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# USING A LIFE-COURSE APPROACH TO BETTER UNDERSTAND DEPRESSION IN OLDER AGE

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# Using a life-course approach to better understand depression in older age

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

By


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*Friday September 28, 2018 | 10:00 am*
*Samuelssonsalen, Karolinska Institutet, Tomtebodavägen 6, Solna*

In memoriam of my mormor Ingrid
1926-10-15 − 2018-01-20

To all women, today and throughout the history, who have fought for women's rights and the possibility to obtain higher education. Your sacrifices and battles will never be forgotten and I am always forever grateful.

# ABSTRACT

This doctoral thesis aimed to explore the prevalence of depression, and to identify risk factors, secular changes, and consequences of depression in late adulthood from a life-course perspective. The four studies in this thesis were based on data from the H-70 study, the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), and the Kungsholmen Project (KP). The major findings of these studies are summarized below.

**Study I.** This study used five-year follow-up data from the H-70 study to examine whether the association between social factors and depression has changed between the 1970s and 2000s in two birth cohorts of septuagenarians. Feelings of loneliness were related to higher depression risk in both of the cohorts. However, infrequent visits with others than children or neighbors (once per month or less), and the perception of having too little contact with others, were related to an increased risk of depression in 75-year-olds examined in the 1970s, but not in those examined in the 2000s.

**Study II.** This study used SNAC-K data to examine to what extent the prevalence of depression varies when using different depression definitions and sub-samples of the population of adults aged 60−104 years. The prevalence of any depression ranged between 4.2% to 9.3% according to the diagnostic criteria (DSM-IV-TR and ICD-10); 9.2% to 10.6% for the rating scales (MADRS and GDS15); and was 9.1% for self-report. Depression prevalence was lower when excluding those having dementia, as compared to the total population. Moreover, being physically dependent or not having a partner were related to higher depression prevalence across the majority of the depression definitions.

**Study III.** This study used nine-year follow-up data from SNAC-K and KP to explore whether low mood was related to an increased risk of dementia in two birth cohorts of adults above 70 years of age, and whether marital status and living situation modify this relationship. Those having low mood at baseline were at an increased risk of dementia in both cohorts combined (hazard ratio [HR] 1.2, 95% confidence interval [CI] 1.0-1.4), compared to those without low mood. However, the higher risk was detected only in those who did not have a partner (HR 1.5, 95% CI 1.2-1.9), or lived alone (HR 1.5, 95% CI 1.2-1.9), but not among those who had a partner or lived with someone (HR 0.8, 95% CI 0.5-1.2).

**Study IV.** This study used six-year follow-up data from SNAC-K to explore whether the experience of negative life events across the life span was related to an increased depression risk later in life. The total number of negative life events was associated with an increased risk of any depression. When further examining timing of the events, the experience of negative events ($\geq 90^{th}$ percentile) in early- (0−18 years, odds ratio [OR] 2.4, 95% CI 1.2-5.0) or late-life (>65 years, OR 2.1, 95% CI 1.1-4.4) were associated with an increased risk of any depression, but not those occurring in early-adulthood (19−40 years, OR 1.4, 95% CI 0.7-2.7) or middle-adulthood (41−65 years, OR 1.3, 95% CI 0.6-3.1).

**Conclusions.** Depression prevalence was similar independent of the depression definitions used, except for ICD-10, showing much lower prevalence. Moreover, the quantity and quality of social contacts with others were related to depression in older adults examined in the 1970s, but not in those examined 30 years later. In addition, marital status and living situation have the possibility to buffer the detrimental effects of low mood on dementia onset. Finally, there are critical time periods in early-life (0−18 years) and late-life (>65 years), when the experience of negative life events exacerbates depression risk in later life.



**Keywords:** depression, geriatrics, epidemiology, population-based study, cohort differences, prevalence, incidence, psychosocial, dementia, low mood, marital status, living situation, negative life events, life-course perspective.

# SAMMANFATTNING

Syftet med denna avhandling var att undersöka förekomsten av depression och att identifiera riskfaktorer, sekulära förändringar och konsekvenser av depression hos äldre utifrån ett livsloppsperspektiv. Fyra studier genomfördes för att undersöka detta och data från H-70 studien, ”the Swedish National Study on Aging and Care in Kungsholmen” (SNAC-K), och ”the Kungsholmen Project” (KP) användes. De viktigaste fynden från dessa studier summeras nedan.

**Studie I.** Data från H-70 studien användes för att undersöka om sambandet mellan sociala faktorer och depression har förändrats mellan 1970- och 2000-talet hos två olika födelsekohorter av sjuttioåringar. Känslor av ensamhet var relaterat till en högre risk för att utveckla depression över en femårig uppföljningsperiod i båda födelsekohorterna. Dock var sällsynta besök med andra än ens barn och grannar (definierat som en gång per månad eller mindre) och upplevelsen av ha för lite kontakt med andra relaterat till en ökad depressionsrisk hos 75-åringar som undersöktes på 1970-talet men inte hos dem som undersöktes på 2000-talet.

**Studie II.** Data från SNAC-K användes för att undersöka om och i vilken utsträckning prevalensen av depression varierar då olika definitioner av depression och subgrupper av studiepopulationen används hos äldre mellan 60–104 år. Depressionsförekomsten fluktuerade mellan 4.2–9.3% utefter de diagnostiska kriterierna (DSM-IV-TR och ICD-10); mellan 9.2–10.6% utefter skattningsskalorna (MADRS och GDS-15); och var 9.1% för självrapporterad depression. Oavsett vilken definition som användes för att klassificera depression så fann vi en högre depressionsförekomst hos de som hade demens, en fysisk funktionsnedsättning eller som inte hade en partner.

**Studie III.** Data från SNAC-K och KP användes för att undersöka om nedstämdhet var associerat med en ökad risk för demens över en nioårig uppföljningsperiod hos två olika födelsekohorter av äldre som är över 70 år. Vidare undersöktes det om civilstånd och boendesituation möjligtvis kunde modifiera detta samband. I båda födelsekohorterna hade de som led av nedstämdhet en ökad risk för demens (hazard ratio [HR] 1.2, 95% konfidensintervall [CI] 1.0-1.4), i jämförelse med dem som inte led av nedstämdhet. Dock förekom den ökade risken bara hos de som inte hade en partner (HR 1.5, 95% CI 1.2-1.9) eller som bodde ensamma (HR 1.5, 95% CI 1.2-1.9), men inte hos dem som hade en partner och bodde tillsammans med någon (HR 0.8, 95% CI 0.5-1.2).

**Studie IV.** Data från SNAC-K användes för att undersöka om upplevelsen av negativa livshändelser var relaterat till en ökad depressionsrisk hos äldre. Det fanns ett samband mellan antalet negativa livshändelser och en ökad risk för att utveckla depression. Vidare undersöktes det huruvida tidpunkten för de negativa livshändelserna påverkade depressionsrisken. Vi fann att upplevelsen av flera negativa livshändelser (≥90: e percentilen) i barndomen (0–18 år, odds ratio [OR] 2.4, 95% CI 1.2-5.0) och sen vuxenålder (>65 år, OR 2.1, 95% CI 1.1-4.4) ökade risken för att utveckla depression, men inte om de inträffade i tidig vuxenålder (19–40 år) eller medelåldern (41–65 år).

**Sammanfattning.** Oavsett vilken definition som använts för att klassificera depression så var förekomsten av depression lika hög. Dock blev prevalensen av depression mycket lägre då den skattades utefter ICD-10. Vidare fann vi att både kvantiteten och kvaliteten på sociala kontakter med andra var relaterat till en ökad risk för depression hos äldre som undersöktes på 1970-talet men inte hos dem som undersöktes 30 år senare. Vi fann även att civilstånd och boendesituation kan motverka de skadliga effekter som nedstämdhet kan ge upphov till och därmed senarelägga debuten av demens. Utifrån ett livsloppsperspektiv så fann vi att barndomen (0–18 år) och sen vuxenålder (>65 år) är kritiska tidsperioder då upplevelsen av negativa livshändelser kan öka risken för att drabbas av depression senare i livet.

**Nyckelord:** depression, geriatrik, epidemiologi, populations-baserade studier, kohortskillnader, prevalens, incidens, psykosociala, demens, nedstämdhet, civilstånd, boendesituation, negativa livshändelser, livsloppsperspektiv.

# LIST OF SCIENTIFIC PAPERS

This doctoral thesis is based on the following original papers, referred to in the text by their respective Roman numerals.

I. **Sjöberg L,** Östling S, Falk H, Sundh V, Waern M, Skoog I. Secular changes in the relation between social factors and depression: A study of two birth cohorts of Swedish septuagenarians followed for 5 years. *J Affect Disord*, 2013; 150(2):245-52. doi: 10.1016/j.jad.2013.04.002.

II. **Sjöberg L,** Karlsson B, Atti AR, Skoog I, Fratiglioni L, Wang H-X. Prevalence of depression: Comparisons of different depression definitions in population-based samples of older adults. *J Affect Disord*, 2017; 221:123-131. doi: 10.1016/j.jad.2017.06.011.

III. **Sjöberg L,** Fratiglioni L, Lövdén M, Wang H-X. Low mood and risk of dementia: The role of marital status and living situation. *Submitted.*

IV. **Sjöberg L,** Fratiglioni L, Karlsson B, Wang H-X. Negative life events across the life-course and risk of depression in later life. *Manuscript.*

# ADDITIONAL PUBLICATIONS NOT INCLUDED IN THE THESIS

I. Sindi S, Kåreholt I, Johansson L, Skoog J, **Sjöberg L**, Wang H-X, Johansson B, Fratiglioni L, Soininen H, Solomon A, Skoog I, Kivipelto M. Sleep disturbances and dementia risk: a multi-centre study. *Alzheimers Dement*, 2018 [In press]. doi: 10.1016/j.jalz.2018.05.012.

II. Sindi S, Johansson L, Skoog J, Darin-Mattsson A, **Sjöberg L**, Wang H-X, Fratiglioni L, Kulmala J, Soininen H, Solomon A, Johansson B, Skoog I, Kivipelto M, Kåreholt I. Sleep disturbances and later cognitive status: A multi-centre study. *Sleep Medicine*, 2017 [In press].
doi: https://doi.org/10.1016/j.sleep.2017.11.1149.

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doi: 10.1080/13607863.2017.1348484.

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doi: 10.1016/j.jagp.2016.03.009.

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AD | Alzheimer' s Disease |
| AD | Anno Domini ("in the year of the Lord") |
| ADL | Activities of Daily Living |
| APOE ε4 | Apolipoprotein E gene |
| ATC | Anatomical Therapeutic Chemical Classification |
| BC | Before Christ |
| BDNF | Brain-Derived Neurotrophic Factor |
| CI | Confidence Interval |
| CPRS | Comprehensive Psychopathological Rating Scale |
| DALYs | Disability Adjusted Life Years |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| GABA | Gamma-Aminobutyric Acid |
| GDS | Geriatric Depression Scale |
| HPA | Hypothalamic Pituitary Adrenal |
| HR | Hazard Ratio |
| ICD | International Classification of Mental and Behavioral Disorders |
| KP | Kungsholmen Project |
| MADRS | Montgomery-Åsberg Depression Scale |
| MCI | Mild Cognitive Impairment |
| MMSE | Mini-Mental State Examination |
| NEO-FFI | Neuroticism Extraversion Openness – Five-Factor Inventory |
| OR | Odds Ratio |
| PI | Principal Investigator |
| SNAC-K | Swedish National Study on Aging and Care in Kungsholmen |
| SSRI | Selective Serotonin Reuptake Inhibitor |
| WHO | World Health Organization |
| WMA | World Medical Association |
| YLD | Years Lost due to Disability |

# 1 INTRODUCTION

## 1.1 DEPRESSION

### 1.1.1 Depression from a historical perspective

"*The tears of the world are a constant quantity.*" – Samul Beckett (1).

In the Western world, the history of depression can be separated into five major periods. Already during the *Classical Antiquity* (from the 8th century BC to 5th century AD), Hippocrates defined depression as an illness of the brain, triggered by imbalances of the four humors (black bile, yellow bile, blood, and phlegm). More explicitly, an excess of black bile (in Greek black bile is *melaina chole*) was believed to cause the state of melancholy in which symptoms of sadness, tendency to suicide, anxiety, moral dejection, sleeplessness, irritability, restlessness, prolonged fear, and dislike toward food were present. Seventy years after the death of Hippocrates, the school of Aristotle emerged. He proposed an integrated theory of the body and soul, where illnesses/disturbances of the soul were thought to affect the body and vice versa. In alignment with Aristotle's theory, from the fourth to the first centuries BC, medicine and philosophy were developed along closely related lines, and seen as intertwined entities of psychiatry. Moreover, the philosophies of Hippocrates and Aristoteles pervaded during the period of the Roman Empire, which reigned from the latter half of the first century BC to the fifth century AD.

During the *Middle Ages* (or Medieval period), which lasted from the 5th to the 15th century and where the rise of Christianity took place, depression was seen as a disgrace to God, as a reprimand for an immoral soul. Moreover, persons suffering from melancholia were seen as possessed by the devil, and if one could not exorcise the evil from the body, they must die. Some believed that proofs to support these ideas were to be found in the Bible since Judas committed suicide due to melancholy. He was therefore believed to be possessed, and subsequently, persons suffering from melancholy were further seen as Judas-like. This theory had severe consequences for those suffering from mental illnesses, and during the Inquisition of the thirteenth century, some were even imprisoned due to their depression and proceeding sins. Until this day, the stigmatization still attached to mental illnesses and depression is believed to be a relic of the Middle Ages.

In the period of the *Renaissance* (from the 14th to 17th century), the view of depression completely shifted, from a punishment due to sinfulness, to a sign of profundity or insightfulness. Marsilio Ficino believed that melancholy was the manifestation of mankind's desire for greatness and the eternity. He further believed that deep thinkers and artists were more likely to experience melancholy than the common man since they had greater capacity and ability to raise their minds over the distractions of everyday life. Thus, the tormented minds were more worthy and were a sign of complexity, depth, and soulfulness. This resulted in melancholy turning into fashion and as an illness of the aristocracy or upper-class.

The *Age of Enlightenment* (from the 17th until the 19th century), was the time period of rationalism and science. During the seventeenth century, Robert Burton was one of the main

thinkers, who further interweaved medicine and philosophy, as well as science and metaphysics. During this time period it was also suggested that mental illnesses or madness could stem from genetic heredity. The eighteenth century is sometimes referred to as the Age of Reason because rationality, reasoning, and enlightenment were superior, and thus church and religion lost some of its powers over the society and academia. During this period, scientific explanations of the mind and body advanced. However, in the age of reasoning, those without reason were socially disadvantaged, and once again stigmatized. As a matter of fact, this time period, along with the Middle Ages, might have been some of the worst for persons suffering from mental illnesses. As an example, those suffering from psychiatric disorders could be seen as animal-like creatures without self-discipline, and should therefore be segregated from society. During the nineteenth century, the Romantic period took place and once again the view of depression completely shifted, from melancholia being stigmatized to it being seen as a sign of insightfulness.

The *Modern Age* began in the twentieth century. The two most influential persons, whose theories and research have come to impact and dominate modern psychiatry, were Sigmund Freud and Emil Kraepelin. They also came to represent two movements of psychiatry and depression; the psychoanalytical/psychological (Freud), and the psychobiological/biochemical approach (Kraepelin). Sigmund Freud believed that melancholy could arise from unconscious conflicts due to an unwilling loss, resulting in internalized anger and the splitting of the ego, which further could turn into self-loathe. Emil Kraepelin believed that the majority of mental disorders had an internal biochemical foundation. He further introduced order in psychiatry by systematically identifying clusters or patterns of symptoms, which he later classified into separate mental disorders, which laid the groundwork for the Diagnostic and Statistical Manual of Mental Disorders, 3d Edition (DSM-III) that was released in 1980. Kraepelin is sometimes referred to as the "father of modern psychiatry" since his work and focus on the classification of depression and other psychiatric disorders (through the clustering of psychiatric signs and symptoms), to this day, is the most legitimate and valid scientific and medical approach (2-4).

### 1.1.2 Definitions of depression

Unipolar depression is mainly characterized by low mood and loss of interest, in contrast to bipolar depression that shifts between manic/hypomanic and depressive episodes. The focus of this thesis is unipolar depression, which will be referred to as "depression" throughout the thesis. Today, the two most common criteria for diagnosing depression are the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR/DSM-5) (5, 6), and the International Classification of Mental and Behavioral Disorders (ICD-10) (7). The following symptoms are included in the DSM-IV-TR/DSM-5 and the ICD-10 diagnostic criteria (**Table 1**).

- Low mood
- Loss of interest or pleasure in activities that normally are pleasurable
- Decreased energy/fatigue

- Significant changes in appetite or weight
- Sleep disturbances
- Psychomotor agitation or retardation
- Feelings of worthlessness, inappropriate guilt, or pessimism
- Concentration difficulties or indecisiveness
- Recurrent thoughts of death, suicide, or suicidal behaviors
- Reduced self-esteem or confidence (only in ICD-10)

**Table 1**. Depressive symptoms included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR/DSM-5), and the International Classification of Mental and Behavioral Disorders (ICD-10).

| | **ICD-10**[a] | **DSM-IV-TR/DSM5**[b] | | **ICD-10**[a] | **DSM-IV-TR/DSM5**[b] |
|---|---|---|---|---|---|
| **SYMPTOMS** | | | **DEFINITIONS** | | |
| 1. Low mood | ● | ○ | Minor depression | | At least ○ and (+) |
| 2. Loss of interest or enjoyment | ● | ○ | | | |
| 3. Decreased energy/fatigue | ● | (+) | Mild depression | At least ●● and ++ | |
| 4. Changes in appetite or weight | + | (+) | | | |
| 5. Sleep disturbances | + | (+) | Moderate depression | At least ●● and ++++ | |
| 6. Psychomotor agitation/retardation | + | (+) | | | |
| 7. Feelings of worthlessness/ guilt/pessimism | + | (+) | Major depression | | At least ○ and (+)(+)(+)(+) |
| 8. Concentration difficulties or indecisiveness | + | (+) | | | |
| 9. Suicidal thoughts | + | (+) | Severe depression | All ●●● and +++++ | |
| 10. Reduced self-esteem/confidence | + | | | | |

Source: Sjöberg et al. (2017) (8), modified by author.

[a] At least 2 of the ● core symptoms and at least 2 + additional symptoms are required for mild depression; at least 2 of the ● core symptoms and at least 4 + additional symptoms are required for moderate depression; and all 3 of the ● core symptoms and at least 5 + additional symptoms are required for severe ICD-10 depression. [b] At least 1 of the ○ core symptoms and at least 1 (+) additional symptom is required for DSM-IV-TR minor depression; and at least 1 of the ○ core symptoms and at least 4 (+) additional symptoms are required for DSM-IV-TR or DSM-5 major depression.

