

SOCIAL DIFFERENTIALS IN THE OUTCOMES OF DEPRESSION

A LONGITUDINAL REGISTER STUDY

Heta Moustgaard

ACADEMIC DISSERTATION

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Department of Public Health
Faculty of Medicine
University of Helsinki

Department of Social Research
Faculty of Social Sciences
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ABSTRACT

Depression is a leading cause of disability worldwide. At worst, it may lead to frequent hospitalisation and even premature death. The risk of suicide is particularly high among the depressed. This study assessed whether social and economic resources protect depressed patients from psychiatric hospital admission and premature mortality. The study also aimed to establish the role of alcohol and the rapidly increased antidepressant treatment of depression in these outcomes. The study used large, longitudinal register samples of the Finnish adult population, combining information from various administrative registers. Depression was inferred from psychiatric hospital care and antidepressant purchases. Treatment and depression outcomes were assessed in 1-10-year follow-ups.

The results indicate that at least in a population already in contact with the healthcare system, antidepressant treatment and depression outcomes vary only modestly according to social factors. However, material aspects of socioeconomic position such as a low income, not owning a home and being unemployed increased the risk of hospital admission for depression by 2040 per cent among those with previous depression treatment, even after controlling for baseline depression severity and psychiatric comorbidity, whereas education and occupational social class were unrelated to admission risk. Having no partner and living without co-resident children also increased the admission risk. None of the social factors studied buffered against excess mortality among the depressed. Educational differences in the prevalence of antidepressant use before and after hospital care for depression were small and mostly limited to the period after discharge. Antidepressant use immediately after discharge was slightly less common among those with a low level of education, but educational differences increased thereafter as antidepressant use decreased more rapidly among this group. Differences in daily antidepressant use that met treatment guidelines were more pronounced than those for any antidepressant use, suggesting a need for improving treatment adequacy and adherence particularly among patients with a low level of education.

The study established the central role of excessive alcohol consumption as a pathway to depression mortality. Alcohol-related causes accounted for about half of the excess mortality of depressed men and around a third of depressed women. Improving the detection and management of substance use problems would thus be critical for reducing depression mortality. Increased antidepressant sales do not seem to have prevented female suicides. However, among men an increase in the proportion of antidepressant users receiving minimally adequate treatment reduced non-alcohol-related suicides. The results suggest that increased adequacy of antidepressant treatment has been more central in reducing suicide rates than the mere increase in per-capita antidepressant sales or prevalence of antidepressant use.

ABSTRAKTI

Masennus on yleinen mielenterveyden häiriö, joka vakavimmillaan vaatii sairaalahoitoa ja voi johtaa jopa ennenaikaiseen kuolemaan. Erityisesti itsemurhan riski on masentuneilla suuri. Tämän tutkimuksen tavoitteena oli selvittää, suojaavatko sosiaaliset ja taloudelliset resurssit, kuten korkea koulutus, korkeat tulot, työssäolo tai perhe, masennuspotilaita psykiatriseen sairaalahoitoon päätymiseltä ja ennenaikaiselta kuolemalta. Lisäksi tarkasteltiin, millainen merkitys yhtäältä alkoholinkäytöllä ja toisaalta nopeasti yleistyneellä masennuslääkkeiden käytöllä on masennuksen ennusteelle. Tutkimuksessa käytettiin laajoja rekisteriaineistoja, joissa masennus pääteltiin psykiatrisen sairaalahoidon ja masennuslääkkeiden käytön perusteella. Masentuneiden lääkkeiden käyttöä ja ennustetta tarkasteltiin 1-10 vuoden seurannassa.

Tutkimuksen perusteella väestöryhmien väliset erot masennuslääkehoidossa sekä masennuksen ennusteessa ovat vähäisiä ainakin jo masennuksen vuoksi hoidon piirissä olevilla. Puolison kanssa asuminen sekä materiaaliset resurssit, kuten korkeat tulot, omistusasuminen ja työssä olo kuitenkin suojasivat masennuspotilaita masennuksen vuoksi sairaalaan päätymiseltä. Sen sijaan korkea koulutus tai korkea ammattiasema eivät suojanneet sairaalahoitoon päätymiseltä. Mitkään tutkituista sosiaalisista ja taloudellisista resursseista eivät suojanneet masennuspotilaita ennenaikaiselta kuolemalta. Koulutusryhmien väliset erot masennuslääkkeiden käytössä ennen masennukseen saatua sairaalahoitoa ja sen jälkeen olivat pieniä ja rajoittuivat sairaalahoidon jälkeiseen aikaan. Lääkekäyttö oli hieman vähäisempää matalasti koulutetuilla heti sairaalajakson jälkeen, mutta erot kasvoivat seurannan aikana, sillä matalasti koulutetut lopettivat lääkekäytön nopeammin. Koulutusryhmien väliset erot korostuivat päivittäisessä, hoitosuosituksen mukaisessa lääkekäytössä. Tulosten perusteella olisi syytä kiinnittää huomiota etenkin matalasti koulutettujen masennuspotilaiden hoidon riittävyteen ja jatkuvuuteen.

Tutkimus osoitti, että alkoholinkäyttö on keskeinen syy masennuspotilaiden korkeaan kuolleisuuteen: miehillä masennuspotilaiden korkeammasta kuolleisuudesta noin puolet ja naisilla noin kolmannes johtui alkoholista. Päihdeongelmien havaitseminen ja hoito ovatkin tutkimuksen perusteella keskeisessä roolissa masennuspotilaiden kuolleisuuden ehkäisyssä. Masennuslääkkeiden käytön yleistymisen ei näytä ehkäisseen naisten itsemurhia. Miehillä hoidon keston vähimmäiskriteerit täyttävän masennuslääkehoidon yleistymisen näyttäisi kuitenkin ehkäisseen sellaisia itsemurhia, joissa uhrin alkoholipäihtymys ei ollut myötävaikuttavana tekijänä. Tulosten perusteella masennuslääkehoidon yleistymisen sinänsä ei näyttäisi ehkäisseen itsemurhia, vaan keskeistä on ollut kestoltaan riittävän hoidon yleistymisen.

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

- I Moustgaard, H., Joutsenniemi, K. & Martikainen, P. 2014. Does hospital admission risk for depression vary across social groups? A population-based register study of 231,629 middle-aged Finns. *Social Psychiatry and Psychiatric Epidemiology* 49, 1, 15–25.
- II Moustgaard, H., Joutsenniemi, K., Sihvo, S. & Martikainen, P. 2013. Alcohol-related deaths and social factors in depression mortality: a register-based follow-up of depressed in-patients and antidepressant users in Finland. *Journal of Affective Disorders* 148, 2–3, 278–285
- III Moustgaard, H., Joutsenniemi, K., Martikainen, P. 2014. A longitudinal study of educational differences in antidepressant use before and after hospital care for depression. Submitted.
- IV Moustgaard, H., Joutsenniemi, K., Myrskylä, M. & Martikainen, P. 2014. Antidepressant sales and the risk for alcohol-related and non-alcohol-related suicide in Finland — an individual-level population study. *PLoS One* 9, 6, e98405.

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ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical Classification System
AUD	Alcohol Use Disorder
BDI	Beck Depression Inventory
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
DDD	Defined Daily Dose
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECT	Electroconvulsive Therapy
GEE	Generalized Estimating Equations
GHQ	General Health Questionnaire
HAM-D	Hamilton Rating Scale for Depression
HR	Hazard Ratio
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
IRR	Incidence Rate Ratio
ISCED	International Standard Classification of Education
KELA	Finnish Social Insurance Institution
NUTS	Nomenclature of Territorial Units for Statistics
RR	Rate Ratio
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Substance Use Disorder
THL	Finnish National Institute for Health and Welfare

1 INTRODUCTION

Most people experience feelings of sadness and loss of enjoyment during their lifetime. This may be a normal reaction to negative life events and difficult circumstances. However, if these feelings are strong and persistent, and significantly impair the ability to function, they may indicate the presence of clinical depression, which is considered a psychiatric disorder. Depression is a major public-health burden globally, accounting for around 10 per cent of life-years lived with disability (Murray et al., 2012). It has been estimated in cross-national studies that around five per cent of people suffer from depression at any given time (Ferrari et al., 2013), and that an average 15 per cent of people in high-income countries and 11 per cent in low-to-middle-income countries suffer from depression during their lifetime (Bromet et al., 2011).

Depression is a pressing public-health issue not only because of its high prevalence but also because of its uneven distribution across the population and thus its contribution to social inequalities in health. Epidemiological studies have consistently reported depression to be more common among people who are not married or living with a partner, and who are unemployed (Andrade et al., 2003; Bijl et al., 1998; Bromet et al., 2011; Goodwin et al., 2006; Joutsenniemi et al., 2006; Paul and Moser, 2009; Pinto-Meza et al., 2013). Many studies also indicate that depression is more common among those in low socioeconomic positions, but the evidence is less consistent (Andrade et al., 2003; Kessler and Bromet, 2013; Lorant et al., 2003; Markkula et al., 2015; Pinto-Meza et al., 2013; Pirkola et al., 2005). Reducing social inequalities in health is a major goal in public-health policy both in Finland and internationally (Sihto and Palosuo, 2013).

Social inequalities in depression are only partly determined by differences in prevalence, however, and may also be caused by differentials in its course and outcomes. Depression frequently has a recurring or chronic course (Hardeveld et al., 2010; Steinert et al., 2014), and the risk of premature mortality, suicide in particular, is high (Harris and Barraclough, 1998; Wulsin et al., 1999). The extent to which economic and social resources protect against the adverse outcomes of depression is not well established. In order to tackle social inequalities in depression a better understanding is needed on whether some social groups manage better with depression than others. The aim in this study is to broaden current knowledge of the extent of social differentials in depression outcomes, and of the underlying mechanisms. It therefore examines how adverse outcomes vary according to social factors such as socioeconomic position, employment status and living arrangements, and sheds light on the role of alcohol and depression treatment in bringing about this variation.

Existing evidence concerning social differentials in depression outcomes is inconsistent, some studies showing worse outcomes among people in a low

socioeconomic position and the unmarried, whereas others report no such differentials (Bjerkeset et al., 2008; Bracke, 1998; Cole et al., 1999; Dowrick et al., 2011; Eaton et al., 2008; Hardeveld et al., 2010; Kessing et al., 1998; Licht-Strunk et al., 2007; Lorant et al., 2003; Steinert et al., 2014). Few studies have assessed social differentials in mortality among depressed people, and differentials according to socioeconomic or living-arrangement factors have rarely been found (Fuhrer et al., 1999; Hawton et al., 2013; Leinonen et al., 2014; Schneider et al., 2001). Most of these earlier studies are based on small samples, however, and may lack the statistical power to detect differentials. There is thus a need for studies based on large population samples.

Reducing premature mortality among people with depression requires a better understanding of the mechanisms behind the excess mortality. Alcohol is one of the leading causes of working-age mortality in Finland (Statistics Finland, 2012), and is a major contributor to socioeconomic differentials in mortality (Martikainen et al., 2014; Tarkiainen et al., 2011). Although it has been suggested that excessive alcohol consumption is a notable pathway between depression and mortality (Wulsin et al., 1999), there is as yet no evidence concerning the contribution of alcohol-related causes to the excess mortality of depression.

Another major cause of death among the depressed is suicide. Psychological autopsy studies have shown 30–90% of suicides to be linked to depression (Lönngqvist, 2000), and better detection and treatment of depression and other mental health problems are key elements in suicide-prevention strategies in Finland and elsewhere (Beskow et al., 1999; World Health Organization, 2014). The most common treatment alternative for depression is antidepressant medication, which has shown a moderate effect in reducing depressive symptoms (Melandar et al., 2008; Turner et al., 2008). However, its effectiveness in suicide prevention is still under debate. The rapid increase in antidepressant treatment since the emergence of new types of antidepressants at the end of the 1980s has coincided with a decrease in suicide mortality in many countries, including Finland (Baldessarini et al., 2007). Some researchers have interpreted this as a medical breakthrough in suicide prevention (Isacsson 2000, Isacsson et al. 2010), whereas others are more sceptical (Isacsson et al., 2010; Safer and Zito, 2007). Despite the abundance of research on the matter, little is known about the effect of increased antidepressant sales on alcohol-related suicides, a substantial subtype particularly among men and those in a low socioeconomic position (Mäki and Martikainen, 2009, 2008). Furthermore, few studies have assessed the impact of increased antidepressant treatment across population subgroups based on gender, socioeconomic position or living arrangements. Given that population subgroups may differ in terms of access to treatment as well as the propensity to seek and adhere to it, it is possible that the increase in treatment has not benefitted all groups equally.

Differential access and adherence to effective depression treatment may be one pathway through which social factors affect depression outcomes.

Inadequate treatment for mental-health problems and its unequal distribution constitute a common concern among public-health professionals, given that treatment seems to be received disproportionately by those with more socioeconomic resources (Bijl et al., 2003; The WHO World Mental Health Survey Consortium, 2004). Whether this applies to antidepressant treatment of depression as well is not clear based on current evidence (Andersen et al., 2009; Butterworth et al., 2013; Colman et al., 2008; Hämäläinen et al., 2009; Hansen et al., 2004a; Kivimäki et al., 2007; Mauramo et al., 2012; Roer et al., 2010). Studies explicitly assessing the need for treatment are scarce, and thus it is difficult to determine whether any observed differences in treatment reflect differences in need or in access. There is also a lack of longitudinal studies comparing long-term trajectories of antidepressant use between social groups that would be able to evaluate differences in both access and adherence to treatment. There is a clear need to enhance understanding of the extent to which social differences in treatment are driven by unequal access or differential continuity, and consequently of the types of intervention that would be most effective in decreasing social differentials in treatment and its outcomes.

The objective of this study is to enhance knowledge about social inequalities in depression through the assessment of social differentials in depression outcomes such as psychiatric hospital care and premature mortality. The investigation also covers educational differentials in longitudinal trajectories of antidepressant use, which constitute a potential pathway for bringing about social differentials in depression outcomes. A further aim is to quantify the contribution of alcohol-related deaths to depression mortality, and to establish the extent to which the increased use of antidepressants has prevented alcohol-related and non-alcohol-related suicides across social groups. The study is based on large, nationally representative population register samples from Finland, with linkages to routinely collected administrative data on socioeconomic and living-arrangement factors, hospital care, medication use and mortality. These register-based data are unique in that they allow the longitudinal assessment of antidepressant use, and even of rare depression outcomes such as psychiatric admission and suicide in large population samples without selective attrition or loss to follow-up. These are problems, which may seriously compromise the quality of survey-based or clinical data that are commonly used in psychiatric epidemiology (Fischer et al., 2001).

2 THE CONCEPTUAL FRAMEWORK OF THE STUDY

2.1 DEPRESSION: DEFINITION AND EPIDEMIOLOGY

A sad mood and a lack of enjoyment are part of human life and normal emotional reactions to loss and other difficult circumstances. Sadness may even serve useful functions, such as prompting sympathy and help from others or motivating the individual to recover what has been lost (Wolpert, 2008). Overwhelming sadness that exceeds the limits of normal reactions, however, has been acknowledged under different names throughout written history (Eaton, 2001). In current psychiatric nosology it is called depression. Where the limit should be set between normal sadness and depression as a psychiatric disorder is a matter of controversy, even within psychiatry (Horwitz and Wakefield, 2007).

According to the two major psychiatric classification systems in use today, the International Statistical Classification of Diseases Tenth Revision (ICD-10) produced by the World Health Organization, and the two most recent versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV and DSM-5) produced by the American Psychiatric Association, the formal diagnosis of depression is purely symptom-based. The different depressive disorders are diagnosed according to the number, type, severity and duration of the presented symptoms (American Psychiatric Association, 2013, 1994; World Health Organization, 1993, 1992). Depression is thus seen as a heterogeneous syndrome (Depression: Current Care Guidelines, 2014; NICE, 2009) rather than a uniform disorder with a clear aetiology (Carney and Freedland, 2000).

The diagnosis of a major depressive disorder in according to DSM-IV and DSM-5 (referred to as depressive disorder in ICD-10 (World Health Organization, 1993, 1992)) requires the presence of a persistent depressive mood or loss of interest and enjoyment for a period of at least two weeks, as well as at least four of the following symptoms: loss of energy, reduced self-esteem, unreasonable feelings of guilt and unworthiness, suicidal ideation or behaviour, reduced concentration, psychomotor agitation or retardation, sleep disturbance, and changes in appetite. Furthermore, the symptoms have to cause clinically significant distress or impairment in functioning (American Psychiatric Association, 2013, 1994). Major depression is further divided into mild, moderate and severe according to the number of symptoms and the extent of impairment. In its most severe form it may include psychotic features such as delusions and hallucinations. Major depressive disorder is diagnosed only among individuals with no history of manic, hypomanic or mixed episodes, which are indicative of bipolar affective disorders. The term unipolar

depression is often used so as to emphasise the distinction from bipolar disorders.

Other unipolar depressive disorders include postnatal depression and dysthymia. Postnatal depression is a major depressive episode occurring within four weeks of delivery. A persistent affective disorder lasting for years with constantly recurring depressed mood and other depressive symptoms, but no or few episodes meeting the criteria for a major depressive episode, is called dysthymia (in ICD-10, DSM-IV) or persistent depressive disorder (in DSM-5) depending on the classification system (American Psychiatric Association, 2013, 1994; World Health Organization, 1993, 1992). Depressive symptoms not meeting the full criteria for a major depressive disorder or dysthymia are often referred to as “subthreshold” or “subclinical” depression (Judd et al., 2002). These milder symptoms have been shown to cause considerable impairment and to have similar outcomes to clinical depression (Cuijpers and Smit, 2002; Judd et al., 2002; Solomon et al., 2001). It is a matter of debate whether there is continuity between subclinical depressive symptoms and clinical depression, or whether clinical depression meeting diagnostic criteria is a qualitatively distinct and categorical entity (Klein et al., 2007; Solomon et al., 2001).

