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SUICIDAL BEHAVIOR IN DEPRESSIVE OR BIPOLAR DISORDERS

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Abstract

This thesis investigates suicidal behavior in its different forms of suicidal ideation, suicide attempts, and death by suicide among patients with depressive disorders or bipolar disorder in psychiatric care.

Explanatory factors for lifetime suicidal ideation and suicide attempts are examined as part of the Helsinki University Psychiatric Consortium (HUPC) study. The study is based on a random sample of 287 patients (mean age 39.9 years) with either depressive disorders (n=188) or bipolar disorders (n=99) in psychiatric secondary care in the Helsinki metropolitan area. Based on clinical diagnoses, each participant was assigned a lifetime principal diagnosis by reviewing medical records. The participants were surveyed by self-reports on early life experiences, personality traits, psychological factors, current and lifetime clinical symptoms, and lifetime suicidal behavior. Information on lifetime suicide attempts was complemented by data from medical records.

Of the HUPC cohort, 34% reported lifetime suicidal ideation, 17% had once attempted suicide, and 28% had repeatedly attempted suicide. Lifetime suicidal behavior was associated with several factors from multiple domains when examined separately. When the effects of other variables were controlled, lifetime suicidal ideation had independent associations with younger age, lifetime principal diagnosis of severe depressive disorder and bipolar disorder (type II), hopelessness, and childhood physical abuse. Lifetime single suicide attempt was independently associated with diagnosis of severe depressive disorder without psychotic symptoms and self-reported borderline personality disorder traits. Lifetime repeated suicide attempts were independently associated with younger age, female sex, diagnosis of severe depressive disorder with and without psychotic symptoms, diagnosis of bipolar disorder (type II), comorbid alcohol dependence, self-reported borderline personality disorder traits, and childhood physical abuse.

As part of the HUPC study, the association between childhood maltreatment and suicidal behavior was investigated in more detail. The total effect of childhood maltreatment on either lifetime suicide ideation or suicide attempt was similar in magnitude. Formal mediation analyses estimated that all of the total effect of childhood maltreatment on suicide attempts, and about one-fifth of the total effect on suicidal ideation, were mediated by borderline personality disorder traits. The mediation effect was independent of current depressive symptoms, and the difference between suicidal ideation and suicide attempt outcomes was statistically significant.

Risk for suicide, its temporal trends and risk factors were longitudinally investigated in a national study of first-hospitalized patients for depression. This register-based study links individual-level data from the Finnish Hospital Discharge Register, the Census Register of Statistics Finland, and Statistics Finland's register on causes of death. A cohort of 56 826 patients (25 188 men, 31 638 women; mean age 44.8 years) hospitalized in 1991-2011 was followed on the registers up to the end of the year 2014.

During a maximum 24-year follow-up 2587 patients (1609 men, 978 women) died by suicide. The overall cumulative risk for suicide was 8.6% in men and 4.1% in women. The risk for suicide was less than half (HR 0.49) among patients first hospitalized in 2006-2011 relative to patients first hospitalized in 1991-1995. The incidence rate was highest during the first year after discharge (2305 per 100 000 person-years in men, 973 per 100 000 person-years in women) and was more than halved during the next year.

The strongest baseline predictors for suicide were male sex and previous suicide attempts. Other predictors included severe depression, psychotic depression, comorbid alcohol dependence, living alone, higher education level, and high family income. Among patients with previous suicide attempts, the cumulative probability for suicide was 15.4% in men and 8.5% in women. Gender differences in risk factors were modest and appeared to inadequately explain the gender disparity in risk. Of those who died by suicide, men died more often by potentially more lethal methods.

In summary, suicidal ideation and suicide attempts in depressive disorders and bipolar disorders may have both shared and unshared risk factors. The differences may be both qualitative and quantitative. Factors that are temporally closer to the suicidal behavior have independent effects. Hopelessness and depressive morbidity are associated with suicidal ideation. Suicide attempters are characterized by more severe clinical characteristics and factors related to a predisposition to act on one's thoughts. Childhood maltreatment is a risk factor for suicidal behavior. The mediating mechanisms between the outcomes of suicidal ideation or suicide attempts appear different. Borderline personality disorder traits may act as a major mediating factor between childhood maltreatment and suicide attempts.

Inpatients with depression have a high risk of suicide over time, particularly during the post-discharge year. The cumulative risk of suicide in depression varies with time and ecological changes. The risk for suicide has declined substantially among clinically severe inpatients from 1991 to 2014 in Finland. Clinical characteristics and sociodemographics predict long-term risk of suicide. Highest risk is associated with previous suicide attempts and male gender. Modest gender differences exist in risk factors, but the choice of potentially more lethal methods by men may explain men's excess risk.

Keywords: suicidal ideation, suicide attempt, suicide, depressive disorder, bipolar disorder, risk factor

Tiivistelmä (Finnish Abstract)

Väitöskirjassa selvitettiin itsetuhokäyttäytymisen esiintyvyyttä ja taustatekijöitä psykiatrisessa erikoissairaanhoidossa masennuksen tai kaksisuuntaisen mielialahäiriön vuoksi hoidossa olleilla potilailla. Tutkimuksessa tarkasteltiin erikseen itsemurha-ajattelua, itsemurhayrityksiä ja itsemurhia.

Itsemurha-ajattelun ja itsemurhayritysten taustatekijöitä selvitettiin osana Helsinki University Psychiatry Consortium (HUPC) tutkimusta. Tutkimusaineiston (N=287) muodostivat 188 masennuksesta ja 99 kaksisuuntaisesta mielialahäiriöstä kärsivää potilasta (keski-ikä 39,9 vuotta). Potilaat valittiin satunnaisotantaan perustuen pääkaupunkiseudun psykiatrisesta erikoissairaanhoidosta. Elämänaikainen päätutkimusdiagnoosi määriteltiin tavanomaisen kliinisen diagnostiikan ja sairauskertomustietojen pohjalta. Tutkimuskyselyllä kartoitettiin potilaiden lapsuuden kokemuksia, persoonallisuuden piirteitä, psykologisia tekijöitä, ajankohtaista sekä elämänaikaista oirekuvaa ja itsetuhokäyttäytymistä. Tietoa itsemurhayrityksistä täydennettiin sairauskertomuksista saatavilla tiedoilla.

HUPC-tutkimukseen osallistuneista potilaista 34% raportoi elämänaikaista itsemurha-ajattelua. Itsemurhaa oli yrittänyt kerran 17% potilaista ja toistuvasti 28%. Lukuisia tekijöitä usealta eri osa-alueelta yhdistyi itsetuhokäyttäytymiseen yksittäin tarkasteltuna. Monimuuttuja-analyysissä riippumattomasti elämänaikaista itsemurha-ajattelua selittivät nuorempi ikä, vakava masennustila, tyypin II kaksisuuntainen mielialahäiriö, toivottomuus ja lapsuudenaikainen fyysinen kaltoinkohtelu. Toistuvia itsemurhayrityksiä selittivät riippumattomasti nuorempi ikä, naissukupuoli, vakava masennustila, psykoottinen masennustila, tyypin II kaksisuuntainen mielialahäiriö, alkoholiriippuvuus, tunne-elämän epävakaat persoonallisuuden piirteet ja lapsuudenaikainen fyysinen kaltoinkohtelu.

Tarkemmassa tarkastelussa todettiin lapsuudenaikaisen kaltoinkohtelun vaikutuksen olevan yhtä suuri itsemurha-ajatteluun ja itsemurhayrityksiin. Mediaatioanalyysin tulosten perusteella lapsuudenaikaisen kaltoinkohtelun vaikutukset välittyivät kokonaisuudessaan itsemurhayritysten osalta tunne-elämän epävakaiden persoonallisuuden piirteiden kautta, kun taas vaikutuksesta itsemurha-ajatteluun välittyi vain viidesosa. Ero oli tilastollisesti merkitsevä ja riippumaton ajankohtaisista masennusoireista.

Koko Suomen kattavassa rekisteritutkimuksessa selvitettiin masennuksen vuoksi ensimmäistä kertaa sairaalahoidossa olleiden potilaiden itsemurhan riskiä, riskitekijöitä sekä riskissä tapahtuneita ajallisia muutoksia. Tutkimuksessa yhdistettiin yksilötason tietoa sairaalahoidon hoitoilmoitusrekisteristä (HILMO), Tilastokeskuksen väestörekisteristä ja kuolinsyirekisteristä. Tutkimuskohortin muodostivat 56 826 masennuksen

vuoksi vuosina 1991-2011 ensimmäistä kertaa sairaalahoidossa ollutta potilasta (25 188 miestä, 31 638 naista; keski-ikä 44,8 vuotta). Potilaita seurattiin enimmillään 24 vuoden ajan vuoden 2014 loppuun asti.

Potilaista 2587 kuoli itsemurhaan (1609 miestä, 978 naista). Itsemurhan kumulatiivinen riski oli miehillä 8,6% ja naisilla 4,1%. Vuosina 2006-2011 ensimmäistä kertaa sairaalahoidossa olleiden potilaiden itsemurhan riski oli puolet pienempi (riskitiheyksien suhde 0,49) kuin vuosina 1991-1995 hoidossa olleilla. Itsemurhan ilmaantuvuus oli korkein ensimmäisenä sairaalahoidon jälkeisenä vuotena (miehillä 23,05 ja naisilla 9,73 per 1000 henkilövuotta) ja laski selvästi yli puoleen toisen vuoden aikana.

Itsemurhakuolemaa ennustivat miessukupuoli, aiempi itsemurhayritys, vakava masennustila, psykoottinen masennus, alkoholiriippuvuus, yksin asuminen, korkeampi koulutus ja perheen korkea tulotaso lähtötilanteessa. Aiemmin itsemurhaa yrittäneiden miesten (15,4%) ja naisten (8,5%) kumulatiivinen todennäköisyys kuolla itsemurhaan oli hyvin korkea. Sukupuolierot riskitekijöissä olivat vähäisiä ja selittivät heikosti sukupuolieroja riskissä. Itsemurhaan kuolleet miehet olivat naisia useammin menehtyneet todennäköisemmin kuolettavaan itsemurhamenetelmään.

Johtopäätöksenä todetaan, että masennuksesta tai kaksisuuntaisesta mielialahäiriöstä kärsivien potilaiden itsemurha-ajattelun ja itsemurhayritysten taustatekijät voivat olla osin jaettuja ja osin erillisiä. Erot voivat olla sekä laadullisia että määrällisiä. Vankimmin itsetuhokäyttäytymistä selittävät ajallisesti sitä lähellä olevat kliiniset tekijät. Itsemurha-ajattelua selittävät sekä masennukseen yhdistyvä sairastavuus että toivottomuus. Itsemurhayrityksiä selittävät vaikeampi oirekuva ja tekijät, jotka voivat liittyä alttiuteen toimia ajatusten mukaisesti. Lapsuudenaikainen kaltoinkohtelu on itsetuhokäyttäytymisen riskitekijä. Tekijät jotka välittävät tätä yhteyttä näyttävät eroavan itsemurha-ajatusten ja itsemurhayritysten välillä. Tunne-elämän epävakaan persoonallisuuden piirteet voivat olla merkittävä yhdistävä tekijä lapsuudenaikaisen kaltoinkohtelun ja itsemurhayritysten välillä.

Masennuksen vuoksi sairaalahoidossa olleiden potilaiden kumulatiivinen riski kuolla itsemurhaan on korkea. Riski on korkein sairaalahoidon jälkeisenä ensimmäisenä vuotena. Tutkimus osoittaa, että masennuksesta kärsivien potilaiden riski kuolla itsemurhaan voi olennaisesti muuttua väestötasolla, ja että masennuksen vuoksi sairaalahoidossa olleiden potilaiden itsemurhan riski on laskenut johdonmukaisesti Suomessa 1990-luvun alusta alkaen vuoteen 2014 asti. Sekä kliiniset että sosiodemografiset tekijät ennustavat itsemurhakuolemaa pitkällä aikavälillä. Riski on korkein miehillä ja aiemmin itsemurhaa yrittäneillä. Sukupuolten väliset erot riskitekijöissä ovat vähäisiä. Miesten taipumus valita todennäköisesti kuolettavampia itsemurhamenetelmiä voi selittää miesten ylikuolleisuutta itsemurhaan.

Avainsanat: itsemurha-ajattelu, itsemurhayritys, itsemurha, masennus, kaksisuuntainen mielialahäiriö, riskitekijä.

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List of original publications

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- I. Aaltonen K, Näätänen P, Heikkinen M, Koivisto M, Baryshnikov I, Karpov B, Oksanen J, Melartin T, Suominen K, Joffe G, Paunio T, Isometsä E. Differences and similarities of risk factors for suicidal ideation and attempts among patients with depressive or bipolar disorders. *Journal of Affective Disorders* 2016;193:318-330.
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- III. Aaltonen KI, Isometsä E, Sund R, Pirkola S. Decline in suicide mortality after psychiatric hospitalization for depression in Finland between 1991 and 2014. *World Psychiatry* 2018;17(1):110-112.
- IV. Aaltonen KI, Isometsä E, Sund R, Pirkola S. Risk factors for suicide in depression in Finland: first-hospitalized patients followed up to 24 years. *Acta Psychiatrica Scandinavica* (published online 27 Nov 2018); doi: 10.1111/acps.12990.

The publications are referred to in the text by their Roman numerals and have been reprinted with the permission of their copyright holders

Abbreviations

ACME	Average Causal Mediation Effect
ADE	Average Direct Effect
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorders Identification Test
BD	Bipolar Disorder
BD-I	Bipolar Disorder, type I
BD-II	Bipolar Disorder, type II
BDI	Beck Depression Inventory
BHS	Beck Hopelessness Scale
BIS-11	Barratt Impulsiveness Scale, version 11
BPD	Borderline Personality Disorder
CANMAT	Canadian Network for Mood and Anxiety Treatments
CAPE	Community Assessment of Psychic Experiences
CBT	Cognitive Behavioral Therapy
CM	Childhood Maltreatment
DBT	Dialectical Behavior Therapy
DCR	Diagnostic Criteria for Research
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
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 th edition
ECR-R	Experiences in Close Relationships, revised
ECT	Electroconvulsive Treatment
FHDR	Finnish Hospital Discharge Register
GAS	Global Assessment Scale
GBD	Global Burden of Disease
GSE	General Self-Efficacy Scale
HR	Hazard Ratio
HUPC	Helsinki University Psychiatric Consortium
ICD-10	International Classification of Diseases, 10 th edition
ISBD	International Society for Bipolar Disorders
JoBS	Jorvi Bipolar Study
LTE-Q	List of Threatening Experiences Questionnaire
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MDQ	Mood Disorder Questionnaire
MSI-BPD	McLean Screening Inventory for Borderline Personality Disorder
NCS-R	National Comorbidity Survey Replication

NOS	Not Otherwise Specified
OASIS	Overall Anxiety Severity and Impairment Scale
pc-VDS	Vantaa Primary Care Depression Study
PRISM	Psychiatric Research Interview for Substance and Mental Disorders
PSSS-R	Perceived Social Support Scale, revised
RCT	Randomized Controlled Trial
rTMS	Repetitive Transcranial Magnetic Stimulation
S ₅	Short Five
SD	Standard Deviation
SDS	Sheehan Disability Scale
S.E.	Standard Error
SGA	Second-Generation Antipsychotic
SPQ-B	Schizotypal Personality Questionnaire, brief version
SUD	Substance Use Disorder
TADS	Trauma and Distress Scale
tDCS	Transcranial Direct Current Stimulation
VDS	Vantaa Depression Study
WMHS	World Mental Health Survey

1 Introduction

Worldwide, approximately 800 000 people die annually by suicide and the number of suicide attempters is about 20-fold higher (World Health Organization, 2014). In the year 2016, about 300 million people were affected by depressive disorders and 40 million people by bipolar disorders (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). More than half of those who die by suicide or have attempted suicide have either depressive disorder or bipolar disorder (Hawton et al., 2013a; Cho et al., 2016).

Suicide is the 18th leading cause of death and accounts for 1.4% of all deaths globally (World Health Organization, 2018). The burden of suicide is highest among young and middle-aged adults. Among youths and young adults, suicide is the second leading cause of death worldwide and the leading cause of death in developed countries. In 2013, the target of the World Health Organization Mental Health Action Plan was to reduce suicide mortality by 10% by the year 2020 (World Health Organization, 2014).

Over the course of a year, about 2.0% of people worldwide have suicidal ideation. Of these, approximately one-third plan a suicide and up to two-fifths make a suicide attempt (Borges et al., 2010). In high-income countries, slightly over half of those having suicidal ideation or attempts receive treatment, with the situation being much worse in low-income countries. The most common barriers for seeking treatment include not perceiving a need for treatment or the wish to cope alone (Bruffaerts et al., 2011). However, most of those who die by suicide have had treatment contact during the previous year, providing an opportunity for prevention. The most common last treatment contact is in primary care. Nearly half of those who die by suicide have had a primary care contact during the month preceding death. About one-fourth to one-third have had mental health treatment contact during the last 12 months (Stene-Larsen & Reneflot, 2017; Walby et al., 2018).

It is most difficult to anticipate or study suicide. The breakdown of suicidal behavior according to Chekroud (2018) among 100 000 primary care or mental healthcare patients in integrated care illustrates this challenge. About 16 600 patients will report having had suicidal thoughts at least several times over the past two weeks. Next month, 53 of these individuals will attempt suicide and four will die by suicide. Of those who died by suicide, in the month preceding death one in three had denied having thoughts of suicide (Simon et al., 2016). Overall, about half of individuals dying by suicide communicate suicidal ideation or intent (Pompili et al., 2016).

Suicidal behavior can be investigated by determining which factors explain formation of suicidal ideation, suicide attempts, and suicides. That most individuals with mental disorders or suicidal ideation never attempt

and much less die by suicide, combined with the low base rate of suicides, generates substantial complexity for research and prevention (Bolton et al., 2015). The most important unresolved questions are as follows: what are the factors that make a person think about suicide, and what factors then contribute to risk to act on one's thoughts (Nock et al., 2009). Because research on risk factors for suicide deaths necessitates very large samples unavailable for most investigations, longitudinal information on risk factors for suicide in depressive or bipolar disorders remains very limited (Hawton et al., 2013a; Schaffer et al., 2015b).

Numerous temporally distal or proximal risk factors for suicidal behaviour have been indentified in the literature from multiple domains. These include familial factors, early life experiences, psychological and behavioural traits, precipitating stressors and current clinical characteristics (Turecki & Brent, 2016). However, the relative magnitude of effect of these factors, mechanisms, and specificity for suicidal ideation or suicide attempts are not well delineated.

The most important mental disorder associated with suicide is depressive disorders. Treatment practices and organization of services in mental health care have undergone major transformations in recent decades. The growth in use of antidepressants has been marked. At the same time the number of psychiatric bed has reduced significantly and the use of outpatient care increased (Organization for Economic Co-operation and Development (OECD), 2017). Whether or not there has been temporal variations in risk for suicide in depression during current treatment era has not been investigated.

This thesis study, as part of the Helsinki University Psychiatric Consortium (HUPC) study, aimed to investigate numerous putative risk factors from multiple domains specifically for suicide ideation and suicide attempts among patients with depressive or bipolar disorder in psychiatric secondary care. In more detail, the hypothesized significance of borderline personality disorder traits in mediating the effect of childhood maltreatment on suicidal behavior was examined.

Another part of this thesis examines in a national cohort of first-hospitalized patients for depression the long-term risk for suicide, temporal variations in risk, and risk factors for suicide. Gender differences were investigated in connection to risk factors and methods for suicide as a possible explanation for gender disparity in risk. In this register-based study, a cohort of all first-hospitalized patients for depression in Finland in 1991-2011 was followed to the end of the year 2014 (24 years at most).

The research projects were conducted in collaboration with the Department of Psychiatry, University of Helsinki and Helsinki University Central Hospital, and the Department of Public Health Solutions, Mental Health Unit, National Institute for Health and Welfare, Helsinki, and in part with the Department of Social Services and Health Care, Psychiatric Services, City of Helsinki, Finland.

2 Review of the literature

2.1 Definition of depressive and bipolar disorders

Depressive disorders and bipolar disorders (BD) are mental disorders characterized by episodic or relatively stable changes in mood and activity with accompanying changes in somatic and cognitive functioning. The disturbances lead to significant functional impairment and represent a marked change from previous functioning.

The two current classification systems for mental disorders are the International Classification of Diseases, 10th edition (ICD-10) (World Health Organization, 1993) and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association, 2013).

2.1.1 Diagnosis of depressive disorders

Depressive disorders are characterized by depressive mood largely uninfluenced by circumstances, significantly reduced interest or pleasure in activities, and accompanying somatic and cognitive changes.

The most characteristic conditions of depressive disorders are the depressive episode in the ICD-10 and the major depressive disorder (MDD) in the DSM-5. At least a two-week depressive episode or major depressive episode (MDE) with concurrent criteria is required for the diagnosis of depressive episode (ICD-10) and MDD (DSM-5), respectively (see Table 1). Both classification systems specify exclusion criteria. The ICD-10 criteria for depressive episode exclude previous hypomanic or manic episodes and episodes attributable to psychoactive substance use or any organic mental disorder. The DSM-5 criteria for MDD exclude symptoms better explained by a schizophrenia spectrum or other psychotic disorder, hypomanic or manic episodes, and symptoms attributable to the effects of substance use or another medical condition. Both classification systems provide separate codes for a single episode and recurrent episodes (at least one previous depressive episode followed by at least a two-month period when the criteria are not met before the current depressive episode).

The ICD-10 classification specifies depressive episodes as mild (four to five symptoms), moderate (six to seven symptoms), and severe (at least eight symptoms, including all three main criteria from 1 to 3 presented in Table 1). The DSM-5 diagnosis of MDD sets no clear cut-off points based on symptom count for specifying severity. In mild MDD, the number of symptoms is not more or is only slightly more than the number required for MDE, causing manageable distress and minor functional impairment. Moderate MDD is characterized by symptoms, distress, and impairment ranging between the mild and severe conditions. In severe MDD, the number of symptoms

substantially exceeds the number required for MDE, causing unmanageable and serious distress with marked functional impairment. The DSM-5 introduced anxious distress and mixed features specifiers applicable for an MDE, which are discussed in more detail in Section 2.1.3.

The ICD-10 classifies psychotic depression as a severe depressive episode, or as a severe episode of recurrent depressive disorder, with psychotic symptoms when the criteria for severe depressive episode are met and there are either (1) delusions or hallucinations (not typical schizophrenia) or (2) depressive stupor. Presence of schizophrenia or schizoaffective disorder, depressive type is excluded. Codes are provided for mood-congruent and mood-incongruent psychotic symptoms. The DSM-5 includes similarly additional specifiers for mood-congruent and mood-incongruent psychotic features.

Table 1 Diagnostic symptom criteria for major depressive episode (DSM-5) and depressive episode (ICD-10-DCR).

DSM-5 MDE	ICD-10-DCR Depressive Episode
During the same 2-week period:	Depressive episode for at least 2 weeks
Five or more symptoms; at least one is either (1.) or (2.) [*]	Four or more symptoms; at least two are either (1.), (2.), or (3.)
1. Depressive mood [†]	1. Depressed mood [†]
2. Markedly diminished interest or pleasure [†]	2. Loss of interest or pleasure in activities
	3. Decreased energy or increased fatigability
3. Significant weight gain or loss [¶] , or decreased or increased appetite [‡]	4. Loss of confidence and self-esteem
4. Insomnia or hypersomnia [‡]	5. Unreasonable feelings of self-reproach or excessive and inappropriate guilt
5. Psychomotor agitation or retardation ^{‡, §}	6. Recurrent thoughts of death or suicide; any suicidal behavior
6. Fatigue or loss of energy [‡]	7. Diminished ability to think or concentrate, indecisiveness or vacillation
7. Feelings of worthlessness or excessive or inappropriate guilt [‡]	8. Change in psychomotor activity, with agitation or retardation
8. Diminished ability to think or concentrate, or indecisiveness [‡]	9. Sleep disturbance of any type
9. Recurrent thoughts of death or suicidal ideation, or a suicide attempt	10. Decreased or increased appetite with corresponding weight change
Causing significant distress or impairment in social, occupational, or other functioning	

^{*} representing a change from previous functioning, [†] most of the day, nearly every day, [‡] nearly every day, [¶] a change of 5% of body weight in a month, [§] observable to others.

Abbreviations: DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; ICD-10-DCR = International Classification of Diseases, 10th edition, Diagnostic Criteria for Research, MDE = Major Depressive Episode

2.1.1.1 The Finnish DSM-III-R

Two substudies of this thesis using register data applied in part the Finnish Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-III-R) based classification (Lääkintöhallitus, 1989), which was in use from 1987 to 1995. At that time, Finland was among the first countries to adopt operationalized DSM-III-R criteria for mental disorders as the basis for the Finnish International Classification of Diseases, 9th edition. The Finnish diagnosis of major depression is based on identical criteria with those of the DSM-III-R. However, the code numbers differ, and the Finnish diagnosis of major depression does not separate single episode or recurrent major depression and includes no additional specifiers (Kuoppasalmi et al., 1989). The severity of major depression in the Finnish DSM-III-R is further classified as unspecified, mild, moderate, severe, and severe without and with psychotic features, partial remission, and full remission. Unspecified depression is classified separately.

2.1.1.2 Dysthymia

The ICD-10 classifies dysthymia as a persistent mood disorder where (1) there is a two-year period of stable or regularly recurring depressive mood and the periods of normal mood are no longer than a few weeks and a history of hypomanic episode is excluded, (2) during the two-year period there have been no or only few depressive episodes severe enough or lasting for two weeks that have warranted a diagnosis of recurrent mild depressive episode, and (3) at least three of the following symptoms have been present while depressed (reduced energy or action; insomnia; reduced self-confidence or feelings of inadequacy; difficulty in concentrating; often in tears; loss of interest or enjoyment in pleasurable activities; hopelessness or despair; perceived inability to cope with responsibilities of daily life; pessimistic views or brooding over the past; social withdrawal; and being less talkative than normal). ICD-10 dysthymia excludes recurrent depressive disorder.

The DSM-5 classifies persistent depressive disorder (dysthymia) as a condition where (1) there is a period of at least two years of depressive mood present for most of the day and more days than not, (2) while depressed, at least two defined symptoms are present (poor appetite or overeating; insomnia or hypersomnia; low energy or fatigue; low self-esteem; poor concentration or difficulty in making decisions; hopelessness), and (3) the symptoms listed in (1) and (2) have not been absent for more than two months at a time. The symptoms cause significant distress or impairment. The criteria for MDD may have been present at the onset or continuously for the two years. Excluded are a history of hypomania, mania, or cyclothymic disorder; symptoms better accounted for by any schizophrenia spectrum or other psychotic disorders, psychoactive substance use, or another medical condition.

2.1.2 Diagnosis of bipolar disorders

The BDs are characterized by episodes of mania, hypomania, depression and episodes with mixed symptoms.

The most characteristic conditions of BD are classified by the DSM-5 to type I and type II disorders. The DSM-5 BD, type I (BD-I) is characterized by at least one lifetime period that meets the criteria for a manic episode. Before or subsequent to this episode, there may have been episodes of hypomania, mania, or major depression. The DSM-5 BD, type II (BD-II) is characterized by at least one hypomanic episode and another of MDE. This hypomanic episode represents an apparent change in functioning, which is observable to others. For both diagnoses excluded are symptoms attributable to any schizophrenia spectrum or other psychotic disorders, psychoactive substance use, or another medical condition.

The ICD-10 does not subcategorize BD into separate entities, but the Finnish national guidelines instruct applying the Diagnostic and Statistical Manual of Mental Disorders (DSM) based classification of type I and II BD (Working group appointed by the Finnish Medical Society Duodecim, 2013). The ICD-10 separates single hypomanic and manic episodes without any other mood episodes (including depressive episodes) from the diagnosis of BD. For an ICD-10 diagnosis of BD at least one manic or hypomanic episode and an additional episode of mania, hypomania, depressive, or mixed episode are required. A diagnosis of psychotic mania is made if delusions or hallucinations are present (excluding delusions completely impossible and hallucinations in the third person or giving running commentary) and presence of schizophrenia or schizoaffective disorder, manic type is excluded. The ICD-10 criteria for a severe depressive episode with psychotic features in BD are identical to the criteria required for a severe depressive episode with psychotic features in depressive disorders. Symptoms due to a psychoactive substance or other medical condition are excluded in all diagnoses.

The diagnostic criteria of ICD-10 and DSM-5 for manic and hypomanic episodes are presented in Table 2. The criteria for an MDE (DSM-5) and depressive episode (ICD-10) are identical to the criteria presented in Table 1. In the ICD-10, a mixed episode of BD can be applied when there is a mixture or rapid alteration of marked symptoms of opposite polarities continuing for at least two weeks. The DSM-5 has introduced a mixed features specifier, which is discussed in the next section.

Table 2. Diagnostic criteria for manic and hypomanic episodes in the DSM-5 and in the ICD-10-DCR.

