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**ADVERSE LIFE EVENTS,
PSYCHIATRIC MORBIDITY, AND MORTALITY**

Epidemiological studies of socioeconomic inequalities
from a life course perspective

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“Genius without education is like silver in the mine.”
(Benjamin Franklin)

ABSTRACT

The overall aim with this dissertation was to increase the knowledge on the association between adverse life events, and psychiatric morbidity and mortality, and the role of socioeconomic position from a life course perspective.

In Study I we examined the association between socioeconomic position, adverse childhood experiences, and psychotropic medication in young adulthood, using parental educational level as measure of socioeconomic position. A cohort of 362 663 individuals born in Sweden between 1985 and 1988 was followed from birth until 2008. Adverse childhood experiences were associated in a dose-response manner with increased risks of psychotropic medication. This relationship was similar in all socioeconomic groups.

In Study II we examined whether juvenile delinquency, defined as being convicted of a crime between the ages of 15 and 19, increased the risk of suicide in young adulthood. Nearly one million individuals were included. We found an increased risk of suicide in juvenile delinquents, where the highest suicide risk was found in repeated juvenile offenders.

In Study III we examined if divorce was associated with an increased risk of psychiatric morbidity. All married or divorced residents in Sweden between the ages of 45 and 54 in 2006, with no history of psychiatric care 1987–2005 were included (n=703 960). Psychiatric morbidity was defined as psychiatric inpatient care, outpatient care and use of psychotropic medication. Divorced women and men had a higher risk for psychiatric inpatient care compared to married. The longer the marriages the lower the risk for psychiatric morbidity. Lower educational level increased the risk for psychiatric inpatient care after divorce.

In Study IV we compared overall and cause-specific mortality and quality of somatic care among psychiatric patients and non-psychiatric patients. All individuals between the ages of 20 and 79 in 2005 (n=6 294 339) were followed with respect to mortality in 2006 and 2007. Psychiatric patients had a substantially increased risk of all studied causes of death as well as death from conditions considered amenable to intervention by the health service, i.e. avoidable mortality. The analysis of the quality of somatic care revealed lower levels of health care quality for psychiatric patients, signaling failures in medical care.

In conclusion, individuals who have experienced adverse life events have a higher prevalence of psychiatric morbidity than those who have not. This increased psychiatric morbidity was observed regardless of whether the adverse life event occurred in childhood, adolescence or in middle age. Adverse life events were more common among individuals in lower socioeconomic groups, and socioeconomic position tended to modify the relationship between adverse life events and psychiatric morbidity.

LIST OF PUBLICATIONS

- I. Björkenstam E, Hjern A, Mittendorfer-Rutz E, Vinnerljung B, Hallqvist J, Ljung R. Multi-exposure and clustering of adverse childhood experiences, socioeconomic differences and psychotropic medication in young adults. *PLoS One*. 2013;8(1):e53551. doi: 10.1371/journal.pone.0053551. Epub 2013 Jan 16.
- II. Björkenstam E, Björkenstam C, Vinnerljung B, Hallqvist J, Ljung R. Juvenile delinquency, social background and suicide--a Swedish national cohort study of 992,881 young adults. *International Journal of Epidemiology*. 2011 Dec;40(6):1585-92.
- III. Björkenstam E, Hallqvist J, Dalman C, Ljung R. Risk of new psychiatric episodes in the year following divorce in midlife: Cause or selection? A nationwide register-based study of 703,960 individuals. *International Journal of Social Psychiatry*. 2012 Oct 15
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LIST OF ABBREVIATIONS

ACE	Adverse Childhood Experiences
APA	American Psychiatric Association
ATC	Anatomical Therapeutic Chemical Classification System
CI	Confidence Interval
DDD	Defined Daily Dose
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Statistical Classification of Diseases and Related Health Problems
IRR	Incidence Rate Ratio
LISA	Longitudinal Integrated Database Predestined for Labor Market and Similar Studies
OR	Odds Ratio
PIN	Personal Identity Number
RD	Risk Difference
RR	Risk Ratio
SCB	Statistics Sweden
SD	Standard Deviation
SI	Synergy Index
TPR	Total Population Register
WHO	World Health Organization

1 INTRODUCTION

Psychiatric morbidity is one of the leading causes of disability worldwide (1, 2). Different types of mental disorder with various severity affects individuals in all age groups, social groups and in women as well as men. Mental disorders account for three of the ten leading causes of disability in people between the ages of 15 and 44, and the other causes are often associated with mental disorders (3). Moreover, suicide is the second most common cause of death among adolescents and young adults in the industrialized parts of the world including Sweden (4).

It is well established that social class is linked to health, where health follows a social gradient: the higher the social position, the better the health (5, 6). In industrialized countries, heart disease and diabetes, mental disorder and chronic respiratory disease, accidents and violence all follow a social gradient – the lower the ranking in society, the higher the risk (5). Studies have shown that individuals in lower social groups more often are affected by psychiatric morbidity (7-9). These socioeconomic inequalities in psychiatric morbidity date back to the early 20th century (9).

A life course approach offers a framework for studying long-term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood and later adult life (10, 11). One purpose with life course epidemiology is to study the contribution of factors in early life jointly with factors later in life to identify risk and protective processes over the life course (11).

An association between experience of adverse life events over the life course, and psychiatric morbidity has been documented (12, 13). Moreover, adverse life events in childhood may have negative long-term health and social consequences (14, 15).

With a life course perspective, this dissertation aims at increasing the knowledge on the association between adverse life events, and psychiatric morbidity and mortality, and the role of socioeconomic position from a life course perspective. Figure 1 illustrates the four studies from a life course perspective.

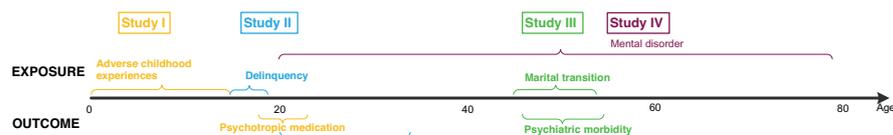


Figure 1. Illustration of the studies from a life course perspective

2 BACKGROUND

2.1 PSYCHIATRIC MORBIDITY – AN OVERVIEW

Mental health has been defined in various ways by scholars from different cultures. According to the World Health Organization (WHO), mental health can be described as: "a state of well-being in which the individual realizes her or his abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community" (16). Mental health is seen as an essential component of general health.

The mental condition of people is determined by a multiplicity of factors, including biological (e.g. genetics, sex), individual (e.g. personal experiences), family and social (e.g. social support, defined as "resources provided by other persons" (17)) and economic and environmental (e.g. social position and living conditions). Mental health could be regarded as a balanced state that is influenced by both past and present events, social interactions and personal resources.

Mental ill health, mental problems, mental disease, psychiatric morbidity, psychiatric disease, and mental disorders are some of the concepts used in an attempt to cover different aspects of mental suffering. These various states have been considered as a continuum, which extends from the most severe mental disorders (e.g. psychotic disorders) to a variety of symptoms (e.g. worry, anxiety and disturbed sleep) of different intensity and duration.

Mental disorders are generally characterized by alterations in thinking; mood or behavior associated with personal distress and/or impaired functioning (1). The American Psychiatric Association (APA) defines mental disorder as a health condition characterized by significant dysfunction in an individual's cognitions, emotions, or behaviors that reflects a disturbance in the psychological, biological, or developmental processes underlying mental functioning (18).

Mental disorders are common, and the milder conditions are very common. In fact, mental disorder is one of the largest public health problems in the world (1, 19), where the most common forms of mental disorders are anxiety and depression (1). According to the WHO, mental disorder (in terms of depression) will be the highest ranking disease problem in the developed world in 2020 (1) and in 2030 (2). It is already one of the leading causes of disability worldwide.

Most prevalence estimates on psychiatric morbidity include lifetime, and 12-month prevalence. Lifetime prevalence is the number of cases at any time during the lifetime of respondents, and 12-month prevalence is the number of cases during the past year. There is substantial variation in the results in studies on lifetime prevalence, mostly depending upon the methodological characteristics of the studies. While some studies have stated that approximately 25% of individuals worldwide develop one or more mental disorder during their life (1, 20), others have presented lifetime prevalence as high as 50% (21, 22). In the United States, the 12-month prevalence is estimated to between 25% and 30% (23, 24). Similar estimates were also found in a European study (22). However this estimate could be even higher as the study only considered adults

between the ages of 18 and 65, and only some of the many mental disorders were considered.

Age is an important determinant of psychiatric morbidity. Mental disorders are known to have much earlier ages of onset than most chronic physical disorders (25). There are however differences in age of onset depending on the type of mental disorder. Anxiety is for instance known to have an earlier age of onset compared to substance use disorders and mood disorders (21, 25). Psychotic disorders rarely occur before age 14, but show a marked increase in prevalence between the ages of 15 and 17. Schizophrenia, accounting for approximately two thirds of all psychotic disorders, usually develops between the ages of 15 and 35 (25). Mental disorders account for three of the ten leading causes of disability in people between the ages of 15 and 44, and the other causes are often associated with mental disorders (3). A review study from the US on children and adolescents shows that approximately one third experience a mental disorder across their lifetime (3). A recent study estimating 12-month prevalence among persons between the ages of 13 and 17 in the US showed that as many as 40% met the criteria for any mental disorder (26). This is a much higher estimate compared to an earlier WHO report from 2001, where 10-20% of youth have one or more mental disorder (1). Data for Sweden indicate a steep increase in self-reported mental ill health among adolescents – especially adolescent girls, since the mid-1980s through 2005 (27). A high prevalence of mental disorders is also seen in old age, typically including individuals ≥ 65 years (28), and the prevalence of some disorders tends to increase with age (1). Among the elderly, depression is the most common type of mental disorder (29, 30).

Psychiatric morbidity is present in women and men at all stages of the life course, and there are gender differences in the occurrence of different types of disorders. Externalizing symptoms refer to a tendency to deal with problems through action, while internalizing symptoms refer to a tendency to respond to problems with inner suffering (31). Women seem especially prone to suffer from internalizing disorders such as anxiety disorder and depression, whereas men more often suffer from externalizing disorders such as alcohol and substance use disorders (31-34). In their overview on epidemiological findings on selected mental disorders, Kohn et al. found similar patterns, i.e. an increased risk for depression and anxiety disorders in women, and strikingly higher rates of alcohol abuse disorders in men (35). A meta-analysis on prevalence of psychiatric morbidity in Europe showed higher rates of psychiatric morbidity in women compared to men (22).

2.2 PSYCHIATRIC MORBIDITY AND MORTALITY

Psychiatric morbidity is associated with increased mortality rates (33, 36, 37). This applies especially to the more severe types of mental disorders such as schizophrenia and bipolar disorder (38-40), though the highest rates have been found among patients treated for substance use disorders (37). Cardiovascular disease is also a major cause of excess death for patients with a psychiatric morbidity, partly due to a higher prevalence of smoking, obesity, and hypertension (41). There are conflicting data on cancer incidence and mortality in psychiatric patients, although most studies suggest that, while cancer mortality is higher, incidence is no different from that of the general population (42, 43).

2.2.1 Suicide

Worldwide almost one million people commit suicide annually (44). In the industrialized parts of the world, suicide is the second most common cause of death among adolescents and young adults (4). Suicide is strongly associated with the presence of psychiatric morbidity (45). Psychiatric disorders are present in about 90% of people who commit suicide (46, 47). Affective disorder is the most common psychiatric disorder, followed by substance use disorder and schizophrenia. More than half of all people who die by suicide meet criteria for current depressive disorder. Between 10% and 15% of patients with bipolar disorder die by suicide. Lifetime suicide risk in schizophrenia is 4-5%, the risk being highest early after onset of the disorder.

Gender differences are present in suicide and suicidal behavior. In most Western countries, suicide is more common in men compared to women (47, 48). Asian countries typically show much lower rates for men than women, however in China more women than men die by suicide (47, 49). Both psychopathologic factors and sex-/gender-related method preferences are considered to contribute to the pattern of these differences (49, 50). Men are more inclined to use more drastic violent methods than women, who are over-represented among suicide attempters using poisonings (50, 51).

2.3 SOMATIC HEALTH CARE INEQUALITIES IN PSYCHIATRIC MORBIDITY

Some severe mental disorders are associated with serious medical comorbidity (52-54). Disparities in access to and utilization of health care, as well as the quality of health care provision, may contribute to inequalities in health (55). Health care inequalities have been observed in people with a diagnosis of a mental disorder (54-60). This has especially applied to individuals with a chronic mental disorder. Studies have reported lower levels in access, provision, and quality of somatic health care (54). Lower quality of diabetes care (57), and cardiovascular procedures (56, 58) has also been documented. One type of unmet need has for instance been the lack of access to medical care (61). These health care inequalities have been shown in all age groups and in both women and men.

The concept of avoidable mortality was first introduced in 1976 as an indicator of quality of health care (62). Avoidable mortality measures deaths that could be argued to have been avoidable either by the healthcare system or by public health interventions and has been applied in comparisons between regions, populations and over time. Psychiatric patients have been shown to have higher avoidable mortality rates compared to the general population (63, 64), and questions have been raised as to whether the medical care of physical disorders provided to psychiatric patients is less adequate than for the population in general (61). The indicators of avoidable mortality are divided into causes of death reflecting the outcome of medical care and causes reflecting the effect of the national health policy.

2.4 SOCIAL DETERMINANTS OF HEALTH

2.4.1 The concept of social determinants of health

In every type of political and social system, differences in health have been noted between different social groups in the population (6, 65). Health follows a social gradient: the higher the social position, the better the health (6). There are however a few exceptions, e.g. malignant neoplasm and breast cancer among women (66, 67). Differentials in health and longevity by socioeconomic position have been identified in a large number of studies over the years. The social gradient in health is not confined to those in poverty. It runs from top to bottom of society, with less good standards of health at every step down the social hierarchy. To understand the causes of this gradient one needs to examine the circumstances in which people are born, grow, live, work and age, i.e. the social determinants of health (6). These circumstances are shaped by the distribution of money, power and resources at global, national and local levels. The social determinants of health are mostly responsible for health inequalities that exist within and between countries (5, 6). Numerous researchers have described the relationship between the social determinants and health. Figure 2 illustrates this relationship according to a model by Dahlgren and Whitehead (68). Social determinants of health include both societal-level influences on health (living and working conditions, and the broader social structures in which they are embedded), as well as individual-level risk factors (such as health behaviors) (69, 70).

