among women than men (Kendler et al. 2002; Kendler et al. 2006a), has been reported from 20% to 45 % (Sullivan et al. 2000), but it has raised higher, nearly up to 80% in severely depressed psychiatric inpatients (McGuffin et al. 2007; Sullivan et al. 2000).

2.1.5 Course and outcome of MDD

Major depressive episode is often foreshadowed by a prodromal phase of illness with only some of DSM-IV symptoms present and followed by residual symptoms with only partial remission (Judd et al. 1998; Melartin et al. 2005). It has been estimated that half of all MDEs resolve in 2 to 4 months in population surveys (Kessler et al. 2003; Kessler et al. 2005; Spijker et al. 2002), where milder episodes are more common, and only one fifth of all individuals with MDE has a chronic course of illness. In a primary care investigation (Oldehinkel et al. 2000) using life chart methodology the median duration of 8 months in acute episodes of depressive disorders was found. In addition 91% reached at least partial remission during the 42 months follow-up. In psychiatric setting numerous reports on course and outcome of depression are to be found. It has been seen as a highly recurrent and often chronic disease (Angst 1986). Longer duration, severity of depression and presence of current comorbidity have been important predictors of the outcome of depression (Melartin et al. 2004; Parker et al. 2000; Ramana et al. 1995; Solomon et al. 2000). In a study of the long-term outcome of MDD in psychiatric care one tenth of patients have poor, one third intermediate and one half having favourable outcome, while achieving total remission lasted 11 months expressed in median (Holma et al. 2008).

2.2 Adverse life events

2.2.1 Stressful life events conceptually

The topic of stress cuts across several disciplines. According to the concept of homeostasis an organism strives to compensate the state of imbalance in some physiological functioning (Selye 1973). The quality of life is depending upon the ability to regulate emotional experiences according to the requirements of the situation (allostasis) (McEwen 1998). In stress, however, the regulation does not succeed. Stress activates HPA-axis so that stress hormones are excessively secreted (McEwen 2007).

In the psychological model of stress, the subjective perception of an objective environmental condition is underlined. Thus a perceived substantial imbalance between appraised demand and response capability under conditions where failure to meet demand has important perceived consequences (McGrath 1970), seems important. Subjective, negative experiences of threat, harm or demand are essential to the aetiological process linking stress and disease (Kasl 1996).

In epidemiological approach stress has been conceptualized more as an environmental condition, for instance as a negative consequence of chronic work stress, occupational burnout (Maslach et al. 2001). While personality factors may influence vulnerability to burnout (Kalimo et al. 2003; Mattila et al. 2007; Zellars et al. 2000), these personality factors may then interact with situational factors, as job demands and job resources

(Schaufeli and Bakker 2004) conducting to burnout. Environmental exposure variables thought to increase the risk of adverse health outcomes have been thought to contain threat or uncertainty or unpredictability or uncontrollability (Kasl 1996).

2.2.2 Investigation methods of life events

Since the 1960s life event research has gradually developed methodologically. In the Schedule of Recent Experience (SRE) (Holmes and Rahe 1967) stressful events were thought to indicate varying degrees of "readjustment demand", but it contains problems of contamination between cause and consequences. The Bedford College Life Events and Difficulties Schedule (LEDS) interview (Brown and Harris 1978) is methodologically more sophisticated. By the use of standard questions about the occurrence of particular life events and the avoidance of questions about reactions to events, it can be established, whether certain events occur irrespective of how a person felt about them or of the interviewer's judgment of what part they may have played in the onset of the psychiatric disorder. The semistructured Interview for Recent Life Events (IRLE; (Paykel 1983), used in the present investigation, is shorter, but it includes Brown's judgments of independence (of the disorder) and contextual threat (which is referred to as objective negative impact of events), in addition to exact timing of life events.

2.2.3 Childhood adversities and MDD

Childhood poor parenting has increased the lifetime risk for depression by 30%. In female twin studies it was associated with coldness and authoritarianism of both mothers and fathers (Kendler and Prescott 2006). No evidence for shared family environment affecting the risk for MDD was found. The writers conclude that individuals may react to parenting in different ways guided in part by genetically influenced characteristics e.g. temperament. Parental death, loss (Kendler and Prescott 2006) and depression (Lieb et al. 2002), as well as childhood physical (Widom et al. 2007) and sexual (Kendler and Prescott 2006; MacMillan et al. 2001; Weiss et al. 1999) abuse have been found to increase the risk for adult MDD. Negative childhood experiences seem to be more predisposing factors to depression in women than in men (Veijola et al. 1998).

It was also concluded in a Finnish study that early adversities may predict certain types of negative life events in adulthood on pathway to depression, but may also lead to HPA-axis-mediated sensitivity manifested in exaggerated stress-related sympathetic responses in adulthood increasing risk for depression (Korkeila et al. 2005). Within the Health 2000 project in Finland, associations between retrospectively self-reported adverse environmental factors during 0-16 years in childhood and adulthood affective-, anxiety- and alcohol use disorders were investigated. More adversities were associated with mental disorders among females than males, and several diagnosis-related patterns in the

associations were found. The investigators conclude that the impact of adversities is probably composed of a wide range of factors from direct causal associations to complex, interacting environmental effects. Variations in associations reflect the differing genetic and environmental transmission mechanisms of mental disorders (Pirkola et al. 2005a).

2.2.4 Adverse life events as precipitators of MDD

Together with genetic vulnerability and temperamental factors, adverse life events are likely to form one of the key domains of liability to major depression (Kendler et al. 1993a; Kendler et al. 2002; Kendler et al. 2006a). The relative risk of depression within six months after the most stressful events is estimated to be about sixfold (Paykel 1978) and the population attributable risk, including all life events, is commonly about 40 % (Cooke 1987).

Interactions between the risk factor domains appear to be important (Caspi et al. 2003; Kendler et al. 2005a). Especially, at high levels of adversity, neuroticism has been a potent predictor for onsets of MDE (Kendler et al. 2004). In addition, about one third of the association between adversities and onset of depression is not causal, but genetically influenced (Kendler and Baker 2007), and individuals may select themselves into high-risk environments (Kendler and Karkowski-Shuman 1997). This may happen through genetical traits of neurotic temperament, which predisposes both to exposure of stressful experiences and to episodes of depression (Kendler et al. 1999a). It has also been found that functional polymorphism in the promoter region of the 5-HTT gene has been found to moderate the influence of stress on depression: individuals with short alleles at the 5-HTT locus have increased sensitivity to the impact of mild stressors (Caspi et al. 2003). Dopamine transporter gene, genotype A2/A2, may also be involved in the development of depressive symptoms in individuals facing adversities (Elovainio et al. 2007). In monoamine-deficiency hypothesis stress is thought to lead to a state of depletion (Belmaker and Agam 2008). It has also been noted that major depression may itself generate further dependent life events (Hammen 1991), which again have been found more heritable than events independent of the respondent's own behaviour (Kendler et al. 1999b).

Gender, age and life events in depression

Because major depression is more common among women (Kessler et al. 1994; Kessler et al. 2003; Kessler et al. 2005), more precipitating life events could also be expected for them. Age differences in prevalence rates of major depression and depressive symptomology also raise questions about differences in triggering life events (Karel 1997). Adversities generally among people, however, have been known risk factors since 1960s and 1970s (Brown and Harris 1978).

Most of the earlier major studies about life events preceding depression have involved predominantly, or even exclusively, female subjects (Brown and Harris 1978; Kendler et al. 1993a), but recently more investigations about life events among males are also to be found (Kendler et al. 2006a). Results have been inconsistent. Compared with males, depressed females may (Bebbington et al. 1988; Sherrill et al. 1997), or may not (Dalgard et al. 2006; Kendler et al. 2001b; Maciejewski et al. 2001; Paykel 1991) experience more life events preceding their depression, react with more symptoms (Uhlenhuth and Paykel 1973), or respond differently to certain specific kinds of stress (Spangler et al. 1996). Kendler et al. (2001b) concluded that the greater prevalence of major depression among women cannot be attributed to differential sensitivity to stressful life events, while Maciejewski et al. (2001) found that women were approximately three times more likely than men to experience depression in response to any examined stressful life events.

Investigations of depression in different age groups have shown that the phase of life may well influence which risk factor domains for depression are most relevant. Pre-illness psychological vulnerability, stress and genetic factors may dominate in young adults, whereas comorbid medical and neurological disorders may contribute more among older adults, who thus are more biologically than psychologically or socially, at a greater risk for major depression (Blazer and Hybels 2005; Karel 1997).

Life events in temporal phases and subtypes of depression

The role of psychosocial stress may vary in different temporal phases of the illness process, and between subtypes of depression. The precipitating role of life events has been suggested to diminish over time in recurrent major depression (Mitchell et al. 2003), at least for the nine first lifetime episodes (Kendler et al. 2000; Kendler et al. 2001a; Post 1992). Furthermore, the temporal association between severe event and depression onset appears less close in recurrent melancholic and psychotic depression than in other types of depression (Brown et al. 1994; Frank et al. 1994).

Life events among comorbid subgroups in depression

Of patients with current DSM-IV major depression in psychiatric settings, about one half suffered from a comorbid anxiety disorder, up to one quarter a substance use disorder, and about one half a personality disorder (Melartin et al. 2002). Presence of clinically relevant syndromes other than depression is a major source of clinical heterogeneity. To what extent the presence of comorbid psychiatric disorders is related to differences in the psychosocial pathway to depression has been little investigated. Comorbidity between depression and anxiety disorders may reflect not only overlapping pathogenic mechanisms, but perhaps also temporally different stages of the same process (Brown et al. 1993; Finlay-Jones and Brown 1981). Depressed patients with co-existing alcoholism may face more adversity than others with depression (Loo et al. 1990), and patients with personality disorders may suffer more divorces, separations and other stressors (Pfohl et al. 1984).

Particularly among those with personality disorders and alcoholism, many of the adverse life events encountered are likely to be dependent on the subject's own behaviour. However, this does not necessarily imply that such events are intentional, nor that they are clinically unimportant in the pathway to depression or its outcome. On the contrary, shame and guilt about one's own actions or hostility by others are unlikely to improve anyone's mood.

Types of life events and precipitation in depression

The idea of Sigmund Freud (Freud 1926), was that anxiety is the reaction to the danger of losing an object, and the pain of mourning the reaction to the actual loss of the object. More recent investigations have given support for his conceptualizations (Brown et al. 1993; Finlay-Jones and Brown 1981). Loss and humiliating events have been particularly demoralizing among depressives (Farmer and McGuffin 2003) and in epidemiologic twin studies (Kendler et al. 2003b). In the former humiliating events were more frequent among males, while in the latter there were no gender differences. Personal stressful life events (assault, financial problems, serious housing problems, job loss, serious difficulties at work, serious illness, serious marital problems, divorce/separation, loss of confidant) and stressful network events (interpersonal conflict with an individual in the network, crises experienced by someone in the network, illness or death of someone in the network) have been associated with increased risk for MDD. Men were more sensitive to divorce, separation and work difficulties and women to their social network events (Kendler and Prescott 2006).

Attributive role of life events

The objective precipitating role of life events may differ from their subjective meaning. According to the attribution theory, symptoms are as far as possible normalized by attributing them to situational causes (Robbins and Kirmayer 1991). However, depressive persons are prone to cognitive, dispositional distortions (Beck et al. 2004). Although life events have been extensively studied, whether depressive patients attribute the onset of depressive episode generally to some life event, has been little investigated, not to speak of differences between clinical subgroups. Life event research, however, has often considered this effort after meaning as merely a methodological problem.

Life events in the prodromal phase of depression

Preceding adverse life events usually seem to have occurred not long before the onset of depression (Brown and Harris 1978; Goodyer et al. 2000; Kendler et al. 1998). Because major depressive episodes (MDEs) are usually foreshadowed by prodromal illness phase, it remains poorly understood whether the psychosocial antecedents of depression actually intermingle with the early phases of the depressive syndrome, occurring not before but

during the presumably vulnerable period of prodromal symptoms. An interaction of prodromal or residual symptoms with life stress (Brown et al. 1993; Fava et al. 1998; Fava 1999), especially with highly proximal events, was suggested to be essential in provoking depressive symptoms above the threshold of a depressive disorder (Goodyer et al. 2000).

2.2.5 Adverse life events in the outcome of MDD

In contrast to the established role in precipitating depressive episodes, the influence of adversities on the outcome of depression remains more obscure. In general, adverse life events before onset of an episode have been found to predict better outcome in some investigations (Monroe and Depue 1991; Reno and Halaris 1990), but not in all (Brugha et al. 1997; Melartin et al. 2004; Monroe et al. 1992). Different patient samples, methods of measurement and time intervals make comparison between investigations difficult. Adversities exerting their influence after the onset of depression, however, may predict long-term outcome more effectively. In a long-term cohort study the presence of stressful circumstances predicted less improvement in depression (Billings and Moos 1985; Swindle et al. 1989). The role of adverse life events has, however, been found to be less important among patients with severe depression (Andrew et al. 1993; Paykel et al. 1996; Sherrington et al. 2001).

2.2.6 Adverse life events on the current level of MDD

Major depressive disorder is a long-term disorder with alternating periods of depression, prodromal or residual symptoms and full remission (Judd et al. 1998; Melartin et al. 2005). To what extent adverse life events as determinants of symptom-level outcome are dependent on the current level of depressive symptoms is not known. The impact of adverse events might well vary depending on the clinical state of the patient. Partial remission, for instance, may indicate a high risk for relapse or recurrence (Paykel et al. 1995), therefore representing a state of increased vulnerability to adversity.

2.3 Social support

2.3.1 Social support conceptually

Researches have put forward a wide variety of complementary definitions of social support (Quick et al. 1996) leading consequently to a variety of ways to measure and operationalize them, - and inconveniences in comparing different results. Genetic factors have been of aetiologic importance for social support in epidemiologic twin studies. The weighted heritability has been estimated to 23% for friend problems, 38% for relative problems, 17% for friend support, 31% for relative support, 31% for confidants and 31% for social integration (Agrawal et al. 2002; Kendler 1997; Kendler and Baker 2007). Genetic investigations have also shown that tryptophan hydroxylase 1 gene (TPH1) may be involved in the development of depressive symptoms by moderating the impact of demoralizing social influences (Jokela et al. 2007), whereas serotonin hydroxytryptamine receptor 2A (HTR2A) gene in the ability of individuals to use environmental support.

In perceptual approach social support is defined as the individual belief that one is cared for and loved, esteemed and valued and belongs to a network of communication and mutual obligation (Cobb 1976).

A developmental approach to social support maintains that secure attachments in childhood are rooted in human behaviour and form the basis for an adult's ability to form effective social relationships (Bowlby 1979). Subjectively perceived social support (Sarason et al. 1991), as opposed to objective availability of it, has been thought to reflect these early attachments in childhood. Subjectively perceived social support may also contain relatively stable personality-like qualities (Lahey and Cassady 1990).

In dynamic terms social support has been defined as interpersonal transactions, an exchange of resources between at least two individuals perceived by the provider or recipient to be intended to enhance the well-being of the recipient (Quick et al. 1996).