As seen in **Table 1**, the DSM-IV-TR research diagnosis for minor depression requires two to four symptoms, and major depression according to DSM-IV-TR or DSM-5 requires at least five out of nine symptoms. Moreover, at least one of the two core symptoms – low mood and loss of interest – has to be present to fulfill the criteria for a minor or major depression (5, 6). A mild depression according to the ICD-10 diagnostic criteria, for research, requires the presence of four out of ten symptoms in which at least two of the three core symptoms – low mood, loss of interest, and decreased energy – have to be present. A moderate depression requires a total of six symptoms, where two of the three core symptoms have to be present, and a severe depression requires a total of eight symptoms, in which all of the three core symptoms have to be present (7). According to both diagnostic criteria, the symptoms must have been present consecutively during a two-week period, but the DSM criteria more explicitly requires clinically significant distress or impairment in important areas of daily functioning.

### 1.1.3 Depression from a global perspective

The World Health Organization (WHO) has estimated that around 322 million individuals are suffering from a depressive disorder globally. Depressive disorders have been ranked as the 13$^{th}$ leading cause of burden of disease globally (7$^{th}$ in high-income and 18$^{th}$ in low-income countries), measured as disability-adjusted life years (DALYs). Moreover, if measured according to healthy years lost due to disability (YLD), depression is ranked as number one globally (9) (**Table 2**). Thus, depression is contributing to a large proportion of the total burden of disease and disability worldwide.

**Table 2.** Leading causes of years lost due to disability (YLD) globally, 2015.

| Cause | YLDs (million) | YLDs (%) |
|---|---|---|
| 1. Depressive disorders | 54 | 7.5 |
| 2. Back and neck pain | 52 | 7.2 |
| 3. Iron-deficiency anaemia | 48 | 6.7 |
| 4. Diabetes mellitus | 33 | 4.6 |
| 5. Migraine | 27 | 3.7 |
| 6. Anxiety disorders | 25 | 3.4 |
| 7. Other hearing loss | 24 | 3.3 |
| 8. Skin diseases | 21 | 2.9 |
| 9. Oral conditions | 17 | 2.4 |
| 10. Asthma | 16 | 2.2 |
| 11. Schizophrenia | 15 | 2.1 |
| 12. Uncorrected refractive errors | 14 | 2.0 |
| 13. Osteoarthritis | 13 | 1.8 |
| 14. COPD | 12 | 1.7 |
| 15. Falls | 12 | 1.6 |
| 16. Autism and Asperger syndrome | 10 | 1.4 |
| 17. Alzheimer disease and other dementias | 10 | 1.4 |
| 18. Drug use disorders | 10 | 1.4 |
| 19. Gynecological diseases | 10 | 1.4 |
| 20. Congenital anomalies | 9 | 1.3 |

Source: World Health Organization (2016) (9), modified by author.

### 1.1.4 Depression in old age

In 2017, there were 962 million individuals aged 60 years and older, which is 13% of the total population worldwide. In 2050, this number is projected to be more than double, rising to 2.1 billion, making up 20% of the total population (except for Africa). Thus, the population aged 60 years and over is growing faster than all other age groups (10). Moreover, non-communicable diseases more frequently affect adults and older individuals, and are the greatest contributor to the world's global health burden (11). In high-income countries this is evident especially in adults 60 years and older (9).

The prevalence of depression in older adults aged 65+ years ranges from around 5% to 10% (1–5% for major depression) (12), which makes depression one of the most prevalent mental disorders in old age. However, the prevalence varies quite substantially across studies. Moreover, depression is a common source of reduced life-satisfaction and functional impairment in older adults (12). The total health care costs (inpatient and outpatient) have been found to be 47% to 51% higher in older adults having minor or major depression, compared to those not having depression, even after adjusting for chronic illnesses (13).

Despite depression being highly prevalent, impairing, and very costly for the society, previous population-based studies have found that only 8% to 35% of older individuals with a depression diagnosis were prescribed an antidepressant (14-16), and 2.7% received any psychotherapy (16). This under-treatment may be due to under-detection by primary health care providers. Specifically, one study found that only 50% of older patients received a correct diagnosis (17). This is in line with a meta-analysis showing that the diagnostic sensitivity of major depression in individuals aged 65+ years was lower than 50% in primary health care settings in Europe, USA, and Australia (18). The same under-detection has been found in primary health care settings in Sweden (19). Thus, half of those older individuals who have a major depression are not identified as having depression.

The under-detection of depression in older adults may be due to that the manifestation of depression in older individuals can differ from younger persons. In detail, older adults are more likely to express somatic symptoms, psychomotor problems, sleep disturbances, lack of energy/fatigue, and cognitive difficulties, rather than primarily affective symptoms such as low mood. This may result in older individuals not meeting the criteria for a major depression diagnosis, even though they have clinically significant symptoms that affect their daily functioning (20). Moreover, health care personnel, as well as older individuals themselves, may interpret depressive symptoms as a ”normal” part of the aging process (12, 21). However, as previously mentioned, unrecognized and untreated depression is a common cause of decreased well-being, as well as increased disability and use of health care services (12, 19, 22). Thus, in view of the global increase of older individuals (23), better knowledge and detection of depression in older adults is highly valuable from clinical, economical, and public health perspectives.

*Prevalence of depression in older adults*

Several studies have investigated depression prevalence in older adults. However, as aforementioned, the estimates from earlier studies vary quite substantially. To illustrate this, one review found that the prevalence ranged from 1% to 16% for major depression, 2% to 19% for minor depression, and 7.2% to 49% for depressive symptoms in older persons living in the community or in nursing homes (15). It is possible that the differences in the prevalence of depression are due to methodological inconsistencies, such as differences in depression definitions, or in the compositions of the study populations (24, 25). However, only a limited number of studies have simultaneously used different definitions of depression (i.e. diagnostic criteria, rating scales, and self-report) and sub-samples of the study population (e.g. by dementia status, living place, and socio-demographics) to explore to what extent the prevalence of depression may differ.

## 1.2 LIFE-COURSE APPROACH TO DEPRESSION IN OLD AGE

The purpose of life-course epidemiology is to link exposures/events occurring across the life-course to later health outcomes (**Figure 1**). Specifically, it helps to identify how psychosocial, behavioral, and biological factors operate across the life span and affect an individual's risk of developing disease or ill-health (26, 27). Overall, the etiology of depression in later life is complex and multifactorial, and possibly stems from several different factors throughout the life-course (28). Hence, to examine depression in old age using a life-course perspective is highly valuable in distinguishing separate and interactive effects of risk factors across the life span, as well as detecting the most efficient and crucial timing for depression prevention (29, 30). Thus, the life-course approach has contributed to the theoretical base of this thesis.

There are three main concepts included in life-course epidemiology: 1. causal pathway of time (accumulation of risk and chains of risk); 2. timing of causal actions (e.g. critical or sensitive periods, and birth cohort effects); and 3. different types of mechanisms (e.g. vulnerability, resilience, and modifying or mediating factors) (27). In this doctoral project we mainly focused on the theories related to an accumulation of risk, sensitive periods, birth cohort effects, and modifying factors.

The accumulation of risk theory is based on the notion that the number, severity, and duration of exposures and insults during the life span cumulatively can cause biological damage. Thus, the accumulation of exposures/insults (such as environmental, behavioral, and socio-economical) is believed to cause long term damage or affect an individual's risk of ill-health. The sensitive time period theory argues there is a time-window or a sensitive period in which an exposure has a greater impact on the development and risk of a disease later in an individual than at other times. A birth cohort refers to the location for individuals in historical time, indexed by their year of birth. Environmental changes (such as improvements or worsening in living standards or working conditions), or cohort variations in risk exposure or behaviors (e.g. sun-bathing or smoking) may have long term effects and influence health

(31). Thus, comparisons between different birth cohorts can be useful to detect differences that may be due to societal or environmental changes and/or alterations in risk behaviors. Modification is when the effect of an exposure on the outcome, varies across different levels of the modifying factor. To test for interaction, the joint effect of two (or more) exposures on the outcome is examined (32). From a life-course perspective, interactions are important since they are common and realistic features of life-course processes (27).

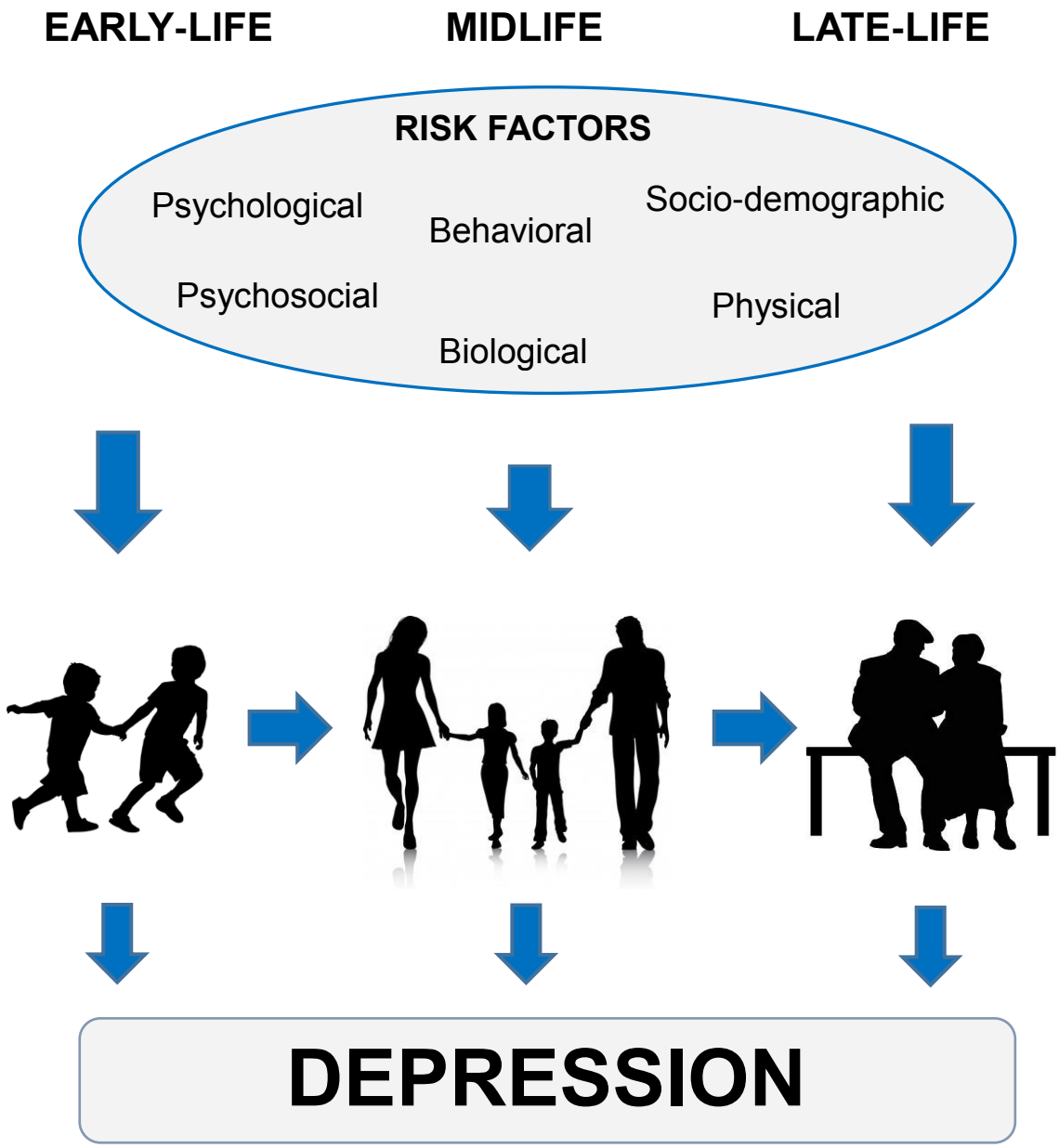


**Figure 1.** A potential model of the hypothesis for depression and depression vulnerability over the life-course. Source: Gudmundsson P (2012) (33), modified by author.

### 1.3 RISK FACTORS OF DEPRESSION IN OLD AGE

Socio-demographic, psychosocial, behavioral, psychological, physical, and biological factors have all been related to depression risk or vulnerability in older adults. Thus, the risk for developing depression is multifactorial, and the risk factors are intertwined across the life span and with each other (**Figure 1**). The major risk factors that have been included in this thesis (either as exposures, covariates, or modifiers) are presented below.

### 1.3.1 Socio-demographics

#### *Age differences of depression*

A 30-year longitudinal study of adults aged 19–95 years found that the prevalence of depressive symptoms followed a U-shaped pattern across adulthood, being highest in young adulthood, decreasing across middle-adulthood, and then increasing again in older adulthood (34). This is in line with the majority of studies reporting an increase of depressive symptoms with age (12, 24, 35). However, studies have found a decline (25, 36) or no change (14) in the prevalence of major depression with age. It has been suggested that the higher levels of depressive symptoms may be explained by health-related problems and functional disabilities (15, 37). Yet, accounting for these problems reduced, but did not eliminate, the increase of depressive symptoms with older age (34).

#### *Sex differences in depression*

The prevalence of depression in older adults has been found to be higher in women than men worldwide (12, 15, 25). This sex difference is present already in puberty and lasts throughout the life span across all age-groups. However, the sex gap seems to decrease with increasing age (among the oldest-old), but still exists (20).

There are several different explanations for the sex differences in the prevalence of depression. First, it has been suggested that physicians may be more likely to detect depressive symptoms in women than men, and that women seek care more often than men when suffering from a depression. Second, men are more likely to under-report or suppress emotional manifestations of depression due to sex stereotypes, such as depression being perceived as feminine and contradictory to society's archetypes of masculinity. Third, men may be more likely to express other depressive symptoms than women, such as aggressiveness, irritability, over-consumption of alcohol, and risk-taking, which differ from those included in the traditional diagnostic criteria. Indeed, one study found that the sex difference in depression prevalence actually disappeared when including these alternative symptoms to a traditional rating scale of depression (38). Fourth, it has also been suggested that the sex difference is due to differences in social and societal factors between the sexes. In detail, women tend to have lower socio-economic status and they are exposed to more psychosocial and psychological stressors (such as sexual harassment, discrimination, and greater societal pressure etc.) than men (39), and these factors have been related to depression. Fifth, the sex difference of depression may also be due to biology since sex hormones (androgen, testosterone, and estrogen) have been found to modulate the neurotransmitters serotonin, dopamine, and noradrenalin. This is supported by the fact that the sex difference of depression is prevalent from puberty onwards (40-42).

#### *Socio-economic status*

Low socio-economic status (e.g. low education and low income) has been related to both the onset and perseverance of depression in older adults (15, 43-46). Overall, as compared to

those with higher education, individuals with lower education are more likely to obtain manual labor jobs. Compared to non-manual workers, individuals in manual labor jobs are more likely to have lower job control (47-50) and wages (51) (consequently resulting in lower retirement pensions), which are factors that also have been associated with a higher risk of developing depression or depressive symptoms (52-55).

### *Marital status and living situation*

Unmarried older adults (widowed, divorced, or never-married) have an increased risk of depression compared to those who are married (56, 57). Moreover, studies have found that widowed individuals have a higher risk of depression than those who never married (56). Overall, individuals without a partner are more likely to live alone, which also has been found to be associated with a higher depression risk (15, 58). In addition, those who are without a partner or live alone are more likely to experience loneliness and poor social support (59), which in turn can increase the risk of depression (15, 59, 60). On the contrary, having a partner or living with someone can provide social stimulation, promote engagement in healthy behaviors (61, 62), and decrease the levels of psychosocial stress through emotional, practical, and economic support (62), factors that can lower the risk of depression (15, 57, 63-65). However, marital difficulties, dissatisfaction, or illnesses of the spouse have been found to be related to depressive symptoms (66) and major depression in older adults (67, 68), indicating that the quality of the relationship is of importance for mental health. At the same time, it is important to bear in mind that depression may also negatively influence one's marital status, quality of the marriage, and also the ability to marry a suitable partner (56, 59).

In addition, some studies have found sex differences in the association between marital status and depression. In detail, unmarried men have been found to have higher depression risk than unmarried women (57). One cross-sectional study found that for women, the greatest association between marital status and depression was found for those who were married, while for men the situation was reversed, i.e., the strongest association was found among the never married (59). This is in line with research showing that women become dissatisfied with their marriage sooner than men do (69), and in heterosexual relationships in Europe, Australia, and USA, women are more likely to file for divorce (70) (e.g. women in the US, nowadays, initiate around 70% of all divorces) (70). Moreover, studies have also found that marital dissatisfaction predicted greater increases in depressive symptoms for women (71), and a stronger association between the marital quality and depressive symptoms was found for women than men (72).

Regarding living place, compared to living in the community, those living in nursing homes or institutions have been found to have a higher risk of depression (58). Individuals living in these settings are more likely to have a higher prevalence of physical illnesses, disabilities, pain, cognitive impairment**,** comorbidities, and nutritional deficits, than those in the community, thus contributing to a higher depression risk (73, 74). In addition, loss of independence or autonomy, social isolation, and loneliness may also further contribute to an increased risk of depression among those living in nursing homes or in institutions (75).

### 1.3.2 Psychosocial factors

#### *Social factors*

Having a poor social network, low participation in social activities, low social support, and feelings of loneliness have been associated with depression (15, 59, 76-78), and the risk of developing depression in old age (15, 60, 79, 80). On the other side, problematic relationships have also been found to be related to depressive symptoms in older adults (66). Thus, it is important to study both the quantity and quality of the social network and support in relation to depression (20). In addition, studies have also found that social support may act as a buffer, thus decreasing the risk of developing depression when exposed to stressors or negative life events (81, 82). However, the relationship between social support/network and depression may be reciprocal, i.e., scarcity of social support and network may be the result of a depression and vice versa (83). Taken together, more longitudinal research is needed to further explore how quantitative and qualitative aspects of social relations affect depression risk in older adults (84-88).

#### *Secular changes*

Rapid societal changes took place during the 20$^{th}$ century in Sweden, predominantly in the later decades (89). These include the introductions of universal child benefits (1947), three weeks of statutory vacation (1951), compulsory health insurance (1955), and improved housing standards and working conditions. Moreover, rapid technological changes have also affected people's lives during the later decades of the 20$^{th}$ century (90-92). In line with the life-course approach, comparisons between different birth cohorts could be beneficial to detect cohort differences that may be linked to societal changes, and to better comprehend the context in which social factors impact the risk of developing depression in older adults.

#### *Negative life events*

There has been an association between the exposure to negative life events and the risk of developing depression in older adults (15, 93). Moreover, the timing of a negative life event has been found to play a crucial role in relation to its impact on the brain, as well as the development of brain-related disorders (94-96). Specifically, the experience of negative life events has been associated with an increased risk of depressive symptoms or a diagnosis of depression (97), especially when events occur in the more sensitive stages of the life span (e.g. early-life) (98). However, most of the previous studies did not explore negative events across the entire life span, i.e., they only focused on either childhood negative events and/or events that occurred during the past years (99, 100). In addition, most studies assessed depression in adolescence or middle aged adults but not in older adults (97, 98, 101). Thus, more studies are needed to examine the impact of negative life events across the entire life span on the risk of developing depression in older adults.