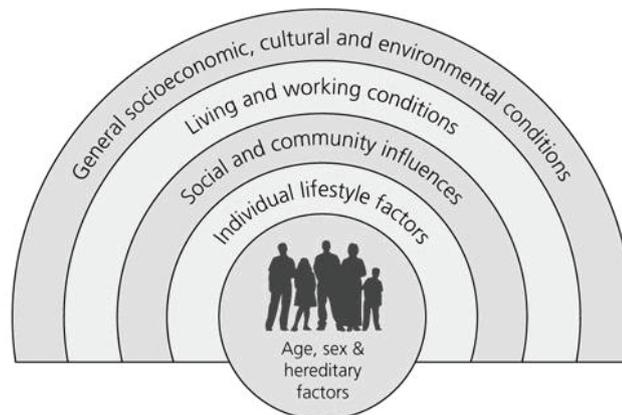


Figure 2. The main determinants of health, adapted from Dahlgren and Whitehead (68)

To describe social stratification, a variety of terms are used in the epidemiological literature including social class, social status, socioeconomic status, and socioeconomic position (71). In an overview of the concept of socioeconomic position in social epidemiology, three major sociological traditions have been discussed: Marxian, Weberian and Functionalist (72). Briefly, the Marxian tradition presents a view of society stratified into “classes”, determined by the nature of exploitative production relations and that this forms a relationship between those who own and those who do not own property in the means of production. The Weberian tradition views society as stratified in multiple ways, i.e. by class, status, and political power. This tradition

argues that this stratification leads to unequal distribution of economic resources and skills. The Functionalist approach to social stratification, developed in the US, views the stratification of society as a natural and necessary feature of complex modern societies (72).

Social class may refer to the position of the individual's occupation in the structure of employment relations, whereas the concept of social status or socioeconomic status more reflect the position in a hierarchy, or social prestige accorded to an individual (73). Throughout this dissertation, the concept "socioeconomic position" is used, described by Lynch and Kaplan to mean "the social and economic factors that influence what position(s) individuals and groups hold within the structure of society" (72).

2.4.2 Across what groups should inequality be measured?

In social epidemiology, different indicators of socioeconomic position aim to describe the social stratification. People in different social categories have various resources and constraints leading to different life chances and living conditions. Socioeconomic position can be measured at three complementary levels: individual, household, and neighborhood (71). An individual's health could for instance be influenced by the socioeconomic characteristics of the neighborhood in which she or he lives, regardless of her or his own individual-level socioeconomic position (74).

Occupation, education, and income are often used as individual-based measures to define socioeconomic position (72). These are indicators of what resources individuals have access to, and what sort of life chances they have (72). The choice of measure should depend on how one believes socioeconomic position is linked to health damaging exposures and health protective resources, and ultimately to health (72). Is it few resources, or lack of prestige that causes poor health, or some combination of these? Occupational categories have been the primary basis for socioeconomic classification in western European countries (75). The occupation-based measures of socioeconomic position often group occupations so that the individuals in these occupations have similar labor market and work situation (72). In Sweden, it is common to use the occupation-based classification used by Statistics Sweden (76), which is similar to the classification of Erikson-Goldthorpe (77). Education, typically measured as completed years of schooling, or in terms of attainment of certain milestones (e.g. high school degree, university degree), is not a direct measure of position within the class structure, but rather a mechanism by which individuals gain access to such locations (73). Education could also reflect several noneconomic social characteristics such as general and health-related knowledge, which could have important health effects (78, 79).

Income as a measure has a broad range from the very poor to the very rich, describing availability of material resources. However, income is a complex measure, as it does not take into account wealth, ownership of property etc. When using income as a measure, it is important to adjust for the number of persons supported by the income.

The three primary indicators of childhood socioeconomic position are parental occupational status, educational level, and financial adversity (80). Throughout this dissertation, highest attained educational level will be used as the measure of socioeconomic position (further described in the methods section 3.3).

The individual-based measures cannot be used interchangeably as they refer to different socioeconomic factors. As a consequence, the effects on various health outcomes may differ as individuals may be classified differently depending on the measure used (75, 81). Occupation is frequently used as a measure of socioeconomic position in Europe, while education and income is more commonly used in the US (75).

Besides these three measures of socioeconomic position, there are other important measures of social stratification. Gender is a critical determinant of both physical and mental health. The term gender is often erroneously used interchangeably with the term sex (82). Gender refers to a social construct regarding culture-bound conventions, roles, and behaviors for, as well as relations between and among, women and men. Sex on the other hand is a biological construct premised upon biological characteristics. It is not self-obvious whether differences in the risk for psychiatric morbidity in women and men are due to biological differences or more social differences. Sometimes it may even be a combination of the two (83). Men tend to die earlier than women, but women tend to have higher rates of morbidity, especially when it comes to psychological distress (84). Gender determines the differential power and control women and men have over the socioeconomic determinants of their mental health and their lives, social position, status and treatment in society and their susceptibility and exposure to specific mental health risks (85).

Historically, when studying socioeconomic disparities in women's health, it has been debated how to measure social position of women, i.e. whether to use women's own socioeconomic position or in the context of their household (86-88). In a study comparing individual-based and household-based measures of social class in women, Krieger *et al.* suggested using the gender-neutral household measure, i.e. the most dominant class position in the household regardless of gender (87).

2.4.3 Socioeconomic inequalities in mental health and explanations

Many studies have shown the influence of social inequality on different health aspects, including both physical and mental health (7-9, 89). In general, individuals in the upper end of the social strata have healthier lifestyle patterns (90), lower prevalence of chronic disease (91), and lower risk of premature death (92). This is true regardless of stratification measure, i.e. for occupation (93), education (92) and income (91, 94).

People from disadvantaged family background are more likely to accumulate risks associated with disadvantage throughout life than those born to more privileged families (95, 96). Socioeconomic variation in the risk of mental disorder may be explained by differential clustering of risk factors by socioeconomic position. Risk factor clustering may be distributed differentially between as well as within socioeconomic groups (97, 98), where between-group clustering refers to clustering of risk factors in different socioeconomic groups, and within-group clustering describes clustering of risk factors within a socioeconomic group (98).

Childhood socioeconomic environment has long-term influences on various health outcomes (96), including psychiatric morbidity in adulthood (15, 26, 80, 99). Research has shown that duration of exposure is strongly associated with health, suggesting that risk to ill health from poor socioeconomic circumstances may accumulate over the life course (96). A cross sectional study on clustering of risk factors by social class in

childhood and adult life showed that co-occurrence of three or four risk factors was greater among more disadvantaged groups (100).

It has also been shown that past socioeconomic factors could act independently on current socioeconomic position on health, which stresses the importance of considering past socioeconomic experiences (96). Childhood socioeconomic position may for instance influence adult health independently of adult socioeconomic position (96, 100). Socioeconomic position in childhood has strong effects on distributions of risk factors in adult life (15). A recent prevalence study on US adolescents showed a higher prevalence of different mental disorders among offspring of parents with less than college education compared to college graduates (26).

In the inverse relationship between the occurrence of severe mental disorder and socioeconomic position, the causal structure of this relationship has been debated (7-9). A question that is often raised is whether the association between socioeconomic disadvantage and mental disorder is a consequence of the disorder itself, leading to a drift down the social class scale (social selection or reverse causation), or whether being in a lower socioeconomic position contributes to developing mental disorder, i.e. social causation (9).

Both hypotheses have been thoroughly studied over the years. Research in favor of the social selection hypothesis as an explanation for the negative socioeconomic position – mental disorder correlation, has suggested that individuals with mental disorder are drawn to low-income communities as a result of their disability (8). Intergenerational drift has been suggested as an explanation for social selection, stating that children and adolescents who are mentally ill fail to maintain the socioeconomic position of their family once they become adults (8).

According to the social causation theory, the stress from occupying the role of an individual in a lower social group increases the likelihood of mental health problems. In other words, the inverse correlation between socioeconomic position and mental disorder is an outcome of stressful economic conditions, such as poverty or unemployment (8).

It has been argued that control over one's life is central to the causal mechanism for psychological distress, and that low social class members have little sense of control over their lives (101). There is evidence that psychosocial factors at work influence the risk of psychiatric morbidity and may play an important role in contributing to the social gradient in ill health (102). Among different approaches to measure work stress, the demand-control model suggests that stressful experience at work results from a specific job task profile, defined by two dimensions – the psychological demands and the degree of control available to the person (101). The effort-reward imbalance model claims that high efforts spent at work that are not met by adequate rewards may cause recurrent stressful experience. This imbalance is likely to occur in people who have no alternative choice or are in highly competitive jobs (101).

Most studies that have found evidence for the social selection hypothesis have done so for severe mental disorders such as schizophrenia (7, 34), whereas social causation has been demonstrated with conditions of lesser severity, such as anxiety disorder and depression (7, 8, 103). In order to avoid problems with social selection, many

researchers have stressed the importance of measuring socioeconomic status long before the onset of the disorder.

2.5 LIFE COURSE EPIDEMIOLOGY

Life course epidemiology has been defined as the study of long-term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood, and later life (10, 11). Life course epidemiology suggests that various biological and social factors throughout life independently, cumulatively and interactively influence health and disease in adult life (104). One purpose with life course epidemiology is to study the contribution of factors in early life jointly with factors later in life to identify risk and protective processes over the life course (11). Life course epidemiology studies how socially patterned exposures during childhood, adolescence, and early adulthood influence adult disease risk and socioeconomic position.

A life course approach emphasizes the importance of time and timing in understanding causal links between exposure and outcome (105). In the life course approach, there are several hypotheses on how the effect of exposure can be linked to health-related outcomes (10). The critical period model stresses the timing of exposure, proposing that an exposure at a specific period in the life course is particularly damaging to the individual (11, 105). Among concepts referring to the causal pathway in relation to time, accumulation of risk has been introduced, suggesting that exposures gradually accumulate to increase the risk of disease (11). The exposure risk may be either independent, or clustered. The *chains of risk model* is a special version of the accumulation model, referring to a sequence of linked exposures that lead to impaired function and increased disease risk because one adverse exposure leads to another and so on. In the chains of risk model, each exposure can increase the risk together, but also independently of each other. A trigger effect describes a chain of risk where it is only the final link in the chain that has any marked effect (10).

Additionally, another concept known as social mobility (34) considers how individuals change between different categories of the social structure once or several times during the life course. Inter-generational social mobility describes the change of socioeconomic positions between generations, from parental to own adult socioeconomic position, while intra-generational social mobility describes mobility within (a certain period of) an individual's own socioeconomic position (34).

Accumulated exposure to low socioeconomic positions across the life course increases the risk for disease (100, 106). Most common measures in studies on accumulated adverse socioeconomic positions are parental socioeconomic position in childhood, followed by one's own position in young adulthood and current position (106, 107).

2.6 ADVERSE LIFE EVENTS

2.6.1 Concept and definition

It has long been debated how different life events affect health. Over four decades ago, a checklist of 43 events (e.g. death of a spouse, divorce) called the Schedule of Recent Experiences was published (108). The purpose of this checklist was to inventory incidents that were found to precede illness onsets.

Adversity refers to a condition of suffering, destitution or affliction, but also misfortune (109). Life events can be important representations of adversity. Adverse life events have been defined as occurrences likely to bring about readjustment-requiring changes in people's usual activities (110). These events are commonly distinguished into early adverse life events, i.e. those occurring during childhood and adolescence, and recent life events, i.e. those that occurred shortly before the onset of a disorder (12).

Since the publication of the Schedule of Recent Experiences by Holmes and Rahe (108), there has been a large increase in the construction of measures in research on the relations between life events and health.

2.6.2 Adverse life events as risk factors for psychiatric morbidity

The association between experience of adverse life events over the life course, and onset of mental disorders has been well documented (12, 13, 111, 112). Studies have reported an excess of adverse life events in the 6-12 months preceding mental disorder in general (12), but also for specific disorders such as depression (113, 114), schizophrenia (115, 116), and anxiety disorders (117, 118).

Adverse life events during childhood (also known as adverse childhood experiences (ACE)), e.g. abuse, neglect, and growing up with parental substance use may have negative long-term health and social consequences (14, 15, 119-123). Biological explanations from neurobiology and epidemiology suggest that early life stress causes enduring brain dysfunction that affects health and quality of life throughout the lifespan (119). Psychological and psychosocial explanations suggest that childhood adversity may damage emotion regulation, and concept of self-worth, reducing the child's self-esteem (15).

Adverse childhood experiences tend to occur in clusters, rather than as single experiences (119, 124). Several studies have shown that clustered adverse experiences during the formative years have a strongly graded relationship to several mental health problems, from adolescence to adulthood (119, 125-127). This is congruent with the allostatic stress theory, which suggests that the neurobiological stress management systems can be permanently altered by cumulative/chronic stress in childhood (128, 129).

In studies on adverse life events, criminal behavior, such as juvenile delinquency has been pointed out as a risk factor for psychiatric morbidity (130-134). It is more common among delinquents to suffer from mental disorder and substance use (135, 136).

Another rather common adverse life event is divorce or separation. Experience of divorce has been shown to increase the risk for psychiatric morbidity (137-139). Different processes have been suggested to explain why married have better health than unmarried. The selection hypothesis, mentioned earlier, suggests here that there is a predominance of mentally healthy individuals who gets and stays married while unhealthy individuals to a larger extent tend to stay single or get divorced, i.e. health problems "select" people in and out of marriage (140). Social integration is mentioned as a protective factor of marriage, indicating that social ties, and social support are more accessible for married people (141). Yet another explanation is social causation,

where stressors associated with a transition into separation and the stress from occupying the role of a separated/divorced person increases the likelihood of psychiatric morbidity (137).

In studies of psychiatric morbidity following adverse life events, it is often debated why some people recover or avoid negative outcomes against these events whereas others do not (142). Research has shown that some individuals have the capacity to overcome extreme adversity, and to show positive adaption in difficult situations (143). This phenomenon is called resilience (95). Resilience is an important concept in the life course perspective on adult health (96). It can be defined as a dynamic process of positive adaption to adversity (95, 144). Resilient individuals are able to utilize their skills and strengths to cope and recover from problems and challenges.

Moreover, the individual's capacity to cope with live circumstances has been proposed as a possible pathway. Over the years, the coping term has come to cover a variety of conceptual meanings (145). Some researchers refer to coping as "any response to external life strains that serves to prevent, avoid or control emotional distress" (146), or specific processes that an individual engages in for the purpose of dealing with stress (147). Pearlin and Schooler suggested a distinction between three kinds of resources important for the emotional impact of social strain: social resources, psychological resources (i.e. coping ability) and specific coping responses (i.e. coping strategies) (146). Coping strategies have been shown to be unequally distributed in society, with individuals in higher socioeconomic positions having higher levels of coping ability (145).

3 AIMS

The overall aim of this dissertation is to increase the knowledge on the association between adverse life events, psychiatric morbidity, and mortality, and the role of socioeconomic position from a life course perspective.