The way depression and depressive disorders in general are conceptualised has implications for how they should be measured in research. If one sees depression as a categorical entity—a disorder with clear limits defining a disordered mood—then a diagnostic schedule is a proper measurement. If one thinks of it as continuous, with increasing severity as symptoms increase, however, then an inventory or a rating scale may be more suitable (Dew et al., 2006). Diagnostic schedules such as the commonly used Composite International Diagnostic Interview (CIDI) distinguish depressive disorders qualitatively from each other and from non-disordered mood based on diagnostic criteria used in current psychiatric classification systems (DSM or ICD). Inventories evaluate the number and severity of depressive symptoms on a continuous scale, and are thus more sensitive than diagnostic schedules to changes in symptomatology across measurements. However, cut-off points are often used with inventories as well to indicate “caseness”. The most widely used inventories include the Beck Depression Inventory (BDI) and the Hamilton Rating Scale for Depression (HAM-D) for assessing depressive symptoms, and the General Health Questionnaire (GHQ) for more general psychological distress (Dew et al., 2006). As discussed below, the prevalence, correlates, course and outcomes of depression vary according to how it is conceptualised and measured.

In this study depression is empirically measured using information from healthcare registers, and depression is used as a broad term ranging from hospital-treated severe depressive disorders with psychotic features to subthreshold depression treated with antidepressants. Thus the concept of depression used in this study is theoretically closer to the notion of depression as a continuous rather than a categorical phenomenon. When the reference is

to previous studies the term depression is used for both clinically assessed depression and depressive symptoms measured on rating scales, and the measurements used are specified when relevant.

Depressive disorders are rather common in the general population, although prevalence estimates across countries and studies vary considerably (Andrade et al., 2003; Weissman et al., 1996). Community epidemiological surveys using the World Health Organization CIDI interview corresponding to the DSM-IV diagnostic criteria for a major depressive episode have indicated a mean 12-month prevalence of 5.5 per cent and a mean lifetime prevalence of 14.6 per cent across 10 high-income countries, and 5.9 and 11.1 per cent, respectively across eight low-to-middle-income countries (Bromet et al., 2011). The 12-month prevalence of CIDI-measured major depression in the Finnish general population in 2000–2001 was 4.9 per cent, and the prevalence of any depressive disorder (including dysthymia) was 6.5 per cent (Pirkola et al., 2005). Recent evidence (2011) from Finland suggests an increase in the prevalence of major depressive disorder to 7.4 per cent, and of any depressive disorder to 9.6 per cent (Markkula et al., 2015), although a dramatic decrease in response rate between the studies hinders reliable comparison. A universally increasing trend in depression has been suggested, but the evidence remains inconsistent (de Graaf et al., 2012; Goodwin et al., 2006; Hidaka, 2012).

The reasons why some people develop depressive disorders and others do not are not well known. Commonly acknowledged risk factors for depression include female gender, a family history of depression, adverse childhood experiences such as neglect or abuse, and stressful life events such as bereavement, divorce or job loss (Goodwin et al., 2006; Kendler et al., 2000, 1999). However, genetic, neurobiological and psychosocial factors have been found to affect vulnerability to stressors in developing depression (Kendler et al., 1995; Southwick et al., 2005). Individuals with no genetic disposition to depression, or with strong social support, may thus be more resilient and less likely to become depressed even when exposed to stress and negative life-events (Southwick et al., 2005). The causal mechanisms linking the observed risk factors with depression are thus likely to be complex and interrelated.

Comorbidity, in other words the co-occurrence of other mental disorders such as anxiety disorders and substance use disorders as well as various physical illnesses, is common in depression (Horwath et al., 2002; Richards and O'Hara, 2014; Swendsen and Merikangas, 2000), and several mechanisms for this have been suggested. Depression may share a common aetiology and risk factors with the comorbid disorders (Swendsen and Merikangas, 2000). Pre-existing mental and physical disorders may also be risk factors for depression onset: depression may be a psychological or physiological reaction to an illness, for example (Wulsin et al., 1999). Finally, depression may increase the risk of other psychiatric and physical disorders via biological or behavioural pathways. Biological dysregulation, such as of the autonomous nervous system and neuroendocrine functions, have been

observed in depression, and they increase the risk of various somatic illnesses such as diabetes mellitus and cardiovascular disease (Cuijpers et al., 2014c; Cuijpers and Schoevers, 2004). Excessive alcohol consumption, smoking and a lack of exercise, which are known risk factors for many psychiatric and physical disorders, are also common in depression (Cuijpers and Schoevers, 2004; Swendsen and Merikangas, 2000). Specifically with regard to psychiatric comorbidity, it has been questioned whether the disorders are comorbid in the true sense, meaning a co-occurrence of two essentially separate disorder entities, or whether the comorbidity is in fact an artefact of the current psychiatric classification system that splits mental disorders into ever smaller subdiagnoses (Bebbington et al., 2000; Eaton, 2001).

2.2 OUTCOMES OF DEPRESSION

Depression tends to have a chronic or recurrent course, although evidence on its course and outcomes seems to be strongly dependent on the study setting (K. M. Holma et al., 2008). It has been found in studies of specialised mental health care that only 15 per cent of depressive patients have no recurrence after 15 years (Hardeveld et al., 2010). However, stable recovery seems more common in the context of community and primary care (Hardeveld et al., 2010; Steinert et al., 2014), probably because patients present with less severe depression in these settings. According to a recent review of prospective studies focused on community and primary care, around 35–60 per cent of people with depression had no recurrence in follow-ups ranging from three to 49 years (Steinert et al., 2014). About 10–20 per cent of the patients had a chronic course with no major improvement during follow-up, and the rest (an average of 39% across the studies) had a recurring course with at least two episodes during follow-up.

Depression sometimes becomes so serious that extensive and recurrent hospital care is needed. At worst, depression may even lead to premature death (Wulsin et al., 1999). There are also various potentially adverse social outcomes such as marital disruption, work disability and exclusion from the labour market (Bulloch et al., 2009; Kessler et al., 1998; Luo et al., 2010; Riihimäki et al., 2014). However, such social outcomes are beyond the scope of this study.

2.2.1 PSYCHIATRIC HOSPITAL CARE

Admission to psychiatric hospital care is used in this study as an indicator of a negative course of depression. Being referred to a psychiatric hospital on the grounds of depression is often related to patient suicidality (Doerfler et al., 2010) and the psychotic features of depression (Vuorilehto et al., 2007), and thus reflects a severe deterioration in mental health. As an individual-level experience psychiatric admission could be considered one of the most

distressing outcomes of a mental-health problem, generating feelings of fear, anger and loss of self-esteem, particularly if admission is involuntary (Morrison et al., 1999). Costly and intensive inpatient care is also an undesirable and adverse outcome of depression from the perspective of the healthcare system, and is sometimes even seen as the failure of previous treatment attempts (Lyons et al., 1997). Although hospital care may be part of a long-term treatment plan for depressive patients, it is uncommon in Finland where the psychiatric care system focuses on outpatient services. In 2013 only around five per cent of psychiatric inpatients had repeated hospital care by pre-arrangement (Rainio and Rätty, 2015).

2.2.2 MORTALITY

Another adverse outcome of depression assessed in this study is premature death. Reviews and meta-analyses of depression mortality suggest an excess in all-cause mortality of about 20–170 per cent compared with the general population (Cuijpers and Smit, 2002; Harris and Barraclough, 1998; Schulz et al., 2002; Wulsin et al., 1999), the excess being evident in psychiatric inpatient as well as community samples (Cuijpers and Smit, 2002; Harris and Barraclough, 1998; Schulz et al., 2002; Wulsin et al., 1999). However, the excess seems to be larger among inpatients, suggesting that depression severity increases the risk of death (Wulsin et al., 1999). Correspondingly, according to a recent meta-analysis, major depression carried a somewhat larger excess risk of death (60%) than sub-threshold depressive symptoms (30%), although the difference was not statistically significant (Cuijpers et al., 2013b).

The causal mechanisms producing the excess mortality are not well established, although some evidence is provided by studies assessing causes of death. A cause of death that is causally linked to depression is suicide. Suicidal thoughts are often present as symptoms of depression, and according to psychological autopsy studies (based on posthumously gathered information from family and friends, medical records and police reports, for example), around 30–90 per cent of suicides are preceded by depression (Lönngqvist, 2000). However, suicide is a rare event, even among depressed individuals: the lifetime prevalence of completed suicide among people with depression ranges from around 0.5 per cent in community samples (Kuo and Gallo, 2001) to around nine per cent among the highest risk group, namely depressed patients previously hospitalised on the grounds of suicidality (Bostwick and Pankratz, 2000). Thus suicide can only explain a small part of overall excess mortality (Cuijpers and Schoevers, 2004), particularly in the case of less severe forms of depression. Elevated levels of other accidental and violent causes of death (often called unnatural or external causes) have also been found among the depressed, particularly among individuals with a history of psychiatric inpatient treatment (Harris and Barraclough, 1998; Hiroeh et al., 2001; Ösby et al., 2001), indicating the significance of behavioural pathways in inducing

depression mortality. However, evidence of increased external-cause mortality from population samples is more scarce and inconsistent, probably due to the low numbers of external-cause deaths observed in survey-based studies (Joukamaa et al., 2001; Markkula et al., 2012; Mykletun et al., 2007).

An extensive body of literature reports higher mortality from cardiovascular disease among the depressed (Wulsin et al., 1999). Depression has been found to increase both the incidence (Steptoe, 2007) and the case fatality of heart diseases (Barth et al., 2004; Lett et al., 2007). Given that cardiovascular disease is the leading cause of death worldwide (World Health Organization, 2011), it is also likely to account for a large proportion of depression mortality. Both biological and behavioural pathways have been suggested to explain the excess mortality from cardiovascular and other diseases among the depressed (Cuijpers et al., 2014c; Cuijpers and Schoevers, 2004; Wulsin et al., 1999). Depression may be a biological or psychological reaction to a pre-existing somatic disorder that increases the risk of death on the one hand (Wulsin et al., 1999), but on the other hand biological dysregulations related to depression may increase the risk for various somatic illnesses (Cuijpers et al., 2014c; Cuijpers and Schoevers, 2004). Suggested behavioural pathways include less treatment-seeking and poorer adherence to treatment for somatic disorders when depressed, as well as detrimental health behaviours such as excessive alcohol consumption, smoking and a lack of physical exercise (Cuijpers and Schoevers, 2004). In particular, it has been argued that excessive alcohol consumption is one of the major pathways inducing depression mortality (Wulsin et al., 1999). Given that alcohol-related deaths are a leading cause of working-age mortality in Finland (Statistics Finland, 2012), their contribution to premature mortality among the depressed is likely to be substantial.

2.3 DETERMINANTS OF DEPRESSION OUTCOMES

2.3.1 SOCIAL FACTORS

The social determinants of depression outcomes are viewed in this study within the wider framework of social inequalities in health (Berkman and Kawachi, 2000; Marmot and Wilkinson, 2006; Townsend and Davidson, 1988). Research on health inequalities focuses on differences in health across population subgroups defined by socioeconomic factors such as education, occupation, income, wealth, home ownership, area deprivation and employment (Elo, 2009; Krieger et al., 1997; Lynch and Kaplan, 2000). These are all aspects of the wider concept of socioeconomic position, which refers to the position of the individual in the social hierarchy. One of the most consistent findings in epidemiology is that a low socioeconomic position is related to worse health according to most measures of morbidity and mortality across time and geographical regions (Krieger et al., 1997; Lynch and Kaplan,

2000; Mackenbach, 2012). The different aspects of socioeconomic position are not interchangeable, however, and may affect health through different pathways (Lahelma et al., 2004).

Education is acquired early in life, and to a large extent determines future occupation and income. It provides people with skills and knowledge that may help in avoiding behaviours and lifestyles that are detrimental to health. Occupation, on the other hand, defines one's position in the social hierarchy, and also determines work-related physical and psychosocial exposures. The more material aspects of socioeconomic position such as income and wealth may protect against stress related to financial insecurity, and facilitate health-enhancing behaviours and access to healthcare (Herd et al., 2007; Lahelma et al., 2004). Home ownership is the most common form of wealth (Brandolini et al., 2008) and reflects material well-being accumulated over the lifespan and across generations. Employment status has also be viewed as one aspect of socioeconomic position (Lynch and Kaplan, 2000). Becoming unemployed may lead to adverse health effects via increased psychosocial stress, loss of social networks, and a deterioration in material circumstances (Martikainen and Valkonen, 1996).

The wider concept of social determinants of health (Marmot et al., 2008; Marmot and Wilkinson, 2006) also encompasses social factors other than socioeconomic position that may influence health, such as marital status and living arrangements. The better health of married compared to nonmarried people is a well-established epidemiological finding (Hu and Goldman, 1990; Koskinen et al., 2007; Martikainen et al., 2005), and research increasingly shows that people living in non-marital partnerships have better health than those living alone or with someone other than a partner (Carr and Springer, 2010; Joutsenniemi et al., 2006; Koskinen et al., 2007). Close relationships are thought to be beneficial to health in providing emotional, social, economic and instrumental support (Carr and Springer, 2010) as well as social control (Umberson, 1992), and may enhance health-promoting behaviour (Lynch and Kaplan, 2000). Living arrangements and marital status also reflect a history (or lack) of stressful life events such as divorce and bereavement that may be detrimental to health.

Various theories have been put forward to explain social differentials in health (Carr and Springer, 2010; Mackenbach, 2012). In general, health inequalities are perceived to result from an unequal distribution of health-damaging exposures and health-protective resources across population subgroups (Lynch and Kaplan, 2000). The various theories differ in terms of which exposures (e.g., material, psychosocial or behavioural) and resources (e.g., financial, cultural, psychosocial or cognitive) are considered the most relevant and in what is assumed about the causal ordering of social circumstances and health (Mackenbach, 2012). Causal explanations emphasise the effect of social circumstances on health, whereas explanations based on selection suggest that people are sorted into socioeconomic groups or living arrangements based on their health ('direct selection'), or on health

determinants such as personal characteristics and health behaviours ('indirect selection').

With regard to depression, much of the research on social inequalities has focused on differentials in prevalence or incidence (Lorant et al., 2003). Overall, evidence indicating social differentials in depression is less consistent than in the case of physical illness, and seems to depend on how depression is conceptualised and measured. Studies comparing different measures of depression and depressive symptoms report more pronounced differentials between socioeconomic and living-arrangement groups for more severe measures of depression, and a less steep or non-existent social gradient for more common depressive symptoms or psychological distress (Andersen et al., 2009; Joutsenniemi et al., 2006; Kosidou et al., 2011a; Lorant et al., 2003). Moreover and in contrast to evidence on physical illness, depression seems to be more strongly related to the material aspects of socioeconomic position such as income and past or current financial difficulties, whereas differentials according to education and occupational social class often turn out to be small or non-existent: this is the case for less severe forms of depression and psychological distress in particular (Andersen et al., 2009; Fryers et al., 2003; Kessler et al., 1997; Kosidou et al., 2011b; Laaksonen et al., 2007; Lorant et al., 2003; Markkula et al., 2015; Pirkola et al., 2005).

Although these observed associations may be attributable in part to the selection of depressed individuals into low socioeconomic positions and to being unpartnered, exposure to stressful life-events appears to have a causal effect on depression onset (Kendler et al., 2000, 1999). Given the evidence that both chronic stress and acute stressful life-events are more common among those with a low socioeconomic position (Lantz et al., 2005; Taylor et al., 1997), social differentials in depression onset could be causally induced via stress exposure. However, the social factors that appear to predict depression onset do not necessarily predict the outcomes. Efforts to reduce social inequalities in depression would therefore benefit from a better understanding of the social processes operating at different stages of the illness (Herd et al., 2007).

A specific theory focusing on the differential effects of social exposures at different stages of depression is the kindling hypothesis of mood disorders (Post, 1992). According to the hypothesis, exposure to major stressful life-events plays a stronger role in the aetiology of first-onset depression than in subsequent episodes because depressive episodes sensitise the individual to stress so that ever smaller stress exposures may eventually inflict subsequent episodes (Kendler et al., 2000; Monroe and Harkness, 2005; Post, 1992). On the basis of the kindling hypothesis one would expect the course of depression to be only weakly related to social exposures, and thus that social factors would have little effect in determining depression outcomes.

Another specific theoretical approach to social differentials in depression outcomes is the buffering hypothesis (Fuhrer et al., 1999). It was originally posited to explain how social support and other resources may modify the

effects of acute or chronic stressors on health (Cohen and Wills, 1985; Stansfeld, 2006) but has also been used in research on depression outcomes to test whether social support buffers against the excess mortality of depression (Fuhrer et al., 1999). Other social and economic resources such as a high level of education, a high income and being in employment could similarly buffer against the excess mortality through better coping skills or better access to treatment, for example.

The differential receipt of and adherence to effective depression treatment is a specific pathway potentially bringing about social differentials in depression outcomes. Treatment may be more affordable to those with more financial resources, for example, and social control exerted by a co-resident partner may enhance treatment adherence (Umberson, 1992). Differentials in seeking treatment and in the interaction between patient and healthcare provider may also produce social differentials in the receipt of appropriate treatment for depression (Butterworth et al., 2013; Comino et al., 2000). New treatment regimens and health interventions may also be more readily adopted by people in higher socioeconomic positions, despite less treatment need, as suggested in the diffusion of innovations theory and the inverse-equity hypothesis (Mackenbach, 2012; Victora et al., 2000).

2.3.2 TREATMENT

The main treatment alternatives for depression include psychotherapy, antidepressants and—in the case of severe and psychotic depression—electroconvulsive therapy (ECT) (American Psychiatric Association, 2010; Depression: Current Care Guidelines, 2014; NICE, 2009). The guidelines recommend treatment in three phases: acute, continuation and maintenance. The target in the acute phase is remission, in other words the partial or preferably full relief of depressive symptoms. The phase lasts until remission is achieved, usually for between six and eight weeks. The next phase, continuation treatment, should last for between four and nine months after remission so as to avoid relapse, in other words the return of depressive symptoms. Antidepressant treatment should continue on the same dosage level that was effective in the acute phase. After this, long-term maintenance treatment may be called for to avoid recurrence among patients with a history of recurring moderate to severe depression (American Psychiatric Association, 2010; Depression: Current Care Guidelines, 2014; NICE, 2009).

Meta-analyses of randomised, controlled trials have shown psychotherapy, antidepressants and ECT to be effective in the acute phase of treatment (Cuijpers et al., 2014a, 2008; Melander et al., 2008; Turner et al., 2008; UK ECT Review Group, 2003), although the effects of psychotherapy and antidepressants compared to placebos are only small to moderate (Cuijpers et al., 2014a; Undurraga and Baldessarini, 2012). Antidepressants and psychotherapy have proved to be equally effective in the treatment of mild to moderate depression (Cuijpers et al., 2014b, 2013a, 2008), and a recent meta-

analysis suggests a combination of the two may be twice as effective as either one in isolation (Cuijpers et al., 2014b).