DSM-5		ICD-10-DCR	
Manic episode	Mania	Hypomanic episode	Hypomania
<p>A distinct (≥ 1 week) period of both:^{†,‡}</p> <ul style="list-style-type: none"> - elevated, expansive, or irritable mood - abnormal and persistently increased activity or energy <p>≥ 3 symptoms; or ≥ 4 if mood is only irritable</p> <ol style="list-style-type: none"> 1. Inflated self-esteem or grandiosity 2. Decreased need for sleep 3. More talkative or pressure to keep talking 4. Flight of ideas or racing thoughts 5. Distractibility (reported or observed) 6. Increase in goal-directed activity or psychomotor agitation 7. Excessive involvement in activities of high potential for adverse consequences <p>Causing marked impairment in functioning: social or occupational, necessitates hospitalization, or presence of psychotic symptoms</p>	<p>A prominent, definitely abnormal and sustained (≥ 1 week) mood change of:[‡]</p> <ul style="list-style-type: none"> - predominantly elevated, expansive, or irritable mood <p>≥ 3 symptoms; or ≥ 4 if mood is only irritable</p> <ol style="list-style-type: none"> 1. Increased activity of physical restlessness 2. Increased talkativeness 3. Flight of ideas or racing thoughts 4. Social disinhibition with inappropriate behavior 5. Decreased need for sleep 6. Inflated self-esteem or grandiosity 7. Distractibility or constant changes in activity or plans 8. Reckless or foolhardy behavior, the risks of which are not recognized 9. Marked sexual energy or indiscretions 	<p>A distinct (≥ 4 consecutive days) period of both:[†]</p> <ul style="list-style-type: none"> - elevated, expansive, or irritable mood - abnormal and persistently increased activity or energy <p>≥ 3 symptoms; or ≥ 4 if mood is only irritable</p> <ol style="list-style-type: none"> 1. Inflated self-esteem or grandiosity 2. Decreased need for sleep 3. More talkative or pressure to keep talking 4. Flight of ideas or racing thoughts 5. Distractibility (reported or observed) 6. Increase in goal-directed activity or psychomotor agitation 7. Excessive involvement in activities of high potential for adverse consequences <p>Not causing marked impairment in functioning (social or occupational); excludes conditions necessitating hospitalization or with psychotic symptoms</p>	<p>An abnormal and sustained period (≥ 4 consecutive days) of:</p> <ul style="list-style-type: none"> - elevated or irritable mood <p>≥ 3 symptoms; some interference with functioning</p> <ol style="list-style-type: none"> 1. Increased activity of physical restlessness 2. Increased talkativeness 3. Difficulty in concentration or distractibility 4. Decreased need for sleep 5. Increased sexual energy 6. Mild spending sprees, or other reckless or irresponsible behavior 7. Increased sociability or over-familiarity

[†]most of the day, nearly every day. [‡] any duration if resulting in admission

Abbreviations: DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; ICD-10-DCR = International Classification of Diseases, 10th edition, Diagnostic Criteria for Research

2.1.3 DSM-5 anxious distress and mixed features specifiers

The DSM-5 introduced anxious distress and mixed features specifiers that can be applied in the most recent hypomanic, manic, or depressive episodes of a BD, type I or type II, or depressive episodes of MDD.

An episode with anxious distress is applicable when there are for most of the days at least two symptoms of either feeling keyed up or tense, feeling unusually restless, having difficulty in concentrating due to worry, feeling that something terrible may happen, or feeling a loss of self-control.

A depressive episode with mixed features can be applied when the full criteria for an MDE are met, and there are at least three symptoms of the opposite polarity (excluding irritable mood and distractibility). A hypomanic or manic episode with mixed features can be applied when the full criteria for either are met, and there are at least three symptoms of the opposite polarity most of the days (other than changes in weight or sleep, or problems in concentration or decision-making).

2.1.4 Comorbidity

The term psychiatric comorbidity was initially coined to describe a manifestation of two or more psychiatric disorders independent of each other. The idea was that the disorders had to be distinct. However, many diagnoses share similar phenomena and the concept of comorbidity has been criticized for merely reflecting shortcomings of contemporary diagnostic classifications. Diagnoses defined by criteria not based on underlying etiological processes allow considerable heterogeneity from one affected individual to the next. In addition, comorbid diagnoses could either be true independent disorders or varying manifestations of one disorder. Among mood disorders, the ambiguity may concern particularly anxious symptoms, which are widely prevalent during mood episodes (Maj, 2005).

General population surveys show high comorbidity between psychiatric disorders (Kessler et al., 2003). Comorbid disorders have a significant negative impact on the course of depressive disorder or BD (Holma et al., 2010; Penninx et al., 2011; Friborg et al., 2014; Riihimäki et al., 2014b; Pallaskorpi et al., 2015; Ten Have et al., 2017; Ten Have et al., 2018).

2.2 Depressive disorders

2.2.1 Epidemiology

A systematic review (Ferrari et al., 2013b) of 116 representative population-based studies estimated an adjusted global point prevalence of MDD of 4.7%. The World Mental Health Survey (WMHS) (Bromet et al., 2011), based on representative population-based data from 18 countries (n=89 037), reported a 12-month prevalence of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) MDD of 5.5% in high-income countries and 5.9% in low- and middle-income countries. The 12-month prevalence rates of individual countries showed marked regional variation, ranging from 2.2% (Japan) to 10.4% (Brazil). The global prevalence of dysthymia within a year has been estimated at 1.55% based on a systematic review and mathematical modeling by the Global Burden of Disease (GBD) 2010 Study (Charlson et al., 2013).

The National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III) is the first national survey of DSM-5 MDD. In this representative sample of the adult civilian US population (N = 36 309), the 12-month prevalence of DSM-5 MDD was 10.4% (Hasin et al., 2018).

Lifetime prevalence rates of MDD should be considered with caution due to risk of recall, selection, and survival biases. Nevertheless, lifetime estimates are provided by several cross-sectional general population surveys. The WMHS findings propose a 15% lifetime prevalence of DSM-IV MDD in developed countries, whereas lower lifetime rates are found in developing countries. The reasons for the divergent results remain unknown (Bromet et al., 2011). The NESARC-III study has reported a 20.6% lifetime prevalence rate of DSM-5 MDD in the US (Hasin et al., 2018).

Complementary information on lifetime risk of depression derives from a Danish longitudinal register-based study on lifetime patterns for being treated for depressive disorder in secondary care (Pedersen et al., 2014). Lifetime risks (i.e. probability) for depressive disorders were approximated by calculating cumulative incidences with competing survival analyses. Estimated lifetime risks for being treated in secondary care for depressive disorders were 9.1% in men and 15.5% in women. However, rates are lower-bound estimations for morbidity since patients in primary care were excluded, and many individuals do not seek treatment or do it with delay.

In contrast to the plentiful data on non-psychotic depression, the literature on epidemiology of psychotic depression is more limited. A recent systematic review, including only four community-based studies, has suggested a lifetime prevalence of psychotic depression to range from 0.35% to 1% (Jääskeläinen et al., 2018).

In Finland, the national Health 2000 study (n = 8028) reported a 12-month prevalence of MDD and dysthymia of 4.9% and 2.5%, respectively (Pirkola et al., 2005). A follow-up of the Health 2000 study (Markkula et al., 2015) reported a 12-month prevalence of 7.4% for MDD and 4.5% for dysthymia by using multi-imputation data. The rates using weighed data were 5.4% for MDD and 2.0% for dysthymia.

Women are about two times more often affected by depressive disorders than men (Seedat et al., 2009). The incidence rates for first onset depressive disorders increases rapidly during teenage years, peaking at about 20 years of age. The rates decline continuously thereafter, rapidly over the third decade of life, until a second rise in incidence in late life (Pedersen et al., 2014). When examining prevalence by age group in the GBD 2010 Study modeling, the prevalence of MDE increases steadily over the second and third decades of life, showing some abatement between 65 and 74 years of age, after which a second increase occurs in late life (Ferrari et al., 2013a).

2.2.1.1 Time trends

There has been controversy about whether time trends in prevalence of depressive disorders truly exist. Increased public awareness of depression and help-seeking and other secondary indicators have supported the general perception of rising trends. The GBD 2010 Study has reported a relatively stable point prevalence of MDD from 1990 to 2010 (Ferrari et al., 2013a). More recently, The Finnish Health 2011 study has documented by using multi-imputation data an increase in 12-month prevalence of depressive disorders (MDD and dysthymia) from 7.3% in 2000 to 9.6% in 2011. The increase in the rate of depressive disorders (or MDD) was significant only in women. The observed increase in the prevalence of MDD based on weighed data indicated only a trend (Markkula et al., 2015). Two recent American studies have also indicated rising trends. First, a large probability sample of US citizens aged 12 years or over indicated a significant rising trend in prevalence of 12-month DSM-IV MDD from 2005 to 2015 (Weinberger et al., 2018). The prevalence rate was on the rise for the two youngest (12-25 years) and the oldest (50 years or older) age groups, and the increase was faster among the youngest age group (12-17 years) relative to the other age groups. The NESARC-III study reported also an increase in 12-month prevalence of DSM-5 MDD from 5.3% in 2001-2002 to 10.4% in 2012-2013 (Hasin et al., 2018).

2.2.2 Multifactorial etiology

The etiology of depressive disorders is complex and depression as a disorder most likely heterogenous (Hasler, 2010; Peterson et al., 2018; Rantala et al., 2018). In addition to interindividual variation, intraindividual

clinical presentation of successive MDEs vary to a high degree (Oquendo et al., 2004a). For the time being, there is no known single causation or universal explanation for depression. Both genetic and environmental factors have an influence (Sullivan et al., 2000). Contributing factors comprise long-term vulnerabilities (genetic, early life experiences, personality) and temporal stress reactions to triggering events, the interrelations of which are complex and dynamic (Kendler & Gardner, 2016).

Meta-analytic evidence from family studies suggests that the heritability of MDD is between 31% and 42% (Sullivan et al., 2000). A large amount of this heritability according to current understanding derives from thousands of single genetic loci with small individual effects. Based on genome-wide association studies, the heritability from single-nucleotide polymorphisms is estimated to be 21-30%. These common genetic variants with small individual effects may account half the heritability (Flint & Kendler, 2014). The genetic variation between individuals exposed and unexposed to adverse experience may partly diverge (Peterson et al., 2018). A recent genome-wide association analysis was first to identify 44 independent and significant loci associated with MDD (Wray et al., 2018). Overall, roughly 2500 loci may account for half of the heritability, and one in five genes expressed in the brain may be involved (Flint & Kendler, 2014).

Pooled estimations from family studies indicate that individual-specific environmental factors account for between 58% and 67% of liability to MDD (Sullivan et al., 2000). A longitudinal study of middle-aged female twins indicated that a large proportion (83%) of environmental risk for adult MDD is explained by current stressors associated with a transient risk elevation. A substantial minority (17%) of environmental risk may be explained by events earlier in life related to a persistent vulnerability (Kendler & Gardner, 2017). Another twin study of men and women (Torvik et al., 2018) found no evidence on long-term environmental effects, but only stable genetic component from ages 18 to 45 together with current stressors exerting their effects over some years.

Current stressors associated with onset of depression over the short term include the ending of or difficulties within an intimate relationship, economic or work problems, assaults, and illnesses (Kendler et al., 1998; Bromet et al., 2011; Kessler & Bromet, 2013). The psychological experiences that ensue may be characterized by humiliation, loss, and entrapment (Kendler et al., 2003). Long-term environmental risk factors for depression are likely characterized by complex bidirectional relations between endogenous predispositions and life experiences during maturation. Life events associated with long-term vulnerability may commonly be qualities of intimate relationships or recurrent breakups, and less often occupational hardships or single dramatic events profoundly altering a person's life (Kendler & Halberstadt, 2013).

The strongest evidence exists for childhood maltreatment (CM) and poor rearing environment being long-term risk factors for adult depression (Li et al., 2016). The characteristics of environmental factors resulting in enduring

effects are, however, unclear, and the possibility of gene-environment correlations renders conclusions uncertain.

Personality traits, responsiveness to environmental threats, and vulnerability to depression are interconnected. Neuroticism, a hereditary personality trait according to the Five Factor Model (Costa & McCrae, 1992), is an established vulnerability factor for depression. Trait neuroticism appears to moderate the effects of stressful experiences on outcome of depression. While both high cumulative stress from early life to adulthood and high levels of neuroticism are associated independently with adult depression, their combination has the most potent effect on depression (Vinkers et al., 2014).

Whether depression as a disorder differs between men and women has been debated. Depression shows higher heritability in women than men and the genetic correlation between genders is 0.6, suggesting significant differences (Flint & Kendler, 2014). Of environmental factors, deficient childhood parenting and adult interrelationships may have stronger impacts on women than on men. Men, in turn, may be more affected by economic and work-related hardships than women (Kendler & Gardner, 2014).

Some evidence suggests that over a longer period in adulthood primary depressive vulnerability and impact of life events may become somewhat less relevant for recurrences, and consequently, self-sustaining factors could exist (Hasler, 2010; Kendler & Gardner, 2016). However, the temporal dynamics and complex interrelations require further elucidation and the self-sustaining aspects remain to be clarified.

The neurobiological processes associated with depression include structural and functional changes in the central nervous system. Several interrelated neurobiological systems associated with stress responses show altered activity in the hypothalamic-pituitary-adrenal axis, monoaminergic neurotransmission, neurotrophic factors, glutamate and gamma-aminobutyric acid mediated neurotransmission, autonomic nervous system, and immune system (Hasler, 2010; Otte et al., 2016). Structural brain imaging findings among adults indicate volume loss in both cortical areas (orbitofrontal cortex, anterior and posterior cingulate, insula, and temporal lobes) (Schmaal et al., 2017) and subcortical areas (hippocampus) (Schmaal et al., 2016). The neural mechanisms are hypothesized to involve emotional processing within subcortical regions and attenuated reciprocal regulation from cortical areas (Disner et al., 2011). However, brain activation studies of emotional or cognitive processing await replicable and consistent findings (Muller et al., 2017).

2.2.3 Comorbidity

Among general population surveys, the US National Comorbidity Survey Replication (NCS-R) reported that 64% of the 12-month DSM-IV cases had a comorbid clinical disorder (Kessler et al., 2003). In the Finnish Health 2000

study, 32% of the 12-month depressive disorder cases had a comorbid anxiety disorder (23%) or alcohol use disorder (AUD) (9%) (Pirkola et al., 2005). In the NESARC-III study, 36% of the 12-month DSM-5 MDD cases had a comorbid anxiety disorder and 22% a comorbid AUD. The survey first investigated DSM-5 MDD and its anxiety/distress specifier in a general population and found that this specifier characterized 70-75% of the DSM-5 MDD cases (Hasin et al., 2018).

In Finland, in screening-based cohorts of the Vantaa Depression Study (VDS) and the Vantaa Primary Care Depression Study (pc-VDS), 57% of the DSM-IV MDD participants in secondary care and 43% of the DSM-IV MDD participants in primary care had a comorbid anxiety disorder. The corresponding rates for AUD were 25% and 9% (Melartin et al., 2002; Vuorilehto et al., 2005).

A few population-based studies have investigated comorbid personality disorders among participants with MDD. Most recently, the NESARC-III study (Hasin et al., 2018) reported that 36% of 12-month and 27% of lifetime DSM-5 MDD cases met the criteria for lifetime borderline personality disorder (BPD). The respective rates were 7-8% for antisocial personality disorder and 14-18% for schizotypal personality disorder. In clinical studies of MDD, a systematic review estimated that 45% of cases with MDD (60% of cases with dysthymia) had a comorbid personality disorder, most often cluster C personality disorder, followed by cluster B personality disorder (Friborg et al., 2014).

In Finnish DSM-IV MDD cohorts, 44% of patients in secondary care and 52% in primary care have met the criteria for a comorbid personality disorder (Melartin et al., 2002; Vuorilehto et al., 2005). The most common comorbid personality disorders were avoidant (24%), paranoid (17%), and borderline (12%) in secondary care, and borderline (25%), avoidant (19%), and obsessive-compulsive (12%) in primary care. However, current depressive and anxious symptoms may inflate estimations of prevalence of personality disorders. The stability of personality disorder traits is moderate, but weak in categorical diagnoses even over a fairly short period (Melartin et al., 2010).

2.2.4 Course

The course of depression may be described in various ways such as the median time of an MDE, remission rates, or conversely rates of chronic course, recurrences rates, or rates for sustained remission, number of lifetime recurrences, and time spent ill. Therefore, estimations vary by time period, sample characteristics, definition of outcome, and study design.

Median length of MDE. Cross-sectional large-scale population surveys have estimated the median duration of an MDE as three months and the mean duration as four to ten months (Kessler et al., 2003; Ferrari et al., 2013a). In the NESARC-III study, the median duration of the longest lifetime

MDE was reported to be about six months (Hasin et al., 2018). A small community-based follow-up study of first-episode MDE found the median length of an episode to be 12 weeks (Eaton et al., 2008). Recently, a general population study using life-chart methods (N=286) disclosed a median MDE duration of six months and a mean duration of 10.7 months (Ten Have et al., 2017).

Remission rate. In a general population study using life-charts, 74% of MDE cases were found to remit at one year, 84% at two years, and 88% at three years (Ten Have et al., 2017). Other community surveys have reported that 75-80% of MDD cases remit within two years (Penninx et al., 2011; Fuller-Thomson et al., 2014), and nearly all (94%) of those screening positive for MDD become negative at least once over a 12-year follow-up (Fuller-Thomson et al., 2014). The Finnish national Health 2011 study reported that 21% of participants with MDD and 27% of participants with dysthymia met the criteria for any depressive disorder 11 years later (Markkula et al., 2016). The recovery rate from psychotic depression may be worse than from depression without psychotic symptoms (Musliner et al., 2016; Jääskeläinen et al., 2018).

There is limited information on the natural course of untreated depression. According to a systematic review of primary care studies, spontaneous remission rates from depression may be 23% within three months, 32% within six months, and 53% within 12 months. Due to the inverse relationship between severity of depression and rates for remission, the findings may not generalize to more severely depressed populations (Whiteford et al., 2013).

Recurrences. A small community-based follow-up study of first episode MDE found that among those who attain remission, half show sustained remission and 35% have recurrences over a 15-year follow-up (Eaton et al., 2008). Longitudinal population-based studies published since have found recurrence rates of 13.2% at five years, 23.2% at ten years, and 42.0% at 20 years (Hardeveld et al., 2013), and recently, more favorable rates of 4.3% at five years, 13.4% at ten years, and 27.1% at 20 years (Ten Have et al., 2018). A chronic course of depression has been estimated to characterize 12% of participants with MDD over 36 months in the general population (Ten Have et al., 2017) and even up to six years (Ten Have et al., 2018). An extended follow-up study of up to 23 years found that about 15% of first-episode MDD cases do not remain free for a year from an MDE in the years to come (Eaton et al., 2008). Another general population study revealed that 6% of cases screening positive for MDD showed a chronic course over 12 years (Fuller-Thomson et al., 2014).

In secondary care, the cumulative rate of recurrence of MDD after remission is high. According to a systematic review (Hardeveld et al., 2010), 60% of patients may have a recurrence within five years, 67% within ten years, and 85% within 15 years. Data from primary care were limited.

In Finnish MDD cohorts, in primary care about 90% of the DSM-IV MDD patients in the pc-VDS attained partial or full remission (70% full remission) during a five-year follow-up (Riihimäki et al., 2014b). The median time to full remission was 20 months. Of remitted patients, half had at least one recurrence; of these patients, 50% had multiple recurrences. In secondary care, virtually all (99%) of the MDD patients in the VDS attained partial or full remission (88% full remission) during a five-year follow-up (Holma et al., 2008). The median time to full remission was 11 months (median time to full or partial remission 5.5 months). Of the patients, 29% had no recurrences, 30% had one recurrence, and 41% had multiple recurrences. Half of the patients had a favorable course with mostly sustained remission, one in three had an intermediate course with partial remission, and 11% had a persistent course with full MDE most of the time.

Time spent depressed. A systematic review of 15 studies with over ten years of follow-up reported that patients with MDD spend 46% of time on average in depressive states (Forte et al., 2015). In the five-year follow-ups of the Finnish VDS and pc-VDS, patients on average spent 42-50% of time in full remission, 24-30% in partial remission, and 20-34% in full MDE (Holma et al., 2008; Riihimäki et al., 2014b).

2.2.5 Treatment

Current Finnish (Working group appointed by the Finnish Medical Society Duodecim, 2016) and foreign (National Institute for Health and Care Excellence, 2009 (Updated 2018)) guidelines for treatment of depression all emphasize the role of evaluation of both severity and recurrence of depression in treatment planning. The Finnish national guideline acknowledges the centrality of antidepressant treatment and psychotherapeutic interventions alone or in combination in treatment. Both therapies are found to be effective in mild and moderate depression, whereas the role of antidepressants and combined pharmaco- and psychotherapies is emphasized in more severe depression. In case of psychotic depression, antipsychotic medication should be combined with an antidepressant. Treatment of depression is divided into acute, continuation, and maintenance phases, where the respective objectives are to reach remission, maintain remission, and prevent recurrences.

A recent meta-analytic study of 21 antidepressants confirmed the long-debated efficacy of medication in acute treatment of depression (Cipriani et al., 2018). All available antidepressants were found as effective, and the differences concerned mainly the likelihood of discontinuation of medication (i.e. acceptability of the antidepressant). The pharmacotherapeutic effect is maintained over six months during the continuation phase, as found by a recent meta-analysis (Henssler et al., 2018).

Psychotherapeutic interventions are effective in treatment of depression (Huhn et al., 2014), and the benefits are maintained for at least six months

after acute treatment (Karyotaki et al., 2016). Although there are no clear differences in therapeutic effects between different psychotherapeutic modalities, the solidness of the evidence base varies considerably among them (Barth et al., 2013). According to the Finnish guidelines (Working group appointed by the Finnish Medical Society Duodecim, 2016), the evidence base is largest for cognitive-behavioral, interpersonal, and psychodynamic therapies and for behavioral activation. Emerging electronically assisted psychosocial treatments efficient in treatment include self-guided computerized cognitive-behavioral therapy without (Karyotaki et al., 2017) or with therapist support (Richards & Richardson, 2012). These are supported for mild depression (Working group appointed by the Finnish Medical Society Duodecim, 2016) and are set among first-line treatment options in some international guidelines supporting stepped care models (National Institute for Health and Care Excellence, 2009 (Updated 2018)). In addition, based on limited data, single-session psychoeducation may be a prompt and cost-effective early intervention bearing modest benefits (Tursi et al., 2013).

Although direct comparisons of efficacy between pharmacotherapy and psychotherapy are anything but simple, pooled data from such studies suggest comparable efficacy (Cuijpers et al., 2013). Early meta-analytic evidence based on limited data indicate that the more severe the depression, the more efficient the antidepressants (Fournier et al., 2010). However, recent more inclusive data show comparable efficiency over the depression severity continuum (Weitz et al., 2015; Furukawa et al., 2018). Based on individual-level meta-analytic data, the efficacy of cognitive-behavioral therapy is comparable for depressions ranging from mild to severe (Weitz et al., 2015; Furukawa et al., 2017). Combined treatment with pharmacotherapy and psychotherapy results in larger treatment effects than either treatment alone (Cuijpers et al., 2014; Huhn et al., 2014). Currently, more research is needed on predictors of outcome for a specific treatment or combination of treatments (Huhn et al., 2014).

Electroconvulsive treatment (ECT) is the most effective available treatment option in severe and psychotic depression. ECT may also alternatively be considered for treatment-resistant moderate-level depression (Working group appointed by the Finnish Medical Society Duodecim, 2016). Among non-invasive brain-stimulation techniques, meta-analytic evidence supports efficacy of repetitive transcranial magnetic stimulation (rTMS) for depression (Mutz et al., 2018). The efficacy of rTMS is comparable to that of pharmacotherapies, and it is also useful in treatment-resistant depression (Working group appointed by the Finnish Medical Society Duodecim, 2016). The rTMS is more tolerable but inferior in efficacy relative to ECT. Evidence on the transcranial direct current stimulation (tDCS) supports its use as a potential treatment for non-treatment-resistant depression (Mutz et al., 2018). A novel but still experimental pharmacotherapy for depression includes ketamine (N-methyl-D-aspartate

antagonist). Parenteral single administration of ketamine relieves symptoms of depression significantly in a few hours, with the effect lasting up to one week (McGirr et al., 2015). However, the long-term safety and efficacy of ketamine remain to be investigated. The drug's potential is currently compromised by the finding of preadministered opioid antagonist naltrexone counteracting its antidepressant effects (Williams et al., 2018).

2.3 Bipolar disorders

2.3.1 Epidemiology

There has been considerable uncertainty in the prevalence rates of BD in the general population. The reasons are manifold and include unidentified hypomanic episodes leading to BD misdiagnosed as MDD and variability in diagnostic instruments or disorders assessed (BD-I and BD-II versus wider bipolar spectrum disorders). Lifetime estimations may also bear a variety of problems, including recall biases. In general, the overall lifetime prevalence of BD is considered to be over 1% (Vieta et al., 2018).

A systematic review of 29 general population studies from 20 countries (Ferrari et al., 2011) estimated a 12-month prevalence of 0.84% for bipolar spectrum disorders. This estimation may be conservative because of the stringent criteria used and pooled studies concerning mostly BD-I or BD-II. In the WMHS published since, the 12-month prevalence was 0.4% for BD-I, 0.3% for BD-II, and 0.8% for subthreshold BD (Merikangas et al., 2011). In the NCS-R Survey (Merikangas et al., 2007), the 12-month prevalence was 0.6% for BD-I, 0.8% for BD-II, and 1.4% for subthreshold BD. In the NESARC-III study, first investigating prevalence according to the DSM-5 in a general population, the 12-month prevalence was 1.5% for BD-I, but this study did not provide data on BD-II or a wider spectrum of BD (Blanco et al., 2017). In a review of 11 European general population studies, the median 12-month prevalence was estimated at 0.7% for BD overall (Wittchen et al., 2011). According to surveys (Merikangas et al., 2007; Merikangas et al., 2011; Blanco et al., 2017), lifetime prevalence rates are 0.6-2.1% for BD-I, 0.4-1.1% for BD-II, and 1.4-2.4% for subthreshold BD.

In Finland, the Psychosis in Finland Study, stemming from the Health 2000 general population study, estimated a lifetime prevalence rate of 0.24% for BD-I for persons 30 years or older (Perälä et al., 2007). Including register diagnoses raised the estimate to 0.42%. The Mental Health in Early Adulthood in Finland study, also stemming from the Health 2000 study, reported among persons 18-29 years of age a lifetime prevalence of 0.53% for BD-I, 0.72% for BD-II, and 0.61% for bipolar spectrum disorders (Suvisaari et al., 2009).

A Danish register-based study of first psychiatric treatment contacts provides complementary but lower-bound estimations of lifetime incidence

of BD (Pedersen et al., 2014). The study approximated the lifetime risk (i.e. probability) of being treated for BD in secondary care by competing survival analyses. According to the register-based data, the projected nationwide lifetime risk was 1.32% in men and 1.84% in women (absolute cumulative risk at 50 years of age was 0.76% in men and 1.07% in women).

The gender distribution in BD is about equal (Seedat et al., 2009; Ferrari et al., 2011; Blanco et al., 2017). The usual age at onset is from the late teens to early 40s, with the mean age at onset being 18 years for BD-I (median < 25 years) and 20 years for BD-II (Merikangas et al., 2007; Merikangas et al., 2011). The incidence is lower in older individuals, but late onsets do occur.

2.3.2 Multifactorial etiology

BDs are currently conceived as heterogeneous in etiology, with mechanisms still unresolved (Grande et al., 2016). Both genetic and environmental factors play a role, and reductionist explanations deriving from either nature or nurture have been rejected (Craddock & Sklar, 2013).

BD ranks high in heritability among all psychiatric disorders. A family history of BD is at present among the most important known predictor of its occurrence in an individual. An offspring of a parent with BD is estimated to have a four- to six-fold relative risk and an absolute risk of 10% of having BD in adulthood (Lichtenstein et al., 2009; Rasic et al., 2014). A large Swedish family study found 59% of the liability for BD to be attributed to additive genetic effects and 38% to individual environmental influences (Lichtenstein et al., 2009). Overall, it is estimated that about 60-85% of the liability may be explained by genetic factors (Smoller & Finn, 2003; Lichtenstein et al., 2009). Genetically, BD has a close relationship with schizophrenia and MDD. The disorders share overlapping common genetic variants (genetic correlation BD-schizophrenia $r = 0.68$; BD-MDD $r = 0.47$) (Lee et al., 2013). Novel findings from post-mortem brains show that this overlap extends to gene expression (Gandal et al., 2018). However, a considerable proportion of genetic variance remains unshared (Lee et al., 2013). A recent and more detailed analysis indicated that BD-I is genetically closer to schizophrenia than BD-II, which in turn has genetically more in common with MDD than BD-I (Stahl et al., 2017). Higher genetic loading with schizophrenia indicates poorer treatment response to lithium in BD, which may enable pharmacogenomic applications (Amare et al., 2018).

Overall, the heritability of BD is largely explained to consist of hundreds or thousands of common genetic variants with weak individual effects. The possible existence of relatively rare variants with large effects remains unclear (Craddock & Sklar, 2013; Geschwind & Flint, 2015). Common genetic variants may account for one-fourth of the heritability for BD (Lee et al., 2013). To date, over 40 individual genetic loci have been identified to be associated with liability for BD (Ikeda et al., 2018). Common genetic variation likely acts indirectly on risk for the disorder via molecular signaling

pathways and neurodevelopment, a process also influenced by environmental effects (Gandal et al., 2018).

The partial (40-60%) concordance rate of monozygotic twins for BD demonstrates the contribution of environmental influences in the etiology (Smoller & Finn, 2003). There is, however, limited knowledge of environmental influences (Bortolato et al., 2017). Perinatal or fetal complications and infections and substance use have been investigated as risk factors, but findings are inconclusive. CM is associated with BD (Palmier-Claus et al., 2016) and with more severe clinical characteristics and comorbidity in BD (Agnew-Blais & Danese, 2016). Firm conclusions are hindered by largely cross-sectional evidence, and longitudinal studies remain sparse.

Stressful life events may trigger onset of a mood episode among BD patients (Lex et al., 2017) or be a consequence of an episode (Koenders et al., 2014). Of types of current stressors, childbirth may be a more important risk factor in BD than in MDD (Lex et al., 2017). Events related to goal attainment and disrupted circadian rhythms may contribute more to onset of (hypo)manic episodes (Proudfoot et al., 2011). Seasonal variation appears to exist to some extent, as risk for manic episodes may be higher during spring-summer (to a lesser extent in autumn), and depressive episodes in early winter (and to a lesser extent in summer) (Geoffroy et al., 2014).

