Depression among Swedish 70-year-olds

Sex differences from a gender perspective

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To my husband Jonathan, my family, and in loving
memory of my grandfather Hans-Åke and my
great-grandparents Gerd and John.
– for your everlasting love
and support.

"I miss my tears, really…
If I get extra happy, they usually appear; the happy tears… but now they never come. If I am very, very sad, no tears will come at all. I feel like… when I cry, everything becomes a bit easier for me."

Source: Quote from a study participant during data collection in focus group discussion no.1, answering the question "How would you describe your latest depressive episode to me?". Illustration made by author.

Abstract

Depression is one of the leading causes of global burden of disease. Due to increased life expectancy, late-life depression is an escalating public health issue. The prevalence is reported to be almost twice as high among women compared to men. Little is known about the role of gender expression (femininity, masculinity, or androgyny) in relation to depression epidemiology, and whether the prevalence of late-life depression may change over time. The overarching aim of this thesis was to study prevalence, time trends, and subjective experiences of depression among older adults, with specific focus towards potential differences by sex and gender expression.

All samples were derived from the population-based Gothenburg H70 Birth Cohort Studies. *Paper 1* describes the examination of 70-year-olds (born 1944) in 2014-16. As all papers are based on this examination, *Paper 1* generates an overall understanding of the data framework. *Paper 2* tests the validity and reliability of the Positive-Negative Sex-Role Inventory (PN-SRI), a measure of gender expression. The findings suggest that PN-SRI is applicable in a Swedish research setting among older adults due to a satisfactory level of internal consistency and face validity. *Paper 3* gives an overview of the prevalence of depression between the 1970s and the 2010s, placing it in a Swedish historical context. We found that depression decreased among women across the study period. *Paper 4* generates an opportunity to deeper understand the experiences of depression by enabling the participants to share their lived experiences in focus group discussions. The participants expressed unmet needs of communication, as well as a lack of trust regarding healthcare for depression. They also desired more knowledge about available treatments, potential side effects, and how to avoid recurrence. *Paper 5* examines sex and gender expression in relation to depression. Irrespective of biological sex, femininity was associated with a greater burden of depressive symptoms. The inverse was observed for androgyny and masculinity.

Perspectives of gender have an important place within mental health research, which is highlighted in this thesis. We found a decreasing time trend in the prevalence of late-life depression among women. The sex ratio in depression is complex, partly linked to gender-related factors such as gender expression. Older adults have expressed limited trust towards healthcare providers in seeking medical help for depression. Also, they have expressed a need for more communication and health knowledge about depression. **Key words**: Depression, time trend, epidemiology, sex, gender, experiences, older adults.

Sammanfattning på svenska

Depression är en av de ledande orsakerna till den globala sjukdomsbördan. Då den förväntade livslängden ökar i världen är depression hos den äldre befolkningen ett växande folkhälsoproblem. Förekomsten rapporteras vara ungefär dubbelt så hög hos kvinnor som hos män. Kunskapen om hur genusuttryck (femininitet, maskulinitet och androgynitet) är relaterat till depressionsepidemiologi är begränsad, även huruvida depressionsförekomst kan förändras över tid. Det övergripande syftet med denna avhandling var att studera förekomsten av depression hos en äldre befolkning, samt deras subjektiva erfarenheter av att ha haft depression. Specifikt fokus riktades mot könskvoten i depressionsförekomst, i relation till genusuttryck.

Materialet utgjordes av urval från den populationsbaserade H70-studien (the Gothenburg H70 Birth Cohort Studies). *Delarbete 1* beskriver 70-årsundersökningen 2014-16, för kohorten född 1944. Då samtliga delarbeten baseras på denna undersökning, genererar detta en övergripande förståelse för avhandlingens datamaterial och ramverk. I *Delarbete 2* testades validitet och reliabilitet av the Positive-Negative Sex-Role Inventory (PN-SRI), som är en mätskala för genusuttryck. Resultaten visade att PN-SRI kan vara lämplig att använda i forskning på äldre personer. *Delarbete 3* ger en historisk överblick av depressionsförekomsten från 1970-talet fram till 2010-talet. Förekomsten av depression hade minskat hos kvinnor under studieperioden. *Delarbete 4* gav möjligheten att ta del av studiedeltagarnas egna beskrivningar av att ha haft depression. Under fokusgruppsdiskussionerna framkom att de upplevt bristande kommunikation och en riktad misstro till hälso- och sjukvården gällande kunskap kring och behandling av depression. De önskade få mer kunskap om tillgängliga behandlingar, potentiella biverkningar, och hur man kunde undvika återfall efter att ha tillfrisknat. I *Delarbete 5* undersöktes kön och genusuttryck i förhållande till depression. Oavsett biologiskt kön var femininitet relaterat till högre depressiv symtombörda. Omvänt samband hittades för androgynitet och maskulinitet.

Avhandlingen belyser genusperspektivets viktiga roll för forskning inom psykisk ohälsa. Vi fann en minskande tidstrend gällande förekomsten av depression hos kvinnor. Könskvoten i depressionsförekomst är komplex och har samband med genus-relaterade faktorer, som exempelvis genusuttryck. Äldre personer har uttryckt låg tillit gentemot hälso- och sjukvården gällande hjälpsökande för depression. De har även uttryckt ett behov av ökad kommunikation och kunskap kring depression.