### 1.3.3 Behavioral factors

Physical inactivity (e.g. infrequently or never engaging in moderate or vigorous activity) has been shown to be a risk factor for developing depression. Among adults aged 64+ years, those who had a higher degree of physical activity at baseline reported less depressive symptoms at two-year follow-up than those who had lower degree of physical activity (63). In addition, being a current smoker has also been related to an increased risk of developing depressive symptoms in older adults (64). Moreover, a strong association between alcohol misuse and depressive symptoms has been found in older adults aged 65+ years (102). However, this relationship seems to be U-shaped, i.e., those who drink moderate levels of alcohol have shown lower risk of developing depressive symptoms as compared to abstainers or heavy drinkers (103).

### 1.3.4 Psychological factors

Personality has been linked to depression (20, 104, 105). In detail, consistent findings of previous studies are that high scores on the personality trait of neuroticism (sub-categories; anxiety, hostility, depressiveness, self-consciousness, impulsivity, stress-vulnerability), and low scores on extraversion (sub-categories: warmth, gregariousness, assertiveness, activity, excitement-seeking, positive emotions) are associated with risk, severity, and new onset of major depression in older adults (104-107).

### 1.3.5 Physical factors

There is an association between cardiovascular diseases and depression (20, 108, 109). In detail, studies have found that the occurrence of heart disease or stroke may increase the risk of developing depression or depressive symptoms in older adults (109). Related to this, the "vascular depression hypothesis" entails that cerebrovascular damages precede, predispose, or precipitate depression or depressive symptoms (110-112). Thus, there is evidence of comorbidity between cardiovascular diseases and its risk factors with later onset of depression (111). Type 2 diabetes (impaired glucose metabolism) has also been related to depression, and studies have found that around 15% of individuals with type 2 diabetes have major depression and around 20% have elevated depressive symptoms (113). In addition, studies have also found that cognitive impairment or dementia may increase the risk for developing depression. However, various explanations of the relationship between depression and dementia are possible (114, 115). As an example, the vascular-depression-dementia hypothesis suggests that cardiovascular and cerebrovascular diseases and their risk factors may link depression with dementia (116). Overall, the number of chronic somatic diseases (117) and multimorbidity (the presence of two or more chronic diseases) (118) have been associated with a diagnosis of depression or the persistence of depressive symptoms (119). In addition, functional limitations or physical disabilities, such as dependency in activities of daily living (ADL) (120), have also been associated with an increased risk of depression or depressive symptoms in older adults (15, 117, 121). Moreover, physical functioning is vital for a good quality of life, and studies have found older persons to be more worried about their capacity to be physically autonomous than physical diseases per se (122).

### 1.3.6 Biological factors

The most well-known biological dysfunction of depression is hyper activation or dysfunction of the hypothalamus-pituitary gland-adrenal cortex (HPA) - axis, which releases glucocorticoids as a reaction to stress/stressors. Protracted high levels of glucocorticoids can lead to structural and functional changes of the stress-reactive brain regions, which are involved in the regulation of the HPA-axis (i.e. hippocampal area, prefrontal cortex, and amygdala). This process can ultimately lead to atrophy and reduced activity of the prefrontal cortex and hippocampus, and/or an increased activity of the amygdala (123, 124), which also have been related to depression (125, 126). Furthermore, immunological mechanisms, such as an up-regulation of pro-inflammatory cytokines, have also been associated with depression (125, 127). Moreover, decreased levels of brain-derived-neurotrophic-factor (BDNF), which is important for neuronal development and survival as well as synaptic plasticity, and the Apolipoprotein E gene (APOE ε4) genotype have also been related to depression (125, 128). Finally, lower levels of the neurotransmitters serotonin, noradrenaline, dopamine, or gamma-aminobutyric acid (GABA) have been linked to depression, and serotonin and noradrenaline are the neurotransmitters that are primarily targeted during antidepressant treatments (125).

## 1.4 CONSEQUENCES OF DEPRESSION IN OLD AGE

The most serious consequence of a depression is mortality (suicide and non-suicide), and there is an increased risk already when having a mild depression. Depression is the most common risk factor for suicide among older adults, and a study found that around 85% of older persons who died from suicide previously had a depression (111). In addition, prospective studies that simultaneously examined physical ill-health and depressive disorders found that older adults who suffered from both a physical disease and depressive disorder (including mild depression), were twice as likely to die, as compared to those who only had a physical disease (19). Studies have also found that there is an increased risk of developing stroke or cardiovascular diseases among older individuals who suffer from a depression (12, 129). Moreover, around 25% of older adults with minor depression developed a major depression within two years if they did not receive treatment for their mild depression (111).

### 1.4.1 Dementia

Dementia is projected to nearly double worldwide every 20 years among adults aged 60+ years, such as from 47 million in 2015 to 75 million in 2030, and to 132 million in 2050 (130). Previous studies have found a positive relationship between depressive symptoms or a diagnosis of depression and dementia (115). There are various explanations for this association as depression may be: a) a prodromal symptom of dementia; b) a risk factor for dementia; or c) a response to cognitive decline. In addition, depression and dementia may co-exist due to mutual underlying pathology or similar symptoms included in both disorders (e.g. reduced ability to think or concentrate/memory complaints). Thus, there are several potential explanations for the relationship between depression and dementia.

Moreover, the dementia process can result in lack of interest/anhedonia, fatigue, changes in sleep patterns, psychomotor agitation/retardation, or weight changes (114), symptoms all included in depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), whereas anhedonia is one of the two core symptoms of depression (6). The other core symptom of depression is low mood. The presence of low mood alone has been shown to be especially prominent in the early stages of cognitive decline (131), and able to better predict the progression from mild cognitive impairment (MCI) to Alzheimer's Disease (AD) than a combined score from a depression rating scale (132). Taken together, low mood may be a better predictor of incipient dementia than a diagnosis of depression or depressive symptoms according to a rating scale.

## 1.5 KNOWLEDGE GAPS AND RESEARCH HYPOTHESIS

Overall, as aforementioned, only a limited number of studies have simultaneously used different definitions of depression (diagnostic criteria, rating scales, and self-report), and sub-samples of the study population (e.g. by dementia status, living place, and socio-demographics) to verify to what extent the prevalence of depression may differ (24, 25). In addition, more longitudinal research is needed to further explore how quantitative and qualitative aspects of social relations affect depression risk in older adults (84, 86-88), and whether having a partner and living with someone could work as a buffer when having low mood, and thus delay the onset of dementia. Furthermore, when exploring these associations (social relations and depression risk, and low mood and dementia), comparisons between different birth cohorts could be beneficial to detect cohort differences, and to better comprehend the societal and environmental context in which psychosocial factors may influence the risk of developing depression or dementia in older adults. Moreover, no previous study has examined the relationship between negative life events across the entire life span, the timing of these events (early-life, early-adulthood, middle-adulthood, or late-life), and depression risk in older adults (97-101, 133).

In accordance with the life-course approach, we hypothesize that risk factors active at early- and late-life (sensitive time periods), an accumulation of risk factors across the lifespan, birth cohort effects, and modifying factors affect the occurrence, risk, and future consequences of depression in older adults.

# 2 AIMS

## 2.1 GENERAL AIM

The overall aim of this doctoral thesis is to estimate the prevalence of depression in late-life and identify risk factors, secular changes, and consequences of depression in late adulthood from a life-course perspective.

## 2.2 SPECIFIC AIMS

The general aim was achieved by four individual studies, and the specific aims of each study are specified below:

1. To test whether the association between social factors and depression in older adults has changed between the 1970s and 2000s (Study I).

2. To examine whether and to what extent the point prevalence of depression varies in older individuals aged 60–104 years when applying different diagnostic criteria (ICD-10 and DSM-IV-TR/DSM-5), rating scales (MADRS and GDS-15), and self-report in sub-samples of the population (by dementia status, living place, and socio-demographics) (Study II).

3. To explore whether low mood is related to an increased risk of dementia in two birth cohorts of older adults of different generations, and whether marital status and living situation modify this relationship (Study III).

4. To assess whether the experience of negative life events across the life span is related to increased depression risk in older adults, and whether the timing of these events (early-life, early-adulthood, middle-adulthood, or late-life) impacts this association differently (Study IV).

# 3 MATERIALS AND METHODS

## 3.1 STUDY POPULATIONS

This thesis is based on data from the H-70 study (study I), the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K, study II, III, and IV), and the Kungsholmen Project (KP, study III).

### 3.1.1 The H-70 study

The Gerontological and Geriatric Study in Gothenburg (H70) is an ongoing longitudinal population-based study with the purpose to study secular trends, health and health-related factors in older individuals in Gothenburg, Sweden. The H-70 study started in 1971–72, including a representative sample of 70-year-olds born 1901–02. Of the 460 individuals who were invited to the baseline examination, 68 refused or did not participate in the psychiatric examination, leaving a final baseline sample of 392 persons (response rate 85.2%). In 2000–01, another population sample of 70-year-olds born in 1930 was examined. Of the 778 individuals who were invited to the baseline examination, 758 were eligible. Out of these, 259 refused or did not participate in the psychiatric examination, leaving a baseline sample of 499 persons (response rate 65.8%) (134). Both samples were examined with identical instruments, and included individuals living in the community and institutions. The samples were systematically derived from the Swedish Population Register that covers names and addresses of all residents in Sweden.

**Figure 2** shows the flow-chart of the participants in study I. For the purpose of this study, ten persons who were examined in 1971–72, and twelve persons who were examined in 2000–01 were excluded due to dementia. This left a total baseline sample of 382 individuals in the 1901–02 birth cohort, and 487 individuals in the 1930 birth cohort. When exploring depression at five-year follow-up, 65 persons born 1901–02, and 65 born 1930 were excluded due to having major or minor baseline depression, leaving 317 born 1901–02 and 422 born 1930. During the follow-up, an additional 38 individuals in cohort 1901–02, and 14 in cohort 1930 died. Among the survivors, 26 persons born 1901–02 and 86 born 1930 declined participation, leaving 253 individuals born 1901–02 (response rate 90.7%) and 322 born 1930 (response rate 78.9%). To study incidence of depression, those who developed dementia (eight persons in cohort 1901–02 and twelve in cohort 1930), were excluded at follow-up. This left a final follow-up sample of 245 persons born 1901–02 and 310 born 1930.

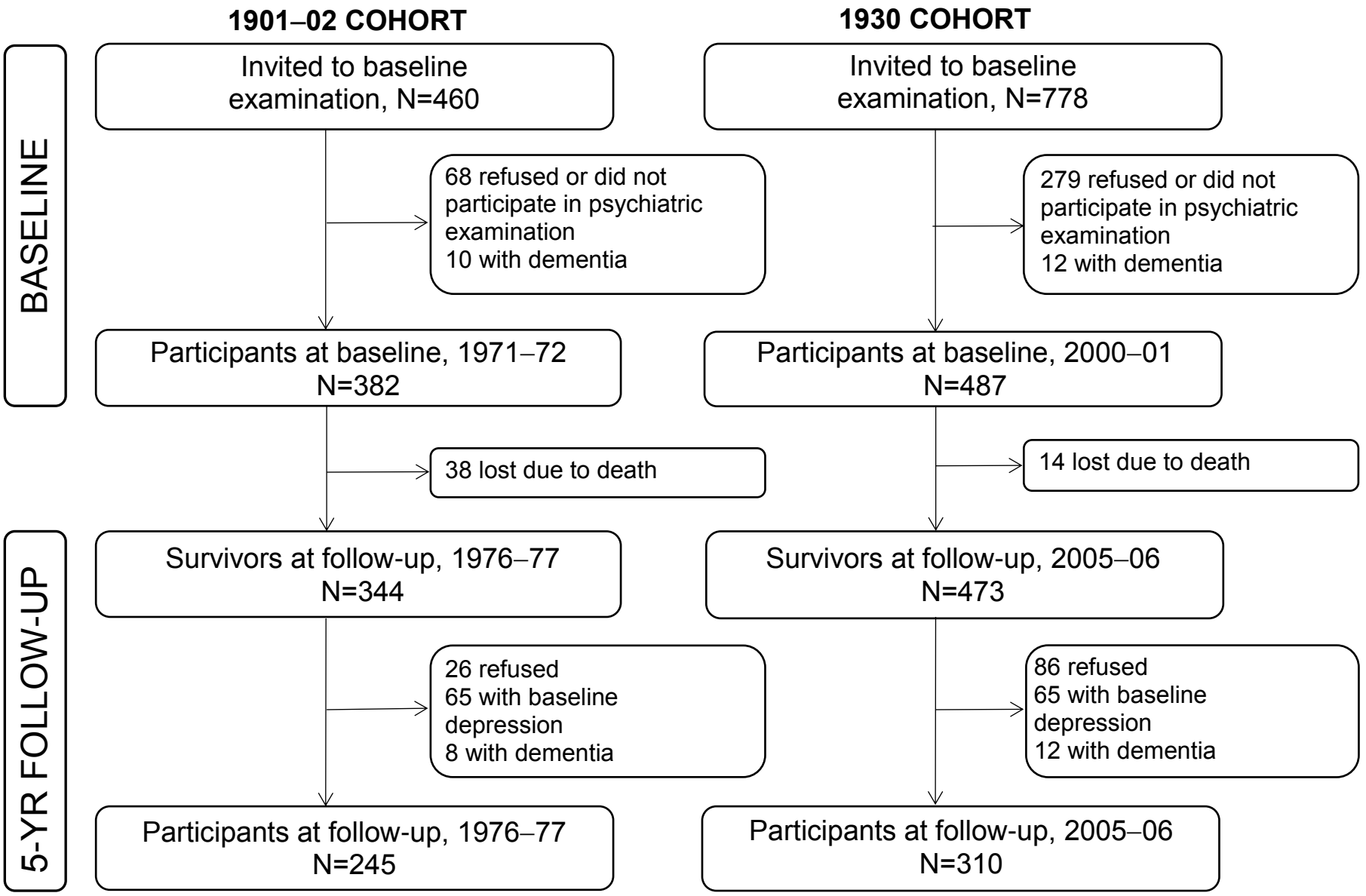


**Figure 2**. Overview of the study population at baseline and five-year follow-up for study I. Source: Sjöberg L (2013) (134), modified by author.

### 3.1.2 The Swedish National Study on Aging and Care in Kungsholmen (SNAC-K)

SNAC-K is an ongoing longitudinal study with the goal of investigating the aging process and improving health and care among older adults by identifying possible preventive strategies (135). During March 2001 to June 2004, a representative population of older adults registered as inhabitants in the district of Kungsholmen in Stockholm, were invited to the baseline examination. The study population was stratified by eleven specific age-cohorts (60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and ≥99 years), and assessment intervals (i.e. three and six years). The follow-ups were performed every six years for the younger age cohorts (60–72 years), and every three years for the older age cohorts (78+), due to more rapid changes in health and greater attrition in the older age groups. Of the 5111 persons who were invited for participation at baseline in 2001–04, 4 were deaf, 32 had moved, 23 did not speak Swedish, 262 were not able to be contacted, and 200 died, leaving an effective sample of 4590. Of these, 3363 participated (73.3%) in the examination at baseline in year 2001–04.

For the purpose of study II, 10 individuals did not undergo the medical examination, which left 3353 individuals in the analyses. To investigate depression in a sample free from dementia, 311 individuals having dementia were excluded. To examine a sample of persons living in the community, 191 who lived in an institution were excluded (**Figure 3).**

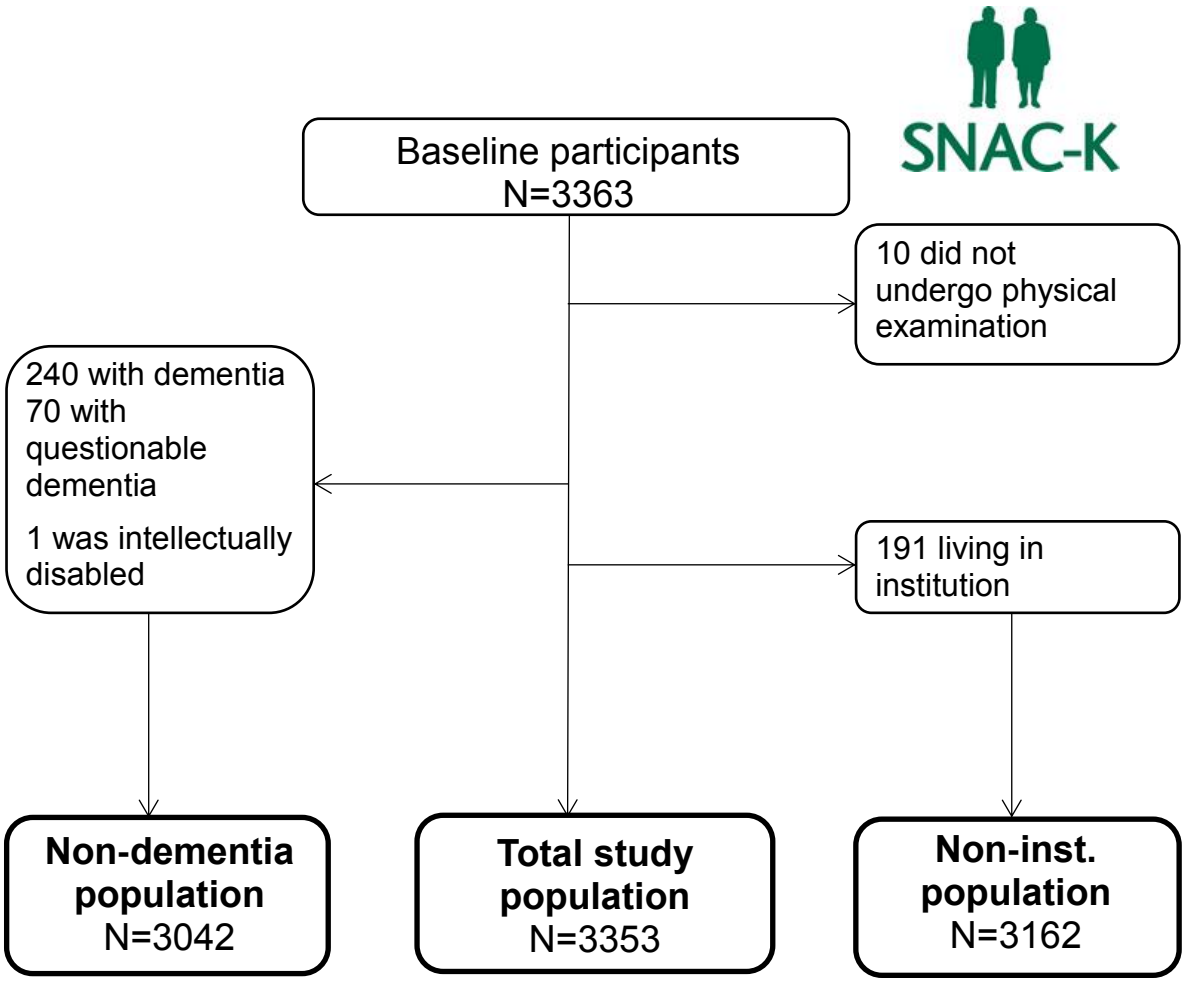


**Figure 3**. Overview of the study participants for study II (SNAC-K).

For the purpose of study III, 10 individuals did not undergo the baseline medical examination, which left 3353 individuals. To harmonize the SNAC-K sample with the KP sample, those below 72 years of age were excluded (n=1300), leaving 2053 individuals. Of these, 307 individuals were excluded due to dementia, leaving 1746 individuals. Participants who were aged 72 years underwent two follow-up examinations (2007–10 and 2010–13), and those aged 78+ years underwent three (2004–07, 2007–10, and 2010–13). Moreover, 31 persons who had a Mini-Mental State Examination (MMSE) score less than 24, and 22 persons who were living in an institution were excluded, leaving a sample of 1693 individuals who were living at home and had intact cognition at baseline. Of these, 98 individuals had missing data on MMSE, 3 persons on low mood, and 22 persons on incident dementia, leaving 1570 individuals. At the first follow-up examination, 168 persons did not participate in the testing (drop-out rate 10.7%), leaving 1402 participants for this study (**Figure 4**).