The neuropathophysiological processes related to BD remain largely unclear. Current investigations have focused on modulation of synaptic and neural plasticity (Vieta et al., 2018), hormonal regulation (corticotrophin-releasing signaling), intra- and intercellular neurotransmission (calcium and glutamergic signaling, and second messenger systems), and neuronal development (Nurnberger et al., 2014). Emerging gene expression findings from a post-mortem study indicate downregulated synaptic function and altered immune and inflammatory activity in the brain (Gandal et al., 2018). Epigenetic alterations are possible mechanisms for the effect of environmental factors (Vieta et al., 2018).

The neural processes in BD are hypothesized to include networks involved in voluntary/involuntary emotional processing/regulation (bilateral prefrontal cortex, hippocampus, amygdala) and reward processing (left ventral striatal-ventrolateral and orbitofrontal cortex) and white matter tracts connecting associated structures (Phillips & Swartz, 2014). Structural neuroimaging findings of BD have found cortical thinning in brain areas involved in emotional processing, including bilateral frontal regions, and in the left cingulate and left superior temporal gyrus (Hanford et al., 2016). A large consortium-based study (Hibar et al., 2018) recently reported BD to be associated with reduced bilateral cortical thickness in frontal, temporal, and parietal regions. No differences emerged between BD-I and BD-II, but in this cross-sectional design the cortical gray matter was thinner among those with longer reported illness duration. Lithium pharmacotherapy was associated with increased, and anticonvulsant and antipsychotic pharmacotherapies

with decreased cortical thickness. Additionally, a history of psychosis was associated with reduced cortical surface area. The findings of the same consortium on subcortical regions in BD show volume loss in the bilateral hippocampus and thalamus and enlarged lateral ventricles (Hibar et al., 2016). No significant volumetric differences were present between BD-I and BD-II, although a trend for larger changes was seen in BD-I.

2.3.3 Comorbidity

Among the general population surveys, the US NCS-R Survey (Merikangas et al., 2007) reported an exceedingly high (96%) rate of psychiatric comorbidity in BD. The most prevalent comorbidities were anxiety disorders and substance use disorders (SUDs). In the WMHS, rates of psychiatric comorbidity were 88% for BD-I and 83% for BD-II (Merikangas et al., 2011).

A meta-analytic review of current anxiety disorders among pooled 2120 euthymic BD patients (Pavlova et al., 2017) estimated a 35% rate of a comorbid anxiety disorder during euthymia. The risk for an anxiety disorder was 4.6-fold that of community controls. The most prevalent anxiety disorders were generalized anxiety disorder (12%), social anxiety disorder (10%), specific phobia (9.7%), and obsessive-compulsive disorder (7%).

SUDs are common among patients with BD, and individuals with SUDs have high rates of BD. According to a systematic review of comorbidity of SUD in BD in the general population (Hunt et al., 2016b), one in three individuals with BD have SUDs, most commonly AUD (24%). Individuals with BD were estimated to have over three-fold risk for an AUD. Conversely, individuals with an AUD were estimated to have over four-fold risk for BD. Rates of SUDs in clinical BD cohorts are slightly higher according to another similar review (Hunt et al., 2016a). Men had over two-fold risk for a lifetime SUD (51% men, 34% women), but rates were similar between types I and II. Of specific SUDs, the highest prevalence rate was estimated for an AUD (35% men, 17% women).

Information on comorbid personality disorders in BD in the general population is largely limited to the data of the NESARC study from the US (Grant et al., 2005). The data proposed a high 71% prevalence rate of any comorbid personality disorder in BD-I. No data for BD-II were available. A systematic review of clinical BD samples (Friborg et al., 2014) estimated a more moderate 42% prevalence rate of comorbid personality disorder in BD, but reported high heterogeneity between studies. Cluster B and C personality disorders were the most prevalent, with comparable rates. The two most common personality disorders in BD were obsessive-compulsive (18%) and borderline (16%). There has been long-lasting controversy on the boundaries between BD and BPD (Bassett et al., 2017; Beraldi et al., 2018). A recent systematic review and meta-analysis of comorbidity and predictors of BD and BPD (Fornaro et al., 2016) estimated that about one in five individuals with BD have comorbid BPD, rates being two- to three-fold higher in BD-II than

in BD-I. The review concluded that although both disorders are risk factors for the presence of the other, literature mostly supports the view of two distinct disorders. According to Post et al. (2018), current manic or depressive symptoms may substantially influence the likelihood of self-reported personality disorder symptoms, which makes clinical assessments intricate.

In the Finnish Jorvi Bipolar Study (JoBS) (Mantere et al., 2006), the overall rate of any comorbidity, including personality disorders, was 70% (60% other clinical disorders and 43% personality disorders). Of the cohort, 45% had a comorbid anxiety disorder, 20% an SUD, and 8% an eating disorder. The most prevalent personality disorders were borderline (22%), obsessive-compulsive (12%), and avoidant (12%).

2.3.4 Course

BDs are characterized by a lifelong vulnerability to recurrent mood episodes with intermittent periods of either euthymia or subthreshold symptoms (Grande et al., 2016; Vieta et al., 2018).

Pre-onset. Before syndromal onset, many patients show symptoms of (sub)syndromal depression, subsyndromal hypomanic symptoms, cyclothymia, or affective lability for several years (Faedda et al., 2015). A study of genetically susceptible youths observed that the symptoms of depression/anxiety and affective lability are constantly present, whereas hypomanic symptoms intensify preceding the onset of the disorder (Hafeman et al., 2016).

First episode and risk for recurrence. The first occurrence of a mood disorder is depressive in polarity in about 50-60% (Mantere et al., 2004; Baldessarini et al., 2014). On the other hand, of patients with an MDD more than one in five (22.5%) may diagnostically convert to BD by having an episode of opposite polarity in the long term (Ratheesh et al., 2017). A meta-analytic review of limited data on recurrence rates after single lifetime manic or mixed episode (Kessing et al., 2018) estimated that about one in three patients will have a recurrence the next year and about 60% within two to four years. Another systematic review of recurrence rates after first episode of mania among BD patients with previous other mood episodes (Gignac et al., 2015) estimated recurrence rates of 26% at six months, 41% at 12 months, and 60% at four years.

Recurrence in clinical BD. Up to 90% of patients with BD will have a recurrence over their lifetime. In the Systematic Treatment Enhancement Program for Bipolar Disorder study, 49% of the patients with heterogeneous illness histories who achieved remission had a recurrence during a two-year follow-up (Perlis et al., 2006). In the five-year follow-up of the Finnish JoBS (Pallaskorpi et al., 2015), 87% of the participants had a recurrence (median interval two years) and half experienced three or more recurrences. A review of randomized controlled trials (RCTs) or naturalistic follow-up studies

(Vazquez et al., 2015) estimated a two-year recurrence rate of 39% in RCTs in active treatment arm (versus 61% in placebo) and 55% in naturalistic studies after remission.

Pre-episode prodromal symptoms. Subsyndromal symptoms of the same polarity, anxiety, or agitation for more than one week may precede full syndromal episodes in about half of cases (Mantere et al., 2008a). However, the fluctuating course of BD and limited sensitivity limit utility of prodromal symptoms for episode prevention.

Median duration of phases and episodes. The natural course of an untreated manic episode varies substantially from a median length of two to six months, most commonly about 3-4 months (Angst & Sellaro, 2000). Estimations from the current treatment era on average duration of episodes are similar, being a few weeks in hypomania, about 2-3.5 months in mania, and 4-5 months in an MDE (Solomon et al., 2010; Tondo et al., 2017). In the Finnish JoBS 18-month follow-up study (Mantere et al., 2008b), the median duration of major depression was 6.5 months, manic phase 2 months, hypomanic phase two weeks, and mixed phase 6 months. The total duration of episodes (median 8.5 months) was substantially longer due to common polyphasic episodes (Mantere et al., 2008b).

Remission rates. The time to a recovery correlates strongly with the polarity of an index episode (Mantere et al., 2008b). Pooled data from follow-up studies after the first episode of mania (Gignac et al., 2015) indicate that a clear majority achieve syndromal remission (84% within six months and 88% within 12 months). However, full symptomatic remissions (62%) occur more rarely within one year. In the Systematic Treatment Enhancement Program for Bipolar Disorder study (Perlis et al., 2006) cohort of 1469 clinical BD patients with various illness histories and index episodes, the full remission rate was 58% within two years. During the five-year follow-up of the JoBS (Pallaskorpi et al., 2015), 96% of patients attained full remission for two months (median time to full remission 6.6 months).

Subsyndromal symptoms. The National Institute of Mental Health Collaborative Depression Study revealed the large amount of time spent in subthreshold symptoms and related long-term morbidity (Judd et al., 2002; Judd et al., 2003). During a 13-year follow-up of BD-I and BD-II patients, subthreshold depressive or hypomanic symptoms were about three times more common than full syndromal mood episodes and accounted for about three-fourths of total time ill.

Depression to mania ratio and time ill. A systematic review of 14 studies with a mean follow-up of seven years (Forte et al., 2015) estimated that on average BD patients spend 45% of their time in syndromal or subsyndromal states (44% in BD-I and 43% in BD-II). Depressive morbidity predominates the course of BD and time ill (70% in BD-I and 82% in BD-II). The proportion of time that individuals with BD-I are in (hypo)mania was 10%; the corresponding figure for individuals with BD-II was 6%. The proportions of mixed or other states were 6% and 3%, respectively. The pooled data

showed high heterogeneity, possibly due to samples from different levels of care. Since the review, two long-term studies have aggregated retrospective and prospective data and estimated the total proportion of time ill in BD at 37% over a 12-year period (Tondo et al., 2017) and 34% over a 19-year period (Serra et al., 2017). The Finnish JoBS five-year follow-up study observed that patients with BD spent about one-third of time in mood episodes and 15% with subthreshold symptoms (Pallaskorpi et al., 2015). Generally, BD-II patients spend proportionally more time depressed than BD-I patients (Forte et al., 2015; Serra et al., 2017; Tondo et al., 2017), a finding that was not observed in the JoBS five-year follow-up (Pallaskorpi et al., 2015). Increasing observational time has been associated with more time spent in euthymia (Forte et al., 2015).

2.3.5 Treatment

Current Finnish (Working group appointed by the Finnish Medical Society Duodecim, 2013) and The Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) (Yatham et al., 2018) guidelines for treatment of BD emphasize the role of evaluation of both polarity of acute phase and a history of longitudinal course of mood episodes in treatment decisions. Treatment of BD is divided into acute and maintenance phases, where the objective is to achieve full remission and prevent recurrences, respectively.

Pharmacological treatments. Psychopharmacological treatments form the basis of treatment. In treatment of mania, several first- and second-generation antipsychotics, and mood stabilizers have demonstrated efficacy for manic symptoms and recovery (Yildiz et al., 2015). Second-generation antipsychotics (SGA), lithium, and valproate are most commonly used and recommended (Working group appointed by the Finnish Medical Society Duodecim, 2013; Yatham et al., 2018). On average, about half of manic patients have a response (defined by symptom reduction of at least 50%) to antimanic drugs without significant differences in efficacy (Yildiz et al., 2015; Baldessarini et al., 2018). Combination treatment with SGA and a mood stabilizer is found to result in superior treatment efficacy and response rates compared with monotherapy, but is associated with more side effects (Ogawa et al., 2014). Bipolar mixed states and hypomania should mostly be treated in a manner similar to manic phases, and if a concomitant antidepressant is in use, this should be discontinued (Working group appointed by the Finnish Medical Society Duodecim, 2013; Yatham et al., 2018). Bipolar depression constitutes a continuous challenge for treatment (Baldessarini et al., 2018). Treatment alternatives include lamotrigine, quetiapine, lurasidone, lithium, valproate, and olanzapine+fluoxetine (Yatham et al., 2018). Antidepressants as adjuvant treatment with SGAs or mood stabilizers show small, but statistically significant treatment effects, whereas long-term use should be avoided due to risk of treatment-emergent (hypo)manic switches or cycle

acceleration (McGirr et al., 2016). Several pharmacotherapies can be used in maintenance treatment for BD, and medications may show somewhat a different spectrum of efficacy in prevention of relapses of mood episodes from different polarities (Working group appointed by the Finnish Medical Society Duodecim, 2013; Miura et al., 2014; Yatham et al., 2018). Lithium and quetiapine are the only pharmacological agents that prevent relapses of both polarities, lithium+valproate combination, olanzapine, and risperidone show more antimanic effects, and lamotrigine demonstrates only prevention of depression (Miura et al., 2014).

Psychosocial treatments. According to the Finnish guidelines (Working group appointed by the Finnish Medical Society Duodecim, 2013), the objective of psychosocial therapies is to provide psychosocial support and psychoeducation and improve treatment adherence. The CANMAT and ISBD guidelines (Yatham et al., 2018) recommend psychoeducation be offered at onset to all patients (and family members) to prevent relapse, to reduce stigma, and to develop individual coping strategies. For acute depression or maintenance treatment, adjuvant psychosocial treatments to pharmacological treatments may be offered based on individual needs. These include cognitive behavioral therapy (CBT) or family-focused therapy as a second-line option and interpersonal and social rhythm therapy or peer support as a third-line option. Overall, studies on psychosocial interventions are for the time being of low- to moderate quality and reveal mixed findings (Oud et al., 2016). Cognitive and functional remediation therapies are emerging adjunctive treatments with preliminary evidence of efficacy (Dean et al., 2018).

ECT and rTMS. According to the Finnish guidelines (Working group appointed by the Finnish Medical Society Duodecim, 2013), ECT may be used in treatment of severe or treatment-resistant manic episodes. ECT is also useful in bipolar depression, and the guidelines instruct use of ECT after two unsuccessful but adequate trials of pharmacological treatment or in depressive episodes with psychotic features. The CANMAT and ISBD guidelines recommend ECT as a second-line treatment for acute BD-I depression or as an adjuvant to pharmacotherapy in mania. Similarly, rTMS adjuvant with pharmacotherapy can be considered a second-line option for acute BD-I depression and a third-line option for mania (Yatham et al., 2018). The evidence for long-term maintenance treatment of ECT in BD is limited (Baldessarini et al., 2018).

2.4 Suicidal behavior

2.4.1 Definition of suicidal behavior

Suicidal behavior is self-initiated and determined by the presence of a self-destructive intention to die (Silverman et al., 2007). The term suicidal

ideation encompasses a variety of suicidal preoccupations, wishes, intentions, or plans (transient-persistent, passive-active). The term suicide attempt denotes a self-inflicted self-destructive behavior where there is either explicit or implicit evidence of some degree of intention to die. The outcome of a suicide attempt may be no injury, injury, or death. Suicide is the outcome of a fatal suicide attempt.

2.4.2 Theories of suicidal behavior

Among early theories, French sociologist Émile Durkheim's (1858-1917) (Durkheim, 1897) pioneering work on suicide in the late 19th century was based on a sociological theory of distorted social integration or regulation. The psychoanalytical model by Sigmund Freud (1856-1939) in the early 20th century was based on the proposed life and death drives. Self-destructive wishes and actions were suggested to originate from anger towards and wishes to destroy another, which are turned inwards and against part of one's own ego due to an internalized object (Barzilay & Apter, 2014). Deriving from psychodynamic theories, the pioneer of modern suicidology as a discipline, Edwin S. Shneidman (1918-2009) viewed suicide as a problem-solving attempt originating from unbearable psychological pain (psychache) drawing from thwarted needs and a constricted mind (Shneidman, 1977). The theory of suicide as an escape from self by Baumeister (1990) viewed suicide as an aspiration to get reptite from an unbearable state of mind and distorted self-awareness, induced by emerging cognitive deconstruction and disinhibition.

Modern psychological theories are mostly based on stress-diathesis models (O'Connor & Nock, 2014). The cognitive-behavioral theory (CBT) emphasizes three main constructs of lasting dispositional vulnerability factors for psychiatric disturbance, and cognitive contents and processes associated with psychiatric disturbance. These two constructs lead to activation of suicidal schema characterized by hopelessness and attentional fixation. Ultimately, possibility and timing of transition from thoughts to a suicidal act depends on individual threshold of distress tolerance (Wenzel et al., 2009). Rooted in behaviorism and biosocial theory, Linehan's dialectical behavior therapy (DBT) emphasizes acceptance and change in treatment of pervasive developmental emotional dysregulation as a core feature (Crowell et al., 2009). A generation of theories belonging to the ideation-to-action framework conceptualizes first formation of suicidal ideation and then transition from ideation to suicide attempts as separate processes. The interpersonal theory of suicide postulates that suicidal desire results from an individual's experience of thwarted belongingness and perceived burdensomeness. The model separates from this desire the capability to engage in suicidal acts that results from lowered fear of death and increased pain tolerance through habituation and opponent processes (Van Orden et al., 2010). The integrated motivational-volitional model of suicidal behavior assumes two main factors: the motivational factor driving suicidal ideation

and characterized by experience of defeat and entrapment, and the volitional factor related to transition to suicidal acts (O'Connor & Kirtley, 2018). The three-step theory of suicide postulates that the experience of pain and hopelessness explains the emergence of suicidal ideation, which is intensified further by low connectedness if present, whereas proceeding to suicide attempts is determined by the capacity for suicidal acts (Klonsky & May, 2015).

According to the medical stress-diathesis model (Mann, 2003), stressors proximal to suicidal acts include exacerbation of a psychiatric disorder and acute psychosocial crisis, whereas the predispositional diathesis, which is independent of psychiatric disorders, includes enduring familial factors, neurobiological dysfunctions, and psychological and behavioral traits.

2.4.3 Epidemiology in the general population

In 2016, the global estimated age-standardized suicide rate was 10.5 per 100 000 and about 1.4% of all deaths worldwide were by suicide. Suicide was the 18th leading cause of death, but the second leading cause among youths and young adults (15-29 years) (World Health Organization, 2018).

In the WMHS (Nock et al., 2008), the cross-national prevalence of lifetime suicidal ideation was 9.2% and suicide plans 3.1%. The estimated lifetime prevalence of suicide attempt was 2.7%. The risk for first onset of suicidal ideation increases rapidly during the teenage years to young adulthood. Approximately two-thirds of all attempts were premeditated and one-third unplanned.

In the WMHS (Borges et al., 2010), the 12-month prevalence rate was 2.0-2.1% for suicidal ideation and 0.6-0.7% for suicide plans. The 12-month prevalence rate for suicide attempts was 0.3-0.4%.

Estimations of the rate of death by suicide among those who have previously attempted suicide vary considerably, mostly depending on the level of care sampled, the method of the index attempt, and the length of follow-up. The rates vary from 3.9% within five years in samples consisting of mostly self-poisonings in primary and secondary care (Carroll et al., 2014) to 12-16% in those who have been hospitalized for attempted suicide in long-term follow-up cohorts (Suominen et al., 2004; Runeson et al., 2010). A nationwide longitudinal study of all hospitalized suicide attempters in Finland estimated a 30% risk for reattempt and a 10% risk for suicide during a maximum 8-year follow-up (Haukka et al., 2008).

The gender paradox of suicide is that while women are more likely to endorse suicidal ideation and to attempt suicide (Haukka et al., 2008; Nock et al., 2008), men die more often by suicide in a ratio of about 3.5:1 in Europe and high-income countries. However, the male-to-female ratio is considerably lower in low- to middle-income countries and the Asian Pacific (Turecki & Brent, 2016).

In a Finnish random telephone-interviewed general population sample (N=4868), the 12-month period prevalence of suicidal ideation was 2.3-2.4% and suicide attempts 0.9-1.1%, without any significant gender differences (Hintikka et al., 1998). In another postal survey of the general population in Eastern Finland (N=1593) in 1998 (Hintikka et al., 2001), the 12-month period prevalence of suicidal ideation was 14.7% in men and 9.2% in women. The corresponding 12-month incidence rates were 4.6% in men and 3.1% in women. The participants (N=1339) were followed up two times in 1999 and 2001 and a point prevalence of suicidal ideation of 11.4-13.7% in men and 7.6-8.4% in women was reported (Hintikka et al., 2009). The gender differences in both studies were significant. In 1989-1992, Helsinki was the only investigated center in 13 European countries that showed higher rates for suicide attempt in men than in women (Schmidtke et al., 1996). In a Finnish national study (Haukka et al., 2008), the incidence of suicide attempts leading to a hospitalization was estimated at 44 per 100 000 person-years.

In 2017 in Finland, a total of 824 people died by suicide, the annual incidence rate being 22 per 100 000 in men and 8 per 100 000 in women (overall 15 per 100 000). The male:female ratio of suicide was about three:one. Overall, the suicide rates in Finland peaked in 1990 and have since declined to about half. From year 2015 (731 suicides), the number of suicides in Finland has increased over two consecutive years (Official Statistics of Finland (OSF), 2018).

2.4.4 Multifactorial etiology

Factors that may predispose to suicide are manifold and likely no single approach will ever be able to provide an all-encompassing explanation. Therefore, etiological research subsumes commonly specific subgroups. Underlying factors are generally classified into three main constructs consisting of: 1) familial and early-life factors, commonly called distal factors, 2) cognitive, psychological, and personality traits, commonly called mediating factors, and 3) acute life events, psychic disturbance, and disinhibition, commonly called proximal or precipitating factors. Additional factors include environmental factors and social cohesion (Turecki & Brent, 2016).

Suicide runs in families. In the largest family study (Tidemalm et al., 2011), the risk for suicide was highest among monozygotic twins, but declined along with decreasing amount of shared genetic and environmental factors. Twin and adoption studies have estimated a 30-50% heritability of suicidal behavior. Suicidal ideation appears to be cotransmitted with mood disorders separately from transmission of heritability for suicide attempts, whereas suicide attempts and suicides show also independent transmission from psychiatric disorders. The heritability of suicidal behavior independent of heritability of psychiatric disorders has been estimated at 17% for suicidal

ideation and at 36% for suicide attempts (Turecki & Brent, 2016). The familial transmission of suicidal behavior may be mediated by transmission of impulsive aggressive traits and early-life abuse, particularly among adolescents and young adults (Brent, 2010). A recent population-based genome-wide association study estimated 4.6% heritability (single-nucleotide polymorphism) for suicide attempt and 1.9% heritability independent of psychiatric disorders (Erlangsen et al., 2018). However, genome-wide association studies have not yet provided significant and replicable findings (Lutz et al., 2017).

Early-life adversity has been consistently associated both cross-sectionally and longitudinally with suicidal ideation and attempts (Zatti et al., 2017; Angelakis et al., 2019) and recently also with suicides (Björkenstam et al., 2017; Castellvi et al., 2017). The long-term effects of early-life adversity on stress responses, cognitive deficits, and personality traits, possibly partly through epigenetic modulation, are assumed to mediate the effects on suicidal behavior (Turecki, 2014; Turecki & Brent, 2016).

The developmental or mediating factors are presumed to affect the diathesis for suicide by predisposing to psychiatric disorders or to suicidal behavior in case of acute psychiatric disturbance (Mann, 2003; Turecki & Brent, 2016). Several factors are identified for diathesis, of which the tendency to react aggressively is the most studied (Mann, 2003). Among other factors are hopelessness (Ribeiro et al., 2018), high neuroticism and low extraversion or agreeableness (O'Connor & Nock, 2014; Batty et al., 2018), and anxiety/agitation and disinhibition (Nock et al., 2009; O'Connor & Nock, 2014; Rogers et al., 2016). Putative neuropsychological traits, among others, include cognitive rigidity or inflexibility (O'Connor & Nock, 2014), overvaluation of emotionally negative signals (e.g. rejection), impaired decision-making, disinhibition of automatic responses, limited problem-solving abilities, and low verbal fluency (Jollant et al., 2011; Richard-Devantoy et al., 2014).

Of all etiological factors, the most comprehensive evidence base exists for psychiatric disorders as proximal factors for suicidal behavior. According to psychological autopsy studies, worldwide about 81% of suicide decedents had suffered from psychiatric disorders. The most prevalent psychiatric disorders were depressive disorders (51%) and alcohol abuse (20%) (Cho et al., 2016). A notably similar 83.9% rate of any clinical psychiatric morbidity was found among patients hospitalized for self-harm by a systematic review (Hawton et al., 2013b). Again, the most prevalent psychiatric disorders were depression (49%) and AUD (26%) (Hawton et al., 2013b). AUDs may exert their influence on suicidal behavior through evolving impulsive-aggressive traits (mediating factor) or proximally through behavioral disinhibition (Turecki & Brent, 2016).

In the Finnish national psychological autopsy study, 93% of the suicide decedents were estimated to have had any psychiatric disorder (in the majority, several) prior to death. The most common psychiatric disorders

were mood disorders (59%), AUD (43%), and personality disorder (31%) (Henriksson et al., 1993).

Negative life events (particularly interpersonal stressors) are associated with suicidal ideation and behavior (Liu & Miller, 2014). The effects of life events are commonly considered as acute precipitants or consequences of acute psychiatric disorders (Mann, 2003; Oquendo et al., 2014).

The most demonstrated neuropathological processes associated with suicidal behavior are deficits in serotonergic and noradrenergic transmission, but also to an increasing extent imbalances in excitatory/inhibitory function of glutamatergic/gamma-aminobutyric acid-ergic systems (Lutz et al., 2017). The hypersensitivity of stress systems and the hypothalamic-pituitary-adrenal axis may be particularly relevant as a consequence of early-life stress (Turecki, 2014). Other neuropathological processes may involve low-grade neuroinflammation and reduced neuroplasticity (Lutz et al., 2017). Structural and functional imaging findings point to brain areas involved in emotional processing and the cognitive appraisal system, and their integration and formation of adaptive actions, and stress reactions (orbital and prefrontal cortices and anterior cingulate cortex) (Jollant et al., 2011; van Heeringen et al., 2014; Lutz et al., 2017).

2.4.5 High-risk periods

Marked temporal variations exist in risk of suicidal behavior both individually and epidemiologically.

For an individual, the intensity of suicidal ideation may vary considerably even over short periods (Kleiman et al., 2017). Over the course of weeks and months, suicidal ideation correlates temporally with concurrent severity of depression (Sokero et al., 2005; Riihimäki et al., 2014a). The full syndromal mood episodes therefore constitute high-risk periods (Isometsä, 2014). Early illness course constitutes a high-risk period for suicide within three months of the first depression diagnosis (Crump et al., 2014). The risk remains high during the early years of onset of a depressive disorder or BD (Ösby et al., 2001; Nordentoft et al., 2011). The majority (60%) of first suicide attempts occur within one year of onset of suicidal ideation (Nock et al., 2008).

From an epidemiological point of view, the highest risk periods are associated temporally with psychiatric hospitalization; this risk exceeds the effect of all other known risk factors. According to a Danish nationwide population-based register study (Qin & Nordentoft, 2005), two peaks in risk exist. Compared with the general population, the risk was 60-82 times higher during the first week after admission and 102-246 times higher during the first week after discharge. The risk was even higher among patients with affective disorders, adjusted relative risks being 208 in men and 168 in women in the week after admission, and 219 in men and 1977 in women in the week after discharge. According to meta-analytic data (Walsh et al., 2015), about one suicide occurs per 676 admissions, the pooled estimate of

suicide incidence being 147 per 100 000 inpatient-years. However, there was high heterogeneity among the studies included, and the risk was inversely proportional to the mean length of an average hospital stay. Another meta-analysis of suicide risk after discharge from a psychiatric hospital (Chung et al., 2017) estimated a pooled risk of suicide of 1132 per 100 000 person-years within three months, 654 per 100 000 from 3 to 12 months, 494 per 100 000 from 1 to 5 years, and still 277 per 100 000 after ten years. Again, the studies included showed high heterogeneity. The highest risk was found among inpatients with suicidal ideation or behavior (2078 per 100 000 person-years).

Another very high-risk period exists shortly after a non-fatal suicide attempt. The risk for reattempting or dying by suicide is highest within the first post-discharge week among those hospitalized for a suicide attempt (Haukka et al., 2008). Over 80% of those who have had a non-fatal suicide attempt and eventually die by suicide do so within one year of the index attempt (Bostwick et al., 2016). The risk and rate probably depend on the method of the index attempt. According to a large Swedish population-based study with a 21- to 31-year follow-up, among those who had attempted suicide by a violent method (hanging/strangulation/suffocation, firearms/explosives, jumping from a height) or drowning and survived, 69-88% of those who eventually died by suicide did so within the first year of the index attempt (Runeson et al., 2010). In another large sample of patients with self-harm followed up to 12 months (Olfson et al., 2017), very high risk was found among those who had used violent methods (2813 per 100 000 person-years), especially firearms (5822 per 100 000 person-years), particularly during the first month since the index event (hazard ratio [HR] 17.5 violent methods overall; HR 33.1 firearms).

2.4.6 Methods of suicide attempts and suicide

Suicide mortality may be viewed as an outcome of incidence of suicide attempts and probability of dying by the method chosen for the attempt (Miller et al., 2012). Violent methods account for a relatively low proportion of the total number of suicide attempts, but a high proportion of suicide deaths (Henriksson et al., 1993; Miller et al., 2012; Bostwick et al., 2016). Efforts have been made to compare the mutual lethality of methods by case fatality ratios (for a given method, the number of suicides divided by the total number of suicide attempts (fatal and non-fatal)). Violent methods, such as suffocation/hanging and firearms, show very high case fatality rates (69-80%) compared with poisonings (2%) (Miller et al., 2012). However, rates are overestimations because the total number of suicide attempts remains always unknown so that incidences represent lower-bound estimations.

Longitudinal studies among people with non-fatal suicide attempts show consistently higher risk of suicide among those who have used self-injurious or violent methods relative to poisonings (Runeson et al., 2010; Bergen et al.,

2012; Miller et al., 2013; Runeson et al., 2016). The risk is found exceedingly high particularly among those who have used firearms (Haukka et al., 2008; Olfson et al., 2017). Those who have used violent methods in non-fatal attempts are very likely to use violent methods in their last fatal attempt, with rates of up to 79-94% among those who die by firearms or hanging versus 41-65% among those who have self-poisoned (Runeson et al., 2010; Bergen et al., 2012; Olfson et al., 2017). However, due to large numbers, the majority (69-82%) of subsequent suicide deaths after non-fatal suicide attempts occur among those who have used self-poisoning (Runeson et al., 2010) and a subsequent switch to more lethal methods may occur (Miller et al., 2013; Olfson et al., 2016). Higher suicide intent has been associated with potentially more lethal methods chosen (Haw et al., 2015), although unequivocal knowledge of potential lethality may not always be present and may be complex among those who have self-poisoned.