List of Papers

This doctoral thesis is based on the following five original papers:

Paper 1. Rydberg Sterner T & Ahlner F, et al. The Gothenburg H70 Birth Cohort Study 2014-16: design, methods and study population. European Journal of Epidemiology 2019:34(2): 191-209

Paper 2. Rydberg Sterner T, Gudmundsson P, Seidu N, Bäckman K, Skoog I, Falk H. A Psychometric Evaluation of a Swedish version of the Positive–Negative Sex-Role Inventory (PN-SRI) – Results from the H70-study. Societies 2018:8 (13)

Paper 3. Rydberg Sterner T, Gudmundsson P, Sigström R, Ahlner F, Seidu N, Zettergren A, Kern S, Östling S, Waern M, Skoog I. Depression and neuroticism decrease among women but not among men between 1976-2016 in Swedish septuagenarians. Acta Psychiatrica Scandinavica 2019:139(4): 381-394

Paper 4. Rydberg Sterner T, Dahlin-Ivanoff S, Gudmundsson P, Wiktorsson S, Hed S, Falk H, Skoog I, Waern M. "I wanted to talk about it, but I couldn't". A focus group study about experiencing late life depression - results from the H70 study (*submitted*)

Paper 5. Rydberg Sterner T, Gudmundsson P, Falk H, Seidu N, Ahlner F, Wetterberg H, Sigström R, Östling S, Zettergren A, Kern S, Waern M, Skoog I. Depression in relation to sex and gender expression among Swedish septuagenarians – results from the H70 study (*submitted*)

Paper 1, 2 and 3 are re-printed with the permission from the publisher:

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Abbreviations

ABC	Affective, biological and cognitive vulnerabilities
ACTH	Adrenocorticotropic hormone
APOE4	ε4 allele of apolipoprotein E
ATC	Anatomical Therapeutic Chemical classification system
BDNF	Brain-derived neurotrophic factor
BSRI	Bem Sex-Role Inventory
CFI	Comparative fit index
CI	Confidence interval (95 %)
CPRS	Comprehensive Psychopathological Rating Scale
CRH	Corticotropin-releasing hormone
CT	Computed tomography
DF	Degrees of freedom
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. revised
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th ed.
ELSA 85	Elderly in Linköping Screening Assessment
EPI	Eysenck Personality Inventory
FEM(+)	Feminine personality traits (socially desirable)
FEM(-)	Feminine personality traits (socially undesirable)
GDS	Geriatric Depression Scale
GLM	Generalized Linear Model
ICD	International Statistical Classification of Diseases and Related Health Problems
H70	The Gothenburg H70 Birth Cohort Studies
HPA axis	Hypothalamic–pituitary–adrenal axis
MADRS	Montgomery-Åsberg Depression Rating Scale
MAS(+)	Masculine personality traits (socially desirable)
MAS(-)	Masculine personality traits (socially undesirable)
MASK	Memory and Aging Study of Koreans
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
N	Sample size
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIMH	National Institute of Mental Health
OR	Odds Ratio
p	p-value

PAQ	Personal Attribute Questionnaire
PN-SRI	Positive-Negative Sex-Role Inventory
PPSW	Prospective Population study of Women in Gothenburg
RMSEA	Root-mean-square error of approximation
SD	Standard deviation
SHARE	Survey of Health, Ageing and Retirement in Europe
SF-36	The Short Form (36) Health Survey
SLC6A4	Serotonin transporter gene
SRMR	Standardized root-mean-square residual
WHO	World Health Organization
X^2	Chi-square
YLD	Years lived with disability
α	alpha
5-HTTLPR	The promotor region of the serotonin transporter gene
♥	Classification of socially desirable or undesirable attributes
☿	Classification of aspects of femininity and masculinity
♂	Men
♀	Women

Definitions in short

Depression	
Depression	Major depression was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), requiring at least 5 out of 9 pre-specified depressive symptom clusters occurring during the past month, of which at least one had to be depressed mood or diminished interest/pleasure. Minor depression required the presence of 2–4 symptoms according to DSM-IV-TR research criteria. For the purpose of this thesis, the term "any depression" was used to denote those fulfilling criteria for either major or minor depression.
Burden of symptoms	Depressive symptom burden was rated according to the Montgomery-Åsberg Depression Rating Scale (MADRS), including ten depressive symptoms. Individual items were rated from 0 (no symptoms) to 6 (severe symptoms), generating a score ranging 0-60.
Sex/Gender	
Sex	The biological distinction between men and women based on the information given by their Swedish personal identity number.
Gender	While sex include the biological distinction between men and women, gender adds to the behavioral, cultural or psychological attributes associated with one sex or the other.
Gender norms	Socially expected patterns of attributes and behaviors that are valued and considered acceptable for men and women within a given culture or social group.
Gender expression	How an individual expresses a sense of being masculine, feminine, neither, or both through behavioral attributes.
Femininity	Behavioral attributes traditionally associated with women
Masculinity	Behavioral attributes traditionally associated with men
Androgyny	Both feminine and masculine behavioral attributes are present without femininity or masculinity being dominant
Epidemiology	
Birth cohort	A group of a population that is born during the same time period (e.g. a certain year) irrespective of age at first examination.
Age effect	Variations linked to individual biological and social processes of aging, but not necessarily related to the time period or birth cohort to which an individual belongs.
Period effect	Variations caused by external factors affecting all age groups at a particular historical time, e.g. war, economic crisis. Period effects in data may also be the result of methodological changes in e.g. outcome classifications.
Cohort effect	Variations in health-related factors and outcomes resulting from the unique exposure of a cohort as they move across time, e.g. vaccination programs or educational systems.
Time trend	Include age, period and cohort effects which plays important roles in understanding time-varying elements in epidemiology.