**Figure 5** shows the flow-chart of participants in study IV. Ten individuals did not undergo the baseline medical examination, and 370 individuals were excluded due to depression or missing information on depression, leaving 2983 individuals. Follow-up examinations were conducted every three years among those aged 78+ years (two assessment periods: 2004–07 and 2007–10), and six years among those aged 60–72 years (one assessment period: 2007–10). For the purpose of this study, individuals with a definite dementia diagnosis at baseline (n=81) were excluded from the sample since they were more likely to misreport negative life events. Of the remaining 2902 individuals, 673 persons had missing data on negative life events and 21 on incidence of depression, leaving 2208 participants. Prior to the next follow-up examination 216 persons died. Among the 1992 survivors, 210 persons refused, moved, or could not be contacted (drop-out rate 10.5%), leaving 1782 participants for the analyses.

### 3.1.3 The Kungsholmen Project (KP)

The Kungsholmen Project is a longitudinal population-based study on aging and dementia. All residents aged 74 years or older (n=2368) in October 1987, living in the Kungsholmen district of Stockholm, Sweden, were asked to participate in the initial examination. Of the 2368 individuals, 181 died and 69 moved, leaving an effective sample of 2118 individuals. Of those, 1810 agreed to participate (85.5%) in the study and underwent the baseline examination in 1987–89 (136).

For the purpose of study III, 110 persons refused/moved/died, and 227 had dementia. This left a sample of 1473 individuals who were identified as not having dementia (137, 138), and they went through the first (1991–93), second (1994–96), and third (1997–98) follow-up examinations. Out of these, 98 persons who had a MMSE score less than 24 or were living in an institution were excluded. This left a study population of 1375 individuals who were living at home and had intact cognition at baseline. Out of these, 7 persons had missing data on low mood, leaving 1368 individuals. At the first follow-up examination, 171 persons refused or moved (drop-out rate 12.5%), leaving 1197 participants for this study (**Figure 4**).

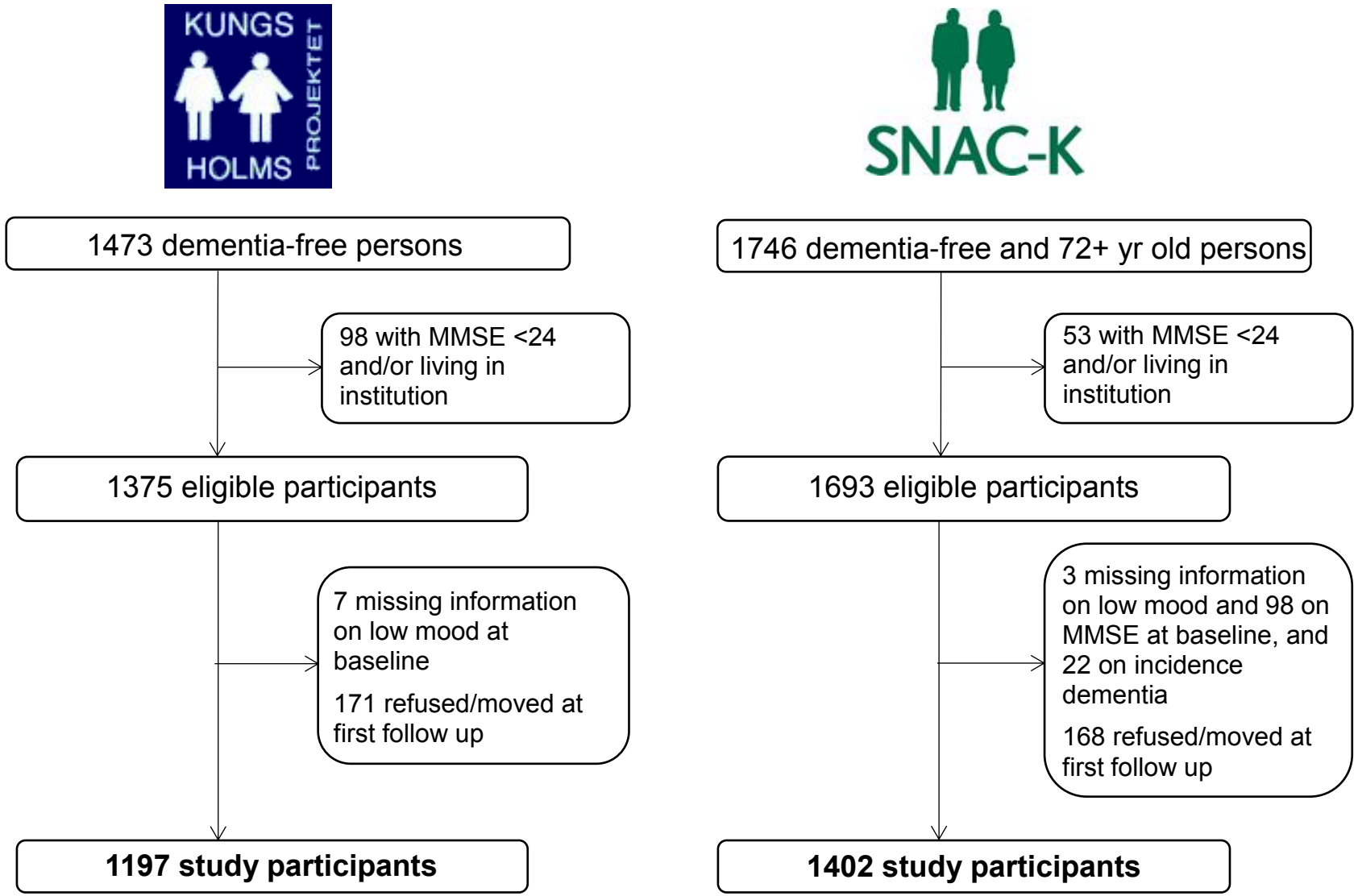


**Figure 4.** Overview of the study participants for study III (KP and SNAC-K).

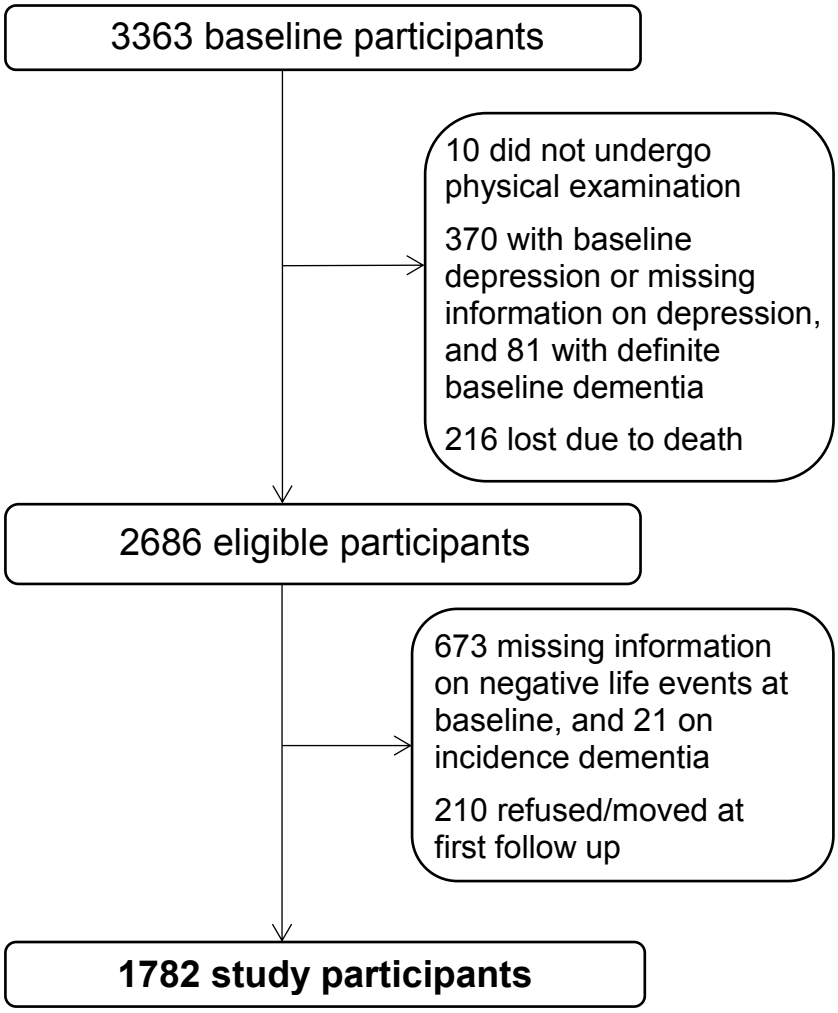


**Figure 5**. Overview of the study participants for study IV (SNAC-K).

## 3.2 DATA COLLECTION

In all studies, during the baseline and follow-up examinations comprehensive information were collected in accordance with standard protocols (available at: http://www.kungsholmenproject.se/ (summary of included variables in KP), and http://www.snac-k.se/ (SNAC-K)) through clinical examinations, interviews, self-administered questionnaires, and cognitive tests administered by nurses, physicians, and psychologists. Information has also been gathered from national patient registers.

## 3.3 ASSESSMENTS OF THE MAIN EXPOSURES

### 3.3.1 Social factors

In study I, quantitative and qualitative aspects of social factors were assessed during the baseline examinations. Contact with individuals other than children or neighbors was classified as having daily contact in person or by telephone or not having it. In 2000-01, the question also included having daily contacts via email. Visits (to visit or be visited) with children or others were classified as having visits once per month or less versus more than that, and visits with neighbors as having regular (often or sometimes) versus not having regular visits (never). The qualitative aspects of these psychosocial contacts were classified as the perception of having too little contact with children, neighbors, or others versus having good enough/sufficient contact. Feelings of loneliness were categorized as often or sometimes versus seldom or never, and having a regular hobby as pursuing the hobby once per month or more versus less than that.

### 3.3.2 Low mood

In study III, low mood was assessed at baseline for KP and SNAC-K. In KP, the participants were asked the following question during a nurse interview: "Do you often feel in a low mood/depressed?" and their answers were dichotomized as yes versus no. In SNAC-K, low mood was assessed during a general medical examination where physicians performed the Comprehensive Psychopathological Rating Scale (CPRS) (139). Two items of this scale were used to measure subjective and objective low mood; sadness (subjective) and apparent sadness (objective) (139). The presence of low mood was specified by a cut-off of $\geq 1$ (131) on the subjective sadness item and $\geq 2$ on the objective sadness item (139), and was dichotomized as fulfilling the criteria of low mood in either of the two items versus not fulfilling the criteria in any of the items.

### 3.3.3 Negative life events

In study IV, negative life events were retrospectively assessed at baseline by a structured questionnaire of 18 pre-defined events, e.g., death of best friend, large financial losses, severe illness of a friend/family member etc. (see Table 1 in study IV for detailed information) (140). Every participant was asked whether they had experienced the event or not, and the age of the occurrence. An event could have occurred several times during an individual's life span and each occurrence was counted as a single event. To examine the events throughout

the life-course, they were categorized according to the age at which the events occurred: at or before 18 years (early-life events); between the ages of 19–40 years (early-adulthood events); between the ages of 41–65 years (middle-adulthood events); and >65 years of age (late-life events) (96). The reported sum of negative life events was used as continuous and categorical variables. For the categorical analyses, all of the life events were categorized as: $\leq 50^{th}$ percentile (reference group); $> 50^{th}$ and $< 90^{th}$ percentile; and $\geq 90^{th}$ percentile (see method-section in study IV for detailed information). In addition, two additional analyses were performed where the life events were categorized into tertiles (≤ first tertile (reference group), second tertile, and ≥ third tertile), or in three groups (no events (reference group), one event, and two or more events).

## 3.4 ASSESSMENTS OF THE OUTCOMES

### 3.4.1 Depression

#### *Assessment of depressive symptoms*

Experienced physicians conducted a general medical examination where the Comprehensive Psychopathological Rating Scale (CPRS) was used to measure the point prevalence of depression during the preceding month. The CPRS is a semi-structured instrument used to assess current psychiatric signs and symptoms (139), and encompasses ratings of each sign or symptom based on its intensity, frequency, and duration. Each item of the CPRS is rated from zero to six, with a rating of two indicating the presence of a depressive symptom, and higher ratings indicating more severe symptoms. The CPRS has been shown to have good applicability and reliability in older individuals (141).

#### *Diagnosis of depression*

Specific items and cut-off levels used for the CPRS were selected in accordance with expert opinion (142) to represent depressive symptoms according to the DSM-IV-TR/DSM-5 (5, 6) (study I, II, and IV) and ICD-10 (7) (study II) diagnostic criteria. The collected data were reviewed by physicians who independently diagnosed depression according to DSM-IV-TR/DSM-5 (minor or major), and ICD-10 (mild, moderate, or severe) (see **Table 3** for detailed information).

#### *Depressive symptoms by rating scales*

In study II, depressive symptoms were also rated according to the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Geriatric Depression Scale (GDS-15 short version). MADRS is a subscale of the CPRS, which includes the ten following items for the rating of depressive symptoms: apparent and reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts (143). MADRS has been validated in adults <80 or >80 years of age, and no variations in sensitivity or specificity were found across the age groups (144). Moreover, the MADRS has also been found to have high inter-rater reliability (ranging from

0.89 to 0.97) (143). The MADRS-score ranges from 0 to 60 and the cut-off for depression was classified as >9 (145). The Geriatric Depression Scale (GDS-15) includes 15 items with answers categorized as yes/no (**Table 4**). The GDS is explicitly aimed at rating depressive symptoms in persons aged 65 years and over (146), and the inter-rater reliability of this scale has been found to be high (0.94) (147). The overall score ranges from 0 to 15 and the cut off for depression was classified as ≥5 (147, 148).

### *Self-reported depression*

In study II, self-reported depression was assessed by the investigating physicians who asked whether the participants were currently suffering from depression. The answers were classified as yes/no.

**Table 3.** The selected Comprehensive Psychopathological Rating Scale (CPRS) items and cut-offs used for diagnosing Depression according to DSM-IV-TR/DSM-5 (study I, II, and IV) and ICD-10 (study II) diagnostic criteria.

| **Depressive symptoms** | **DSM-IV-TR/DSM-5**[a] (study I, II, and IV) | **ICD-10**[b] (study II) |
|---|---|---|
| **1. Low mood (subjective or observed)** | CPRS-item: 1 Sadness (2-6)<br>CPRS-item: 41 Apparent Sadness (4-6)<br>An individual is considered to fulfill the symptom of "low mood" if fulfilling the criteria for either CPRS-item 1 or 41. | CPRS-item: 1 Sadness (2-6)<br>CPRS-item: 41 Apparent Sadness (4-6)<br>An individual is considered to fulfill the symptom of "low mood" if fulfilling the criteria for either CPRS-item 1 or 41. |
| **2. Loss of interest or enjoyment** | CPRS-item: 5 Inability to feel (2-6) | CPRS-item: 5 Inability to feel (2-6) |
| **3. Change in appetite** | CPRS-item: 18 Reduced appetite (2-6) | CPRS-item: 18 Reduced appetite (2-6) |
| **4. Sleep disturbances** | CPRS-item: 19 Reduced sleep (3-6)<br>CPRS-item: 20 Increased sleep[c] (4-6) | CPRS-item: 19 Reduced sleep (3-6) |
| **5. Psychomotor agitation/ retardation (observed)** | CPRS-item: 54 Reduced speech (2-6)<br>CPRS-item: 60 Slowness of movement (3-6)<br>CPRS-item: 61 Agitation (3-6)<br>An individual is considered to fulfill the symptom of "Psychomotor agitation/retardation" if fulfilling the criteria for either CPRS-item 54, 60, or 61. | CPRS-item: 54 Reduced speech (2-6)<br>CPRS-item: 60 Slowness of movement (3-6)<br>CPRS-item: 61 Agitation (3-6)<br>An individual is considered to fulfill the symptom of "Psychomotor agitation/retardation" if fulfilling the criteria for either CPRS-item 54, 60, or 61. |
| **6. Decreased energy/fatigue** | CPRS-item:14 Lassitude (3-6)<br>"During the past 3 months did you suffer from fatigue?": Yes[d]<br>CPRS-item: 15 Fatigability[e] (3-6) | CPRS-item: 14 Lassitude (3-6)<br>"During the past 3 months did you suffer from fatigue?": Yes[d] |
| **7. Feelings of** | CPRS-item: 6 Pessimistic thoughts (3-6) | CPRS-item: 6 Pessimistic thoughts (3-6) |

| | | |
|---|---|---|
| **worthlessness/guilt/pessimism** | | |
| **8. Concentration difficulties or indecisiveness** | CPRS-item: 16 Concentration difficulties (4-6)<br>CPRS-item: 13 Indecision (3-6)<br>CPRS-item 48 Distractibility[f] (4-6) | CPRS-item: 16 Concentration difficulties (4-6)<br>CPRS-item: 13 Indecision (3-6) |
| **9. Suicidal thoughts** | CPRS-item: 7 Suicidal thoughts (2-6) | CPRS-item: 7 Suicidal thoughts (2-6) |
| **10. Reduced self-esteem/confidence** | - | Sense of worthlessness[g] (2-6) |

Source: Sjöberg et al. (2017) (8), modified by author.

[a] Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision and 5th Edition, [b] The ICD-10 classification of mental and behavioral disorders: diagnostic criteria for research. [c] CPRS-item 20 was only available in study I (H-70 study). Thus, in the H-70 study, an individual fulfilled the symptom of "sleep disturbances" if fulfilling the criteria for either CPRS-item 19 or 20. [d] This question was only used in study II and IV (SNAC-K), [e] The CPRS-item 15 was only available in study I (H-70 study). Thus, in SNAC-K an individual fulfilled the symptom of "decreased energy/fatigue" if fulfilling the criteria for either CPRS-item 14 or answering yes to the fatigue question, and in the H-70 study if fulfilling the criteria for either CPRS-item 14 or 15. [f] The CPRS-item 48 was only available in study I (H-70 study). Thus, in the H-70 study, an individual fulfilled the symptom of "concentration difficulties or indecisiveness" if fulfilling the criteria for either CPRS-item 16, 13, or 48, and in SNAC-K if fulfilling the criteria for either CPRS-item 16 or 13.