Antidepressant treatment in the continuation and maintenance phases has also been found to effectively reduce the risk of relapse and recurrence in meta-analyses of randomised controlled trials among patients who achieved remission in acute-phase antidepressant treatment (Geddes et al., 2003; Williams et al., 2009). Conversely, observational community studies assessing long-term outcomes of depression such as recovery, chronicity and recurrence report no significant associations between antidepressant or other treatments and outcomes (Steinert et al., 2014). There may be at least two reasons for this discrepancy. Observational studies may underestimate the positive effect of treatment if being treated is correlated with the initial severity, chronicity and comorbidity of the depression, all of which are strong predictors of an adverse course (Hardeveld et al., 2010; Steinert et al., 2014). On the other hand, continuation trials may overestimate the positive long-term effect of treatment because they only include patients who responded positively during the acute phase. In sum, continuation and maintenance antidepressant treatment seems to prevent relapse among patients who benefitted from it in the acute phase, whereas evidence concerning the benefits of continued antidepressant use across all patients remains unclear.

Given that the available treatment options show at least a small-to-moderate effect in the acute phase of symptom reduction, as well as in preventing recurrence, a potential factor affecting outcomes is the lack of adequate treatment. Population studies from Finland and elsewhere have shown that only around 30–60 per cent of individuals meeting the diagnostic criteria for major depression receive any treatment (Bijl and Ravelli, 2000; Härmäläinen et al., 2009, 2004; Kessler et al., 1999; Spijker et al., 2001a; Wang et al., 2005). This implies that the detection and treatment of first-onset episodes in the general population may be delayed and inadequate. Furthermore, there is evidence to suggest that the degree to which depressed patients follow the treatment as recommended—referred to as patient compliance or adherence (Mitchell and Selmes, 2007)—is low (Lingam and Scott, 2002). It was found in a Finnish study on psychiatric inpatient and outpatient care that although almost 90 per cent of the depressed patients received acute-phase antidepressant treatment, early discontinuation was common and only about a quarter of them completed a continuation phase of at least four months (Melartin et al., 2005). The most common self-reported reason given for discontinuation was the patient's autonomous decision, possibly reflecting a willingness to cope without medication (Melartin et al., 2005). Less common reasons included side-effects, poor response and subjective recovery. It has also been reported that maintenance treatment is of inadequate duration in Finland (I. A. Holma et al., 2008).

Depression seems to be particularly suboptimally treated among patients with comorbid substance use disorders (SUD) (Blanco et al., 2012; ten Have et al., 2004), despite the fact that antidepressant treatment has proved

effective for both of the comorbid disorders, in particular when combined with psychological treatment (Davis et al., 2010; Nunes and Levin, 2004). Treatment for depression in Finland has also been found to be suboptimal among suicidal patients (Suominen et al., 1998).

While unmet need for treatment is a common problem, the majority of all mental-health treatment goes to mild and minor cases (Bijl et al., 2003; The WHO World Mental Health Survey Consortium, 2004). Furthermore, medicalization, in other words the process of defining an ever widening range of behaviours as medical problems (Conrad, 1992; Eaton, 2001), may lead to the over-treatment of normal emotional responses to adverse social circumstances, such as unemployment or bereavement (Buffel et al., 2015; Wakefield, 2013). One concern is that this process may be at least partly driven by aggressive marketing by the pharmaceutical industry, which has profited from increases in the prescribing of psychotropic medication (Eaton, 2001). Antidepressant sales have risen dramatically worldwide since the end of the 1980s when a new group of antidepressants, selective serotonin reuptake inhibitors (SSRI) was introduced, gradually followed by other new-generation antidepressants (Baldessarini et al., 2007). Both SSRIs and these other new-generation antidepressants are better tolerated and less toxic in overdose than the older tricyclic antidepressants that have been in use since the 1950s, and this has led to easier prescribing and monitoring in primary care (Reseland et al., 2006). The consumption of antidepressants in Finland increased from around seven daily doses per 1,000 inhabitants in 1990 to over 70 in 2010 (National Agency for Medicines and Social Insurance Institution, 2012), and the role of general practitioners as prescribers has increased markedly (Sihvo et al., 2010). It is not known how this increased use has been allocated with respect to treatment need. Around a quarter of Finnish antidepressant users studied in 2000 had no known psychiatric morbidity (Sihvo et al., 2008).

2.3.3 THE ROLE OF ANTIDEPRESSANTS IN SUICIDE PREVENTION

A particular question regarding the effects of treatment on depression outcomes concerns suicide prevention. Given that depression is one of the main risk factors for suicide, its better detection and treatment could well have a preventive effect. Antidepressants and interpersonal psychotherapy have been found to reduce mild suicidal ideation more than placebos among depressed patients, largely as a consequence of their more general effects on depression (Weitz et al., 2014). However, treatment trials, the gold standard for proving medication effects, have been unable to show positive effects on completed suicide—largely for methodological reasons such as a lack of statistical power and short follow-ups (Gunnell et al., 2005).

Several countries, including Finland, have witnessed a marked decline in suicide mortality rates since the expansion in the use of new-generation antidepressants (Baldessarini et al., 2007; Bramness et al., 2007; Reseland et al., 2006). It would therefore be plausible to assume that the increased level of

treatment for depression could have led to a decline in the rates of completed suicide. This could be attributable to specific treatment effects, but also to nonspecific mechanisms such as a growing awareness of depression as well as increased treatment optimism among physicians and patients following the emergence of the new treatment alternatives. Changes in treatment adequacy in particular could be a mechanism affecting suicide rates, the duration of antidepressant treatment spells having increased in Finland (Sihvo et al., 2010). However, thus far the causal connection between increased antidepressant sales and a decline in suicide mortality remains open to debate (Isacsson et al., 2010; Safer and Zito, 2007).

3 EMPIRICAL EVIDENCE

3.1 SOCIAL DIFFERENTIALS IN DEPRESSION OUTCOMES

The most consistent predictors of a negative course in depression seem to be factors related to the depression itself: the severity of the index episode, the number of previous episodes, early age at onset and psychiatric comorbidity (Hardeveld et al., 2010; Steinert et al., 2014). Substance use disorders (SUD), and alcohol use disorders (AUD) in particular, are common in depression (Pirkola et al., 2005; Sullivan et al., 2005) and have been found to predict worse prognosis and suicidality (Blanco et al., 2012; Davis et al., 2008; Najt et al., 2011; Sullivan et al., 2005).

Evidence of social differentials in depression outcomes remains inconsistent. Reviews of studies using primary-care and community samples report little or no evidence of differentials according to socioeconomic factors or marital status in the recurrence or persistence of depression among adults (Cole et al., 1999; Hardeveld et al., 2010; Licht-Strunk et al., 2007; Steinert et al., 2014). On the other hand, a meta-analysis of large population studies (Lorant et al., 2003) as well as more recent single population studies have indicated that depression is more persistent among the unemployed (Bjerkeset et al., 2008; Bracke, 1998), those with a low level of education (Bjerkeset et al., 2008; Eaton et al., 2008; Lorant et al., 2003), a low income (Lorant et al., 2003) and a low occupational social class (Lorant et al., 2003), and those not owning their home (Dowrick et al., 2011).

Methodological differences are likely to go some way in explaining these inconsistencies. The reviews showing no social differentials only included studies with rather small samples ($n < 500$), which may not have had sufficient statistical power to detect significant differences (Cole et al., 1999; Hardeveld et al., 2010; Licht-Strunk et al., 2007). They were also based on more stringent measurements, only including studies in which depression was diagnosed according to DSM or ICD criteria, or with clinically relevant depressive symptoms. In contrast, most studies included in the meta-analysis reporting significant differentials used unspecific measures of psychological distress such as the GHQ, and in only one study was depression measured in accordance with a schedule based on DSM criteria. This study also showed the smallest social-group differences in persistence (Lorant et al., 2003), possibly indicating smaller social-group differentials in the persistence of depression meeting diagnostic criteria.

Most studies assessing admission to psychiatric inpatient care, an indicator of an unfavourable course of depression, report no differentials according to socioeconomic or living-arrangement factors (Aro et al., 1995; Callahan and Wolinsky, 1995; Lauber et al., 2006; Lin et al., 2007; Morrow-Howell et al.,

2006; Vogel and Huguelet, 1997), although one large register study revealed a higher risk of readmission for depression among never-married individuals (Kessing et al., 1998).

Empirical evidence of social differentials in depression mortality is largely lacking. Most of the available studies focus on the predictors of suicide among depressed patients. Research on suicide has yielded mixed results, some showing higher and some lower risks among the unemployed, those who are married or cohabiting, and those living alone (Hawton et al., 2013). As a result, no significant social predictors were found in a meta-analysis of these studies (Hawton et al., 2013). The few studies assessing causes other than suicide generally reveal no modification of excess mortality in depression. According to one study conducted among older French adults, the excess all-cause mortality of depression was unmodified by the number of social relations (Fuhrer et al., 1999), whereas according to another one conducted among discharged inpatients with depression, the excess risk of mortality for internal and external causes was unmodified by marital status or education (Schneider et al., 2001). A large register study on mortality after disability retirement on the grounds of depression reports a largely similar excess in internal-cause mortality across occupational social classes and living arrangements, whereas the excess in external-cause and alcohol-related mortality was significantly larger in the upper non-manual class and among those living with a partner and children (Leinonen et al., 2014). These results provide little support for the hypothesis that beneficial socioeconomic or family situations buffer against the risk of premature mortality posed by depression.

Although excessive alcohol use has been suggested as one of the major pathways inducing depression mortality (Wulsin et al., 1999), few studies have focused on alcohol-related mortality among the depressed, probably because of a lack of suitable data. One Finnish study reported a roughly three-fold increase in mortality from alcohol-related diseases and accidental alcohol poisoning after disability retirement for depression, compared to non-retired men and women (Leinonen et al., 2014), and another Finnish study based on an employee sample reported a five-fold alcohol-disease mortality among antidepressant users (Kivimäki et al., 2007). However, no studies have explicitly assessed the contribution of alcohol-related causes to the excess mortality associated with depression.

3.2 SOCIAL DIFFERENTIALS IN ANTIDEPRESSANT TREATMENT

Inadequate and unequally distributed mental health care is a commonly raised concern. It has been found that people with a high educational level (Andrews et al., 2001; Blumenthal and Endicott, 1996; ten Have et al., 2004; Wang et al., 2005) and a high income are more likely to seek and receive treatment for their mental health disorders (Alegria et al., 2000; Wang et al., 2005). In

particular, receiving care that meets treatment guidelines and is given in specialised settings appears to be more common among those with a higher socioeconomic position (Alegria et al., 2000; Wang et al., 2005; Young et al., 2001). With regard to depression, evidence from Finnish population studies suggests few social differentials in the receipt of treatment. It was found in a sample of 557 depressed individuals that marital status, education, occupational social class, household income and employment status were all unrelated to the use of any or specialised healthcare for their major depressive episode when severity of the episode was controlled for (Hämäläinen et al., 2004). In a smaller population sample of 288 individuals with major depressive disorder the only predictor of antidepressant use was being single, and of psychological treatment was being divorced, whereas education, income and employment status were unrelated to receiving treatment (Hämäläinen et al., 2009).

Empirical evidence of social differentials specifically with regard to antidepressant treatment is mixed, and varies according to which aspects of socioeconomic position have been assessed. According to most, but not all (Bocquier et al., 2013; Hämäläinen et al., 2009; Harris et al., 2011) studies, material aspects of a low socioeconomic position such as a low income (Andersen et al., 2009; Hansen et al., 2004a; Mauramo et al., 2012) and financial difficulties (Butterworth et al., 2013; Mauramo et al., 2012), as well as unemployment (Andersen et al., 2009; Buffel et al., 2015; Colman et al., 2008; Hansen et al., 2004a; Roer et al., 2010) predict a higher incidence and prevalence of antidepressant use. However, analyses of aspects of socioeconomic position related less directly to material resources and more directly to knowledge, status and occupational exposure, namely education and occupational social class, indicate either no gradient (Butterworth et al., 2013; Colman et al., 2008; Hämäläinen et al., 2009; Harris et al., 2011; Kivimäki et al., 2007; Mauramo et al., 2012), or more antidepressant use among those with a high socioeconomic position (Andersen et al., 2009; Kivimäki et al., 2007; Roer et al., 2010).

The key challenge in assessing the extent of unequal access to antidepressant treatment is the evaluation of differences in treatment need, in other words differences in the prevalence and severity of depression. Most studies do not have indicators for treatment need, although some infer unequal access to antidepressant treatment by comparing their own results with social differentials in depression incidence and prevalence from external sources (Bocquier et al., 2013), or in depression outcomes such as suicide and alcohol-related mortality (Kivimäki et al., 2007). These may be inappropriate comparisons given that antidepressants are often prescribed for other indications than depression (Gardarsdottir et al., 2007; Sihvo et al., 2008). If the social patterning in these other indications differs from depression patterns, small social-group differentials in antidepressant use are likely to emerge.

Studies explicitly controlling for depression severity as an indicator of treatment need have reported equal use of antidepressants across educational and occupational groups (Butterworth et al., 2013; Colman et al., 2008; Hämäläinen et al., 2009; Harris et al., 2011), and either increased use among those with fewer material resources such as a low income (Buffel et al., 2015; Butterworth et al., 2013; Colman et al., 2008) or equal use across income and employment groups (Hämäläinen et al., 2009; Harris et al., 2011). In contrast with the hypothesis of unequal access to treatment, these findings have been interpreted as an indication of an effective social safety net actually allowing better access to treatment among the socially disadvantaged (Butterworth et al., 2013).

Although social differentials in the incidence and prevalence of any antidepressant use may be small, social inequalities may arise from differentials in the adequacy of the dosage and the duration of the treatment. In particular, common predictors of non-adherence such as a low level of medical information, a lack of social support and concerns about treatment costs (Mitchell and Selmes, 2007) are likely to be more common among patients with a low socioeconomic position. Accordingly, some studies, although not all (Sihvo et al., 2008), report that early discontinuation is more common (Hansen et al., 2004b; Jeon-Slaughter, 2012; Sundell et al., 2013) and long-term antidepressant use less common (Bocquier et al., 2013) among those with a low socioeconomic position. However, few studies have assessed social differentials in the longitudinal course and adequacy of antidepressant treatment among depressed individuals.

3.3 ANTIDEPRESSANTS AND SUICIDE MORTALITY

Interest in whether antidepressant treatment prevents suicides is widespread, and researchers have used various designs in attempting to resolve the question. Randomised controlled trials, the gold standard of proving both medication effects and causal effects more generally, have been largely unhelpful in assessing such a rare outcome as suicide, and a lack of statistical power has been a problem even in large meta-analyses of trials (Gunnell et al., 2005). As a result, more prevalent outcomes such as suicidal ideation and behaviour have been assessed. These outcomes appear to be more common in patients treated with SSRIs (Fergusson, 2005; Gunnell et al., 2005), particularly among children and adolescents (Hammad et al., 2006). However, the elevated levels of suicidal thoughts and behaviour at the beginning of antidepressant treatment have been found to decrease in follow-up as depressive symptoms dissolve (Gibbons et al., 2012). Consequently, the short follow-up times (8–10 weeks) in treatment trials may hinder the assessment of potential long-term benefits (Gunnell et al., 2005).

A meta-analysis of individual-level observational studies with longer follow-ups ranging from two months to seven years revealed that the odds of

completed suicide were 40 per cent lower among depressed adults and elderly people using SSRIs (Barbui et al., 2009). Causal inference from observational studies is challenged by the fact that patients are not randomised to treatment groups. Antidepressant use is likely to be influenced by suicide-risk factors such as depression severity, suicidal ideation and personal characteristics that are difficult fully to control for (Barbui et al., 2009). This problem, referred to as confounding by indication, is somewhat alleviated in aggregate-level studies in which suicide rates are predicted by regional or national antidepressant sales. The logic is on the population level: if antidepressants are effective in suicide prevention, then increased antidepressant sales should translate into a decline in suicide rates.

Most aggregate-level studies, although not all (Baldessarini et al., 2007; Safer and Zito, 2007; Zahl et al., 2010), indeed report declining suicide rates as sales of antidepressants increase (Baldessarini et al., 2007; Gibbons et al., 2005; Grunebaum et al., 2004; Gunnell et al., 2003; Gusmão et al., 2013; Kelly et al., 2003; Ludwig et al., 2009). However, few of these studies control for time, and thus it is difficult to establish whether the two trends are causally connected or merely co-occurring. Controlling for time is essential in inferring causality between trends in that it removes the confounding effects of all other co-occurring trends in observed or unobserved factors such as other aspects in the provision of mental health care, the national economy, alcohol consumption and divorce rates, which may influence suicide rates irrespective of antidepressant sales. National studies from Sweden and Finland report no beneficial effect after controlling for time (Dahlberg and Lundin, 2005; Korkeila et al., 2007), whereas it was found in a Norwegian study that increased sales reduced suicide rates in times of low antidepressant sales but not when sales were high (Bramness et al., 2007). Ludwig and his colleagues, in their time-controlled cross-national study, used between-country variation in how rapidly new medication is adopted and diffused nationally as an instrument for antidepressant sales in predicting suicide rates (Ludwig et al., 2009). They found a more rapid decline in suicide rates in countries with early and quick diffusion of new medications—because antidepressants were also introduced more rapidly in these countries. Their results suggest a decrease of five per cent in suicide rates for an increase of one pill per capita per day. An instrumental variable approach is a strong test for causality because an instrument is only assumed to influence the outcome via its effect on the exposure of interest, and thus lacks problems related to confounding.

The evidence of a causal connection between increasing antidepressant sales and decreasing suicide rates in national populations seems compelling. However, it is unclear from the existing research whether increased antidepressant sales have benefitted all population subgroups equally. Subgroup-specific evidence is relevant given that the increase in antidepressant treatment is likely to prevent suicides only among groups that are adequately treated. Suicides are committed predominantly by men in a low socioeconomic position (Mäki and Martikainen, 2009, 2008), whereas

antidepressants are consumed primarily by women and the socioeconomic patterning of antidepressant use is less clear (see Chapter 3.2. *Social differentials in antidepressant treatment*). According to a review of aggregate-level studies, the decline in female suicide rates has been less strongly related to the introduction of new antidepressants than in male suicide rates (Baldessarini et al., 2007), but none of the studies contributing to this result controlled for time and thus causal inference is problematic. No previous studies have assessed the effects of antidepressant use on suicide across socioeconomic and living-arrangement groups.