1. Introduction

1.1 Definition of late-life depression

Focus for this thesis is late-life depression, which is mainly characterized by low mood and loss of interest. Depression is defined and diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. The diagnostic criteria and the differentiation between major depression, minor depression and burden of depressive symptoms are further described in the Method section (*4.3.3 Depression diagnosis; 4.3.4 Burden of depressive symptoms*) and in Appendix 1. Early onset depression is defined as having experienced the first depressive episode earlier in life (childhood, adolescence or adulthood), while late onset depression refers to having experienced the first depressive episode during late life, approximately after the age of 60.[1] It has been suggested that early onset and late onset depression may differ in terms of risk factors and symptom presentations. While early onset depression may have a stronger association with family history of depression[2] and neuroticism,[3] late onset depression may be more related to vascular risk factors, cognitive decline, and inflammation.[4,5] Still, late onset characteristics may also occur for depression among older persons having had prior episodes of depression earlier in life,[6] making the differentiation between early and late onset depression difficult. For the purpose of this thesis, "late-life depression" may therefore include both early onset and late onset depression, however experienced during later life. In the text, late-life depression, depression and depression among older adults will be used interchangeably.

1.1.1 Depressive symptoms

Symptoms included in the DSM diagnostic criteria for depression is shown in Table 1, which are described in detail in Appendix 1. In summary, the DSM-IV-TR research criteria for minor depression requires two to four symptoms, while the DSM-5 criteria for major depression requires at least five out of nine symptoms. For both minor and major depression, at least one of the core symptoms (depressed mood or diminished interest/pleasure), has to be present in order to fulfill the diagnostic criteria.

Table 1. Depressive symptoms included in the DSM [a] diagnostic criteria for major [b] and minor depression [c]

1. Depressed mood	**4**. Insomnia/ hypersomnia	**7**. Feelings of worthlessness or guilt
2. Diminished interest/pleasure	**5**. Psychomotor agitation/retardation	**8**. Diminished ability to think /concentrate or indecisiveness
3. Change in weight or appetite	**6**. Fatigue or loss of energy	**9**. Recurrent thoughts of death or suicidal ideation

[a] Diagnostic and Statistical Manual of Mental Disorders (DSM); [b] DSM-5; [c] DSM-IV-TR. In order for a depression diagnosis to occur, either '1. depressed mood' or '2. diminished interest/pleasure' needs to be present, together with a combination of symptom no. 3 to 9.

Late-life depression may display different symptom patterns compared to depression earlier in life.[1,7] Some report that feelings of worthlessness or guilt may be less prevalent in older age, while sleep disturbance, thoughts about death, concentration difficulties, and memory deficiency may be more prevalent.[1] Others have found that depressive symptoms tend to change from being mainly mood-related in younger ages to being more somatic with increasing age.[7] Studies regarding sex differences in symptom expression among older adults are scarce.[1,8,9] Some suggest that appetite disturbances is more common in older women (compared to men), while agitation is more common in older men (compared to women).[9] Others have found that suicidal ideation was more common among older men, while psychomotor disturbance was more common among older women.[8]

1.2 **Global burden of depression**

Globally, about 260 million people suffer from depressive disorders, and about 160 million people suffer from major depression.[10] Depression is one of the most common mental disorders in old age,[11] and is one of the leading causes of global burden of disease in both men and women.[12] This burden does not only have a negative effect on individual and population health, but also on global economy. Depression has been associated with higher direct costs for all age groups[13] (e.g. emergency treatment or medications) and indirect costs for adults[14] (e.g. lost productivity or premature death by suicide). During the past decade, depression has been ranked as the third-to-fifth most common cause for years lived with disability (YLD), see Table 2.

Table 2. Top 5 leading causes for Years Lived with Disability (YLD) 1990-2017

	Women			Men		
	1990	2007	2017	1990	2007	2017
1	Low back pain	Low back pain	Low back pain	Low back pain	Low back pain	Low back pain
2	Headache disorders	Headache disorders	Headache disorders	Headache disorders	Headache disorders	Headache disorders
3	Dietary iron deficiency	Depressive disorders	Depressive disorders	Dietary iron deficiency	Diabetes	Diabetes
4	Depressive disorders	Dietary iron deficiency	Dietary iron deficiency	Depressive disorders	Depressive disorders	Age-related hearing loss
5	Anxiety disorders	Anxiety disorders	Diabetes	Age-related hearing loss	Age-related hearing loss	Depressive disorders

Source: The Global Burden of Disease Study 2017,[15] modified by author.

The World Health Organization (WHO) have acknowledged that the social gradient in mental health is severely gendered.[16] Although incidence and prevalence estimates vary among studies,[17] a consistent finding is that the prevalence of depression is about twice as high among women compared to men.[18] As populations are ageing world-wide,[19] most of the projected gains in life expectancy will occur among those above age 65 years.[20] Thus, late-life depression is an escalating public health problem.

1.2.1 **Incidence and age of onset**

The mean age of onset for major depression has been reported to not differ between men and women (men: age range 15-83 with mean age 45; women: age range 15-89 with mean age 46).[21] However, the incidence rates for women is reported to be higher compared to men across the lifespan. For older adults, the incidence of late-life depression between age 70-85 has been shown to be 22.6 per 1 000 risk-years (11.9 per 1 000 risk-years in men; 29.9 per 1 000 risk-years in women).[22] Over time, incidence rates may change. Among 55-64 year young-old adults, the incidence rates have declined between the 90's and 00's, which is suggested to be caused by improvements of protective factors for depression in later born cohorts, such as educational level.[23]

1.2.2 **Point prevalence**

Among older populations (>65 years), the prevalence of depression is approximately 10 %,[11,24] including 1-5 % with major depression.[1,11] Approximately 1.5 % of older women, and 0.2 % of older men, have

experienced major depression within the past month.[25] Data from The Survey of Health, Ageing and Retirement in Europe (SHARE), has shown that the prevalence of depression, and its sex ratio, were lower in Northern Europe, compared to Southern Europe.[26] The global prevalence of major depression for combined ages and both sexes has been shown to increase.[27] However, age- and sex-specific projections are uncertain as the prevalence of depression may change over time[28] and vary by geographical area.[29,30] Birth cohort comparison of the point prevalence of depression in the Gothenburg H70 Birth Cohort Studies (the H70 studies) is shown in thesis *Paper 3*.