3.1 RESEARCH QUESTIONS

1. Is there an association between adverse childhood experiences, socioeconomic position, and psychotropic medication in young adulthood? Does the risk of psychotropic medication increase with an increasing number of adverse childhood experiences? Do adverse childhood experiences cluster between and within socioeconomic groups? (Study I)
2. Does juvenile delinquency increase the risk of suicide in young adults? Is the relationship modified by socioeconomic position? (Study II)
3. Is divorce associated with an increased risk of psychiatric morbidity? Can the occurrence of psychiatric morbidity after divorce be explained by social causation or a selection of vulnerable individuals? (Study III)
4. Do psychiatric patients have higher overall and cause-specific mortality? Is the quality of somatic care for psychiatric patients different from the care provided to patients with no concurrent psychiatric morbidity? (Study IV)

4 MATERIAL AND METHODS

4.1 DATA SOURCES

The studies in this dissertation were based on data from several Swedish population-based registers. The unique personal identity number (PIN), assigned to each Swedish citizen or permanent resident was used to link information from the different registers (148).

The National Patient Register (Study I-IV)

The National Patient Register, held by the National Board of Health and Welfare, was established in 1964 (149). It includes all individuals admitted to any psychiatric or general hospital, with complete coverage for psychiatric care since 1973 and for somatic care since 1987. Since 2001, all visits to specialized outpatient physicians are included. The register is updated once a year and it comprises approximately 1.5 million discharges a year, and nearly 10 millions visits to outpatient physicians.

The register includes patient data, administrative data, and medical data (e.g. diagnoses and procedures). The National Patient Register has close to complete coverage for all inpatient care (149). However, in 2010, around 25% of visits to psychiatric outpatient physicians were not included (150). In all studies, the National Patient Register was used to obtain information on hospital discharge, either with a diagnosis for mental disorder, or hospitalization at a psychiatric clinic. We used the National Patient Register to obtain information on principal and secondary diagnostic codes, sex, date of birth, date of admission and discharge, and procedure codes.

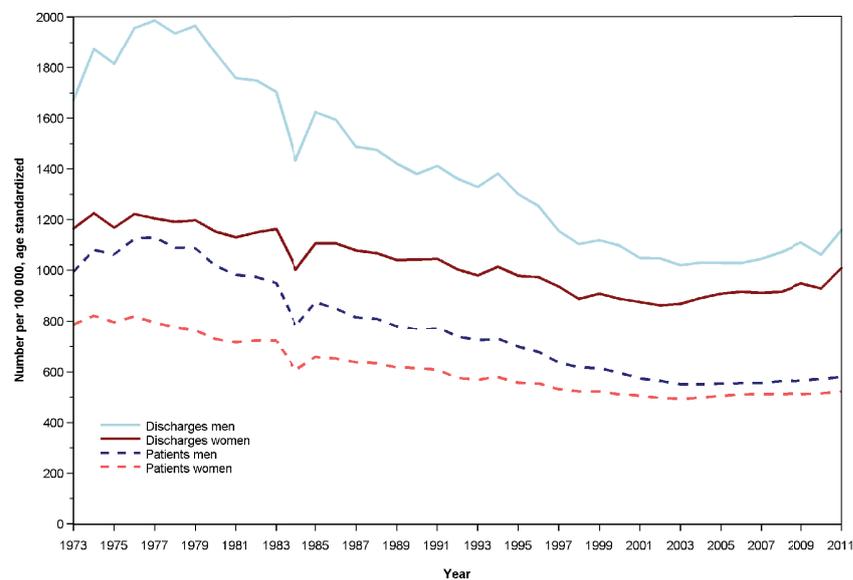


Figure 3. Number of discharges from psychiatric inpatient care 1973-2011*

Figure 3 illustrates the number of discharges from psychiatric inpatient care reported to

* Insufficient data in the National Patient Register in 1984

the National Patient Register between 1973 and 2011. In Sweden, inpatient care has to a great extent been replaced by outpatient treatment, and the accessibility to inpatient care has decreased. Therefore, the decrease in discharges over the years is a result of a shift in the responsibility for inpatient care from psychiatric hospitals at the county council level to institutions at the community level (151). In the year of 1984, several county councils in Sweden had difficulties in reporting data to the National Patient Register (152), which explains the decrease this year shown in Figure 3.

The Causes of Death Register (Study I-II, IV)

The Causes of Death Register contains information on all deceased individuals recorded as residents in Sweden at the time of death, irrespective of whether the death occurred in Sweden or abroad. The register is held by the National Board of Health and Welfare and comprises all deaths of Swedish residents since 1952. The register has very high coverage. However, the proportion of deceased with a lack of medical information increased between 2008 and 2011 from 0.5% to 1.8% (153). The basis for the register is the death certificates executed in each case by a physician. Underlying cause of death together with date of death was obtained from the Causes of Death Register.

The Prescribed Drug Register (Study I, III)

The Prescribed Drug Register contains patient characteristics for all prescribed drugs, dispensed in Swedish pharmacies to the entire population since 1999 (154). Since July 1st 2005, the personal identity number is included. The register includes information about the drug (type and amount), the patient (PIN, age, sex and place of residence), date of purchase and drug costs. Drugs utilized in hospitals or purchased over-the-counter are not included. Pharmaceuticals are grouped according to the Anatomical Therapeutic Chemical Classification System (ATC) (155). As a statistical measure of drug consumption, WHO has defined the daily dose (DDD) (155).

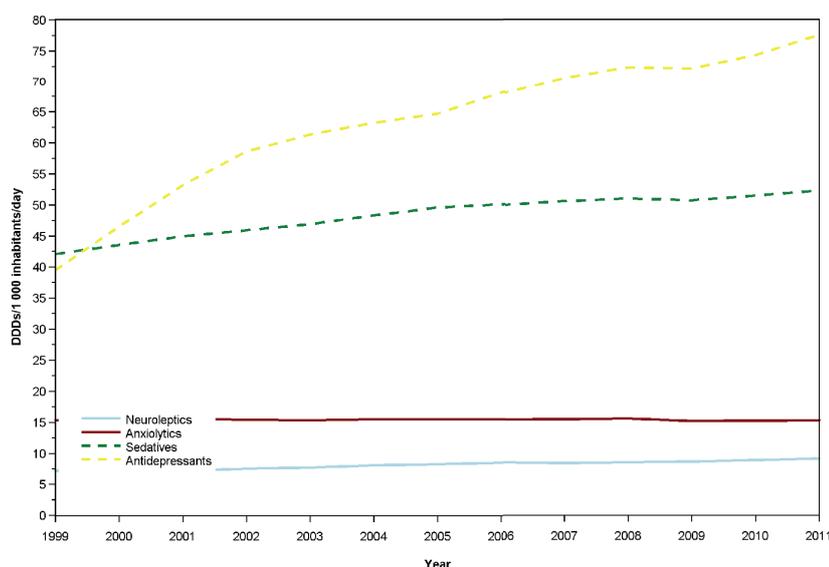


Figure 4. DDDs per 1000 inhabitants/day for psychotropic drugs, 1999-2011

DDD is the assumed average dose per day for a drug used for its main indication in adults. Figure 4 presents the defined daily dose (DDD) per 1 000 inhabitants/day in Sweden from 1999-2011 for the major classes of psychotropic drugs studied in this dissertation. In Study I and III, we used the Prescribed Drug Register to obtain information about prescribed drug type and amount.

The Medical Birth Register (Study I)

The Swedish Medical Birth Register, established in 1973, is held by the National Board of Health and Welfare. The register contains information on standardized antenatal, obstetric, and neonatal records. Almost all births in Sweden are included, only 1-2% of the records are missing annually (156). The Medical Birth Register, including personal identity number, sex and date of birth, was used in Study I to define the study population.

The Swedish Register of Children and Young Persons Subjected to Child Welfare Measures (Study I-II)

The Swedish Register of Children and Young Persons Subjected to Child Welfare Measures was established at Statistics Sweden in 1968. Since 1994, the register is held by the National Board of Health and Welfare. The register includes records on out-of-home care, foster family and residential care. In order to define child welfare intervention, type of intervention, type of out-of-home-care, and legal ground for the intervention were obtained.

The Total Population Register (Study II-IV)

The Total Population Register, held by Statistics Sweden, was established in 1968. It includes all individuals with permanent residence in Sweden. The Total Population Register is based on data from the Swedish Tax Agency and contains information on age, sex, marital status, country of birth and place of residence (157). This register was used to identify the subjects in Study II-IV.

The Population and Housing Censuses and the Longitudinal Integration Database for Health Insurance and Labor Market Studies (Study II-III)

The Population and Housing Census, held by Statistics Sweden, was a mandatory nationwide census conducted every 5 years between 1960 and 1990. Every household in Sweden was obligated to respond to and return the census questionnaire. Among other items, the censuses gathered information on age, sex, occupation, employment, and education (157). No census has been conducted after 1990. Similar data is today collected via a selection of different administrative registers and compiled into the database Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA by Swedish acronym) (158). This longitudinal database, established in 1990 under the acronym LOUISE, was renamed LISA in 2004. Updated annually, the register included all individuals 16 years of age or older that were registered in Sweden as of December 31st for the respective year. The database integrates existing data from the labor market, educational and social sectors. In Study II, we used the Population and Housing Censuses of 1990 to obtain information on single household. LISA was used in Study I to obtain single household and parental separation, number of changes in place of residency, and place of residence. In the third study, marital status was obtained from LISA.

The Swedish Register of Education (Study I-III)

The Swedish Register of Education, established by Statistics Sweden in 1985, is annually updated with information on the highest formal education attained by each individual, from elementary to post-graduate level (157). From this register information on highest attained educational level was collected.

The Total Enumeration Income Survey (Study I-II)

The Total Enumeration Income Survey, performed by Statistics Sweden, contains data on the income of, and governmental benefits (including social assistance and disability pension) provided to the entire Swedish population (157). This register was used in the first studies to obtain information on parental social assistance reciprocity and parental disability pension.

The Multi-Generation Register (Study I-II)

The Multi-Generation Register, held by Statistics Sweden, contains links between children and parents (biological and adoptive). The register includes all known relationships between children (born in 1932 and onwards) and parents who were alive 1961 or later (157). In the first two studies, parents and siblings were identified in the Multi-Generation Register.

The Crime Register (Study I-II)

The Crime Register, held by the Swedish National Council for Crime Prevention, contains information on all court convictions in Sweden for persons 15 years of age or older (159). The criminal code in Sweden determines that individuals are convicted as guilty regardless of mental disorder. Therefore, it also includes individuals transferred to forensic hospitals (e.g. individuals who were psychiatrically assessed and found to have had psychosis at the time of the offense). Conviction data also include cases in which the prosecutor decides to caution or fine. Because plea-bargaining is not permitted in Sweden, the data also accurately reflect the extent of the officially resolved criminality. We used the register in Study II to retrieve information on convictions and penalties.

4.2 MEASURES OF PSYCHIATRIC MORBIDITY

There are currently two diagnostic systems for classification of mental disorders in use. The Diagnostic and Statistical Manual of Mental Disorders (DSM), with its present version DSM-IV, is published by the American Psychiatric Association (18). The International Statistical Classification of Diseases and Related Health Problems (ICD), produced by the World Health Organization (WHO), is another commonly used manual which includes criteria for mental disorders (160). Diagnoses in the Swedish registers are coded according to ICD. However, since 2009, diagnoses according to DSM may also be reported to the National Patient Register.

Another way to measure psychiatric morbidity is by using prescriptions for drugs treating mental disorder. Psychotropic drugs are commonly used in the adult population (161, 162). Among the major classes of psychotropic drugs, neuroleptics are used to treat psychotic disorders, e.g. schizophrenia. Anxiolytics are used to treat anxiety disorders. Sedatives are commonly used to treat sleep disorder and also to relieve anxiety. Antidepressants, which are the most commonly prescribed psychotropic drugs,

are most often used to treat mood disorders, followed by anxiety disorders (162). Even though most prescribing of psychotropic drugs is for psychiatric conditions, there are other indications as well that they may be used for (162).

The first study used prescriptions for drugs treating psychiatric morbidity as the outcome variable. In Study II, suicide, which may be regarded as a consequence of psychiatric morbidity, was the outcome measure. In Study III psychiatric morbidity was the outcome and defined as psychiatric inpatient care, psychiatric outpatient visit, and medical treatment with psychotropic drugs. In Study IV, psychiatric diagnoses after psychiatric inpatient care or visits to specialized psychiatric outpatient physicians were used to obtain the exposure.

4.3 SOCIOECONOMIC CLASSIFICATION

Throughout this dissertation we used education in the analyses where we investigate whether socioeconomic position modifies the association between the studied exposure and outcome. Effect-measure modification refers to the situation in which a measure of effect changes over values of some other variable (163). A variable modifies the association between exposure and outcome when the effect of the exposure of interest differs across levels of the modifying factor (11). In the first three studies we investigated if socioeconomic position modified the relationship between exposure and mental disorder.

In the first two studies, our subjects are young individuals. As these persons are too young to have achieved a measurable occupation, education or income by themselves, we used parental socioeconomic position as a measure of the social stratification. In both studies, highest attained parental education level was measured when the child was 15 years old. For households with two adults, we chose the highest educational level to characterize the household. In Study I, educational level was classified into five categories: 1) nine years of compulsory school, 2) 10-12 years of education (equivalent to senior high school), 3) 13-14 years of education (i.e. university education less than 3 years), 4) > 14 years of education, 5) Missing. In Study II, we used the following three categories: 1) 9 years of compulsory school, 2) 10–12 years of education, 3) >12 years of education.

In Study III, educational level was used as a measure of socioeconomic position. As the cohort comprised individuals between the ages of 45 and 54, educational level was classified into two categories representing distinct levels in the Swedish educational system for this age cohort: 1) ≤ 12 years of education, 2) ≥ 13 years of education.

4.4 DESIGN OF THE STUDIES

The designs and methods used in each study are presented in table 1.

Study I

Study I was a register-based cohort study in which the study population was defined as all individuals born in Sweden and recorded in the Medical Birth Register between 1985 and 1988 with at least one parent born in Sweden (n=382 154). Individuals who had ever migrated (n=15 012), been adopted (n=227), had been diagnosed with mental

retardation during the ages 0-17 years (n=392), and those who died before the 31st of December 2008 (n=3 954) were excluded. The final cohort (n=362 663) was followed for use of psychotropic medication from January 1st 2006 until December 31st 2008.

Study II

Study II was a register-based cohort study where we included all Swedish residents born between 1972 and 1981 (n=1 067 202). Children who had been diagnosed with mental retardation during the age of 0 and 17 (n=1 834), as well as children who died before the age of 20 (n=4 443) were excluded. An inclusion criterion was to be a Swedish resident during the age of 7 to 19 years. After excluding children who immigrated or emigrated during this period (n=68 328), the final cohort comprised 992 881 individuals. The follow-up period lasted from their 20th birthday until 31st of December 2006. Thus, the incidence of suicide was measured from the age of 20 to 25 years for those born in 1981, and up to the age of 34 years, for those born in 1972.