In the Finnish psychological autopsy study in 1987-1988, men died more often by potentially more lethal methods and were more likely to have died in their first attempt than women (62% vs. 38%). Most suicide decedents (82%) had used at least two different methods (fatal method included) (Isometsä & Lönnqvist, 1998; Pirkola et al., 2003).

2.5 Suicidal behavior in depressive disorders

2.5.1 Epidemiology

Worldwide, about half of those who have died by suicide (Cho et al., 2016) or been hospitalized for self-harm (Hawton et al., 2013b) have suffered from depressive disorders. Patients with depression have nearly a 20-fold (standardized mortality ratio) risk for dying by suicide compared with the general population (Chesney et al., 2014). Numerous studies have aimed to estimate the ('true') lifetime suicide risk in depression. Early studies indicated implausibly high risks and were followed by studies providing markedly lower estimates (Bostwick & Pankratz, 2000). The most thorough and recent estimates derive from a Danish population-based study that followed patients with depression from secondary care (hospitalized, or since 1995 treated in secondary care) during 1970-2006 (median follow-up 18 years) (Nordentoft et al., 2011). The study observed a cumulative incidence of 6.7% in men and 3.8% in women for suicide. The risk of suicide in depression shows a strong gradient with level of care (Simon & VonKorff, 1998; Bostwick & Pankratz, 2000), a likely proxy for illness severity. A recent meta-analysis (Dong et al., 2018) estimated an overall 31% rate of lifetime suicide attempts in MDD, but rates vary depending on patient setting. Surprisingly, no gender differences in rates of suicide attempts in MDD was found.

In the VDS, the majority (58%) of patients with MDD reported suicidal ideation and 15% had attempted suicide during the index episode (Sokero et

al., 2003). In the Vantaa Primary Care Depression Study (pc-VDS), 37% of the participants reported lifetime suicidal ideation (24% current) and 17% had attempted suicide (Vuorilehto et al., 2006).

2.5.2 Risk factors for suicidal ideation

A common limitation in the literature on suicidal behavior is non-segregation of risk factors for suicidal ideation and attempts as an outcome. Moreover, research on suicidal ideation among specific diagnostic groups is relatively limited.

The most consistent evidence base exists on the association between severity of depression and suicidal ideation (Sokero et al., 2003; Vuorilehto et al., 2006; Keilp et al., 2012; Ribeiro et al., 2018). In fact, suicidal ideation without clinically significant depression is rare, although not all patients with severe depression have suicidal ideation (Uebelacker et al., 2010; Riihimäki et al., 2014a). The subjective experience of depression rather than its somatic symptoms may be more essential for emergence of suicidal ideation (Keilp et al., 2012). Severity of hopelessness has repeatedly been correlated with suicidal ideation (Sokero et al., 2003; Vuorilehto et al., 2006; Ribeiro et al., 2018). Longitudinally, hopelessness has stable trait and temporal state-related aspects, of which state hopelessness is associated with concurrent depressive and anxious symptoms and level of social support (Baryshnikov et al., 2018). Consistently, in longitudinal studies resolution of depressive symptoms and hopelessness (Sokero et al., 2006; Keilp et al., 2018) has been associated with a decline in suicidal ideation.

Other factors that have been associated with suicidal ideation in MDD include male gender, younger age, SUDs, comorbid psychiatric disorders including cluster B and C personality disorders, chronic medical illness, functional impairment, low subjective social support (Sokero et al., 2003; Vuorilehto et al., 2006), and childhood physical abuse (McHolm et al., 2003). There are currently no quantitative systematic reviews on risk factors for suicidal ideation in depression.

2.5.3 Risk factors for suicide attempts

Suicidal ideation appears as a precondition for suicide attempt among patients with MDD (Sokero et al., 2003; Vuorilehto et al., 2006). Over 80% of suicide attempts occur during an MDE and less than 5% during full remission (Holma et al., 2010; Riihimäki et al., 2014a).

The most recent systematic review on risk factors for suicide attempts in depression was published over ten years ago (Oquendo et al., 2006). The study was narrative, and no meta-analysis was possible due to limited data. According to the review, the most robust predictors of suicide attempts were previous suicide attempts, more persistent or recurrent depressive morbidity, and comorbid AUD. The role of these predictors has since been

confirmed by several major longitudinal studies (Bolton et al., 2010; Holma et al., 2010; Riihimäki et al., 2014a; Eikelenboom et al., 2018).

Individual longitudinal studies have identified several other risk factors for suicide attempt in depression. Of sociodemographic factors, these include female sex (Oquendo et al., 2014; Wang et al., 2015), younger age (Holma et al., 2010; Wang et al., 2015; Eikelenboom et al., 2018), low education and unemployment (Wang et al., 2015; Eikelenboom et al., 2018), sick leaves (Wang et al., 2015), low income (Bolton et al., 2010; Holma et al., 2010; Eikelenboom et al., 2018), and lack of a partner (Holma et al., 2010; Eikelenboom et al., 2018).

In addition to family history of suicidal behavior (Oquendo et al., 2007), developmental or mediating risk factors for suicide attempts include impulsive-aggressive traits or hostility (Oquendo et al., 2004b; Oquendo et al., 2007; Eikelenboom et al., 2018), high neuroticism and low extraversion or agreeableness (Eikelenboom et al., 2018), and avoidant attachment style (Grunebaum et al., 2010).

Of proximal or clinical factors, suicide attempts in depression have been predicted by severity of depression (Oquendo et al., 2004b; Holma et al., 2010; Riihimäki et al., 2014a; Eikelenboom et al., 2018), concurrent anxiety symptoms or disorders (Bolton et al., 2010; Holma et al., 2010; Riihimäki et al., 2014a), psychotic depression (Holma et al., 2010), hopelessness and severity of suicidal ideation (Holma et al., 2010; Riihimäki et al., 2014a), few reasons for living (Oquendo et al., 2007), comorbid personality disorder, particularly BPD (Oquendo et al., 2004b; Oquendo et al., 2007; Bolton et al., 2010; Holma et al., 2010; Oquendo et al., 2014; Jylhä et al., 2015), insomnia (Eikelenboom et al., 2018), functional impairment (Holma et al., 2010), antidepressant and anxiolytic prescription (Wang et al., 2015; Eikelenboom et al., 2018), history of inpatient treatment (Wang et al., 2015), life events (Oquendo et al., 2014), physical illness (Isometsä, 2014), and low subjective social support (Holma et al., 2010; Riihimäki et al., 2014a).

Total number of risk factors (Eikelenboom et al., 2018) and increasing level of comorbidity (Bolton et al., 2010) have been found to prospectively predict suicide attempts.

Marked temporal changes exist in risk for suicide attempts among patients with MDD. In the 18-month follow-up study of VDS, in comparison to being in full remission, patients had nearly eight-fold higher relative risk for a suicide attempt during an MDE and 2.5-fold higher relative risk during partial remission (Sokero et al., 2005). In the five-year follow-up of the VDS (Holma et al., 2010), in comparison to being in full remission, the incidence rate per 1000 patient-years was 21-fold higher during an MDE and four-fold higher during partial remission. In the five-year follow-up study of pc-VDS (Riihimäki et al., 2014a), the incidence rate per 1000 patient-years was 107 during an MDE and 5.8 during partial remission. Similarly, Oquendo et al. (2002) have reported over seven-fold increased risk related to an MDE, whereas another study found nearly five-fold higher odds for a suicide

attempt during the month spent in an MDE and 2.5-fold higher odds in the following month (Oquendo et al., 2014). In the Finnish studies, the time spent in depressive states was noted to be a major contributor to the incidence of suicide attempts (Holma et al., 2010; Riihimäki et al., 2014a).

2.5.4 Risk factors for suicide

According to the Finnish psychological autopsy study in 1987-1988, most (85%) of the suicide decedents with MDD had psychiatric (SUD, anxiety, or personality disorders) or physical illness comorbidities before death. Of those who died by suicide, about two in three were men. Overall, 68% had used violent methods, which were more common among those with psychotic MDD than among those with non-psychotic MDD. Compared with women, men who died by suicide died more often by violent methods and had had more often a comorbid SUD and less often a history of psychiatric treatment or hospitalization. Physical illnesses were more prevalent among older subjects. At that time, most suicide decedents had received inadequate treatment for depression (Isometsä et al., 1994a; Isometsä et al., 1994b).

Risk factors for suicide in depressive disorders have been recently reviewed (Hawton et al., 2013a). According to the meta-analysis, suicides in depression were predicted by male gender, family history of psychiatric disorders, previous suicide attempts, higher severity of depression, hopelessness, comorbid anxiety disorders, comorbid SUD, and comorbid personality disorders (mainly cluster B). The pooled evidence was inconclusive on some clinically highly important risk factors, including psychotic features and family history of suicide, as well as such markers as a history of psychiatric hospitalization or involuntary admission. One of the major findings of the review was highlighting the relatively limited evidence base of risk factors for suicide in depression. Most of the pooled studies were small case-control or cohort studies. Evidence on only three of the reviewed 29 putative risk factors was based on more than one thousand events as an outcome (male gender, psychiatric admissions, and SUD). Three larger studies were identified, but none of these examined more than five putative risk factors. The review was not able to investigate adjusted affects due to lack of individual-level data. The authors of the review called for large-scale longitudinal studies on risk factors for suicide in depression.

Two population-based studies on risk factors for suicide in depression have been published since the review by Hawton et al. (2013a). A Danish nationwide study of 34 671 patients with in- or outpatient contacts with psychiatric hospitals due to severe psychotic or non-psychotic depression between 1994 and 2010 followed these patients on the registers up to end of the year 2010 (755 suicides) (Leadholm et al., 2014). The study found risk factors for suicide in adjusted analyses to be older age, male gender, and previous suicide attempts. There was no difference in risk between psychotic and non-psychotic severe depression. However, in the analyses individual

patients could have belonged to either group, which may have limited the ability to demonstrate differences, and no time-to-event analyses were conducted. Another population-based study from Sweden followed 21 096 in- and outpatients treated for depressive disorders up to 1-5 years (152 suicides) (Wang et al., 2015). The study found male sex, combined antidepressant and anxiolytic medication prescription, previous suicide attempts, and a history of psychiatric hospital treatment as risk factors for suicide, whereas living in a marriage with children was a protective factor. The study reported two gender differences in risk factors, comprising medium-level education and previous suicide attempts, showing higher risks in men.

2.6 Suicidal behavior in bipolar disorders

2.6.1 Epidemiology of suicidal behavior

About 3.4-14% of all individuals dying by suicide (Schaffer et al., 2015c) and 6.4% of those hospitalized for self-harm (Hawton et al., 2013b) have suffered from BD. Patients with BD have been estimated to have 17-fold (standardized mortality rate) higher risk for suicide than the general population (Chesney et al., 2014). A recent review by the ISBD Task Force (Schaffer et al., 2015c), reported a pooled suicide rate of 164 per 100 000 person-years in BD with a male:female ratio of 1.7:1. About 23-26% of patients with BD have attempted suicide in community-based samples. Another meta-analysis estimated an overall 31% risk for a suicide attempt in BD (Tondo et al., 2016). These two systematic reviews have estimated that women have either 54% higher odds (Schaffer et al., 2015b) or 35% higher relative risk (Tondo et al., 2016) for attempting suicide relative to men. The risk for attempting suicide is about equal in BD-I and BD-II (Tondo et al., 2016).

A large Danish register-based study has followed first-hospitalized patients for BD between 1970 and 2006 (or who had in 1995-2006 first psychiatric outpatient treatment) up to the end of the year 2006 (median follow-up 18 years). The study reported a cumulative incidence of suicide among BD patients of 7.8% in men and 4.8% in women (Nordentoft et al., 2011). During a mean five-year follow-up after a hospital-treated suicide attempt Runeson et al. (2016) observed that about 20% of BD patients who had used a self-injurious method died by suicide compared with 7-8% of those after a self-poisoning index event.

In the JoBS – a Finnish screening-based secondary care BD cohort – 61% of the participants reported having had during the index episode suicidal ideation (77% lifetime) and 20% having attempted suicide (51% lifetime) (Valtonen et al., 2005). By the follow-up period of five years, 57% of the cohort had a lifetime suicide attempt (Pallaskorpi et al., 2017).

2.6.2 Risk factors for suicidal ideation

Limited evidence exists on risk factors for suicidal ideation, specifically in patients with BD. The Finnish JoBS found lifetime suicidal ideation (no suicide attempts) to be independently predicted by current depressive symptoms and hopelessness (Valtonen et al., 2005). The results concerning comorbid anxiety disorders are mixed (Simon et al., 2007; Nakagawa et al., 2008), and may be confounded by comorbid cluster B personality disorder (Nakagawa et al., 2008).

In longitudinal studies with various lengths of follow-up, suicidal ideation has been predicted by baseline severity of depression (Kohler-Forsberg et al., 2017), depressive recurrences, melancholic features and more mixed episodes per year (Undurraga et al., 2012), affective lability (Ducasse et al., 2017), and psychological traits of self-criticism, negative cognitive style, and rumination (Stange et al., 2015). In a six-month maintenance treatment study of 482 BD outpatients, 14% of the subjects reported persistent suicidal ideation despite medication (Kohler-Forsberg et al., 2017). Overall, the limited knowledge on risk factors of suicidal ideation in BD mainly consider depressive course of illness, hopelessness and mood switches.

2.6.3 Risk factors for suicide attempts

Suicidal ideation appears as a prerequisite for suicide attempt among patients with BD (Valtonen et al., 2005). Among BD patients, suicide attempts are very rare without concurrent clinical mood symptoms. In the Finnish five-year follow-up of JoBS, 72% of the observed suicide attempts occurred during an MDE, 9% during depressive mixed episodes, 8% during a mixed state, 9% during depressive symptoms, and only 2% during euthymia (Pallaskorpi et al., 2017).

A recent systematic review by the ISBD Task Force (Schaffer et al., 2015a) on risk factors for suicide attempts in BD included 141 studies on 20 putative factors. According to the review, suicide attempts in BD were found to be significantly associated – at least in one study – with numerous factors including sociodemographics, clinical characteristics of BD, psychiatric comorbidity, and other clinical variables.

The sociodemographics that were associated with suicide attempts were female gender, younger age (older age with violent methods), single or divorced marital status, and religious affiliation.

The clinical characteristics of BD that were associated with suicide attempts included young age at onset, depressive/mixed polarity of first episode (manic with violent methods), depressive predominant polarity, depressive episodes or mixed states, mixed features, rapid cycling, greater number or severity of episodes, anxiety, atypical features, and suicidal ideation.

Psychiatric comorbidities associated with suicide attempts were comorbid SUDs, anxiety disorders, eating disorders, borderline or cluster B personality disorders, aggression, and irritability; mixed results were seen for impulsivity.

Other factors that were associated with suicide attempts included family history of a mood disorder (including BD) or suicide, prior suicide attempts, CM or adversity, interpersonal or occupational problems, bereavement, smoking, coffee intake, obesity, and sexual dysfunction.

In another systematic review by the ISBD Task Force (Schaffer et al., 2015b), the authors were able to quantitatively estimate by meta-analysis the association of 13 putative risk factors and suicide attempts in BD. This meta-analytic data showed a significant association between suicide attempts and female sex, early illness onset, depressive polarity of first, current, or most recent episode, comorbid anxiety, SUD, or AUD, illicit substance use, comorbid cluster B or borderline PD, and family history of suicide (first degree).

In the Finnish five-year follow-up of JoBS (Pallaskorpi et al., 2017) published since the two reviews, the authors presented two adjusted models for suicide attempts based on either subjective or objective ratings. In the subjective model, suicide attempts were independently predicted by baseline hopelessness and neuroticism. In the objective model, independent predictors included higher depressive symptoms at baseline and younger age. However, the authors investigated also risk factors during an MDE and found that during MDEs suicide attempts were predicted by longer duration of MDEs, cluster C personality disorders, and baseline severity of depressive symptoms.

There are marked temporal variations in risk for suicide attempts in BD according to the illness phase. In the JoBS five-year follow-up, the highest incidence rate for suicide attempts was 765 per 1000 person-years during mixed phases, followed by 354 per 1000 person-years during an MDE, 70 per 1000 person-years during depressive symptoms, and 6 per 1000 person-years during euthymia (Pallaskorpi et al., 2017). Overall, the highest risk of suicide attempts was associated with relatively short-duration mixed states, while the most important risk factor is length of MDEs, during which most suicide attempts in BD occur (Pallaskorpi et al., 2017).

2.6.4 Risk factors for suicide

According to the Finnish psychological autopsy study including 31 BD-I suicide decedents in 1987-1988 (Isometsä et al., 1994c), 79% died during an MDE, 11% during a mixed state, and 11% after psychotic mania. Compared with women, men died 11 years younger and had more often (56%) comorbid alcohol dependence. Most suicide decedents showed high comorbidity (71%), and the clear majority had received insufficient treatment prior to death.

A recent systematic review by the ISBD Task Force (Schaffer et al., 2015a) on risk factors for suicide in BD reviewed a total of 141 studies. According to the review, suicide in BD was found to be significantly associated – at least in one study – with male sex, current depressive episodes and mixed states, current manic state with psychotic features, hopelessness, comorbid anxiety disorder, previous suicide attempts, psychosocial stressors during the last week before death, and family history of a mood disorder (including BD) or suicide.

In another systematic review by the ISBD Task Force (Schaffer et al., 2015b), the authors were able to quantitatively estimate by meta-analysis the association of four putative risk factors and suicide in BD. According to the meta-analytic data, there were only significant associations between suicide in BD and male gender and family history of suicide (first degree).

Two large register-based studies have been published since the meta-analytic review. A Finnish population-based study followed up to four months 52 747 discharged BD patients in 1987-2003 (Isometsä et al., 2014) and observed an eight-fold HR for suicide among those with a suicide attempt at index episode. Men showed 3.6-fold higher risk, whereas lithium treatment was associated with lower risk. Overall, the highest but sharply declining risk was observed after index hospitalizations for depression and the lowest but more stable risk after manic or other episodes, with the risk after mixed episodes situated between the above extremes. A Swedish cohort study of 12 850 patients with BD based on quality registers (Hansson et al., 2018) found predictors for suicide over a median four-year follow-up to be male sex, living alone, criminal conviction, mood episodes (particularly depressive) during the previous year, previous suicide attempts, comorbid anxiety, SUD, or personality disorders, psychiatric hospitalizations, and involuntary treatment.

2.7 Prevention of suicidal behavior

Suicide prevention strategies comprehend multifaceted measures i) at the population level (universal), ii) among high-risk groups and periods (selective), and iii) among specific individuals with suicidal ideation or who have previously attempted suicide (indicated) (Bolton et al., 2015; Zalsman et al., 2016).

Among population-level strategies, the most substantial evidence base exists for restricted access to the most lethal and prevalent means (applies also to individual-level strategies). Although some substitution may occur, the net effect appears positive (Yip et al., 2012; Zalsman et al., 2016). Ecological data suggest declining suicide rates after implementation of national suicide prevention programs (Matsubayashi & Ueda, 2011). More accessible mental health services (Zalsman et al., 2016), particularly outpatient services (Pirkola et al., 2009), have been found to be associated

with lower suicide rates. School-based mental health programs have been associated with a decrease in suicidal ideation and attempts. Insufficient research knowledge exists on primary care screening, internet and helpline support, gate-keeper training, and public awareness campaigns (Zalsman et al., 2016). Quality of media reporting on suicides may be associated with either increased (epidemiological facts, expert opinions) or decreased (personal, managing distress) short-term suicide rates (Niederkrotenthaler et al., 2010).

Service and quality changes in mental health services (assertive outreach policies and 24-hour crisis teams, ward safety measures, training of mental health personnel, and policy implementations for the period immediately after discharge and for non-compliant outpatients or dual-diagnosis patients) have been associated with declining suicide rates, especially among clinical populations (While et al., 2012). Dealing with high-risk periods after discharge from hospital or emergency department is considered an important component of suicide prevention strategies (Bolton et al., 2015). However, according to a time series analysis (Gunnell et al., 2012), implementation of national policy changes in England to have first outpatient follow-up within seven days of hospital discharge and enhanced care during the first three months had no effect on post-discharge risk of suicide. Nonetheless, the relative risk for self-harm episodes declined by 14% at one week and by 11% at one month.

Since the original Gotland study (Rutz et al., 1989), accumulated evidence supports primary care doctor education programs targeted at enhancing recognition and treatment of depression as effective population-based interventions for lowering regional suicide rates (Zalsman et al., 2016). However, continued education and support for primary care doctors may be required to maintain the effects (Turecki & Brent, 2016).

Recognizing the major role of mental disorders in risk of suicide and particularly treating depressive disorders form the cornerstones for suicide prevention. An ecological study in 28 European countries (including Finland) has shown an association between increasing sales of antidepressants and declining suicide mortality (Gusmao et al., 2013). Based on pooled individual-level data from RCTs among adult depressive patients, suicidal ideation and risk of suicide attempts have been found to decline during acute-phase treatment through a decline in depressive symptoms. Neither reduction nor increment in suicidal behavior was observed among youths (Gibbons et al., 2012). A recent meta-analysis based on clinical study reports (Sharma et al., 2016) has indicated a higher risk among children and adolescents related to antidepressant treatment (3.0%) versus placebo (1.1%) in composite outcome of suicide, suicide attempts, suicidal ideation, or self-harm. The difference between active treatment (2.3%) and placebo (1.1%) in outcomes of suicide or suicide attempts did not reach statistical difference among children or adolescents. The possible increased risk of suicidal ideation associated with antidepressants should be considered among

children and adolescents; nevertheless, use does not necessarily need to be avoided in this population (Zalsman et al., 2016). Among adults, the systematic review by Zalsman et al. (2016) on prevention of suicidal behaviour concluded that antidepressant use is associated with reduced risk for suicide. However, this conclusion was not supported by another systematic review of RCTs (Riblet et al., 2017). Observational literature (Kessing et al., 2005; Song et al., 2017) and some systematic reviews (Zalsman et al., 2016; Smith & Cipriani, 2017) support the concept of lithium being preventive against suicidal ideation and suicide attempts, particularly in mood disorders. However, another meta-analysis of RCTs of lithium indicated only a trend, thus warranting further studies (Riblet et al., 2017). A systematic review by the ISBD (Schaffer et al., 2015c) likewise more cautiously concluded that current literature supports anti-suicidal effects of lithium (and anticonvulsants) in BD, but called for more prospective, randomized, and comparative trials for this specific population. Administration of intravenous ketamine or intranasal esketamine is associated with rapid resolution of suicidal ideation within hours up to a week (Canuso et al., 2018; Wilkinson et al., 2018). The relief of imminent risk may provide a bridge over the delayed onset of effects for standard pharmacotherapies, as demonstrated in small 4- to 6-week RCTs. (Canuso et al., 2018; Grunebaum et al., 2018). Notwithstanding promising potential of ketamine, more wide-spread use and long-term safety remains open. Preliminary findings indicate also that adjunctive low-dose buprenorphine may relieve suicidal ideation within 2-4 weeks (Yovell et al., 2016). Systematic reviews provide mixed results on antisuicidal effects of clozapine in psychotic disorders (Zalsman et al., 2016; Riblet et al., 2017).

Among neuromodulation therapies, rTMS delivered in 15 sessions for 3 weeks may relieve suicidal ideation partially independently from resolution of depressive symptoms (Weissman et al., 2018). The effectiveness of ECT is based on observational uncontrolled studies, but showed an 82% resolution rate of suicidal ideation in completers of a three-week course of ECT among severely depressive patients with high rates of suicidal ideation (Kellner et al., 2005). According to a nationwide observational study, unipolar or bipolar patients with depression receiving ECT had 20% lower risk of suicide than matched controls (Liang et al., 2018).

Psychotherapeutic or other psychosocial interventions have been mostly investigated among high-risk individuals with mental disorders, suicidal ideation, or previous suicide attempts. Psychosocial treatments for suicidal behavior share common elements in evaluating a patient's behavior, supporting positive and discouraging negative behaviors, exploring emotional and cognitive precipitants, improving problem-solving skills, promoting an active stance among therapists, and explicitly addressing suicidal behavior (Turecki & Brent, 2016). A recent meta-analytic review of RCTs (Meerwijk et al., 2016) estimated that psychosocial and behavioral interventions directly addressing suicidal behavior (mainly CBT and DBT)

reduced the risk of suicide attempts by 35% (number needed to treat 7-8). The direct interventions showed better improvement at the end of treatment and over a longer term follow-up (mean 13.6 months) than indirect interventions, which were effective only in the long term. However, the differences between direct and indirect interventions were not statistically significant and firm conclusions were limited by the heterogenic group of indirect interventions. Another systematic review of psychosocial interventions after self-harm (includes acts without suicidal intent) (Hawton et al., 2016) found CBT (includes problem-solving therapy) to reduce the rate of participants' self-harm episodes at six and twelve months. DBT significantly reduced the frequency of repeat self-harm among patients with BPD. In prevention of suicides, recent meta-analytic evidence from RCTs of CBT indicated a trend for an association between CBT and lower risk for suicide suggesting need for more research (Riblet et al., 2017). Among new psychosocial interventions, preliminary findings from an RCT of the Attempted Suicide Short Intervention Program indicated considerably lower (83%) suicide re-attempt risk compared with treatment as usual (8.3% vs. 26.7%) (Gysin-Maillart et al., 2016).

A chain of care for recent suicide attempters with follow-up contacts and active outreach is recommended (Bolton et al., 2015; Turecki & Brent, 2016; Zalsman et al., 2016). Among these individuals, the need for appropriate psychopharmacological or psychological treatments for mental disorders should be evaluated, considering the high rate of such disorders among previous suicide attempters (Hawton et al., 2013b). Pooled evidence from RCTs show that the World Health Organization's 'Brief Intervention and Contact' intervention (includes educational session and regular follow-up contacts up to 18 months) is associated with significantly lower risk for suicide. However, the evidence is derived solely from low- and middle-income countries (Riblet et al., 2017). A study of Safety Planning Intervention among patients with suicidal behavior in the emergency department found a 45% reduced risk of suicidal behavior in the intervention group relative to the control condition during a six-month follow-up (3.0% vs. 5.3%) (Stanley et al., 2018). Among emergency department attendees with current suicidal ideation or suicide attempt, an interrupted time series analysis indicated a 20% reduction in relative risk (absolute 5%) for suicide attempt during a 52-week follow-up after implementation of both emergency department-based and follow-up (via telephone) intervention (close screening for risk of suicide, provision of a safety plan and information, phone calls for 52 weeks) (Miller et al., 2017).

2.8 Summary of the review

Depressive disorders and BD are impairing disorders characterized by recurrent mood episodes and intermittent periods of full remission or

subthreshold symptoms. Patients experience nearly half of the time syndromal or subsyndromal mood symptoms. Depressive states predominate also the course of BD. The annual prevalence of MDD is about 5%. Lifetime, over 1% of the population is affected by BD. Depressive disorders are twice as common among women than men, whereas BD is equally common. A thorough explanation for the etiology and pathophysiology of both disorders is missing. The proportion explained by genetic or environmental factors appears to be inverse between the disorders. Early adversity is a long-term vulnerability factor for both. Known neurobiological alterations manifest at various levels and are often associated with stress responses.

Depressive disorders are the mental disorder most clearly associated with suicidal behavior, although the risk in BD may be even higher. Of those who attempted suicide or died by suicide, more than half had suffered from depressive disorder or BD. Up to one-third of patients with depressive disorder or BD may have attempted suicide. The cumulative probability for dying by suicide among patients with depressive disorders is estimated at 7% in men and 4% in women. The corresponding rates in BD are 8% and 5%.

Risk factors for depressive disorders or BD and suicidal behavior overlap. By definition, a suicide attempt requires suicidal ideation and thus both share risk factors. Research on suicidal behavior should aim to clarify the factors explaining formation of suicidal ideation and those explaining suicide attempt separately. In depressive disorders suicidal ideation is rare without concurrent clinically significant depression. Less is known of formation of suicidal ideation in BD but mainly concern depressive morbidity and mood lability. Additionally, hopelessness contributes to suicidal ideation.

The factors most consistently associated with suicide attempts in depressive disorders or BD include previous suicide attempts, more severe characteristics of depressive morbidity, hopelessness or suicidal ideation, aggression, comorbid anxiety disorders, cluster B personality disorders, substance misuse, family history of suicidal behavior, life events or physical illness, and low social support. The majority of suicide attempts in depressive disorder or BD cluster in high-risk mood episodes, consisting of MDEs and mixed episodes specific to BD. Mental disorders as criteria-based syndromes appear to explain formation of suicidal ideation, but not satisfactorily suicide attempts among suicide ideators. Conditions characterized by agitation and disinhibition may, however, better characterize suicide attempters.

Suicide attempts are commonly investigated as a proxy for suicide due to low base rate of suicides. However, these two populations have some distinct characteristics, because suicides are associated more often with male sex, older age, more severe clinical characteristics, and death by first attempt. The strongest evidence of risk factors for suicide in depression pertain to male sex, family history of psychiatric disorder, previous suicide attempt, severity of depression, hopelessness, comorbid anxiety and personality disorders, and SUDs. In BD, the only risk factors identified for suicide in a meta-analysis include male sex and first-degree family history of suicide.

Suicidal behavior has complex longitudinal associations between temporally distal and proximal factors. Presumably, mediating factors link the effects between them. The diathesis for suicidal behavior includes familial susceptibility and adversities during development. Personality traits, psychological factors, cognitive deficits, behavioral dispositions, and long-lasting alterations in stress responses may contribute to this diathesis as potential mediators. Proximal precipitants for suicidal behavior include emergence of mood episodes, hopelessness, substance use, life stressors and lack of protective factors like interpersonal support. Exceptionally high-risk periods for suicide are those temporally close to psychiatric hospitalization and non-fatal suicide attempt. The acceptability and availability of a method for attempted suicide is probably a major determinant of its outcome.