Social support has also been described structurally according to the types and sources of social support. Emotional support, especially from family and close friends, is the most often recognized form of social support. Appraisal support, again, means transmission of affirmation, feedback or social comparison. Informational support includes advice, suggestions, or directives for responding to personal or situational demands, and instrumental support includes concrete forms of support, such as money or time.

In functional approach social support has protective, informational, evaluative, modelling and emotional functions (Quick et al. 1996), partly overlapping with other definitions. While the conceptualization of Finfgeld-Connett (2005) also combines many elements of those mentioned earlier, it has some new aspects to it: social support is composed of emotional and instrumental support. It is an advocative interpersonal process

characterized by reciprocal exchange of information. It is context specific, and it results in a number of improved health outcomes. Antecedents of emotional and instrumental support include a perceived need, a social network and climate that are conducive to the exchange of social support (Finfgeld-Connett 2005).

2.3.2 Social support as a risk and protective factors of MDD

Poor social support, as broadly defined, seems to be a risk factor for depression (Brown and Harris 1978; Cooper and Paykel 1994; Kendler et al. 2002; Paykel 1978). Social support as a protective factor, however, has been thought to lower the risk of depression by modifying the impact of risk situations (buffering effect), but social relationships may also have beneficial effects regardless of whether individuals are under stressful risk situations (main effect) (Aro 1994; Cohen and Wills 1985) or not. It has been suggested that embeddedness of individual social networks within the broader social structure (the social capital of the person) may operate via main effects, whereas functional aspects of social relationships (as perceived support) operates through a stress-buffering mechanism (Kawachi and Berkman 2000).

Women have larger and more intimate social networks compared with men, and they have been more sensitive than men to the demoralizing effects of low levels of social support in a longitudinal study of opposite-sex twins (Kendler et al. 2005b) and more vulnerable than men without social support when exposed to life events in a cross-sectional, multinational community survey from five European countries using Beck Depression Inventory as a measure of depression (Dalgard et al. 2006). Social factors appear to be weaker predictors for depression onset among older adults (George 1994). Different comorbid groups of alcoholism or personality disorders in the pathway to depression have had weaker social support or more social difficulties than MDD patients without these comorbidities (Loo et al. 1990; Pfohl et al. 1984).

The structure of the family, the basic source of social support, may also vary with gender and age, and the family may protect depressive men more than women (Bebbington 1987), who may be able to maintain alternative sources of support such as non-marital friendships despite depressive symptoms (Salokangas et al. 1988). Social support in the families of patients with MDD is reported weaker overall (Miller et al. 1986), even after symptomatic remission (Keitner and Miller 1990). The authors, however, assume no single linear causality between depression and family functioning, but instead a mutually reinforcing negative pattern of interaction.

2.3.3 Social support in the outcome of MDD

Poor social support after the onset of depression may effectively predict worse outcome of MDD, and the presence of more supportive social resources has predicted more improvement in depression in a long-term cohort study (Billings and Moos 1985; Swindle et al. 1989). Furthermore, having more independence and less arguments and conflicts within the family

and more helpful friends and activities with them outside the family were found to predict stable remission (Moos et al. 1998), while having fewer closer relationships predicted partial or non-remission (Cronkite et al. 1998). Social support has, however, had less meaning among patients with severe depression (Andrew et al. 1993; Paykel et al. 1996; Sherrington et al. 2001).

2.3.4 Social support on the current level of MDD

Like adverse events, objective and subjective social support might well vary depending on the clinical state of the patient. Social resources may also be reduced in partial remission and during a depressive episode, because symptoms create a burden for family and friends and often elicit criticism (Moos et al. 1998). Thus, being depressed may provoke depression-dependent events. On the other hand, family members and friends may also adapt to patients' episodes of depression and remain supportive (Hooley et al. 1994; Moos et al. 1998).

2.3.5 Impact of MDD on social support

Even though all studies (Burton et al. 2004; Kessler et al. 1994; Wade and Kendler 2000a) do not support the idea of a specific buffering role for social support against depression when facing adversity, low social support per se, is likely to be a predisposing factor for depression (Kendler et al. 2002). Depression per se, however, may in turn have important negative consequences for social support available to the patient (Coryell et al. 1993), which then could even progressively predispose the patient to later recurrences or chronicity.

Current interpersonal difficulties and weak social support are closely connected with the onset of depression. To some extent, these may actually reflect the premorbid vulnerability of a depression-prone individual. For example, deficits in interpersonal functioning may in part reflect temporary symptoms of depression and remit along with the depressive episode, and in part may well have been present before onset (Petty et al. 2004). From several perspectives, however, researchers have proposed that the presence of depression could undermine various forms of social support. In addition, a 'scar' hypothesis (Lewinsohn et al. 1981) proposes, that depressive episodes may leave erosive psychosocial (Rohde et al. 1990), cognitive (Nolen-Hoeksema et al. 1992) or personality (Kendler et al. 1993c) scars presumably encoded at the biological level (Burcusa and Iacono 2007), but these views have not received unequivocal empirical support (Jylhä et al. 2007; Oldehinkel et al. 2003; Shea et al. 1996; Zeiss and Lewinsohn 1988).

T.E. Joiner Jr. has suggested several active, self-propagating interpersonal processes that might contribute to chronicity of depression (Joiner 2000). A depressive person may self-generate interpersonal stress when depressed (Hammen 1991), so that negative feedback-seeking (Coyne et al. 1987; Joiner et al. 1997; Swann 1996), excessive reassurance-seeking, or avoiding of interpersonal conflicts may precipitate rejection and

lead to social withdrawal (Joiner 2000). Recently, it has been investigated the relationship of the components of depressive symptoms on perceived social support and demand among elderly, and found that in particular the cognitive component, depressiogenic beliefs, predicted negative changes in social support and demand prospectively (Maher et al. 2006).

Clinical studies lend some empirical support to perspectives outlined above. The NIMH Collaborative Depression Study found occupational, economical and psychosocial impairment to persist for years among patients with major affective disorder, even after resolution of clinical symptoms, suggesting that recurrences one after another may lead to long-term psychosocial impairment (Coryell et al. 1993). Also in a cross-sectional study of major depressive outpatients, a longer duration of current episode was related to patients' perceptions of low support from friends (Gladstone et al. 2007). In contrast, a general population study (Petty et al. 2004), found no evidence for recurrent episodes producing interpersonal scars. Moreover, in female twin investigations (Wade and Kendler 2000a; Wade and Kendler 2000b) it was found that major depression lowered social support and social support again influenced risk for major depression while both reflected a common genetic liability. Thus, whether depressive episodes actually lead to long-term psychosocial consequences persisting after recovery still remains unclear due to methodological limitations in the previous studies, as only a few comprise clinical samples and involve longitudinal designs (Lara and Klein 1999). Comparison of studies is also difficult, because social support is measured with variable methods focusing on somewhat different aspects of social support. A clear view of the impact of severity, duration, recurrence or chronicity of major depressive disorder on social support is still missing.

2.4 Personality

2.4.1 Dimensions of personality

The concept of temperament has been seen as the early appearing core of later adult personality. It remains relatively stable, is inherited and based in biological processes (Bates 2000; Pervin et al. 2005). Theories of temperament differ as to dimensions and the number of them. In the theory of Cloninger (Cloninger et al. 1993), four adult dimensions of temperament are discerned: novelty seeking, harm avoidance, reward dependence and persistence, whereas Strelau emphasizes six temperamental traits: briskness, perseverance, sensory sensitivity, emotional reactivity, endurance and activity (Strelau and Zawadzki 1993). The theories of childhood temperament describe temperament more from the developmental point of view (Buss and Plomin 1975; Kagan et al. 1986; Thomas and Chess 1977).

Personality, instead, can be conceptualized as a large entity of individual differences including values, motives, attitudes, needs, coping mechanisms, capabilities, attainments and self-esteem. Personality develops from temperament through experiences, maturation and

interaction with environment. In the trait theories of personality specific responses in behaviour are linked together as habits, and habits grouped as traits, and traits are linked together as higher-order factors using statistical technique of factor analysis (Pervin et al. 2005).

The number of traits in personality theories has varied including, for instance, the 16 factor-model (Cattell 1965), the three factors model (Eysenck and Eysenck 1975) and the five-factor model (Costa Jr. and McCrae 1992). Two widely studied personality dimensions, Neuroticism and Extraversion (Watson et al. 1999) have also been included in the largely supported Big Five factor model, together with the factors of Agreeableness, Conscientiousness and Openness to new experience.

A person with high neuroticism (N) is prone to be anxious, emotionally unstable and self-conscious. He/she worries, sleeps badly, has psychosomatic diseases, allows emotions to affect judgements and is preoccupied with things that might go wrong. A person with low N, instead, is calm and unworried generally, and recovers quickly after an emotionally upsetting experience (Eysenck and Eysenck 1964). Sensitivity to negative stimuli (Clark et al. 1994) is essential in neuroticism (N), negative emotionality (NE) (Tellegen et al. 1988) and negative affectivity (NA) (Watson et al. 1988), and N/NE/NA is linked with aversive motivational system inhibiting behaviour (Clark et al. 1994).

Extraversion contains positive emotionality, energy and dominance. An extravertive person is sociable, likes parties and people, while an introvert is quiet, sits more willingly over books and is reserved except to intimate friends (Eysenck and Eysenck 1964). Extraversion (E), positive emotionality (PE) (Tellegen et al. 1988) and positive affectivity (PA) (Watson et al. 1988) all have affective core reflecting tendency to positive mood states, and E/PE/PA is linked with behavioural activation system facilitating behaviour (Clark et al. 1994).

A comprehensive framework for understanding the whole person has recently been proposed (McAdams and Pals 2006). It strives to integrate the Big Five model of personality traits with those self-defining features of psychological individuality constructed in response to situated social tasks and the human need to make meaning in culture. Five fundamental principles are expressed. Personality is (1) an individual's unique variation on the general evolutionary design for human nature, expressed as a developing pattern of (2) dispositional traits, (3) characteristic adaptations and (4) self-defining life narratives, complexly and differentially situated in (5) culture and social context.

2.4.2 Personality as a direct and indirect risk factor for MDD

Personality dimensions have been found to influence the risk for depression and also to modify its outcome in several ways. High neuroticism, for instance, has been considered a risk factor for depression in prospective epidemiological twin (Fanous et al. 2007; Kendler et al. 1993b; Kendler et al. 2002; Kendler et al. 2006a; Kendler et al. 2006b),

general population (Ormel et al. 2004) and clinical (Angst and Clayton 1986; Boyce et al. 1991; Hirschfeld et al. 1989; Nyström and Lindegård 1975) studies. Moreover, low extraversion has been suggested to be a vulnerability factor for depression (Hirschfeld et al. 1983; Kendler et al. 2006b), and high extraversion to exert some protective effects against depression (Farmer et al. 2002). However, premorbidly started prospective epidemiological studies among male conscripts (Angst 1986) and women (Kendler et al. 1993b), as well as two prospective clinical studies (Boyce et al. 1991; Hirschfeld et al. 1989) have not proved this to be a risk factor.

Personality may also have indirect influences on risk for and outcome of depression through interpersonal influences (Kendler et al. 1993b; Roberts and Gotlib 1997). Neuroticism has been found to mediate the relation between support and depression (Henderson 1981). Indirect influences of introversion on risk and outcome of depression remain somewhat obscure, but may arise resulting from introverts failing to obtain adequate social support (Roberts and Gotlib 1997). Shy and unsupported university students were likely to experience increases in depressive symptoms and the effect was mediated by an internal experience of loneliness (Joiner 1997). However, how personality influences the psychosocial resources available to the patient is not well known, and the scant research conducted has comprised cross-sectional, non-clinical studies of stress and coping (Holahan et al. 1999; Holahan et al. 2000).

2.4.3 Impact of personality on social support in MDD

Personality has an impact on social support (Kendler et al. 2003a), because people differ in their ability to create and maintain adequate social support networks (Roberts and Gotlib 1997). Twin studies support this view. Genetically influenced personality traits also play a role in influencing how individuals create their own social world (Agrawal et al. 2002; Kendler 1997; Kendler et al. 2003a; Kendler and Baker 2007). In addition, perceived social support has been suggested to partly be a variable with personality-like qualities (Lakey and Cassady 1990). Furthermore, personality characteristics, such as negative self-concept and dependence, may lead to unsupportive relations and negatively affect the quality of relationships with persons who might otherwise be supportive (Joiner et al. 1993). However, the influence of the personality traits of neuroticism and extraversion on social functioning among patients with major depression has been studied little. Because these patients are prone to have high neuroticism and low extraversion (Jylhä et al. 2007), pronounced effects could be expected. It is also conceivable that patients with lower neuroticism or higher extraversion might be more flexible in recreating social resources that were impaired during depressive episodes. As far as we know only one cross-sectional study of tertiary care depressive patients exists (Ranjith et al. 2005). In this study, after adjusting for clinical and demographic variables, extraversion made the largest contribution to social functioning, and neuroticism did not persist as a significant predictor.

3 AIMS OF THE STUDY

The aim of this prospective, medium-term investigation is to clarify the role of adverse life events and social support among patients with DSM-IV major depression and:

I to examine the differences in the prevalence, number, negative impact, independence (of MDE), attribution, and type of life events in addition to objective and subjective support among subgroups of patients. It was also expected that life events are clustering more into time before depression and prodromal phase, and less into time of ongoing depression.

II to investigate whether greater severity of life events and less subjective and objective social support would predict poorer outcome in all patients, but most among those currently in partial remission, because of their higher sensitivity to these aspects. Those in full remission were expected to be more resilient and those in major depressive episode less responsive to adversities and poor social support.

III to investigate whether objective and subjective social support decline as a consequence of time spent in MDE, and are sensitive to improvement.

IV to examine whether objective and subjective social support are influenced by neuroticism and extraversion. Regarding between-subject differences, it was firstly hypothesized that the lower the neuroticism or the higher the extraversion, the higher the level of objective and subjective social support; conversely, the higher the neuroticism or the lower the extraversion, the lower the level of social support. Secondly, it was hypothesized that the lower the neuroticism or the higher the extraversion, the greater the within-subject positive changes in objective and subjective social support; conversely, the higher the neuroticism or the lower the extraversion, the smaller these changes.

4 MATERIALS AND METHODS

4.1 General study design

The Vantaa Depression Study (VDS) is a prospective, naturalistic cohort study of patients with DSM-IV MDD. A control group of patients without depression was not used.

Context of the study

The Vantaa Depression Study (VDS) is a collaborative depression research project between the Department of Mental and Alcohol Research of the National Public Health Institute, Helsinki, Finland, and the Department of Psychiatry of the Peijas Medical Care District (PMCD), Vantaa, Finland. The catchment area comprises the city of Vantaa (population 169 000 in 1997), bordering Helsinki. The PMCD Department of Psychiatry offers secondary care psychiatric services to all Vantaa citizens. These include a psychiatric inpatient unit, a general hospital outpatient clinic, six community mental health care centres - each covering a specific catchment area - and two day hospitals.