Another limitation in the current literature is that little is known about the effects of antidepressant use on alcohol-related suicides, in other words suicides in which alcohol intoxication is a contributory cause. This is a significant subtype, particularly in Finland where around 30–40 per cent of all suicides are alcohol-related (Mäki and Martikainen, 2009, 2008). Furthermore, evidence from earlier studies suggests that depression is suboptimally treated among patients with suicides attempts or comorbid alcohol use disorders (AUD) (Blanco et al., 2012; Suokas and Lönnqvist, 1995; Suominen et al., 2002). Although not all alcohol-related suicides are committed by people with AUD, increased antidepressant treatment in this high-risk group could have a beneficial effect in preventing alcohol-related suicides. However, no previous studies on this are available.

4 THE CONTEXT AND THE AIMS OF THE STUDY

4.1 THE FINNISH CONTEXT

This study is set in Finland, a Nordic welfare state with tax-funded universal healthcare and a nationwide health insurance scheme covering all permanent residents irrespective of age, wealth or region of residence (National Agency for Medicines and Social Insurance Institution, 2012; OECD, 2012; Wahlbeck et al., 2008). Despite the intention to provide equally accessible healthcare, concerns have been raised particularly related to the various pathways to care, namely public outpatient services, occupational health services and private health services, the latter two being available only to the employed and more affluent sections of the population (Wahlbeck et al., 2008).

With regard to depression, Finland is a rather average European country. The 12-month prevalence of depressive disorders (6.5% in Finland vs. a 6.9% median across European studies) and differences in prevalence according to education, employment and marital status are similar to those reported in other European countries (Lindeman et al., 2000; Pinto-Meza et al., 2013; Pirkola et al., 2005; Wittchen and Jacobi, 2005). Finland has a relatively high suicide rate—in 2010 the age-standardised rate was 16.8 per 100,000 persons compared with the European average of 12.3 (OECD, 2012). An extensive, nationwide suicide-prevention programme was implemented in Finland in 1992–1996, one of the major goals of which was to improve the detection and treatment of depression (Beskow et al., 1999). The programme has been evaluated as highly successful (Beskow et al., 1999; Upanne, 1999): the detection and pharmacotherapy of depression have improved (Sorvaniemi et al., 2006) and suicide rates have declined since the beginning of the 1990s, although the causal connection between these developments has not been empirically tested (Beskow et al., 1999; Upanne, 1999). Alcohol consumption in Finland is below the European average (OECD, 2012), yet Finland has one of the highest alcohol-related mortality in Western Europe (Ramstedt, 2002), possibly because of more harmful drinking habits. Both alcohol consumption and alcohol-related mortality increased during the study period (Herttua et al., 2007; National Institute for Health and Welfare, 2013).

Overall, the treatment of depression in Finland has been judged inadequate. Less than a third of depressed people received any treatment for their depression at the turn of the millennium (Hämäläinen et al., 2009, 2004), and only 60 per cent of the patients who were given any treatment had used specialist mental-health services in municipal psychiatric outpatient clinics, mental-health centres, private psychiatrists or psychiatric hospitals (Hämäläinen et al., 2004). Antidepressants are the most common treatment for depression in Finland (Hämäläinen et al., 2009). They are sold to the

public only by authorised pharmacies against a prescription issued by a doctor—no over-the-counter medication is available (National Agency for Medicines and Social Insurance Institution, 2012). All residents are eligible for the reimbursement of antidepressant costs as part of the public-health-insurance scheme. The reimbursement level during the study period was 42 per cent. Drug costs are directly reimbursed at the time of purchase, the reimbursement covering a maximum prescription period of three months at a time (National Agency for Medicines and Social Insurance Institution, 2012). There is also an annual payment ceiling for out-of-pocket drug costs, after which all further costs are fully reimbursed. A computerised individual-level register of all reimbursed medications was created in 1994 to administer the accumulation of out-of-pocket costs for patients (Klaukka, 2001). This national Prescription Register is updated monthly from all retail pharmacies and the information can be linked with other administrative registers using personal identity codes given to all Finnish residents.

The availability of publicly financed psychotherapy was limited during the study period. The demand far exceeded the supply in terms of available funds, and there was also a shortage of psychotherapists outside urban areas (Wahlbeck et al., 2008). Less than 20 per cent of depressed individuals in the general population received any psychological treatment in 2000–2001 (Hämäläinen et al., 2009), and the proportion is suggested to be even lower (around 10%) among people granted a disability pension on the grounds of depression (Honkonen et al., 2007).

The Finnish system of mental health care has been described as fragmentary and complex (Harjajärvi et al., 2006; Korkeila, 2009). It has become highly decentralised since the deinstitutionalisation of psychiatric care from the beginning of the 1990s (Korkeila, 2009). The municipalities are currently responsible for arranging mental-health services for their residents, either as part of their primary care provision or via services purchased from larger hospital districts, private care providers and non-profit organisations (Harjajärvi et al., 2006; Wahlbeck et al., 2008). There is large variation between municipalities in the extent and type of psychiatric outpatient services available (Harjajärvi et al., 2006; Korkeila, 2009). Psychiatric inpatient care is provided in psychiatric hospitals, the psychiatric wards of general hospitals, and psychiatric wards under the administration of municipal health services (Harjajärvi et al., 2006; Kaltiala-Heino et al., 2001). There are no private psychiatric hospitals in Finland, but most residential services for psychiatric patients are privately run with municipal funding (Harjajärvi et al., 2006).

Treatment of substance use disorders in Finland has traditionally been separate from mental healthcare, and services are mainly provided by municipal social-care departments (Tammi and Stenius, 2014). Some types of service such as discussion therapies and the treatment of somatic diseases caused by substance use are also provided by the healthcare sector (National Institute for Health and Welfare, 2013). The national plan for mental health

and substance abuse work promotes the integration of outpatient services for mental health and substance use disorders (Ministry of Social Affairs and Health, 2012). However, the decentralised provision of services compromises the potential for government steering and there are wide differences in service integration among the municipalities (Tammi and Stenius, 2014). Alcohol use disorders comprise the vast majority of substance use disorders in Finland. For example, alcohol-related causes accounted for about 86 per cent of all substance-related inpatient care episodes in 2012, and over 90 per cent of all substance-related deaths (National Institute for Health and Welfare, 2013).

This study covers a period of constant economic growth between two large-scale economic downturns: the great recession at the beginning of the 1990s and the recession following the financial crisis in 2008.

4.2 THE AIMS OF THE STUDY

The overall aim of this study was to examine how the adverse outcomes of depression vary according to social factors such as socioeconomic position, employment status, and living arrangements, and to establish the role of alcohol and antidepressant treatment in bringing about this variation. The study used large longitudinal register-based data for representative samples of working-age and older Finns.

The specific aims were:

1. To assess the social differentials in the psychiatric admission risk for depression, in the excess mortality of depression, and in antidepressant use (Sub-studies I-III).
2. To quantify the contribution of alcohol-related causes of death on the excess mortality of depression (Sub-study II).
3. To establish whether increased sales of antidepressants caused the fall in suicide rates in Finland, and whether the effect was similar across population subgroups and for alcohol-related and non-alcohol-related suicides (Sub-study IV).

5 MATERIALS AND METHODS

5.1 DATA SOURCES AND STUDY DESIGNS

The analyses were based on longitudinal individual-level population register samples combining information from various administrative registers. The personal identity codes given to all permanent residents of Finland were used to link the different information. Annually updated data on socioeconomic position, employment status, living arrangements, and dates and causes of death were obtained from Statistics Finland. Hospital discharge records including the diagnoses and exact dates of entry and exit came from the national Hospital Discharge Register held by the National Institute for Health and Welfare (THL). The Social Insurance Institution (Kela) provided information on all purchases of prescription medication from retail pharmacies, including dates, amounts and type, drawn from the national Prescription Register, as well as information on the right to reimbursement for drug costs under the Special Refund Categories due to certain diagnosed chronic conditions. Information on alcohol-related deaths was based on the underlying and contributory causes of death given on the death certificate and came from the Statistics Finland Cause of Death Register. Register data facilitate the longitudinal assessment of depression outcomes in a large population-based sample, with minimal attrition or loss to follow-up that may be critical problems in clinical and survey-based studies (Fischer et al., 2001). Validity studies have shown these register sources to have good quality and practically complete national coverage (Haukka et al., 2007; Lahti and Penttilä, 2001; Mathers et al., 2005; Rikala et al., 2010; Sund, 2012; Sund et al., 2014).

The first two sub-studies were based on a 14-per-cent random sample of the Finnish population aged 40 years and older at the end of 1997, whereas the third and fourth were based on an 11-per-cent sample of the Finnish population aged 15 years and older in 1987-2007. The latter sample was further supplemented with an oversampling of people who died, covering 80 per cent of all deaths occurring during the study period. The register holders approved of the use of these linked datasets for research purposes (permission numbers TK-53-574-04 and TK-53-373-09 for sub-studies I and II, and TK-53-1519-09 for sub-studies III and IV). Table 1 summarises the main characteristics of the study samples and designs.

Sub-study I was based on a cohort design with a baseline population of people aged 40–64 years, living in private households at the end of 1997 (n=237,469). Those living in institutions were not included because information on antidepressant purchases (one of the main indicators of depression used in this sub-study) was not available for this group. People aged 65 and older were not included either because many of the social factors

of interest, such as employment status and co-residence with minor children, generally applied to the working-age population. Furthermore, it has been shown that the relationship between antidepressant use and depression is weaker among older adults (Sihvo et al., 2008), and antidepressant use would thus have been a less valid indicator of depression than among the working-age population. The sample was assessed for baseline psychiatric morbidity in 1996-1997 using data on primary diagnoses of inpatient hospital care, the right to special reimbursement for drug costs for certain diagnosed conditions, and purchases of psychotropic medication (see Chapter 5.2.2 *Psychiatric and somatic comorbidity* for details). In order to focus on the outcomes of unipolar depression, individuals with more serious psychiatric disorders such as schizophrenia and bipolar disorders (n=5,658) as well as those with any missing data (n=118) were excluded. Finally those in psychiatric hospital care at baseline (n=64) were excluded as, by definition, they were not at risk for hospital admission for unipolar depression, the outcome of interest in this sub-study. The remaining sample (n=231,629) was divided into three groups according to depression status in the two years preceding baseline: those with inpatient care for unipolar depression, those with antidepressant purchases and those with neither in 1996–1997. These groups were followed up separately for inpatient hospital admission with a primary diagnosis of unipolar depression in 1998–2003.

The baseline sample and study design in sub-studies I and II were broadly similar. However, those in psychiatric inpatient care at baseline were not excluded in sub-study II. The sample was followed up for cause-specific mortality in 1998–2007, during which a total of 15,081 deaths were observed. The mortality rates were compared according to depression status at baseline, and in order to establish whether or not economic and social resources buffered against the detrimental effect of depression, the magnitude of the excess mortality of depressed patients was compared between social groups. The contribution of alcohol-related and other causes of death to the excess mortality was also calculated in this study.

The focus in sub-study III was on educational differences in the prevalence of antidepressant use among people aged 25–64 living in private households, and having at least one hospital-care episode with a primary diagnosis of unipolar depression in 1998–2007 (n=7,249). Antidepressant use was assessed in consecutive three-month periods before and after the *first* hospital-care episode for depression. If this episode was immediately preceded or followed by another hospital episode, with no days back in the community in between, the episodes were treated as a single episode and the three-month periods were calculated before and after this combined episode. One individual could be observed for up to 40 periods, five years before admission and five years after discharge. However, only periods between the beginning of 1998 and the end of 2007, when the individual was alive, aged 25–64 and living in the community, were included in the analyses, and thus an individual could contribute less than 40 periods of observation time. The prevalence of

antidepressant use was calculated for each period only among individuals eligible for that period.

Adults aged 20 and older in 1995–2007 (n=950,158) were followed up yearly for alcohol-related (n=2,859) and non-alcohol-related (n=8,632) suicide in sub-study IV. Suicide risk was predicted by regional antidepressant sales controlling for regional differences and national-level time trends that may influence suicide risk irrespective of the regional sales. The effects of antidepressant sales on suicide risk were assessed across relevant population subgroups to establish whether the increased sales affected all groups similarly.

Table 1. *Data sets used in the sub-studies*

Sub-study	Sample	Ages	Study period	N	Dependent variables
I	14% community sample from 1997	40–64	1997–2003	231,629	Psychiatric hospital admission for depression
II	14% community sample from 1997	40–64	1997–2007	231,695	Cause-specific mortality
III	11% population sample from 1998–2007 and 80% of those dying in 1998–2007 (only non-institutionalised individuals with at least one hospital episode for depression)	25–64	1998–2007	7,249	Antidepressant use
IV	11% population sample from 1995–2007 and 80% of those dying in 1995–2007	20+	1995–2007	950,158	Alcohol-related and non-alcohol-related suicide

5.2 VARIABLES

5.2.1 DEPRESSION

In this study depression was assessed indirectly using data on hospital care and antidepressant purchases, which are the main indicators available in register data (Thielen et al., 2009). Baseline depression status was measured in the two years (1996–1997) preceding baseline in sub-studies I and II, and during the whole follow-up period (1998–2007) in sub-study III. The exact

criteria and terminology varied somewhat across the sub-studies, and this is indicated in the text when appropriate.

Inpatient hospital care with a primary diagnosis of depression in psychiatric or general hospital wards was used to measure depression in sub-studies I–III. *Depressed inpatients* had hospital care for the following diagnoses, coded according to the International Classification of Diseases Tenth Revision (ICD-10): depressive episode (F32), recurrent depressive episode (F33), dysthymia (F34.1), recurrent brief depressive episodes (F38.1), and postpartum depression (F53.0). A subject who had hospital care for depression was defined as an inpatient irrespective of his or her antidepressant purchases.

Purchasing antidepressants was used as a proxy measure for being in outpatient care for depression in sub-studies I and II. *Depressed outpatients* had purchases of antidepressants but no inpatient hospital care. Antidepressants included codes N06A in the Anatomical Therapeutic Chemical Classification (ATC). In order to focus on depression, tricyclic antidepressants (codes N06AA but not N06AA22) were excluded as they are often used for non-psychiatric indications (Gardarsdottir et al., 2007). Although also non-tricyclic antidepressants have indications other than depression, such as anxiety, eating disorders, pain, incontinence, and insomnia (Gardarsdottir et al., 2007) the main use in Finland is for depression (Sihvo et al., 2008).

In sub-study II depressed outpatients were defined as having made at least one non-tricyclic antidepressant purchase in the two years preceding baseline. The definition was stricter in sub-study I: depressed outpatients had to have a minimum of two yearly purchases or purchases of at least 90 Defined Daily Doses (DDD) of any non-tricyclic antidepressant in the two-year period preceding baseline. DDD is the assumed average daily dose of a given drug for its main indication in adults, set by the World Health Organization (WHO Collaborating Centre for Drug Statistics Methodology, 2013), and information on the number of DDDs purchased was obtained from the Prescription Register held by Kela.

Depression severity was assessed in sub-studies I and III. The psychotic features of depression (F32.3 and F33.3) were used as a proxy for depression severity among depressed inpatients (sub-studies I and III). The number of DDDs was used in sub-study I as a proxy for the baseline severity of depression among outpatients with larger amounts, indicating more severe depression. The categories were less than 90, 90–179, 180–359, 360–719 and over 720 DDDs in the two-year period preceding baseline. These categories reflect daily use for less than three months, between three and six months, between six and 12 months, for a year to two years, and for over two years, respectively.

Subjects with neither inpatient care for depression nor the required number of antidepressant purchases were defined as *non-depressed* in sub-studies I and II. It should be noted that this group included non-depressed

people but also depressed individuals with no inpatient or antidepressant treatment.

In sub-study I depressed inpatients were termed as having a '*baseline history of inpatient treatment*', depressed outpatients as having a '*baseline history of antidepressant treatment*', and the non-depressed as having '*no baseline history of inpatient or antidepressant treatment*'. However, for the sake of clarity and consistency the terminology used in sub-studies II and III is applied in this summary. All the dependent and independent variables used in the sub-studies are listed in Table 2.

5.2.2 PSYCHIATRIC AND SOMATIC COMORBIDITY

Psychiatric comorbidity was assessed in sub-studies I–III, its measurement being based on primary hospital diagnoses and purchases of psychotropic medication. Chronic somatic disorders were controlled for in the mortality analyses of sub-study II, and were based on hospital diagnoses, purchases of prescription medication, and the right to reimbursement for drug costs using algorithms adapted for Finnish health registers (Nihtilä et al., 2008; Sund, 2003). Psychiatric and somatic morbidity were measured in the two years preceding baseline (1996–1997) in sub-studies I and II, and during the whole follow-up period (1998–2007) in sub-study III.

In order to focus on unipolar depression in sub-studies I and II, individuals with more serious psychiatric disorders than depression (schizophrenia, or manic, bipolar or non-affective psychotic disorders) at baseline were excluded irrespective of comorbid unipolar depression. The exclusion was based on hospital care (ICD-10 codes F20–F29, F30.1–F31, F53.1) and on the right to special reimbursement for drug costs due to diagnosed psychosis. Individuals with hospital care for other psychiatric disorders but not for unipolar depression were also excluded because defining them as non-depressed or as depressed outpatients using antidepressants would have made these groups less meaningful.

Once individuals with more serious psychiatric disorders had been excluded, as described above, other psychiatric comorbidity was assessed. The measurement of comorbid *substance use disorders (SUD)* differed slightly across the sub-studies. In sub-study III it only included hospital care for substance-induced psychiatric disorders (ICD-10 codes F10–F19) and alcohol intoxication (X45), whereas purchases of prescription medication for SUD (ATC codes V03AA and V03AB30) were also included in sub-study I. A more comprehensive definition was used in sub-study II to capture all alcohol-related morbidity and thus also hospital care for substance-induced somatic disorders (K29.2, K70, K86.0, I42.6, O35.4, G31.2, G40.51, G62.1, and G72.1), and a more comprehensive list of prescription medications (N02AC02, N02ACXX, N02AC06, N02AE01, N07BB, N07BC) was included.