Suicidal prevention involves universal population level, selective high-risk group, and high-risk individual level strategies. Restriction of access to lethal methods for suicide and more accessible mental-health services form main population-level strategies. Effective treatment of depressive episodes and dealing with high-risk post-discharge periods form the core of high-risk group strategies. Among high-risk individuals adequate pharmacotherapy for mood episodes remain the most readily available measure in both depressive and bipolar disorder. Treatment of depressive disorders with appropriate psychotherapies focusing directly on suicidal behavior should be considered for high-risk individuals. Neuromodulative treatments complement treatment options. Provision of a safety plan, follow-up contacts and active outreach may reduce the risk for suicide attempts among high-risk individuals.

Overall, treatment practices for depression have undergone major transformations in recent decades. Concurrently with an outbreak in the use of antidepressants, deinstitutionalization and emphasis on community-based services have resulted in a substantially reduced number of psychiatric beds. These ecological changes may have had an influence on suicide risk in depression, but temporal trends have not been investigated.

Several limitations exist in the scientific literature on risk factors for suicide. Studies with a narrow focus on investigated putative risk factors are susceptible to unobserved confounding. In addition, the relative magnitude of effects and comparative significance of factors for suicidal behavior remain unknown. Suicidal ideation and suicide attempts are too often not examined as separate outcomes. As a result, the relevance of factors for either formation of suicidal ideation or predisposition to suicide attempts among ideators remain insufficiently understood. Investigations on the mutual mechanisms between temporally distal factors, including CM, and suicidal behaviour remain scarce. The evidence base on risk factors for suicide in depressive disorder and BD is surprisingly limited and longitudinal studies are needed. Lastly, the gender disparity in risk for suicide is established, but its explanations, including the role of gender differences in risk factors, require clarification.

3 Aims of the study

This study investigates clinical epidemiology of and risk factors for suicidal ideation, suicide attempts, and suicide among patients with depressive disorder or BD in Finnish psychiatric secondary care.

Specific aims were as follows:

1. To investigate a) differences and similarities in multiple domains of putative risk factors for suicidal ideation or suicide attempts specifically, and b) independence of the effects of several putative distal, mediating, and proximal risk factors in a secondary care sample of patients with depressive disorder or BD (Study I).
2. To investigate the effect of BPD traits as a mediator between CM and either suicidal ideation or suicide attempts among patients with depressive disorder or BD (Study II).
3. To investigate cumulative risk of suicide and temporal trends in risk in a Finnish nationwide cohort of first-hospitalized patients with depression in 1991-2011 followed up to the end of the year 2014 (Study III).
4. To investigate risk factors for suicide and gender differences in risk factors and methods of suicide in a Finnish nationwide cohort of first-hospitalized patients with depression in 1991-2011 followed up to the end of the year 2014 (Study IV).

4 Materials and methods

4.1 Design and setting of Studies I and II

Studies I and II were conducted as part of the HUPC study, a collaborative research project between the Department of Psychiatry, University of Helsinki and Helsinki University Central Hospital; the Department of Public Health Solutions, Mental Health Unit, National Institute for Health and Welfare; and the Department of Social Services and Health Care, Psychiatric Services, City of Helsinki. The Ethics Committee of Helsinki University Central Hospital and the research committees of the organizations above approved the study design.

The study was implemented as a web-based survey in psychiatric secondary services within the Helsinki metropolitan area (cities of Helsinki, Espoo, Vantaa, Kauniainen, Kerava, and the municipality of Kirkkonummi). The mean population of the catchment area in 2012 was 1 139 222. Eligible participants were sampled from all ten community mental health centers, in 24 of the 35 psychiatric inpatient units, in one of the eight day-care hospitals, and in two residential communities of the area.

4.2 Design and setting of Studies III and IV

Studies III and IV were conducted as part of the MERTTU research project (Pirkola et al., 2009). These register-based studies merged national-level data from 1) the Finnish Hospital Discharge Register (FHDR), 2) the census register maintained by Statistics Finland, and 3) Statistics Finland's register on causes of death. The Ethics Committee of the National Institute for Health and Welfare approved the study design.

From the study database, all patients with a first-time hospitalization due to depression in Finland between 1991 and 2011 were identified and followed on the registers up to 31 December 2014 (maximum 24 years). Sociodemographic information from the census register was obtained from 31 December of the year preceding the index hospitalization. All data were linked with the Finnish personal identity codes at the individual level.

4.3 Participants and sampling in Studies I and II

The objective of the HUPC study sampling was to derive a representative cohort of mood disorder patients in psychiatric care in the area. Patients were sampled from the mood disorder units between 12 January 2011 and 20 December 2012 in proportion to the size of the population of the area. One-

half of the participants were sampled from the Department of Psychiatry at Helsinki University Central Hospital, and one-half from the Psychiatric Services at the Helsinki City Department of Social Services and Health Care.

All patients aged 18 years and over were considered eligible. The exclusion criteria were a diagnosis of neurodevelopmental or neurodegenerative disorder and insufficient Finnish language skills. Patients were sampled with a stratified sampling method from the regional units. Eligible study participants were randomly drawn either from patient lists or by selecting all patients on a certain day or week in a unit. In hospital setting, every fifth voluntary admission was identified. All participants were thoroughly informed of the study and provided their informed consent. The participants were asked to answer a browser-based survey on specific laptops using mobile access, with an option for a paper-and-pencil version.

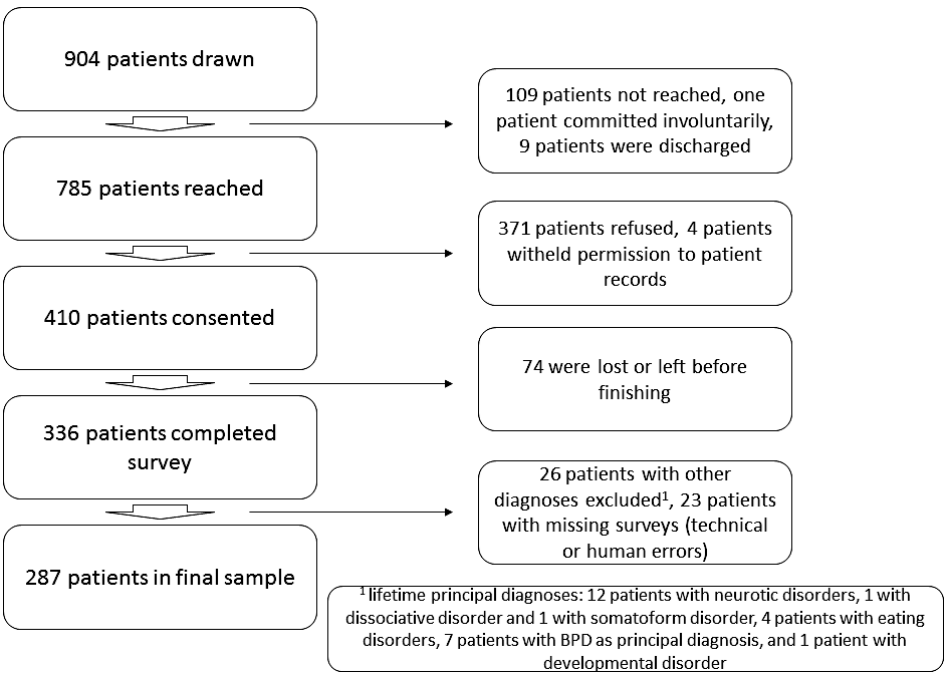


Figure 1 Flowchart of the Helsinki University Psychiatric Consortium (HUPC) sampling process.

The sampling process is outlined in Figure 1. The final study sample (N=287) consists of 188 patients with depressive disorder (includes five patients with dysthymia) and 99 patients with BD. Of the patients with BD, 36 had BD-I, 55 had BD-II, and eight had BD not otherwise specified (NOS). Patients with other lifetime principal diagnoses were excluded from the analyses. The

clinical and sociodemographic characteristics of the sample are presented in Table 3. Of the total sample, 55 (19.2%) were inpatients at the time of survey and 151 (52.6%) had a lifetime history of psychiatric hospitalization. The mean number of psychiatric hospitalizations was 4.16 (standard deviation [SD] 5.9) among those ever hospitalized. Patients had a mean of 5.7 (SD 6.2) years from the first contact with psychiatric care.

Table 3 Clinical and sociodemographic characteristics of the HUPC sample.

Characteristic	Depressive disorder		Bipolar disorder		Total sample	
	n	%	n	%	n	%
	188	100	99	100	287	100
Depressive disorder ^a						
Severe with psychotic symptoms	14	7.4	-	-	14	4.9
Severe without psychotic symptoms	105	55.9	-	-	105	36.6
Moderate or dysthymia	69	36.7	-	-	69	24.0
Bipolar disorder ^{a, b}						
Type I	-	-	36	36.4	36	12.5
Type II and NOS	-	-	63	63.6	63	22.0
Alcohol harmful use or dependence	33	17.5	31	31.3	64	22.3
Comorbid emotionally unstable personality disorder, borderline type	43	22.9	17	17.2	60	20.9
Men	42	22.3	36	36.4	78	27.2
Women	146	77.7	63	63.6	209	72.8
Marital status ^c						
Not cohabiting / Unmarried	79	42.5	32	32.3	111	38.9
Married or cohabiting	68	36.6	37	37.4	105	36.8
Divorced	36	19.4	29	29.3	65	22.8
Widowed	3	1.6	1	1.0	4	1.4
Education ^c						
University	30	16.1	22	22.2	52	18.2
College	45	24.2	27	27.3	72	25.3
Vocational or apprenticeship	46	24.7	22	22.2	68	23.9
No professional education	65	34.9	28	28.3	93	32.6
Employment status ^c						
Unemployed	20	10.8	10	10.1	30	10.5
Sick leave	66	35.5	22	22.2	88	30.9
Disability pension	32	17.2	38	38.4	70	24.6
Working or studying	54	29.0	27	27.3	81	28.4
Other	14	7.5	2	2.0	16	5.6
	Mean (SD)		Mean (SD)		Mean (SD)	
Age, years	39.1	(13.3)	41.3	(12.3)	39.9	(13.0)

Abbreviations: HUPC = Helsinki University Psychiatric Consortium, NOS = not otherwise specified, SD = Standard Deviation

^a All diagnoses according to the International Classification of Disease, 10th edition, Diagnostic Criteria for Research (ICD-10-DCR)

^b ICD-10-DCR bipolar affective disorder diagnoses subclassified applying Diagnostic and Statistical Manual of Mental Disorders (DSM) compatible classification of type I and type II disorders

^c Data missing for two patients with depressive disorder, 0.7% of the total sample

4.4 Participants of Studies III and IV

Study participants include all patients 18 years and older with first lifetime hospitalization for depression as a first diagnosis in a psychiatric hospital or a psychiatric unit within a general hospital between 1991 and 2011. The Finnish DSM-III-R (Lääkintöhallitus, 1989) codes 2961A-G and 2968A and ICD-10 codes F32-33 (World Health Organization, 1993) were used to derive the patient cohort from the FHDR. Excluded were patients who had a previous psychiatric hospitalization between 1980 and 1990 or who had at baseline a hospitalization discharge record of a comorbid diagnosis of a major psychotic disorder (identified and excluded with the following DSM-III-R codes 2951-2953 A-F, 2954A, 2956 A-F, 2957A, 2959 A-F, 2971A, 2973A, 2988A, 2989X, 3012C; and ICD-10 codes F20-29).

Living patients at discharge (excluding patients who died during the baseline hospitalization by suicide or another cause) were followed on the registers until death by suicide or another cause (regardless of place of death) or until 31 December 2014, whichever came first. Altogether 56 826 patients (25 188 men and 31 638 women) were followed for 628 514 person-years (mean 11.1 years, median 10.7 years, and maximum 24 years of follow-up). The follow-up was naturalistic by design and represents treatment as usual with possible re-hospitalizations. The sociodemographic and clinical characteristics of the cohort are presented in Table 4.

Table 4 Sociodemographic and clinical characteristics of patients first hospitalized for depression in Finland from 1991 to 2011 at baseline.

Characteristic	Total Cohort		Men		Women	
	N = 56 826 (n / %)		n = 25 188 (n / %)		n = 31 638 (n / %)	
Marital status						
Not married	21080	37.1	10340	41.1	10740	33.9
Married	22665	39.9	10377	41.2	12288	38.8
Divorced	8831	15.5	3720	14.8	5111	16.2
Widowed	4250	7.5	751	3.0	3499	11.1
Lives alone	16704	29.4	7244	28.8	9460	29.9
Lives with others	40122	70.6	17944	71.2	22178	70.1
Children 0-7 years old _a						
No	32250	56.8	14443	57.3	17807	56.3
Yes	7699	13.5	3205	12.7	4494	14.2
Education level						
Basic _b	24774	43.6	10703	42.5	14071	44.5
Upper secondary	21983	38.7	10363	41.1	11620	36.7
Tertiary _c	10069	17.7	4122	16.4	5947	18.8
Employment status						
Employed	23767	41.8	11238	44.6	12529	39.6
Unemployed	7723	13.6	4121	16.4	3602	11.4
Studying	5332	9.4	1991	7.9	3341	10.6
Retired	14750	26.0	5611	22.3	9139	28.9
Conscript	183	0.3	179	0.7	4	0.0
Disability pension	394	0.7	156	0.6	238	0.8
Out of labor force (other)	4677	8.2	1892	7.5	2785	8.8

Table 4 (continued)

Family income level						
Lowest third	18654	32.8	7568	30.0	11086	35.0
Middle third	18779	33.0	8326	33.1	10453	33.0
Highest third	19393	34.1	9294	36.9	10099	31.9
Depression severity						
Moderate _d	21630	38.1	10341	41.1	11289	35.7
Severe	24699	43.5	10691	42.4	14008	44.3
Psychotic	10497	18.5	4156	16.5	6341	20.0
Alcohol dependent	6734	11.9	4472	17.8	2262	7.1
GAS value						
0 – 47	8938	15.7	3791	15.1	5147	16.3
47 – 63	25446	44.8	11502	45.7	13944	44.1
63 – 100	14555	25.6	6259	24.8	8296	26.2
Missing data _e	7887	13.9	3636	14.4	4251	13.4
Admission type						
Voluntary	43029	75.7	18744	74.4	24285	76.8
Involuntary	6875	12.1	3223	12.8	3652	11.5
Missing data _e	6922	12.2	3221	12.8	3701	11.7
Previous suicide attempt _f						
At admission	2908	5.1	1281	5.1	1627	5.1
Over past 4 years	2402	4.2	1124	4.5	1278	4.0
	Mean	SD	Mean	SD	Mean	SD
Age, years	44.8	17.5	43.4	16.0	45.8	18.6

Sociodemographic information obtained from the final day of the year prior to baseline hospitalization and clinical information from the hospital discharge records at baseline.

_a for those living in family, data missing for 29.7% of patients, n = 16 877.

_b contains missing information

_c consists of lowest level tertiary education or higher

_d includes all other types of depression (from mild to moderate, partial remissions, other specified, and unspecified)

_e information missing prior to 1994 when psychiatric care-specific additional information notifications were established in the FHDR.

_f subcategories mutually exclusive, individuals may be categorized in both.

Abbreviations: FHDR = Finnish Hospital Discharge Register, GAS = Global Assessment Scale.

4.5 Explanatory variables

4.5.1 Diagnostics of the HUPC study (Studies I and II)

HUPC study diagnostics were based on diagnostic assessments carried out by clinical doctors and documented in patient records. The national guidelines instruct applying ICD-10 Diagnostic Criteria for Research (DCR) criteria for clinical diagnoses. The study investigators reviewed the rationale for clinical diagnoses by reviewing all available information from the patient's medical histories and specifying the diagnosis when needed. The group of investigators consisted of three psychiatric residents and one specialist in psychiatry. In uncertain diagnostics, senior investigators specialized in psychiatry were consulted (42 cases, 12.5% of the sample). Each patient was given in hierarchical order one lifetime principal diagnosis, which was considered the most severe and pervasive disorder over the lifetime. Severe depressive disorder, BD, and psychotic disorders were considered as primary

conditions over others. BD diagnoses of the study follow national guidelines (Working group appointed by the Finnish Medical Society Duodecim, 2013) that instruct applying DSM-compatible classification of type I and type II disorders. Patients with lifetime recurrent antidepressant treatment-induced (hypo)manic episodes were classified as BD NOS and combined in the analyses with BD-II patients. When applicable, additional lifetime comorbid diagnoses were assigned for lifetime substance misuse or dependence and comorbid BPD (ICD-10 code F60.31). Background clinical information from patient records was collected on the number of lifetime hospitalizations and the date of the first and current contact with psychiatric services.

4.5.2 The HUPC Survey (Studies I and II)

The sociodemographic data of the HUPC study were collected as part of the survey. The HUPC survey via self-report scales inquired about multiple domains of putative explanatory factors, including childhood experiences, adult attachment styles, psychological factors, personality traits, current clinical symptoms, lifetime clinical symptoms, substance abuse, recent life events, current perceived social support, and ability to function.

4.5.2.1 Childhood experiences and adult attachment style

The Trauma and Distress Scale (TADS) (43 items) is a self-report scale (Patterson et al., 2002; Klosterkotter et al., 2005) of CM and distressing experiences. The five subdomains of the scale (25 items) inquire about childhood physical, sexual, and emotional abuse and emotional and physical neglect. The formulation of questions probes gradually more severe experiences and for each the scale rates the frequency (Likert scale 0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = nearly always). The TADS provides subscores for the five subdomains and a total sum score. The TADS has been validated in a Finnish community sample. The findings have shown good internal consistency, reliability between self-reported and interview-based TADS, and concurrent validity with self-reported depressive symptoms and treatment-seeking as proxies for traumatization (Salokangas et al., 2016). The validation study proposed slightly revised items, however, this study used the original scales to maintain comparability. In this study, Cronbach's alpha for the sum score was 0.92, and for the subscales of emotional abuse 0.84, physical abuse 0.75, sexual abuse 0.91, emotional neglect 0.90, and physical neglect 0.68.

The Experiences in Close Relationships, revised (ECR-R) (36 items) is a self-report scale (Fraley et al., 2000) of adult romantic attachment-related anxiety and avoidance. The two subdomains of the scale (18 items each) are rated on a seven-point Likert scale from 1 (strongly disagree) to 7 (strongly agree). Exploratory and confirmatory factor analyses have shown a distinct

two-factor structure and high temporal stability over a short time period (Sibley & Liu, 2004). In the HUPC survey, the questions of the scale were presented after a conditioned question about ever having an intimate relationship in adulthood. Cronbach's alphas were 0.94 for adult anxious and 0.91 for adult avoidant attachment subscores.

4.5.2.2 Personality traits and psychological factors

The Short Five (S5) (60 items) is a brief self-report scale (Konstabel et al., 2012) of the 30 facets of the Five-Factor Model personality traits (Costa & McCrae, 1992). The S5 consists of positive and negative single items measuring the six facets of each of the five factors of neuroticism, extraversion, agreeableness, conscientiousness, and openness (to new experiences). The S5 shows good congruence with the standard Revised Neo Personality Inventory developed by Costa and McCrae (1992) and similar external validity. In this study, Cronbach's alphas were for neuroticism 0.88, extraversion 0.86, agreeableness 0.68, conscientiousness 0.82, and openness 0.78.

The General Self-Efficacy Scale (GSE) (10 items) is a self-report scale (Schwarzer & Jerusalem, 1995) of perceived general beliefs of personal agency, optimism, and coping in demanding life circumstances. The questions are rated on a four-point Likert scale from 1 (not at all true) to 4 (exactly true). The scale has been found to be reliable, universal, and unidimensional. Higher scores indicate greater beliefs in self-efficacy and correlate positively with optimism, active coping, and positive emotions, but inversely with depressive and anxiety symptoms (Scholz et al., 2002; Luszczynska et al., 2005). In this study, Cronbach's alpha for the scale was 0.86.

The Barratt Impulsiveness Scale, version 11 (BIS-11), (30 items) is a self-report scale (Patton et al., 1995) of the multifaceted construct of impulsiveness. The questions are rated on a four-point Likert scale from 1 (rarely/never) to 4 (almost always), with higher scores indicating greater impulsivity. The BIS-11 shows strong test-retest reliability at one month, high convergent validity with similar self-reports, and a total score of ≥ 72 indicates a highly impulsive person and shows concurrent validity with harmful impulsive behavior (Stanford et al., 2009). In this study, Cronbach's alpha for the scale was 0.88.

The McLean Screening Inventory for Borderline Personality Disorder (MSI-BPD) (10 items) is a self-report screening instrument (Zanarini et al., 2003) for BPD. Each question probes for the presence of a BPD symptom and is rated as true/false. A cut-off score of 7 or more indicates the presence of BPD with good sensitivity (0.81) and specificity (0.85), and the scale shows good internal consistency and high test-retest reliability (Cronbach's alpha = 0.74). A validation study of the Finnish version of the scale (Melartin et al., 2009) reported a sensitivity of 0.82 and specificity of 0.72 for an

optimal cut-off score of 7 or more, and a Cronbach's alpha of 0.77 for the internal consistency of the scale. In this study, Cronbach's alpha was 0.75.

The Schizotypal Personality Questionnaire, brief version (SPQ-B) (22 items) is a brief self-report instrument (Raine & Benishay, 1995) screening for the presence of DSM-III-R-based schizotypal personality traits. Each question of the SPQ-B probes for the presence of schizotypal personality traits and is rated true/false. The original validation study by Raine and Benishay (1995) supported the existence of three factors (cognitive-perceptual, interpersonal, and disorganized), good reliability of the scales, and moderate convergent validity with independent clinical ratings. Others have found equal fit for a one-dimensional solution and moderate convergent validity with semistructured interview-based assessments (Compton et al., 2007). In this study, Cronbach's alpha for the unidimensional scale was 0.92.

4.5.2.3 Current clinical symptoms

The Beck Depression Inventory (BDI) (21 items) is a self-report instrument (Beck et al., 1961) screening for the presence and severity of current depressive symptoms, which are rated on a four-point Likert scale. The BDI show good internal consistency and convergent validity with a clinical rating for depression (Beck et al., 1988). In this study, Cronbach's alpha for the scale was 0.92.

The Beck Hopelessness Scale (BHS) (21 items) is a self-report scale (Beck et al., 1974) screening for hopelessness and pessimistic attitudes about the future, which are rated as true/false. Higher scores on the scale indicate more severe hopelessness and pessimistic views. The original validation study indicated excellent internal consistency and good convergent validity with clinically rated hopelessness. The construct validity of the BHS was supported by associations with severity of depression and suicidal intent, confirmed by a Finnish general population study (Haatainen et al., 2004). In this study, Cronbach's alpha for the scale was 0.92.

The Overall Anxiety Severity and Impairment Scale (OASIS) (5 items) is a self-report instrument (Norman et al., 2006) for anxiety symptoms over the past week. The items rate the severity, frequency, anxiety-related avoidance behavior, and impairment on a five-point Likert scale from 0 (not at all) to 4 (extreme/all the time). The test-retest reliability and convergent and discriminative validity were found to be good to excellent. A cut-off score of 8 or more indicates the presence of an anxiety disorder with a sensitivity of 0.69 and a specificity of 0.74 (Norman et al., 2006; Norman et al., 2011). In this study, Cronbach's alpha for the scale was 0.90.

4.5.2.4 Lifetime clinical symptoms

Subjective lifetime most severe anxiety and depressive symptoms were retrospectively inquired with modified questions of the BDI (21 items) and OASIS (5 items) scales, respectively. In the HUPC survey, the modified scales were presented after first asking the respondent to recall the most severe episode of anxiety or depression over the lifetime and report the year and month of occurrence. The respective items of the BDI and OASIS scales were then presented to inquire about the symptoms during this most severe lifetime episode of anxiety or depression. Cronbach's alphas were for the modified BDI 0.88 and for the modified OASIS 0.84.

The Community Assessment of Psychic Experiences (CAPE) (46 items) is a self-report instrument (Stefanis et al., 2002) for positive, negative, and depressive symptoms of psychotic-like experiences. Each item of the scale is rated on a four-point Likert scale for frequency from 0 (never) to 3 (nearly always), and if present, for associated distress from 0 (not distressed) to 3 (very distressed). The CAPE provides a total sum score and subscores for frequency and distress on each subdomain of positive, negative, and depressive symptoms. The CAPE shows good test-retest reliability and predictive validity for other equivalent interview-based or self-reported assessments (Konings et al., 2006). In this study, the Cronbach alphas of the frequency scores were for positive symptoms 0.86, negative symptoms 0.88, and depressive symptoms 0.85.

The Mood Disorder Questionnaire (MDQ) (15 items) is a screening instrument (Hirschfeld et al., 2000) for lifetime presence of BD (hypo)manic symptoms and behaviors. The first part of the MDQ (13 items) probes for lifetime BD (hypo)manic symptoms rated as yes/no. The second part (1 item) inquires whether these symptoms occurred during the same period of time (rated yes/no). The third part (1 item) inquires about the severity of problems caused on a four-point Likert scale from 1 (no problems) to 4 (severe problems). In the validation study, a clinical cut-off score of 7 or more in the first part when symptoms have occurred at the same time and have caused moderate to severe problems indicated the presence of BD with a sensitivity of 0.73 and a specificity of 0.90 (Hirschfeld et al., 2000). The translated Finnish version has shown high sensitivity (0.85), but only moderate specificity (0.47) with this standard cut-off score in a psychiatric care sample (Isometsä et al., 2003). In this study, Cronbach's alpha for the first part of the scale was 0.90.

4.5.2.5 Substance abuse

The Alcohol Use Disorders Identification Test (AUDIT) (10 items) is a self-report instrument (Saunders et al., 1993) screening for hazardous and harmful alcohol consumption over the past year. The questions of AUDIT cover alcohol consumption, drinking behavior, dependence symptoms, and

alcohol-related problems, each rated from 0 to 4 with different scoring options. The original validation study presented a cut-off score ≥ 8 (0.92% sensitivity, 0.94% specificity) for detecting alcohol harmful use. Since then, accumulating evidence has indicated a sensitivity of 31–89% and a specificity of 83–96% in primary care. In Finland, a cut-off score of ≥ 8 for men and ≥ 6 in women is recommended (Working group appointed by the Finnish Medical Society Duodecim, 2018). In this study, Cronbach's alpha for the scale was 0.89.

Two questions adopted from the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (Hasin et al., 1996) screened for recent non-alcohol substance abuse or dependence. The first question asks about any substance use other than alcohol at least six times and the second question for use most of the day for at least three consecutive days over the past six months. For both scales, the questions provide a list of nine psychoactive substances with an additional open-ended option and are rated yes/no.

4.5.2.6 Current life circumstances

The List of Threatening Experiences Questionnaire (LTE-Q) (12 items) is a self-report questionnaire (Brugha et al., 1985) of life events over the past 12 months. The 12 questions inquire about life stressors and the month of occurrence. The LTE-Q displays high test-retest reliability and convergent validity with informant-based information (Brugha & Cragg, 1990).

The Perceived Social Support Scale, revised (PSSS-R) (12 items) is a self-report scale (Blumenthal et al., 1987) of current perceived social support. The questions are rated on a five-point Likert scale from 1 (not at all true) to 5 (exactly true). In this study, Cronbach's alpha for the scale was 0.94.

4.5.2.7 Ability to function

The Sheehan Disability Scale (SDS) (3 items) is a self-report measure (Sheehan, 1983; Sheehan et al., 1996) for current subjective functional ability in work, family, and social life. Each item rates impairment in one of these domains from 0 (not at all) to 10 (very seriously). The SDS displays high internal consistency, acceptable test-retest reliability, and convergent validity with clinical-rated functional status (Leon et al., 1997; Arbuckle et al., 2009). In this study, Cronbach's alpha for the scale was 0.83.

4.5.2.8 Family history of mental health and substance use

Familial mental disorders or substance abuse were probed by two questions inquiring whether a first-degree relative of the respondent had ever had mental disorder or substance use problems requiring treatment or causing

considerable impairment. In positive cases, a list of examples was provided and the participant was asked to answer open-entry questions about the explicit relationship, type of mental disorder, or main substance abused.

4.5.3 The Finnish Hospital Discharge Register

The FHDR contains information on all inpatient psychiatric and somatic hospitalizations in Finland since 1969. In Finland, all psychiatric hospitals are publicly funded. The coverage of the FHDR is complete (Sund, 2012). The diagnoses in the FHDR during 1987-1995 were based on the nationally applied DSM-III-R criteria (Lääkintöhallitus, 1989) and since then on the ICD-10-DCR criteria (World Health Organization, 1993).

The FHDR diagnoses are clinical diagnoses assigned by the attending doctor. The diagnoses of mental disorders in the register show good accuracy (Sund, 2012). Baseline hospitalizations were obtained by the DSM-III-R codes 2961A-G and 2968A, and ICD-10 codes F32-33. Comorbid diagnoses of alcohol dependence were identified with the DSM-III-R 3039X and ICD-10 F10.2 codes. Data on previous suicide attempts registered in the FHDR were identified with the following DSM-III-R codes E950-E959 and ICD-10 codes X60-X84, Y87.0, and Z91.5. Two mutually exclusive categories were then formed of previous suicide attempts (however, an individual may have both): 1) a suicide attempt at baseline episode (a somatic hospitalization due to a suicide attempt that led directly to the baseline psychiatric hospitalization or a psychiatric hospitalization with a record of a suicide attempt [the latter encompasses also suicide attempts without somatic hospitalization prior to admission or attempted in psychiatric hospital care, which are identically coded in the FHDR]), or 2) a suicide attempt within four years prior to the baseline admission (and necessitating somatic hospitalization).