[g] Sense of worthlessness (No original CPRS item)

Representing feelings of inferiority, that one is nothing worth. Rate according to social capacities, intensity, and degree of incapacities. Distinguish from pessimistic thoughts (CPRS-item: 6).

0 Representing feelings of temporary feelings of inferiority that may occur in some circumstances

1

2 Exaggerated feelings of inferiority and worthlessness, situations where one does not feel inferior/worthless may occur

3

4 Pervasive feelings of worthlessness, present also in everyday life; recurring thoughts of inferiority throughout interview

5

6 Constant painful feelings of inferiority that are socially incapacitating and may lead to paranoid delusions

**Table 4.** The Geriatric Depression scale: short form (GDS-15).

| | | |
|---|---|---|
| 1. Are you basically satisfied with your life? | YES | NO |
| 2. Have you dropped many of your activities and interests? | YES | NO |
| 3. Do you feel that your life is empty? | YES | NO |
| 4. Do you often get bored? | YES | NO |
| 5. Are you in good spirits most of the time? | YES | NO |
| 6. Are you afraid that something bad is going to happen to you? | YES | NO |
| 7. Do you feel happy most of the time? | YES | NO |
| 8. Do you often feel helpless? | YES | NO |
| 9. Do you prefer to stay at home, rather than going out and doing new things? | YES | NO |
| 10. Do you feel you have more problems with memory than most? | YES | NO |
| 11. Do you think it is wonderful to be alive now? | YES | NO |
| 12. Do you feel pretty worthless the way you are now? | YES | NO |
| 13. Do you feel full of energy? | YES | NO |
| 14. Do you feel that your situation is hopeless? | YES | NO |
| 15. Do you think that most people are better off than you are? | YES | NO |

Answers in grey indicate depressive symptoms. Every highlighted answer in grey gives 1 score and the total score ranges from 0−15.

### 3.4.2 Dementia

*Diagnosis of dementia*

In study III, the diagnosis of clinical dementia was made according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised (DSM-III-R) (149) for KP, and Fourth Edition-Revised (DSM-IV-TR) (5) for SNAC-K, following the same three-step practice. First, a preliminary diagnosis was autonomously made by the examining physicians, followed by a second preliminary diagnosis by the reviewing physician. In case of discrepancies between the first and the second diagnosis, a third opinion was solicited by a physician who was external to the data collection, and this was accepted as the final diagnosis (137, 150). To ascertain possible dementia diagnoses among those who died between the follow-up examinations, clinical charts were collected and examined by physicians following the same procedure and diagnostic criteria as described above (138). Overall, the agreement between the DSM-III-R and DSM-IV diagnosis of dementia has been shown to be high (kappa=0.8) (151). In both studies (SNAC-K and KP), the incident dementia cases over nine years were those who developed dementia during the first, second, or third follow-up periods.

In study II and IV (using SNAC-K), a clinical diagnosis of dementia was used to either examine depression prevalence in individuals with or without dementia (study II), or as an exclusion criterion (study IV), following the aforementioned procedures. In study I (H-70 study), dementia was used as an exclusion criteria according to DSM-III-R (149). However, since it was not possible to diagnose DSM-III-R dementia in the earlier-born cohort

examined 1971–72, the historical criteria by Kay et al (1964) (152) was used. Nevertheless, the agreement between the dementia diagnosis using the historical or DSM-III-R criteria has been found to be high (kappa=0.81) (151).

## 3.5 COVARIATES

### *Socio-demographics*

In all studies, information on age, sex, education, marital status, and living situation or place were assessed during the baseline examinations. Education was categorized as compulsory education or less versus more than compulsory education. Marital status was categorized as having a partner (married, cohabitant, or having a partner but live-apart) versus being single, divorced, or widowed (study II, III, and IV). In study I, marital status was classified as single versus married/cohabiting, and widowed versus not widowed. In study I, other partner-related factors such as the perception of the marriage (happy or very happy versus ordinary or unhappy), partner's physical health (healthy versus unhealthy), and sexual activity (having sexual intercourse during the past year versus not having it) were also assessed.

In study III, marital status and living situation were used as potential modifiers of the association between low mood and dementia. Living situation was dichotomized as living alone versus living with someone (i.e. living with a partner, children, grandchildren, siblings, sister- or brother-in-law, or other persons). In study III, a combined variable was further created and was classified as the following: 1) having a partner and living with someone; 2) not having a partner and living alone; and 3) not having a partner and living alone/with someone or having a partner but living alone.

In study II and III, living place was classified as community-dwelling versus living in an institution, and was used to examine depression prevalence in those living in the community or in institutions (study II), or as an exclusion criterion (study III).

### *Psychosocial and behavioral factors*

In study III and IV, contacts with friends, relatives, or children were assessed at baseline and were grouped as having less than daily to weekly contacts and/or being unsatisfied with these contacts (infrequent or unsatisfied) versus having daily to weekly satisfying contacts. In study IV, social support was also assessed and was classified as low versus average or high on reporting whether having access to personal support. Global leisure activities were assessed in study III and was the sum of social (e.g. attending art exhibitions, theatres, or social meetings), physical (e.g. physical exercise, walking or biking), and mental (e.g. writing, reading books/newspapers or playing chess) activities as described previously (153). The participation in these activities was reported as daily, weekly, monthly, or less than monthly. The score for each activity ranged from zero to two and the total global leisure activity scores ranged from zero to six, and were defined as low (zero to one), moderate (two to three), or high (four to six).

In study IV, physical activity was defined as inactive (no or inadequate) versus active if engaging in health- or fitness-enhancing activities several times per week or every day (154). Moreover, smoking status was categorized as current versus non-current, and alcohol consumption as no or occasional, light to moderate (drinks per week: 1–14 for men and 1–7 for women), or heavy (drinks per week: >14 for men and >7 for women) (155).

### *Psychological and physical factors*

In study IV, the personality traits of neuroticism and extraversion were assessed at baseline using 24 items from the NEO Five-Factor Inventory (NEO-FFI). A scale ranging from 1 (disagree), 2 (neither agree nor disagree), and 3 (agree) were used to create the sum scores categorized as: low (<45), moderate (45–55), and high (>55) (156). Neuroticism was classified as average or high versus low, and extraversion as low versus average or high.

Global cognition was measured using the MMSE (157) during the baseline examinations. In study II, the MMSE scores were separated into three groups: 0–23; 24–26; and 27–30, to demonstrate the different levels of cognitive functioning. In study III, the MMSE scores were dichotomized as 24–26 versus 27–30 (those with MMSE scores below 24 were excluded from the study sample), and was also used as continuous variables, as in study IV.

Dependency in activities of daily living (ADL) (120) was defined as being dependent in one or more ADL items: bathing, dressing, toileting, transferring in and out of bed and from bed to chair, and eating versus no dependencies (study II, III, and IV). In study I, three of these activities of daily living were included (dressing, toileting, and eating), and being dependent was defined as needing help in any of these activities otherwise being independent.

In study I, chronic diseases were defined as having none or any of the five diseases listed below. Chronic diseases included coronary heart disease, which was defined as angina pectoris according to the criteria by Rose et al (1962) (158), or documented myocardial infarction or ECG evidence of ischemia; chronic obstructive pulmonary disease, which was defined as morning cough or use of asthma medication; hypertension (systolic blood pressure ≥160 mmHg and/or diastolic pressure ≥90 mmHg in sitting position after five minutes of rest, or the use of antihypertensive medication); and diabetes mellitus or stroke, which was defined as being told by a physician.

In study III and IV, multimorbidity was classified as having two or more versus one or less of the disease diagnoses listed below. The disease diagnoses were based on the International Classification of Diseases Eighth Revision (ICD-8) for KP (159), and Tenth Revision (ICD-10) for SNAC-K (160). In study III, coronary heart disease/ischemic heart diseases (KP, ICD-8 codes: 410–414 and SNAC-K, ICD-10 codes: I20–I22, I24, I25, Z95.1, Z95.5); cerebrovascular disease (KP, ICD-8 codes: 430–438 and SNAC-K, ICD-10 codes: G45, G46, I60–I64, I67, I69); diabetes mellitus (KP, ICD-8 code: 250 and SNAC-K, ICD-10 codes: E10, E11, E13, E14, E89.1 and ATC-code A10), and malignancy/solid neoplasms (KP, ICD-8 codes: 140–208 and 230–239 and SNAC-K, ICD-10 codes: All C (excl. C81–C96),

D00–D09, D32.0, D32.1, D32.9, D33.0–D33.4, and Q85) were included (161). In study IV, 54 chronic diseases, which previously have been described (161), were included. However, for the purpose of study IV, dementia (ICD-10 codes: F00–F03, F05, G30, G31), depression and mood diseases (ICD-10 codes: F30–F34, F38, F39, F412), neurotic, stress-related, and somatoform diseases (ICD-10 codes: F40–F45, F48), other psychiatric and behavioral diseases (ICD-10 codes: e.g., F04, F06–07, F09, F102, F106–107, F112, F116–117 etc., see Calderon et al for detailed information (161)), and sleep disorders (ICD-10 codes: F510–F513, G47) were excluded (161).

### *Biological factors*

The APOE and BDNF genotypes were obtained by sequencing DNA from blood samples, this procedure has previously been described in detail (162). The APOE genotype was dichotomized as APOE ε4 carrier (at least one ε4 allele) versus non-ε4 carrier (no ε4 alleles) (study III and IV), and the BDNF genotype as met/met, val/met, or val/val carriers (study IV).

### *Medication*

In study II, antidepressants were assessed at baseline during the medical examination, and they were categorized according to the international classification system "Anatomical Therapeutic Chemical Classification" (ATC) (163). The antidepressants with ATC-codes: N06AA (non-selective monoamine reuptake inhibitors), N06AB (selective serotonin reuptake inhibitor, SSRIs), N06AF (Monoamine oxidase inhibitors, non-selective), N06AG (monoamine oxidase A inhibitors), and N06AX (other antidepressants such as mirtazapine and venlafaxine) were included, and were dichotomized as use of any antidepressant versus no use.

## 3.6 STATISTICAL ANALYSES

In all studies, statistical tests were two-tailed and P-values <0.05 were considered statistically significant. The statistical analyses were conducted using IBM SPSS Statistics version 19, 22, or 25 (IBM Corp., Armonk, N.Y., USA), or STATA version 15 (StataCorp, College Station, Texas) for Windows. **Table 5** shows an overview of the methods of statistical analyses used for the four studies included in this thesis.

**Study I.** Fisher's exact test was used to test differences in proportions. In each of the cohorts, multiple logistic regression models were used to estimate the odds ratios (OR) of psychosocial factors at baseline in relation to depression at baseline and incidence of depression at five-year follow-up. The basic-adjusted models were adjusted for sex and marital status, and education and ADL-dependency were additionally controlled for. To avoid an excessive number of parameters in relation to the number of cases, chronic diseases were separately added to the basic-adjusted models. In a second step, both cohorts were combined and interactive effects were tested to examine whether birth cohort significantly modified the associations between psychosocial factors and depression.

**Study II.** Multiple logistic regressions were used to explore the odds ratios (OR) of socio-demographic and health-related factors in relation to depression. All of the analyses were adjusted for age, sex, education, marital- and dementia status, living place, and ADL-dependency. To explore the prevalence of depression in different sub-samples, the analyses were further stratified by dementia status, living place, and socio-demographics. Multiple imputations of missing data were carried out using a random number generator program with 40 imputations. Age, education, sex, marital status, living place, diagnosis of dementia, use of antidepressants, ADL-dependency, cognitive function, diagnosis of any depression, and self-reported depression, were taken into account when imputing missing data.

**Study III.** Chi-Square tests were used to test differences in proportions. Cox proportional hazards regression models were used to estimate the hazard ratios (HR) of baseline low mood associated with incidence of dementia over nine years. Stratified analyses were performed to examine whether marital status and living situation modified the association between low mood and dementia. Age, sex, education, ADL-dependency, multimorbidity, and global cognition (MMSE), were controlled for in our models, and age and MMSE scores were used as continuous variables. The APOE ε4 genotype, contacts with friends, relatives or children, and global leisure activities were further controlled for in additional analyses. The additive interactive effects (relative excess risk due to interaction) were tested to explore whether marital status, living situation, study cohort, or global cognition significantly modified the associations between low mood and risk of dementia, and p-values <0.1 were considered statistically significant (164). Overall, the participants were followed from baseline up until the date of dementia diagnosis, date of death, or until the end of the follow-up period. The time of dementia onset was assumed to be the midpoint between the follow-up examinations or the time of death.

**Study IV.** Multiple logistic regression models were used to examine the odds ratios (OR) of the number of negative life events (used as continuous and categorical variables) associated with incidence of depression over six years. Age, sex, education, and follow-up time were controlled for in the basic-adjusted models. In a second step, marital status, multimorbidity, physical dependency or activity, social support, social contacts with children, relatives, or friends, global cognitive function, smoking status, alcohol consumption, BDNF met and APOE ε4 carrier status, and personality (neuroticism and extraversion), were separately added to the basic-adjusted models. Age and global cognition (MMSE) were used as continuous variables, and the covariates with more than one category were dichotomized, if only one category was significantly associated with depression risk. The confounders with a P-value <0.2 were kept in the final multi-adjusted models, which included multimorbidity, social support, social contacts, cognitive function, alcohol consumption, and personality traits. Overall, participants were followed from the date of the baseline examination up until the date of a depression diagnosis at three or six years of follow-ups, or until the end of the follow-up period (if they had not developed depression).

**Table 5.** Title, data sources and design, exposures, outcomes, potential confounders, and statistical analyses used in the four studies included in this thesis.

| Study | Title | Data sources and design | Exposures | Outcome | Potential confounders | Statistical analysis |
|---|---|---|---|---|---|---|
| **Study I** | Secular changes in the relation between social factors and depression: A study of two birth cohorts of Swedish septuagenarians | H-70 study Cross-sectional and longitudinal | Psychosocial factors | Depression at baseline and at 5-year follow-up | Sex, marital status, education, ADL-dependency, chronic diseases | Logistic regression models |
| **Study II** | Prevalence of depression: Comparisons of different depression definitions | SNAC-K Cross-sectional | - | Depression at baseline | Age, sex, education, marital-and dementia status, living place, and ADL-dependency | Logistic regression models |
| **Study III** | Low mood and risk of dementia: The role of marital status and living situation | SNAC-K and KP Longitudinal | Low mood | Dementia over 9 years follow-up | Age, sex, education, ADL-dependency, multimorbidity, MMSE, APOE ε4, social contacts, and global leisure activities | Cox regression models using follow-up time (days) as the time scale |
| **Study IV** | Negative life events across the life-course and risk of depression in later life | SNAC-K Longitudinal | Negative life events | Depression over 6 years follow-up | Age, sex, education, multimorbidity, social support and contacts, MMSE, alcohol consumption, and personality traits | Logistic regression models, controlling for follow-up time in days. |

Abbreviations: SNAC-K= Swedish National Study of Aging and Care; KP= Kungsholmen Project study; ADL= Activities of Daily Living; MMSE= Mini Mental State Examination; APOE ε4= Apolipoprotein E gene.

## 3.7 ETHICAL CONSIDERATIONS

All of the included studies in the thesis (H-70, SNAC-K, and KP) follow the Helsinki Declaration, which is a statement of ethical principles for medical research involving human subjects by the World Medical Association (WMA) (165), and the guidelines of the Swedish Council for Research in the Humanities and Social Sciences, which includes: the principles of autonomy and integrity, and the rules for consent, demand, and use of research.

In all of the studies, participants received written information about the nature of the study including the aim, study design, duration, examinations, and the role and importance of the participant. Before the start of the study, written informed consent was obtained directly from all participants. In case of severe cognitive impairment, informed consent was collected from a proxy, usually from a family member or close relative. As part of the informed consent procedure, participants were further guaranteed that their data would be anonymous and confidential. The participants were also informed that participation was voluntary and that they could withdraw or end their participation at any time, without having to justify their withdrawal. With regards to confidentiality, the collected data are stored in locked rooms or drawers. Moreover, the data have been entered into the database system, following the rules for privacy and security. Furthermore, permission must be given from the Principal Investigators (PIs) in order to receive data and conduct research on the H-70, KP, or SNAC-K studies, and researchers are only given decoded data so that the participants' name and personal identification remain anonymous.

During the examinations, the safety and well-being of every participant have been considered e.g., the examinations were performed in friendly and comfortable atmospheres and environments. Moreover, the tests have been designed to minimize distress experienced by the participants. However, if a participant expressed discomfort or anxiety, the interview ended immediately. Overall, in case of detection of a disease/disorder, the examining physicians are obliged to ensure that the participant receives adequate information so that they are able to seek help and treatment from their family doctor or other physician.

The Ethics Committee for Medical Research at the University of Gothenburg has approved all phases of the H-70 study (Date: 1976-04-05 (earlier-born cohort), and Dnrs: S377-99 and T453-04 (later-born cohort). In addition, the Ethics Committee at Karolinska Institutet and the Regional Ethics Review Board in Stockholm have approved the baseline and follow-ups of the Kungsholmen Project study; Dnrs: 87:148, 87:234, 90:251, 94:122, 97:413, 99:025, 01-020 (patient registers), and the SNAC-K study; Dnrs: 01-114, 04-929/3, Ö 26-2007, 2010/447-31/2, 2009/595-32 (patient registers).

# 4 MAIN RESULTS

Below are the main results presented for each of the four individual studies included in the thesis. For more detailed information on the results, please see the published papers and manuscripts at the end of this thesis.

## 4.1 STUDY I

### Secular changes in the relation between social factors and depression: A study of two birth cohorts of Swedish septuagenarians followed for 5 years

At baseline, the prevalence of any depression was 17% (n=65) (major: 1.8%, n=7; minor: 15.2%, n=58) among the 382 septuagenarians born 1901–02, and 13.3% (n=65) (major: 3.9%, n=19; minor: 9.4%, n=46) among the 487 septuagenarians born 1930. The incidence of depression at five-year follow-up was 7.8% (n=19) (major: 3.3%, n=8; minor: 4.5%, n=11) in the earlier-born cohort, and 14.2% (n=44) (major: 1.3%, n=4; minor: 12.9%, n=40) in the later-born cohort.

**Table 6** shows the association between psychosocial factors at baseline in relation to the incidence of depression at five-year follow-up in the two birth cohorts. Overall, feelings of loneliness at baseline were related to higher incidence of depression in both of the birth cohorts. However, having visits once per month or less with others than children or neighbors, and the perception of having too little contact with others at baseline were related to an increased risk of depression in the earlier but not in the later-born cohort. These associations could not be explained by socio-demographic or health-related factors, such as ADL-dependency or the presence of any chronic diseases.