Further psychiatric comorbidity among depressed inpatients was defined in sub-study I as inpatient treatment for other psychiatric disorders (other

ICD-10 codes F30–F69, F99, excluding unipolar depression, SUD and more serious psychiatric disorders). Purchases of other psychotropic medication (ATC codes N05A–N07, excluding non-tricyclic antidepressants) were used as a measure for comorbid psychiatric problems among depressed outpatients and non-depressed individuals.

5.2.3 SOCIAL FACTORS

Social factors were measured at baseline at the end of 1997 in sub-studies I and II, and as time-varying and updated annually in sub-studies III and IV. In practice, measuring covariates as time-varying means reallocating each individual annually according to changes in their status. An individual can thus contribute to the population at risk and to the number of events in different groups in different years. For example, an individual may be alive and employed for one year and thus contribute a year of person-time to the employed group. If the same individual is unemployed in the next year, and commits suicide, he or she contributes less than a year of person-time and one event of suicide to the unemployed group. It should be kept in mind that treating covariates as time-varying does not provide an estimate for the effect of status change such as job loss, but only allocates events and populations at risk more accurately.

Education was based on the highest achieved qualification, classified according to the International Standard Classification of Education (ISCED) as tertiary (ISCED levels 5–6), secondary (3–4) and basic (0–2) (UNESCO Institute for Statistics (UIS), 2012). The two highest levels were collapsed in sub-study IV. In sub-study III those enrolled in education for a higher degree than the one already achieved were included in the higher categories, and the two lower-level categories were collapsed. Thus the educational groups in sub-study III were any and no post-secondary education.

Occupational social class was based on the classification of Statistics Finland (1989) and included non-manual, manual and other. Economically inactive persons were classified according to their previous occupation, and homemakers were classified according to the occupation of the head of the household.

Household net income per consumption unit was calculated by first summing up all the taxable income of all household members (including wages, capital income and taxable income transfers, and excluding taxes), and then dividing the sum by the number of consumption units in the household. Consumption units were defined as 1.0 for the first household member and 0.7 for each of the other members. Household income was presented in quartiles.

Individual taxable income included wages, capital income and taxable income transfers, without excluding taxes, and was divided into tertiles. The two highest tertiles were collapsed and compared to the lowest.

Home ownership was categorised as owner and renter.

Employment status was classified as employed, unemployed, on disability pension and other. The three last-mentioned groups were collapsed in sub-studies III and IV, and compared with the employed group.

Living arrangements were based on information regarding co-residence and official marital status, categorised in sub-study I as living with a marital or non-marital partner, not living with a partner and never having been married, and not living with a partner and having previously been married. The two latter categories were collapsed in sub-studies II and IV, and the partnered were compared to the non-partnered. Those living alone were compared with all the others in sub-study III. Co-residence with minor children was also assessed in sub-study I.

The demographic variables included gender, age, region of residence and study year. All the analyses were either controlled for or stratified by gender. Age was controlled for as categorical in sub-studies I, II and IV, and birth year as continuous in sub-study III. Region of residence was categorised according to the Nomenclature of Territorial Units for Statistics (NUTS) level 3 in sub-studies I and IV, and level 2 in sub-study III (Eurostat, 2013).

5.2.4 OUTCOMES OF DEPRESSION

The measurement used in sub-study I for the unfavourable course of depression was admission to hospital care with a primary diagnosis of unipolar depression (ICD-10 codes F32–F33, F34.1, F38.1, F53.0).

Sub-studies II and IV assessed suicides and other mortality as depression outcomes. Deaths were classified as suicides (ICD-10 codes X60–X84, Y87.0), all accidental and violent deaths including suicides (V01–X44, X46–Y89), and disease deaths including accidental alcohol poisoning (A00–T98, X45). They were further divided into alcohol-related and non-alcohol-related based on whether alcohol poisoning (X45) or an alcohol-related disease (F10, G312, G4051, G621, G721, I426, K292, K852, K860, O354, P043) was stated on the death certificate as an underlying or contributory cause. Suicides were considered alcohol-related if alcohol intoxication was stated as a contributory cause on the death certificate.

5.2.5 ANTIDEPRESSANT TREATMENT

Sub-study III focused on antidepressant treatment received in consecutive three-month periods before and after hospital care for unipolar depression. In order to capture the pharmacotherapy of depression as comprehensively as possible all antidepressants (ATC codes N06A), including tricyclic antidepressants (N06AA), were assessed. Sensitivity analyses excluding tricyclic antidepressants yielded highly similar results. An individual was defined as having *any antidepressant use* in a given three-month period if he or she had purchased antidepressants at least once during the period, and

as having *daily antidepressant use* if the purchases amounted to 90 DDDs or more.

Yearly individual-level data on non-tricyclic antidepressant purchases were aggregated in sub-study IV to produce regional antidepressant sales. Three sales measures were assessed: (1) the regional number of DDDs sold per capita per year to capture the amount of antidepressant medicine sold overall; (2) the regional prevalence of antidepressant users to capture the proportion of the population actually using antidepressants; and (3) the proportion with purchases of at least 90 DDDs per year among all antidepressant users. The last measure was used as an indicator of the proportion of antidepressant users with minimally adequate treatment as it corresponds to a prescription of three months or more, which is the general length of the acute-phase treatment of depression (Hirschfeld, 2001). Given that current guidelines recommend continuation treatment of between four and nine months after acute symptom resolution (American Psychiatric Association, 2010; Depression: Current Care Guidelines, 2014), sensitivity analyses were also conducted using the proportion of individuals making purchases of at least 180 DDDs per year.

It should be noted that DDDs do not measure prescribed daily doses as such, but are a computational measure. The true prescribed daily doses depend on patient characteristics such as age and weight, and may be larger or smaller than the DDD (WHO Collaborating Centre for Drug Statistics Methodology, 2013).

Table 2. Study variables in the sub-studies

Sub-study	Dependent	Independent
I	Hospital admission for depression	Gender; Age (categorical 5-year age-groups) Region of residence: NUTS3 Previous treatment: inpatient/antidepressant/neither; Educational attainment: tertiary/secondary/basic; Occupational social class: non-manual/manual/other; Household net income quartile; Home ownership: owner/renter; Employment status: emp./unemp./disability pension/other; Living arrangements: with partner/never marr./previously marr.; Co-residence with children; Severity of depression; Substance use disorder; Other psychiatric comorbidity;
II	Suicide; Accidental and violent deaths; Disease deaths; divided into alcohol-related and non-alcohol related	Gender (stratified); Age: categorical 1-year age-groups; Depression status: inpatient/antidepressant/neither; Educational attainment: tertiary/secondary/basic; Home ownership: owner/renter; Employment status: emp./unemp./disability pension/other; Living arrangements: with partner/without partner; Substance use disorder; Chronic somatic disorders as dummy variables;
III	Any antidepressant use; Daily antidepressant use	Gender; Year of birth (continuous); Region of residence: NUTS2; Study year: continuous; Educational attainment and enrolment: any post-secondary/no post-secondary; Employment status: employed/unemployed/other; Living arrangements: alone/with others; Substance use disorder; Severity of depression;
IV	Alcohol-related and non-alcohol-related suicides	Gender (stratified); Age (categorical 15-year age-groups); Region of residence: NUTS3; Study year: categorical; Regional non-tricyclic antidepressant sales (continuous): Doses per capita; prevalence of users; proportion of users with minimally adequate treatment; Education: 9+ years/9 or less Individual taxable income tertile: 2nd or 3rd/lowest Home ownership: owner/renter Employment status: emp./other Living arrangements: with partner/without partner

5.3 STATISTICAL METHODS

Social differentials in admission risk for depression (sub-study I) were studied using Cox proportional hazards regression models (Singer and Willett, 2003). Hazard ratios (HR) and their 95-per-cent confidence intervals were calculated from multivariate models, controlling for demographic factors, baseline severity of the depression, psychiatric comorbidity, and the social factors. The analyses were performed separately for depressed inpatients (n=846), depressed outpatients (n=8,754), and non-depressed individuals (n=222,029) at baseline. Given that few gender interactions were significant, both genders were combined in the analysis in order to gain statistical power. Individual follow-up times started at the end of 1997 and ended at hospital admission for depression (the outcome of interest), hospital admission for a more severe psychiatric disorder, emigration, death or the end of 2003, whichever came first.

Mortality in depression was assessed in sub-study II by calculating gender- and cause-specific mortality rates per 100,000 person-years during 1998–2007 for depressed inpatients (n=897, 165 deaths), depressed outpatients (n=13,658, 1,356 deaths) and the non-depressed population (n=217,140, 13,560 deaths) at baseline. The contribution of each cause to the total excess mortality of depressed inpatients and outpatients was calculated from these rates. The relative excess mortality was quantified in terms of mortality-rate ratios with 95-per-cent confidence intervals for the combined depressed inpatient and outpatient population compared with the non-depressed population. Rate ratios were calculated using the Mantel-Haenszel method (Clayton and Hills, 1993) controlling for age, inpatient status, SUD and other chronic somatic disorders at baseline. To assess whether social factors such as a high level of education, home ownership, employment or living with a partner buffered against the excess mortality of depression, the Mantel-Haenszel method was used to test the effect modification by these factors, controlling for age and inpatient status. Individual follow-up times were censored at death attributable to a cause other than the one studied, and at the end of 2007.

Educational differences in the prevalence of antidepressant use were assessed in sub-study III by means of logistic regression using generalised estimating equations (GEE). GEE models take into account the dependency of within-individual repeated measurements by assuming a correlation structure between them (Twisk, 2004, 2003). An unstructured working correlation was applied because it sets fewest restrictions on the correlation structure between measurements (Twisk, 2004). The results are presented as crude and adjusted differences between educational groups in the prevalence of antidepressant use across time, and the 95-per-cent confidence interval for the difference. Gender, study year, year of birth, region of residence, comorbid SUD, depression severity, employment status and living alone were controlled for in the adjusted model.

Individual-level Poisson regression models (Loomis et al., 2005) were used in sub-study IV to examine the extent to which regional antidepressant sales predicted suicide risk in 1995–2007 among men and women aged 20 and older (n=950,158). The yearly follow-ups were censored at death or end of year. Robust standard errors were calculated using the cluster-option in Stata to account for the non-independence of yearly follow-ups of the same individuals. A region and time fixed-effects approach was applied to control for regional differences and national-level time trends that may influence suicide risk irrespective of regional antidepressant sales. The region fixed effects control for all time-invariant regional characteristics such as the prevalence of depression, whereas time fixed effects (as single-year dummy variables) controls for variation in suicide risk common to all regions in a given year irrespective of their antidepressant sales (Allison, 2009). Analyses were conducted separately for different measures of antidepressant sales and for alcohol-related and non-alcohol-related suicides, as well as for population subgroups by gender, education, home ownership, employment status, income and living arrangements. The results are presented as suicide-incidence rate ratios (IRR) and their 95-per-cent confidence intervals per one-unit increase in regional antidepressant sales adjusted for age, region and year fixed effects.

The analyses in sub-studies III and IV were weighted to account for the oversampling of deaths in the data. The weighting produced similar estimates as would have been obtained by analysing the 11-per-cent random sample alone (without the oversampling of deaths), but the precision was greatly increased. Stata 8 and 11 (StataCorp, 2009, 2003) was used for all the analyses.

6 RESULTS

6.1 HOSPITAL ADMISSION FOR DEPRESSION (SUB-STUDY I)

Among middle-aged Finnish men and women 0.4 per cent had inpatient care for depression in 1996–1997 and were thus defined as depressed inpatients. Around three per cent of men and five per cent of women were depressed outpatients (defined as having purchased at least 90 DDDs of antidepressants or at least twice annually in 1996–1997). The risk of subsequent hospital admission for depression was strongly dependent on baseline depression status: almost 30 per cent of depressed inpatients were readmitted during the five-year follow-up against admission of only around five-per-cent of depressed outpatients, and less than one per cent among the non-depressed population (Table 3).

Among depressed inpatients (Figure 1, Panel A), having the lowest income, living in rented housing, being on disability pension and being never or previously married increased the risk of readmission by 20–50 per cent. However, these effects did not reach statistical significance in the full model in which baseline severity, psychiatric comorbidity, demographics and all social factors were controlled for simultaneously. Education, occupational social class, unemployment and having coresident children were unrelated to readmission risk among depressed inpatients.

The results were fairly similar for depressed outpatients (Figure 1, Panel B). Again, education and occupational social class were unrelated to admission risk. Having the lowest income, living in rented housing, not being employed, being previously married and not having coresident children increased the risk by 25–60 per cent when only demographics were controlled for. However, these effects were largely attenuated and failed to reach statistical significance in the full model. Around half of the attenuation was due to adjustment for baseline severity and psychiatric comorbidity (35–70% depending on the variable), and half was due to mutual adjustment for all social factors.

Social differentials in admission risk were larger among the non-depressed population than among depressed inpatients and outpatients following adjustment only for demographics (Figure 1, Panel C). All the measures of a low socioeconomic position as well as not being employed, not living with a partner and not having coresident children were strongly related to the risk of hospital admission for depression. However, the effects were of similar magnitude as among the depressed groups in the full model. As there were no measures for baseline severity in this group, most of the attenuation between the models was due to mutual adjustment for all social factors.

Table 3. *Distribution of the study population in 1997 and the proportions admitted to hospital for depression in 1998–2003 by depression status in 1996–1997 and social factors in 1997: Finnish community-dwelling men and women aged 40–64 in 1997*

	Depression status					
	Inpatients		Outpatients		Non-depressed	
	Distribution %	Admitted %	Distribution %	Admitted %	Distribution %	Admitted %
Gender						
Men	47.8	23.7	38.3	5.4	50.2	0.5
Women	52.2	34.6	61.7	5.0	49.8	0.6
Education						
Tertiary	20.9	27.1	29.0	5.1	25.7	0.5
Secondary	32.5	32.0	34.4	5.6	33.6	0.7
Basic or less	46.6	28.7	36.6	4.7	40.6	0.6
Occupational Social Class						
Non-manual	38.5	30.1	53.5	4.8	46.5	0.5
Manual	43.6	29.0	30.4	5.6	36.5	0.7
Other	17.8	29.2	16.1	5.5	17.1	0.5
Household income quartile						
Highest	15.7	24.8	24.7	4.4	25.4	0.4
3rd	20.6	28.7	23.9	4.1	25.3	0.5
2nd	24.5	29.9	23.0	4.7	25.1	0.6
Lowest	39.2	31.4	28.4	7.1	24.1	0.9
Home ownership						
Owner	62.3	25.8	72.1	4.6	79.9	0.5
Renter	37.7	35.4	27.9	6.6	20.1	0.9
Employment status						
Employed	31.8	26.8	50.6	4.8	65.6	0.5
Unemployed	15.5	28.2	15.1	7.0	12.1	0.9
Disability pension	43.1	31.3	26.1	4.6	12.2	0.8
Other	9.6	32.0	8.3	6.1	10.1	0.6
Living arrangements						
With partner	52.1	25.6	61.8	4.5	74.0	0.5
Never married	13.6	31.3	11.6	5.6	10.4	0.7
Previously married	34.3	34.5	26.6	6.5	15.6	0.9
Coresident minors						
Yes	22.8	30.1	27.3	5.3	32.5	0.6
No	77.2	29.2	72.7	5.1	67.5	0.6
All	100.0	29.4	100.0	5.2	100.0	0.6
N	846	249	8,754	452	222,029	1,320

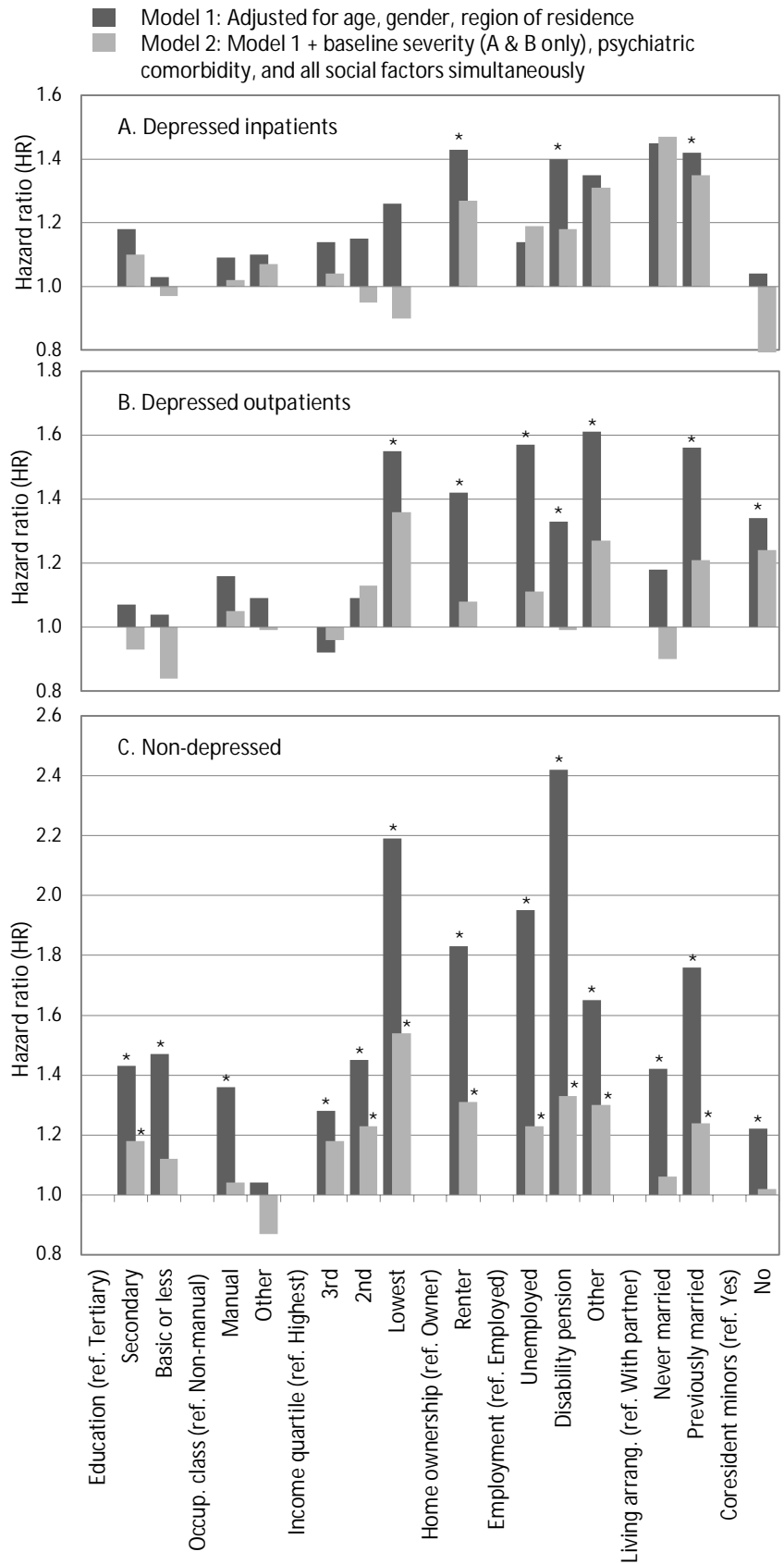


Figure 1 Hazard ratios of hospital admission for depression in 1998–2003 by social factors in 1997 and depression status in 1996-1997. Finnish community-dwelling men and women aged 40–64 in 1997, *Statistically significant at the .05 level.