The FHDR data provided information on the date of admission and discharge, and since 1994, on the overall functioning at discharge global assessment scale (GAS) value based on the assessment of the doctor in charge) and on whether the patient was involuntarily admitted. According to the Finnish Mental Health Act (1116/1990, 8§; 438/2014 9§), an individual may be involuntarily referred for evaluation in a psychiatric hospital if all of the following three conditions are suspected to be fulfilled: 1) the patient has a mental illness (i.e. psychotic), 2) the patient needs treatment for the mental illness, and if not receiving treatment, the condition of the mental illness would deteriorate or the patient's or another individual's safety would be in severe danger, and 3) all other mental health services are regarded as inappropriate or insufficient.

4.5.4 The Census Register (Study IV)

The sociodemographic data for Study IV was obtained from the Census Register of Statistics Finland. The data were matched on 31 December of the year prior to the index hospital admission. The sociodemographic variables (and pertinent categories) were as follows: 1) marital status (not married, married, divorced, and widowed), which since 2002 also includes same-sex partners), 2) household (lives alone or with others), 3) has children aged ≤ 7 years (for those living in a family), 4) relative income of the family living together (as thirds), 5) educational level (basic, upper secondary, and tertiary), and 6) employment status (at work, unemployed, studying, disability or old age pension, conscript, approved for unemployment pension due to long-term unemployment, or not in labor force for other reasons).

4.6 Suicidal behavior outcomes

4.6.1 Lifetime suicidal ideation and suicide attempts (Studies I and II)

The HUPC survey inquired about lifetime suicidal behaviors with translated questions from the National Comorbidity Survey (Kessler et al., 1999). The first question inquired about lifetime suicidal ideation ("Have you ever seriously thought about committing suicide?"), the second about making any plans ("Have you ever made a plan for committing suicide?"), and the third about lifetime suicide attempts ("Have you ever attempted suicide?"). In case of a positive answer for the last question, the number of lifetime attempts was asked with options ranging from one to six (or more).

To enhance the comprehensiveness of information about lifetime suicidal behaviors, survey data were complemented by a review of all available information from patient records on documentations on lifetime suicide attempts. When judging whether to count an act as a suicide attempt, by definition, this had to have at least some degree of intention to die described in the records (excluding self-harm behaviors without intention to die).

An individual's total number of lifetime suicide attempts was integrated from the survey and patient record data by selecting the one showing a higher count and classified from one to six (or more).

4.6.2 Suicides and Causes of Death Register (Studies III and IV)

For the cohort, the dates and causes of death during the entire follow-up were obtained from Statistics Finland's register on causes of death. Next, the suicide deaths were identified with the following DSM-III-R E950-E959 and ICD-10 X60-X84, Y87.0, and Z91.5 codes.

4.7 Statistical methods

4.7.1 Statistical methods of Study I

Bayesian imputation method using Mplus 7.1 software (Muthén & Muthén, 2012) was applied for imputation of missing data. The unobserved variables were predicted by observed variables using the covariance between variables (Enders, 2010). Instruments with a very large number of items were imputed in sections (10-20 items at a time) to reduce excessive computer calculation times. Scales with 20% or more missing data were excluded from imputation and further analyses.

The lifetime principal diagnostic variables for mood disorders were categorized into one of the following non-overlapping categories: 1) severe depressive disorder with psychotic symptoms, 2) severe depressive disorder without psychotic symptoms, 3) moderate depressive episodes or dysthymia (henceforth ‘moderate’), 4) BD-I, and 5) BD-II (including patients with BD NOS). Comorbid diagnosis of lifetime alcohol harmful use or dependence was combined into a single variable (AUD).

Lifetime suicidal behavior as a response variable was categorized into four non-overlapping categories: 1) no lifetime suicidal ideation or attempts, 2) lifetime suicidal ideation but no suicide attempts, 3) one lifetime suicide attempt, and 4) multiple suicide attempts.

Statistical tests of univariate analyses included χ^2 -, Mann–Whitney U-, Kruskal–Wallis, and One-Way ANOVA tests. Due to multiple testing, a threshold of $p < 0.01$ was applied. Dummy-coding was used for categorical variables. A multivariable multinomial regression model was used to examine associations between explanatory variables and different categories of lifetime suicidal behavior as a response variable. The non-suicidal category was used as a reference. In the multivariable models, preset explanatory variables included age, gender, and lifetime principal diagnostic variables (moderate depressive disorder group as reference). Other explanatory variables were then added or omitted one at a time from domains of putative risk factors by balancing and selecting the variables with the strongest association and omitting variables showing non-significant associations. Independent effects were examined by adding all selected variables simultaneously to the final model. Due to circularity, suicidal items in BDI, worst lifetime BDI, and MSI-BPD, as well as a lifetime comorbid diagnosis of BPD were excluded from the analyses. IBM SPSS Statistic, version 21 was used for analyses.

4.7.2 Statistical methods of Study II

The “mediation” package (version 4.4.5.) of R software (version 3.2.2.) (2015-08-14) (Imai et al., 2010; Tingley et al., 2014; R Core Team, 2016) was used to test the hypothesis of MSI-BPD score mediating the effect of TADS

score on lifetime suicidal behavior. Logistic regression models (Gelman & Hill, 2007; Tingley et al., 2014) were used to model three separate outcomes of lifetime suicidal behavior: (1) lifetime suicidal ideation but no lifetime suicide attempts, (2) lifetime suicidal ideation and/or suicide attempt, and (3) lifetime suicide attempt. Linear regression model was used to predict MSI-BPD as a mediating variable by age, sex, and TADS scores.

Differences between the models of (1) and (3) in mediation statistics were examined by random permutation tests (1000 random permutations). Mediation analyses were run with 2000 simulations and non-parametric (bootstrap) tests (Imai et al., 2010; Tingley et al., 2014). The difference in outcome between the modeled "exposure" (highest TADS mean scores) and "control" (lowest TADS mean scores) conditions was used to define the total effect. This total effect of TADS on suicidal behavior outcome was separated then as the Average Causal Mediation Effect (ACME) and the Average Direct Effect (ADE), representing, respectively, the mediated effect through MSI-BPD and the direct (not mediated by MSI-BPD) effect of TADS on the suicidal behavior outcome.

Whether this hypothesized mediation effect of TADS on suicidal behavior via BPD traits arises as a single construct of items reflecting all DSM-IV BPD criteria or specifically involves some separate subdomains was then studied by comparing the models using the MSI-BPD total score and models based on three subdomains of BPD traits. For these analyses, as presented by others (Gunderson et al., 2011; Reichborn-Kjennerud et al., 2013), the MSI-BPD items were categorized as four separate subcomponents consisting of an affective component (items "increased anger", "mood instability", "feeling of emptiness"), an interpersonal component (items "troubled relationships", "avoidance of abandonment"), a behavioral component (items "suicidal behavior", "impulsivity"), and a cognitive component (items "dissociative symptoms", "distrustfulness", "identity disturbance"). After excluding the suicidal item in the behavioral component, the remaining single item of "impulsivity" was coalesced with the cognitive component for statistical reasons. The total score of MSI-BPD and the sum of subcomponents were set to the same unit before examining the differences in mediation statistics using the MSI-BPD total score and subscores.

Data were analyzed without imputation of missing data (listwise deleted) because 96.5% of the sample had complete data for mediation analyses. Only ten patients had any missing values in one or more of the scales in the mediation analyses (eight patients had more than two missing TADS items, one patient had more than one missing MSI-BPD item, and two patients had more than two missing BDI items) and were assigned as missing cases pertinent to the total score of TADS, MSI-BPD, or BDI, respectively. Otherwise, the scores were calculated by averaging the non-missing items. All analyses were conducted by omitting the suicidality items of MSI-BPD and BDI. Composite variables were created for parental history of any mental disorder or substance abuse and were used for adjusting.

4.7.3 Statistical methods of Studies III and IV

A national cohort of discharged first-hospitalized patients with depression was followed on the registers until death (by suicide or another cause) or up to 31 December 2014, whichever came first. The time-to-event analyses censored (Study III) or treated as competing risks (Study IV) the deaths by causes other than suicide and ignored the diagnostic switches to a major psychotic disorder or BD because of the possibility of inducing survival bias in the analyses (only diagnoses of living patients can change).

The Kaplan-Meier product limit estimator was used in survival analyses to calculate the probability of not dying by suicide and the cumulative risk of suicide (Study III). Competing survival analyses were used to derive the cumulative probability of dying by suicide taking into account that patients may die of other causes (Study IV).

Time-trend analyses were conducted by forming five-year cohorts by admission year sequentially over the study period. The age- and gender-adjusted Cox proportional hazards for suicide were evaluated for each five-year cohort by the cohort of 1991-1995 serving as the reference. These time-trend analyses were estimated for three years post-discharge (individual follow-ups equal in length) and for the maximum (up to 24 years) available follow-up (individual follow-ups differing in length) periods.

The association between explanatory variables and risk for suicide was estimated in unadjusted (sex, age, baseline year only) and adjusted analyses using cause-specific Cox proportional hazard regression models. Cox models generated for the total cohort and then for men and women separately. The variables added to the adjusted models were selected a priori (gender, type of depression diagnosis, comorbid alcohol dependence, previous suicide attempts, family income, educational level, and living alone). This selection was based on previous literature on putative risk factors for suicide and an aim to limit as much as possible interrelations or changes over time among the selected variables. In the Cox models, the admission year was used as a stratification variable and the proportional hazard assumption was fulfilled based on the Schoenfeld residuals. Gender interactions were tested by adding an interaction term one by one for each variable into the model.

The study diagnoses from the DSM-III-R era were transformed into comparable ICD-10-DCR codes. The conversions were made by creating three non-overlapping categories of depression severity: 1) moderate category (reference) (mild, moderate, remissions of recurrent depression, other specified, and unspecified types; DSM-III-R codes 2961A, 2961B, 2961C, 2961F, 2961G, 2968A and ICD-10 codes F32.0*, F32.1*, F32.8, F32.9, F33.0*, F33.1*, F33.4, F33.8, F33.9), 2) severe depressive disorder without psychotic features or symptoms (DSM-III-R 2961D and ICD-10 F32.2, F33.2 codes), and 3) severe depressive disorder with psychotic features or symptoms (DSM-III-R 2961E and ICD-10 F32.3, F33.3 codes).

The analyses were run with software packages R (www.r-project.org) and Survo (www.survo.fi).

5 Results

5.1 Suicidal behavior in patients with depressive or bipolar disorder (Study I)

5.1.1 Lifetime prevalence of suicidal ideation and suicide attempts

Overall, 62 (21.6%) of the 287 patients in the HUPC secondary care sample had no lifetime suicidal behavior. Of the 97 patients (33.8%) who had lifetime suicidal ideation without attempts, 62 (63.9%) had made a suicide plan. Of the 128 patients (44.6%) who had attempted suicide, 49 (17.1%) had made one suicide attempt, and 79 (27.5%) had made two or more suicide attempts. Among suicide attempters, only 8 patients (6.3%) did not disclose lifetime suicidal ideation.

5.1.2 Explanatory factors for lifetime suicidal ideation and suicide attempts

The age, gender, and clinical characteristics of the HUPC sample (N=287) are presented according to the classification of lifetime suicidal behavior in Table 5. Along with the lifetime suicidal behavior continuum (no suicidal behavior, suicidal ideation without attempts, single suicide attempt, and recurrent suicide attempts), groups showed significant differences in age, lifetime principal diagnostics, comorbidity (AUD and BPD), being an inpatient at the time of the survey, and lifetime psychiatric hospitalizations.

The results of the HUPC survey are presented according to lifetime suicidal behavior in Table 6. The groups of patients classified according to lifetime suicidal behavior showed differences in multiple domains of risk factors, including CM, anxious adult attachment style, neuroticism, borderline and schizotypal personality disorder traits, self-efficacy, impulsivity, current depressive and anxiety symptoms, hopelessness, retrospective lifetime most severe depressive and anxiety symptoms, frequency of positive, negative, and depressive symptoms, alcohol use over the past year, and benzodiazepine use over the past six months. In addition, several putative risk factors in the analyses remained narrowly outside the pre-set $p \leq 0.01$ statistical significance level, including childhood emotional neglect, personality traits of agreeableness and conscientiousness, lifetime (hypo)manic symptoms or behaviors, and ability to function.

Table 5 Characteristics of the patients in the Helsinki University Psychiatric Consortium (HUPC) sample (N = 287) according to lifetime suicidal behavior.

Characteristic	No lifetime suicidal behavior		Lifetime suicidal ideation without attempts		Single lifetime suicide attempt		Recurrent lifetime suicide attempts		Statistics
	n	%	n	%	n	%	n	%	
<i>Patients</i>	62	21.6	97	33.8	49	17.1	79	27.5	
Men	20	32.3	29	29.9	12	24.5	17	21.5	$\chi^2=2.628$; df 3; $p=0.453$
Women	42	67.7	68	70.1	37	75.5	62	78.5	13.446; df 3; $p=0.004^*$
<i>Clinical diagnosis</i>									$\chi^2=40.022$; df 12; $p<0.001^{**}$
Severe DD with psychotic symptoms	2	3.2	4	4.1	1	2.0	7	8.9	
Severe DD without psychotic symptoms	12	19.4	45	46.4	21	42.9	27	34.2	
Moderate DD or dysthymia	24	38.7	22	22.7	12	24.5	11	13.9	
BD-I	16	25.8	4	4.1	4	8.2	12	15.2	
BD-II or NOS	8	12.9	22	22.7	11	22.4	22	27.8	
Comorbid AUD	6	9.7	16	16.5	10	20.4	32	40.5	$\chi^2=22.802$; df 3; $p<0.001^{**}$
Comorbid BPD	3	4.8	12	12.4	12	24.5	33	41.8	$\chi^2=35.135$; df 3; $p<0.001^{**}$
Inpatient when surveyed	9	14.5	8	8.2	12	24.5	26	32.9	$\chi^2=18.862$; df 3; $p<0.001^{**}$
Lifetime psychiatric hospitalization	29	46.8	37	38.1	26	53.1	59	74.7	$\chi^2=24.431$; df 3; $p<0.001^{**}$
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age, years	44.0	11.4	39.4	13.1	40.8	13.5	36.7	12.9	$F_{3, 283}=3.925$; $p=0.009^*, \dagger$
No. of psychiatric hospitalizations _a	2.41	1.701	2.0	1.394	3.54	4.13	6.64	8.306	17.313; df 3; $p<0.001^{**}, \dagger$

Abbreviations: AUD = Alcohol Use Disorder, BD-I = Bipolar Disorder, type I, BD-II = Bipolar Disorder, type II, BPD = Borderline Personality Disorder, DD = Depressive Disorder, NOS = Not Otherwise Specified, SD = Standard Deviation

Lifetime principal clinical diagnoses based on the International Classification of Disease, 10th edition, Diagnostic Criteria for Research (ICD-10-DCR)

Bipolar Disorder classified according to the national guidelines into type I and type II disorders

_a among those ever hospitalized

* significant at ≤ 0.01 level, ** significant at ≤ 0.001 level.

\dagger analysis of variance (ANOVA), \dagger Kruskal-Wallis test. All other statistical tests with the Chi-square test.

Table 6 Results of the Helsinki University Psychiatric Consortium (HUPC) Survey according to lifetime suicidal behaviors.

Domains of risk factors	No lifetime suicidal behavior		Lifetime suicidal ideation without attempts		Single lifetime suicide attempt		Recurrent lifetime suicide attempts		Statistical analysis
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
<i>Childhood adversity and adult attachment style</i>									
TADS _a	19.1	11.9	27.1	17.4	24.9	16.8	30.0	18.4	13.101; df 3; p=0.004*
Emotional abuse _a	4.9	4.2	7.1	4.9	6.0	5.0	7.9	5.4	13.421; df 3; p=0.004*
Physical abuse _a	1.7	2.1	3.2	3.5	2.9	2.8	4.1	4.2	13.446; df 3; p=0.004*
Sexual abuse _b	1.1	2.9	1.8	3.9	2.4	4.9	2.3	4.1	5.092; df 3; p=0.165
Emotional neglect	7.7	4.7	10.0	5.5	9.1	6.0	10.1	5.3	8.729; df 3; p=0.033
Physical neglect	3.9	3.0	5.0	3.8	4.5	3.6	5.6	4.2	6.401; df 3; p=0.094
ECR-R: anxious _c	3.3	1.3	3.9	1.4	4.0	1.5	4.6	1.3	22.498; df 3; p<0.001**
ECR-R: avoidant _c	3.3	1.2	3.4	1.2	3.7	1.2	3.6	1.2	3.220; df 3; p=0.359
<i>Personality and psychological factors</i>									
S5: neuroticism	1.5	14.4	9.9	12.8	7.9	12.8	12.6	12.8	F _{3, 283} =8.781; p<0.001***
S5: extraversion	-2.0	12.9	-4.8	14.7	-3.8	13.8	-2.3	13.1	F _{3, 283} =0.755; p=0.520 [†]
S5: openness	9.6	10.4	9.4	11.3	8.0	11.3	10.3	12.1	F _{3, 283} =0.405; p=0.750 [†]
S5: agreeableness	15.8	7.0	12.4	9.9	11.1	9.2	11.7	9.8	F _{3, 283} =3.226; p=0.023 [†]
S5: conscientiousness	4.7	11.7	1.7	11.5	1.8	10.4	-1.8	13.3	F _{3, 283} =3.499; p=0.016 [†]
MSI-BPD _i	3.7	2.6	5.4	2.4	6.1	2.5	7.1	2.2	39.901; df 3; p<0.001**
BIS-11 _d	56.0	12.4	59.8	12.4	61.3	12.4	64.0	13.6	F _{3, 282} =4.682; p=0.003*, [†]
GSE _d	22.6	6.0	19.5	6.3	19.4	6.5	18.5	6.2	17.111; df 3; p=0.001**
SPQ-B _d	6.8	4.5	9.4	5.5	10.0	5.2	11.5	4.8	F _{3, 282} =9.987; p<0.001**
<i>Current clinical</i>									
BDI _{d, m}	18.9	11.6	27.2	11.5	24.6	12.0	29.4	12.4	F _{3, 282} =9.094; p<0.001**, [†]
OASIS _a	8.8	4.6	11.2	4.6	10.9	4.2	12.4	4.4	F _{3, 281} =7.736; p<0.001**, [†]
BHS _d	7.4	5.6	11.9	5.2	10.6	5.8	11.5	6.1	25.191; df 3; p<0.001**
<i>Lifetime clinical</i>									
BDI most severe _{e, m}	34.8	10.4	43.4	9.4	38.1	11.2	45.9	9.9	F _{3, 276} =13.453; p<0.001**, [†]
OASIS most severe _e	14.6	4.0	16.7	2.6	16.3	34.3	17.1	2.8	16.873; df 3; p=0.001**
CAPE total _f	126.4	39.5	149.7	37.4	144.6	34.2	159.3	34.0	F _{3, 269} =9.348; p<0.001**, [†]
frequency of positive symptoms _a	25.9	5.1	28.6	7.3	28.8	5.9	30.9	7.5	22.149; df 3; p<0.001**
frequency of negative symptoms _g	30.2	7.8	34.4	8.0	33.9	8.3	34.1	7.1	F _{3, 279} =4.264; p=0.006*, [†]
frequency of depressive symptoms _h	17.5	4.4	20.7	4.4	19.7	4.7	21.9	4.6	F _{3, 277} =11.556; p<0.001**, [†]
MDQ _{a, n}	6.1	4.4	6.5	4.3	6.0	4.3	8.1	4.0	11.085; df 3; p=0.011
<i>Current life circumstances</i>									
PSSS-R _d	42.0	12.3	39.1	12.7	38.7	12.6	40.5	13.1	F _{3, 282} =0.866; p=0.459 [†]
LTE-Q	1.8	1.7	2.1	1.8	2.0	1.9	2.4	1.9	5.020; df 3, p=0.710
<i>Ability to function</i>									
SDS _i	17.0	8.2	20.3	8.0	20.1	6.6	20.4	7.6	7.852; df 3; p=0.049

Table 6 (continued)

Substance abuse

AUDIT _b	7.4	7.0	5.4	5.6	7.1	8.1	9.9	8.8	13.028; df 3; p=0.005*
PRISM BZD use past 12 months	n	%	n	%	n	%	n	%	
At least 6 times _j	13	25.0	26	28.6	19	39.6	38	51.4	$\chi^2=12.706$; df3; p=0.005**
On 3 consecutive days _k	6	12.0	13	14.6	14	29.2	15	20.3	$\chi^2=6.098$; df 3; p=0.107 [†]

^a data missing for 0.7% of patients, n = 285; ^b data missing for 1.7% of patients, n = 282; ^c data missing for 23.0% of patients, n = 221; ^d data missing for 0.3% of patients, n = 286; ^e data missing for 2.4% of patients, n = 280; ^f data missing for 4.9% of patients, n = 273; ^g data missing for 1.4% of patients, n = 283; ^h data missing for 2.1% of patients, n = 281; ⁱ data missing for 3.5% of patients, n = 277; ^j data missing for 7.7% of patients, n = 265; ^k data missing for 9.1% of patients, n = 261.

^l item 2 excluded from the analyses, ^m item 9 excluded from the analyses.

ⁿ sum of the first part (13 items) of the questionnaire asking about hypomanic or manic symptoms or behaviors

[†] analysis of variance (ANOVA), [‡] Chi-square test. All other statistical tests with the Kruskal-Wallis test.

* significant at ≤ 0.01 level, ** significant at ≤ 0.001 level.

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, BDI = Beck Depression Inventory, BHS = Beck Hopelessness Scale, BIS-11 = Barrat Impulsiveness Scale, Version 11, BZD = benzodiazepine, CAPE = Community Assessment of Psychic Experiences, ECR-R = Experiences In Close Relationships, Revised, GSE = General Self-Efficacy Scale, LTE-Q = List of Threatening Experiences Questionnaire, MDQ = Mood Disorder Questionnaire, MSI-BPD = McLean Screening Instrument for Borderline Personality Disorder, OASIS = Overall Anxiety Symptoms and Impairment Scale, PRISM = Psychiatric Research Interview for Substance and Mental Disorders, PSSS-R = Perceived Social Support Scale, Revised, SD = Standard Deviation, SDS = Sheehan Disability Scale, SPQ-B = Schizotypal Personality Questionnaire, Brief Version, S5 = Short Five, TADS = Trauma and Distress Scale.

5.1.2.1 Multivariable multinominal regression model for lifetime suicidal behavior

The adjusted effects of the variables from multiple domains of risk factors for lifetime suicidal behavior in the final model are presented in Table 7. Significant variables in the final model for lifetime suicidal ideation without attempts were younger age, diagnosis of severe depressive disorder without psychotic symptoms, BD-II/NOS, hopelessness, and TADS physical abuse score.

Significant variables in the final model for a single lifetime suicide attempt were diagnosis of severe depressive disorder without psychotic symptoms and MSI-BPD score.

Significant variables in the final model for lifetime repeated suicide attempts were female sex, younger age, diagnosis of severe depressive disorder with or without psychotic symptoms, BD-II/NOS, diagnosis of comorbid AUD, MSI-BPD scores, and TADS physical abuse scores.

To examine differences in predictors between the lifetime suicidal ideation group and the two lifetime suicide attempter groups, the multivariable multinominal regression models were repeated by setting the lifetime suicidal ideation without suicide attempt group as a reference category. In these models, there were no statistically significant variables for a single lifetime suicide attempt. For lifetime repeated suicide attempts, significant variables were age ($\beta = -0.030$, standard error [S.E.] 0.015, $p = 0.043$), diagnosis of severe depressive disorder with psychotic symptoms ($\beta = 1.907$, S.E. 0.808, $p = 0.018$), diagnosis of BD-I ($\beta = 2.038$, S.E. 0.730, $p = 0.005$), diagnosis of comorbid AUD ($\beta = 1.549$, S.E. 0.414, $p < 0.001$), and MSI-BPD scores ($\beta = 0.253$, S.E. 0.085, $p = 0.003$). Female sex remained narrowly outside the statistical significance level ($\beta = 0.792$, S.E. 0.411, $p = 0.054$).

The effect of the ECR-R anxious and avoidant scores in the multivariable multinominal regression models was examined in a subsample of 221 participants with a complete dataset (23% missing data largely because participants living alone disclosed no lifetime intimate relationship in adulthood). Due to lower numbers and more variables, some statistical power was lost. The BD-II/NOS category was no longer statistically significant in predicting lifetime suicidal ideation without attempts, and neither was the MSI-BPD score for the single lifetime suicide attempt category. The included ECR-R anxious scores in the models showed positive, but statistically non-significant, adjusted effects with the lifetime repeated suicide attempts group ($\beta = 0.364$, S.E. 0.195, $p = 0.062$).

Table 7 Adjusted effects of multiple domains of risk factors in multivariable multinomial regression models for different types of lifetime suicidal behavior.

Variable	No suicidal behavior	Lifetime suicidal ideation only				Single lifetime suicide attempt				Recurrent lifetime suicide attempts			
		β	OR	OR 95% CI	S.E.	Wald χ ²	p	β	OR	OR 95% CI	S.E.	Wald χ ²	p
Women	1.0	0.31	1.36	0.58 - 3.19	0.44	0.50	0.479	0.68	1.97	0.78 - 5.23	0.50	1.82	0.177
Age, years	1.0	-0.04	0.96	0.93 - 0.99	0.02	5.52	0.019*	-0.02	0.98	0.95 - 1.01	0.02	1.51	0.219
Severe DD with psychotic symptoms	1.0	1.76	5.80	0.76 - 44.41	1.04	2.87	0.090	0.87	2.38	0.17 - 33.66	1.35	0.41	0.520
Severe DD without psychotic symptoms	1.0	1.61	4.98	1.86 - 13.36	0.50	10.16	0.001***	1.54	4.68	1.55 - 14.13	0.56	7.49	0.006**
BD-I	1.0	-0.83	0.44	0.11 - 1.68	0.69	1.46	0.227	-0.41	0.67	0.16 - 2.71	0.72	0.32	0.570
BD-II or NOS	1.0	1.38	3.98	1.26 - 12.54	0.59	5.54	0.019*	1.15	3.15	0.88 - 11.37	0.65	3.09	0.079
Comorbid AUD _a	1.0	0.86	2.36	0.74 - 7.58	0.59	2.09	0.148	1.10	3.01	0.87 - 10.38	0.63	3.05	0.081
TADS physical abuse	1.0	0.15	1.17	1.01 - 1.34	0.07	4.48	0.034*	0.11	1.12	0.96 - 1.31	0.08	1.93	0.165
BHS	1.0	0.10	1.10	1.03 - 1.18	0.04	7.43	0.006**	0.05	1.05	0.97 - 1.13	0.04	1.37	0.241
MSI-BPD	1.0	0.14	1.15	0.96 - 1.38	0.09	2.20	0.138	0.27	1.31	1.07 - 1.60	0.12	6.55	0.011*

Lifetime principal clinical diagnoses based on the International Classification of Disease, 10th edition, Diagnostic Criteria for Research (ICD-10-DCR)

Bipolar Disorder classified according to the national guidelines into type I and type II disorders

_a diagnosis of alcohol harmful use or dependence

* significant at ≤ 0.05 level, ** significant at ≤ 0.01 level, *** significant at ≤ 0.001 level

Abbreviations: AUD = Alcohol Use Disorder, BD-I = Bipolar Disorder, type I, BD-II = Bipolar Disorder, type II, BHS = Beck Hopelessness Scale, DD = Depressive Disorder, MSI-BPD = McLean Screening Instrument for Borderline Personality Disorder, NOS = Not Otherwise Specified, S.E. = Standard Error, OR = Odds Ratio, TADS = Trauma and Distress Scale

5.2 Relationship between childhood maltreatment and suicidal behavior (Study II)

The direct effects of TADS and the mediated effects via MSI-BPD scores on three lifetime suicidal behavior outcomes (lifetime suicidal ideation excluding suicide attempts, lifetime suicidal ideation and/or suicide attempt, and lifetime suicide attempt) are illustrated in Figure 2.

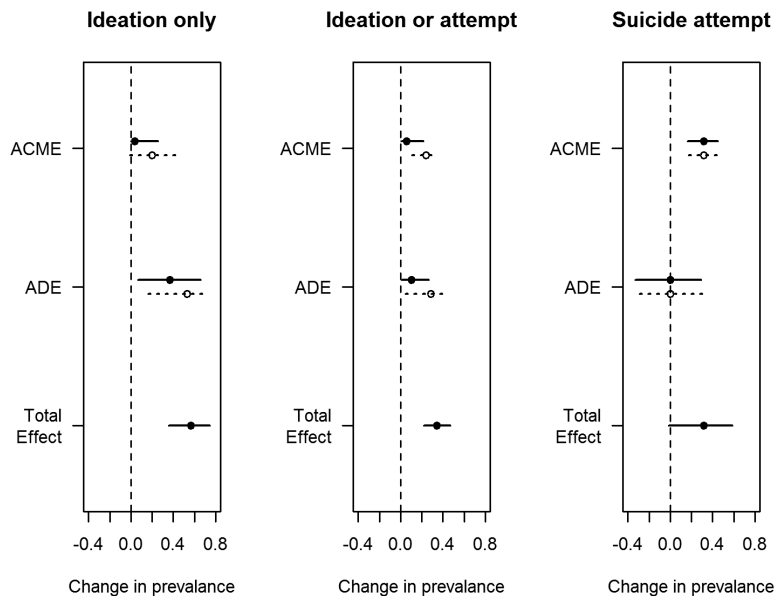


Figure 2 Mediation of the Trauma and Distress Scale (TADS) effects on lifetime suicidal behavior by borderline personality disorder traits (MSI-BPD). Abbreviations: ACME = Average Causal Mediation Effect; ADE = Average Direct Effect; Total Effect = ACME + ADE. ACME and ADE are depicted both for maximal TADS score (dots; answer 4 on all items) and minimum TADS score (circles; no trauma or distress). Confidence intervals (95%) depicted by whiskers. Reproduced with permission from Elsevier (doi:10.1016/j.eurpsy.2017.03.011).