Time trends in depression prevalence

Several time trend studies examining incidence and prevalence of depression have included children and young adults,[31-35] late middle-aged adults,[36,37] mixed ages without age stratifications,[38-48] or mixed ages including stratification for older adults > 65 years.[28,49-60] Apart from *Paper 3* in this thesis, only a few have solely focused on time trends in depression prevalence for older adults > 65 years.[24,61,62] An increase in depression is suggested for younger,[32] and middle-aged[36] populations. Among older adults the prevalence of major depression has been found to be stable,[51] while milder forms of depression have been reported to increase,[61] decrease[28] or fluctuate[52] over time. Studies also show inconclusive time trend results.[56] When reporting (and comparing) results regarding time trends in depression prevalence, it is important to consider that results may vary due to differences in study contexts, e.g. number of measuring points, sample ages, study periods and geographical areas. In order to further understand time-varying elements in depression epidemiology, age, period and cohort effects may each play an important role.[63] An **age effect** is a variation linked to individual biological and social processes of aging, but not necessarily related to the time period or birth cohort to which an individual belongs. A **period effect** may be described as a variable variation caused by external factors affecting a population (irrespective of age) at a particular historical time, e.g. war, societal economic crisis. A **(birth)cohort effect** is variations in health-related factors and outcomes resulting from the unique exposure of a birth cohort as they move across time, e.g. vaccination programs or educational systems. These concepts will be further problematized in relation to depression during the general discussion (*6.4.2 Time trends in depression and gender equality).*

1.2.3 **Chronicity and recurrence**

Few population-based studies with long-term follow-ups have reported rates of depression recurrence.[64-66] Although studies focusing on long-term courses of depression among older adults are lacking, a meta-analysis showed that having had a prior depressive episode increased the risk for late-life depression.[67] To date, one of the longest follow-ups reported that about 50 % of those with first depressive episodes had recovered, and did not experience recurrence during the 23-year-long study period (age 10-65+).[68] Also, on average, men had shorter depressive episode durations compared to women. However, there are discrepant results regarding sex differences in the chronicity of depression. Some suggest that once depression has occurred, women have a greater risk for chronicity than men.[69] Others report no consistent sex differences in neither chronicity nor recurrence of depression.[70-72] Instead, the risk of recurrence have been reported to be higher for those with early onset depression (compared to later onset),[72] and to increase with the number of depressive episodes.[71]

1.2.4 **Subjective experience of depression in late life**

A meta-synthesis[73] identified five qualitative publications focusing on older adults' subjective descriptions of experiencing depression.[74-78] The results showed that older adults experienced negative feelings toward oneself, including self-blame, hopelessness and lack of self-worth, while suffering from depression. Many expressed feeling persistent sadness and losing the sense of life being meaningful. Many feared an inability to recover, and felt powerless and isolated. Beyond the year of 2010, further studies have focused on experiences of depression among older African Americans,[79-81] Korean Americans,[82] Hispanic immigrants in the United States,[83] older adults in Japan,[84,85] the United Kingdom,[86-88] Sweden,[89] and older males in Canada.[90,91] With a few exceptions,[74,81,82,89] the majority of previous studies have included samples from primary care or inpatient settings. Only two studies have included samples derived from a population-based epidemiological study, as in thesis *Paper 4*. The first involved a sample derived from the Memory and Aging Study of Koreans (MASK)[82] (mean age 67). They found that the majority of participants (with clinically significant depressive symptoms) did not identify themselves as having depression. The second involved a sample from the Elderly in Linköping Screening Assessment (ELSA 85) study[89] (mean age 88). Based on the descriptions from older adults with depression, the authors suggested that milder forms of depression may be part of progresses in normal

ageing. Previous studies have reported that lower mood was expected by young-old adults in their late 60s,[79] frail older adults in their late 70s,[87] and older-old adults in their late 80s from the general population.[89] Having low mood was normalized alongside of declining physical health,[86] and was 'simply something to live with' during later life. Although symptoms such as reduced appetite or sleep disturbances may overlap between depression and e.g. physical disorders during late life,[7,11] others have proposed that depression is not part of normal aging.[1] Instead, overlapping symptoms and normative preconceptions about depression and aging may lead to underdiagnosis of late-life depression.[7,11]

1.2.5 **Lifetime prevalence**

Compared to men, women have about twice the lifetime risk of developing depression.[70] Approximately 5 % of older men, and 13 % of older women will have experienced major depression during their lifetime[25] (see Table 3).

Table 3. Lifetime prevalence [a] estimate of major depression by age and sex

	All ages	**18-34**	**35-49**	**50-64**	**≥65**[b]
N (♀/♂)	*5 143/4 139*	*1 658/1 375*	*1 522/1 343*	*1 068/854*	*894/567*
Total	19.2 (0.5)	19.4 (0.8)	22.7 (0.9)	20.7 (1.2)	9.8 (0.9)
Women	22.9 (0.6)	23.7 (1.1)	26.7 (1.0)	24.6 (1.5)	13.0 (1.3)
Men	15.1 (0.8)	15.1 (1.2)	18.6 (1.4)	16.2 (1.4)	5.3 (1.2)

Source: Kessler, et al.,[25] modified by author. [a] % (SD). [b] Age range not specified in original publication.