6.2 MORTALITY IN DEPRESSION (SUB-STUDY II)

When the focus turned to mortality, depressed outpatients were defined more broadly than in the study of psychiatric admission for depression. Thus the proportion of depressed outpatients, defined as having made at least one antidepressant purchase in the two years preceding baseline, was larger: 4.4 per cent among men and 7.4 per cent among women (Table 4). All-cause mortality was three-fold among depressed male inpatients and four-fold among depressed female inpatients compared with non-depressed men and women, respectively. In the case of depressed outpatients, all-cause mortality was around two-fold compared with the non-depressed in both genders.

Table 4. Study population, number of deaths, mortality rate (per 1000 person years), and deaths by cause in 1998–2007. Finnish community-dwelling men and women aged 40–64 in 1997

Men	Inpatients	Outpatients	Non-depressed
%	0.4	4.4	95.2
N	432	5061	109819
Number of deaths	103	788	9514
Mortality rate	27.5	16.9	9.0
Deaths by cause (%)			
Suicides			
Alcohol-related	6.8	2.9	1.6
Non-alcohol-related	10.7	4.9	2.3
Other accidental and violent deaths			
Alcohol-related	6.8	8.2	4.2
Non-alcohol-related	4.9	6.0	3.8
Disease deaths			
Alcohol-related	25.2	27.9	18.7
Non-alcohol-related	45.6	49.6	69.0
Unknown cause	0.0	0.4	0.3
<hr/>			
Women	Inpatients	Outpatients	Non-depressed
%	0.4	7.4	92.2
N	465	8597	107321
Number of deaths	62	568	4046
Mortality rate	14.3	6.8	3.8
Deaths by cause (%)			
Suicides			
Alcohol-related	3.2	1.4	0.3
Non-alcohol-related	27.4	5.1	1.5
Other accidental and violent deaths			
Alcohol-related	6.5	4.2	1.6
Non-alcohol-related	4.8	5.5	3.1
Disease deaths			
Alcohol-related	12.9	15.8	8.7
Non-alcohol-related	45.2	67.8	84.6
Unknown cause	0.0	0.2	0.2

Of this excess mortality suicides accounted for around 10 per cent among outpatient men and women, and around 25 and 40 per cent among inpatient men and women, respectively (Figure 2). The majority (60–70%) of the excess mortality was accounted for by disease deaths in all the other groups except inpatient women. However, a large proportion of the excess disease deaths were alcohol-related (45–60% among men and 30–35% among women).

Overall, alcohol-related causes accounted for 45–55 and 25–35 per cent of all excess deaths among men and women, respectively. All alcohol-related excess deaths combined with non-alcohol-related accidental and violent deaths accounted for around 70 per cent of the total excess among inpatient men and women, and around 70 and 55 per cent among outpatient men and women, respectively.

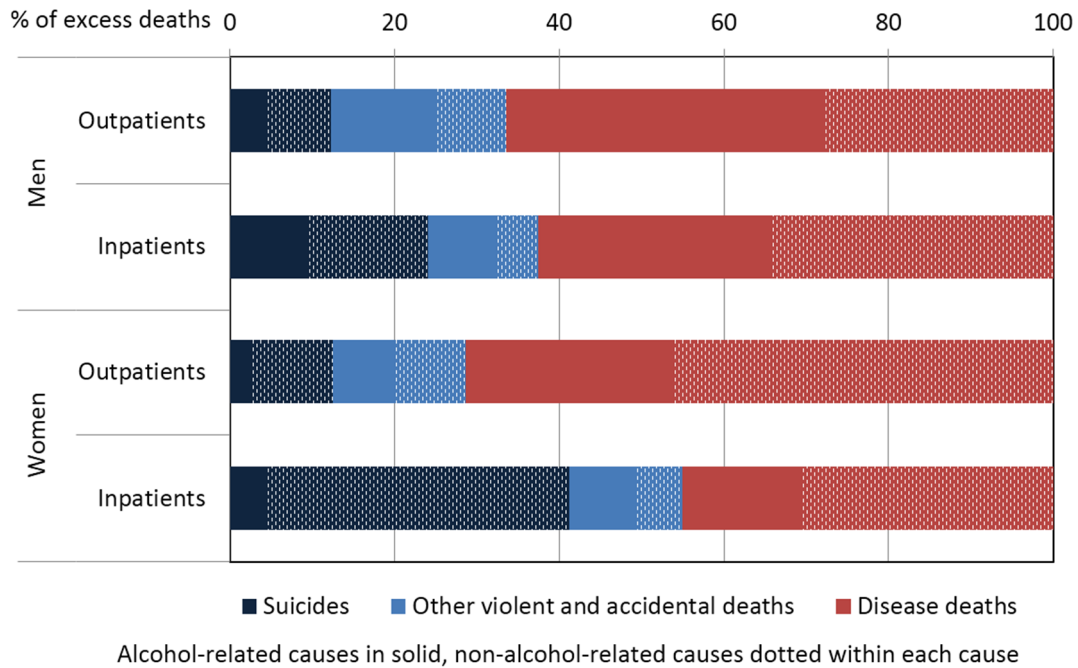


Figure 2 Proportion of excess mortality in 1998–2007 among depressed inpatients and outpatients compared with the non-depressed population accounted for by different causes of death. Finnish community-dwelling men and women aged 40–64 in 1997

Mortality rates in the non-depressed population were consistently higher among those who had a low level of education, did not own their home, were not employed, and were not living with a partner (Table 5). The social patterning of mortality was less clear in the depressed population (combining inpatients and outpatients), and the differences between the social groups were smaller. The relative excess mortality for all alcohol-related causes among the depressed was significantly larger among men and women with higher levels of education and employment. Furthermore, the excess mortality for alcohol-related diseases was larger among those owning their home. The relative excess mortality of the depressed was not significantly modified by social factors in the case of non-alcohol-related causes.

Table 5. Absolute mortality rates^a and mortality rate ratios (RR) in 1998–2007 by cause of death, depression status in 1996–1997, and social factors in 1997. Finnish community-dwelling men and women aged 40–64 in 1997

	Alcohol-related						Non-alcohol-related					
	Men			Women			Men			Women		
	Dep. ^b	Non-dep.	RR ^c	Dep. ^b	Non-dep.	RR ^c	Dep. ^b	Non-dep.	RR ^c	Dep. ^b	Non-dep.	RR ^c
Accidental and violent deaths												
Education												
Tertiary	157	28	4.92	49	3	16.50	114	33	2.94	93	11	5.04
Secondary	285	54	5.18	34	8	4.86	233	58	3.57	92	18	4.63
Basic	163	66	2.20	48	10	3.84	242	69	3.35	90	21	3.35
Home-ownership												
Owner	136	41	3.13	36	5	6.58	173	46	3.42	68	16	3.26
Renter	369	98	3.55	64	18	3.37	279	97	2.70	154	24	5.19
Employment status												
Employed	115	29	3.75	28	4	6.16	120	36	2.73	45	13	2.99
Unemployed	463	157	2.69	49	17	2.22	308	105	2.90	139	16	7.16
Disability	175	75	1.65	53	16	2.48	265	108	2.14	149	44	2.33
Living with partner												
Yes	114	32	3.53	42	6	6.38	120	37	2.94	72	16	3.59
No	367	119	2.86	45	12	3.56	355	116	2.88	123	22	4.38
Disease deaths												
Education												
Tertiary	321	72	3.98	66	14	4.24	620	374	1.44	283	201	1.29
Secondary	564	172	3.16	139	29	4.82	663	482	1.31	370	256	1.39
Basic	546	229	2.33	118	50	2.23	1245	899	1.41	674	464	1.46
Home-ownership												
Owner	359	114	2.90	86	21	3.69	799	559	1.34	440	297	1.40
Renter	815	389	2.12	184	86	2.17	1052	879	1.26	558	436	1.27
Employment status												
Employed	269	72	3.54	66	16	3.90	380	323	1.17	233	184	1.21
Unemployed	842	493	1.65	197	98	1.71	593	755	0.87	377	342	1.18
Disability	559	358	1.27	163	71	1.93	1823	1927	1.05	1008	1043	1.05
Living with partner												
Yes	267	89	2.81	99	27	3.67	805	527	1.40	417	283	1.39
No	897	425	2.10	132	50	2.30	993	928	1.14	560	436	1.33

Significant excess mortality in bold

Effect modification significant at level * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

^a Per 100,000 person-years

^b Depressed outpatients and inpatients combined

^c Depressed vs. non-depressed, adjusted for age and inpatient status.

6.3 ANTIDEPRESSANT USE TRAJECTORIES (SUB-STUDY III)

Men and women with at least one hospital episode for depression in 1998–2007 were followed up for up to 10 years, splitting the follow-up into consecutive three-month periods before admission and after discharge. Of these periods around 25 per cent were spent in any post-secondary education, defined as high education (Table 6). The proportions of periods with any antidepressant use and with daily antidepressant use were slightly larger among those with a high as opposed to a low educational level (43% vs. 42% and 31% vs. 29% for any and daily use, respectively). The highly educated were more likely to be female and younger, and to have psychotic depression and less likely to have had hospital care for substance use disorders (SUD) during follow-up. Those with a high education were also more likely to be employed and less likely to live alone than those with a low-level education.

Table 6. *Characteristics of the study population (n=7,249) as means and proportions of observed three-month periods by education. Finnish community-dwelling men and women aged 25–64 with at least one hospital episode for depression in 1998–2007*

	Education	
	Low	High
Any antidepressant use (%)	41.8	42.7
Daily antidepressant use (%)	28.6	30.8
Women (%)	53.3	61.0
Age (mean)	45.1	43.5
Psychotic depression (%)	11.4	15.6
Substance use disorder (%)	20.1	14.4
Employed (%)	39.5	61.6
Unemployed (%)	17.1	9.5
Living alone (%)	31.9	28.6
Weighted %	75.2	24.8
N (periods)	129,869	40,798

In the five years preceding hospital admission for depression there were no differences between the educational groups in the prevalence of any antidepressant use (defined as having made at least one purchase of antidepressants in a given three-month period) (Figure 3). However, there was a significant three-to-four-percentage-point excess in the prevalence of antidepressant use among the highly educated in the three-month periods immediately preceding admission and following discharge. The difference widened further in the three-to-six-month period after discharge as the prevalence of any antidepressant use decreased more rapidly among the less

highly educated. This excess, ranging from three to six percentage points, lasted for 2.5 years after discharge.

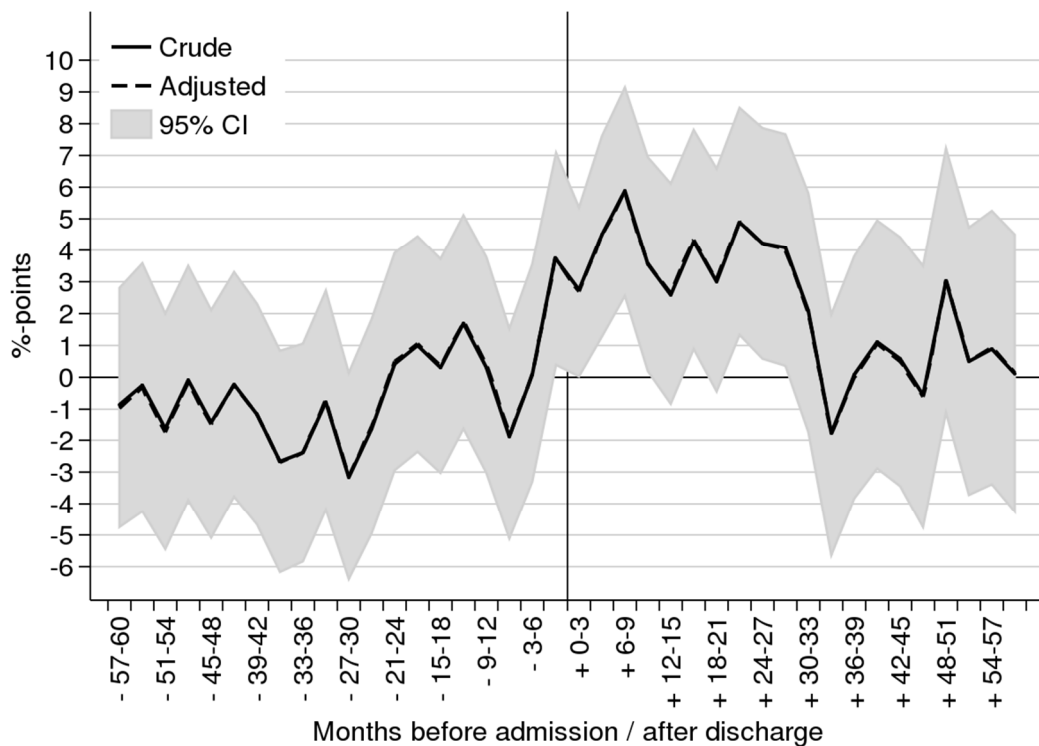


Figure 3 Excess in the prevalence of any antidepressant use among those with a high vs. a low level of education before and after hospital care for depression with 95% confidence intervals (CI). Finnish community-dwelling men and women aged 25–64 in 1998–2007. The adjusted model includes gender, birth year, study year, region of residence, psychotic features, SUD, employment status, and living alone

Educational differences in the prevalence of daily antidepressant use (defined as at least 90DDD of antidepressant purchases in a given three-month period) were largely similar to any use (Figure 4). However, the prevalence of daily use was much lower. Even at its peak, immediately after discharge, it was only 63 per cent among the highly educated and 55 per cent among those with a low educational level, compared with 81 and 78 per cent, respectively for any antidepressant use (data not shown). The differences between the educational groups were also larger: between three and eight percentage points up to 2.5 years after discharge.

Despite the large differentials in clinical and socio-demographic characteristics, controlling for these factors had a negligible impact on educational differences in antidepressant treatment (Figures 3 and 4).

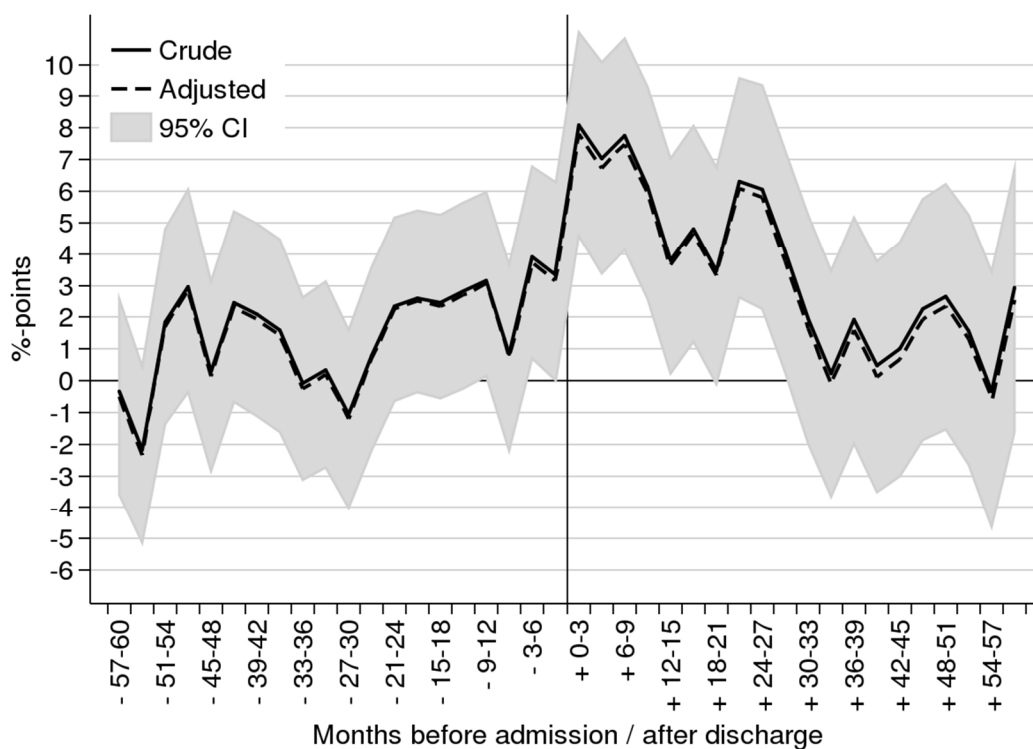


Figure 4 Excess in the prevalence of daily antidepressant use among those with a high vs. a low level of education before and after hospital care for depression with 95% confidence intervals (CI), Finnish community-dwelling men and women aged 25–64 in 1998–2007. The adjusted model includes gender, birth year, study year, region of residence, psychotic features, SUD, employment status, and living alone

6.4 ANTIDEPRESSANTS AND SUICIDE (SUB-STUDY IV)

Sales of non-tricyclic antidepressants increased rapidly in Finland in 1995–2007. The number of daily doses sold per capita per year rose from five to 18 among men and from seven to 30 among women aged 20 and older. The prevalence of antidepressant users more than doubled, reaching over six per cent among men and over 10 per cent among women in 2007. The proportion of antidepressant users with doses reflecting minimally adequate treatment (defined as having purchased at least 90 DDDs of non-tricyclic antidepressants in a given year) increased from around 60 to 80 per cent among both men and women. Simultaneously with this increase in antidepressant sales, suicide rates declined among both men and women. The age-adjusted rates fell from 56 to 38 suicides per 100,000 person-years among men and from 16 to 11 among women. Around 30 per cent of suicides were alcohol-related among men and around 10 per cent among women.