Of the total effect of TADS on suicide attempt outcome, 99.7% was mediated via MSI-BPD scores. Of the total effect of TADS on suicidal ideation outcome, by contrast, only 21.2% was mediated via MSI-BPD scores. The respective proportion for ideation and/or attempt outcome was 43.3%. The formal random permutation tests showed no significant differences in total effect of TADS on suicidal behavior outcomes between lifetime ideation and lifetime suicide attempt outcomes ($p = 0.379$). However, the MSI-BPD scores mediated substantially more of the effect of TADS on suicide attempts than on suicide ideation (ACME was greater for suicide attempts than for suicidal

ideation, $p = 0.002$). Conversely, the effects of TADS on suicide ideation outcome showed mainly effects unmediated by MSI-BPD scores (ADE was smaller for suicide attempts than for suicidal ideation, $p = 0.003$). The differences in estimates for proportion mediated by MSI-BPD indicated only a trend ($p = 0.195$) because of the joint influence of uncertainty in both ACME and ADE. The similar divergence in mediation statistics between suicidal ideation and suicide attempt outcomes was detected in both patients with depressive disorders and patients with BD, although the estimates were more imprecise due to small sample sizes in these stratified analyses. In the mediation model, no interaction was detected regarding BD diagnosis and other variables.

The proportion-mediated estimates, ADE, and ACME of the effect of TADS via MSI-BPD on suicidal behavior outcomes and their sensitivity analyses are presented in Table 8.

Table 8 Mediation analyses of the impact of childhood maltreatment on lifetime suicidal behavior via borderline personality disorder traits.

		Mediated	ACME	ADE
Adjusting variables		Estimate	Estimate	Estimate
Suicidal ideation only	Gender and age (baseline)	21%	0.120	0.441
	Gender, age, parental psychiatric disorder	21%	0.123	0.467
	Gender, age, parental substance abuse	23 %	0.135	0.452
Suicidal ideation, or suicide attempt	Gender and age	43%	0.149	0.195
	Gender, age, parental psychiatric disorder	41%	0.147	0.208
	Gender, age, parental substance abuse	42 %	0.158	0.217
Suicide attempt	Gender and age	100%	0.316	0.001
	Gender, age, parental psychiatric disorder	97%	0.321	0.011
	Gender, age, parental substance abuse	90 %	0.331	0.036

Abbreviations: ACME = Average Causal Mediation Effect; ADE = Average Direct Effect

Controlling for BDI had a negligible effect on the mediation estimates of the TADS on suicide attempt by MSI-BPD (adjusted proportion-mediated 100%, ACME 0.24, and ADE 0.00). Adjustments for maternal and paternal mental problems including their interaction had marginal effects on the mediation estimates.

The results of the mediation models using the three subcomponents derived from the MSI-BPD (“affective”, “interpersonal”, and “behavioral/cognitive”) yielded similar results to the models using the total score of MSI-BPD (original Study II, Figure 2). Permutation tests revealed that the ACME for suicide attempt outcome was stronger for the “behavioral/cognitive” subcomponent than for the “interpersonal”

subcomponent ($p = 0.006$), whereas ADE showed no differences ($p = 0.978$). The mediation estimates of TADS on suicide attempt outcome by “affective” or “behavioral/cognitive” subcomponents showed no statistically significant differences.

5.3 Risk of suicide (Studies III and IV)

5.3.1 Risk of suicide after first hospitalization up to 24 years

By the end of the follow-up, altogether 15 063 patients of this national cohort of first-hospitalized patients for depression died, 2587 (17%) of whom died due to suicide (1609 men, 978 women). The overall cumulative risk of suicide was estimated at 6.13% (95% CI 5.80-6.46%), being higher (8.64%) in men (95% CI 8.00-9.27%) and lower (4.14%) in women (95% CI 3.83-4.45%). When deaths by other causes during the follow-up were considered as competing risks, the overall cumulative probability of dying by suicide was 5.6% (95% CI 5.3-5.9%) (men 7.7% [95% CI 7.2-8.2%] and women 3.9% [95% CI 3.6-4.3%]). At the time of suicide, the mean age in men was 46.2 years (SD 13.9) and in women 48.4 years (SD 14.7) (overall 47.0 years; SD 14.3).

The suicide incidence rate within three years post-discharge was in men over the first 12 months 23.05 per 1000 person-years (95% CI 21.20-25.02), over 12 to 24 months 8.84 per 1000 person-years (95% CI 7.69-10.10), and over 24 to 36 months 6.12 per 1000 person-years (95% CI 5.17-7.20). The corresponding suicide incidence rates in women were over the first 12 months 9.73 per 1000 person-years (95% CI 8.68-10.87), over 12 to 24 months 3.82 per 1000 person-years (95% CI 3.17-4.57), and over 24 to 36 months 3.19 per 1000 person-years (95% CI 2.60-3.88).

Figure 3 depicts the temporal patterns of not dying by suicide after discharge during the maximum 24-year follow-up.

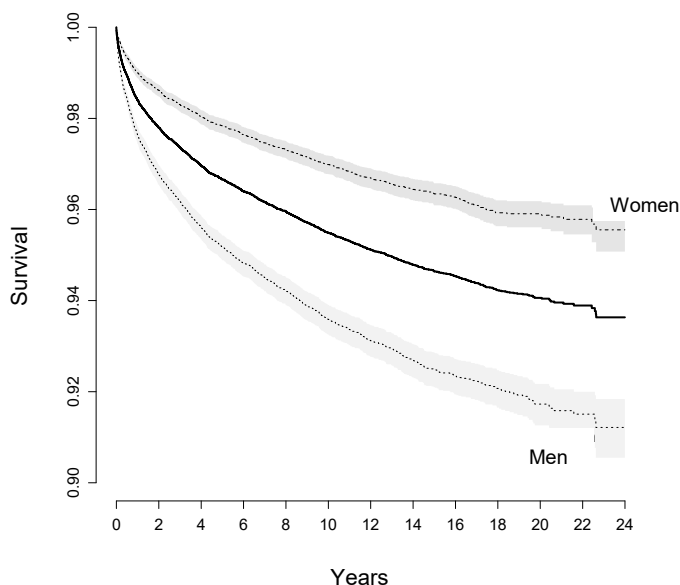


Figure 3 Cumulative probability of not dying by suicide in men and women after first lifetime psychiatric hospitalization for depression followed for a maximum of 24 years.

5.3.2 Temporal trends in risk for suicide in 1991-2014 (Study III)

The temporal patterns for risk of suicide among consecutive five-year cohorts by admission year with appropriate lengths of follow-up are plotted in Figure 4. Relative to the cohort of 1991-1995, the HR for risk of suicide within three years post-discharge declined consistently among successive cohorts and was reduced among the cohort of 2006-2011 to 0.48 (95% CI 0.42-0.56) (Table 9).

Table 9 Age- and sex-adjusted hazard ratios for suicide for consecutive cohorts by admission year after first lifetime psychiatric hospitalization for depression in Finland between 1991 and 2011.

Period	3 years postdischarge ^a			Maximum 24-year follow-up ^b		
	HR	95% CI	p	HR	95% CI	p
1991-1995	1.0			1.0		
1996-2000	0.69	0.61 - 0.79	<0.0001	0.70	0.63 - 0.77	<0.0001
2001-2005	0.54	0.47 - 0.63	<0.0001	0.57	0.51 - 0.64	<0.0001
2006-2011	0.48	0.42 - 0.56	<0.0001	0.49	0.43 - 0.55	<0.0001

Abbreviations: HR = hazard ratio, CI = confidence interval, p = p-value

^a equal length of individual follow-ups, ^b varying length of individual follow-ups
significant findings in boldface

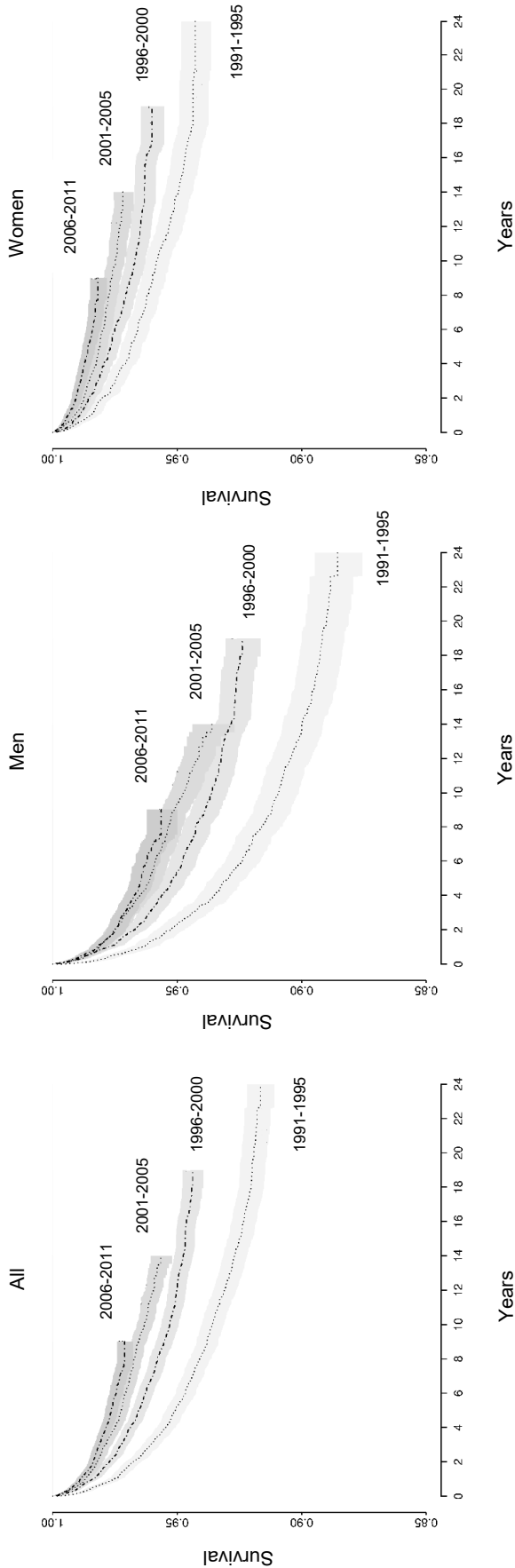


Figure 4 Cumulative probability of not dying by suicide for all patients and for men and women separately in consecutive cohorts by admission year after first lifetime psychiatric hospitalization for depression with varying lengths of follow-up.

5.4 Risk factors for suicide after first hospitalization (Study IV)

Tables 10 and 11 present the age-only adjusted and multivariable-adjusted models, respectively, for proportional hazards of suicide for all patients and for men and women separately.

Table 10 Age-adjusted hazard ratios of individual variables for suicide among first-hospitalized patients for depression followed for 628 514 person-years.^a

Characteristic	All (N = 56 826)			Men (n = 25 188)			Women (n = 31 638)		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Men	2.097	1.936-2.271	<0.0001	-			-		
Depression severity									
Moderate ^b	1.0			1.0			1.0		
Severe	1.187	1.083-1.302	0.0003	1.231	1.099-1.382	0.0004	1.103	0.948-1.285	n.s.
Psychotic	1.375	1.235-1.532	<0.0001	1.406	1.223-1.617	<0.0001	1.317	1.112-1.561	0.001
Alcohol-dependent	1.263	1.134-1.408	<0.0001	1.146	1.010-1.301	0.035	1.695	1.383-2.077	<0.0001
Suicide attempt ^c									
At admission	2.308	2.040-2.610	<0.0001	2.205	1.878-2.589	<0.0001	2.450	2.021-2.971	<0.0001
Over the past 4 years	2.331	2.043-2.659	<0.0001	2.323	1.966-2.746	<0.0001	2.332	1.881-2.890	<0.0001
Education level									
Basic ^d	1.0			1.0			1.0		
Upper secondary	1.165	1.066-1.273	0.0007	1.148	1.029-1.281	0.014	1.191	1.026-1.384	0.022
Tertiary ^e	1.355	1.219-1.505	<0.0001	1.179	1.025-1.356	0.022	1.615	1.372-1.901	<0.0001
Family income level									
Lowest third	1.0			1.0			1.0		
Middle third	1.062	0.960-1.175	n.s.	1.036	0.910-1.180	n.s.	1.095	0.932-1.287	n.s.
Highest third	1.229	1.109-1.363	<0.0001	1.156	1.013-1.319	0.031	1.348	1.143-1.590	0.0004
Lives alone	1.092	1.002-1.190	0.044	1.144	1.027-1.274	0.014	1.031	0.893-1.190	n.s.
Marital status									
Not married	1.0			1.0			1.0		
Married	1.056	0.956-1.167	n.s.	0.990	0.873-1.124	n.s.	1.165	0.987-1.374	n.s.
Divorced	1.084	0.958-1.227	n.s.	0.976	0.831-1.146	n.s.	1.270	1.041-1.549	0.019
Widowed	0.794	0.629-1.000	n.s.	0.924	0.646-1.322	n.s.	0.819	0.597-1.123	n.s.
Children 0-7 years old ^f	1.006	0.996-1.016	n.s.	1.013	1.001-1.025	0.035	0.995	0.979-1.012	n.s.
Employment status									
Employed	1.0			1.0			1.0		
Unemployed	0.981	0.877-1.097	n.s.	1.000	0.874-1.145	n.s.	0.949	0.778-1.158	n.s.
Studying	0.884	0.754-1.036	n.s.	0.851	0.687-1.053	n.s.	0.925	0.729-1.174	n.s.
Pension ^g	0.834	0.736-0.945	0.004	0.861	0.736-1.007	n.s.	0.800	0.650-0.984	0.035
Conscript	0.291	0.109-0.778	0.014	0.302	0.113-0.811	0.017	-	-	-
Unemployment pension	1.024	0.654-1.603	n.s.	1.323	0.773-2.264	n.s.	0.665	0.294-1.502	n.s.
Out of labor force (other)	0.796	0.679-0.934	0.005	0.774	0.626-0.956	0.018	0.824	0.645-1.049	n.s.
GAS value									
0 - 47	1.0			1.0			1.0		
47 - 63	0.919	0.815-1.038	n.s.	0.906	0.775-1.060	n.s.	0.948	0.783-1.147	n.s.
63 - 100	0.825	0.721-0.943	0.005	0.897	0.756-1.064	n.s.	0.719	0.579-0.893	0.003
Missing data ^h	1.060	0.873-1.286	n.s.	1.135	0.882-1.460	n.s.	0.965	0.713-1.305	n.s.

Table 10 (continued)

Admission status									
Voluntary	1.0			1.0			1.0		
Involuntary	1.316	1.172-1.478	<0.0001	1.195	1.028-1.390	0.020	1.531	1.275-1.838	<0.0001
Missing data ^g	1.087	0.920-1.302	n.s.	1.046	0.830-1.319	n.s.	1.165	0.876-1.550	n.s.

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, FHDR = Finnish Hospital Discharge Register, p = p-value, n.s. = not significant

^a adjusted only for age (and sex); stratified over baseline admission year

^b includes all other types of depression (from mild to moderate, partial remissions, other specified, and unspecified)

^c subcategories mutually exclusive, individuals may have been categorized in both.

^d contains missing information.

^e consists of lowest level tertiary education or higher.

^f for those living in family.

^g includes disability pension, occupational pension, and old age pension

^h before 1994, when psychiatric care-specific additional information notifications were established in the FHDR.

Table 11 Adjusted hazard ratios for suicide among first-hospitalized patients for depression followed for 628 514 person-years.^a

Characteristic	All (N = 56 826)			Men (n = 25 188)			Women (n = 31 638)		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Men	2.069	1.908-2.243	<0.0001	-			-		
Depression severity									
Moderate ^b	1.0			1.0			1.0		
Severe	1.188	1.083-1.303	0.0003	1.230	1.095-1.382	0.0005	1.115	0.956-1.299	n.s.
Psychotic	1.451	1.301-1.619	<0.0001	1.470	1.276-1.694	<0.0001	1.423	1.198-1.692	<0.0001
Alcohol-dependent	1.261	1.129-1.409	<0.0001	1.147	1.008-1.306	0.038	1.647	1.338-2.026	<0.0001
Suicide attempt ^c									
At admission	2.110	1.862-2.391	<0.0001	2.000	1.700-2.355	<0.0001	2.248	1.849-2.733	<0.0001
Over the past 4 years	2.111	1.845-2.415	<0.0001	2.116	1.783-2.510	<0.0001	2.083	1.673-2.592	<0.0001
Education level									
Basic	1.0			1.0			1.0		
Upper secondary	1.147	1.049-1.253	0.003	1.128	1.010-1.260	0.032	1.177	1.013-1.369	0.034
Tertiary ^{d **}	1.295	1.160-1.445	<0.0001	1.137	0.984-1.315	n.s.	1.536	1.295-1.823	<0.0001
Family income level									
Lowest third	1.0			1.0			1.0		
Middle third	1.065	0.961-1.180	n.s.	1.060	0.929-1.210	n.s.	1.059	0.899-1.248	n.s.
Highest third	1.191	1.068-1.329	0.002	1.169	1.018-1.343	0.027	1.207	1.011-1.442	0.038
Lives alone	1.124	1.029-1.227	0.009	1.165	1.044-1.301	0.007	1.069	0.923-1.238	n.s.

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, p = p-value, n.s. = not significant

^a adjusted for each other and age; stratified over baseline admission year

^b all other types of depression (from mild to moderate, partial remissions, other specified, and unspecified)

^c subcategories mutually exclusive, individuals may have been categorized in both.

^d consists of lowest level tertiary education or higher.

5.4.1 Risk of suicide among previous suicide attempters

The overall cumulative probability of suicide among those with previous suicide attempts was 15.4% (95% CI 13.7-17.3%) in men (suicide attempts at admission 15.5%; 95% CI 13.2-17.9%; and during the previous four years 16.0%; 95% CI 13.5-18.6%) and 8.5% (95% CI 7.3-9.7%) in women (suicide attempts at admission 8.4%; 95% CI 6.9-10.0%; and during the previous four years 8.8%; 95% CI 7.1-10.7%). Of those suicide attempters who died by suicide, about three in five died during five years since discharge (cumulative probability 9.7% in men and 5.0% in women).

The cumulative probability of not dying by suicide during the follow-up in men and women with previous suicide attempts is depicted in Figure 5.

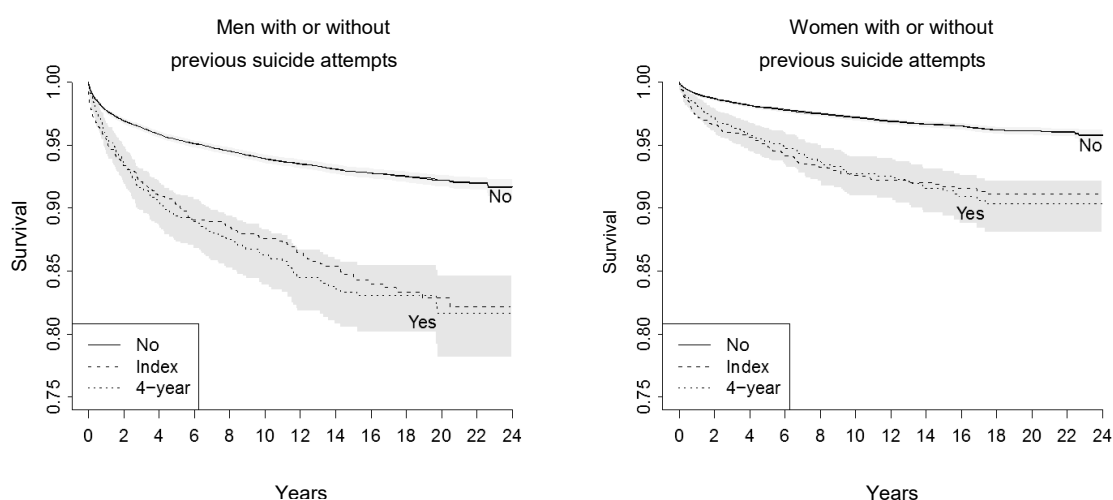


Figure 5 Cumulative probability of not dying by suicide after a suicide attempt, either during the previous four years or at the index (baseline) episode, in men and women after first hospitalization for depression followed for up to 24 years.

5.4.2 Gender differences in risk factors

Risk factors for suicide showed mainly similarities between genders. However, a diagnosis of comorbid alcohol dependence was a stronger risk factor in women than in men (gender interaction term, $p = 0.002$). Having a tertiary level education elevated the risk of suicide only in women (gender interaction, $p = 0.01$), and having young children in the family elevated the risk of suicide only in men (gender interaction, $p = 0.03$). In addition, admission type showed a partial gender interaction, as involuntary admission appeared to be a stronger risk factor in women than in men (gender interaction, $p = 0.11$; pairwise interaction, $p = 0.046$). Previous suicide attempts and family income showed the least gender differences.

5.4.3 Gender differences in methods of suicide

The methods of suicide in men and women are shown in Table 12. Compared with women, men died more often by potentially more lethal methods of suicide.

Table 12 Methods of suicide in men and women (n = 2587) who died by suicide after first hospitalization for depression over a maximum follow-up period of 24 years.

Method of suicide	Men (n = 1609)		Women (n = 978)	
	n	%	n	%
By exposure to gases*	74	4.6	8	0.8
By hanging, strangulation, or suffocation*	540	33.6	192	19.6
By drowning*	77	4.8	115	11.8
By firearms or explosives*	193	12.0	19	1.9
By jumping from a high place	73	4.5	54	5.5
By sharp object	42	2.6	15	1.5
By self-poisoning*	475	29.5	495	50.6
By crashing or throwing oneself before moving object	105	6.5	72	7.4
By other methods or sequelae of self-harm	30	1.9	8	0.8

$\chi^2 = 265.7$; df 8; $p < 0.0001$.

* Statistically significant ($\alpha < 0.0001$) difference in relative frequency between men and women (z-test)

By exposure to gases: DSM-III-R codes E951* and E952*; ICD-10 code X67

By hanging, strangulation, or suffocation: DSM-III-R code E953*; ICD-10 code X70

By drowning: DSM-III-R code E954*; ICD-10 code X71

By firearms or explosives: DSM-III-R code E955*; ICD-10 codes X72-X75

By jumping from a high place: DSM-III-R code E957*; ICD-10 code X80

By sharp object: DSM-III-R code E956*; ICD-10 code X78

By self-poisoning: DSM-III-R code E950*; ICD-10 codes X60-X66, X68-X69

By crashing or throwing oneself before moving object: DSM-III-R codes E959A, E959B, and E959C; ICD-10 codes X81-X82

By other methods or sequelae of self-harm: DSM-III-R code E959X; ICD-10 codes X76, X77, X79, X83-X84, Y870, and Z915

6 Discussion

6.1 Main findings

This study investigated a continuum of suicidal behavior and pertinent risk factors among patients with depressive disorder or BD in Finnish psychiatric care. The two HUPC studies (Studies I and II) investigated lifetime suicidal behavior among secondary care patients (N=287) with depressive disorder or BD. The main objective was to investigate the specificity, comparative strength, and mutual mechanisms of a comprehensive array of putative risk factors for suicidal ideation and attempts. Studies III and IV followed a Finnish population-based cohort of 56 826 first-hospitalized patients due to depressive disorder in 1991-2011 up to a maximum of 24 years. The main objective was to elucidate the long-term risk of suicide, including its temporal trends and risk factors.

In the HUPC cohort (Study I), the lifetime prevalence of suicidal behavior was 78.4% (33.8% suicidal ideation without attempts, 17.1% single lifetime suicide attempt, and 27.5% repeated suicide attempts). Lifetime suicidal ideation or attempts were correlated in univariate analyses with multiple factors including CM, personality and psychological traits, and current and lifetime clinical characteristics and symptoms. The independence of the effects of variables was then examined by multivariate models: a) lifetime suicidal ideation without attempts was associated with younger age, lifetime diagnosis of severe depressive disorder without psychotic symptoms, lifetime diagnosis of BD-II, current hopelessness, and childhood physical abuse, b) single suicide attempt was associated with lifetime diagnosis of severe depressive disorder without psychotic symptoms and BPD traits, and c) repeated suicide attempts were independently associated with female sex, younger age, and severe depressive disorder with or without psychotic symptoms, lifetime diagnosis of BD-II, lifetime AUD, BPD traits, and childhood physical abuse.

In the HUPC data (Study II), the mechanisms of the association between CM and suicidal behavior were further investigated. The total effect of CM on lifetime suicidal ideation without attempts or lifetime suicide attempts was of the same magnitude. However, according to formal mediation analyses, BPD traits mediated 100% of the total effect of CM on suicide attempts, but only 21% of the total effect on lifetime suicidal ideation without suicide attempts. This difference in mediation effects via BPD traits on different suicidal behavior outcomes was statistically significant.

Based on national registers (Study III), the overall cumulative risk of suicide was 6.1% among first-hospitalized patients for depression in Finland in 1991-2011 who were followed up to 24 years. The cumulative risk of suicide was over two-fold higher in men (8.6%) than in women (4.1%). Between

those hospitalized in 1991-1995 and in 2006-2011, the risk of suicide declined to one-half (HR 0.49) during the study period.

Long-term risk for suicide among first-hospitalized patients for depression (Study IV) was highest, with an adjusted risk of over two-fold, in men and among previous suicide attempters. Among those with previous suicide attempts, the cumulative probability of suicide was 15.4% in men and 8.5% in women. Suicides were predicted by severe depression, psychotic depression, comorbid alcohol dependence, higher education, high family income, and living alone. Gender differences in risk factors were modest. However, men died markedly more often than women by potentially more lethal methods.

6.2 Lifetime prevalence of suicidal ideation and suicide attempts (Study I)

Of the patients with depressive disorder or BD in the HUPC cohort, 78% reported lifetime suicidal behavior. The lifetime rate for suicidal ideation without attempts was 34% and for suicide attempts 45%. Of those with suicide attempts, 62% had attempted suicide twice or more. These rates are comparable to the rates found in previous secondary care screening-based cohorts from the area (Sokero et al., 2003; Valtonen et al., 2005). In the VDS, 61% of the participants with an MDD described suicidal ideation during the index episode, and 15% had attempted suicide (Sokero et al., 2003). No lifetime prevalence rates were presented in the study. In the JoBS, 80% of the participants with BD reported lifetime suicidal behavior. Of the BD participants, 77% reported lifetime suicidal ideation and 51% had attempted suicide (Valtonen et al., 2005). By the five-year follow-up of the JoBS, 57% of the BD cohort had a lifetime suicide attempt (Pallaskorpi et al., 2017).

6.3 Explanatory factors for lifetime suicidal ideation and suicide attempts (Study I)

Consistent with previous research (Schaffer et al., 2015a; Turecki & Brent, 2016), univariate analyses revealed suicidal ideation and suicide attempts to be associated with numerous factors from multiple domains, including developmental factors, personality and psychological traits, and clinical characteristics. Developmental factors comprised abusive emotional, physical, and sexual early experiences. Personality or psychological traits that were associated with suicidal behavior included neuroticism, anxious adult attachment style, self-efficacy, impulsivity, BPD traits, and schizotypal personality disorder traits. Temporally proximal clinical factors associated with suicidal behavior included lifetime principal mood disorder diagnoses, comorbidity with AUD or BPD, retrospectively rated lifetime most severe

depressive and anxiety symptoms, psychotic-like experiences, current severity of depressive and anxiety symptoms, hopelessness, recent alcohol and benzodiazepine use, and psychiatric hospitalizations.

Outcomes of suicidal ideation and suicide attempts were specifically examined in non-overlapping categories in multivariate models. Lifetime suicidal ideation without attempts were independently associated with younger age, principal diagnoses of severe depressive disorder without psychotic symptoms or BD-II, hopelessness, and childhood physical abuse. These findings are in accordance with previous studies, which have also observed younger age, more severe depression, and hopelessness to correlate with suicidal ideation (Sokero et al., 2003; Valtonen et al., 2005; Vuorilehto et al., 2006; Keilp et al., 2012; Riihimäki et al., 2014a; Ribeiro et al., 2018). Overall, the findings are consistent with the concept of depression, hopelessness, and suicidal ideation having shared constructs (Shahar et al., 2006). Hopelessness and suicidal ideation also vary longitudinally according to levels of depressive symptoms (Sokero et al., 2006; Baryshnikov et al., 2018; Keilp et al., 2018). However, despite the strong connection, other factors are likely to exist because not all patients with severe depression have suicidal ideation (Uebelacker et al., 2010; Riihimäki et al., 2014a). A recent systematic review and meta-analysis showed that CM is associated with suicidal ideation in heterogeneous samples, but literature concerning specifically depressive disorders and particularly BD was limited (Angelakis et al., 2019). Hence, the results of this study are consistent with the general evidence-base and show that CM is associated with suicidal ideation in a clinical cohort of patients with depressive disorder or BD.

Multivariate models for lifetime suicide attempts revealed independent associations with female gender, younger age, principal diagnosis of severe depressive disorder with and without psychotic symptoms, BD-II, AUD, BPD traits, and childhood physical abuse. The evidence for women and young people being over-represented among suicide attempters in mood disorders has been well-established (Isometsä, 2014; Schaffer et al., 2015b). However, a recent meta-analysis of MDD cohorts surprisingly found no gender differences in rates (Dong et al., 2018). In this study, psychotic depression was associated with the highest adjusted odds (>39) for suicide attempts. The relative risk between psychotic and non-psychotic depression for suicide attempts has long been debated. Recently, a meta-analysis found evidence for higher risk in psychotic depression than in non-psychotic depression (Gournellis et al., 2018). Severity of depression is associated with persistent course of depression, both of which increase the risk of suicide attempts (Oquendo et al., 2006; Holma et al., 2008; Holma et al., 2010; Riihimäki et al., 2014a). The finding that BD-I was inversely associated with lifetime suicidal ideation without attempts was slightly unexpected. Because the emergence of suicidal ideation is mostly associated with depressive morbidity, this finding may be explained by a some subgroup of BD-I participants having mainly manic course of illness. However, among suicide

ideators BD-I was strongly (adjusted odds >7) associated with suicide attempts, which may represent a novel finding. The findings concerning BD-I are nevertheless based on low numbers and require replication. However, the finding of BD-I strongly increasing the risk of a suicide attempt among suicide ideators is consistent with the results of the WMHSs and the hypothesis of mental disorders with poor impulse control being associated with suicide attempts (Nock et al., 2009). Characterized also by disinhibition, comorbid AUD (adjusted odds > 11) and BPD traits were strongly associated with multiple suicide attempts. By calculation, the adjusted odds among patients scoring seven or more in the MSI-BPD (however, suicidality item omitted) was over a 6.5-fold (1.307 raised to the seventh power) for belonging to the single suicide attempter group and over a 15-fold (1.478 raised to the seventh power) for the group of multiple suicide attempts. Similarly, BPD symptoms have been found to increase the suicide attempt rate ratio by 33% in a sample comprising mostly patients with depressive disorders (Stringer et al., 2013). Findings are also consistent with earlier results of repeated suicide attempts being associated with AUD (Lopez-Castroman et al., 2011) and BPD (Soloff et al., 2000; Garino et al., 2005).