4.2 Screening

The first phase of patient sampling for the VDS cohort study involved screening all patients in the PMCD with a possible new episode of DSM-IV MDD between 1 February 1997, and May 31, 1998. During that period, every patient (N=806) aged 20-59 years 1) seeking treatment at, 2) being referred to, or 3) already receiving care and now showing signs of deteriorating clinical state in the department of psychiatry, but without a clinical diagnosis of ICD-10 schizophrenia or bipolar I or II disorders, was screened for the presence of depressive symptoms by their attending mental health professional. The screening instrument included the five screening questions for depression from the WHO schedules for clinical assessment in neuropsychiatry (SCAN), version 2.0 (Wing et al. 1990). The scale for suicidal ideation (SSI) (Beck et al. 1979) was also completed to identify cases with moderate to severe suicidal ideation or plans. After either 1) a positive response to any of the SCAN screening questions, or 2) a score of six or more in the SSI, irrespective of the presence of depressive symptoms, the patient was fully informed about the study project, and written consent requested. Of the 703 eligible patients, 161 (22.9%) refused to participate in the study, but 542 (77.1%) agreed and gave written informed consent. The patients who refused did not differ significantly ($p>0.05$) in age and gender from those who consented. The research protocol for the VDS was approved by the Ethics Committee of the PMCD in December 1996.

4.3 Baseline evaluation

4.3.1 Diagnostic measures

In the second phase of sampling, the 542 participating patients were interviewed face-to-face by one of the researchers (UL, PL-M, TM, HR or PS) using the WHO SCAN (Wing et al. 1990). The interviewers had all received training by a WHO certified training centre. Based on the interview, 269 patients diagnosed with DSM-IV MDD were included in the MDD cohort study. Diagnostic reliability was investigated using 20 videotaped diagnostic interviews; the kappa coefficient for MDD was 0.86 (0.58-1.0), with a 95% observed agreement rate (Melartin et al. 2002).

The decision to include a patient in the study cohort was made by the researcher during the interview, after which the entire SCAN interview (Wing et al. 1990) was conducted to achieve a full picture of axis I comorbid disorders. In addition, the Structured Clinical Interview for DSM-III-R personality disorders (SCID-II) (Spitzer et al. 1989) was used to assess diagnoses on axis II.

4.3.2 Exclusion criteria

All patients who had earlier received a diagnosis of schizophrenia, schizo-affective disorder or another psychosis, or of DSM-IV bipolar I or II disorder or substance-induced mood disorder, were excluded even if they currently fulfilled the criteria of MDD.

4.3.3 Observer and self-report scales

At the baseline phase 17-item Hamilton Rating scale (Hamilton 1960) and the 21-item Beck Depression Inventory (Beck et al. 1961) was used to assess the severity of depression, Beck Anxiety Inventory (Beck et al. 1988) to assess anxiety symptoms, the Beck Hopelessness Scale (Beck et al. 1974) to assess hopelessness, and Eysenck Personality Inventory (Eysenck and Eysenck 1964) to assess neuroticism and extraversion.

4.3.4 Measurement of life events at baseline

The Interview for Recent Life Events (IRLE) (Paykel, 1983) was used. This measures 64 life events in categories including work, education, finance, health, bereavement, migration, courtship and cohabitation, legal, family and social relations, and marital relations. Events are inquired using a semistructured interview, and rated according to their objective negative impact from severe (value 1) to no negative impact (value 5), independence of the psychiatric illness from almost certainly independent (value 1) to almost certainly dependent (value 5), and the month of their occurrence. The IRLE has been found to have good reliability and validity (Paykel 1983).

In our study the scale of objective negative impact, however, was inverted so that score 1 signified "no negative impact", 2 "slight negative impact", 3 "moderate negative impact", 4 "remarkable negative impact" and 5 "serious negative impact". In statistical comparisons of impact, higher values were also given more weight using geometric weighting (1,2,4,8,16) to emphasize more serious events. The independence of the event from the MDD (but not from comorbid disorders) was assessed in order to improve reliability. To exclude the possible bias through including life events that are caused by depression, all statistical analyses were repeated, including only events almost certainly independent or probably independent of depression (values 1 or 2 in the independence scale). The period of measurement comprised the 12 months before the first baseline interview. The timing of events occurred with an accuracy of a calendar month (resulting in 12.5 months on average). The onset of the prodromal phase of depression was defined as the onset of the first criteria symptom of depression before the current mood episode fulfilled the criteria for (unipolar) DSM-IV Major Depressive Disorder. In the interview it was also asked whether the patients considered some life event as having triggered their state of depression and also their view about the presence of any positive event neutralizing earlier adversities or heralding a fresh start in their life.

4.3.5 Measurement of social support at baseline

Two instruments, the Interview Measure of Social Relationships (IMSR) (Brugha et al. 1987), and the Perceived Social Support Scale - Revised (PSSS-R) (Blumenthal et al. 1987) were used. IMSR is a semistructured interview designed to collect data on the number of contacts, and the presence of attachment figures of a person, on the presence of negative and intense interaction, and on the number of members known by each person in the primary group containing relatives and friends. The network size of primary group was used as a measure of objective social support. Questions were made only about primary groups containing close relatives and friends contacted within the two weeks before the interview. Brugha himself found differences in the stability of the questions, but the overall reliability of the IMSR has been found good. In addition, questions were asked about social support sought and offered in the context of life events, and whether the respondent had been criticised by someone close. The PSSS-R questionnaire of perceived social support was the measure of subjective social support. It provides a total score ranging from 12-60 and factor-analytically derived subscale scores for family, friends and a significant other. The reliability of the PSSS-R has been found good (Blumenthal et al. 1987). The shortened 12-question version with a 1-5 Likert scale was used.

4.4 Follow-up procedure

Of the 269 patients with current MDD initially included in the cohort (Melartin et al. 2002), 229 participated in the 6-month, and 207 in the 18-month follow-up. Patients participating in the 18-month, but not in the 6-month interview (N=5), or those whose diagnosis switched to bipolar disorder between the follow-ups (N=9) were excluded from the analyses. Thus, 193 patients participated in both the 6- and 18-month follow-ups. Of the original 269 patients, 76 were excluded from the investigation; these patients were younger (median 32.9 years vs. 42.9 years, $Z=-3.61$, $p<0.001$), had higher scores on the BAI (25.3 vs. 21.0, $Z=-2.24$, $p=0.025$), and were more often living alone (46/76, 60.5% vs. 88/193, 45.6%, Chi-square=4.283, $df=1$, $p=0.038$) than those participating in both follow-ups. These patients did not, however, differ from the participants in terms of the number of life events (Mann-Whitney, $Z=-1.281$, $p=0.200$) and IMSR baseline network size (Mann-Whitney, $Z=-0.678$, $p=0.497$) or PSSS-R baseline perceived social support (Mann-Whitney, $Z=-0.301$, $p=0.763$).

All diagnostic measures and observer and self-report scales were repeated at 6- and 18-month follow-ups. Patients were divided into three mutually exclusive groups on the basis of DSM-IV criteria using graphic life chart methodology: a) those in a state of full remission (none of the 9 MDE criteria symptoms), b) those in a state of partial remission (1-4 of the 9 symptoms), and c) those in a state of full MDE (5+ of the 9 symptoms) at 6 months. Relapse was defined, when symptoms fulfilling the DSM-IV MDE criteria have returned after a period of less than two months (but more than two weeks), and recurrence, when these symptoms have returned after at least two consecutive months of full or partial remission.

The median times to follow-up interviews were 6.5 and 18.8 months for interviews at 6- and 18-months, respectively. Most (174/198, 88%) of the patients at baseline have received antidepressants at an adequate dosage (154/198, 78%) (Melartin et al. 2004).

4.4.1 Measurement of life events in the follow-up

The Interview for Recent Life Events (IRLE) was used again (Paykel 1983) to measure events from baseline to 6-month and from 6- to 18-month in the same way as in baseline. The reliability of the measurement of life events using IRLE was not tested. Although the study design was prospective, life events have to be assessed retrospectively.

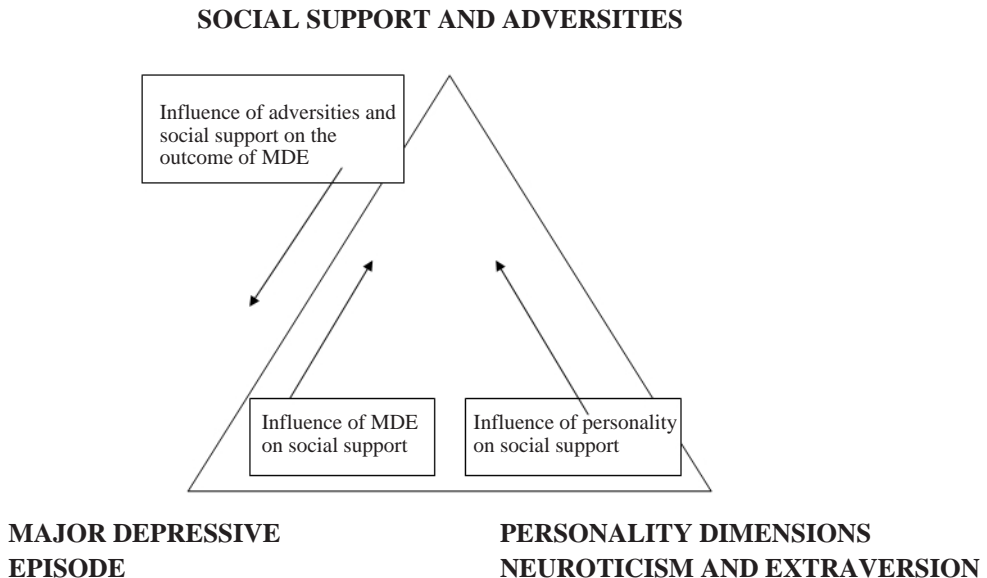
4.4.2 Measurement of social support in the follow-up

At 6- and 18-month interviews objective social support two weeks before and subjective, perceived social support cross-sectionally were assessed in the same way as in baseline. Because the distribution of PSSS-R at 18 months was skewed, it was recoded into eight classes (class intervals: 12-18, 19-24, 25-30, 31-36, 37-42, 43-48, 49-54, 55-60) which resulted in a more normal distribution. Although the reliability of IMSR or PSSS-R was not tested, Cronbach's alpha coefficient for internal consistency for IMSR primary network size was 0.90 at baseline, 0.90 at 6 months and 0.89 at 18 months, and for PSSS-R respectively 0.94, 0.95 and 0.96.

4.4.3 Study design and outcome measures of follow-up studies

Investigated relationships between major depression, adversities, social support and personality in the follow-ups are seen in a triangle. Figure 1.

Figure 1. Relationships investigated between variables in the follow-ups depicted using a triangle.



4.4.3.1 Influence of adversities and social support on the outcome of MDD

The main interest was in the period between the 6- and 18-month follow-up interviews, in order to find out whether greater severity of life events and less subjective and objective social support among patients with different current levels of MDD at 6 months predict poorer outcome of depression at 18 months, although life events during the first six months after the baseline interview are also reported.

The measures of social support were prospectively repeated at the 6- and 18-month follow-ups. The adverse life events and social support factors as predictors of later outcome were investigated by stratifying patients into three mutually exclusive groups on the basis of DSM-IV criteria in graphic life chart methodology: a) those in a state of full remission (none of the 9 MDE criteria symptoms), b) those in a state of partial remission (1-4 of the 9 symptoms), and c) those in a state of full MDE (5+ of the 9 symptoms) at 6 months.

The main outcome measure was the score on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1960) at the 18-month follow-up interview. This method is largely used producing thus comparable quantified results of an interview. It has also been devised for use on patients already diagnosed as suffering from affective disorder of depressive type (Hamilton, 1960).

4.4.3.2 Influence of MDD on social support

Objective (IMSR network size) and subjective (PSSS-R perceived social support) social support in addition to demographic characteristics are reported at baseline, at 6 and at 18 months generally and specifically within a subgroup of chronically depressed patients because persisting in MDE throughout the whole 18-month period can be expected to result in most clear deterioration in social support. In addition 18-month objective and subjective social support are reported among subgroups of fully remitted, partially remitted and MDE.

The exact duration of the index episode and the timing of possible relapses or recurrences were examined by gathering all available data which were then integrated into the form of a graphic life chart. Life chart was based on DSM-IV criteria. Time expressed in months after the first baseline interview were divided into three periods: (1) state of full remission (none out of 9 MDE criteria symptoms), (2) state of partial remission (1-4 symptoms) or (3) state of MDE (5+ out of 9 symptoms).

The main outcome measures were the 18-month IMSR network size as a measure of objective social support and the 18-month PSSS-R perceived social support as a measure of subjective social support.

4.4.3.3 Influence of personality on social support

Firstly, the levels of objective and subjective social support at baseline, at 6 and at 18 months, and secondly, the changes from baseline to 6 months, from 6 to 18 months and from baseline to 18 months in IMSR network size and in PSSS-R perceived social support among patients with high vs. low neuroticism and high vs. low extraversion in the Eysenck Personality Inventory (EPI) are to be reported. EPI neuroticism at index interview was categorized as high, if ≥ 15 and low, if ≤ 14 . EPI extraversion at index interview was high, if ≥ 11 and low, if ≤ 10 . To minimize the effect of depression in this study, the scores of neuroticism and extraversion at index interview were used, i.e. the interview, when scores on the Hamilton Depression Scale were at a minimum (Jylhä et al. 2007).

Between-subject differences in social support potentially may reflect stable between-subject differences also in other respects (Roberts and Gotlib 1997). Therefore, in the linear regression models, the outcome measures were firstly the levels of baseline IMSR network size and baseline PSSS-R perceived social support between the patients, but secondly the change in 18-month IMSR network size as a measure of objective social support within the patient and thirdly the change in 18-month perceived social support in PSSS-R as a measure of subjective social support within the patient.

4.5 Statistical analyses

In the baseline study the statistical methods included non-parametric and parametric univariate analyses, and also linear and logistic regression models. Because of the high number of statistical comparisons, only the significance level of $p < 0.005$ was accepted, with the exception of multivariate analyses. SPSS software, version 9.0, was used (Statistical Package for the Social Sciences for Windows, Release 9.0.1, 1989-1999).

In the second investigation about the influence of adversities and social support on the outcome of major depressive disorder, parametric and non-parametric methods were also used to examine group differences in means and proportions. Pearson product-moment correlation was applied to zero-order bivariate associations over groups and within groups. In linear regression models the severity of HAM-D at 6 months as a predictor was controlled for, because of its variation within every subgroup. Several other potentially confounding factors such as gender, age, neuroticism at six months (Kendler et al. 2004), Beck Anxiety Inventory at six months, Beck Hopelessness scale at six months, IMSR network size at six months, proportion of patients with antidepressant medication at six months, presence of alcoholism at six months, number of earlier episodes before the 6-month follow-up (Post, 1992; Kendler et al. 2000), and times to full and partial remission before the 6-month follow-up were adjusted for.