Study III

The study population included all individuals born between 1952 and 1961, alive and registered in Sweden on December 31st 2005 as well as on December 31st 2006 who were either married or divorced in 2005 and 2006 (N=833 629). In order to be able to measure incidence of psychiatric morbidity, we excluded 129 669 individuals with a history of psychiatric care 1987–2005 (measured as psychiatric inpatient care 1987-2005 or as psychiatric outpatient care 2001-2005 or as medical treatment with psychotropic drugs during July 1st through December 31st 2005). Our final study cohort, comprising 703 960 individuals, was followed for new episodes of psychiatric care utilization from January 1st to December 31st 2007.

Study IV

The study population comprised individuals alive and registered in Sweden in December 31st 2004 and 2005, between the ages of 20 and 79, i.e. those born between 1926 and 1985. After excluding individuals diagnosed with mental retardation, the study population comprised 6 294 339 individuals. The cohort was followed with respect to mortality from January 1st 2006 until December 31st 2007.

Table 1. An overview of the four studies

	STUDY I	STUDY II	STUDY III	STUDY IV
Aim	To examine the association between adverse childhood experiences, and risk of psychotropic medication	To examine whether juvenile delinquency increases the risk of suicide in young adults and whether the relationship is modified by socioeconomic position.	To examine if divorce is associated with an increased risk of mental disorder, and to investigate whether the occurrence of mental disorders after divorce is explained by social causation or a selection of vulnerable individuals.	To investigate whether psychiatric patients have higher overall and cause-specific mortality, and whether the quality of somatic care for psychiatric patients is different from the care provided to patients with no concurrent mental disorder.
Study population	Individuals born in Sweden between 1985 and 1988 with at least one parent born in Sweden (n=362 663), followed from January 1 st 2006 through December 31 st 2008	Swedish residents born between 1972 and 1981 (n=992 881), followed from age 20 until December 31 st 2006	Individuals born between 1952 and 1961, registered in Sweden in 2004 and 2005 (n=6 294 339), followed from January 1 st 2006 through December 31 st 2007	Individuals born between 1926 and 1985, registered in Sweden in 2004 and 2005 (n=6 294 339), followed from January 1 st 2006 through December 31 st 2007
Design	Population-based cohort study	Population-based cohort study	Population-based cohort study	Population-based cohort study
Data source	Medical Birth Register, Prescribed Drug Register, National Patient Register, Crime Register, Total Enumeration Income Survey, Swedish Register of Children and Young Persons Subjected to Child Welfare Measures, Causes of Death Register, Swedish Register of Education,	National Patient Register, Causes of Death Register, Swedish Register of Children and Young Persons Subjected to Child Welfare Measures, Total Population Register, National Population and Housing Censuses, Swedish Register of Education, Total Enumeration Income Survey, Multi-Generation Register, Crime Register	National Patient Register, Prescribed Drug Register, Total Population Register, LISA	National Patient Register, Causes of Death Register, Prescribed Drug Register, Total Population Register
Exposures	Adverse childhood experiences: severe criminality among parents, parental alcohol or drug abuse, social assistance receipt, parental separation or single household, child welfare intervention before age 12, mentally ill or suicidal parents, familial death, number of changes in place of residency	Juvenile delinquency: being convicted of a crime between the ages of 15 and 19	Marital transition (divorce, marriage)	Mental disorder, defined as being hospitalized or treated in outpatient care with a principal psychiatric code
Outcome	Prescribed psychotropic medication	Suicide including deaths with undetermined intent	Psychiatric morbidity, measured as psychiatric inpatient care, outpatient care and prescribed psychotropic medication	Underlying cause of death, grouped as: ischemic heart disease, cancer, suicide and death with undetermined intent, external causes of death (suicide excluded), and indicators of avoidable mortality. Health care quality indicators: avoidable hospitalization, 28-day case fatality rate after myocardial infarction, and treatment with lipid lowering drugs.
Statistical analysis	Descriptive analysis, synergy index, odds ratios using logistic regression.	Descriptive analysis, incidence rate ratios using Poisson regression	Descriptive analysis, incidence rate ratios using Poisson regression	Descriptive analysis, age-standardized proportions, incidence rate ratios using Poisson regression

4.5 EXPOSURES

Study I

In Study I we used eight measures of adverse childhood experiences. All these experiences alone have been shown to be risk factors for later psychiatric morbidity. All adverse childhood experiences were measured between birth and age 14.

Children growing up with criminal parents have increased risk for psychiatric morbidity (164). *Severe criminality among parents* was measured from birth until age 14, and was defined as parents who received custodial or noncustodial sentences or individuals transferred to forensic hospitals.

Death of a family member is regarded as a traumatic life event that increases stress levels in children (165-167). *Familial death* was defined as death of either parent or sibling. This adverse childhood experience was measured from birth until age 14.

As a commonly used measure of adverse childhood experience, we defined *parental alcohol or drug abuse* as parents hospitalized with a main diagnosis for alcohol and/or narcotic-related substance use (ICD-9: 291, 303, 305A, 357F, 425F, 535D, 571A, 571B, 571C, 571D, 292, 304, 648D, 655F, 969G, 969H, and 965A; ICD-10: E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86, O35.4, T51, Z50.2, Z71.4, Z72.1, F11-16, F18-19, O35.5, P04.4, T40, T43.6, Z50.3, Z71.5, and Z72.2), or parents who had received an alcohol or narcotic-related drug conviction. This adverse childhood experience was measured from 1987 until the age of 14.

Children of mentally ill parents are at greater risk for psychiatric morbidity (168). *Parental psychiatric morbidity* included parents hospitalized with a main diagnosis of mental disorder (ICD-9: 290-319 (substance use disorders excluded); ICD-10 F00-F98 (substance use disorders excluded)). Suicidal parents included parents hospitalized with a diagnosis for deliberate self-harm (ICD-9: E950-E959, E980E-989; ICD-10: X60-X84, Y10-Y34). This adverse childhood experience was measured from 1987 until age 14.

It has been shown that children in families receiving long-term social assistance face less satisfactory health (169). To fulfill the criterion of “*social assistance reciprocity*”, at least one parent must have received social assistance at least during one year (measured when the child was between 5 and 14 years old), where more than 50% of the yearly income constituted social assistance.

Growing up in a single-parent family has disadvantages for the health of the child (170). *Single household* and *parental separation* was measured when the child was between 5 and 14 years old.

Experience of child welfare intervention before age 12 is a well-known risk factor for psychiatric morbidity (171, 172). *Child welfare intervention* was defined as out-of-home care or provision of respite care before the age of 12.

Frequent changes of residence during childhood are associated with an increased risk of psychiatric morbidity (173). We defined this adverse childhood experience as two or more changes of residence between municipalities when the child was between the ages 6 and 14, i.e. year of compulsory school.

Study II

The exposure *juvenile delinquency* was defined as being convicted of a crime between the ages of 15 and 19 years. All convictions from the Crime Register between the age of 15 and 19 were summarized, categorizing the cohort into four exposure groups: Group 0, comprising those who have never been convicted of a crime at the age of 15–19 years; Group 1 consisted of individuals with one conviction only; Group 2 included individuals with two to four convictions; and Group 3 was considered as severe delinquency and consisted of individuals with five or more convictions and individuals with less than five convictions, but with more severe penalties, i.e. probation or imprisonment.

In a sub analysis we studied violent crime separately. Violent crime was defined as homicide, assault, robbery, arson, sexual offence (rape, sexual coercion, child molestation, indecent exposure or sexual harassment), illegal threats or intimidation. Hence, burglary and other property offences, traffic offences and drug offences were excluded. When the analysis was dichotomized to violent and non-violent convictions, a subject with both types of conviction was placed in the 'violent' group. This definition was based on the work by Fazel *et al* (174, 175).

Study III

In order to study the relationship between marital transition and psychiatric morbidity, marital status for the years 1990 to 2006 was obtained from LISA. Four mutually exclusive categories for marital transition were created as: *i*) individuals who were married in 2005 as well as in 2006. *ii*) individuals married in 2005 and divorced in 2006. *iii*) divorced in both 2005 and 2006. *iv*) individuals divorced in 2005 and remarried in 2006. In order to handle marital duration, we calculated number of married years between 1990 and 2004 and created three groups: 0-5 years, 6-14 years, and 15 years). A dichotomous variable for earlier divorce, i.e. during 1990 to 2004 was created.

Study IV

We identified all individuals recorded in the National Patient Register with a principal psychiatric diagnostic code (ICD-10: F00-F99 (dementia excluded)) in inpatient or specialized outpatient care in 2004 or 2005. If a patient had more than one discharge or outpatient visit, the principal diagnoses from all discharges and outpatient visits were kept to further categorize patients. Five mutually exclusive exposure groups were created according to a hierarchy of diagnoses: *i*) schizophrenia and other non-affective psychoses (ICD-10: F20-F29), *ii*) affective disorder (ICD-10: F30-F39), *iii*) anxiety disorder (ICD-10: F40-F48), *iv*) other psychiatric diagnoses, (ICD-10: F04-F99 except for diagnoses above)), *v*) persons without inpatient and outpatient care due to mental disorder served as the reference group.

Psychiatric in- or outpatient care due to substance use disorder was also studied in a sub analysis and was divided into categories according to whether the substance use was attributed to alcohol (ICD-10: F10), narcotic-related drugs (ICD-10: F11-F19), or both.

Schizophrenia/other non-affective psychoses, affective or anxiety disorder were analyzed with and without a coexisting substance use disorder (attributed to either

alcohol or narcotics-related drugs). In these analyses, persons without inpatient and outpatient care due to mental disorder served as the reference group.

4.6 OUTCOME MEASURES

Study I

In the first study filled prescriptions for psychotropic drugs was used as a proxy for psychiatric morbidity. Pharmaceuticals were grouped as: neuroleptics (ATC: N05A), anxiolytics and sedatives (N05B-N05C), and antidepressants (N06A). An individual was considered to have received drug treatment if at least one prescription for psychotropic medication was dispensed between January 1st 2006 and December 31st 2008.

Study II

Suicide was defined as having an underlying cause of death in the Causes of Death Register (ICD-9: E950–E959, ICD-10: X60–X84) or as death with undetermined intent (ICD-9: E980–E989, ICD-10: Y10–Y34). With our definition of suicide including deaths with undetermined intent, our aim was to reduce spatial and secular trends in detecting and classifying cases of suicide (176).

Study III

The cohort in Study III was followed from January 1st until December 31st 2007 for three mutually exclusive indicators of psychiatric morbidity: (1) psychiatric inpatient care, (2) psychiatric outpatient visit and no inpatient care, and (3) filled prescription of psychotropic drugs but without in- or outpatient care. Inpatient care was considered as an indicator of severe psychiatric disorders. Outpatient care was used as an indicator of milder psychiatric disorder. Psychotropic medication without in- or outpatient care was used as an indicator of an even milder form of psychiatric disorder or distress. We referred to all of these measures as psychiatric morbidity. Individuals treated in inpatient- and outpatient psychiatric care were identified in the National Patient Register. Information on medical treatment was obtained from the Prescribed Drug Register. Pharmaceuticals were grouped as: antipsychotics (ATC: N05A), antidepressants (N06A), and anxiolytics and sedatives (N05B-N05C). An individual was considered receiving medical treatment if at least one prescription for psychotropic medication was dispensed during the studied period.

Study IV

The underlying cause of death was obtained from the Causes of Death Register. The classifications of the different causes of death are shown in Table 2. The indicators of avoidable mortality were divided into causes of death reflecting the outcome of medical care, and causes reflecting the effect of the national health policy. In the analyses of indicators reflecting aspects of health care quality, the indicator *avoidable hospitalization* measures efficiency, availability and treatment for selected conditions in outpatient care, such as preventive public health and primary care. The assumption is that unnecessary hospitalizations can be avoided if patients with these selected conditions receive proper outpatient care.

Table 2. Classification of outcomes in Study IV

Outcome	ICD-10
Causes of death	
All-cause mortality	All diagnoses
Ischemic heart disease	I20-I25
Suicide and death with uncertain intent	X60-X84, Y10-Y34
Deaths from external causes (suicide excluded)	V01-Y89 (except for the diagnoses X60-X84, Y10-Y34)
Cancer	C00-C99
Avoidable causes of death	
<i>Medical care indicators:</i>	
Typhoid	A01.0
Tetanus	A35
Tuberculosis	A15-A19, B90
Malignant neoplasms of cervix uteri	C53
Hodgkin's disease	C81
Diabetes	E10-E14
Chronic rheumatic heart disease	I05-I09
Hypertensive disease	I10-I15
Stroke	I60-I69
Respiratory diseases	J00-J99
Asthma (part of respiratory diseases)	J45-J46
Appendicitis	K35-K38
Abdominal hernia	K40-K45
Cholelithiasis and cholecystitis	K80-K81, K83.0
Maternal deaths	O00-O99
Osteomyelitis	M86-M87
<i>National health care indicators:</i>	
Malignant neoplasms of the oesophagus	C15
Malignant neoplasms of trachea, bronchus, lung	C34
Cirrhosis of liver	K70, K73-K74
Motor vehicle accident	V00-V99
Avoidable hospitalization	
<i>Chronic conditions*</i>	
Anaemia	D50.1, D50.8, D50.9
Asthma	J45, J46
Diabetes	E10.1-E10.8 (primary or secondary diagnosis) E11.0-E11.8 (primary or secondary diagnosis) E13.0-E13.8 (primary or secondary diagnosis) E14.0-E14.8 (primary or secondary diagnosis)
Heart failure	I50, I11.0, J81
Hypertension	I10, I11.9
Chronic obstructive lung disease	J41, J42, J43, J44, J47 (primary diagnosis) J20 together with J41, J42, J43, J44, J47 as secondary diagnosis
Angina pectoris	I20, I24.0, I24.8, I24.9
Acute conditions	
Bleeding ulcers	K25.0, K25.1, K25.2, K25.4, K25.5, K25.6, K26.0, K26.1, K26.2, K26.4, K26.5, K26.6, K27.0, K27.1, K27.2, K27.4, K27.5, K27.6, K28.0, K28.1, K28.2, K28.4, K28.5, K28.6
Diarrohea	E86, K52.2, K52.8, K52.9
Epileptic seizures	O15, G40, G41, R56
Inflammatory diseases of female pelvic organs	N70, N73, N74
Pyelitis	N39.0, N10, N11, N12, N13.6
Ear, nose and throat infection	H66, H67, J02, J03, J06, J31.2

* Cardiac surgery discharges excluded

The indicator regarding 28-day case fatality rate after myocardial infarction describes how well the health care system handles acute care after myocardial infarction. It was defined as the proportion of deceased within 28 days after myocardial infarction (ICD-10: I21, I22). This indicator has been described more thoroughly elsewhere (177).

The third indicator, proportion on treatment with lipid lowering drugs, was measured among patients receiving diabetes drugs. The indicator was defined as the proportion of individuals using diabetes drugs (ATC: A10), that received at least one prescription of lipid lowering drugs (ATC: (C10)) (177).