Despite this temporal connection, regional sales of non-tricyclic antidepressants were not significantly related to the risk of any suicide or alcohol-related suicide among men when age, region and year were controlled

for (Figure 5). This was true for all measures of antidepressant sales: the number of doses sold per capita, the prevalence of antidepressant users and the proportion among antidepressant users who had purchased doses reflecting minimally adequate treatment. However, the risk of non-alcohol-related male suicide was reduced by one per cent (incidence rate ratio, IRR=0.987, 95% confidence interval 0.976–0.998) when the proportion receiving minimally adequate treatment increased by one percentage point. This significant result was not replicated in sensitivity analyses in which minimally adequate treatment was defined as having purchased at least 180DDDs (data not shown).

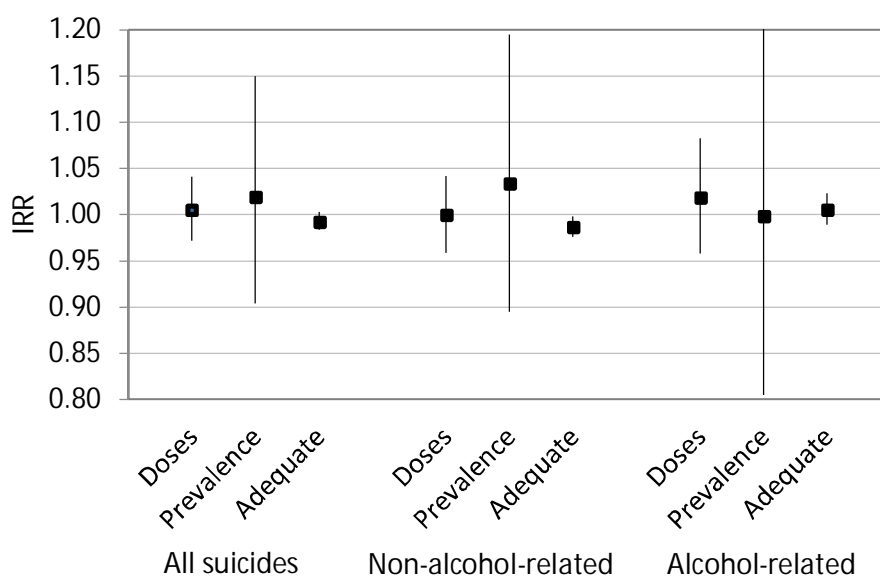


Figure 5 Relative changes in suicide risk as incidence rate ratios (IRR) and 95% confidence intervals per one-unit increase in regional non-tricyclic antidepressant sales (doses sold per capita, prevalence of antidepressant users, proportion of antidepressant users with doses reflecting minimally adequate treatment) controlled for age, region and year fixed effects in Finland, 1995–2007, **men** aged 20+.

No measure of regional antidepressant sales was related to the risk of any, alcohol-related or non-alcohol-related suicide among women when age, region and year fixed effects were controlled for (Figure 6).

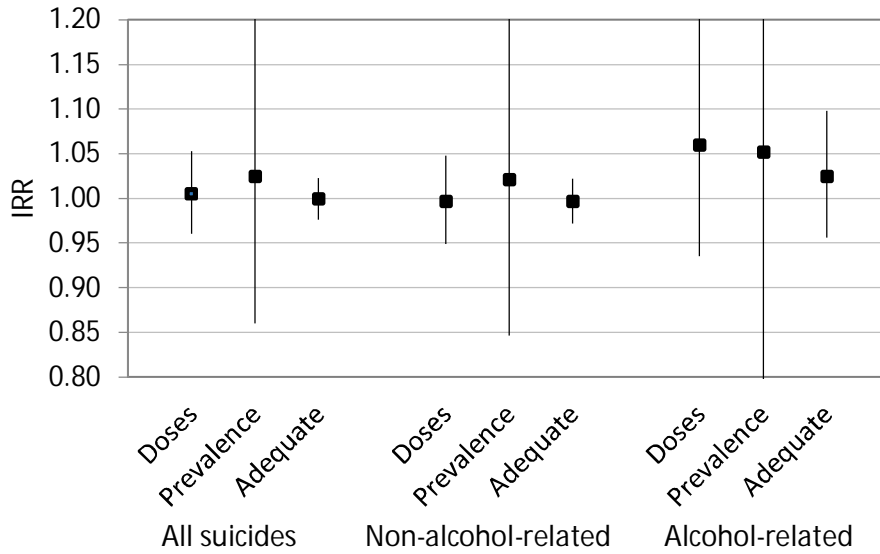


Figure 6 Relative change in suicide risk as incidence rate ratios (IRR) and 95% confidence intervals per one-unit increase in regional non-tricyclic antidepressant sales (doses sold per capita, prevalence of antidepressant users, proportion of antidepressant users with doses reflecting minimally adequate treatment) controlled for age, region and year fixed effects in Finland, 1995–2007, **women** aged 20+.

Further investigation into social-group differentials in the effect of antidepressant sales on suicide risk was limited to the association between non-alcohol-related male suicide and the proportion of antidepressant users with minimally adequate treatment, because none of the other associations were significant in the overall model. The reduction in suicide risk was only significant among men who did not own their home and were not living with a partner (Figure 7). The reduction was borderline significant among men with higher levels of education, employment and income. There was no reduction in suicide risk in the other groups.

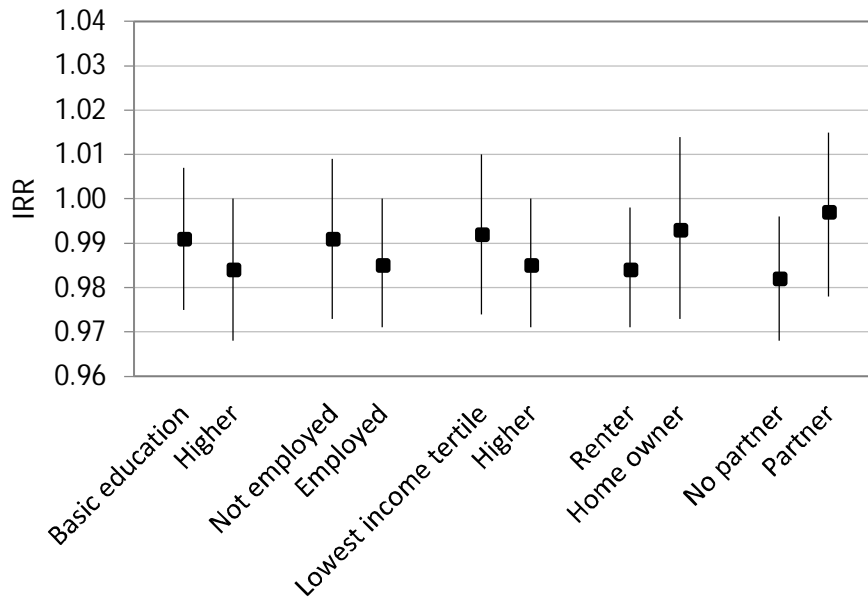


Figure 7 Relative change in non-alcohol-related suicide risk as incidence rate ratios (IRR) and 95% confidence intervals per one-unit increase in the proportion of antidepressant users with doses reflecting minimally adequate treatment by social factors controlled for age, region and year fixed effects in Finland, 1995–2007, *men* aged 20+.

7 DISCUSSION

7.1 A SUMMARY OF THE MAIN RESULTS

This study used Finnish longitudinal data-sets combining information from different administrative registers to investigate the outcomes of depression. The overall objective was to assess the extent to which adverse outcomes vary according to social factors, and the role of alcohol and depression treatment in bringing about this variation. The specific aims were to examine social differentials in psychiatric hospital admissions for depression, the excess mortality of depression, antidepressant use and the effect of antidepressant sales on suicide mortality. Further aims were to quantify the contribution of alcohol-related causes to depression mortality, and to disentangle the causal impact of increased sales of antidepressants on the risk of alcohol-related and non-alcohol-related suicide.

Social differentials in psychiatric hospital admissions for depression, the excess mortality of depression and antidepressant use were mainly small and often non-significant. The most consistent predictors of hospital admission were the material aspects of socioeconomic position, income, home ownership and unemployment, as well as living without a partner. The excess mortality of depression was not buffered by a higher socioeconomic position, being employed, or having a partner. In contrast, the relative excess mortality attributable to alcohol-related causes was somewhat larger in men and women with a high level of education, the employed, and those owning their home. In the case of non-alcohol-related causes the excess mortality was unmodified by social factors. Antidepressant use before and after hospital care for depression varied little across the educational groups, although the highly educated were somewhat more likely to use antidepressants after hospital discharge. The differences were more pronounced in the case of daily rather than any use, suggesting more below-guideline use among those with a low educational level.

The findings demonstrate the important role of alcohol in depression mortality. The contribution of alcohol-related causes to the excess mortality of depressed in- and out-patients was high, accounting for around half of the excess mortality among men and around a third among women. The beneficial effect of increased antidepressant sales in preventing suicides was limited to non-alcohol-related male suicides, and was related to the increased proportion of antidepressant users receiving minimally adequate treatment. These results are discussed in more detail below.

7.1.1 MODEST EFFECTS OF SOCIAL FACTORS

Psychiatric admission for depression

According to the results of this large, population-based study including both depressed inpatients and outpatients with antidepressant purchases, social factors such as socioeconomic position, employment status and living arrangements have only modest predictive power in psychiatric admission for depression. These results further strengthen the findings from mainly small clinical and community samples (Cole et al., 1999; Hardeveld et al., 2013, 2010; Lauber et al., 2006; Licht-Strunk et al., 2007; Lin et al., 2007; Morrow-Howell et al., 2006; Spijker et al., 2004, 2001b; Steinert et al., 2014; Vogel and Huguelet, 1997) and larger population studies (Aro et al., 1995; Callahan and Wolinsky, 1995) that social factors play a modest role in determining depression outcomes such as recurrence, persistence and psychiatric admission.

The results are somewhat at odds with those of previous large-scale population studies showing substantial differentials in depression persistence according to education, occupational social class, income and employment status (Bjerkset et al., 2008; Bracke, 1998; Lorant et al., 2003; Melchior et al., 2013), and a higher risk of hospital readmission for depression among never-married individuals (Kessing et al., 1998), possibly reflecting methodological differences in the measurement of depression and its outcomes. Most importantly, depression status was inferred in the current study from healthcare use, and social differentials in outcomes may be smaller among depressed individuals who are already in contact with the healthcare system.

The small social differentials in depression outcomes are broadly consistent with the kindling model of affective disorders, which predicts a diminishing effect of life stressors on the recurrence of depression compared with first onset (Monroe and Harkness, 2005; Post, 1992). Although the social factors assessed in this study did not directly measure stressors, they indicate differential exposure to life stressors such as union dissolution, job loss and financial strain.

With regard to the relative importance of the different aspects of socioeconomic position and living arrangements, the more material aspects of socioeconomic position (income, home ownership and employment) and living without a partner seemed to be the most influential risk factors for admission, whereas differentials between educational and occupational groups were negligible. A similar pattern has typically emerged in studies assessing the incidence and prevalence of depression (Andersen et al., 2009; de Graaf et al., 2012; Eaton et al., 2008; Hughes and Waite, 2002; Joutsenniemi et al., 2006; Kessler et al., 1997; Kosidou et al., 2011a; Laaksonen et al., 2007; Lorant et al., 2003; Pirkola et al., 2005). There may be at least two explanations for this finding. First, the social factors that were

more strongly related to depression outcomes (income, home ownership, employment and living arrangements) are more dynamic than education or occupational social class and are thus more likely to be affected by reverse causality. In other words, an unfavourable course of depression may lead to union dissolution or exclusion from the labour market, but cannot change previously obtained educational qualifications or occupation (at least when measured retrospectively from previous occupation among those not currently employed, as in the current study). It may also be that residual confounding by the severity of baseline depression and psychiatric comorbidity, which could not be fully accounted for, affected both the dynamic social factors and the depression outcome. It was found in a Belgian study, for example, that the higher risk of depression persistence among highly educated and divorced individuals was fully accounted for by differences in baseline depression severity (Bracke, 1998).

On the other hand, economic resources and living with a partner could well have a stronger causal impact on depression outcomes than education and occupational class. Economic resources such as employment and income may be particularly critical to coping with depression on account of lower levels of stress related to financial difficulties and economic insecurity, better access to occupational health services, and better affordability of treatment. A high education and a non-manual occupational social class may provide few additional resources. In contrast, psychosocial exposures such as demanding and stressful work among the highly educated and in non-manual occupations could, in fact, make it more difficult to cope with depression in these groups. The lower prevalence of depression among people living with a partner has previously been found to be partly mediated through social support and better health behaviours (Joutsenniemi et al., 2006), and the same could apply in the case of depression outcomes. Specifically, co-resident partners may encourage care-seeking and enhance treatment adherence. The emotional support and optimistic outlook provided by a partner are also likely to have a direct positive effect on coping with depression. Further research is needed to disentangle the causal direction and the specific pathways bringing about the observed social differentials in psychiatric admission for depression.

The excess mortality of depression

The findings related to depression mortality provided little support for the hypothesis that social and economic resources would buffer against the detrimental effect of depression. Excess mortality among the depressed varied relatively little by social factors, particularly for non-alcohol-related causes. This further strengthens the evidence from previous studies based on smaller samples (Fuhrer et al., 1999; Schneider et al., 2001). In contradiction of the buffering hypothesis, in fact, the relative excess mortality of depression in the case of alcohol-related-causes was significantly larger among those with a higher education, those owning their home and the employed. It could be that

fulfilling labour-market-related expectations when depressed is more challenging in these groups (Agerbo, 2007), resulting in excessive alcohol consumption. However, in these socioeconomic groups alcohol-related mortality was very low in the non-depressed comparison group, which resulted in a large relative excess. The absolute excess in death rates was, in contrast, generally larger among those with a low socioeconomic position, the unemployed and those living without a partner. In accordance with these findings, a study on excess mortality after disability retirement for depression indicated that socioeconomic resources and family ties may be less protective among people who have already developed depression than in the general population (Leinonen et al., 2014). The results on both mortality and psychiatric admission indicate that efforts to tackle social inequalities in depression should focus on the primary prevention of its onset, given that social differentials in outcomes, at least in a population already in contact with the healthcare system, are small. Furthermore, the impact of delayed or altogether lacking healthcare contact on social differentials in depression outcomes should be investigated in future studies.

Antidepressant use

The educational differences in antidepressant use before and after hospital care for depression identified in this study were small, and mostly driven by earlier discontinuation and below-guideline treatment among those with a low level of education. Differences in antidepressant use were assessed among people with hospital care for depression in order to overcome a common setback in earlier studies, namely the lack of information on treatment need across socioeconomic groups (Andersen et al., 2009; Hansen et al., 2004a; Kivimäki et al., 2007). Hospital care for depression was considered an indication of an evident need for treatment that would be reasonably homogenous across educational groups. The small educational differences in any antidepressant use in the three months following hospital discharge suggests rather equitable access to at least some treatment at the time of evident need. This is in accordance with findings from previous studies controlling for depression severity as an indicator of treatment need (Butterworth et al., 2013; Hämäläinen et al., 2009; Roer et al., 2010). However, in line with earlier evidence showing higher discontinuation rates among those with a low socioeconomic position (Bocquier et al., 2014; Hansen et al., 2004b; Sundell et al., 2013), the prevalence of antidepressant use declined more rapidly among those with a low level of education.

Furthermore, daily antidepressant use was more common among those with a high education, and the differentials were more pronounced than for any use. The differentials were particularly large immediately after discharge, suggesting a need for improved treatment adherence among the less highly educated. It has been concluded in earlier Finnish studies that continuity is the main challenge in the treatment of depression (I. A. Holma et al., 2008;

Melartin et al., 2005), and this seems to be particularly true among those with a low level of education.

Although the educational differences in antidepressant use were significant, especially after discharge from hospital care for depression, the differences in prevalence were quite small, eight percentage points at the highest. This may reflect the fact that the national public health insurance and social security system in Finland lowers the financial barriers to treatment among those with a low educational level. Public health insurance covers 42 per cent of the price of antidepressants for all patients irrespective of wealth (National Agency for Medicines and Social Insurance Institution, 2012). Furthermore, the costs of medicines and healthcare services may be fully covered by social assistance, a last-resort form of economic assistance provided by municipalities for individuals and families whose income does not suffice to cover living expenses (National Agency for Medicines and Social Insurance Institution, 2012; Wahlbeck et al., 2008).

It should be noted that this study only assessed antidepressant treatment, information on other forms of depression treatment being unavailable. Treatment guidelines recommend combining antidepressants with psychotherapy as the most effective treatment (Cuijpers et al., 2014b; Depression: Current Care Guidelines, 2014). Differentials between socioeconomic groups could be larger when it comes to psychotherapy and other types of psychological treatment provided by occupational health services, private healthcare providers and municipal outpatient services. In particular, the shortage of publicly funded psychotherapy (Wahlbeck et al., 2008) as well as financial barriers to private psychotherapy may prevent its use among those in a low socioeconomic position. It was found in a British study that a high level of education, a high income and a high occupational social class were all associated with higher usage of privately purchased psychotherapy, whereas differences in publicly funded psychotherapy were smaller and even reversed (Jokela et al., 2013). In contrast, a Finnish study reported no differences according to education, income or employment status in any (private or public) psychological treatment among individuals with major depression in the previous 12 months (Hämäläinen et al., 2009).

Given that the Finnish study only assessed depressed persons and controlled for measures of depression severity and comorbidity, it is likely to give a more thorough insight into differentials in depression treatment, whereas the British study covering the general population and with no controls for depression reflects differentials in care use more generally. It is a common finding that the majority of mental-health treatment is received by people with mild or sub-clinical symptoms (Bijl et al., 2003; The WHO World Mental Health Survey Consortium, 2004). In fact, the British study revealed that most people using private psychotherapy had only low levels of psychological distress as measured by the GHQ (Jokela et al., 2013). It could thus be that, in the general population, those in higher socioeconomic positions seek more treatment for minor symptoms because they have the financial resources to do

so. However, this does not necessarily imply inequalities in access to treatment among those with major depression. Accordingly, studies reporting that antidepressant use is more common among those with a high level of education or in a high occupational social class (Andersen et al., 2009; Kivimäki et al., 2007; Roer et al., 2010) may be detecting differentials in its use for minor symptoms. The present study overcame this problem in assessing antidepressant use only among people with inpatient hospital care for depression. However, further studies are needed to assess social differentials in the initiation and continuation of antidepressant use, as well as in antidepressant treatment combined with psychotherapy, among depressed people in the general population: they may differ from those observed in people already in contact with specialised psychiatric care.