A general linear model gave the basis to statistical control, and the results were expressed in terms of partial correlations. Some of the distributions were skew. These effects were checked in several ways (original raw score, normalizing the distributions, dropping out the extreme values, winzorizing the distributions, and looking at the bivariate graphs and the regression diagnostics). The discrepancies between the different procedures were small in respective coefficients, and did not affect their significances. So it seems that skewness and outliers did not produce artefacts. To make the overall and groupwise results comparable, and to remove the effects of differing group means from the correlations, within groups standardized scores were used in multiple partial calculations. The results are expressed in terms of correlations and partial correlations. Two of the main results are depicted as graphs. Analyses were carried out with SPSS 13 for Windows.

In the study about the influence of major depression on social support, parametric and non-parametric methods were again used for group differences in means and proportions. For repeated measures at three points of time, non-parametric Friedman Test for continuous variables and Cochran's Q for dichotomous variables were applied. In linear regression models the IMSR network size at baseline, the Hamilton depression score at baseline, and time spent in MDE served as predictors for the 18-month IMSR network size, whereas perceived social support in PSSS-R at baseline, the Hamilton depression score at baseline and time spent in MDE served as predictors for the 18-month perceived social support in PSSS-R. Three cases were missing from data concerning perceived social support at baseline, where N remained 190. Other possible confounding clinical, personality and sociodemographic variables, such as number of earlier episodes before baseline, neuroticism at baseline, inpatient/outpatient status, age and gender were controlled for. The non-significant variables were stepwise omitted from the final model, but age, gender and baseline Hamilton score were retained as predetermined covariates. As an alternative to neuroticism at baseline, baseline anxiety disorder, baseline alcoholism, baseline personality disorder and the number of comorbid mental disorders at baseline were also used as confounding factors. In addition to linear regression models, logistic regression models were used. To confirm the robustness of the findings, a logistic regression model with a dichotomised dependent variable expressing subjective social support under vs. above the median value was used. Analyses were carried out with Statistical Package for the Social Sciences for Windows, Release 12.0.1 (1999-2002).

In the last study about the influence of personality on social support, mean differences between groups of high (above median) vs. low (below median) neuroticism and similarly, high vs. low extraversion were examined and reported. Mann-Whitney U-test for non-parametric and ANOVA F-test for parametric data was used. In addition Spearman's ρ (r_s) between variables of personality and social support was used. For repeated measures at different points of time, non-parametric Friedman Test for continuous variable was applied. In linear regression models, index neuroticism and extraversion served as predictors firstly for the level of baseline IMSR network size and baseline PSSS-R perceived social

support between patients. Secondly, index neuroticism and extraversion together with IMSR network size at baseline served as predictors for change from baseline to 18 months in IMSR network size within patients. Thirdly, index neuroticism and extraversion together with PSSS-R perceived social support at baseline served as predictors for the change in PSSS-R perceived social support from baseline to 18 months within patients. As confounding factors baseline alcoholism, change in BAI anxiety symptoms from baseline to 18-month interview, change in BDI depression score from baseline to 18-month interview, duration of MDD after baseline, marital status at baseline, employment at baseline, gender and age were controlled for in linear regression models. Analyses were carried out with Release 14.0 (21 Apr 2006). Copuright © SPSS 1989-2005. Inc. Chicago, III: SPSS.

5 RESULTS

5.1 Life events, social support and onset of MDE in subgroups of patients

Generally life events were common, as 91% (246/269) out of all patients reported them and there were on average 4.1 ± 3.0 events per preceding year. The objective unweighted negative impact of life events was somewhat more than moderate (mean 2.7 ± 1.6) and the events were probably independent of MDD (mean 2.03 ± 1.0). Correlation between the total frequency of life events and the severity of depression was found weak with the BDI (Pearson's $r = .139$, $p = 0.024$) and non-significant with the HAM-D (Pearson's $r = -.081$, ns.).

Differences between genders

No significant differences were found between men and women in the prevalence of subjects with any reported events (96% vs, 90%, respectively), frequency of events (mean, 3.8 vs. 4.2), the sum of weighted negative impacts of events (mean, 30.7 vs. 36.8). No marked differences in the 12 specific life event categories between genders were found. The objective social network averaged 7.4 people, differing non-significantly between men and women (mean 6.9 vs. 7.6). However, females perceived significantly more total social support (median 43 vs. 34, $Z = -3.92$, $p < .0001$), support from a significant other (median 16 vs. 11, $Z = -4.12$, $p < .0001$) and friends (median 13 vs. 10, $Z = -3.81$, $p < .0001$), but only slightly more support from the family (median 14 vs. 13, $Z = -1.96$, $p = 0.051$) in the PSSS-R.

Differences between older and younger patients

In terms of age, the younger had significantly more life events. Frequency in the categories of education, migration and courtship and cohabitation, and prevalence of the first two were significantly greater among the younger, whereas in no life event category the prevalence or frequency were greater among the older subjects. The younger subjects had received significantly more criticism, but they also perceived more support from a significant other or friends (Table 1).

Table 1. Characteristics of life events according to the IRLE 12 months before baseline and social support according to the IMSR and PSSS-R in MDD patients.

Category of event	Younger subjects 20 - 39 yrs N=135		Older subjects 40 - 59 yrs N=134		Total N=269	
	Prevalence N (%)	Mean M±Sd	Prevalence N (%)	Mean M±Sd	Prevalence N (%)	Mean M±Sd
Work	73 (54.1)	0.8±1.0	63 (47.0)	0.7±0.9	136 (50.6)	0.8±0.9
Education	43 (31.9) ^a	0.4±0.5 ^b	9 (6.7) ^a	0.075±0.3 ^b	52 (19.3)	0.3±0.6
Financial	49 (36.3)	0.4±0.5	31 (23.1)	0.2±0.4	80 (29.7)	0.3±0.5
Health	44 (32.6)	0.4±0.6	60 (44.8)	0.6±0.7	104 (38.7)	0.5±0.7
Bereavement	35 (25.9)	0.3±0.5	32 (23.9)	0.3±0.6	67 (24.9)	0.3±0.5
Migration	58 (43.0) ^f	0.5±0.6 ^d	20 (14.9) ^c	0.2±0.4 ^d	78 (29.0)	0.3±0.6
Courtship and cohabitation	36 (26.7)	0.3±0.6 ^e	18 (13.4)	0.1±0.3 ^e	54 (20.1)	0.2±0.5
Legal	7 (5.2)	0.067±0.3	12 (9.0)	0.097±0.3	19 (7.1)	0.082±0.3
Family and social relationships	43 (31.9)	0.5±0.9	41 (30.6)	0.5±1.0	84 (31.2)	0.5±0.9
Marital relationships	46 (34.1)	0.5±0.8	28 (20.9)	0.3±0.8	74 (27.5)	0.4±0.8
Other	29 (21.5)	0.2±0.5	24 (17.9)	0.2±0.4	53 (19.7)	0.2±0.4
Positive	26 (19.3)	0.2±0.5	28 (20.9)	0.2±0.5	54 (20.1)	0.2±0.5
Total	128 (94.8)	4.6±3.0 ^f	118 (88.1)	3.5±2.9 ^f	246 (91.4)	4.1±3.0
<u>Objective social support</u>						
IMSR, social network size		7.2±3.0		7.6±4.0		7.4±3.6
IMSR, criticism, N=265	66 (49.3) ^g		37 (28.2) ^g		103 (38.9)	
<u>Subjective social support</u>						
PSSS-R, total support		41.2±11.1		37.0±13.9		39.1±12.7
PSSS-R, significant other, N=268		14.8±4.6 ^h		12.6±5.5 ^h		13.7±5.2
PSSS-R, family, N=268		13.0±4.9		13.1±5.3		13.0±5.1
PSSS-R, friends, N=268		13.2±4.6 ⁱ		11.2±5.4 ⁱ		12.2±5.1

a Chi-Square = 25.66, df=1, p<.0001;

b Mann-Whitney, Z= -5.31, p<.0001;

c Chi-Square= 23.33, df=1, p<.0001, after controlling for gender (OR=0.23[0.13-0.42], p<.0001), for income (OR=0.24[0.13-0.45], p<.0001), or for the existence of spouse (OR=0.24[0.13-0.42], p<.0001);

d Mann-Whitney, Z=-5.05, p<.001;

e Mann-Whitney, Z=-2.86, p=.004;

f Mann-Whitney, Z=-3.61, p=.001;

g Chi-Square=11.44, df=1, p=.001;

h Mann-Whitney, Z=-3.19, p=.001;

i Mann-Whitney, Z=-3.13, P=.002.

Recurrent depression and melancholic features

There were no significant differences in the prevalence, number, categories of all events, or variables of social support between patients having their lifetime first or recurrent episode. Neither were found differences in these respects between patients with or without melancholia, or between the melancholic patients with a first (N=28), second (N=29) or third or more than third (N=39) episode. Only in single vs. recurrent MDD episode the difference in weighted, objective, negative impact of events was greater in the prodromal phase (median 22.5 vs. 16, Z=-2.87, p=0.004).

Comorbid Mental Disorders

Subjects with pure MDD without any comorbid disorder (N=56) did not differ from those with comorbid MDD in terms of the prevalences, median numbers, median weighted objective negative impacts of any life events, specific life event categories, or objective social support. However, they perceived more PSSS-R family support (median 16 vs. 13; $Z=-2.72$; $p=0.007$), and support from friends (median 14 vs. 12; $Z=-2.86$; $p=0.004$).

The median number of events was significantly greater among patients with (N=152) than without a comorbid anxiety disorder (median 4 vs. 3, $Z=-2.91$, $p=0.004$), but the prevalence, impact of all events, specific life event categories, or objective/subjective social support were not.

No significant differences were detected in the prevalence, frequency, impact of all life events and specific event categories between those with (N=66) or without alcoholism (alcohol dependence or abuse). However, alcoholics perceived significantly less total support (median 38 vs. 42, $Z=-2.9$, $p=0.003$) and family support in the PSSS-R (median 12 vs. 14, $Z=-3.88$, $p<.0001$).

No significant differences in the prevalence, frequency, impact of all life events or specific life event categories between those with (N=118) or without comorbid axis II personality disorder, or between those with a cluster A (N=51), B (N=39) or C (N=85) disorder or without them. In cluster B no significant differences were observed in the prevalence (21% [8/31] vs. 24% [55/175], Chi-Square=.067, $df=1$, $p=0.795$), frequency (median 0 vs. 0, $Z=-.34$, $p=0.731$) or impact (median 14 vs. 10, $Z=-1.52$, $p=0.128$) of life events involving separation or divorce. Patients with a comorbid axis II personality disorder had significantly less support from friends in the PSSS-R (median 11 vs. 13, $Z=-3.42$, $p=0.001$), cluster A patients significantly less perceived social support (median 35 vs. 42, $Z=-3.10$, $p=0.002$) and support from friends (median 10 vs. 13, $Z=-3.10$, $p=0.002$), and in cluster C support from friends was significantly less (median 11 vs. 13, $Z=-3.20$, $p=0.001$) than those without respective disorders.

A linear regression model with the frequency of life events as the dependent variable, and gender, age, severity of depression, recurrent depression, melancholic features, anxiety disorder, alcoholism and axis II clusters A, B or C as independent variables was created. After removing the non-significant predictors, in the final model the frequency of events was significantly associated with younger age (Beta=-.231, $t=-3.894$, $p=0.000$), anxiety disorder (Beta=.174, $T=2.898$, $p=0.004$) and slightly to those with higher BDI score (Beta=.122, $t=2.034$, $p=0.043$), and almost significantly with cluster C (Beta=-.105, $t=-.1751$, $p=0.081$).

In the linear regression models with gender, age, severity of depression, frequency of events, recurrent depression, melancholic features, anxiety disorder, alcoholism, axis II clusters A, B or C, as independent variables, smaller network was significantly associated with smaller frequency of life events (Beta=.187, $t=2.979$, $p=0.003$), with those with higher BDI score (Beta=-.140, $t=-2.287$, $p=0.023$) and almost significantly with younger age (Beta=.118, $t=1.899$, $p=0.059$) whereas weaker perceived support again was significantly associated with male gender (Beta=.232, $t=3.968$, $p<.0001$), older age (Beta=-.166, $t=-2.897$, $p=0.004$), to those with higher BDI score (Beta=-.186, $t=-3.251$, $p=0.001$), cluster A (Beta=-.172, $t=-2.989$, $p=0.003$) and almost significantly with alcoholism (beta=-1.854; $p=0.066$) in the final models.

Events attributed as precipitants

Altogether, 76% (203/266) of the patients personally attributed some life event to having precipitated their depression. The attributed precipitating events were evenly distributed in all categories of the IRLLE, and 81% of them had occurred within 12 months of baseline. One third (30% [45/149]) had occurred at the precise onset of the MDE symptoms, the beginning of prodromal phase. There were no differences in the tendency to attribute between clinical subgroups.

5.2 Baseline life events in different phases of MDD

Life events overall

The mean lengths of time before MDD, the prodromal phase and MDE proper were 5.3 months, 2.9 months and 4.4 months, respectively. The respective incidents of events were 74, 98 and 97 per patient-month. Analyzing the distribution of events month by month before vs. after the onset of prodromal phase (data available upon request) provided no evidence for clustering. However, the observed versus expected (if temporally random) distribution of life events in the three periods differed significantly, although not markedly, in some of the IRLLE life event categories: the occurrence of events related to work (46.5% vs. 20.3% vs. 33.2%, Chi-Square=10.8354, $df=2$, $p=0.01$), health (38.9% vs. 33.3% vs. 27.8%, Chi-Square=7.2131, $df=2$, $p=0.05$) and migration (51.1% vs. 18.2% vs. 30.7%, Chi-Square=9.4721, $df=2$, $p=0.01$) appeared to cluster somewhat in time before MDE, whereas events related to family and social relationships (22.6% vs. 32.8% vs. 44.5%, Chi-Square=10.2898, $df=2$, $p=0.01$) or to marital relationships (28.2% vs. 20.9% vs. 50.9%, Chi-Square 6.8058, $df=2$, $p=0.05$) clustered in the MDE proper phase. As mentioned already before, the median objective negative impact of life events in the prodromal phase was found to be higher among patients in their lifetime first episode compared with those having recurrent depression.

Independent life events

Altogether 63.3% (695/1098) of life events were almost certainly or probably independent of depression. Altogether, 81% (217/269) of patients reported independent life events, on average 2.6 events per preceding year. The unweighted objective negative impact was 2.8 ± 1.7 . Results were similar, albeit expectedly statistically weaker overall. Some exceptions appeared. The prevalence (26% [52/145] vs. 7% [5/67]; Chi-Square=10.810, df=1, p=0.001) and frequency (median 0 vs. 0, Z=-3.48, p=0.001) of family events were now greater among women. Also the tendency for higher impact among those with single episode compared with recurrent depression lost now significance (median 9 vs. 8, Z=-.195, p=0.846).