4.7 POTENTIAL CONFOUNDERS

There are other factors that may influence the results. We were able to take several other factors into consideration in the analyses.

The definition of a confounder is that it influences the association between exposure and outcome (163). A confounding factor is associated with the exposure but is also an independent risk factor for the outcome. Confounding can lead to an under or over estimation of the effect. The following variables were considered as potential confounders: Year of birth (Study I-IV), place of residence (Study I), parental psychiatric morbidity, including inpatient care for mental disorder and inpatient care for deliberate self-harm (part of the methodology in Study I), inpatient care for mental disorder and substance use (Study II), parental inpatient care for substance use (Study II), parental inpatient care for mental disorder (Study II), single parenthood (Study II), social assistance reciprocity (Study II), disability pension reciprocity (Study II), adoption (Study II), foster care (Study II), country of birth (own and parental) (Study II), parental educational level (part of the methodology in Study II), and earlier divorce (part of the methodology in Study III).

4.8 MEASURES OF DISEASE OCCURRENCE

Risk refers to the number of individuals developing disease during a defined time period divided by the total number of subjects followed during the time period. It requires that all individuals are followed for the entire time period. Risk may also be referred to as the incidence proportion (163). Incidence rate is similar to the incidence proportion, i.e. the numerator is the same. The denominator however is instead the total time experienced from the subjects that are followed. Both incidence proportion and incidence rate are measures assessing the frequency of disease onset, whereas prevalence proportion is a measure of disease status.

In epidemiology, effects can be measured either on the absolute or on the relative scale (163). In order to study the causes of disease, two commonly used measures are the risk difference (RD) and risk ratio (RR). RD would be the difference in incidence proportion or incidence rate between the exposed and unexposed group. RR on the other hand is a measure on the relative scale; RR is defined as the risk among the exposed divided by the risk among the unexposed. If two incidence rates are divided we obtain the incidence rate ratio (IRR). In general, the phrase *relative risk* refers to either a risk ratio or an incidence rate ratio. RD always expresses the absolute difference between the exposed and unexposed, whereas the magnitude of the RR depend on the baseline level of the reference group (89).

4.9 STATISTICAL ANALYSIS

Throughout this dissertation, estimates are presented with 95% confidence interval (CI) in order to display significance, but also to indicate the precision of the estimates. The

precision is influenced by the amount of random variation, and can be estimated by observing the width of the confidence intervals around the point estimate (178).

4.9.1 Logistic Regression (Study I)

In Study I, logistic regression analyses were used to statistically evaluate the association between adverse childhood experiences and psychotropic medication utilization. We calculated odds ratios (ORs) including 95% confidence intervals as estimates of incidence rate ratios (IRRs). SAS Logistic procedure in SAS v. 9.2 was used.

The OR may be interpreted as an estimate of IRR. The OR and IRR will always point in the same direction, however it has been argued that, when the prevalence of the outcome is high (over 10%) there is a risk for overestimation of the ORs (179). This was not the case in our study though.

4.9.2 Synergy Index (Study I)

In Study I, we calculated the synergy index (SI), a measure on the biological or public health interaction between two risk factors. SI is expressed as the ratio of the relative excess risk for the combined effect of the risk factors and the sum of the relative excess risks for each separate effect of the two risk factors (178). An SI greater than 1 indicates that the absolute excess risk for those exposed to both risk factors is greater than the sum of the absolute excess risks for those exposed to each separate risk factor. RR_{00} are the jointly unexposed ($RR=1$); RR_{11} is the rate ratio for those exposed to both risk factors; RR_{01} and RR_{10} are the rate ratios for those exposed to only one risk factor.

$$SI = \frac{RR_{11} - 1}{[RR_{10} - 1] + [RR_{01} - 1]}$$

4.9.3 Observed-to-expected ratio (Study I)

In Study I, we calculated age-standardized observed and expected prevalence for each adverse childhood experience for the whole cohort as well as for each stratum of parental socioeconomic position. We derived expected frequencies of co-occurrence of adverse childhood experiences for all combinations of adverse childhood experiences by combining probabilities, assuming a binomial distribution and independence between them. For the between-group clustering analyses the prevalence in the total population was used. For within-group clustering analyses, the prevalence in each specific stratum was used. Clustering is indicated when individuals are more likely to have no or many adverse childhood experiences and thus are less likely to have a single or few adverse childhood experiences than would be expected if the distribution of adverse childhood experiences was independent (thus observed-to-expected ratio greater than one indicates clustering).

4.9.4 Age-standardized proportion calculation (Study IV)

In Study IV, we calculated age-standardized percentages for the indicators *avoidable hospitalization*, *myocardial infarction – 28-day case fatality rate*, and *diabetic patients receiving lipid lowering drugs therapy*, to analyze differences in health care quality.

Data was age-standardized in order to correct for differences in the age structure among the diseased compared to the general population. The same standard population was used for women and men.

4.9.5 Poisson Regression (Study II-IV)

Poisson regression analysis was used in Study II-IV to evaluate the association between the studied exposures and outcomes. Poisson regression analysis is a commonly used statistical model applied in case of time-to-event data, also known as survival analysis. Time-to-event data are generated when the response measurement of interest is the time from a defined origin of measurement to occurrence of an event of interest.

The results in Study II-IV are presented as IRRs with corresponding 95% CI. We assessed person-years at risk by adding up the years the individuals were alive and living in Sweden during the follow-up period. In Studies II-IV, SAS Genmod procedure was used in SAS v. 9.1.

5 REVIEW OF RESULTS

5.1 STUDY I: MULTI-EXPOSURE AND CLUSTERING OF ADVERSE CHILDHOOD EXPERIENCES, SOCIOECONOMIC DIFFERENCES AND PSYCHOTROPIC MEDICATION IN YOUNG ADULTS

The results in Study I showed that adverse childhood experiences were common, 40% had been exposed to at least one adverse childhood experience and nearly 20% had two or more experiences. Exposure to adverse childhood experiences was found to be more common among individuals whose parents had a low socioeconomic position.

The main result in this study was that adverse childhood experiences were associated with an increased risk of psychotropic medication. The OR for more than three adverse childhood experiences and risk of psychotropic medication was 2.4 (95% CI 2.3-2.5) for women and 3.1 (95% CI 2.9-3.2) for men. Besides the clustering effect, each adverse childhood experience on its own increased the risk of psychotropic medication (Table 3).

Table 3. Risk of psychotropic medication 2006-2008 (OR, 95% CI) by adverse childhood experiences and sex*

Adverse childhood experience	Women	Men
Severe crime parents	1.7 (1.6-1.8)	2.2 (2.0-2.3)
Parental alcohol and/or drug abuser	1.8 (1.7-1.8)	2.0 (1.9-2.2)
Parental separation and/or single household	1.6 (1.6-1.7)	1.8 (1.8-1.9)
Household receiving social assistance	1.8 (1.7-1.9)	2.1 (2.0-2.2)
Child welfare intervention before the age of 12	2.3 (2.2-2.5)	3.1 (2.9-3.4)
Mentally ill or suicidal parent	1.9 (1.8-2.0)	2.3 (2.2-2.4)
Familial death	1.3 (1.2-1.3)	1.4 (1.3-1.5)
Two or more changes in place of residence	1.8 (1.6-1.9)	2.0 (1.9-2.2)

* Adjusted for age and place of residence

In order to adjust for potential confounding by population density, the individuals' place of residence in the year of 2006 was studied, showing that the distribution was approximately similar across all pharmaceutical groups (Figure 4).

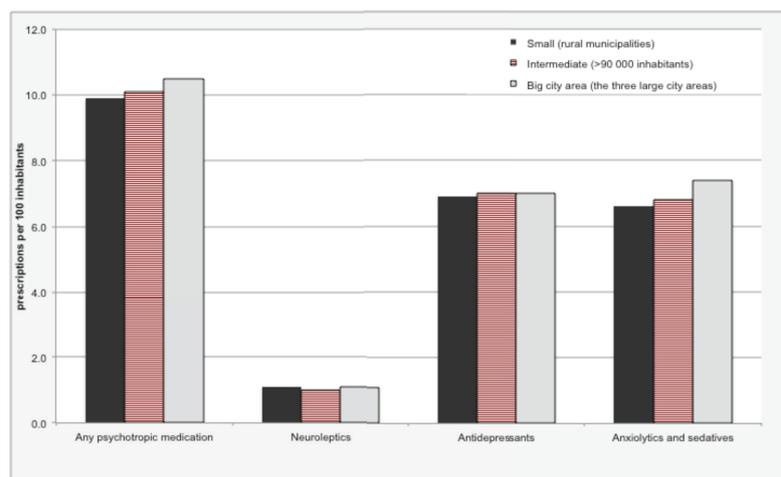


Figure 5. Prescription rates 2006-2008 per 100 inhabitants, by place of residence

Women had higher rates of psychotropic medication compared to men, regardless of the type of drug (Table 4). As the number of adverse childhood experiences increased, rates of at least one filled prescription of psychotropic medication increased gradually. This relationship was similar in all socioeconomic groups.

Table 4. Rates per 100 individuals (with 95% CI) of at least one filled prescription with psychotropic medication during 2006-2008

Number of adverse childhood experiences	Antidepressants	Neuroleptics	Anxiolytics and sedatives	All
Women				
0	7.6 (7.5-7.8)	0.9 (0.8-0.9)	7.1 (7.0-7.3)	10.8 (10.6-11.0)
1	10.4 (10.1-10.7)	1.3 (1.2-1.4)	10.0 (9.7-10.3)	14.6 (14.2-14.9)
2	12.5 (12.0-13.0)	1.8 (1.6-2.0)	12.1 (11.6-12.6)	17.3 (16.7-17.8)
3+	16.5 (15.9-17.1)	2.7 (2.4-3.0)	16.2 (15.6-16.8)	22.6 (21.9-23.2)
Men				
0	3.3 (3.2-3.4)	0.6 (0.5-0.6)	3.6 (3.4-3.7)	5.3 (5.2-5.4)
1	4.9 (4.7-5.1)	1.0 (0.9-1.1)	5.2 (5.0-5.5)	7.7 (7.5-8.0)
2	6.6 (6.3-7.0)	1.4 (1.3-1.6)	7.1 (6.8-7.5)	10.3 (9.9-10.8)
3+	9.6 (9.1-10.0)	2.4 (2.1-2.6)	10.2 (9.7-10.7)	14.6 (14.1-15.2)

In a sub analysis we calculated synergy index in order to measure the interaction between educational level and adverse childhood experiences (Table 5). We merged all individuals with any adverse childhood experience into one group. The four groups for parental education were reduced to two groups: 9-12 years of education and >12 years of education. We found that the risk of psychotropic medication for those exposed to at least one adverse childhood experience *and* having parents with 9-12 years of education was higher than would be expected from the additive effect of the two exposures (SI: 1.4 (95% CI 1.2-1.5) when adjusting for year of birth and sex.

Table 5. Synergy Index with 95% CI

Educational group	Women		Men		All	
	0 ACE	1+ ACE	0 ACE	1+ ACE	0 ACE	1+ ACE
High education (>12 years)	1 (REF)	1.6 (1.5-1.6)	1 (REF)	1.7 (1.6-1.8)	1 (REF)	1.6 (1.6-1.7)
Low education (≤ 12 years)	1.0 (1.0-1.1)	1.8 (1.7-1.9)	0.9 (0.9-1.0)	2.0 (1.9-2.1)	1.0 (1.0-1.0)	1.9 (1.8-1.9)
Synergy index		1.3 (1.2-1.5)		1.4 (1.2-1.7)		1.4 (1.2-1.5)

5.2 STUDY II: JUVENILE DELINQUENCY, SOCIAL BACKGROUND AND SUICIDE – A SWEDISH NATIONAL COHORT STUDY OF 992 881 YOUNG ADULTS

This cohort study, comprising 484 375 (49%) women and 508 506 (51%) men, showed that nearly 6% of the women had one conviction when between 15 and 19 years old, whereas 0.7% had between two and four convictions. Of the 226 women in conviction group 3, 31% had more severe penalties and 69% had more than five convictions. Nearly 12% of the men had one conviction, and 5% had between two and four convictions. Of the 1.2% in the final conviction group, 39% had more severe penalties.

Both women and men with repeatedly convictions had more often a psychiatric morbidity and problems with substance use. Over half of the women in conviction group 3 had a history of psychiatric inpatient care. In the same conviction group, one in ten women were brought up in foster care.

Our results showed increased suicide risks in both female and male convicts. The crude IRRs, where we only adjusted for year of birth, displayed a gradual increase in suicide

risk, i.e. the risk increased as the number of convictions increased. Several separate regression models were analyzed. In the final model, where we included all potential confounders, the conviction group gradient still remained for both sexes.

Table 6. Conviction group and risk of suicide in women and men

Conviction group	Number of suicides	Suicide Rate (No/100 000 person years)	Adjusted IRRs (95% CIs)			
			Model I *	Model II **	Model III ***	Model IV ****
Women						
Never convicted	321	6.9	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Convicted (no violent crime)	37	14.8	2.2 (1.6-3.1)	1.6 (1.2-2.3)	1.8 (1.3-2.5)	1.5 (1.0-2.1)
Convicted for violent crime	38	87.3	12.9 (9.2-18.0)	5.2 (3.6-7.6)	8.1 (5.7-11.6)	4.2 (2.8-6.1)
Men						
Never convicted	563	13.4	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Convicted (no violent crime)	238	33.9	2.5 (2.2-3.0)	2.4 (2.1-2.8)	2.3 (2.0-2.7)	2.2 (1.9-2.6)
Convicted for violent crime	285	82.1	6.1 (5.3-7.1)	4.9 (4.2-5.7)	4.9 (4.2-5.7)	4.2 (3.6-4.9)

* Adjusted for year of birth

** Adjusted for year of birth, substance use, and mental illness 0-19 years of age

*** Adjusted for year of birth, parental education, lone parental household, household receiving social welfare, household receiving disability pension, adoption, foster care, place of residence, country of birth (own and parental)

**** Model I+II+III

When we categorized the conviction groups into non-violent and violent crimes (Table 6), female non-violent offenders had, in the fully adjusted model, an IRR of 1.5 (95% CI 1.0–2.1) and violent offenders an IRR of 4.2 (95% CI 2.8–6.1), the IRRs for men were 2.2 (95% CI 1.9–2.6) and 4.2 (95% CI 3.6–4.9), respectively.

A secondary analysis where we investigated whether the relationship between delinquency and suicide was modified by parental socioeconomic position, showed tendencies of higher risks for adolescents whose parents had lower levels of education. However, these tendencies were no longer evident when adjustments were made for all potential confounding factors. We did however find evidence for higher suicide rates among individuals with parents in lower socioeconomic groups.