7.1.2 IMPORTANT ROLE OF ALCOHOL IN DEPRESSION MORTALITY

Several reviews suggest that alcohol use is a major mediator in the depression-mortality association (Cuijpers and Schoevers, 2004; Wulsin et al., 1999), but studies controlling for self-reported alcohol use have rarely found it to markedly attenuate the excess mortality (Anda et al., 1993; Morris et al., 1993; Mykletun et al., 2007; Shekelle et al., 1981). However, the under-reporting of alcohol intake in self-reports as well as the under-representation of heavy drinkers in surveys are common problems (Gray et al., 2013) that may lead to underestimating the contribution of alcohol in these studies. This is the first study to explicitly quantify the contribution of alcohol-related deaths in depression mortality without the problems of distorted self-reporting or selective non-response, and it demonstrates the important role of alcohol in bringing about depression mortality. Around half of the excess mortality of depressed patients among men and around a third among women was attributable to alcohol-related causes. Most of the deaths were attributable to alcohol diseases, suggesting long-term excessive alcohol consumption is a major pathway from depression to mortality, particularly among men.

However, it should be kept in mind that it was impossible in this study to disentangle the temporal or causal ordering of depression and excessive alcohol consumption, and the depressed patients dying of alcohol-related causes could have been suffering from depression preceded or even caused by alcohol use disorders. The causal association between alcohol use disorders and depression seems to be complex and bidirectional: on the one hand alcohol use disorders may result from self-medication for depressive symptoms, and on the other hand excessive alcohol consumption may cause depression via social or physiological pathways (Swendsen and Merikangas, 2000). The disorders may also share common genetic and environmental risk factors (Prescott et al., 2000). Irrespective of the reasons for comorbidity, the results indicate that the detection and management of alcohol use disorders and excessive alcohol consumption more generally are prerequisites in reducing depression mortality.

Overall, the results highlight the importance of behavioural and life-style pathways in depression mortality among depressed inpatients and outpatients using antidepressants. Alcohol-related causes, suicides and other violent and accidental causes together accounted for around 70 per cent of the excess mortality of depressed men, and 55–70 per cent among depressed women. This could be considered a lower limit for the contribution of behavioural pathways in that unhealthy lifestyles may also be linked to many non-alcohol-related disease deaths. For example, smoking-related deaths have previously been found elevated among Finnish women with depression (Joukamaa et al., 2001): these were categorised as non-alcohol-related disease deaths in the current study and were thus considered “non-behavioural”. A more detailed decomposition of the causes of death contributing to the excess mortality of depression would better capture the different pathways. Specifically, assessing the contribution of alcohol-related deaths to the frequently observed excess cardiovascular mortality among the depressed (Wulsin et al., 1999) could be a fruitful direction for future study. Quantifying the extent to which excessive alcohol consumption is behind the observed association would be particularly interesting given that cardiovascular disease is the cause for which some of the most plausible biological pathways have been suggested (Cuijpers and Schoevers, 2004; Wulsin et al., 1999).

With respect to the external validity of the results, it may be that alcohol is particularly significant as a pathway for depression mortality in Finland, where alcohol-related mortality overall is one of the highest in Western Europe (Ramstedt, 2002). Self-medication of depression by means of alcohol could be more common in Finland than in other countries, for example. This claim is not, however, strongly supported by the finding that the 12-month prevalence of comorbid alcohol use disorders among the depressed in Finland, at around 12 per cent (Pirkola et al., 2005), seems to be similar to those in the Netherlands (13–17%; Boschloo et al., 2011) and the United States (14%; Hasin et al., 2005). The contribution of alcohol-related causes to depression mortality in the general population could also differ from that found in the current study of depressed patients in treatment. Further research is needed to establish the contribution of alcohol-related causes to depression mortality across countries with different levels of alcohol consumption and alcohol-related mortality, in different treatment settings and in the general population.

7.1.3 LIMITED EFFECT OF ANTIDEPRESSANTS ON SUICIDE

The study findings show that the improved adequacy of antidepressant treatment may have prevented non-alcohol-related suicides among men in Finland in 1995–2007. A one-percentage-point increase in the regional proportion of antidepressant users receiving doses reflecting minimally adequate treatment was related to a one-per-cent reduction in the risk of non-alcohol-related male suicides when controlling for all time-invariant regional characteristics and all national-level year-specific characteristics that could

affect suicide risk irrespective of regional antidepressant sales. On the national level this would suggest that increased adequacy of antidepressant treatment could account for over half (63%; 95% confidence interval 11%–105%) of the decrease in non-alcohol-related suicides, given the almost 20 percentage-point increase in the proportion of men receiving minimally adequate treatment. Finland implemented an extensive national suicide-prevention programme in 1992–1996 (Beskow et al., 1999), which may have enhanced the detection and adequacy of pharmacological treatment for depression (Sorvaniemi et al., 2006). Enhanced treatment adequacy could be related to increased adherence, given earlier findings that nonadherence is a major determinant of early continuation (Melartin et al., 2005). However, further research is needed to establish trends in antidepressant adherence.

Other aspects of regional mental-health service provision in addition to regional antidepressant sales, such as the density of general practitioners and psychiatrists, and of available outpatient services, may affect suicide risks. It has been found that Finnish municipalities with versatile, community-based mental-health services have lower-than-expected suicide rates even when socioeconomic and mental-health differentials between municipalities are controlled for (Pirkola et al., 2009). Regional differences in mental-health service provision could be reflected in differential antidepressant sales, and thus confound the antidepressant effect. Controlling for all stable differences between regions in the region fixed effects reduced this confounding somewhat in the analyses. However, co-occurring regional changes in service provision were not controlled for. Consequently, their effects on suicide risk will be attributed to changes in antidepressant sales, which may overestimate the beneficial effect of increased sales.

Unlike some previous studies using similar methodology (Bramness et al., 2007; Ludwig et al., 2009) this study did not reveal any beneficial effect of increased overall per-capita sales or prevalence of antidepressant use. Given that short-term and non-psychiatric antidepressant use is common (Sihvo et al., 2008), a mere increase in overall sales or user prevalence may have little impact on suicide risk—in particular if much of the increase is accounted for by treatment of mild and subclinical symptoms. The study also failed to show a beneficial effect of increased antidepressant sales on alcohol-related or female suicides. There may be methodological reasons for these null findings, such as insufficient statistical power to detect beneficial effects (see Chapter 7.2.3. *Fixed effects regression*). More substantive explanations relate to the study period and the targeting of treatment.

Previous studies with longer observation periods going back to 1980 have shown a beneficial effect of increased overall sales only when antidepressant sales were low (Bramness et al., 2007; Gusmão et al., 2013). The current study covered a later period, 1995–2007, during which increases in already relatively high antidepressant sales may no longer have reduced the number of suicides. This may be particularly true for women, among whom prevalence and per-

capita sales were at a higher level than among men throughout the study period.

At least two reasons could explain why alcohol-related suicides were not affected by the increased sales. First, antidepressants may be less effective in the presence of excessive alcohol use. However, this is not strongly supported by evidence from studies on comorbid depression and substance use disorders suggesting that antidepressants are effective in the treatment of both disorders (Davis et al., 2010; Nunes and Levin, 2004). Second, there may have been less increase in antidepressant treatment among people with a high risk of alcohol-related suicide. The treatment of depression has previously been found inadequate among patients with comorbid substance use disorders (Blanco et al., 2012; Suominen et al., 2002). The detection may be hindered by comorbid alcohol use disorders, and current treatment guidelines recommend the postponement of antidepressant treatment initiation until substance use is under control (Depression: Current Care Guidelines, 2014). Although more research is needed to establish how treatment adequacy has evolved in this group following the expansion in antidepressant treatment, the current results suggest that the increased availability of antidepressant treatment may not adequately cover this group. Alcohol-related suicides are particularly common among men and women with a low socioeconomic position, the unemployed, and those not living with a partner (Mäki and Martikainen, 2009, 2008). More rigorous preventive strategies focusing on alcohol-related suicides would therefore also help in tackling social differentials in suicide mortality. In the case of non-alcohol-related suicide mortality, the increased adequacy of treatment had a beneficial effect among men living without a partner and not owning their home. This result implies success in the targeting of antidepressant treatment among these high-risk groups.

7.2 METHODOLOGICAL CONSIDERATIONS

7.2.1 REGISTER DATA

This study was based on large register samples representative of the Finnish adult population, with long follow-ups. Individual-level records from various administrative registers were linked using the unique personal identification codes given to all permanent residents of Finland. These data carry both strengths and weaknesses in assessing the outcomes of depression. One of the biggest strengths is that they do not suffer from non-response or attrition, which can pose immense problems in clinical and survey studies of depression outcomes in that they tend to be associated with depression severity, demographic and social factors (Fischer et al., 2001), as well as high mortality (Harald et al., 2007; Jousilahti et al., 2005). Register data also circumvents problems of recall bias and misreporting. Specifically, information on the studied outcomes of depression, namely psychiatric hospital care for

depression, suicide, and other premature mortality, is based on the national Hospital Discharge Register and the Finnish Cause of Death Register, both of which have been shown to have good quality and practically complete coverage (Lahti and Penttilä, 2001; Mathers et al., 2005; Sund, 2012). The same applies to the national Prescription Register (National Agency for Medicines and Social Insurance Institution, 2012) from which the information on purchases of antidepressants and other medication was drawn. Several Finnish studies report high concordance between registered antidepressant purchases and self-reported antidepressant use (Haukka et al., 2007; Rikala et al., 2013, 2010). Although the accuracy of depression diagnoses in Finnish healthcare registers has not been explicitly assessed (Sund, 2012), the universal public health insurance should minimise the incentives to biased diagnosing, such as for reimbursement reasons. Finally, extensive register data are well suited to the study of rare outcomes such as suicide. The major limitations of register data concern the measurement of depression. These limitations are discussed below.

7.2.2 THE MEASUREMENT OF DEPRESSION

Depression was measured by hospital care with a depression diagnosis (depressed inpatients) in sub-studies I–III, and in sub-studies I and II also by registered purchases of antidepressants (depressed outpatients), which means that all individuals categorised as ‘depressed’ were in treatment. This has significant implications for the interpretation of the results because studies from the turn of the millennium indicate that only about a third of depressed individuals in Finland used any healthcare services for their depression (Hämäläinen et al., 2004), and only a quarter used antidepressants (Hämäläinen et al., 2009). The propensity to seek treatment increased with depression severity, duration, and perceived disability and healthcare use was around 60 per cent among those with the most severe depressive episodes (Hämäläinen et al., 2004). Although data from Denmark implies the possibility of differential misclassification across social groups when register-based measures of depression are used, resulting in underestimation the excess prevalence of depression in low social groups (Thielen et al., 2009), this seems not to be the case in Finland: no differences were found in antidepressant use according to education, income, employment status or living arrangements among individuals with clinically assessed depression when its severity was controlled for (Hämäläinen et al., 2009). Moreover, the non-psychiatric use of antidepressants seems to be unrelated to education, employment status or living arrangements (Sihvo et al., 2008). Taken together, the proxy measures for depression used in this study are not highly sensitive, and mostly capture the more severe cases, but they are likely to do this rather similarly across social groups. They will also capture depressed individuals who are not picked up in the surveys due to selective non-response (Markkula et al., 2015). Sensitivity in future register studies on depression

could be increased by obtaining data from additional register sources covering areas such as state-funded rehabilitation psychotherapy (available from 1994 onwards), specialised psychiatric outpatient care (available from 1998 onwards) and primary healthcare (available from 2011 onwards), although the quality of such sources is unclear.

In terms of specificity, hospital diagnoses are likely to be rather accurate as measures, although validation studies of the hospital discharge register have not assessed depression diagnoses specifically (Sund, 2012). However, not all people making antidepressant purchases are depressed. Antidepressants are prescribed for many indications including anxiety, eating disorders, sleep problems, incontinence and pain, although depression is the most common (Gardarsdottir et al., 2007; Sihvo et al., 2008). Unfortunately, information on the diagnoses for which antidepressants were prescribed was not available in the data. In order to minimise the misclassification of non-depressed people as depressed, tricyclic antidepressants were excluded because they are commonly used for non-psychiatric indications (Gardarsdottir et al., 2007; Sihvo et al., 2008). Furthermore, sub-studies I and II, in which antidepressant purchases were used as a proxy for depression, excluded people aged 65 and older, among whom non-psychiatric use is more common (Sihvo et al., 2008; Thielen et al., 2009). Additional analyses conducted for sub-study II comparing registered antidepressant purchases to Finnish population-based survey data with clinical assessment of depression (Sihvo et al., 2008) revealed that 64 per cent of middle-aged Finns making non-tricyclic antidepressant purchases had either current major depression or a self-reported history of doctor-diagnosed depression. Thus, although not perfect, non-tricyclic antidepressant purchases could be considered a reasonable proxy for having outpatient treatment for depression.

The use of register data limited the analysis of depression outcomes and treatment to those in contact with healthcare services, and social differentials may be larger in the general population. Relying on register data also prevented the assessment of positive outcomes such as recovery from depression, given that the reasons for discontinuing antidepressants are not known, for example. In particular, early discontinuation may well be related to non-adherence and worse outcomes than early recovery (Melartin et al., 2005).

7.2.3 FIXED-EFFECTS REGRESSION

When the causal connection between rising antidepressant sales and declining suicide rates was evaluated, a region and time fixed-effects design was used to control for all time-invariant regional characteristics and national time trends that could influence the suicide risk irrespective of regional antidepressant sales. This model is a stronger test of causality between two trends than an ordinary regression model controlling for observed confounders because it removes the confounding effects of all other co-occurring trends, both

observed and unobserved (Allison, 2009). In practice this means that effects are only inferred from the variation between regions in how antidepressant sales and suicide risk changed over time, whereas the differences in levels between regions and years are controlled for.

Some authors argue that controlling for time (i.e. removing all year-to-year variation, which is common across regions) is an over-adjustment and prevents analysis of other predictors such as antidepressant sales (Gusmão et al., 2013). The model cannot identify whether the year-to-year variation common to all regions, namely the decreasing national trend in suicide risk, was, in fact, brought about by increased antidepressant sales. Thus if there was little regional variation around the national trend, controlling for everything that is common across regions could mask the beneficial effect of increased sales.

Another limitation of fixed-effect models is the imprecision of estimates due to reduced statistical power compared with ordinary regression models (Allison, 2009; Kaufman, 2008; Madsen and Osler, 2009). It is therefore difficult to draw a firm conclusion that antidepressants do not have a beneficial effect, even with this large sample of almost one million individuals and 11,491 suicides. This is particularly true for alcohol-related and female suicides, which are less common than non-alcohol-related male suicides. These limitations could be overcome by combining individual-level data from other Nordic countries with comparable registers. Such data would provide more statistical power and likely more variation in regional trends of antidepressant sales and suicide mortality for detecting *or rejecting* the beneficial effect of increased antidepressant sales on less common events such as female and alcohol-related suicide.

8 CONCLUSIONS

This study examined social differentials in depression outcomes and antidepressant treatment, using large longitudinal sets of register data that are representative of the general adult population of Finland. The findings strengthen the existing evidence from mainly small samples that the risk for psychiatric hospital care and the excess mortality of depression vary only moderately according to social factors such as socioeconomic position and living arrangements. However, through the simultaneous assessment of various aspects of socioeconomic position the results revealed the relative importance of material factors such as low income, not owning a home and unemployment in increasing the risk for an adverse course of depression, whereas education and occupational social class had little to no effect. Although confounding by depression severity and reverse causality cannot be ruled out, these results imply that financial strain is a major obstacle to managing with and recovering from depression. Given that depression is a common cause of work disability (Gould et al., 2007) and thus of a reduction in income, this poses a challenge for the adequacy of social-security benefits such as disability pensions in preventing the adverse outcomes of depression.

The study produced new information about the contribution of alcohol-related deaths to depression mortality. About half of the excess deaths among depressed men, and around a third among depressed women, were attributable to alcohol, mostly involving alcohol diseases, particularly among depressed outpatients. All in all, alcohol-related causes, suicides and other violent and accidental causes of death accounted for around 70 per cent of the excess mortality among depressed men, and 55–70 per cent among depressed women, emphasising the importance of behavioural pathways in bringing about the higher mortality among the depressed. Targeting hazardous health behaviours, alcohol abuse in particular, should thus be a priority in the prevention of depression-related mortality.

The results did not support the claim of unequal access to antidepressant treatment at a time of evident need, namely immediately before and after hospital care for depression: educational differences in any antidepressant use during these periods were small. However, the prevalence of antidepressant use declined more rapidly after hospital discharge among the less highly educated, suggesting less treatment adherence in this group. Furthermore, the daily use of antidepressants was less common among those with a low educational level, and educational differences were more pronounced than for any antidepressant use. Improving adherence among the low educated group thus seems to be the key challenge for reducing social differentials in antidepressant treatment, at least among depressed patients already in contact with the healthcare system. Social differentials in contacting healthcare services in the first place, as well as differentials in access to non-

pharmacological treatments such as psychotherapy, may also contribute to the unequal provision of depression treatment, and require further investigation.

Improved antidepressant adherence, reflected in the increasing proportion of antidepressant users with minimally adequate treatment, may have accounted for over half of the decrease in non-alcohol-related male suicides in Finland in 1995–2007. On the other hand, the study failed to show any beneficial effect of increased antidepressant sales on alcohol-related or female suicides. Apart from methodological reasons that may hinder the detection of an effect in these less common types of suicide, the lack of effect may relate to the targeting of antidepressant treatment. In particular, depression treatment has been found inadequate among patients at high risk for alcohol-related suicide, namely those with comorbid substance use disorders (Blanco et al., 2012; Suominen et al., 2002), and thus increased antidepressant treatment may not have benefitted this group equally.

Overall, the results of the study highlight the need to improve the detection and appropriate management of comorbid substance use disorders in depression. A better understanding of the role of alcohol in depression is vital in the planning of integrated mental healthcare and social services as well as in designing preventive strategies with regard to depression and suicide.

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