The measurements of lifetime prevalence of depression may be limited,[92] due to e.g. survival effects, recall bias, or by collecting retrospective data at only one occasion. Thus, rates may be underestimated,[64] especially in studies with retrospective design.[93] Compared to the lifetime prevalence of 15 % for men and 23 % for women (Table 3, all ages), others have reported 36 % in men and 40 % in women (age 20-50),[94] and 23-30 % in men and 40-45 % in women (age 15-65).[95] The National Comorbidity Survey from the US (year 1990-1992; age 15-54), showed increasing lifetime prevalence in successive cohorts (for both sexes).[40] Although the sex ratio is present across the life course (after puberty),[96] some suggest that it decreases with age,[97] starting with a post-menopausal decline in women,[98] and continue to decrease between 65-75+.[99] Thus, the sex ratio is still present in late life, yet at a lower level.[100,101] The prevalence of depression is lower among older, compared to younger, adults.[1] Still, due to personal suffering as well as increased risk of suicide, comorbidity, and mortality, late-life depression is an important public health issue.

1.3 **Risk and protective factors for depression**

Late-life depression is a multifactorial disease with a complex and unclear etiology. The risk and protective factors span from biological mechanisms to social phenomena, which interplay throughout the life course. Although biological mechanisms are not the focus for any of the five papers in this thesis, a brief summary of common hypotheses is given below. As detailed descriptions of these are beyond the scope of this thesis, the aim is merely to generate a brief understanding of the link between risk/protective factors and the sex ratio in late-life depression, within which gender-related factors play a role. Following this section, potential explanations for the sex ratio in late-life depression are given.

1.3.1 **Biological mechanisms and factors**

Research on biological risk factors for depression is extensive.[102] Still, the precise biological mechanisms remain unknown.[103] Suggested biological mechanisms and factors include (1) the monoamine hypothesis; (2) HPA axis dysregulation and stress-vulnerability hypothesis; (3) the inflammation hypothesis; (4) the neuroplasticity hypothesis; and (5) genetic factors.

First, **the monoamine hypothesis**[103,104] was proposed in the 1960's. This neurochemical theory suggests that depression is caused by a deficit in the regulation of monoamine transmitters (serotonin, noradrenaline, dopamine). This also includes changes in the downregulation and desensitization of the receptors for noradrenaline and serotonin. The monoaminergic systems are involved in the regulation of e.g. mood, sleep, and appetite; which are some of the functions that are impaired during depression. Hence, a dysfunction in the monoaminergic systems is suggested to induce depressive symptoms. However, despite that monoamine transmitters have been shown to have a role in the pathophysiology, they cannot alone explain the etiology of depression.[103]

Second, **the hypothalamic–pituitary–adrenal (HPA) axis** is a neuroendocrine unit consisting of the hypothalamus located in the brain, the pituitary gland at the base of it, and the adrenal glands on top of the kidneys. The HPA axis plays a key role in stress reactivity and stress hormone regulation. (Figure 1).[103] Stress (from e.g. physical or psychological stressors) is perceived by the brain cortex and amygdala, and transmitted to the hypothalamus. This leads to HPA activation, comprising a chain reaction of hormone releases from

the hypothalamus (corticotropin-releasing hormone, CRH), which in turn stimulate the pituitary gland to release adrenocorticotropic hormone (ACTH) that finally stimulates the adrenal glands. The adrenal glands releases glucocorticoids (e.g. cortisol). In turn, in a negative feedback mechanism, cortisol induces feedback inhibition on the hypothalamus and the pituitary gland, signaling them to suppress the release of CRH and ACTH. Studies have shown that persons having depression may have an HPA axis dysfunction, especially a hyperactive HPA axis (revealed by e.g. increased cortisol levels).[105] This hyperactivity includes a suppressed cortisol response, where the feedback signaling to the hypothalamus and pituitary gland does not result in suppressed release of CRH and ACTH. Instead, the chain of hormone releases does not break. An excess in glucocorticoids may have neurotoxic effects,[106] which has been suggested to be a mechanism for the reduced hippocampus volume found among those having depression. Further, the stress-vulnerability model[107] includes the theoretical interaction between a persons' predisposed vulnerability and their subsequent stress-response (from e.g. life events), and risk for depression.