5.3 STUDY III: RISK OF NEW PSYCHIATRIC EPISODES IN THE YEAR FOLLOWING DIVORCE IN MIDLIFE: CAUSE OR SELECTION? A NATIONWIDE REGISTER-BASED STUDY OF 703 960 INDIVIDUALS

In the cohort comprising 349 423 women and 354 537 men, 1.2% divorced during the studied years (0.5% of the women and 0.7% of the men). Table 7 shows that, among the divorced, 15 % had been divorced at least once before the period 1990-2004. Nearly 15 % of the women and 8 % of the men who divorced in 2006 received some kind of psychiatric treatment in the following year.

Table 7. Cohort characteristics for Study III

	Married 2005/2006	Divorced 2005/2006	Married 2005, divorced 2006	Divorced 2005, remarried 2006
Women				
N	264 485	79 150	3 771	2 017
%	37.6	11.2	0.5	0.3
Age category				
45-49	128 632 (48.6 %)	38 245 (48.3 %)	2 328 (61.7 %)	1 091 (54.1 %)
50-54	135 853 (51.4 %)	40 905 (51.7 %)	1 443 (38.3 %)	926 (45.9 %)
Number of married years 1990-2004				
0 to ≤ 5	18 570 (7.0 %)	42 253 (53.4 %)	477 (12.6 %)	1 015 (50.3 %)
5 to ≤ 14	55 248 (20.9 %)	34 433 (43.5 %)	1 096 (29.1 %)	945 (46.9 %)
15 years	190 667 (72.1 %)	2 464 (3.1 %)	2 198 (58.3 %)	57 (2.8 %)
Earlier divorce				
	19 355 (7.3 %)	3 426 (4.3 %)	535 (14.2 %)	139 (6.9 %)
Educational level				
12 years or less	157 098 (59.4 %)	51 309 (64.8 %)	2 180 (57.8 %)	1 280 (63.5 %)
13 years or more	106 091 (40.1 %)	27 463 (34.7 %)	1 553 (41.2 %)	722 (35.8 %)
Missing	1 296 (0.5 %)	378 (0.5 %)	38 (1.0 %)	15 (0.7 %)
Measures of psychiatric morbidity				
Treated in psychiatric inpatient care	189 (0.1 %)	145 (0.2 %)	9 (0.2 %)	3 (0.1 %)
Treated in psychiatric outpatient care	1 128 (0.4 %)	746 (0.9 %)	43 (1.1 %)	20 (1.0 %)
Prescribed psychotropic medication	22 122 (8.4 %)	8 981 (11.3 %)	478 (12.7 %)	241 (11.9 %)
Men				
N	273 989	72 953	4 819	2 776
%	38,9	10,4	0,7	0,4
Age category				
45-49	131 647 (48.0 %)	33 965 (46.6 %)	2 704 (56.1 %)	1 461 (52.6 %)
50-54	142 342 (52.0 %)	38 988 (53.4 %)	2 115 (43.9 %)	1 315 (47.4 %)
Number of married years 1990-2004				
0 to ≤ 5	26 900 (9.8 %)	35 201 (48.3 %)	665 (13.8 %)	1 175 (42.3 %)
5 to ≤ 14	77 584 (28.3 %)	35 192 (48.2 %)	1 772 (36.8 %)	1 493 (53.8 %)
15 years	169 505 (61.9 %)	2 560 (3.5 %)	2 382 (49.4 %)	108 (3.9 %)
Earlier divorce				
	23 128 (8.4 %)	3 610 (4.9 %)	745 (15.5 %)	225 (8.1 %)
Educational level				
12 years or less	174 219 (63.6 %)	53 289 (73.0 %)	3 157 (65.5 %)	1 844 (66.4 %)
13 years or more	98 286 (35.9 %)	19 225 (26.4 %)	1 618 (33.6 %)	909 (32.7 %)
Missing	1 484 (0.5 %)	439 (0.6 %)	44 (0.9 %)	23 (0.8 %)
Measures of psychiatric morbidity				
Treated in psychiatric inpatient care	276 (0.1 %)	188 (0.3 %)	16 (0.3 %)	8 (0.3 %)
Treated in psychiatric outpatient care	1 075 (0.4 %)	630 (0.9 %)	56 (1.2 %)	12 (0.4 %)
Treated in psychiatric outpatient care	12 845 (4.7%)	4 309 (5.9%)	331 (6.9%)	153 (5.5%)

Analysis of psychiatric morbidity following divorce

Results showed that those who divorced or remarried were at higher risks for psychiatric morbidity compared to married. Newly divorced men had 3.3 (95% CI 2.0-5.4) times higher risk for psychiatric inpatient care, the corresponding risk for newly divorced women was 3.2 (95% CI 1.6-6.3). Both women and men who were divorced in 2005 and 2006 had 2.6 times higher risk for psychiatric inpatient care compared to married.

The analysis of number of married years on psychiatric morbidity for the different transition groups, in which psychiatric in- or outpatient care were considered, showed

that those with fewer years as married had higher risk for psychiatric morbidity, when adjustments were made for age, sex, and earlier divorce. Newly divorced, and married for less than five years had more than six times higher risk for psychiatric morbidity the year following divorce.

Regardless of marital transition between 2005 and 2006, individuals with at least one divorce during 1990–2004 had a higher risk for psychiatric morbidity (Table 8).

Table 8. Marital transition, earlier divorce and risk of psychiatric morbidity (IRRs with 95% CI)

Marital transition	Earlier divorce			
	Women		Men	
	No	Yes	No	Yes
Married 2005 and 2006	1 (REF)	1.4 (1.1-1.6)	1 (REF)	1.4 (1.1-1.6)
Divorced 2005 and 2006	1.5 (1.4-1.7)	2.0 (1.5-2.7)	1.7 (1.6-2.0)	2.9 (2.2-3.7)
Married 2005 and divorced 2006	2.1 (1.5-3.0)	4.9 (3.0-7.9)	2.6 (2.0-3.5)	4.6 (2.9-7.2)
Divorced 2005 and remarried 2006	1.5 (1.0-2.4)	2.0 (0.5-8.1)	1.1 (0.7-1.8)	1.4 (0.4-5.8)

* Adjusted for year of birth and number of married years

Table 9 shows IRRs for the association between marital transition, educational level, and psychiatric morbidity. We found tendencies that lower educational level increased the risk for psychiatric morbidity for males. For females, however, this was true only for psychiatric inpatient care.

Table 9. Marital transition, educational level, and risk of psychiatric morbidity (IRRs with 95% CI)*

Marital transition and educational level	Psychiatric inpatient care	Psychiatric outpatient care	Psychotropic medication
Women			
Married, ≥ 13 years of education	1 (REF)	1 (REF)	1 (REF)
Married, ≤ 12 years of education	1.1 (0.8-1.5)	1.1 (1.0-1.2)	1.1 (1.1-1.1)
Divorced, ≥ 13 years of education	2.1 (1.4-3.1)	2.4 (2.0-2.8)	1.3 (1.3-1.4)
Divorced, ≤ 12 years of education	3.1 (2.3-4.1)	2.4 (2.1-2.7)	1.5 (1.5-1.6)
Newly divorced, ≥ 13 years of education	2.8 (0.9-8.9)	3.2 (2.0-5.0)	1.7 (1.5-1.9)
Newly divorced, ≤ 12 years of education	4.0 (1.7-9.2)	2.5 (1.6-3.8)	1.7 (1.5-1.9)
Remarried, ≥ 13 years of education	-	2.1 (0.9-4.6)	1.6 (1.3-2.0)
Remarried, ≤ 12 years of education	3.5 (1.1-11.0)	2.7 (1.6-4.6)	1.6 (1.3-1.8)
Men			
Married, ≥ 13 years of education	1 (REF)	1 (REF)	1 (REF)
Married, ≤ 12 years of education	1.4 (1.1-1.9)	1.2 (1.1-1.4)	1.0 (0.9-1.0)
Divorced, ≥ 13 years of education	1.9 (1.3-3.0)	2.0 (1.7-2.5)	1.2 (1.1-1.3)
Divorced, ≤ 12 years of education	3.8 (2.9-5.0)	2.7 (2.4-3.2)	1.3 (1.2-1.3)
Newly divorced, ≥ 13 years of education	2.4 (0.7-7.5)	2.0 (1.1-3.6)	1.3 (1.1-1.6)
Newly divorced, ≤ 12 years of education	5.2 (2.9-9.4)	4.1 (3.0-5.6)	1.6 (1.4-1.8)
Remarried, ≥ 13 years of education	-	0.3 (0.0-2.3)	1.1 (0.8-1.5)
Remarried, ≤ 12 years of education	5.5 (2.7-11.4)	1.6 (0.8-3.0)	1.2 (1.0-1.5)

* Adjusted for year of birth

5.4 STUDY IV: QUALITY OF MEDICAL CARE AND EXCESS MORTALITY IN PSYCHIATRIC PATIENTS – A NATIONWIDE REGISTER-BASED STUDY IN SWEDEN

In this study of more than 6 million individuals, 1.6% of all women and 1.4% of all men were treated for psychiatric morbidity during the study period. Among all psychiatric patients, 5 498 (2.9% in all, 2.0% in women and 3.8% in men respectively) died during the follow-up period compared to 66 689 (1.1% in all, 0.9% in women and 1.3% in men) among persons without episodes of treatment for

psychiatric morbidity.

The results showed that psychiatric patients had a substantially increased mortality risk compared to individuals with no episodes of treatment for psychiatric morbidity. Regardless of psychiatric morbidity, those with comorbid substance use disorders had the highest mortality risk. Women diagnosed with both schizophrenia and substance use had an IRR of 10.8 (95% CI 7.1-16.6) for all-cause mortality, whereas women diagnosed with schizophrenia without a concurrent diagnosis for substance use had an IRR of 3.6 (95% CI 3.6-4.0) compared to women with no diagnosis for psychiatric morbidity. Psychiatric patients also had increased risk for death from conditions considered amenable to intervention by the health service, i.e. avoidable mortality. Women diagnosed with schizophrenia had an IRR of 3.5 (95% CI 2.5-4.9) for causes of death reflecting the outcome of medical care; the corresponding IRR for men was 3.4 (95% CI 2.4-4.9).

As seen in Table 10, risk of mortality was higher among those hospitalized than the ones treated in outpatient care only.

Table 10. Associations of mental disorder in relation to mortality (IRRs with 95%CI)*

Mental disorder group	N (%)	All-cause mortality
Women		
No mental disorder	3 042 494 (96.8%)	1 (REF)
Schizophrenia and other non-affective psychoses, inpatient care	5 560 (0.2%)	4.4 (3.8-5.1)
Schizophrenia and other non-affective psychoses, outpatient care	5 605 (0.2%)	3.2 (2.7-3.7)
Affective or Anxiety disorder, inpatient care	15 290 (0.5%)	3.5 (3.2-3.9)
Affective or Anxiety disorder, outpatient care	54 645 (1.7%)	2.0 (1.8-2.2)
Other mental disorder (including substance use disorder), inpatient care	7 021 (0.2%)	7.8 (7.0-8.7)
Other mental disorder (including substance use disorder), outpatient care	10 839 (0.3%)	3.1 (2.7-3.5)
Men		
No mental disorder	3 063 887 (97.1%)	1 (REF)
Schizophrenia and other non-affective psychoses, inpatient care	5 860 (0.2%)	6.2 (5.5-7.0)
Schizophrenia and other non-affective psychoses, outpatient care	6 133 (0.2%)	3.3 (2.9-3.8)
Affective or Anxiety disorder, inpatient care	10 556 (0.3%)	3.9 (3.6-4.3)
Affective or Anxiety disorder, outpatient care	34 415 (1.1%)	2.3 (2.1-2.5)
Other mental disorder (including substance use disorder), inpatient care	16 926 (0.5%)	6.6 (6.3-7.0)
Other mental disorder (including substance use disorder), outpatient care	15 108 (0.5%)	3.0 (2.7-3.2)

* Adjusted for year of birth

Analysis of the different health care quality indicators revealed lower levels of health care quality for psychiatric patients. Compared to individuals without episodes of treatment for psychiatric morbidity, psychiatric patients had a higher 28-day case fatality rate for myocardial infarction and they had more avoidable hospitalizations. This was true for both sexes. The indicator for lipid-lowering drug therapy showed that psychiatric patients with diabetes were given lipid-lowering drugs to a lesser extent than diabetic patients with no diagnosis for mental disorder. Approximately 40% of women with diabetes and concurrent diagnosis for schizophrenia were given lipid-lowering drugs compared to 56% of women with no concurrent diagnosis for psychiatric morbidity. The corresponding proportion for men was 42% with diabetes and schizophrenia versus 56% of men without a diagnosis for psychiatric morbidity.

6 DISCUSSION

6.1 MAIN FINDINGS

The overall aim of this dissertation was to increase the knowledge about the association between adverse life events, psychiatric morbidity, and mortality, and the role of socioeconomic position from a life course perspective. The main findings from the four studies can be summarized as follows:

- Accumulation of adverse childhood experiences increases the risk of psychiatric morbidity in young adults. The higher risk for future mental health problems among children from lower socioeconomic groups compared to peers from more advantaged backgrounds, seems to be linked to a higher rate of exposure to adverse childhood experiences.
- Individuals with delinquent behavior in late adolescence have an increased risk of suicide as young adults. Repeatedly convicted youth have strikingly higher suicide risks that remain high even after adjusting for substance use and psychiatric morbidity.
- Marital transition, especially divorce, is associated with an increased risk of psychiatric in- and outpatient care as well as psychotropic medication in midlife.
- Individuals treated for psychiatric morbidity have increased risk for premature death compared with individuals with no episodes of treatment for psychiatric morbidity. Findings suggest lower quality of health care in the treatment for somatic diseases among psychiatric patients.

6.2 ADVERSE LIFE EVENTS AND PSYCHIATRIC MORBIDITY (STUDY I-III)

All the first three studies focus on investigating the association between different adverse life events and the risk of psychiatric morbidity at different stages of the life course. While Study I and II explored life events occurring during childhood and adolescence, Study III focused more on life events occurring later in life and shortly before the onset of the disorder. Study I sought to examine whether accumulation of several adverse life events in childhood was associated with psychiatric morbidity, whereas Study II and III focused on more specific events – juvenile delinquency and marital transition respectively, in the risk of psychiatric morbidity.

6.2.1 Accumulation of adverse life events in childhood in the risk of psychiatric morbidity

The results in Study I showed that adverse life events tend to occur in cluster, often associated with each other. These findings are supported by other studies showing that adverse childhood experiences are interrelated rather than occurring independently (119, 124). Thus, these kinds of events should not be assumed to be isolated events in children's lives.

Every adverse event on its own increased the risk of psychiatric morbidity, measured as a filled prescription of psychotropic drugs. The dose-response relationship between

the burden of adverse childhood experiences and the risk of psychotropic medication was seen for all groups of psychotropic drugs, indicating that adverse childhood experiences are associated with a broad range of negative psychological consequences. These findings are consistent with other studies showing that clustered adverse experiences during childhood have a strongly graded relationship to several mental health problems (119, 125-127).