Incidences of events per patient-month were now 56 before depression, 54 in the prodromal phase, and 56 during MDE. Finally, the observed vs. expected (if random) distribution of life events in the three periods changed markedly only in the category of marital relationships in which the majority of events were dependent. In contrast with the analyses with all events, the independent marital events clustered bimodally in the time before depression and depression proper (55% vs. 5% vs. 40%; Chi-Square=6.44, df=2, p=0.05).

5.3 Basic characteristics, life events, social support and symptom scores at 6-month follow-up with different levels of depressive symptoms

At the 6-month follow-up, 35.2% (68/193) of the patients were in full remission, 38.9% (75/193) in partial remission and 25.9% (50/193) in MDE. Those in MDE were significantly older compared with the other two groups (means, 43.3 ± 10.7 vs. 41.9 ± 11.8 vs. 38.3 ± 10.2 , ANOVA: p<0.05). Regarding gender or cohabitation there were no significant differences.

Out of the total of 193 patients, 157 (81.3%) reported life events during the preceding six months from baseline. The prevalence, frequency and weighted severity of events did not differ significantly between the three groups at the 6-month interview. However, those in MDE perceived significantly less social support (Kruskal-Wallis, median 33/45/48.5, $\chi^2=26.467$, df=2, p<0.0001) and had a significantly smaller network (Kruskal-Wallis, median 5/7/7, $\chi^2=11.356$, df=2, p=0.003). The occurrence of intense interaction at 6 months was significantly less common among those in MDE (60% vs. 83% vs. 79%, Chi-Square 9.174, df=2, p=0.010). In accordance with the stratification, the mean of HAM-D (19.6 ± 4.5 vs. $8.3-4.4$ vs. 3.0 ± 3.2), Beck Depression Inventory (BDI) (24.2 ± 6.4 vs. 12.5 ± 6.4 vs. 4.2 ± 4.1), Beck Anxiety Inventory (BAI) scores (22.7 ± 8.3 vs. 12.3 ± 8.0 vs. 7.3 ± 7.2) and Beck Hopelessness scale (12.1 ± 4.8 vs. 7.3 ± 4.6 vs. 4.5 ± 3.5) were highest in the MDE group. Those in MDE also had a significantly higher EPI neuroticism score (17.8 ± 3.5 vs. 15.0 ± 4.9 vs. $12.8-5.4$) than their peers in the other groups. Analysis of variance (ANOVA) brought a significant result: p<0.001 in all these clinical symptoms and neuroticism score.

5.4 Life events and symptom scores at the 18-month follow-up with different levels of depressive symptoms

At the 18-month interview, only the frequency of events during the preceding 12 months was almost significantly smaller among those in MDE compared with the other groups (mean 2.3 ± 1.8 vs. 3.1 ± 2.6 vs. 3.4 ± 2.3 , $F=2.982$, $df=2$, $p=0.053$).

The symptom variables at 18-month interview were significantly greater in the MDE group (HAM-D score: 13.5 ± 8.2 vs. 7.4 ± 5.3 vs. 4.9 ± 6.2 , $F=25.896$, $df=2$, $p<0.001$; BDI score: 18.9 ± 11.4 vs. 10.0 ± 7.4 vs. 6.5 ± 8.1 , $F=29.409$, $p<0.001$; BAI score: 16.5 ± 11.0 vs. 11.8 ± 9.6 vs. 7.8 ± 9.0 , $F=11.452$, $p<0.001$; Beck Hopelessness scale: 9.4 ± 5.7 vs. 6.1 ± 4.1 vs. 4.6 ± 3.8 , $F=16.827$, $p<0.001$; EPI neuroticism score: 16.2 ± 4.8 vs. 14.3 ± 5.2 vs. 11.4 ± 5.8 , $F=12.420$, $p<0.001$, among those in MDE, partial remission, or full remission, respectively).

5.5 Influence of adversity and social support on the outcome of MDD

Predictors among all patients

In the overall linear regression model, expressed using original zero-order, within-group standardized and within-group partial correlations, the significant predictors for the level of depressive symptoms (HAM-D) at 18 months were the weighted sum of the severity of life events between 6 and 18 months, the 6-month HAM-D and the EPI neuroticism score (Table 2). Also perceived social support at 6 months predicted the 18-month HAM-D significantly in original zero-order correlation and within-group standardized correlations, and the same was true for Beck Hopelessness scale. Because these two variables correlated (collinearity), multiple within-standardized partial correlation between perceived social support or Beck Hopelessness scale to HAM-D at 18 months was not significant. Presence of antidepressant at 6 months predicted significantly HAM-D at 18 months in zero-order raw scores correlation, but not, when expressed using within-group standardized or within-group partial correlations (Table 2).

Table 2. Original zero-order, within-group standardized, and within-group partial correlations between predictors and HAM-D 18-month score among all patients, N=190^a.

Predictors	Zero-order raw scores correlation ^b		Zero-order within-standardized correlation ^c		Multivariate within-standardized partial correlation ^d	
	r	p	r	p	r	p
Gender	-0.131	(0.073)	-0.137	(0.059)	-0.127	(0.088)
Age	0.118	(0.105)	0.052	(0.480)	0.078	(0.294)
Perceived Social Support in PSSS-R ^e	-0.392***	(0.000)	-0.230***	(0.001)	0.102	(0.170)
Weighted severity of life events in IRLE ^f	0.306***	(0.000)	0.403***	(0.000)	0.369***	(0.000)
HAM-D ^e	0.525***	(0.000)	0.296***	(0.000)	0.170*	(0.022)
EPI Neuroticism Score ^c	0.454***	(0.000)	0.342***	(0.000)	0.237***	(0.001)
Beck Hopelessness Scale ^c	0.420***	(0.000)	0.212**	(0.003)	0.014	(0.848)
Antidepressant at Six Months	0.185*	(0.011)	0.064	(0.382)	-0.020	(0.785)

Analysis of variance (ANOVA): *p<0.05, **p<0.01, ***p<0.001

- a Number of cases only 190 because three cases are missing in EPI neuroticism score
b Group means differ, group covariances differ. Degree of freedom is 188.
c Group means centred to same mean, group covariances standardized to be equal. Degree of freedom is 188.
d Correlation between predictor and HAM-D 18-month score, when other variables are statistically controlled/kept constant, scores are the same as in the middle column, i.e. standardized within groups. Degree of freedom is 181.
e Cross-sectional measures at six-month follow-up.
f Negative life events one year between the follow-ups are geometrically weighted 1,2,4,8,16.

Predictors in the groupwise analyses

In groupwise zero-order correlations and in multiple controlled partial correlations containing the subgroup of patients in full remission at 6 months, the weighted severity of life events between 6 and 18 months, perceived social support and EPI neuroticism score significantly predicted the 18-month HAM-D. Hamilton Rating Scale at 6 months and Beck Hopelessness scale predicted significantly the 18-month HAM-D only in univariate groupwise correlations (Table 3).

Table 3. Zero-order correlations (above) and multivariate controlled (partial) correlations (below) between predictors and HAM-D 18-month score.

Predictors	Major depression N=49 ^a		Group Partial remission N=74 ^a		Full remission N=67 ^a		Significance of differences in correlations
	r	p	r	p	r	p	
Gender	-0.074	(0.613)	-0.033	(0.782)	-0.298*	(0.014)	n.s.
Age	-0.055	(0.730)	-0.278*	(0.022)	-0.115	(0.383)	n.s.
Perceived Social Support in PSSS-R ^b	0.112	(0.445)	0.094	(0.425)	-0.039	(0.753)	n.s.
Weighted severity of life events in IRLE ^c	0.151	(0.339)	0.033	(0.792)	-0.047	(0.723)	n.s.
HAM-D ^c	-0.352*	(0.013)	0.042	(0.725)	-0.411**	*(0.000)	** (0.008)
EPI Neuroticism Score ^c	-0.211	(0.179)	0.204	(0.098)	-0.321*	(0.012)	*(0.020)
Beck Hopelessness Scale ^c	0.177	(0.222)	0.416***	(0.000)	0.553**	*(0.000)	n.s.
Antidepressant at Six Months	0.160	(0.312)	0.480***	(0.000)	0.422**	*(0.001)	n.s.
HAM-D ^c	0.259	(0.072)	0.259*	(0.026)	0.364**	(0.002)	n.s.
EPI Neuroticism Score ^c	0.230	(0.142)	0.175	(0.157)	0.224	(0.086)	n.s.
Beck Hopelessness Scale ^c	0.216	(0.136)	0.336**	(0.003)	0.442**	*(0.000)	n.s.
Antidepressant at Six Months	0.217	(0.167)	0.331**	(0.006)	0.259*	(0.045)	n.s.
HAM-D ^c	0.298*	(0.037)	0.091	(0.440)	0.284*	(0.020)	n.s.
EPI Neuroticism Score ^c	0.179	(0.256)	-0.060	(0.627)	-0.185	(0.157)	n.s.
Beck Hopelessness Scale ^c	0.150	(0.313)	-0.015	(0.899)	0.088	(0.479)	n.s.
Antidepressant at Six Months	0.059	(0.708)	-0.004	(0.974)	-0.099	(0.449)	n.s.

Analysis of variance (ANOVA): *p<0.05, **p<0.01, ***p<0.001

- a One case is missing in EPI neuroticism score.
b Negative life events one year between the follow-ups are geometrically weighted 1,2,4,8,16.
c Cross-sectional measures at six-month follow-up.

In the subgroup of patients in partial remission at 6 months the weighted severity of negative life events between 6 and 18 months, and the 6-month EPI neuroticism score were significant predictors of 18-month HAM-D, both in groupwise zero-order correlations and in multiple controlled partial correlations. Gender became significant in multiple correlations and HAM-D at 6 months only in univariate analysis (Table 3).

In the subgroup of patients in MDE at 6 months, only perceived social support significantly predicted the level of depression at 18 months in the groupwise zero-order correlations.

Graphic presentation of the main results, and interaction between subgroups and predictors

The main results are illustrated by Figure 2 and Figure 3, where raw score correlations between HAM-D at 18 months and weighted severity of life events and also between HAM-D at 18 months and perceived social support are depicted as graphs. The three subgroups of patients differed significantly in their correlation between perceived social support at 6 and HAM-D at 18 months (Table 3).

Independent life events as predictors

In otherwise similar linear models containing only independent events (N=389, dependent events excluded), the significant predictors were the same as those using all adverse life events (data available upon request).

Figure 2. The groupwise association between Negative Life Events and Hamilton 18-month score.

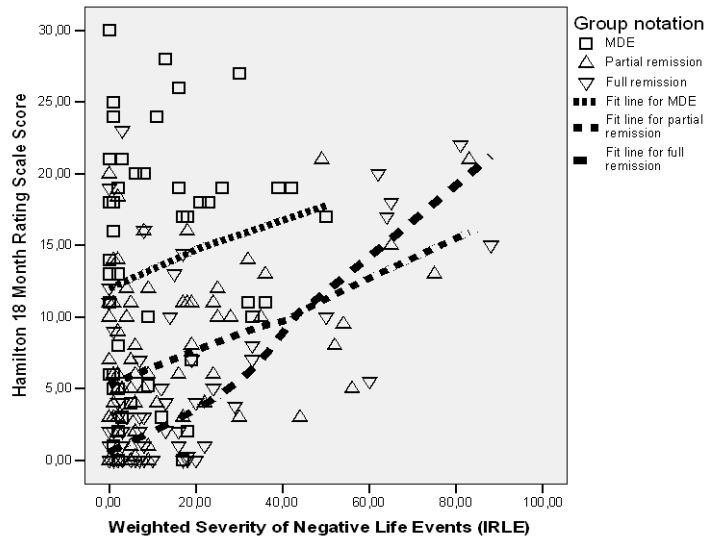
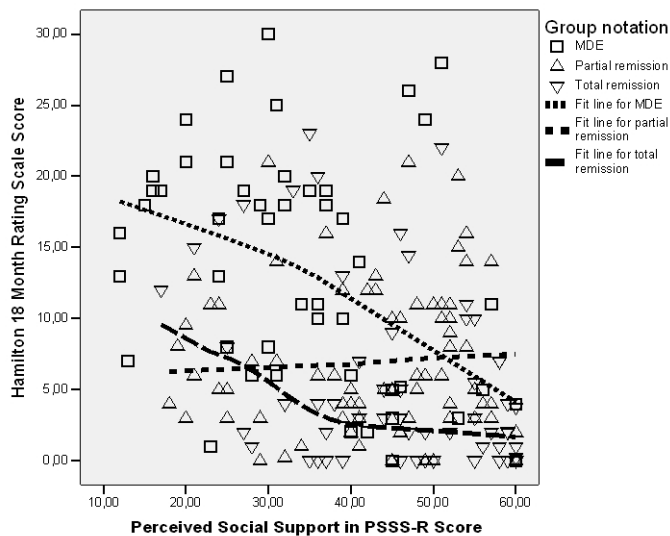


Figure 3. The groupwise association between perceived social support and the Hamilton 18-month score.



5.6 Social support and ability to work during the follow-up

MDD patients overall in the cohort during the prospective follow-up

Objective social support among all patients (N=193) did not change much from baseline, via 6 to 18 months, whereas subjective social support improved significantly (mean 39.2 ± 12.9 vs. 41.9 ± 12.9 vs. 42.6 ± 13.5 , Friedman Test, Chi Square=20.011, $df=2$, $p < 0.001$). The proportions of those living in marital relationships or alone did not change significantly during follow-up. Of the 193 patients, 12 (6.2%) divorced during the follow-up. The proportion of employed patients increased significantly (35% vs. 46% vs. 49%, Cochran's Q, Chi-Square 19.000, $df=2$, $p < 0.001$) and fewer patients took sickleave (28% vs. 20% vs. 6%, Cochran's Q, Chi-Square 44.984, $df=2$, $p < 0.001$). However, the proportion of patients on disability pension for psychiatric reasons also grew significantly (5% vs. 7% vs. 16%, Cochran's Q, Chi-Square 35.524, $df=2$, $p < 0.001$). About one third of all patients were consistently employed, another third was not employed, and in one third, the ability to work fluctuated throughout the 18-month follow-up period.

Patients with full remission, partial remission or in MDE cross-sectionally at 18 months

When patients were classified and retrospectively analysed according to their remission status cross-sectionally at the 18-month interview, both objective and subjective social support were found to have been significantly weaker throughout the follow-up among patients in MDE than among those in full or partial remission (Table 4). This was true regarding the network size and sum of contacts, whereas the other IMSR measures, such as the presence of close attachment figure, negative interaction, criticism, and intense interaction between these clinical groups, did not differ significantly (data not shown). Those in MDE were also more often unemployed. Of those in full remission, a significantly greater proportion was working. No significant differences were found in the proportions of those living in marital relationships or alone (Table 4).