When further examining these differences, it was found that birth cohort significantly modified these associations (interaction effects: P=0.04 for having visits with others than children or neighbors once per month or less; P=0.009 for the perception of having too little contact with others) (**Table 6**).

**Table 6.** Psychosocial factors at age 70 in relation to incident depression at five-year follow-up[a] in two birth cohorts of Swedish septuagenarians.

| | **Cohort 1901-02** (N=245) | **Cohort 1930** (N=310) | Interaction cohort[b] |
|---|---|---|---|
| | OR (95% CI)[a] | OR (95% CI)[a] | P-value |
| **Demographics** | | | |
| Unmarried | 0.48 (0.16-1.49) | 1.39 (0.70-2.78) | 0.059 |
| Widowed | 0.39 (0.09-1.83) | 0.64 (0.24-1.66) | 0.438 |
| Compulsory education or less | 0.64 (0.19-2.06) | 1.07 (0.56-2.06) | 0.369 |
| Female sex | 1.26 (0.46-3.49) | 1.80 (0.88-3.69) | 0.215 |
| **Partner relation** | | | |
| Happy marriage[c] | 2.73 (0.76-9.82) | 0.70 (0.31-1.58) | 0.079 |
| Healthy partner[c] | 0.73 (0.22-2.44) | 0.41 (0.16-1.01) | 0.390 |
| Sexually active | 1.97 (0.64-6.00) | 1.24 (0.57-2.67) | 0.130 |
| **Contact with others** | | | |
| Daily personal or phone contact | 0.28 (0.07-1.16) | 1.04 (0.51-2.09) | 0.175 |
| Infrequent visits with children, neighbors, or others | -[d] | 1.77 (0.86-3.63) | 0.997 |
| - Children | 2.72 (0.65-11.42) | 1.57 (0.58-4.26) | 0.861 |
| - Neighbors | 1.38 (0.50-3.78) | 1.18 (0.58-2.40) | 0.712 |
| - Others | **5.15 (1.79-14.75)**** | 1.60 (0.77-3.31) | **0.037** |
| **Perceived contacts** | | | |
| Feelings of loneliness | **3.81 (1.10-13.20)*** | **2.80 (1.23-6.39)*** | 0.678 |
| Too little contact with children, neighbors, or others | 2.59 (0.96-6.97) | 1.52 (0.68-3.39) | 0.388 |
| - Children | 0.44 (0.05-3.75) | 1.57 (0.58-4.24) | 0.243 |
| - Neighbors | 3.28 (0.79-13.57) | 1.44 (0.29-7.00) | 0.517 |
| - Others | **8.10 (2.84-23.14)**** | 1.16 (0.38-3.59) | **0.009** |
| Having a regular hobby | 1.02 (0.39-2.65) | 1.33 (0.64-2.75) | 0.640 |

Source: Sjöberg et al. (2013) (134), modified by author. [a] Multiple logistic regressions presented as odds ratios (OR) with 95% CI, adjusted for sex and marital status. * P<0.05, **P<0.01. [b] The interaction effects with birth cohort are presented as p-values. [c] Unmarried and non-cohabitants excluded. [d] Model not estimable due to zero cell count.

## 4.2 STUDY II

### Prevalence of depression: Comparisons of different depression definitions in population-based samples of older adults

In a population of 3353 adults aged 60 to 104 years, the prevalence of any depression ranged between 4.2% and 9.3% according to the diagnostic criteria (DSM-IV-TR and ICD-10); 9.2% to 10.6% for the rating scales (MADRS and GDS-15); and was 9.1% for self-reported depression (**Figure 6**). When exploring more severe forms of depression, the prevalence was 1.6% for ICD-10 (moderate/severe depression), and 2.1% for major depression according to DSM-IV-TR/DSM-5.

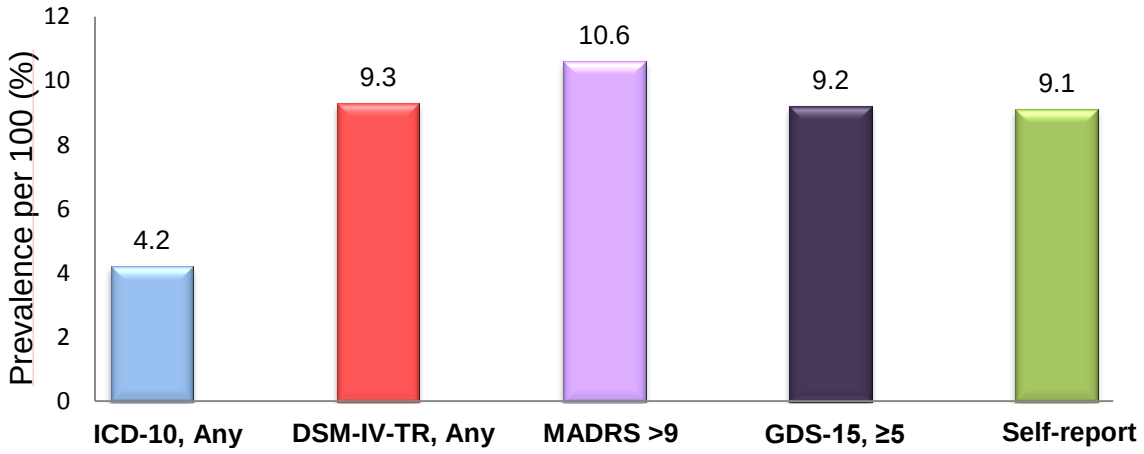


**Figure 6**. Prevalence of depression per 100 by different depression definitions, N=3353.
Abbreviations: ICD-10= International Classification of Mental and Behavioral Disorders; DSM= Diagnostic and Statistical Manual of Mental Disorders; MADRS= Montgomery-Åsberg Depression Scale; GDS= Geriatric Depression Scale.

Apart from self-reported depression, depression prevalence was lower when excluding those having dementia, or living in institutions, as compared to the total population (**Figure 7**).

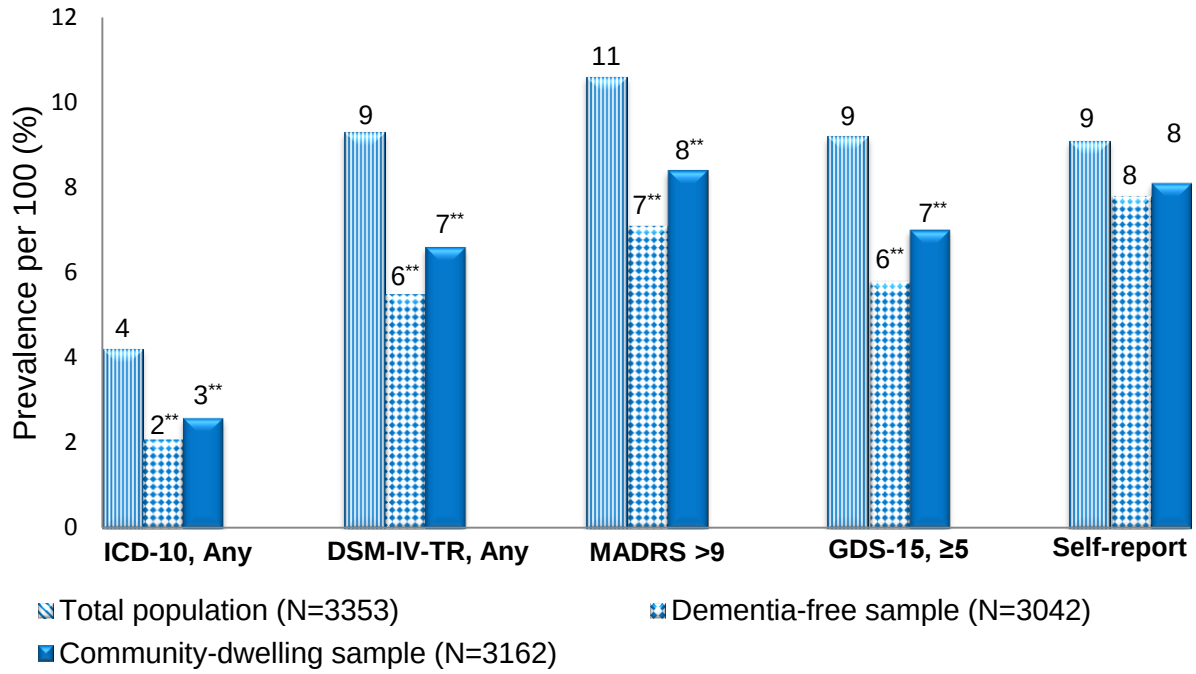


**Figure 7**. Prevalence of depression per 100 by different depression definitions in the different samples.
Abbreviations: ICD-10= International Classification of Mental and Behavioral Disorders; DSM= Diagnostic and Statistical Manual of Mental Disorders; MADRS= Montgomery-Åsberg Depression Scale; GDS= Geriatric Depression Scale. ** P-value <0.01. Source: Sjöberg et al. (2017) (8), modified by author.

Moreover, having dementia (adjusted OR: 1.8 to 4.7), being physically dependent (adjusted OR: 2.4 to 3.2), or not having a partner (adjusted OR: 1.9 to 2.1) were related to a greater depression prevalence, across the majority of the depression definitions.

## 4.3 STUDY III

### Low mood and risk of dementia: The role of marital status and living situation

Low mood was present in 372 (31.1%) individuals in KP and in 206 (14.7%) individuals in SNAC-K (birth cohort difference: P≤0.001). During the nine-year follow-up, 387 (32.3%) dementia cases were identified in KP, and 335 (23.9%) cases were identified in SNAC-K.

Compared to individuals without low mood, those having low mood at baseline were at higher risk of developing dementia in both cohorts. Yet, the risk only existed in those who did not have a partner or lived alone, but not among those who had a partner or lived with someone (interaction effect with marital status: P=0.01 (KP) and P=0.07 (SNAC-K), and living situation: P=0.02 (KP) and P=0.06 (SNAC-K)), adjusting for age, sex, and education. There were no significant interactions between the two cohorts (P≥0.5), therefore the study samples were merged together to increase the power (n=2599, **Figure 8**). In the fully adjusted models, the associations remained in the total sample i.e., low mood increased the risk of dementia (HR 1.2, 95% CI 1.0-1.4, P=0.058) among those who did not have a partner or lived alone, but not among those who were married or lived with someone (**Figure 8**) (interaction effect with marital status: P=0.007, and living situation: P=0.007). When marital status and living situation were simultaneously taken into account, low mood was associated with an increased risk of dementia only in those who did not have a partner (irrespective of living situation) or who had a partner but lived alone (HR 1.4, 95% CI 1.1-1.8, P=<0.01), but not in those who had a partner and lived with someone (HR 0.7, 95% CI 0.4-1.1, P=0.10) (interaction effect, P=<0.009). Additional analyses were performed for individuals with available data on the APOE gene, global leisure activities, and frequency/satisfaction of contacts with friends, relatives, or children. All of the results remained the same or only slightly attenuated.

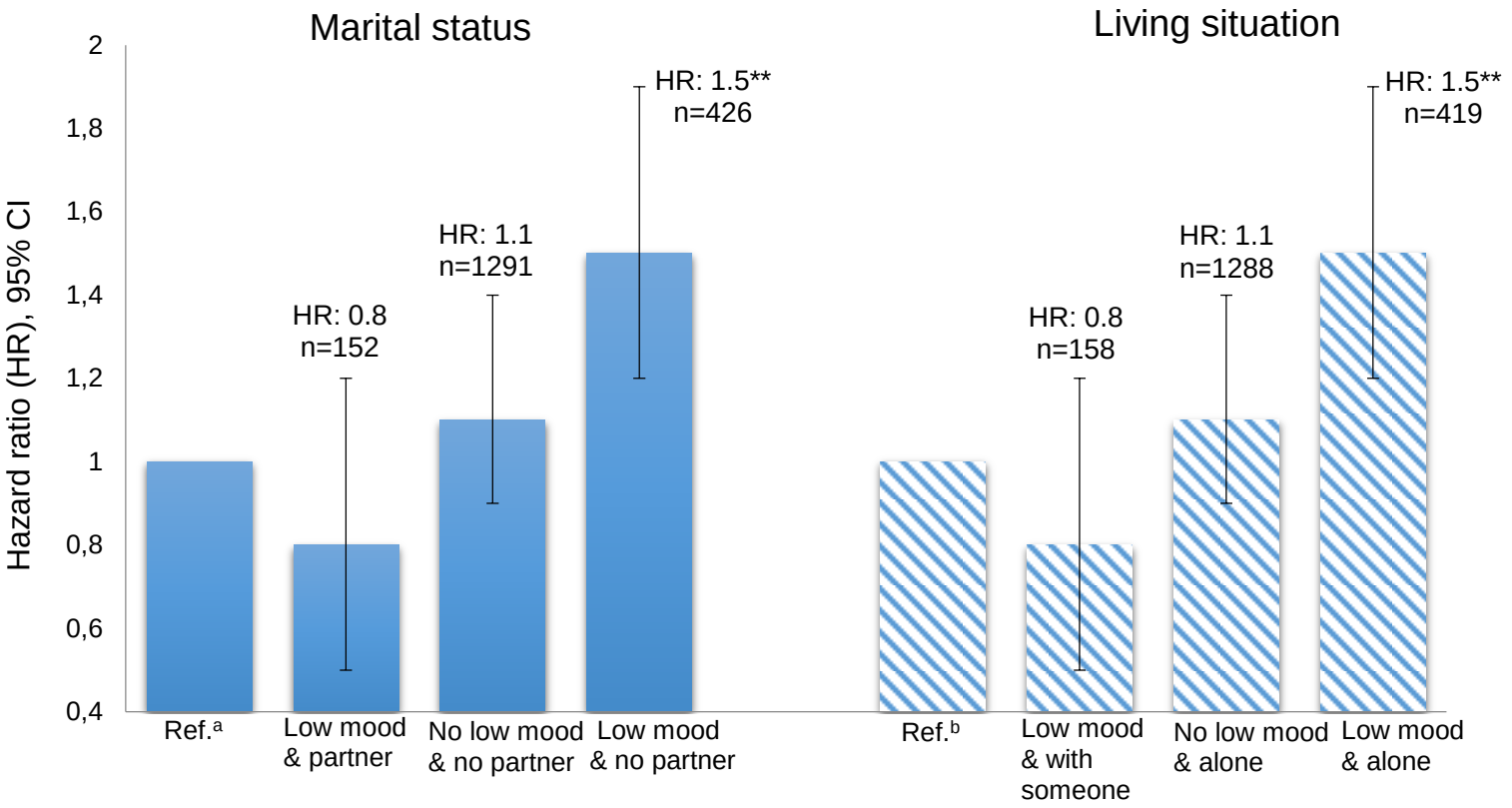


**Figure 8.** Multi-adjusted hazard ratios (HR) with 95% confidence intervals (CI) for the association between low mood at baseline and risk of dementia over nine years in both cohorts combined (KP and SNAC-K, N=2599) by marital status and living situation.
Adjusted for age, sex, education, ADL-dependency, multimorbidity, and MMSE. Reference groups: [a] No low mood and having a partner; [b] No low mood and living with someone. ** P-value <0.01.

## 4.4 STUDY IV

### Negative life events across the life-course and risk of depression in later life

Across the entire life span, the risk of developing any depression increased by 20% for every additional occurrence of a negative life event (OR 1.2, 95% CI 1.1-1.3). However, when exploring age of the occurrence, only the number of early-life (OR 1.5, 95% CI 1.2-1.9) negative events was associated with an increased risk of depression, but not those occurring in early-adulthood (OR 1.1, 95% CI 0.9-1.3), middle-adulthood (OR 1.1, 95% CI 0.9-1.3), or late-life (OR 1.2, 95% CI 1.0-1.5, P=0.1) (multi-adjusted models).

To further explore the association with depression risk, negative life events were also used in a categorical manner. Across the entire life span, the occurrence of eight or more negative life events (≥ 90$^{th}$ percentile) was associated with an increased risk for any (minor and major) or minor depression only in the fully adjusted models (**Figure 9**). The numbers for major depression only are not presented in the figure since only four persons experienced six to seven events, and two experienced eight or more events.

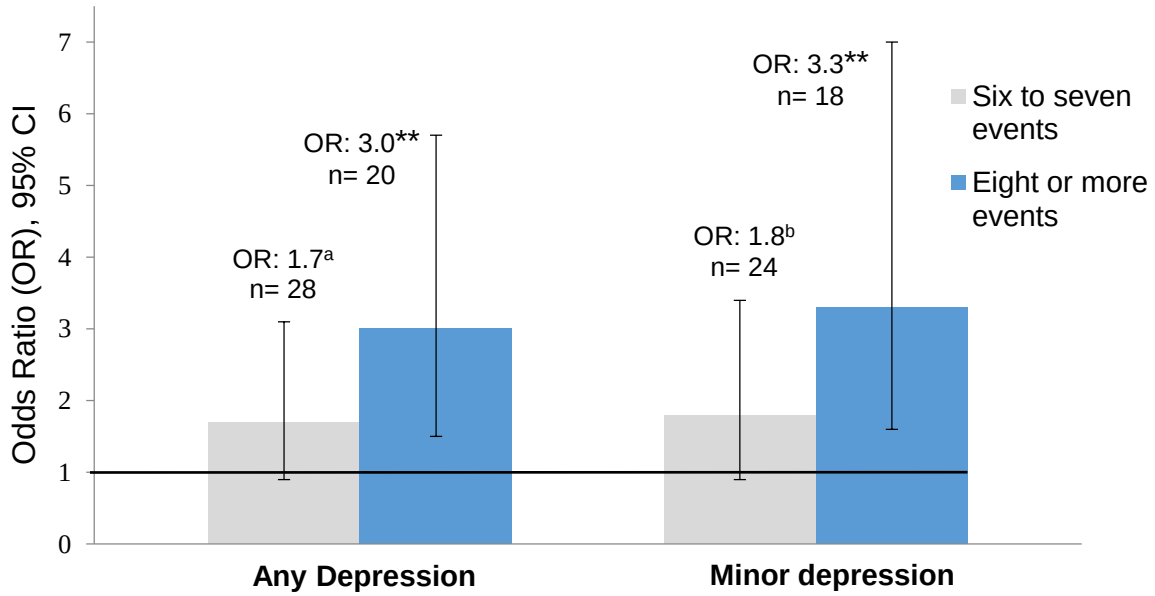


**Figure 9**. Multi-adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for the association between the total number of negative life events across the entire life span and risk of depression over six years by any or minor depression, N=1782. The negative life events were categorized as: ≤ 50$^{th}$ percentile = zero to five events (reference group, OR= 1); > 50$^{th}$ percentile and < 90$^{th}$ percentile = six to seven events; and ≥ 90$^{th}$ percentile = eight or more events. [a] P-value = 0.07; [b] P-value = 0.08; ** P-value <0.01. Adjusted for age, sex, education, follow-up time, multimorbidity, social support, contacts with children/relatives/friends, cognitive function, alcohol consumption, neuroticism, and extraversion.