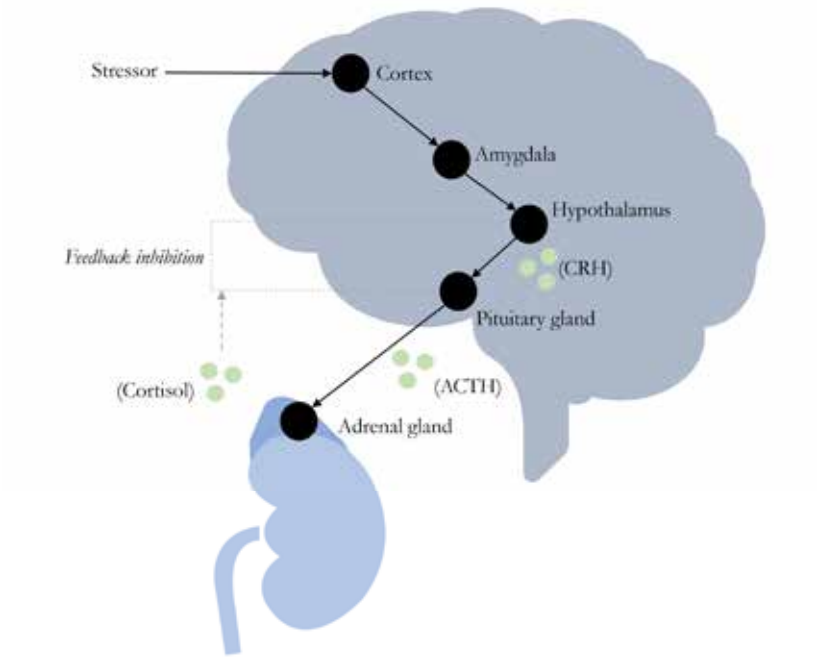


Figure 1. The Hypothalamic-Pituitary-Adrenal axis. Source: Figure inspired by Belmaker et al.,[106] modified by author. The figure is a simplified presentation of the functionality of the HPA axis. It is not anatomically precise regarding the scale, exact locations or shapes of organs or brain regions.

Third, **inflammatory processes** (e.g. increased number of immune cells and inflammatory markers) has been suggested to be associated with the incidence, progression and recurrence of major depression,[108] also among older adults.[109] Some have suggested that this association entails that inflammation is a mediating factor in the relationship between stress and late-life depression.[109] Others suggest that inflammatory cytokines (signaling molecules playing a role in the immune response) can alter neuroplasticity or dopaminergic and serotonergic systems,[110] which are relevant in relation to depression. Studies have also suggested that inflammation partly can be caused by psychological stress.[111]

Fourth, **neuroplasticity** (neuronal survival and synaptic plasticity) is related to the brain-derived neurotrophic factor (BDNF).[106] BDNF may be negatively affected by stress,[103] and show decreased levels among those having depression.[103] Findings from magnetic resonance imaging studies have suggested that grey-matter abnormalities (e.g. volume reduction of hippocampus) are part of the pathophysiology of late-life depression.[112] Thus, studies suggest that BDNF is a link between stress (which refers back to the HPA axis dysregulation hypothesis above), neuroplasticity and hippocampal atrophy in depression.[103]

Fifth, **genetic risk** is suggested to have a stronger effect on depression occurring earlier in life, compared to late onset depression.[113] Twin studies have suggested a heritability of about 37 % for early onset depression,[106] and 23 % for late-life depression.[114] Genetic studies have found a possible association between depression and the serotonin transporter gene (*SLC6A4*),[103] more specifically, a polymorphism occurring in the promotor region (*5-HTTLPR*). The short allele polymorphism may cause reduced uptake of serotonin[106] (which refers back to the monoamine hypothesis above), and is suggested to moderate the influence of stressful life events on depression.[115,116] However, there are inconclusive results among studies regarding a potential association between specific genes and late-life depression.[117] Specific attention has been given to the ε4 allele of apolipoprotein E (*APOE4*), a known risk factor for Alzheimer's disease.[118] Some suggest an association between depression and *APOE4,*[117,119,120] while others do not.[121] A meta-analysis showed that, besides *SLC6A4* and *APOE4*, *BDNF Val66Met* was also associated with late-life depression.[117] *BDNF* regulates neuronal survival and plasticity, and codes the

BDNF protein (which refers back to the neuroplasticity hypothesis above). However, studies conclude that the complex genetic features for depression is still not clear.[106]

1.3.2 **Psychological factors**

A relationship between personality and depression has been proposed. Studies have reported that higher levels of the personality traits of neuroticism is associated with increased risk of late-life depression.[122] Possible explanations to this association include that (1) personality and depression may share etiological factors, but personality does not have a causal influence on depression (and vice versa); (2) personality may have causal effects on increasing the risk of depression; and (3) depression may have a causal influence on personality.[123] In addition to these suggested models, it may be important to consider that personality may show plasticity across the lifespan.[123-125] Further, rumination is a coping style comprising repetitive and passive focus on negative emotions or problems, and on their possible causes and consequences.[126] It is related to depression among older adults,[127] and has been suggested to mediate the effect of neuroticism on depression.[128]

1.3.3 **Lifestyle factors**

There is a growing literature on the benefits of physical activity in relation to depression,[129] in which lower levels of physical activity have been associated with higher levels of depressive symptoms among older adults.[130,131] In addition, reduced physical activity may be a long-term result from having had depression. Theories about why exercise may have positive effects on depression comprise biological processes (e.g. reduced inflammation, increased levels of endorphins and neurotransmitter production, or a reduced HPA axis stress-response) and increased self-efficacy (i.e. one's belief in one's ability to succeed in specific situations).[129] Results from a meta-analysis showed that a healthy diet such as a "Mediterranean diet" (e.g. fruits/vegetables, fish, monounsaturated fats), or avoiding a pro-inflammatory diet (e.g. carbohydrates and saturated fats), could reduce the risk of depression.[132] Further, obesity and depression share biological mechanisms (e.g. inflammatory dysregulation).[133] The two have a bidirectional relationship, where obesity is a risk factor for depression, and depression is a risk factor for obesity.[134] In addition,

smoking,[135] a high intake of alcohol,[135,136] and sleep disturbance[67] have been associated to higher prevalence of depression among older adults.