Objective and subjective social support among persistently depressed patients

Objective social support, i.e. IMSR network size, diminished significantly from baseline to 18 months among the chronically depressed patients (N=12) who remained in MDE throughout the 18-month follow-up (mean 6.6 ± 3.9 vs. 5.8 ± 3.2 vs. 5.0 ± 2.4 , Friedman Test, Chi-Square 6.465, $df=2$, $p=0.039$). At the same time, symptom scores of BDI, BAI and HAM-D within these patients declined slightly, but not significantly, and the proportions of those living in marital relationships or alone did not change significantly at different points of time. With regard to work status, however, the amount of sickleaves decreased (33% vs. 58% vs. 8%, Cochran's Q, Chi-Square 9.000, $df=2$, $p=0.011$) and disability pensions based on psychiatric reasons increased significantly (0% vs. 0% vs. 58%, Cochran's Q, Chi-Square 14.000, $df=2$, $p=0.001$).

It was also found that the proportion of friendless chronic patients was no greater than that of the other patients at baseline (33.3% vs. 16.0%, Fisher's Exact Test, $df=1$, $p=0.128$), but at the 6-month follow-up, the difference in this proportion nearly approached significance (41.7% vs. 18.2%, Fisher's Exact Test, $df=1$, $p=0.062$), and at the 18-month follow-up was significantly greater (50.0% vs. 13.8%, Fisher's Exact Test, $df=1$, $p<0.001$) among chronic patients.

The chronically depressive patients perceived significantly less subjective social support cross-sectionally at baseline than did the non-chronic patients (median 32.0 vs. 41.5; $Z=-3.03$; $p=0.002$). The difference increased consistently at 6 months (median 30.0 vs. 45.0; $Z=-3.70$; $p<.0001$) and again at 18 months (median 22.0 vs. 47.0; $Z=-4.40$; $p<.0001$). Prospectively, the weakening of perceived social support was also to be seen, but it did not reach significance among the chronically depressed patients.

When investigated from baseline to only 6 months, patients persistently in MDE had significantly smaller network size ($N=31$, mean 6.4 ± 3.4 vs. 5.4 ± 2.4 , Friedman Test, Chi-Square 6.000, $df=1$, $p=0.014$) and they perceived significantly less social support ($N=30$, mean 33.2 ± 11.7 vs. 30.9 ± 10.5 , Friedman Test, Chi-Square 4.172, $df=1$, $p=0.041$) than other patients.

Table 4. Subjective and objective social support in addition to demographic characteristics among 193 patients with MDE, partial remission or full remission at the 18-month follow-up.						
	MDE N=45		Partial remission N=60		Full remission N=88	
Subjective social support	Mean \pm SD		Mean \pm SD		Mean \pm SD	
Perceived social support in PSSS-R at baseline, ^{a,b}	30.5 \pm 11.8		42.1 \pm 11.8		41.6 \pm 12.4	
Perceived social support in PSSS-R at 6 months ^c	32.7 \pm 12.6		42.1 \pm 11.5		46.6 \pm 11.5	
Perceived social support in PSSS-R at 18 months ^d	30.5 \pm 12.4		45.2 \pm 11.4		47.1 \pm 11.7	
Objective social support						
Network size in IMSR at baseline	6.8 \pm 4.4		7.6 \pm 3.8		8.3 \pm 3.8	
Network size in IMSR at 6 months ^e	6.5 \pm 3.6		6.8 \pm 3.5		8.1 \pm 3.8	
Network size in IMSR at 18 months ^f	5.8 \pm 3.2		7.6 \pm 3.2		8.4 \pm 3.7	
Sum of contacts at baseline ^g	5.2 \pm 3.3		6.0 \pm 3.1		7.0 \pm 3.3	
Sum of contacts at 6 months ^h	4.1 \pm 2.6		4.7 \pm 2.8		6.1 \pm 3.6	
Sum of contacts at 18 months ⁱ	4.4 \pm 3.3		6.1 \pm 2.8		7.0 \pm 3.2	
Demographic characteristics	N	%	N	%	N	%
Married	22	48.9	35	58.3	50	56.8
Cohabiting	28	62.2	42	70.0	62	70.5
Work status						
Unemployed ^j	13	28.9	6	10.0	11	12.5
Sick leave ^k	5	11.1	6	10.0	1	1.1
Pensioned, psychiatric reason	11	24.4	9	15.0	10	11.4
Pensioned, somatic reason	1	2.2	1	1.7	1	1.1
Employed ^l	12	26.7	28	46.7	55	62.5
Student	3	6.7	3	5.0	7	8.0
Others	0	0.0	7	11.7	3	3.4

a In Major depression $N=44$ and in Full Remission $N=86$.

b Kruskal-Wallis, Chi-Square 26.332, $df=2$, $p<0.001$.

c Kruskal-Wallis, Chi-Square 32.663, $df=2$, $p<0.001$.

d Kruskal-Wallis, Chi-Square 44.395, $df=2$, $p<0.001$.

e ANOVA, $F=3.581$, $df=2$, $p=0.030$.

f ANOVA, $F=8.612$, $df=2$, $p<0.001$.

g Kruskal-Wallis, Chi-Square 8.887, $df=2$, $p=0.012$.

h Kruskal-Wallis, Chi-Square 12.519, $df=2$, $p=0.002$.

i Kruskal-Wallis, Chi-Square 21.192, $df=2$, $p<0.001$.

j Pearson Chi-Square 8.130, $df=2$, $p=0.017$.

k Pearson Chi-Square 7.217, $df=2$, $p=0.027$.

l Pearson Chi-Square 15.524, $df=2$, $p<0.001$.

5.7 Influence of MDE on social support

Predictors for 18-month objective social support

After adjusting for age, neuroticism at baseline, the Hamilton depression score at baseline and the number of earlier episodes before baseline, it was found that the baseline IMSR network size, male gender and also the time spent in MDE remained significant predictors for 18-month objective social support (Table 5). The results were the same when neuroticism was replaced by baseline variables of anxiety disorder, alcoholism, personality disorder, or number of comorbid disorders.

Predictors for 18-month subjective social support

After controlling for age, gender, neuroticism at baseline, the Hamilton score at baseline, and the number of earlier episodes before baseline, it was found that the PSSS-R score of perceived social support at baseline and the time spent in MDE during the 18-month follow-up period remained significant predictors for 18-month subjective social support (Table 6). The results were the same when neuroticism was individually replaced by baseline variables of anxiety disorder, alcoholism, personality disorder, number of comorbid disorders or inpatient/outpatient status in alternative models. The findings persisted even after adjusting for the Hamilton depression score at 18-month interview, which moderately correlated with concurrent perceived social support ($r=-0.447$, $p<0.001$), but being more an outcome itself than a predictor, the 18-month HAM-D was excluded from the final linear analysis (Table 6). Because of the skewed distribution of perceived social support at 18 months, also used was an alternative logistic regression model, which gave similar results.

Table 5. Predictors of 18-month IMSR network size among 193 patients with MDD in Linear Regression Model.							
Variables	B	95% CI for B		S.E.	Beta	t	p
Male gender	1.040	0.188;	1.891	0.432	0.131	2.407	0.017
Age	-0.030	-0.065;	0.006	0.018	-0.092	-1.657	0.099
IMSR network size at baseline	0.565	0.466;	0.663	0.050	0.625	11.314	<0.001
Time spent in MDE , months	-0.082	-0.161;	-0.004	0.040	-0.116	-2.065	0.040
HAM-D at baseline	-0.001	-0.066;	0.065	0.033	-0.001	-0.017	0.986

Table 6. Predictors of 18-month PSSS-R perceived social support among 193^a patients with MDD in Linear Regression Model.

Variables	B	95% CI for B	S.E.	Beta	t	p
Gender	0.215	-0.269; 0.698	0.245	0.047	0.877	0.382
Age	-0.001	-0.020; 0.019	0.010	0.003	-0.066	0.947
PSSS-R perceived social support at baseline ^a	0.092	0.074; 0.110	0.009	0.572	10.151	<0.001
Time spent in MDE, months	-0.113	-0.157; -0.068	0.022	-0.278	-5.008	<0.001
HAM-D at baseline	0.008	-0.017; 0.053	0.018	0.024	0.443	0.659

a Three cases missing; missing data replaced with mean.

5.8 Correlations between personality dimensions and social support

Correlations between neuroticism and the levels/changes in objective/subjective social support

Neuroticism correlated significantly and negatively, albeit weakly, with the levels of IMSR network size at baseline ($r_s = -0.185$, $p = 0.010$), at 6 months ($r_s = -0.150$, $p = 0.038$) and at 18 months ($r_s = -0.162$, $p = 0.025$); and the levels of perceived social support in PSSS-R at baseline ($r_s = -0.155$, $p = 0.033$), at 6 months ($r_s = -0.295$, $p < 0.001$) and 18 months ($r_s = -0.372$, $p < 0.001$). Its correlation was non-significant with both baseline marital status ($r_s = -0.093$, $p = 0.203$) and the change in perceived social support from baseline to 6 months ($r_s = -0.136$, $p = 0.063$), but significantly negative with the change in perceived social support from baseline to 18 months ($r_s = -0.229$, $p = 0.002$). Correlations with change in IMSR network size at 6 months ($r_s = 0.021$, $p = 0.772$) and at 18 months ($r_s = 0.036$, $p = 0.619$) were non-significant.

Correlations between extraversion and the levels/changes in objective/subjective social support

Extraversion correlated significantly and positively with the levels of IMSR network size at baseline ($r_s = 0.340$, $p < 0.001$), at 6 months ($r_s = 0.323$, $p < 0.001$) and at 18 months ($r_s = 0.327$, $p < 0.001$); and the levels of perceived social support in PSSS-R at baseline ($r_s = 0.345$, $p < 0.001$), at 6 months ($r_s = 0.415$, $p < 0.001$) and at 18 months ($r_s = 0.422$, $p < 0.001$). Its correlations were only small and non-significant with baseline presence of marital status ($r_s = -0.065$, $p = 0.369$), with changes in IMSR network size at 6 months ($r_s = -0.041$, $p = 0.540$) and at 18 months ($r_s = -0.024$, $p = 0.744$); and with changes in perceived social support in PSSS-R at 6 months ($r_s = 0.045$, $p = 0.541$) and at 18 months ($r_s = 0.122$, $p = 0.077$).

Patients with high vs. low neuroticism/extraversion differed consistently in their current levels and changes in their IMSR network size and perceived social support (PSSS-R) during follow-up (Table 7; Table 8; Table 9).

Table 7. IMSR network size and PSSS-R perceived social support at baseline, at 6 months and at 18 months among major depressive patients with high vs. low neuroticism at index interview^a, N=193^b			
	High neuroticism N=96	Low neuroticism N=95	Total N=191
IMSR network size	Mean ± SD	Mean ± SD	Mean ± SD
At Baseline ^c	7.1 ± 3.8	8.4 ± 4.0	7.7 ± 4.0
At 6 months ^d	6.5 ± 3.2	8.1 ± 4.0	7.3 ± 3.7
At 18 months ^e	6.8 ± 3.2	8.2 ± 3.8	7.5 ± 3.6
Perceived Social Support in PSSS-R			
At Baseline, ^f N=94	36.5 ± 13.2	41.5 ± 12.0	39.2 ± 12.9
At 6 months ^g	37.8 ± 13.0	45.9 ± 11.5	41.9 ± 12.9
At 18 months ^h	37.2 ± 13.5	45.1 ± 13.4 ⁱ	42.6 ± 13.5

a EPI neuroticism score is high, if its score is => 15 and low, if =<14.

b Two cases are missing.

c Z=-2.480, p=0.013.

d Z=-2.757, p=0.006.

e Z=-2.569, p=0.010.

f Z=-2.644, p=0.008.

g Z=-4.276, p<0.001.

h Z=-5.609, p<0.001.

i Repeated measures of perceived social support in PSSS-R at baseline, at 6 and at 18 months among patients with low neuroticism at index interview, Friedman Test, Chi-Square 29.902, DF=2, p<0.001

Table 8. IMSR network size and PSSS-R perceived social support at baseline, at 6 months and at 18 months among major depressive patients with high vs. low extraversion at index interview^a, N=193^b			
	High extraversion N=108	Low extraversion N=83	Total N=191
IMSR network size	Mean ± SD	Mean ± SD	Mean ± SD
At Baseline ^c	8.7 ± 4.1	6.4 ± 3.4	7.7 ± 4.0
At 6 months ^d	8.3 ± 4.0	6.0 ± 2.9	7.3 ± 3.7
At 18 months ^e	8.5 ± 3.6	6.1 ± 3.1	7.5 ± 3.6
Perceived Social Support in PSSS-R			
At Baseline, ^f	42.8 ± 11.7 ^g	34.1 ± 12.8 ^h	39.2 ± 12.9
At 6 months ⁱ	45.7 ± 11.6	36.7 ± 12.9	41.9 ± 12.9
At 18 months ^j	46.7 ± 11.6 ^k	37.1 ± 14.1 ^l	42.6 ± 13.5

a EPI extraversion is high, if its score is => 11 and low, if =<10.

b Two cases are missing.

c Z=-4.056, p<0.001.

d Z=-4.038, p<0.001.

e Z=-4.412, p<0.001.

f Z=-4.519, p<0.001

g Two cases are missing at baseline perceived social support.

h One case is missing at baseline perceived social support.

i Z=-4.762, p<0.001.

j Repeated measures of perceived social support in PSSS-R at baseline, at 6 and at 18 months among patients with high extraversion at index interview, Friedman Test, Chi Square 18.336, df=2, p<0.001.

k Repeated measures of perceived social support in PSSS-R at baseline, at 6 and at 18 months among patients with low extraversion at index interview, Friedman Test, Chi Square 4.831, df=2, p=0.089.

l Z=-4.781, p<0.001.

Table 9. Changes in IMSR network size and PSSS-R perceived social support from baseline to 6 months, from 6 months to 18 months and from baseline to 18 months among major depressive patients with high vs. low neuroticism or extraversion at index interview^a. N=193^b

Change in network size	High neuroticism N=96 Mean ± SD	Low neuroticism N=95 Mean ± SD	High extraversion N=108 Mean ± SD	Low extraversion N=83 Mean ± SD
From baseline to 6 months	-0.54 ± 3.0	-0.26 ± 2.8	-0.39 ± 2.8	-0.42 ± 3.0
From 6 to 18 months	0.27 ± 2.7	0.12 ± 3.1	0.22 ± 3.1	0.16 ± 2.7
Total change from baseline to 18 months	-0.27 ± 3.3	-0.15 ± 3.1	-0.17 ± 3.4	-0.27 ± 2.9
Change in perceived social support	High neuroticism N=94 Mean ± SD	Low neuroticism N=94 Mean ± SD	High extraversion N=106 Mean ± SD	Low extraversion N=82 Mean ± SD
From baseline to 6 months ^c	1.4 ± 9.1	4.4 ± 11.4	3.2 ± 10.3	2.5 ± 10.7
From 6 to 18 months	-0.7 ± 10.1	1.9 ± 9.2	0.7 ± 9.7	0.4 ± 9.9
Total change from baseline to 18 months ^d	0.7 ± 9.8	6.3 ± 11.2 ^e	4.0 ± 11.4 ^f	2.9 ± 10.2

a EPI neuroticism is high, if its score is ≥ 15 and low, if ≤ 14 . EPI extraversion is high, if its score is ≥ 11 and low, if ≤ 10 .

b Two cases are missing.

c Change in perceived social support at 6 months between high vs. low neuroticism is significant: ANOVA, $F=3.919$, $df=1$, $p=0.049$.

d Change in perceived social support at 18 months between high vs. low neuroticism is significant: ANOVA, $F=13.186$, $df=1$, $p<0.001$.

e Repeated measures of perceived social support in PSSS-R at 6 and again at 18 months among patients with low neuroticism at index interview, Friedman Test, Chi-Square 5.313, $df=1$, $p=0.021$.

f Repeated measures of perceived social support in PSSS-R at 6 and again at 18 months among patients with high extraversion at index interview, Friedman Test, Chi-Square 4.546, $df=1$, $p=0.033$.