When further examining the events throughout the life-course, the analyses showed that the experience of two or more negative events ($\geq 90^{th}$ percentile) in early-life (0–18 years, OR 2.4, 95% CI 1.2-5.0) or late-life (>65 years, OR 2.1, 95% CI 1.1-4.4) were associated with an increased risk of any depression. However, this was not the case for early-adulthood (19–40 years, $\geq 90^{th}$ percentile = three or more events, OR 1.4, 95% CI 0.7-2.7) or middle-adulthood events (41–65 years, $\geq 90^{th}$ percentile = five or more events, OR 1.3, 95% CI 0.6-3.1). Further analyses by type of depression revealed that these associations were maintained for minor but not for major depression. In addition, the experience of one event in early-life ($>50^{th}$ percentile, OR 2.0, 95% CI 1.0-3.7) was also associated with an increased risk for minor depression (multi-adjusted models). In the two additional analyses where different categorizations for negative life events were applied (1. $\leq$ first tertile (reference group), second tertile, and $\geq$ third tertile; 2. no events (reference group), one event, and two or more events), all of the results remained, i.e., the highest tertile and the experience of two or more events in early- or late-life were associated with an increased risk of any or minor depression, but not those occurring in early- or middle-adulthood (multi-adjusted models).

# 5 DISCUSSION

This thesis included four individual studies where we examined: 1) to what extent different definitions of depression and sub-samples of the study population influenced depression prevalence in old age; 2) whether quantitative and qualitative aspects of social relations influenced depression risk in two cohorts of older adults of different generations; 3) whether having a partner and living with someone could work as a buffer when having low mood, and thus delay the onset of dementia in two cohorts of older adults of different generations; and 4) whether the experience of negative life events (across the entire life span, and in early-life, early- or middle-adulthood, or late-life) influenced depression risk in old age.

Overall, the main findings of these studies are summarized below:

1) The prevalence of any depression ranged between 4.2% to 9.3% according to the diagnostic criteria (DSM-IV-TR and ICD-10); 9.2% to 10.6% for the rating scales (MADRS and GDS-15); and was 9.1% for self-reported depression. Moreover, having dementia, being physically dependent, or not having a partner were related to greater depression prevalence, across the majority of the depression definitions.

2) Feelings of loneliness were related to higher depression risk in both of the cohorts from Gothenburg. However, infrequent visits with others than children or neighbors (once per month or less), and the perception of having too little contact with others, were only related to an increased depression risk in 75-year-olds examined in the 1970s, but not in those examined in the 2000s.

3) Those having low mood at baseline were at an increased risk of dementia in both cohorts combined from Stockholm, as compared to those without low mood. However, the higher dementia risk was detected only in those who did not have a partner, or lived alone, but not among those who had a partner or lived with someone.

4) Across the entire life span, the total number of negative life events was associated with an increased risk of any depression. When further examining the events throughout the life-course, the analyses showed that the experience of negative events in early- (0–18 years) or late-life (>65 years) were associated with an increased risk of any depression, but not those occurring in early- (19–40 years) or middle-adulthood (41–65 years).

### Prevalence of depression: Comparisons of different depression definitions and sub-samples of older adults

In an urban population of older adults aged 60–104 years, the prevalence of any depression (independent of depression severity) was similar across all depression definitions (9.1–10.6%) apart from ICD-10, showing much lower figures (4.2%). These results were anticipated since more symptoms are needed to fulfill the criteria for a mild depression by

ICD-10 (at least four symptoms), as compared to a minor depression according to DSM-IV-TR (at least two symptoms). Nevertheless, when comparing more severe forms of depression, the prevalence was similar across ICD-10 and DSM-IV-TR criteria (moderate/severe by ICD-10: 1.6%, and major by DSM-IV-TR/DSM-5: 2.1%).

Our prevalence of moderate/severe (ICD-10) and major depression (DSM-IV-TR/DSM-5) are in line with two prior epidemiological studies on older adults (57, 166). Yet, our prevalence was lower as compared to the majority of earlier studies (14, 24, 167, 168). In addition, when exploring milder forms of depression, the prevalence found in our study (ICD-10: 2.7% and DSM-IV-TR: 7.1%), was similar to two population studies (168, 169), but lower than those reported in most other studies (170, 171). When further exploring differences in characteristics between our study population and those that reported higher depression prevalence, we found that some had poorer education levels and/or cognitive functioning, when compared to our population (73, 168, 170). Since both lower educational levels and cognitive function have been related to depression in older adults (15), this may explain our lower depression prevalence. Moreover, our population consists of urban individuals that may have had greater access to health-care and depression treatment, which subsequently could result in lower depression prevalence.

When examining depression prevalence according to the rating scales (MADRS and GDS-15), our depression prevalence (MADRS: 10.6% and GDS-15: 9.2%) was similar to those reported in other population studies (172, 173), even though one study reported higher prevalence (24). However, it is challenging to compare depression prevalence across studies since there are discrepancies in the rating scales and cut-offs that have been used.

Overall, the prevalence of depression was lower when excluding persons having dementia or living in institutions, as compared to the total population (where they were included). These findings have been supported by other studies (58, 174, 175). However, most previous population studies have not included individuals with dementia or cognitive impairment. Moreover, if included, separate figures for those with and without dementia were not reported. Similar findings have been found for living place since few studies simultaneously reported depression prevalence in those living in institutions and the community. Taken together, when exploring depression prevalence, our results highlight the importance of taking both living place and cognitive status into account, to accurately represent and provide a comprehensive picture of the general population of older adults. Considering the global increase of older individuals (11), it is important to further examine and detect potential modifying mechanisms and effective prevention programs in those having dementia or living in institutions.

We found that not having a partner or having dependency in physical functioning were related to depression across the majority of the depression definitions. These results have similarly been found in previous studies (12, 15). Several studies have also demonstrated the importance of social support in relation to depression (37). Thus, our relationship between marital status and depression can partially be explained by the social support that a marriage

can provide. Moreover, older adults are more likely to be worried about their capacity to be physically autonomous, than physical diseases per se, and physical functioning is important for older individuals' perception of quality of life (122).

### Secular changes in the relation between social factors and depression

In two cohorts of 70-year olds, born 30 years apart and followed for five years, we found that low frequency of social contacts, and the perception of having too little contact with others than children or neighbors, were related to an increased risk of depression in the earlier (examined in 1971–72) but not in the later-born cohort (examined in 2000–01). These findings are in line with previous studies on earlier-born cohorts of older adults that were examined in 1993–94 (59, 176). Moreover, our results showing that social contacts may be of less importance in relation to depression in later-born cohorts of older individuals, are consistent with a cross-sectional study that found no association between subjective social contacts and depressive symptoms in older adults examined in 2005–06 (65–85 years) (177). In line with this, a five-year follow-up study that examined adults aged 50–68 years in 2002–06, also found that social support did not predict changes in depressive symptoms (79).

The birth cohort differences in social contacts and depression, found in our study, may be due to various societal changes that occurred during the 20$^{th}$ century. First, the rapid pace of technological advancement (e.g. development and progress of radio broadcasting, television, cell-phones, and internet) has altered entertainment modalities, and the way in which individuals socialize and communicate. This has generated a society where entertainment and social contacts, to a greater extent, can be accessed via mass media (178). These changes have shaped socio-technological relationships that may be able to compensate for the lower frequency of social interactions in later-born cohorts of older adults. We have previously proposed that later-born cohorts of older adults have greater cognitive and physiological reserve (179, 180). The findings of our study also indicate that later-born cohorts have access to a greater social reserve due to technological expansions. Second, later-born cohorts of older adults have to a larger extent been affected by the "second modernization", characterized by an amplification of the individualization progress, where traits such as independence, autonomy, and self-fulfillment are prominent (181-184). Thus, lower frequency of social interactions may be seen as more acceptable for later than earlier-born cohorts of older adults. Hence, it is possible that such shifts in principles and values have influenced the impact of social contacts on depression risk. Third, later-born cohorts of older adults have lived in societies with greater economic advancement, employment security, and access to higher education (182, 185), which have all contributed to higher socio-economic status (SES). Previous studies have found that psychosocial resources have greater impact on depression in individuals with lower SES (186). Taken together, the lack of an association between social contacts and depression in the later-born cohort of older adults may be due to their higher SES.

Overall, in the earlier-born cohort, contact with others was associated with an increased risk of depression, while contacts with children or neighbors were not. These results are in line with various cross-sectional studies, showing that the support from friends were more important than support from children or family-members in relation to depressive symptoms (177, 187, 188). In general, social contacts with others than neighbors or children are voluntary (181, 189-191), in contrast to family relations, which are more likely to be built on responsibilities and normative principles (192).

### Low mood and risk of dementia: The role of marital status and living situation

In two cohorts of urban older adults >70 years of age, but born and examined 15 years apart (1987–89 to 1997–98 versus 2001–04 to 2010–13), we found an increased risk of dementia over nine years among those who had low mood at baseline, but not in those without low mood. However, the increased risk existed only in those who did not have a partner or lived alone, but not among those who were married or lived with someone.

Our findings of a positive relationship between low mood and an increased dementia risk, are similar to the majority of earlier population studies, which found an association between depressive symptoms and a higher risk of dementia (193, 194) (median follow-up time: 5 years, ranging from 2 to 17), but in contrast to some studies (195, 196) (follow-ups: 2 and 4 years). In general, none of the aforementioned studies explored the association between low mood only and risk of dementia. Low mood may be more beneficial to examine in relation to dementia since some depressive symptoms coincide with those included in a diagnosis of dementia (e.g. weakened ability to think or concentrate), and some may be a consequence of the dementia process (e.g. alterations in sleep patterns or psychomotor agitation/retardation).

Among individuals having low mood, we found that the increased risk of dementia only existed in those who were without a partner or lived alone, but not in those who had a partner or lived with someone. These findings are not surprising since we have previously found that those who were single and lived alone had an increased risk of dementia over a three-year follow-up period, as compared to those who were married and lived with someone (197). Moreover, the majority of earlier studies also found never- or non-married individuals to be at an increased risk of developing dementia (198-201) (follow-ups ranging from 3.5 up to 21 years). Furthermore, when marital status and living situation were simultaneously taken into account, we found that those who had a partner but lived alone or who did not have a partner (regardless of living situation) were at a higher risk of developing dementia, but not those who were married and lived with someone. The fact that our results did not change when additionally adjusting for contacts with children, relatives, or friends, and participation in mental, physical, or social activities provides further robustness to our findings.

In general, having a partner or living with someone can provide both mental and social stimulation, and encourage engagement in healthy activities (61, 62), which may increase the cognitive reserve capacity. Individuals with greater cognitive reserve may have more effective and flexible brain networks, and thus cope better with depressive symptoms (e.g.

low mood), and brain pathology or damage, which subsequently could postpone the onset of dementia (202, 203). Moreover, those having a partner may have greater levels of psychosocial support (e.g. emotionally, practically, and economically) (62), which is very important when suffering from low mood. Thus, this may partly explain why those not having a partner (regardless of living situation), were at an increased risk of dementia when experiencing low mood. Moreover, it is possible that those who did have a partner, but lived alone, had their partner living in an institution or hospital, which may result in greater psychological stress and burden, which subsequently can contribute to a higher risk of developing dementia.

### Negative life events across the life-course and risk of depression in later life

In urban older adults aged 60–99 years, we found that the total number of negative life events across the entire life span was related to an increased depression risk in older adults over six years of follow-up. However, when exploring timing of the events, we found that the experience of two or more negative events ($\geq 90^{th}$ percentile) in early-life (0–18 years) or late-life (>65 years) were associated with an increased risk of depression, but not those occurring in early-adulthood (19–40 years) or middle-adulthood (41–65 years).

Our findings that the total number of negative life events across the entire life span was linked to an increased depression risk are similar to prior population-based studies (204-206). Yet, all of these studies were of cross-sectional design, and either assessed depression in adolescent or middle-aged adults (204), only assessed depressive symptoms (205, 206), or did not state the age of when the life events occurred (206). In our study, the positive relationship between the total number of negative life events and greater risk of depression, is in line with the "cumulative damage hypothesis" (207). This hypothesis proposes that the accumulation of negative events may disrupt the physiological systems dealing with stress (e.g. the hypothalamic-pituitary-adrenal (HPA)- axis), and thus further increase the risk of mental disorders (123, 207).

We also found that the occurrence of two or more negative events ($\geq 90^{th}$ percentile) in the earlier or later stages of life were related to an increased risk of depression, but not those occurring in early- or middle-adulthood. These findings are similar to previous studies that found childhood adverse events to be linked with higher depression risk in both younger (mean age: 42 years) (204) and older samples (mean age: 60 or 70 years) (208, 209), and those reporting an association between late-life negative events and an increased risk of depressive symptoms (mean age: 60 or 72 years) (208, 210). Nevertheless, only one other study explored negative life events across the entire life span (and specified the age of occurrence) in relation to depression in older age (205). Moreover, they found that the total number of events occurring in adulthood (16 to 49 years), but not childhood, was related to depressive symptoms in older adults aged 65 to 94 years, which was in contrast to our findings. However, this study was cross-sectional with a reply rate of 28% and only assessed

depressive symptoms (205). Thus, more studies are needed to further explore and confirm these results.

Overall, our findings highlight the importance of the timing of negative events in the development of depression (i.e. only early- and late-life events were related to depression), which suggests there are critical or sensitive time periods when the brain is particularly vulnerable to negative stressors. This is in line with research that found that the early and later stages of life to be especially susceptible to stress due to the major alterations in the brain during these periods (i.e. developmental phases in early-life and deterioration in later-life) (124). Moreover, this is further supported by our previous findings that the exposure of two or more early-life negative events worsened the age-related reduction in the hippocampal and amygdala volumes, and that the experience of late-life negative events was associated with a larger amygdala volume in older adults (96). However, more longitudinal studies, assessing negative life events across the entire life span, are needed to further explore and confirm whether the accumulation and timing of negative events are related to an increased risk of depression in older adults.

## 5.1 METHODOLOGICAL CONSIDERATIONS

### 5.1.1 Study design

This thesis is based on four population-based observational studies of cross-sectional (study II) and longitudinal (study I, III, IV) study designs. In the cross-sectional study, the exposures (socio-demographics and health-related factors) and outcomes (different depression definitions) were measured simultaneously at the same point of time (at baseline). Thus, in study II, temporality of the associations between the exposures and outcomes could not be verified. In the longitudinal studies, the exposures were measured at the baseline assessments (study I: social factors; study III: low mood; and study IV: negative life events) and the outcomes (study I and IV: depression; and study III: dementia) were assessed at a later point in time, during the follow-up examinations. Thus, in study I, III, and IV, a temporal relationship between the exposures and the outcomes could be established.

### 5.1.2 Internal validity

Overall, when conducting this type of research there are typically two major sources of errors: 1) **systematic error** related to the design and the conduct of a study, which typically includes selection bias, information bias, and confounding, and 2) **random error** or lack of precision that are often related to population sampling variability or mismeasurement (211, 212). Overall, it is important to be aware, to consider, and to try to reduce these errors as much as possible when conducting research. An overview of systematic and random errors, and a discussion on their impact and relation to the studies included in this thesis are presented below.

*Systematic errors*

**1) Selection bias**

Selection bias can occur when there is a systematic error of the recruitment of participants into a study and/or in the possibility to retain them in the study. This can be the result of procedures related to the selection of subjects, as well as factors related to study participation (self-selection), which in turn will influence the magnitude of the study results since they are conditioned on participation. In detail, if the association between the exposure and outcome of interests differs between those who did participate in the study and those who did not participate (or were theoretically eligible to participate), this will lead to distortion of the results. Overall, in all of the three populations (H-70, SNAC-K, and KP), the study subjects were systematically and randomly selected from the general population of older adults living in Gothenburg (H-70) and Kungsholmen in Stockholm (SNAC-K and KP), which has helped to minimize selection bias related to recruitment or selection of the participants. However, it is known that those agreeing to participate in population-based studies tend to be healthier (both physically and mentally) than those who decline, which can be referred to as the healthy respondent effect or self-selection bias (213). As an example, previous studies have found that older individuals having depression or psychiatric disorders are more likely to decline participation in population-based studies (213). Moreover, when conducting research on older individuals, it is important to be aware of survival selection, which refers to the idea that survivors into old age may be more "robust" than those who die, which subsequently can affect the observed associations (214).

Overall, in the H-70 study, the response rate was 85.2% (68/460) in the 1901–02 cohort, and 65.8% (259/758) in the 1930 cohort at baseline. In contrast to the healthy respondent effect, participants and non-participants were similar regarding three-year mortality according to the Swedish Population Register, previous outpatient and inpatient psychiatric care (cohort 1901–02) (215, 216), or previous inpatient psychiatric care during the past two years according to the Swedish Hospital Discharge Register (cohort 1930) (217), and sex in both of the cohorts. However, marital status was similar between participants and non-participants in cohort 1901–02, but non-participants in cohort 1930 were less likely to be married (217). In KP, at baseline the response rate was 85.5% (308/2118), and the non-participants and participants were similar regarding most demographic characteristics (218). Finally, in SNAC-K, the baseline response rate was 73.3% (1227/4590). In line with the healthy respondent effect, the non-participants aged 60–87 years, had a shorter time to death after the beginning of the study, as compared to the participants. However, no differences between participants and non-participants were found related to age or sex (219).

In the cross-sectional analyses of study II, there were individuals who had missing data at baseline (ICD-10 depression diagnosis (n=170); DSM-IV-TR/DSM-5 diagnosis (n=148); any of the MADRS (n=284) or GDS-15 (n=1226) items; self-reported depression (n=119); education (n=32); and use of antidepressants (n=5)). Overall, the persons with missing data

on any of the depression definitions were more often older, without a partner, had lower education, global cognition (MMSE), or ADL-dependencies, than those with complete data. Thus, the data were not missing completely at random (MCAR). To avoid selection bias due to drop-out, multiple imputations were performed using an automatic statistical imputation monotone method, which has been proposed when dealing with data not missing at random. After the imputation, our depression prevalence was closer to those reported in previous studies, as compared to the observed figures, supporting our decision for imputing data. Moreover, since the SNAC-K population has an oversampling of the youngest old (60–66 years) and oldest old (90+), age-standardized prevalence of depression was calculated using censored data representative of the district of Kungsholmen, Stockholm from year 2001 to 2003. The age-standardized prevalence of depression was slightly increased, as compared to the unstandardized prevalence across all depression definitions.