1.3.4 **Negative life events**

Negative life events have been associated with increased risk of depression among older adults.[17] The association is suggested to be stronger when the event occurs at more sensitive stages during the lifespan (e.g. emotional neglect in early life).[137] Childhood trauma exposure has been suggested to have long-term effects in relation to elevated risk of depression among adults.[138] Suggested mechanisms behind this association include that a dysregulation (increased sensitivity) of the HPA axis reactivity may occur after negative life event exposure. Studies among older populations have showed that bereavement-related (e.g. death of or severe illness of significant other), health-related (e.g. illness or injury) or economy-related (e.g. financial hardships) events were associated with higher prevalence of late-life depression.[139-141]

1.3.5 **Marital status, loneliness and social support**

Marital status may affect the risk of having depression among older adults. Those who are not married may have an increased risk for depression compared to those that are married.[142] This association may partly be due to that married persons often live with their spouses, while those not married more often live alone. However, marital status does not say anything about the relationship per se. Feeling lonely and depression have been shown to have a bidirectional relationship among older adults,[143] where feeling lonely is a risk factor for depression,[141] and depression is a risk factor for feeling lonely.[143] Living with someone (e.g. spouse, friend or family member) may decrease levels of psychosocial stress through emotional or economic support.[144] Social support given by spouse, friends or family members is reported to be protective against late-life depression.[145,146] It is also suggested to act as a buffer by decreasing the risk of depression when exposed to negative life events.[147] On the contrary, having a partner may also be a risk factor for emotional, physical or financial abuse,[148,149] or marital dissatisfaction,[150] which may contribute to elevated risk for depression. The negative aspects of social relationships (with spouse, or social network at large) may be important to consider in order to capture its complex relationship to depression.

1.3.6 **Income inequality and socio-economic status**

Having low socio-economic status (including e.g. low education and low income) has been associated to higher prevalence of depression.[151,152] Studies have reported that the risk of depression was higher in populations with greater income inequality compared to populations with less inequality.[153] This association was also shown for older populations. Suggested explanations for this association comprise a mediation effect by psychological stress, i.e. income inequality leads to psychological stress, which in turn, elevates the risk of depression.[154] Further, comparing oneself to those with higher economic or social status may create feelings of status anxiety or shame.[153] Income inequality may also coexist with material deprivations relevant to health, such as societal investments in education, healthy food availability, or access to healthcare.[153]

1.4 **The sex ratio in depression - possible explanations**

> "As women or men, we slip our feet into different shaped shoes, button our shirts on opposite sides, buy our pants in separate shops, and take them off in separate toilets. These arrangements are so familiar that they can seem part of the order of nature."
> – *Raewyn Connell & Rebecca Pearse in Gender in World Perspective (p. 5)*[155]

1.4.1 **Definition of sex and gender**

In this thesis, **sex** is defined as the biological distinction between men and women based on the information given by their Swedish personal identity number. While sex include the biological distinction between men and women, **gender** adds to the behavioral, cultural or psychological attributes associated with one sex or the other according to societal norms, which can change over time and differ between cultures.[156,157] The theoretical framework is founded in the extended version of sex role theory, in which the psychologist Sandra Bem launched the concept of psychological androgyny in 1974.[158] Within this context, the term **gender expression** constitutes how an individual expresses a sense of being masculine, feminine, neither, or both through behavioral attributes. A persons gender expression may not be fixed by nature, nor solely imposed from societal norms.[155] However, it is suggested to include actively learning and incorporating gendered patterns into the self-concept, across the life course.[155,156] Even though masculinity is stereotypically associated to men, and femininity to women, the majority combine masculine and feminine characteristics in different blends.[155] With this in mind, masculinity and femininity are not on opposite sides of a continuum. Instead, they compose a two-dimensional construct where masculinity and femininity comprise one dimension each.[159]

There is an ongoing discussion whether femininity, masculinity and androgyny should be called 'gender identity', 'gender role orientation', 'sex role' or 'gender expression'. This generates discrepancies among studies, also among studies included in this thesis. However, based on theoretical discussions published in the 2019 Lancet series 'Gender equality, norms and health'[160-170], 'gender expression'[170] is used when discussing femininity, masculinity and androgyny, measured with **the Positive-Negative Sex-Role Inventory (PN-SRI)**,[159,171]

in this thesis. Illustrative combinations of sex and gender expressions in shown in Figure 2. PN-SRI is further described in the Method section (*4.3.5 Gender expression*).

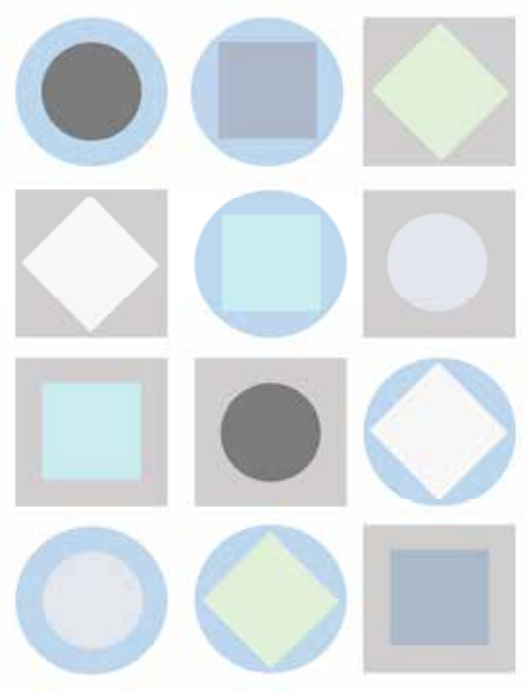


Figure 2. Illustrative combinations of sex and gender expressions. Blue circles and grey squares in the background represents male/female sex, while in the foreground, aspects of femininity (circles), masculinity (squares), and androgyny (tilted squares) are represented. Source: Inspired by illustrations made by Piroska von Gegerfelt, published in Wijma et al.,[172] modified and extended by author to add the possible sex/gender expression combinations when utilizing PN-SRI.