5.9 Social support prospectively in high vs. low neuroticism/extraversion

Levels of objective and subjective social support

Among patients with high (N=96) and low (N=95) neuroticism, the mean levels of IMSR network size between patients in repeated measures from baseline via 6- to 18-month interview did not change significantly (Table 7) and the same was true among patients with high (N=108) and low (N=83) extraversion (Table 8).

The mean level of perceived social support in PSSS-R among those with low neuroticism increased significantly (Friedman Test, Chi Square 29.902, $df=2$, $p<0.001$), but not among those with high neuroticism (Table 7). Among patients with high extraversion, however, it increased significantly from baseline via 6- to 18-month interview (Friedman Test, Chi Square 18.336, $df=2$, $p<0.001$) and among patients with low extraversion, almost significantly (Friedman Test, Chi Square 4.831, $df=2$, $p=0.089$) (Table 8).

Changes of objective and subjective social support

The mean IMSR network size change within a patient, from baseline to 6 months was -0.40 ± 2.9 , from 6 to 18 months 0.19 ± 2.9 and from baseline to 18 months -0.21 ± 3.2 . The intraindividual changes from baseline to 6, and from baseline to 18 months were not significant in any of the subgroups investigated (Table 9).

The mean within-subject PSSS-R perceived social support non-significant changes were from baseline to 6 months 2.9 ± 10.4 , from 6 to 18 months 0.6 ± 9.8 and from baseline to 18 months 3.5 ± 10.9 . These changes from baseline to 6 and to 18 months were neither significant among those with high neuroticism or low extraversion. However, significant within-subject changes were found among those with low neuroticism (Friedman Test, Chi-Square 5.313, $df=1$, $p=0.021$) and those with high extraversion (Friedman Test, Chi-Square 4.546, $df=1$, $p=0.033$) (Table 9).

5.10 Influence of personality on social support

Predictors for the levels of baseline objective and subjective social support in linear regression models

After adjusting for age, gender, baseline employment, baseline symptoms of anxiety (BAI), baseline symptoms of depression (BDI), baseline alcoholism and marital status, it was found that older age, presence of no baseline alcoholism and higher extraversion ($B=0.329$, 95%CI 0.205; 0.453, S.D.=0.063, $Beta=0.368$, $t=5.246$, $p<0.001$) remained the significant predictors for greater baseline IMSR network size in linear regression models. Female gender, no baseline alcoholism and higher extraversion ($B=0.952$, 95%CI 0.579; 1.325, S.D.=0.189, $Beta=0.329$, $t=5.039$, $p<0.001$) at index interview were significant predictors for higher baseline perceived social support in PSSS-R. Neuroticism at index interview did not remain significant in these models predicting social support (data available upon request).

Predictors for change in objective social support from baseline to 18 months

After controlling for baseline alcoholism, change in BAI anxiety symptoms from baseline to 18 months and baseline presence of marital status, neither neuroticism nor extraversion were significant predictors for IMSR network change from baseline to 18-month interview. Baseline IMSR network size, change in BDI depression symptoms from baseline to 18 months and baseline employment significantly predicted it (Table 10).

Predictors for change in subjective social support from baseline to 18 months

After adjusting for age, gender, baseline employment, marital status at baseline, baseline alcoholism, and change in BAI anxiety symptoms from baseline to 18 months, both neuroticism and extraversion as well as the change in BDI depression symptoms from baseline to 18 months and baseline perceived social support (PSSS-R) persisted as significant predictors for change in perceived social support from baseline to 18-month interview (Table 11). The findings largely persisted also when using time in MDE after baseline (instead of change in BDI depression score from baseline to 18-month interview) as a predictor. In this alternative model, time in MDE ($B=-0.478$, 95%CI -0.769 ; -0.186 , S.E.=0.148, Beta=0.210, $t=-3.230$, $p=0.001$) and neuroticism ($B=-0.478$, 95%CI -0.769 ; -0.186 , S.E.=0.148, Beta=-0.210, $t=-3.230$, $p=0.001$), baseline perceived social support ($B=-0.405$, 95%CI -0.514 ; -0.295 , S.E.=0.055, Beta=-0.482, $t=-7.297$, $p<0.001$) were significant predictors of change in the PSSS-R; extraversion ($B=0.309$, 95%CI -0.036 ; 0.654 , S.E.=0.175, Beta=0.127, $t=1.768$, $p=0.079$) approached significance.

Table 10. Predictors for change in 18-month IMSR network size from baseline to 18 months interview among 193 patients with MDD in Linear Regression Model.							
Variables	B	95% CI for B		S.E.	Beta	t	p
Gender	0.771	-0.072;	1.614	0.427	0.109	1.805	0.073
Age	-0.027	-0.063;	0.009	0.087	-0.095	-1.502	0.135
Neuroticism at index interview	0.021	-0.058;	0.099	0.040	0.035	0.520	0.603
Extraversion at index interview	0.044	-0.057;	0.145	0.051	0.061	0.856	0.393
Change in BDI depression score from baseline to 18-month interview	0.056	0.021;	0.092	0.018	0.201	3.103	0.002
IMSR network size at baseline	-0.446	-0.547;	-0.346	0.051	-0.553	-8.764	<0.001
Employed at baseline	0.807	0.019;	1.595	0.399	0.121	2.021	0.045

Table 11. Predictors for change in PSSS-R perceived social support from baseline to 18 months interview among 193 patients with MDD in Linear Regression Model.							
Variables	B	95% CI for B		S.E.	Beta	t	p
Gender	0.670	3.773;	2.434	1.573	0.028	0.426	0.671
Age	-0.040	0.085;	-0.166	0.064	-0.042	-0.636	0.525
PSSS-R perceived social support at baseline ^a	-0.385	-0.500;	-0.271	0.058	-0.459	-6.643	<0.001
Change in BDI depression score from baseline to 18-month interview	0.158	0.286;	0.030	0.065	0.168	2.438	0.016
Neuroticism at index interview	-0.421	-0.700;	-0.141	0.142	0.213	-2.968	0.003
Extraversion at index interview	0.381	0.022;	-0.741	0.182	0.157	2.092	0.038

^a N=190. Missing data replaced with mean.

6 DISCUSSION

6.1. Main findings

In contrast to expectations, only some differences in recent life events and social support between several sociodemographically and clinically heterogeneous subgroups of patients with MDD were found. Life events did not cluster in the time before depression or in the prodromal phase. Nevertheless, patients commonly attributed their depression to a life event.

Adverse life events and poor perceived social support predicted the medium-term prospective outcome of psychiatric MDD patients. Somewhat contrary to the second hypothesis, the outcome of the subgroup in partial remission at onset was not predicted by social support, although the impact of negative life events was pronounced in this group. Overall, adversity and perceived social support had the strongest predictive roles in the subgroup of patients currently in full remission.

Among psychiatric MDD patients, the time spent in MDEs during follow-up significantly predicted 18-month subjective and objective social support. Subjective, but not objective, social support improved among most patients. However, within a small subgroup of chronic patients persisting in a major depressive episode throughout follow-up, the objective social network size diminished progressively.

Among psychiatric MDD patients, the personality dimensions of neuroticism and extraversion were related to level and changes in patients' social support. Across all time points, particularly level of extraversion predicted between-subject differences in levels of objective and subjective social support. Furthermore, levels of neuroticism and extraversion predicted the 18-month change of subjective, but not objective social support.

6.2 Methods

6.2.1 General study design

VDS is a prospective and naturalistic cohort study. The main limitation was that it was carried out without a representative control group of subjects without depression. Thus it is not known whether life events or lack of social support truly were risk factors for depression.

6.2.2 Representativeness of the sample

This study included a non-selected, representative, secondary treatment level psychiatric sample of out- and inpatients with MDD, interviewed at baseline (N=269), at 6 and 18 months after baseline (N=193), in the city of Vantaa, Finland. This sample represents two thirds of all depressed subjects in the general population of Vantaa seeking psychiatric treatment (Rytsälä et al. 2001). Most of the patients (88%) at the 18-month interview had antidepressants, and for the majority (78%) the dosages were at adequate levels for the acute phase in baseline (Melartin et al. 2004). As in any naturalistic study, the treatment was not under the control of the investigators.

6.2.3 Diagnostic measures and life chart methodology

The diagnoses of MDD and comorbid disorders were made using structured interviews (SCAN, SCID-II), and the interrater reliability in the diagnosis of MDD was excellent ($\kappa=0.86$), but that for comorbid disorders was unknown (Melartin et al. 2002). The course of depression during the follow-up was assessed using life chart methodology by inquiring change points in the clinical state according to DSM-IV, with important life events as probes. This Longitudinal Interval Follow-up Evaluation (LIFE) was introduced to investigate the outcome of depression in the form of graphic life chart (Keller et al. 1987).

6.2.4 Dropouts

After baseline, only patients who participated in all three interview phases, remained unipolar and had complete data available, were included; thus the 193 cases included represent 71.7% of the original cohort of 269 patients. Those who dropped out exhibited more symptoms of anxiety, lived alone somewhat more often and were younger. The changes in symptoms of anxiety from baseline to 18 months, the presence of marital relationship and age were adjusted for in the linear regression models. So they are unlikely to produce major bias in the results. In terms of the amount of life events, objective or subjective social support, however, those who dropped out did not differ significantly from those who remained in follow-up.

6.2.5 Measurement of life events and social support

Life events and social support were assessed by both semi-structured interview methods (IRLE, IMSR) and a questionnaire (PSSS-R) with good overall reliability. The reliability of interview measurements in the study was not formally tested but internal consistency for the measures of network size and perceived social support was excellent. The study was carried out in the absence of a representative control group of subjects without depression. Thus it is not possible to estimate whether the life events or social support investigated truly represented risk factors for the onset of depression.

As the patients were studied while clinically depressed, state effects due to depression or comorbid disorders might have biased the findings regarding life events and social support. However, these bias could be minimized by adjusting for psychopathology in the regression models.

In addition, clinical status, life events and social support were assessed by the same investigator, although during a different appointment session. Some contamination of findings may have occurred, although this is unlikely to be a major factor, given so few strong positive findings in the first study. In the second study, as the correlation between HAM-D and observed severity of preceding life events at 6 months was low (0.221), it is unlikely that contamination would have much occurred. The correlation between HAM-D and perceived social support at 6 months was a little stronger (-0.399), therefore statistical adjustment for level of depression was necessary.

The study was also limited by the known bias of any retrospective study, including less than perfect recall, fall-off in reporting more distant life events in IRLE, imprecise timing of events, and possible effort after meaning by the patient (Cooper and Paykel 1994). Some of the life events were dependent from depression. After taking that into consideration only minor changes in the results were to be seen.

Social support in the IMSR focused on the two weeks before the baseline interview; whether major changes had occurred earlier remains unknown. The PSSS-R score, an estimate of perceived social support, may also contain relatively stable, trait-like elements (Lakey and Cassady 1990), but gives no information about variations during the progression to MDE.

It might finally be argued that scarcity of positive findings in the first study, implies insufficient statistical power and thus a type II error, particularly as a more stringent definition for significance (<0.005) was applied in order to protect from spurious associations. However, the sample was relatively large ($N=269$), and none of the observed differences between subgroups was remarkable; most of the statistically significant subgroup differences were too small to be clinically relevant.

6.3 Results

6.3.1 Life events, social support and onset of MDE

Because of remarkable sociodemographic and clinical heterogeneity among patients with MDD, it was respectively expected many differences between gender and age groups in life events and social support and more events and support among patients with their first MDE, in non-melancholic/non-psychotic patients and in the Axis I and Axis II comorbid groups of patients with DSM-IV MDD.

Generally women, compared with men, had not experienced more events at the onset of depression, which was more in line with the investigations of Dalgard et al. (2006), Kendler et al. (2001b), (Maciejewski et al. 2001) and Paykel (1991). There were no differences in the types of events with exception of more family events when including only independent events. Women, however, perceived more social support despite a similar size of social network.

As to age, younger patients had experienced more life events and perceived more social support. Older patients reported somewhat more severe life events. Disparities between younger and older patients were more qualitative than quantitative, and seemed to reflect the phase of life.

Those having recurrent depression had not fewer life events as in many previous studies (Kendler et al. 2000; Post 1992), only more severe impact of events in prodromal phase among those with single episode, was to be found. Within the subgroup of patients with melancholic features there were no differences between single versus recurrent patients. This sample included younger patients than the study of Frank et al. (1994) and fewer inpatients than Brown et al. (1994). After stratifying the data according to these variables, the findings remained the same.

Patients with comorbid anxiety disorder had somewhat more life events, as was expected, while those with comorbid alcoholism had not, compared with patients without respective comorbidity. Perceived social support was weaker among patients with comorbid alcoholism. Although marked differences were supposed between those with or without personality disorder, even the life event measures of separations or divorces were not greater among patients with cluster B personality disorder. Perceived social support, however, was weaker, especially among cluster A patients. The differences between the record-based findings of Pfohl et al. (1984) and the present investigation may be at least in part caused by different samples because in the latter there were more outpatients. These diagnostic differences of comorbid mental disorders, although important in planning treatment of the patients, did not separate subjects with substantially different psychosocial pathways into depression.

Contrary to the expectations, the clustering of independent events into the phases before depression and the prodrome was not to be found. Events tended to pervade all the temporal phases in the progress into depression. Work events may yet have occurred more often before the onset of depression, while family events may have been more common as a consequence of pre-existing depression. The finding of higher objective negative impact of life events during the period of prodromal symptoms among those with their lifetime first episode, may suggest some precipitating role among the first-timers. The major cause for not finding major clustering of events in the two phases may be the chronic and comorbid nature of psychopathology among psychiatric patients. Comorbid disorders are often long-term disorders, intertwined with the course of depression. Therefore depression was unlikely a discrete episode related to a single major life event.

The majority of patients attributed their depression to be triggered by a life event, but in fact, only one third of the attributed events occurred immediately at the onset of the prodrome.