In the longitudinal analyses (study I, III, and IV), additional selection bias may have arisen from missing data due to attrition (death) and non-response (drop-outs) during the follow-up periods. As aforementioned, the baseline drop-out rates were fairly low across all of the four studies (ranging between 14.5 to 34%). In study I, during the follow-up period of 5 years, the attrition rates were 12% in cohort 1901–02 (38/317), and 3.3% in cohort 1930 (14/422), and the drop-out rates were 9.3% for cohort 1901–02 (26/279), and 21.1% in cohort 1930 (86/408). The baseline characteristics of the non-participants (n=64 in cohort 1901–02, and n=100 in cohort 1930) and the participants (n=245 in cohort 1901–02, and n=310 in cohort 1930) at five-year follow-up were similar regarding marital status, number of chronic diseases, basic ADL-dependencies, daily personal or phone contact with others, participation in hobby activities, and the perception of having too little contacts with children or others. However, in the 1930 cohort, the non-participants had lower education, more often felt lonely, and that they had too little contact with their neighbors, as compared to the participants, while in the 1901–02 cohort no differences in these characteristics were found between the non-participants and participants. In study III, during the nine-year follow-up, no individuals were lost due to attrition since we had the possibility to ascertain dementia diagnoses among those who died through clinical charts. However, the drop-out rates were 12.5% for KP (171/1368) and 10.7% for SNAC-K (168/1570). The baseline characteristics between the drop-outs (KP, n=171 and SNAC-K, n=168) and the participants (KP, n=1197 and SNAC-K, n=1402) were similar regarding sex, education, global cognition (MMSE), and low mood. However, in KP the drop-outs were younger, and had less dependency in the ADLs, while in SNAC-K there were no differences in age or ADL-dependency between the drop-outs and participants. In study IV, during the six-year follow-up, the attrition rate was 9.8% (216/2208), and the drop-out rate was 10.5% (210/1992). At baseline, non-participants (n=426) were more often older, men, and had multimorbidity, lower education, lower scores on MMSE or extraversion, low social support, and were more likely to not consume alcohol, as compared to the participants (n=1782). However, no differences were found between non-participants and participants regarding the occurrence of negative life events, marital status, and neuroticism.

Taken together, since the non-participants were more often in a disadvantaged situation than the participants (except in the longitudinal analyses for KP in study III), the potential selection bias that may have occurred at baseline and during the follow-up periods may, if anything, have resulted in an underestimation of the associations between the exposures and outcomes across the four studies.

### 2) Information bias

Information bias can result from different types of measurement errors when collecting information about the subjects included in the study. When categorizing data/variables, there is a risk that subjects are inaccurately categorized, thus leading to misclassification. Overall, misclassification can be categorized as: 1) **non-differential**, or 2) **differential** (211, 212).

- **Non-differential misclassification** occurs when the study subjects' have the same probability to be misclassified, independent of the other variables included in the study (i.e. exposure, outcome, covariates). For example, the misclassification of an exposure variable does not depend on a study subject's status related to the other covariates or outcome and vice versa, i.e., the misclassification of an outcome does not depend on the subject's status on the other covariates or the exposure. Non-differential misclassification is more likely to lead to weakening of a true association (toward the null-hypothesis).

- **Differential misclassification** occurs when the study subjects' probability to be misclassified differs depending on the other variables included in the study. For example, the misclassification of an exposure variable depends on the study subject's status of the other covariates or outcome, and vice versa (misclassification of an outcome variable depends on the subject's status on the other covariates or the exposure variables). Differential misclassification can lead to both weakening of a true association or strengthening of a false association.

In this thesis, all of the exposures (except for in study II) were ascertained before the outcome, thus reducing the risk for differential misclassification of the exposures (e.g. recall bias). However, non-differential misclassification may have occurred, e.g., most of the exposures used in this thesis were assessed by self-report, which may have led to respondent bias. Nevertheless, the nurses, physicians, and psychologists who collected the data underwent training prior to the data-collection, and different individuals detected the exposures (by nurse interviews or self-reported questionnaires), and outcomes (assessed through medical examinations or psychological batteries). In addition, standardized study protocols and procedures were used, and the turnover rate of the data-collection personnel was low across all of the studies, thus reducing the risk of interviewer bias. Overall, the outcomes (depression and dementia diagnoses) were assessed using semi-structured psychiatric protocols, conducted by experienced physicians. Moreover, established diagnostic criteria were used to diagnose depression and dementia by physicians who were external to

the data-collection (except for the first step of diagnosing dementia in study III), thus minimizing the risk of systematic errors (e.g. observer bias). Overall, if a participant was unable to respond, e.g. due to cognitive impairment, a proxy (next-of-kin) was asked instead. This may have led to inaccurate information; however the use of a proxy (or different sources of information) also helped to reduce systematic errors.

### 3) Confounding

A confounder is a third variable that is associated with the exposure and is a risk factor for the outcome. However it should not be on the casual pathway between the exposure and outcome (i.e. a mediator) (212). If a confounder is not taken into account, it may lead to under- or overestimations of the association between the exposure and outcome, thus producing misleading results. As in all epidemiological studies, one can never exclude the possibility of unknown or unmeasured confounding. However, in this thesis, the major potential confounders (e.g. socio-demographics, psychosocial, behavioral, and other health-related factors) were considered and adjusted for in all of the four studies.

#### *Reversed causality*

Reverse causation can be defined as the outcome preceding and causing the exposure instead of the other way around, i.e., the exposure causing the outcome (211, 212). Since neuropathological changes can occur 20–30 years before the clinical onset of dementia (220), it is important to consider this potential temporal bias when studying dementia. Thus, in study III, the positive association between low mood at baseline and incident dementia over nine years, may be influenced by reverse causation. To address this, we conducted sensitivity analyses by excluding those with dementia at the first-follow up examinations. Interestingly, these analyses revealed that the magnitude of the associations between low mood and dementia became stronger in both cohorts combined and separately.

#### *Random errors*

Random errors or lack of precision can be defined as errors that are left after systematic errors have been taken into account. These errors are often related to sampling variability of the population or mismeasurement, and are hard to predict (212). Random errors due to sampling variability can be reduced (or precision can be increased) by increasing the sample size. Moreover, confidence intervals can be used as a tool to estimate the degree of precision since narrower confidence intervals can reflect higher precision (less random error) and vice versa. Thus, in study II, III, and IV, the fairly large sample sizes ($n \geq 1100$) and the narrow confidence intervals of the analyses, mirrors less random errors due to sampling variability in these studies. However, in study I, the sample size was smaller (n=245, cohort 1901–02, and n=310, cohort 1930) and some of the confidence intervals were wider, as compared to the other studies included in this thesis. Moreover, when stratifying the results by marital status (study III), or type of depression (study I, II, and IV), some of the subgroups became fairly small. Thus, we cannot exclude the possibility of errors due to sampling variability, which

may have led to some false negative results in the stratified analyses. Random errors due to mismeasurement are the result of random variability in the assessment of the exposure, outcome, or covariates included in the study. Mismeasurement can be increased by averaging multiple measurements of the same variables. However, the variables included in this thesis were only measured once at baseline and during the follow-ups. Yet, across all of the four studies, the use of standardized questionnaires as well as experienced nurses and physicians to conduct the examinations, reduced the risk of random errors when collecting the data.

### 5.1.3 External validity

External validity (or generalizability) refers to what extent unbiased inferences from a study can be generalized to other populations, beyond the study population. Thus, two key components of external validity are internal validity, and representativeness, i.e., the study population should be representative of the target population. Yet, no study can be entirely representative of all other populations since every population has unique characteristics (212).

The H-70 study is comprised of individuals living in different parts of Gothenburg, which is the second largest city in Sweden. Except for marital status in cohort 1930, there were no differences between the study and target population regarding mortality, inpatient psychiatric care, or sex in the two cohorts (see "selection bias" for detailed information) (217). However, individuals with dementia were excluded in study I. Moreover, a previous report stated that the results from the H-70 study only should be generalized to other urban populations, since population characteristics regarding education and socio-economics tend to differ between larger and smaller cities in Sweden (221, 222). Thus, caution should be taken when generalizing the results from study I to older adults living in rural areas, those having dementia, or living outside the Western societies.

The KP and SNAC-K studies are comprised of older individuals living in an urban area in Kungsholmen, Stockholm, which is the largest city in Sweden. Overall, older individuals living in this area have been found to have higher education and socio-economic status; and more likely to be retired after age 65, or unmarried or divorced, as compared to older adults living in other communities in Sweden (218, 223-225). Moreover, in SNAC-K, there may have been a healthy participation bias since the non-participants aged 60–87 years had a shorter time to death, as compared to the participants at baseline. Taken together, we can expect our study populations to have lower figures of depression and dementia than the national average. Overall, caution should be taken when generalizing the results from study II, III, and IV to older individuals living in rural areas, outside the Western society, and those having lower education or socio-economic status. However, this may, if anything, have led to an underestimation in the magnitude of the associations in study II–IV.

# 6 CONCLUSIONS

The main conclusions of the four individual studies included in this thesis are presented below.

1) In older adults aged 60–104 years, depression prevalence was similar independent of the depression definitions used, except for ICD-10, showing much lower prevalence. Moreover, the prevalence of any depression varies greatly by dementia status, physical functioning, and marital status. These findings can be useful for researchers when exploring and comparing depression prevalence across studies (study II).

2) In two cohorts of septuagenarians, quantitative and qualitative aspects of social contacts with others were related to depression in those examined in the 1970s, but not in those examined 30 years later. This may reflect societal- or period changes in the ways of socializing, communicating, and entertaining (study I).

3) In two cohorts of older adults above 70 years of age, marital status and living situation have the possibility to buffer the detrimental effects of low mood on dementia onset. Thus, specific attention from health care should target individuals having low mood and who do not have a partner or live alone (study III).

4) In older adults aged 60–99 years, there are critical time periods in early-life (0–18 years) and late-life (>65 years), when the experience of negative life events exacerbates depression risk in later life. Thus, specific attention from health care should target older adults who have been exposed to early- or late-life negative events (study IV).

# 7 RELEVANCE AND IMPLICATIONS

According to the WHO, around 322 million individuals are suffering from a unipolar depressive disorder globally, which makes depression one of the largest contributors to the total burden of disease and disability worldwide (9). More specifically, in older adults, depression is one of the most prevalent mental disorders, and a common cause of reduced life-satisfaction and functional impairment (12). Furthermore, the total health care costs are 47% to 51% higher in older adults having minor or major depression, compared to those not having depression (13). Despite depression being highly prevalent, impairing, and very costly for the society, the under-detection has been found to be large in older individuals (14-19). Moreover, with the increasing aging population (23), one of the most relevant health consequences of depression is dementia, which is projected to double worldwide every 20 years in older adults, reaching 132 million cases by 2050. Thus, better detection and understanding of depression and its consequences is highly valuable from clinical, economical, and public health perspectives. Taken together, the findings from this thesis is highly relevant in finding effective interventions to counteract depression or delay the onset of dementia in old age. Moreover, the theoretical life-course approach adds further value, since this perspective can help provide further information on the most crucial time periods when the implementation of public health strategies may be most useful (29, 30).

In line with this, the results from this thesis have several clinical implications. First, the findings of similar depression prevalence across different definitions of depression, except for ICD-10 showing much lower figures, can be useful for clinicians when assessing and detecting depression in older adults. Second, our findings of the long-term impact and consequences of early-life negative events (0–18 years) on depression later in life, suggests the importance of establishing preventive actions for children who have been exposed to adverse life events. Moreover, health care personnel may pay particular attention to older individuals who have been exposed to recent or several negative life events across the life span, or who feel lonely, since this may increase the risk of developing depression. Third, we found that the prevalence of depression was higher in older adults who have dementia, disabilities, or are without partner. In addition, marital status and living situation was also found to buffer the detrimental effects of low mood on dementia onset. Taken together, specific attention from health care should target individuals who have cognitive impairment or disabilities. Moreover, the importance of psychosocial factors in relation to depression risk and the postponement of dementia onset, emphasizes the importance of establishing preventive strategies aimed at increasing social interactions among older adults. Since older individuals are more prone to experience loneliness with increasing age, health care should also pay special attention to the very old.

# 8 FUTURE DIRECTIONS

In this doctoral thesis, a better comprehension of depression in old age was obtained by exploring to what extent depression prevalence differs by various depression definitions and sub-samples, and by identifying risk factors, secular changes, and consequences of depression in late adulthood from a life-course perspective. In conclusion, large-scale national population studies are needed to better understand whether depression prevalence and incidence further differ by various geographical- and socio-economical areas. Moreover, larger study samples are also advantageous when exploring the results in smaller sub-groups (e.g. by type of depression and marital status), due to reduced sampling variability (or an increase in statistical power). Furthermore, prospective longitudinal studies in which individuals are followed before birth and onwards would be beneficial to better understand depression risk from a life-course perspective, and detect the most efficient timing for prevention. Further research on possible factors that may modify the relationship between negative life events and depression is also warranted. Overall, giving the worldwide expansion in the number and proportion of older adults, the demand for depression- and dementia care is expected to increase. Thus, it is highly relevant to continue to explore and identify possible modifying mechanisms, and to implement effective prevention strategies for depression and dementia in older adults.

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# 11 APPENDIX

## Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991-2018

**1991**

**Herlitz Agneta.** Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

**1992**

**Borell Lena.** The activity life of persons with a dementia disease.

**1993**

**Fratiglioni Laura.** Epidemiology of Alzheimer´s disease. Issues of etiology and validity.

**Almkvist Ove.** Alzheimer´s disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

**Basun Hans.** Biological markers in Alzheimer´s disease. Diagnostic implications.

**1994**

**Grafström Margareta.** The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

**Holmén Karin.** Loneliness among elderly - Implications for those with cognitive impairment.

**Josephsson Staffan.** Everyday activities as meeting-places in dementia.

**Stigsdotter-Neely Anna.** Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

**Forsell Yvonne.** Depression and dementia in the elderly.

**1995**

**Mattiasson Anne-Cathrine.** Autonomy in nursing home settings.

**Grut Michaela.** Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

**1996**

**Wahlin Åke.** Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

**Wills Philippa.** Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

**Lipinska Terzis Beata.** Memory and knowledge in mild Alzheimer's disease.

**1997**

**Larsson Maria.** Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

**Almberg Britt.** Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

**1998**

**Agüero-Eklund Hedda.** Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

**Guo Zhenchao.** Blood pressure and dementia in the very old. An epidemiologic study.

**Björk Hassing Linda.** Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)
**Hillerås Pernilla.** Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

**1999**

**Almberg Britt.** Family caregivers caring for relatives with dementia – Pre- and post-death experiences.
**Robins Wahlin Tarja-Brita.** Cognitive functioning in late senescence. Influences of age and health.
**Zhu Li.** Cerebrovascular disease and dementia. A population-based study.

**2000**

**Hillerås Pernilla.** Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)
**von Strauss Eva.** Being old in our society: Health, functional status, and effects of research.

**2001**

**Jansson Wallis.** Family-based dementia care. Experiences from the perspective of spouses and adult children.
**Kabir Nahar Zarina.** The emerging elderly population in Bangladesh: Aspects of their health and social situation.
**Wang Hui-Xin.** The impact of lifestyles on the occurrence of dementia.

**2002**

**Fahlander Kjell.** Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.
**Giron Maria Stella.** The rational use of drugs in a population of very old persons.

**2003**

**Jönsson Linus.** Economic evaluation of treatments for Alzheimer's disease.

**2004**

**Berger Anna-Karin.** Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer´s disease.
**Cornelius Christel.** Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.
**Qiu Chengxuan.** The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.
**Palmer Katie.** Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.
**Larsson Kristina.** According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

**2005**

**Derwinger Anna.** Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.
**De Ronchi Diana.** Education and dementing disorders. The role of schooling in dementia and cognitive impairment.
**Passare Galina.** Drug use and side effects in the elderly. Findings from the Kungsholmen Project.
**Jones Sari.** Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.
**Karp Anita.** Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.
**Nilsson Jan.** Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

**2006**

**Klarin Inga.** Drug use in the elderly – are quantity and quality compatible.

**Nilsson Erik.** Diabetes and cognitive functioning: The role of age and comorbidity.

**Ngandu Tiia.** Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

**Jonsson Laukka Erika.** Cognitive functioning during the transition from normal aging to dementia.

**2007**

**Ferdous Tamanna.** Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

**Westerbotn Margareta.** Drug use among the very old living in ordinary households-Aspects on well-being, cognitive and functional ability.

**Rehnman Jenny.** The role of gender in face recognition. (Stockholm University)

**Nordberg Gunilla.** Formal and informal care in an urban and a rural population. Who? When? What?

**Beckman Gyllenstrand Anna.** Medication management and patient compliance in old age.

**2008**

**Gavazzeni Joachim.** Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

**Marengoni Alessandra.** Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

**Rovio Suvi.** The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

**Xu Weili.** Diabetes mellitus and the risk of dementia. A population-based study.

**Meinow Bettina.** Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)

**Agahi Neda.** Leisure in late life. Patterns of participation and relationship with health.

**Haider Syed Imran.** Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

**2009**

**Thilers Petra.** The association between steroid hormones and cognitive performance in adulthood.

**Masud Rana AKM.** The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

**Paillard-Borg Stéphanie.** Leisure activities at old age and their influence on dementia development.

**Livner Åsa.** Prospective and retrospective memory in normal and pathological aging.

**Atti Anna-Rita.** The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

**2010**

**Fors Stefan.** Blood on the tracks. Life-course perspectives on health inequalities in later life.

**Keller Lina.** Genetics in dementia. Impact in sequence variations for families and populations.

**2011**

**Schön Pär.** Gender matter. Differences and changes in disability and health among our oldest women and men.

**Caracciolo Barbara.** Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.

**Rieckmann Anna.** Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

**2012**

**Haasum Ylva.** Drug use in institutionalized and home-dwelling elderly persons.

**Mangialasche Francesca.** Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

**Lovén Johanna.** Mechanism of women's own-gender bias and sex differences in memory for faces.

**2013**

**Hooshmand Babak.** The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

**Rizzuto Debora.** Living longer than expected: protective and risk factors related to human longevity.

**2014**

**Sjölund Britt-Marie.** Physical functioning in old age: Temporal trends and geographical variation in Sweden.

**Wastesson Jonas.** Unequal drug treatment: age and educational differences among older adults.

**2015**

**Sköldunger Anders.** Dementia and use of drugs: Economic modelling and population-based studies.

**Craftman Åsa Gransjön.** Medicine management in municipal home care; delegating, administrating and receiving.

**Svärd Joakim.** Emotional facial processing in younger and older adults.

**Wang Rui.** Cardiovascular risk factors, brain structure, and cognitive decline in old age.

**Pantzar Alexandra.** Cognitive performance in old-age depression.

**2016**

**Kelfve Susanne.** Gotta survey somebody: methodological challenges in population surveys of older people.

**Heap Josephine.** Living conditions in old age: Coexisting disadvantages across life domains.

**Håkansson Krister.** The role of socio-emotional factors for cognitive health in later life.

**Shakersain Behnaz.** Impact of nutritional status and diet on cognitive decline and survival.

**Bellander Martin.** Plasticity of memory functioning: genetic predictors and brain changes.

**2017**

**Ferencz Beata.** Genetic and lifestyle influences on memory, brain structure, and dementia.

**Köhncke Ylva.** Lifestyle, cognitive aging, and brain correlates.

**Santoni Giola.** How well are we aging? Capturing the complexity of health trajectories of older adults.

**Becker Nina.** Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

**2018**

**Nilsen Charlotta.** Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.

**Darin-Mattsson Alexander.** Set for life? Socioeconomic conditions, occupational complexity, and later life health.

**Marseglia Anna.** The Impact of diabetes on cognitive aging and dementia.

**Heiland Emerald.** Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.