Meta-analytic evidence demonstrates an association between CM and suicide attempts (Agnew-Blais & Danese, 2016; Angelakis et al., 2019). In this study, the effects of childhood physical abuse on suicidal ideation or suicide attempts were independent after controlling for clinical diagnoses, hopelessness, BPD traits, and comorbid AUD. Whether CM shows independent (Bruffaerts et al., 2010) or mainly mediated effects via mental disorders (Fergusson et al., 2000; Bebbington et al., 2009) on suicidal behavior remains a subject of investigation. CM has been significantly associated with severity and complicated course of depressive disorder and BD, (Nanni et al., 2012; Agnew-Blais & Danese, 2016), impulsive-aggressive traits (Brodsky et al., 2001), and affective lability in BD (Aas et al., 2017), which may also explain the association with suicidal ideation or suicide attempts.

6.4 Relationship between childhood maltreatment and suicidal behavior (Study II)

This study aimed to directly investigate the link between CM and suicidal behavior. Specifically, BPD traits were separately examined as a mediator for outcomes of suicidal ideation and suicide attempts. The main findings of the study are that while the total magnitude of CM on either lifetime suicidal ideation or suicide attempts is similar, the mediating processes may differ. The mediation effects via BPD traits on lifetime suicidal ideation were modest, but on lifetime suicide attempts they were substantial.

The study investigated more specifically whether BPD traits mediated the effect of CM on suicide attempts as a single construct or emphasized more

some of its affective, interpersonal, and cognitive/behavioral subcomponents. The results indicate that the mediating processes involve mainly BPD traits as a single construct, although the affective and cognitive/behavioral subcomponents may be somewhat more influential than the interpersonal.

The modest role of BPD traits in mediating the effects of CM on lifetime suicidal ideation is expected. The limited literature on suicidal ideation stresses mainly an association with depression and hopelessness (Sokero et al., 2003; Valtonen et al., 2005). In a single study of suicide attempters, hopelessness was found to mediate the effects of childhood sexual abuse on suicidal ideation (Spokas et al., 2009). More research on the mechanisms between CM and suicidal ideation is clearly needed.

The data showed that BPD traits mediated 100% of the effects of CM on lifetime suicide attempts. This mediation effect was not influenced by current depressive symptoms. The major role of BPD traits in mediation is in contrast to a previous study that found independent effects for CM controlling for BPD diagnosis among patients with MDD (Brodsky et al., 2001). However, that study controlled only for comorbid BPD diagnosis as a categorical variable, whereas this study modeled continuous self-reported traits, which may explain the differences. Since the publication of the results of this study, one small study (N=124) has provided supporting evidence among psychiatric adult outpatients (Bach & Fjeldsted, 2017). The study found that DSM-5 BPD symptoms mediated 67% and DSM-5 BPD traits 82% of the total effect of CM on level of suicidal risk. The limitation of the study is non-segregation of current suicide ideation and previous suicide attempts as outcome, but strengths include diagnostic assessment of BPD by structural interviews. In addition, another study among BD patients noted that the association between CM and suicidal attempts was mediated by affective lability (Aas et al., 2017), the phenotype of which may sometimes be difficult to distinguish from features of BPD. The mutual relationships between BD and BPD have long been debated (Bassett et al., 2017; Beraldi et al., 2018).

A cross-sectional study does not permit causal inferences, but the findings are congruent with what is previously known about one-to-one relationships between CM, BPD, and suicidal behavior. CM associates with suicide attempts (Agnew-Blais & Danese, 2016; Angelakis et al., 2019). Among patients with depression, CM has been associated with a diagnosis of comorbid BPD (Brodsky et al., 2001). In the HUPC data, a dose-response relationship exists between CM and BPD traits (Baryshnikov et al., 2017). According to longitudinal studies, children exposed to CM are at increased risk for BPD as adults (Johnson et al., 1999; Widom et al., 2009). The core phenotype of BPD involves impaired self-control and dysregulation of emotions (American Psychiatric Association, 2013). Transition from suicidal ideation to action is hypothesized to be in part influenced by impaired self-control (Nock et al., 2009). Further, BPD traits among patients with

depression (Stringer et al., 2013) and comorbid BPD in BD (Schaffer et al., 2015b) increase substantially the risk for suicide attempts.

However, interpretations should also take into consideration the complex relationships between CM, BPD, and suicidal behavior including possible confounding by impulsive-aggressive traits (Brodsky et al., 2001), hereditary factors (Berenz et al., 2013; Bornovalova et al., 2013), familial psychiatric disorders and substance use (Kessler et al., 2010). Familial transmission of suicidal behavior may be cotransmitted with, and mediated by, familial transmission of impulsive aggression and early abuse (Brent, 2010).

6.5 Risk of suicide and temporal trends (Study III)

A national cohort of 56 826 first-hospitalized patients for depression were followed up to 24 years (median 10.7 years). The observed cumulative risks of 8.6% in men and 4.1% in women for suicide are slightly higher than the cumulative incidences reported by a similar Danish study (Nordentoft et al., 2011). The differences may be explained by suicide mortality being higher in Finland than in Denmark, and the cohort of exclusively inpatients in Finland. Studies based on hospital data may overestimate the risk of suicide in depression by 33-57% (Crump et al., 2013). The incidence of suicide during the first year after discharge was considerably higher than the pooled one-year incidences of a recent meta-analysis of post-discharge suicides (Chung et al., 2017). As in this study, clinical studies report commonly a smaller gender ratio in risk relative to the general population. The discrepancy requires further clarification, but may be related to gender differences in comorbidities like SUDs and selection effect (Isometsä et al., 1994b; Arsenault-Lapierre et al., 2004).

During the study period from 1991 to 2014 the risk for suicide between the first (1991-1995) and last (2006-2011) hospitalized cohorts declined to one-half (HR 0.49). This downward trend was continuous throughout the period. This result is in sharp contrast to the findings of a recent meta-analysis (Chung et al., 2017), which reported higher rates since 1995. Post-discharge short-term risk of suicide has declined in Scandinavia (Qin et al., 2006; Pirkola et al., 2007; Madsen & Nordentoft, 2013), but rising risks have been reported in England (Kapur et al., 2013). In Finland, the long-term rise of suicide rates since 1940s peaked in 1990 and was approximately halved by 2014 (Official Statistics of Finland (OSF), 2018). The decline found in the study is not only congruous with this overall pattern, but shows that this decline has also occurred in a population of patients first hospitalized for depression, likely severe. Numerous ecological changes since 1990 may have either contributed to or opposed this trend. First, during the early phase of the study in 1992-1996 the national Suicide Prevention Project was implemented after a research stage. Second, between 1991 and 2014 the utilization of antidepressants has risen eight-fold (Organization for

Economic Co-operation and Development (OECD), 2017). Of antidepressants, about 59% are prescribed for depression (Sihvo et al., 2008). The Finnish psychological autopsy study in 1987-1988, a few years before the beginning of the study period here, found that roughly one in ten suicide decedents with MDD had received either adequate pharmacotherapy, weekly psychotherapy, or ECT prior to death (Isometsä et al., 1994b). The extent to which the increase in the use of antidepressants has contributed to the decline remains unknown, but ecological associations exist between the rise in the use of antidepressants and declining suicide mortality (Gusmao et al., 2013). Findings from Denmark indicate that risk of suicide has declined over the past decades at a population level among those who have been in mental health treatment, but not among those without such history (Erlangsen et al., 2017). Third, between 1990 and 2005, the consumption of alcohol per capita has risen, but since 2009 has been in a downtrend (National Institute for Health and Welfare, 2016b). Population-level consumption of alcohol has been found to be associated with national male suicide rates (Hintikka et al., 1999). Fourth, two economic downturns have occurred in the early 1990s and in 2008, with concurrently rising unemployment rates (Official Statistics Finland (OSF), 2018a, 2018b). Fifth, between 1993 and 2011, the number of psychiatric beds has diminished by 60% due to deinstitutionalization, equalling in 2011 the average of countries belonging to the Organisation for Economic Co-operation and Development (OECD) (71 per 100 000 vs. 70 per 100 000) (Organization for Economic Co-operation and Development (OECD), 2017). Between 1994 and 2011, the number of inpatient days of care per 1000 inhabitants halved, and the number of treated patients and hospitalizations per 1000 inhabitants reduced by 10% (National Institute for Health and Welfare). Despite shortening of the lengths of inpatient stays and a possibly elevated threshold for admission likely resulting in more severe patients being treated for shorter periods, long-term suicide mortality has declined. Lastly, contemporarily with the deinstitutionalization process, psychiatric outpatient care has become more available (National Institute for Health and Welfare, 2016a), and associations exist between outpatient-oriented care services and lower suicide mortality (Pirkola et al., 2009).

6.6 Risk factors for suicide (Study IV)

This hitherto largest longitudinal nationwide study examined a wider range of 13 putative risk factors for suicide in depression than before, providing also information on adjusted effects. A dose-response pattern was found for severity of depression with an added influence of psychotic depression for long-term risk for suicide. A previous study suggested similar findings, but was probably under-powered to observe significant differences (Kessing, 2004). The results here substantiate the previous limited meta-

analytic findings of severity of depression as risk factor for suicide in depression, which were based on less than 300 suicides (Hawton et al., 2013a). Moreover, the original studies included were apart from one small community-based study derived from samples of advanced age, only men, and psychological autopsy studies (retrospective study design). Since the Hawton et al. (2013a) meta-analysis, one large community-based study has found severity of depression measured by the Patient Health Questionnaire (PHQ-9) to predict suicide during the following month (Simon et al., 2016). Meta-analytic evidence indicates that psychotic symptoms in depression have an added influence on the risk for suicide attempts (Gournellis et al., 2018), but evidence has been lacking for suicides (Hawton et al., 2013a). Since the review, a recent Danish national study reported no difference in risk for suicide between severe psychotic and non-psychotic depression (Leadholm et al., 2014). However, the study may have had methodological constraints (individuals were allowed to belong to both groups and the design omitted censoring for other events). Earlier, a Finnish national study found psychotic depression to increase the risk for suicide after a suicide attempt compared with non-psychotic MDD (Suominen et al., 2009). According to other studies, severity of depression predicts recurrence and persistence of depression (Melartin et al., 2004; Holma et al., 2008) and severity of suicidal ideation (Riihimäki et al., 2014a), all of which may be more burdensome and severe in psychotic depression (Zalpur & Rothschild, 2016; Jääskeläinen et al., 2018). Like dose-response relationship, more time spent in more severe episodes could be a major determinant for suicide risk (Isometsä, 2014).

Alcohol dependence increased the risk for suicide by 26% during follow-up. Despite AUDs being commonly considered as a risk factor for suicide attempts in depression (Isometsä, 2014), not all studies have found such an association with suicides (Hoyer et al., 2004; Large et al., 2011). Based on limited data, the meta-analysis of Hawton et al. (2013a) estimated 2.5-fold higher odds for suicide related to alcohol misuse in depression. The findings have been recently confirmed by a large Danish register-based study of 72 530 patients with depression and a maximum 42-year follow-up, which reported an unadjusted two-fold higher risk associated with AUD (Ostergaard et al., 2017). Overall, the findings agree with those of the Finnish psychological autopsy study (Isometsä et al., 1994b), and that AUDs rank as the second most common mental disorder among suicide decedents (Cho et al., 2016).

Previous suicide attempts were associated with highest (over two-fold) risk for suicide. By the end of the follow-up, 15% of men and 8.5% of women with previous suicide attempts died by suicide. About 10% of men and 5% of women with previous suicide attempts died by suicide within five years of discharge. Previously, Suominen et al. (2009) longitudinally followed a national Finnish cohort of patients with MDE hospitalized for a suicide attempt for up to four years and reported an overall risk for suicide of 6%. Based on relatively limited pooled data, the Hawton et al. (2013a) meta-

analysis reported nearly five-fold higher odds associated with previous suicide attempts among patients with depression. Another meta-analysis of heterogeneous self-harm studies found a considerably lower risk (3.9%) within five years of the index attempt (Carroll et al., 2014). The discrepancies likely reflect differences in sample characteristics, lengths of follow-up, and potential lethality of methods and severity of intent of index attempts. Violent methods are known to be associated with very high risk of suicide in the short term (Runeson et al., 2010; Olfson et al., 2017). However, the majority (56-59%) of suicide decedents die in the first attempt, limiting the sensitivity as a risk marker (Isometsä & Lönqvist, 1998; Bostwick et al., 2016).

Factors associated with life situation were associated with long-term risk for suicide. Living alone, and unexpectedly, higher family income and higher educational level increased the risk. At the community level, suicides have conversely been associated with being unmarried, unemployment, sickness absence, low education and low income (Crump et al., 2014; Wang et al., 2015). However, two Danish nationwide longitudinal cohort studies of previously hospitalized patients with heterogeneous psychiatric disorders have found similar results as in this study. Madsen et al. (2013) found that higher education predicted suicide after discharge among psychiatric hospitalized patients who had attempted suicide during the previous year. Agerbo (2007) found in a first-hospitalized cohort of psychiatric patients that postgraduate education, employment, high income, and marriage were risk factors for suicide within five years after discharge. Moreover, this elevated risk was related to a subsequent loss of an intimate relationship, job, or income during the follow-up. An alternative hypothesis could include a survival bias among individuals with low socioeconomic status if those dying by suicide were less likely to be admitted at all due to marginalization. However, psychiatric secondary services in Finland receive funding through tax revenue providing more equal access to care regardless of socioeconomic status. The pooled evidence on living alone in depressive patients has been inconclusive (Hawton et al., 2013a). The results of this study substantiate the previously limited evidence base.

The large data enabled the first longitudinal investigation of gender differences in several risk factors for suicide in depression. Alongside gender differences in risk factors, gender differences in methods for suicide were compared. Comorbid alcohol dependence was a stronger risk factor among women than among men. Previously, Hintikka et al. (1999) reported that alcohol abuse was associated with higher risk for suicide attempt in women than in men, supporting the findings here. However, according to the Finnish psychological autopsy study of suicides in major depression (Isometsä et al., 1994b), compared with women, men had more often comorbid alcohol dependence and less often psychiatric hospitalizations. The data here showed higher risks among women with a high education level, whereas previous national studies have found low (Crump et al., 2014) or medium education

level, or unmarried status (Wang et al., 2015) being stronger risk factors in men than women. In contrast to the findings of Wang et al. (2015), the data here showed no evidence of gender differences related to previous suicide attempts. The magnitude of the effect of having small children on men at risk for suicide was negligible. In contrast to these modest gender differences in risk factors, gender differences in suicide methods were prominent. Congruent with the findings of the Finnish psychological autopsy studies (Isometsä & Lönnqvist, 1998; Pirkola et al., 2003), men died more often than women by potentially more lethal methods.

To what extent the findings are generalizable to patients with depression in primary or outpatient care settings is currently uncertain. The findings are, however, in accord with those of the Finnish psychological autopsy study (Isometsä et al., 1994b). Moreover, male sex, previous suicide attempts, more severe depression, and comorbid substance use have also been substantiated as risk factors in large cohorts including in- and outpatients (Nordentoft et al., 2011; Leadholm et al., 2014; Wang et al., 2015; Simon et al., 2016; Ostergaard et al., 2017). Information on living alone, education, and income specific to depression as risk factors for suicide is limited (Hawton et al., 2013a) but several studies indicate that the risk for suicide associated with socioeconomic factors may be inverse between inpatient and general population samples (Agerbo, 2007; Madsen et al., 2013; Crump et al., 2014). Otherwise, a recent very large study based on mental health or primary care records was able to predict suicide within 90 days with an accuracy of 0.86. The most significant predictors for suicide were similar in psychiatric secondary care and primary care (Simon et al., 2018). The findings therefore support the generalizability of the findings here.

6.7 Study strengths

6.7.1 Studies I and II

Among the main strengths of the HUPC study design are that the cohort is a random stratified sample of patients with depressive disorder or BD from psychiatric care in the Helsinki metropolitan area. In this representative clinical sample, the study investigated concurrently perhaps the most inclusive set of putative explanatory factors from multiple domains for suicidal behavior. Included were predisposing early life experiences, mediating or developmental traits, and proximal clinical characteristics as risk factors. A theoretically and clinically important distinction was made in identifying separately explanatory factors/mediators for suicidal ideation and suicide attempts. A sample of patients with depressive disorder or BD allows mutual comparison.

Most of the participants in the HUPC survey reported lifetime suicidal behavior. Data on explanatory variables were mainly based on continuous

ratings, increasing statistical sensitivity. For example, the TADS assesses exposure to gradually more severe childhood adverse experiences and rates the frequency of each. The TADS rates summary scores for overall severity of CM and for each subscale. The survey information on lifetime suicide attempts was complemented by examining all data in available medical records, increasing validity. The applied general approach to causal mediation in Study II is ideal for handling non-continuous outcome data such as lifetime suicide attempts.

6.7.2 Studies III and IV

This national two-part study of suicide and depression is presumably the largest of its kind to date. The cohort consists of all 56 826 Finnish first-hospitalized patients due to depression over the current treatment era in 1991-2011. The patients were longitudinally followed on the registers up to the end of the year 2014 (maximum 24 years). During this extended follow-up there were 2587 suicides.

The study first investigates temporal trends in risk for suicide in depression over a period when psychiatric treatment and organization of services have undergone major transformations. The results provide current estimations of cumulative risk for suicide after hospitalization for depression. The maximum follow-ups of previous studies on risk of suicide in depression have rarely exceeded 20 years (Ösby et al., 2001; Hoyer et al., 2004; Nordentoft et al., 2011).

This study investigated longitudinally a total of 13 putative risk factors for suicide in depression in a national cohort. The study responds to the considerable need for large-scale longitudinal studies on risk factors for suicide in depression (Hawton et al., 2013a) and provides longitudinal information on gender differences in several putative risk factors. By comparison, a recent meta-analysis (Hawton et al., 2013a) of risk factors for suicide in depression included three larger cohorts, none of which examined more than five putative factors. The data of this study also enabled investigation of adjusted effects. The meta-analysis included only one national sample (Hoyer et al., 2004) from a period in 1973-1993, largely before the current diagnostic and treatment era. The pooled evidence was mostly based on small case-control or cohort studies and rarely included more than a few hundred suicides per examined factor (Hawton et al., 2013a). The systematic review (Large et al., 2011) of risk factors for suicide after hospitalization for diverse psychiatric reasons was based on a total of 1544 suicides.

The data were based on Finnish high-quality national registers on hospitalizations and on census data. The diagnoses registered in the FHDR were made without knowledge of outcome. The Finnish identity codes provide accurate linking of register data at an individual level. A sound longitudinal investigation of suicides requires that complete information on

suicide mortality is available, as provided by the causes of death register. The high Finnish medicolegal death investigation standards result in reliable identification of suicides, leaving only a few undetermined deaths (Lunetta et al., 2007). Data on methods of suicide enable also consideration of pertinent gender differences.

6.8 Limitations

6.8.1 Studies I and II

Among the limitations of the HUPC study are that the cross-sectional and retrospective design is insufficient for making causal inferences and it is prone to unobserved confounding. The study aimed at a higher response rate than the 43% eventually obtained. As a result, it remains unknown whether the sample was susceptible to selection biases. However, the mean age and gender distribution of the sample did not statistically differ from all patients in the respective healthcare organizations with corresponding mood disorder diagnoses. The demographics also correspond to those of the previous screening-based representative cohorts of VDS and JoBS (Melartin et al., 2002; Mantere et al., 2004). The reasons for the lower-than-expected response rate may be manifold. Eligible patients were sampled from busy secondary care clinics and wards in everyday practice. Due to comprehensive assessments, the survey was time-consuming. Limited research staff resources led in a loss of some eligible participants. Some completed surveys were lost due to technical difficulties. If selection bias existed, the effect on findings on risk factors and their magnitude would be only to the degree these were different between participants and nonparticipants.

Of explanatory variables, the study diagnoses were based on clinical ICD-10-DCR diagnoses, which may have produced uncertainty in the accuracy or evaluation of severity of the diagnoses. Nonetheless, the diagnoses were made in psychiatric specialized care and the rationale was reviewed and specified if needed by the study physicians. All participants most likely had a mood disorder, but, for example, bipolar diagnoses are often underestimated due to a well-known delay in the diagnosis (Mantere et al., 2004). Some circularity may remain between study diagnoses and outcome variables if individuals with lifetime suicidal behavior were more likely to be diagnosed with more severe depression, BD-II, or AUD. The HUPC survey was based on self-reports and rating scales. Weaknesses in participants' self-reflection or recall biases may have produced inaccuracies (Atkinson et al., 1997). Known correlations between the MDQ and MSI-BPD scores exist in the data (Baryshnikov et al., 2015), which may have produced confounding between mood instability of BD and emotional dysregulation of BPD in these scales. Likewise, concurrent depressive symptoms may have inflated the predisposition to report BPD symptoms (Melartin et al., 2010). Attentional

biases related to depression or the propensity to seek explanations for difficulties may have resulted in retrospective recall biases in reports on childhood experiences. The validity of retrospective reports of childhood experiences has long been debated. Retrospective reports may identify more readily those with the most severe exposures or current comorbidities (Shaffer et al., 2008), and resilient individuals may underreport adversity (Hardt & Rutter, 2004). Concurrent depressive symptoms may influence whether adverse childhood experiences are reported (Colman et al., 2016). However, both prospective and retrospective study designs yield similar results on various outcomes, including risk of mental disorders (Scott et al., 2012). Retrospective reports are easy, time-saving, and cost-effective compared with decade-long follow-up studies and are therefore accepted with their limitations. The respondents' age at exposure to CM was not assessed in our survey. However, current research does not provide much support for the existence of sensitive periods for CM, of which effects appears to be mostly immediate and accumulating (Gomez et al., 2017; Dunn et al., 2018). Uncertainties in the lifetime suicidal behavior outcome variable include possible incomplete information on lifetime suicide attempts and lifetime suicide ideators may attempt suicide in the future.

The HUPC survey was extensive. Nevertheless some factors remained uninvestigated. These include well-known high-risk bipolar mixed and depressive mixed episodes (Pallaskorpi et al., 2017) and a possible role of agitated depression or depression with mixed specifier in unipolar depression (Tondo et al., 2018). Hostile or impulsive-aggressive traits were not covered and diagnostics on post-traumatic stress disorder as a potential outcome of CM were not available (Bentley et al., 2016). Participants had received treatment-as-usual, and its effect on results is unknown. Lastly, findings on suicide attempts may not generalize in a straightforward manner to suicides.

6.8.2 Studies III and IV

Among the limitations are that the FHDR does not provide detailed data on clinical characteristics of the patients. The diagnoses are based on routine clinical assessments in the everyday practice of different treatment units. Structural interview-based diagnostics would be preferable, but are unattainable for the very large-scale samples required for suicide research. Inaccuracies likely exist in assessments of severity of depression, in poorly recognized delusional hopelessness or guilt of psychotic depression, and in missing diagnoses of alcohol dependence. The lifetime course of depression and the clinical status at the time of suicide are not known. For the aforementioned reasons, the findings are likely underestimations of the actual effects. The cohort probably includes undiagnosed patients with BD. The information on previous suicide attempts was limited to those requiring somatic hospitalization and occurring within the previous four years. The

degree of suicide intent involved cannot be verified on the register data. As the attempts likely contributed to the physician's decision to admit the patient or the patient needed to be admitted due to somatic consequences, some degree of suicidal ideation at the time of the attempt can be assumed. The registers do not provide data on hopelessness, impulsive-aggressive traits, cluster B traits, or family history of suicide, which are considered risk factors for suicide (Hawton et al., 2013a; Isometsä, 2014). Sociodemographic information represents circumstances at the end of the previous year before baseline, and these circumstances, apart from the highest level of education if already attained at baseline, were mostly susceptible to change over a long-term follow-up.

A cohort of hospitalized patients likely consists of patients with the most severe clinical characteristics. The extent to which risk factors for suicide in depression in community-based, outpatient, and inpatient populations differ remains uncertain. However, the findings are consistent with the findings of general population studies. The follow-up did not take into account the possibility of migration, which may have inflated or biased risk estimations, but the effect is likely to be small (Nordentoft et al., 2011). In addition, 20 suicides in Study III were accidentally omitted during data management and analyses, but were included in Study IV. Patients with previous hospitalizations were excluded over a backward clearance period of 11-31 years. Some members of the cohort may have had hospitalizations even earlier, but this proportion is probably negligible because the interval between consecutive admissions in the FHDR data is longer than 11 years in 3% of the admissions, and longer than 21 years (median length of the clearance period) in 0.5% of consecutive admissions. The findings on cumulative risk of suicide and age at the time of suicide are lower-boundary estimations, as all cohort members were not followed until death. Treatment during inpatient stay and after discharge was treatment as usual, which may have had an effect on the findings. Regional differences in treatment exist in Finland (Pirkola et al., 2009), but whether gender differences in clinical practices or access to mental healthcare services contributed to the higher risk of suicide in men is unknown.

7 Conclusions

7.1 Conclusions and clinical implications

The results of the HUPC study reaffirm the high rate of suicidal behavior among patients with depressive disorder or BD in psychiatric secondary care. The main findings show that risk factors for suicidal ideation and suicide attempts display both differences and similarities, and there are both dose-response and qualitative patterns. Confirmed by the study, depressive morbidity and hopelessness are salient explanatory factors for suicidal ideation. A single suicide attempt was associated with severe depression and BPD traits. Patients who have repeatedly attempted suicide show more severe clinical characteristics and factors associated with impaired self-control such as BPD traits and AUD.

Both suicidal ideation and suicide attempts were associated with CM. The mediating mechanisms between the two outcomes appear to differ. The mechanisms between CM and suicidal ideation remained largely unexplained and warrant further studies. The results indicate that the effect of CM on suicide attempts may be substantially mediated through BPD traits.

Overall, the results of the HUPC study reveal that several factors, including early adversity, personality traits, and proximal clinical characteristics, are associated with suicidal behavior, but factors temporally closer to suicidal behavior have independent effects. Proximal clinical characteristics may provide meaningful targets for prevention of suicidal behavior among patients with depressive disorder or BD.

The long-term risk of suicide after first hospitalization for depression was estimated at 7.7-8.6% in men and 3.9-4.1% in women. The study is the first to show that the risk for suicide has declined among severely symptomatic inpatients similar to the overall pattern observed in the general population. The cumulative risk for suicide in depression demonstrates thus amenability for change over time and ecological transformations. The first post-discharge year was a particularly high-risk period for suicide. Improving post-discharge policies, long-term continuity of care, close monitoring, and active efforts are warranted for this population.

Long-term risk for suicide after discharge was predicted by more severe clinical characteristics, comorbid alcohol dependence, male gender, previous suicide attempts, higher socioeconomic status, and living alone. Hospitalized patients with previous suicide attempts form a particularly high-risk group. The effect of gender differences in risk factors appeared modest. Men died markedly more often by potentially more lethal methods for suicide than women. For risk of suicide, the weight of the influence of gender differences in choice of methods for suicide is difficult to establish for any study. However, the results of this study are consistent with men's choice of

potentially more lethal methods for a suicide attempt contributing to the gender disparity in risk of suicide.

Overall, the results provide up-to-date information on risk and risk factors for suicide among first-hospitalized patients for depression during the current treatment era. The study is the largest of its kind and substantiates the limited evidence base on risk factors. Findings of this national study are directly applicable to the Finnish healthcare system and treatment practices.

7.2 Implications for future research

While this investigation identified some differences and similarities in explanatory factors for suicidal ideation and suicide attempts, future studies should continue to work towards identifying novel additional factors contributing to these two outcomes. Differentiation of characteristics of individuals who have suicidal ideation and those who are in risk of acting on these thoughts continues to be the main research task in the field of suicidal behavior. In investigating novel risk factors for suicide, studies should control for the effect of known proximal clinical factors due to potential confounding associations. Literature on the complex relationships and mechanisms between distal, mediating, and proximal factors in risk for suicidal behavior is only just starting to emerge. Whether temporally more remote factors lead to, interact, or become activated by more proximal factors remains open for further studies (Malhi et al., 2018). Clearly, large prospective studies are needed to confirm the predictive potential of the findings of the HUPC study for different outcomes of suicidal behavior.

The finding of the substantial decline in risk for suicide among previously hospitalized patients for depression is encouraging, but the reasons for this change and the preventive measures that are the most effective remain obscure. The large disparity in risk for suicide between men and women in depression warrants further investigations. In addition, the gender disparity in risk for suicide in this clinical cohort appears to be less than that observed in the general population. Exposing the factors underlying this discrepancy could be an interesting research objective. The evidence base on risk factors for suicide in depression is still relatively limited, and more large-scale longitudinal studies are needed. The main methodological challenge continues to be addressing the time-dependent quality of putative risk factors. Risk factors can predict longer exposure to high-risk syndromal mood episodes through more persistent or relapsing course of depressive disorder or BD. Differentiating and clarifying the risk factors operating at the time of a mood episode should be an important aim for future studies. Finally, intervention studies are required to investigate the potential role of modifying factors identified by the study in prevention of suicidal behavior.

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