It should be kept in mind that rates of adverse childhood experiences vary considerably between societies, depending on affluence, child rearing patterns and welfare system. A recent comparison of rates of child maltreatment between six high-income countries, for instance, showed that Sweden had the lowest rates (180), and Sweden is also known to have a comparably generous welfare system for families with children. Thus, one might expect that the importance of adverse childhood experiences for the health of young adults is even greater in many other high-income countries.

Our study seems to support the allostatic stress theory in its claims that accumulation of stress, not only extreme deprivation, during childhood may permanently alter brain function (128, 129). We conclude that accumulation of adverse childhood experiences increases the risk of psychotropic medication in young adults.

6.2.2 Juvenile delinquency and suicide

Our findings showed that juvenile delinquency is a risk factor for suicide. This association may in part be explained by comorbid psychiatric morbidity, a finding that should be considered in future research, as psychiatric morbidity represent one of the strongest risk factors for suicide (45-47, 130). The association between delinquency and suicide decreased when substance use was accounted for. Substance use is a risk factor for suicide (47, 181), but also for criminal behavior (136, 175), which stresses the importance of controlling for this profound confounder in future research.

The results showed a gradient in the association between delinquency and suicide, where the repeatedly convicted had highest risk of suicide. The exposure was measured during adolescence, but the effect still showed at the age of 34 years.

Delinquency as a risk factor for suicide has also been shown in other settings (132, 134). These studies were limited in size though. A recent study examining the suicide risk in people with history of criminal convictions showed that suicide risk was particularly high in violent offenders (182). When we categorized the conviction groups into non-violent and violent crimes, we found a similar relationship, where individuals convicted for violent offences had significantly higher suicide risks compared to non-violent offenders. One explanation for the higher suicide risk for violent offenders is the possibility of a shared, common biological mechanisms for homicidal and suicidal behavior through serotonin dysfunction, which is related to several impulse disorders (183).

In general, convictions were much more common among men, 17.9% of all men had at least one conviction compared to 5.9% for women. Other studies have also shown that females constitute a minority of detained juvenile delinquents (130, 131, 184). Earlier research has shown that female offenders have significantly higher rates of

self-destructive behavior compared to delinquent men (132, 185). In young delinquent populations, it appears that females overall present a higher psychiatric morbidity than males, which have also been shown in this study. When it comes to completed suicide in the general adolescent population, males exhibit higher rates than females (47). However, this male predominance is not as evident among delinquent adolescents (130, 182). In our study, delinquent males had higher risks for completed suicide in general. However, in the conviction group comprising those with five or more convictions and individuals with severe penalties, females showed higher suicide rates compared to males.

6.2.3 Marital transition and psychiatric morbidity

We found that middle-aged individuals who experience a marital transition have an increased risk of psychiatric morbidity. Our results showed that married people had lower risk for psychiatric morbidity than those who had experienced marital breakup. Regardless of outcome measure, psychiatric morbidity was worse the year following divorce, which is supported by others (138).

Our findings, where we consider trajectories of marital status over the life course, reveal that there are differences among married individuals, where those who have been married for a longer period of time show better mental health than those married for fewer years. This could support the selection hypothesis suggesting that there is a predominance of mentally healthy individuals who gets and stays married (137, 141).

Our results are also coherent with previous research implying an association between previous experience of divorce and psychiatric morbidity (137, 138). Newly divorced had higher risk for psychiatric morbidity than all other groups, supporting the social causation hypothesis, i.e. the transition into separation in itself increases the risk for psychiatric morbidity.

Widowhood is another kind of marital transition, and also an adverse life event. We have previously shown that the risk of psychiatric morbidity among individuals 75 years of age or older increases the year after being widowed (186), which is consistent with the fact that marital transitions leading to separation increases the risk for psychiatric morbidity.

Our study showed a higher prevalence of psychotropic medication in women than in men, regardless of marital status. However, the risk of psychiatric morbidity following divorce was similar for both sexes, in part contradictory to the previous studies that have suggested that women exhibit more vulnerability to psychiatric morbidity than men when losing a spouse (138).

We conclude that marital transition affects the risk of psychiatric in- and outpatient care as well as psychotropic medication, in particular the year following divorce. Study III supports both the selection hypothesis, linking healthy individuals to long and stable marriages and the social causation hypothesis, linking the stress of recent divorce to increased psychiatric morbidity.

6.3 SOMATIC HEALTH CARE INEQUALITIES AND EXCESS MORTALITY IN PSYCHIATRIC MORBIDITY

Individuals treated for psychiatric morbidity had a substantially increased risk of mortality, regardless of the cause of death. Psychiatric patients had an elevated risk of premature death from conditions considered amenable to intervention by health care services, i.e. avoidable mortality. These findings are in line with previous research, which has reported up to four times higher mortality risks for avoidable causes of death among psychiatric patients, however, with slightly different psychiatric populations (63, 64).

Psychiatric patients with a coexisting substance use disorder had significantly higher risk for premature death. Consistent with previous research, substance use disorders strongly contributed to premature death among both female and male psychiatric patients, especially for those with both alcohol and drug-related abuse (37, 64, 187, 188).

A slight risk increase was also seen in cancer mortality, especially in patients treated for schizophrenia spectrum disorders and substance use disorders. A recent review study on cancer in people with severe mental disorder showed evidence that individuals suffering from severe mental disorders are less likely than other groups to receive screening for a range of cancers (42). Psychiatric patients often had more limited access to diagnostic and treatment services for physical complaints (42). Findings in our study also suggest a lower quality of health care in the treatment of somatic diseases in psychiatric patients. When studying a set of indicators aimed to reflect the outcome of healthcare quality, we found that patients with a psychiatric morbidity had higher rates of potentially avoidable hospitalizations. Under some circumstances, hospitalization is necessary and well motivated, but for most studied diseases, it is a failure of the health care system (189). A recent study on avoidable hospitalization demonstrated that the quality of physical healthcare received by patients with schizophrenia was poorer than that of the general population, signaling failures in public health and medical care (189). Another finding in our study was the low percentage of lipid-lowering drugs given to diabetic patients with a concurrent psychiatric morbidity. As drug therapy against lipid disorders is particularly important in diabetic patients (190), this is an indication of inequality in healthcare. The indicator where we studied 28-day case death rate after myocardial infarction showed worse outcome for those with a psychiatric morbidity. In a Danish study (41), less somatic hospitalization than needed, and less use of invasive heart disease procedures among persons with severe mental disorder, than among the general population, were suggested as additional explanations for the excess mortality in heart disease in people with severe mental disorder.

In conclusion, our study is in conjunction with previous studies showing a marked increase in mortality in patients with a psychiatric morbidity. This was especially evident in individuals with a comorbid substance use disorder. The findings also suggest a lower quality of healthcare in the treatment of somatic diseases in psychiatric patients.

6.4 SOCIOECONOMIC INEQUALITIES IN MENTAL HEALTH (STUDY I-III)

All studies in which we investigated the role of socioeconomic position on mental health showed tendencies of inequalities by socioeconomic position, i.e. that the risk of outcome was higher for individuals in lower socioeconomic groups.

As socioeconomic variation in the risk of psychiatric morbidity may be explained by differential clustering of risk factors by socioeconomic position, our first study aimed at examining whether adverse childhood experiences cluster between and within socioeconomic groups. The results showed that, for those with more than two adverse childhood experiences, between-group clustering was more common in lower socioeconomic groups, whereas within-group clustering was similar in all socioeconomic groups. Coherent with previous research (97, 98, 100, 191), we concluded that clustering of risk factors occurs within all social classes showing no evidence that the extent of within-group clustering is greater among those in lower socioeconomic groups.

Results from Study I did show that exposure to adverse childhood experiences was more common among individuals in lower socioeconomic groups. In the highest socioeconomic group, around 3% had experienced more than two adverse childhood experiences compared to 22% of individuals in the lowest socioeconomic group. These results suggest that adverse life events are more common in lower socioeconomic groups. Also, in Study II, delinquent behavior was more common for individuals in lower socioeconomic position. Among adolescents with no conviction, 64% came from lower socioeconomic groups compared to 85% of individuals with more than three convictions. In Study II, we also found social adversity during childhood to be more common in delinquent adolescent women and men. Similar findings have been observed in other studies as well, children from a relatively disadvantaged family background are more likely to accumulate risks associated with that disadvantage throughout life than children born to more privileged families (95, 96). A large Swedish cohort study found social adversity in childhood to be associated with the risk of developing schizophrenia and other psychoses later in life (192).

Level of parental education is a commonly used measure of socioeconomic position in childhood (26, 80, 96). In Study II, we also used other measures of social stratification, such as social assistance reciprocity and disability pension reciprocity. The results in Study II stress the importance of using more than just one indicator to capture the whole spectrum of the social situation. As we adjusted for several indicators of social adversity in childhood, the risk of suicide was reduced, suggesting that social adversity in childhood is part of the explanation for the increased suicide risk among delinquent youth.

Results from Study III showed that divorce was more common in lower socioeconomic groups, which has been shown by others (193). Similar results were found in Study I, where parental divorce or separation was more common in children from lower socioeconomic environments. We also found that experience of a recent divorce increased the risk of psychiatric inpatient care even more for individuals in lower socioeconomic groups.

In our analyses of the effect of socioeconomic position on psychiatric morbidity, we conclude that exposure to adverse life events or adverse childhood experiences is more common among individuals in lower socioeconomic groups. Socioeconomic position tended to modify the relationship between adverse life events and psychiatric morbidity over the life course, which support the assumption that those in a lower socioeconomic position who experience an adverse life event have a higher risk for psychiatric morbidity.

6.5 GENDER DIFFERENCES

As there are gender differences in the occurrence of psychiatric morbidity, we either controlled for, or stratified the analyses by sex in all studies. Study I revealed no differences between young women and men in the association between adverse childhood experiences and risk of psychotropic medication. However, women had nearly twice as high rates of dispensed prescriptions for psychotropic medication compared to men. These findings have also been shown in other settings (28, 154, 194, 195). Among different types of psychotropic drugs, women more often received treatment with antidepressants and anxiolytics, whereas sex differences were not as pronounced for antipsychotics (196).

Findings in Study II on the other hand revealed major differences in occurrence of juvenile delinquency between women and men. Compared to females, young males were much more often convicted of a crime (18% vs. 6%). Where most studies on delinquency have been able to study a small sample of women, we were able to study a large cohort of almost 30 000 female delinquents. The most severe delinquent females were clearly more exposed to childhood social adversity than anyone else, including corresponding males in the most severe conviction group. For instance, 11.5% had been in foster care (corresponding percentage for men was 6.2%), which is a known risk factor for suicidal ideation (172, 197). Women also had more inpatient care due to both psychiatric morbidity and alcohol and substance use. One possible reason for this marginalization among these women could be that non-normative behavior is more stigmatizing for women (132). Earlier research has shown that female delinquents have significantly higher rates of deliberate self-harm and psychiatric morbidity than delinquent boys (184).

Results in Study IV are in line with earlier findings, that depression as well as anxiety disorders are more common in women. Both biological differences and differences in exposure to environmental stressors has been suggested as possible explanations (31, 83). Psychological and social factors are also important explanations (83). Men on the other hand have higher rates of substance use (31-33), which was seen in Study IV. Lahtinen *et al.* explained these differences to be based on psychosocial rather than biological factors (33). Gender differences exist in the pattern of help seeking for mental health problems. Results in Study III revealed that women had a slightly higher proportion of outpatient care whereas men had slightly higher proportion of inpatient care. In general, women are more likely to visit doctors and use psychotropic medication (32), whereas men have higher suicide rates and are the primary users of psychiatric inpatient care (85).

6.6 POTENTIAL EXPLANATIONS FOR THE MAIN FINDINGS

The studies show that the more adverse life events an individual is exposed to, the higher the risk for psychiatric morbidity. It is important to consider that it does not have to be the stressful event *per se* that leads to morbidity, but rather the way in which the individual copes with it. Several studies have demonstrated the importance of different coping strategies in managing adverse life events (145, 146, 198). Those who were exposed to several adverse life events and later experienced psychiatric morbidity may have been less able to control or handle these events compared to others. The associations found between childhood adversities and psychiatric morbidity may be due to increased stress sensitivity that persists into adulthood. Individuals with a history of these types of events might be more vulnerable to psychiatric morbidity (120, 121). When discussing these kinds of individual differences, personality also needs to be considered. Different personalities might explain the different ways in which people handle adverse events (198). Skodol proposed that personality traits and coping strategies may interact with stressful events in ways to either contribute to the development of psychiatric morbidity or help to protect against it (198). Low self-esteem, which may be a result of disadvantage during the formative years, could lead to lower degrees of resilience (142, 143).

Lack of social support may be another explanation for the increased risk for psychiatric morbidity among individuals that have experienced adverse life events (17). Especially lack of support at the time of the adverse event seems particularly to increase the risk (199). However, measure of social support was not available in the register-based data that we used.

Possible biological mechanisms have also been discussed as explanations for the increased risk for psychiatric morbidity among individuals being exposed to adverse events early in life. Some severe life events may have enduring negative effects on brain development (120). This explanation is in line with the allostatic load theory, stating that events may permanently altered brain functions (128, 129). The presence of a family history of psychiatric morbidity is to also predictor of own psychiatric morbidity (168, 200).

One could wonder why adverse life events tend to be more common in lower socioeconomic groups. Again, coping strategies may be mentioned as one possible explanation, as it has been shown that individuals in higher socioeconomic positions have higher levels of coping ability (96, 145). Moreover, it appears that certain risk factors, such as greater environmental adversity and stress tend to be more present in lower socioeconomic groups (95). Lower socioeconomic position could mean exposure to adverse working conditions, which contributes to the burden of disease in many ways (101). Socioeconomic position may also determine a wide range of life chances. With a high socioeconomic position comes a greater possibility to control one's life. At work for instance, a lower socioeconomic position may imply high demands and low control together with high strain (101).

Disparities in access to and utilization of healthcare, as well as the quality of healthcare provision, may also contribute to inequalities in health. One reason for these disparities, especially for individuals with more severe mental disorders such as

schizophrenia, could be the limited ability of people with psychiatric morbidity to recognize and communicate their symptoms. The high mortality from natural causes could partly be explained by an unhealthier lifestyle, e.g. smoking, dietary habits, which is more common among people with more severe mental disorders (61, 201). Also, medications used to treat severe mental disorder may increase the risk of diabetes and cardiovascular disease as some psychotropic drugs are associated with weight gain (202). Psychiatrists and other mental health providers may also prioritize psychiatric issues and neglect physical problems (55). There is also some evidence of inequalities in case recognition and quality of medical care for psychiatric patients. General practitioners might underestimate the clinical significance of physical complaints when assessing and treating patients with a psychiatric morbidity, a process known as diagnostic over-shadowing (203). The causes for the excess mortality have been debated, where some researchers have suggested that it is the mental disorder itself together with health-related behaviors that increase the mortality risk (38, 201). Other potential explanations for the increased mortality are differences in access, provision, and quality of somatic health care (54). Our findings of elevated mortality risks in diagnoses reflecting the outcome of medical care also indicate less efficient medical treatment of psychiatric patients.