6.3.2 Influence of adversity and social support on the outcome

As to adversities it was firstly hypothesized that severity of life events between the two follow-ups would predict subsequent level of depression in general. This was confirmed and is also in accordance with several earlier investigations (Billings and Moos 1985; Cronkite et al. 1998; Moos et al. 1998; Swindle et al. 1989). However, the second more specific hypothesis, suggesting that because of their particular vulnerability (Paykel et al. 1995), those in partial remission would be more affected than the other groups by adverse life events, did not seem to be true. In either the 6- or the 18-month univariate analyses, no significant mean differences in the severity of life events between the three clinical subgroups were found. In linear regression models the severity of life events was an important predictor also for patients in full remission, not only for those in partial remission, as was expected. Thus, no evidence in terms of adversities for those in partial remission to be a particularly vulnerable subgroup was found. Adversity, by contrast, seemed to have only small effect on those with an ongoing major depressive episode.

As to social support it was firstly anticipated that both objective and subjective social support would be significant predictors of the outcome among all patients. Only subjective social support was significant, thus partly confirming the hypothesis. Qualitative aspects of support may be of importance. Network size, as a measure of objective social support, may be more dependent on the clinical state of the patient. Perceived social support, however, is theoretically rooted in the theory of attachment (Bowlby 1979) and may thus also reflect permanent personality features (Lakey and Cassady 1990). The three subgroups, however, did not differ regarding the presence of a close attachment figure. The quality of the relationship with significant others seemed to be more important. It is noteworthy that significance of perceived social support persisted after adjusting for severity of depression as well as neuroticism. Contrary to the second, more specific hypothesis subjective social support did not predict the outcome of depression among patients in

partial remission, but did so among patients in full remission. Although those in stable, full remission had somewhat better resources at the outset, they seemed to be more sensitive to the negative influence of poor social support during follow-up. Among those in partial remission, neuroticism was a significant predictor for later level of depression, not subjective social support. By contrast, those with an ongoing MDE at 6 months had poor objective social support, namely the smallest network size, were more alone and had fewer interactions with other people. In addition subjective social support was weaker in this group. However, also among this group, only subjective, and not objective, social support significantly predicted the outcome of depression.

6.3.3 Influence of MDD on social support

The aim of the study was to find out whether 1) objective and subjective social support decline as a consequence of time spent in MDE and 2) whether they are sensitive to improvement among patients with DSM-IV MDD.

Objective social support

The longer the patient remained depressed during the follow-up, the smaller the 18-month network size. This was most apparent in the small subgroup of patients who suffered from persistent major depressive episodes throughout the follow-up period. In answer to the second question, it is worth noting that the network size persisted more sparse, even though the clinical state of the patients improved. The influence of clinical or personality characteristics other than those directly related to depression on the outcome of objective social support appeared limited. However, whether the network size later could return to the baseline size after the 18-month interview remains unknown. The aspects of objective social support most related to depression seem to have a smaller network and fewer contacts, whereas no differences in having a close attachment figure, or in negative interactions, criticism or intense interactions between the clinical groups at different points of time, were to be found. This finding could perhaps be best clinically understood in terms of fatigue and diminished interest in social interactions. Consistently with this, the type of objective social support that deteriorated most from depression appeared to be friends, whereas no major changes in the marital status or in the proportion of patients living alone were to be seen. In general, these results resemble those of Coryell et al. (1993) in showing the decline in objective social support. A more detailed comparison, however, is difficult because the patients in the Coryell et al. (1993) study had a longer follow-up time, different measures of objective social support and more inpatient tertiary care patients, of whom 35% were married at the endpoint. About half of the secondary care, medium-term follow-up patients in this VDS study were married at the endpoint, and only some had divorced during the follow-up period. Overall, these two clinical studies support the notion that clinical depression deteriorates objective social support.

Subjective social support

More time depressed had a negative impact on subjective social support. Unlike objective social support, subjective social support improved along with the recovery. Within the small subgroup of chronic patients, a non-significant progressive decline in subjective social support was to be seen. Coryell et al. (1993) measured relationships with spouse, children, important relatives, and friends (i.e. variables rather similar to the subscales of family, friends and significant other in PSSS-R used in VDS). The deteriorative effects of depression were found in both of these studies, but the influence of recovery on subjective social support was found only in this medium-term study on patients with less severe MDE. Furthermore, neuroticism at baseline had no influence on subjective social support, which was in contrast to the cross-sectional, general population sample of Petty et al. (2004). However, these investigators documented the state effect of depression on subjective, perceived social support, just as in this VDS study, too. Overall, the depressed patient's perceptions on subjective, perceived social support appear to be related in part to the patient's current level of depression; so as the patient's depression diminishes, so the patient's outlook on social support becomes more positive. Nevertheless, these multivariate analyses suggest that, even taking this into account, persistent depression leads to inferior subjective social support.

6.3.4 Influence of personality on social support

Level of support between individuals

Regarding between-subject differences, it is firstly hypothesized, that the lower the neuroticism, or the higher the extraversion, the higher also the level of objective and subjective social support; conversely, the higher the neuroticism, or the lower the extraversion, the lower the level of social support. Correlations in this fairly large sample between social support and neuroticism were negative but low, and between extraversion positive and somewhat stronger. Patients with low neuroticism and high extraversion had, in accordance with the hypothesis, higher levels of objective and subjective support at each time point, when compared with patients with high neuroticism or low extraversion. At every time point, patients with low neuroticism or high extraversion had on average one or two, respectively, more persons in their social network and perceived more social support than those with high neuroticism or low extraversion. In the cross-sectional tertiary care study of Ranjith et al. (2002), only extraversion, but not neuroticism, made an important contribution to patient's self-perception and motivation towards social functioning. When depression alleviated, the levels of subjective social support improved among patients with low neuroticism and high extraversion. Among those with high neuroticism, however, objective and subjective social support persisted at low

levels over time. Among those with low extraversion, the hypotheses were only partly confirmed, as the level of objective support remained the same, while the level of subjective social support somewhat improved concurrently with alleviating depression. Overall, among patients with depression, the role of extraversion is more important in influencing differences between individuals in level of social support, whereas neuroticism may be more important for determining their potential change.

Changes of support within individuals

It was secondly hypothesized, that the lower the neuroticism, or the higher the extraversion, the greater the within-subject positive changes in objective and subjective social support; conversely, the higher the neuroticism or the lower the extraversion, the smaller these changes. At all points of time, the within-subject changes of subjective, but not objective social support, were more marked among patients with low neuroticism vs. high neuroticism, but between those with low vs. high extraversion the changes remained non-significant. Prospective changes were found only in subjective, not in objective social support, and only among those with low neuroticism or high extraversion, which thus only partly confirms the hypotheses. In this prospective study with secondary care MDD-patients, the influence of neuroticism on within-subject improvement seemed more apparent. As in some non-clinical studies (Holahan et al. 1999; Holahan et al. 2000; Joiner 1997), the influence of these personality traits among depressive patients with MDD seemed negative with regard to their social resources. Patients with low neuroticism and high extraversion were able to regain and create new social contacts when depression was alleviated. In contrast, patients with high neuroticism seemed less capable of doing so; their social resources remained consistently weaker. Factors such as negative affects (Clark and Watson 1991) and maladaptive cognitions (Schutte 1992) among individuals with high neuroticism may hinder the development of social support. As suggested by Roberts and Gotlib (1997), patients with low extraversion may have weaker objective and subjective social support possibly due to fewer opportunities for social reinforcement. Social self-efficacy and social support have both been negatively associated with depression (McFarlane et al. 1995), but whether self-efficacy is a factor mediating the influences between personality and social support remains unknown. Future research is needed to investigate whether neuroticism and extraversion have similar or different interpersonal pathways mediating influences on risk for and outcome of depression, but these influences are likely stronger for subjective than objective aspects of social support.

7 CONCLUSIONS

7.1 Conclusions and clinical implications

At the onset of depression life events were common and distributed equally in time before depression, prodromal phase and MDE proper. Thus, events may take different roles in different phases. Before MDE they may precipitate depression, in the prodromal phase increase symptoms and in MDE slow down recovery from depression. Life events may also be consequences of depression, and a depressive patient may self generate them. Two thirds of the patients, however, attributed their depression to some event, although only one third of events had occurred immediately at the onset of prodromal phase. Consequently, it is clinically important to grasp the real role of an event in a unique treatment situation.

Comorbid personality disorder and alcoholism among patients with major depressive disorder at the onset of depression were related to weaker perceived social support. These patients may thus also have more difficulties to form collaboration and adherence to treatment. It is important from the beginning of the treatment to pay attention to these aspects among these depressed patients.

Adverse life events and poor perceived social support after baseline had an impact on the outcome of depression among all patients, and mostly among those in full remission. So it is necessary to pay attention to this group of patients to prevent recurrence of MDE. In addition, partially remitted patients were sensitive to adversities and MDE patients to poor perceived social support. From the clinical point of view, the quality of social relationships and coping with difficulties are to be improved by means of psychotherapeutic approaches.

The persistence of MDD appears to weaken both objective and subjective social support. Along with recovery only subjective social support was sensitive to improvement. It is important that depressive patients recover soon, because a vicious circle between major depressive episode and poor social support may develop and predispose to the chronic course of the illness.

Personality had an impact on the social world of the patients. When depression alleviated, patients with high extraversion and low neuroticism regained and created social contacts, in contrast to patients with high neuroticism or low extraversion. The neuroticism may be important in determining potential for change, and especially high neuroticism may hinder the development of social support. Neuroticism and extraversion, by affecting social support, possibly modify and indirectly influence future vulnerability to depression.

7.2 Implications for future research

In this research, interrelationships between life events, social support, major depression and personality were complex and often reciprocal: the influencing agent may be under the influence of the influenced. However, the scope of study should be still wider. Future research, for instance, should take more into account the contribution of genetic factors, because genetic liability may indicate vulnerability to depression, and genes have been found to moderate the influence of stress on depression and the impact of depressiogenic social influences. People may also select themselves into high-risk environments through genetical traits of neurotic temperament. In addition, personality features, as for instance, self-esteem should be paid more attention to, and different coping strategies and self-efficacy. After considering important interrelations more widely, future research should investigate how significant connections are functioning and find different mechanisms to explain the role of psychosocial factors in major depression.

More research is needed to find out whether heterogeneous subgroups of major depression truly do not differ as to adverse life events and social support. In addition to accurate dating of life events and phases of depression, life chart method should also encompass phases of major consumption of alcohol, phases of anxiety, personality disorders and somatic diseases of the patients. Careful investigation should explain what was the first reaction, if any, to an adverse life event. Was it depression, more consumption of alcohol, increasing anxiety or more disturbances in personality?

The scope of investigation should also be widened to major depressive disorders in primary care, where recurrency, chronicity and comorbidity also bring heterogeneity among major depressive patients. It is not known whether these results are to be generalized to primary care, where depression often is less deep and has impaired cognitive coping abilities to a smaller degree.

The results come from medium-term, 18-month follow-up. A longer-term follow-up should confirm the main results, i.e. whether psychosocial factors influence the outcome of depression most among those in full, but not as much in partial remission or in MDE, whether persistence of MDE results in progressively weakening of social support thereby lowering the threshold for future depressive episodes and what is the long-term role of neuroticism and extraversion in modifying vulnerability to depression through interpersonal channels.

8 ACKNOWLEDGEMENTS

This study was carried out at the Department of Mental Health and Alcohol Research of the National Public Health Institute, in Helsinki, and at the Department of Psychiatry at Helsinki University Central Hospital (HUCH), Peijas Hospital, Vantaa. I wish to thank both the former and the present Director General of the National Public Health Institute, Professor Jussi Huttunen, M.D., Ph.D., and Professor Pekka Puska, M.D., Ph.D., for the facilities provided to me by the Institute. I am also very grateful to the former head of the Psychiatric Department of HUCH, Peijas Hospital, Dr. Juhani Solantaus, M.D., for the opportunity of joining this research work and for his warm and valuable support for my work. As an Academic Dissertation, this work took place in the Department of Psychiatry, at the University of Helsinki, for which opportunity I am most grateful.

I wish to express my sincere gratitude to Professor Jouko Lönnqvist, M.D., Ph.D. for the privilege of working and developing my research at the Department of Mental Health and Alcohol Research.

I owe the most profound gratitude to my supervisor, Professor Erkki Isometä, M.D., Ph.D., Department of Psychiatry, University of Helsinki and Research Professor, Head of Mood Disorders Research at the Department of Mental Health and Alcohol Research of the National Public Health Institute. In his guidance I learned to combine intellectual approach to deeply emotional problems. Without his patience and insightful and bright advice in all theoretical and practical questions, it would not have been possible to accomplish this work.

I would like to thank the reviewers of this thesis, Professor Mika Kivimäki, Ph.D. and Docent Juha Veijola, M.D., Ph.D. for their valuable contribution to this thesis and clarifying contents of it.

Especially I want to thank warmly my fellow-researchers and co-authors in Vantaa Depression Study, Paula Lestelä-Mielonen, M.A., Tarja Melartin, M.D., Ph.D., Heikki Rytsälä, M.D., Ph.D., and Petteri Sokero, M.D., Ph.D., for scientific collaboration for more than ten years. I am extremely grateful to Tarja Melartin who, full of excellent ideas lended a helping hand whenever some problem arose and her work for the reliability of the data we all used. I also sincerely thank Heikki Rytsälä for his logic in theoretical questions and mastering of computers.

I have further the pleasure to thank co-authors Docent Martti Heikkinen M.D., Ph.D. for his contribution in the selection of valid and reliable measures for life events and social support, Professor Erkki Komulainen, Ph.D., who gave clear and thorough instruction in statistics for many hours and Pekka Jylhä M.D., Ph.D. for making me acquainted with personality problems in depression.

Sincere thanks to Professor Mauri Marttunen, M.D., Ph.D. for his contribution to the educational and developmental part of the study project, to Antti Karila, Ph.D. for warm encouragement during the study project and Maria Vuorilehto, M.D., Ph.D. for rich and rewarding conversations with humour and new insights.

I also warmly thank Eevaliisa Orelma for her assiduous work in Vantaa Depression Study and kind assistance whenever it was asked. Also Marjut Grainger and Olli Kiviruusu have offered me quite indispensable help in statistical affairs and data procedures. Thanks to them, and also to Sirkka Laakso, Tiina Hara and Tuula Koski for help in many practical matters, to the library personnel at the national Public Health Institute, and also to the personnel of Peijas Hospital and outpatients Clinics for practical help and positive attitude toward the research.

I am grateful to my late mother and father, and to Mirja, who has been like a mother to me. I also warmly thank my sister Tytti for many years of growing together, my sister Tiina for her profound and honest philosophical attitude, and my brother-in-law, Esa, for his imaginative drawing of depressive mind on the cover of my thesis. To you my husband Pekka, I owe the deepest meaning and love of my life, now as many times before. You have stayed by my side again in this research process, and I could not have done it without your countenance. I also thank my children, Anna-Elina, Leealaura and Antti. From you I have learned that life is really worth of loving, defending - and researching. I am happy to thank also you, my grandchildren, Jeremias, Samuel, Rasmus, Vienna and Henrik. You have reminded me that life is not only work and research. You are a joy to me and the world of scientific processes is left far behind with you.

Finally I express my deepest appreciation to all the patients who participated in this study.

This study has been financially supported by the Academy of Finland.

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