6.7 METHODOLOGICAL CONSIDERATIONS

The population-based registers that are used provide an opportunity to perform retrospective cohort studies. The strength of the studies includes the population-based design, using national registers with high completeness and validity. The nationwide register-based design counteracts recall and selection bias. A number of issues arose during the research process that may have influenced the results. These issues are discussed below.

6.7.1 Measures

Psychiatric morbidity

When using diagnoses for classification of psychiatric morbidity, we relied upon register-based diagnoses. The quality register-based data can be debated, but studies have shown that the validity in Swedish registers is appropriate for these types of epidemiological studies (149, 204, 205). The effect of missing data in the register on the studies is described in the validity section below.

Socioeconomic position

We used only education when analyzing the role of socioeconomic position on the risk of psychiatric morbidity in the different studies. In theory, the choice of measure should depend on assumptions of how socioeconomic position is linked to health (72). However, in reality information about a characteristic of interest is not always available. In these studies, the occupation-based measure of socioeconomic position was not available. We used educational level as measure, due to its easiness to measure compared to income. The use of educational level as an indicator of socioeconomic position has several advantages. It allows classification of individuals who do not work (unlike occupational class measure). Older women and men who do not work constitute a large part of the population. Further, level of education is an individual measure of socioeconomic position. Education does seldom change during

adulthood. It does however also have some disadvantages. For example, individuals usually achieve their final level of education early in adult life, thus their educational level might not accurately indicate their current socioeconomic position. Additionally, if measuring education in years, it is like treating all educational institutions equally. Knowing the number of years of education tells nothing about the quality of that education or how it is socially and economically valued. In our analyses, we measured education in terms of attainment of certain milestones, i.e. nine years compulsory school, senior high school, and university education.

One limitation with our studies is that we only measure socioeconomic position at one stage in life. One must bear in mind that individuals may change social positions over time. Several studies have stressed the importance of measuring socioeconomic position at more than one stage of the life course for fully understanding the contribution of socioeconomic factors to health (75, 106, 107).

One problem when studying socioeconomic inequalities in adolescents is that young persons most often do not have a measureable socioeconomic position due to their age. It is therefore most common to use the socioeconomic information of their parents (26, 80, 99). Socioeconomic characteristics earlier in life may not always be reflected in measures of current socioeconomic position or the position later in life (75). In our first two studies we aimed at examining socioeconomic position during childhood in order to mirror the social environment during upbringing.

Adverse life events

Research on life events has often employed a checklist approach, with “external” events such as parental loss or move to a new home. The types of life events included in these checklists are often easy to measure. We used a similar approach by using register-based information.

6.7.2 Reverse causation

When studying the association between socioeconomic disadvantage and psychiatric morbidity, it is important to always be careful in the interpretation of the causal direction. Severe mental disorders may have social effects that could precede the onset of the disorder and could result in social downward drift. As mentioned earlier, it is of great importance to measure socioeconomic status long before the onset of the disorder in order to avoid problems with social selection.

When studying the risk of marital transition on psychiatric morbidity, we excluded individuals with a history of psychiatric care in order to minimize the problem with reverse causation. However, using only psychiatric inpatient care as the exclusion criterion, there could still be individuals with mental health problems included. It could be that their former psychiatric morbidity makes them more prone to marital problems, and also to future mental health problems. This might lead to a higher proportion of divorced having mental health problems, when in fact the psychiatric distress could be due to their former psychiatric morbidity. If mentally ill individuals would be included, divorce should rather be regarded as a mediator in the association between former and future psychiatric morbidity. In the first two studies, we considered parental

educational level when studying the potential modifying effect of socioeconomic position. Doing so could reduce the risk for reverse causation.

6.7.3 Precision

Two broad types of error affect epidemiologic studies, random error and systematic error (Figure 7). Random error, i.e. the error that remains after systematic error is eliminated, is the variability in the data that cannot be readily explained with the available information. The term precision is used in epidemiology as a measure of random error. A common way to reduce random error, or increase precision is to increase the study size. The study sizes in all studies are large, and the precision of the estimates was high in most analyses, which are indicated by the narrow confidence intervals.

6.7.4 Validity

The validity in an epidemiological study may be defined as the degree of systematic error resulting in an incorrect estimate of the association between exposure and outcome. The validity in a study is usually separated into two components, internal and external validity, where internal validity is defined as the validity of the conclusions drawn as they relate to those included in the study base. External validity is defined as the validity of the conclusions as they relate to those outside the study population. Systematic errors, also called bias, are often classified into three broad categories (Figure 6).

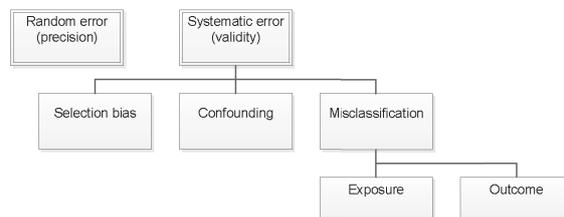


Figure 6. Schedule illustrating the systematic error and its components

6.7.4.1 Selection bias

Selection bias is a systematic error that stems from the procedures used to select subjects and from factors that influence study participation (163). Selection bias is present when the association between exposure and outcome differs for those who participate in the study and those who do not (163). Selection bias is not a major problem in population-based register studies.

6.7.4.2 Confounding

We were able to take several potential confounders into consideration in the analyses. In Study II, we controlled for a number of potential confounders by including them in the multivariate analysis. However, there could still be unmeasured confounding factors affecting our results. This applies especially to Study II where one major limitation was the incomplete information on psychiatric morbidity and substance use. A major part of the increased suicide risk for delinquent youth was explained by comorbid psychiatric morbidity and substance use. Mental health problems as well as

substance use represent important risk factors for suicide. We believe that the measured increased risk would probably decrease if we could adjust for all psychiatric morbidity and substance use.

6.7.4.3 Misclassification of exposure

Misclassification arises when the information collected are not always correct for the study subjects (163). Exposure misclassification is called non-differential if it is unrelated to the outcome classification, and differential if it is different for those with and without the outcome of interest. Differential misclassification can either exaggerate or underestimate an effect (163).

In Study I there are several important adverse childhood experiences that we cannot capture when using register data. Therefore, individuals who have experienced an adverse life event that is not captured are classified as unexposed. Given that exposed individuals have an increased risk, this non-differential misclassification can only lead to an underestimation of the true risk.

In Study II we only measure convicted youth, leading to the possible risk of non-differential misclassification of exposure, i.e. some individuals engaged in delinquent behaviour are not registered and convicted and hence misclassified. The consequence of this misclassification would be a dilution of the results.

In Study III there is a potential non-differential misclassification of cohabitants as divorced, as there might be divorced individuals who have been cohabiting for several years. As cohabiting has been shown to be protective for mental health, this misclassification would lead to an underestimation of the true risk.

In Study IV, as we do not capture patients treated for psychiatric morbidity in primary care, these individuals are classified as unexposed. Assuming a similar effect for patients in primary care as for psychiatric patients selected by a more strict definition of mental health problems, i.e. patients who have seen a psychiatrist, this misclassification will dilute our results towards the null.

6.7.4.4 Misclassification of outcome

Similarly to exposure misclassification, outcome misclassification is differential if it is different for those exposed and unexposed to the variables studied.

Study I uses treatment with psychotropic drugs as a proxy for psychiatric morbidity. Thus, we only capture mental health problems that are treated with psychotropic drugs. Some of these drugs also have other indications than psychiatric morbidity. Hence, individuals treated with psychotropic drugs for other indications are classified as having mental health problems. However, if our studied exposures are less associated with these non-psychiatric indications this misclassification of disease will lead to an underestimation of the association between childhood adverse events and psychotropic drug use.

One limitation in Study III is that we do not capture all kinds of mental health problems. When using the National Patient register, we lack information on primary care together with missing data in psychiatric outpatient care. We do not believe this misclassification of outcome to be dependent on marital status, hence this misclassification will lead to an underestimation of the studied association.

7 CONCLUSIONS

In conclusion, individuals who have experienced adverse life events have a higher prevalence of psychiatric morbidity than those who have not. This increased psychiatric morbidity was observed regardless of whether the adverse life event occurred in childhood, adolescence or in middle age. Experience of adverse life events was more common among individuals in lower socioeconomic groups.

Socioeconomic position tended to modify the relationship between adverse life events and psychiatric morbidity over the life course, which supports the assumption that those in a lower socioeconomic position who experience an adverse life event have a higher risk for psychiatric morbidity.

Accumulation of adverse childhood experiences increases the risk of psychotropic medication in young adults. Adverse life events in childhood tend to occur in cluster often associated with each other. Comparing clustering between different socioeconomic groups showed that clustering was more common among those whose parents had lower educational level. Within group clustering was similar in all educational groups. The higher risk for future mental health problems among children from lower socioeconomic groups, compared to peers from more advantaged backgrounds, seems to be linked to a higher rate of exposure to more adverse childhood experiences.

Adolescents with delinquent behavior in late adolescence have an increased risk of suicide as young adults. Regardless of causality issues, repeated juvenile offenders should be regarded by professionals in health, social and correctional services who come into contact with this group as a high-risk group for suicide.

Divorce is associated with an increased risk of psychiatric in- and outpatient care as well as being prescribed psychotropic medication. Previous experience of divorce and being married for a short time increase the risk of mental health problems. Results support both the selection hypothesis, linking healthy individuals to long and stable marriages, and the social causation hypothesis, linking the stress of recent divorce to increased psychiatric morbidity.

Psychiatric patients have a substantial increased risk of mortality compared to individuals with no episodes of psychiatric morbidity. Psychiatric patients seem to receive a lower quality of somatic healthcare. Careful medical examination of psychiatric patients together with efforts to promote a healthier lifestyle may be of great importance in order to prevent, detect, and treat somatic disease among psychiatric patients.

7.1 FUTURE STUDIES

Based on the findings in Study I, future studies on adverse childhood experiences in the risk of psychiatric morbidity would benefit from studying specific psychiatric diagnoses separately as outcome to further explore this association.

It would also be worthwhile with the use of a qualitative approach to further analyze the association between adverse life events and psychiatric morbidity, to capture mechanisms not possible within register studies.

Childhood and adolescence are particularly important life stages for health-related behavioral development. In order to increase the knowledge on the consequences of childhood adversity on health and social outcomes, future studies should address other health measures, such as somatic disorders.

In order to fully understand the relationship between delinquency and suicide, future research needs to improve measurements of the strong confounders psychiatric morbidity and substance use disorder. Including primary care, and improving the quality of specialized outpatient care in the National Patient Register would increase these measures.

The fact that childhood socioeconomic factors could act independently on adult socioeconomic position on health stresses the importance of considering both. Future studies would benefit from including current socioeconomic position in order to further clarify to what extent the relationship between adverse life events and psychiatric morbidity is modified by socioeconomic position.

Based on a selected set of indicators, we found that psychiatric patients seem to receive a lower quality of somatic healthcare. Future studies should address other indicators of somatic health care in order to examine if this inequality exist in other parts of somatic healthcare as well.

8 SVENSK SAMMANFATTNING

Det övergripandet syftet med avhandlingen var att öka kunskapen om sambandet mellan olika typer av ogynnsamma livshändelser och psykiatrisk sjuklighet, samt dödlighet. Ur ett livsförloppsperspektiv belystes även dessa samband i relation till socioekonomiska förhållanden. Alla fyra studier är registerstudier.

I den första studien analyserade vi huruvida unga vuxna som upplevt ogynnsamma livshändelser i barndomen har en ökad risk för att få psykofarmaka förskrivet. I studien undersöktes även om sambandet såg olika ut beroende på föräldrarnas utbildningsnivå. En kohort med 362 663 individer födda i Sverige mellan 1985 och 1988 följdes upp från födseln till 2008. Vi fann att ogynnsamma livshändelser var vanligare bland personer vars föräldrar hade kortare utbildning. De som hade upplevt ogynnsamma livshändelser i barndomen hade en ökad risk för förskrivning av psykofarmaka. Risken ökade också med antal ogynnsamma livshändelser. Relationen mellan ogynnsamma livshändelser och psykofarmaka var densamma oavsett föräldrars utbildningsnivå.

Syftet med den andra studien var att undersöka om ungdomsbrottslighet, definierad som lagförd för minst ett brott mellan 15 och 19 års ålder, ökar risken för suicid. Studien omfattade närmare en miljon personer. Vi fann en ökad suicidrisk hos de som blivit lagförda, i synnerhet hos de som hade lagförts vid upprepade tillfällen. De som lagförts fler än fem gånger löpte högst risk för suicid.

I den tredje studien undersökte vi om civilståndsförändring, med fokus på skilsmässa, ökar risken för psykiatrisk sjuklighet. Studien inkluderade alla personer i Sverige i åldersspannet 45-54 år 2006 som antingen var gifta eller skilda. Personer som tidigare hade slutenvårdats för psykisk sjukdom exkluderades. Totalt följdes 703 960 personer upp med avseende på psykisk sjuklighet, definierad som psykiatrisk slutenvård, öppenvård eller förskrivning av psykofarmaka. Skilda kvinnor och män hade en förhöjd risk för psykiatrisk sjuklighet jämfört med gifta. Effekten av skilsmässa på psykiatrisk sjuklighet tycktes minska i takt med att antal år som gift ökade. Resultaten indikerade en förhöjd risk för psykiatrisk slutenvård bland de med kortare utbildning.

Med den fjärde studien avsåg vi att utvärdera dödligheten samt kvaliteten av somatisk vård för psykiatriska patienter. Alla individer i åldersspannet 20-79 som år 2005 fanns registrerade i Sverige (n=6 294 339) följdes upp med avseende på dödlighet under 2006 och 2007. De som hade vårdats delades in i olika psykiatriska diagnosgrupper. Resultaten visade att psykiatriska patienter har en påtagligt förhöjd dödlighetsrisk jämfört med den övriga befolkningen. Analyserna av kvaliteten på den somatiska vården visade att psykiatriska patienters vård var av sämre kvalitet. Grundlig medicinsk undersökning av psykiatriska patienter tillsammans med satsningar för att främja en hälsosammare livsstil är av stor vikt för att förebygga, upptäcka och behandla somatisk sjukdom i den här patientgruppen.

Sammantaget visar avhandlingen att ogynnsamma livshändelser ökar risken för psykiatrisk sjuklighet, en risk som delvis varierar beroende på socioekonomisk position i samhället.

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