Adding the theoretical macro, meso and micro levels onto this framework, gender-related aspects may be divided into gender expression and gender roles (micro), gender relations (meso) and institutional gender (macro).[155,170,173] These are displayed in Figure 3, together with the potential factors underlying the sex ratio in depression, which are explained in more detail below.

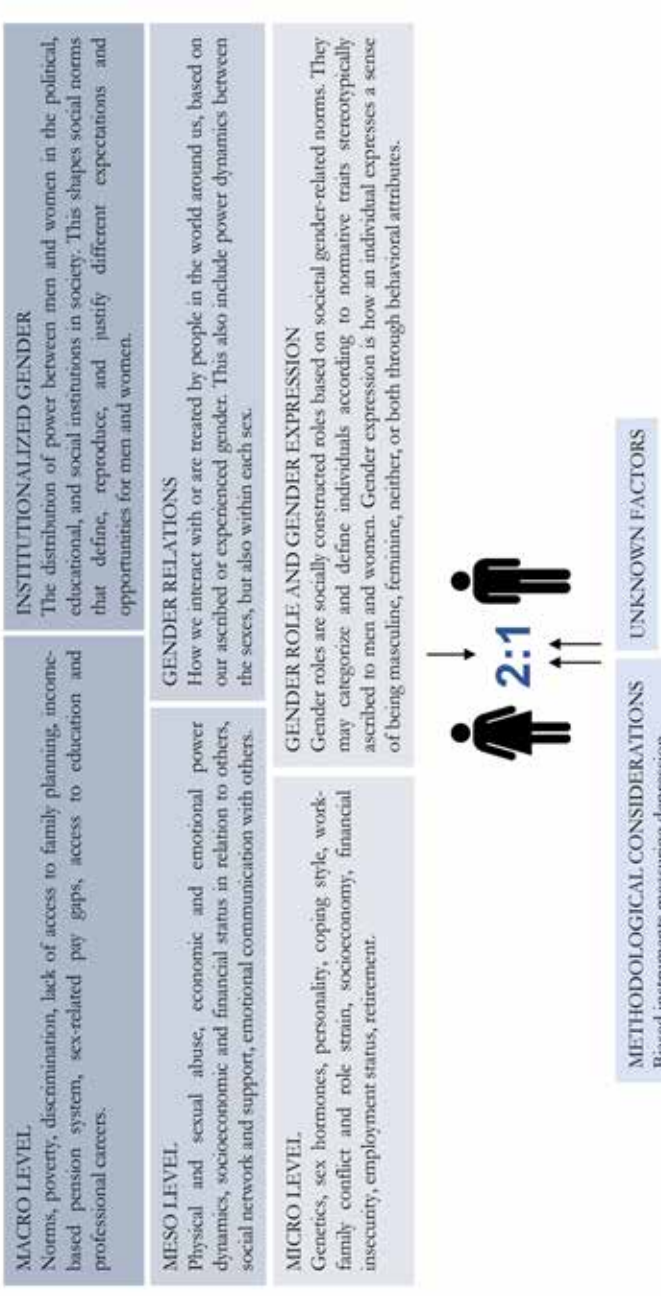


Figure 3. Sex-ratio in late-life depression: potential sex and gender-related factors. Source: Inspired by Connell & Pearse,[155] Darmstadt et al.,[170] Tannenbaum et al.,[173] made by author.

1.4.2 **Factors underlying the sex ratio**

What do we know about the underlying factors for the approximate 2:1 (female:male) sex ratio in depression? The potential origin of this sex difference has previously been described,[174] and is highly debated.[175] While some have suggested that the sex ratio may be due to methodological artefacts,[176] others argue that the observed sex difference in prevalence rates reported by population-based studies is genuine.[70] In short, common explanatory models include that women report symptoms more often while men do not perceive or report them,[176] the presence of biological differences[102] such as hormones[177] or genetics,[178] methodological difficulties (e.g. biased instruments),[179,180] or social or gender-related factors (e.g. gender roles).[181] A simplified display including examples of risk and protective factors, which may underlie the sex ratio in late-life depression, is shown in Figure 3, and are further presented below.

Biological factors

Suggested biological factors underlying the sex ratio in depression include sex hormones and genetics. First, **sex hormones** (e.g. testosterone and estrogen) have been suggested to interact with the HPA axis and with neurotransmitter systems,[177] and with the immune system (pro or anti-inflammatory effects).[111] These interactions are complex,[111] and detailed descriptions goes beyond the scope of this thesis. In summary, while reduced levels of estrogen in women have been suggested as a risk factor for depression, the sudden appearance of high estrogen levels in adolescent girls have seemed to be related to low mood. Further, the HPA axis functional maturation occurs during adolescence. Due to the interaction with sex hormones, females may develop a hypersensitivity to stress, while males may be more protected by their higher testosterone levels. Thus, for example, females would have a higher incidence of depression during adolescence, generating a continuously higher prevalence rate (compared to men) across the life span due to the high risk of recurrence. Also, in general, high levels of testosterone and estrogen has been suggested to be anti-inflammatory, while low levels of estrogen have been suggested to have pro-inflammatory effect.

Second, some evidence suggests that parts of the **genetic vulnerability** for depression may be sex specific.[102] However, the findings are inconclusive. First, results from a population-based twin study (mean age 33),[182] concluded that

even if there may be a sex ratio in the prevalence of depression, the genetic factors that predispose men and women to depressive symptoms are not different. In addition, the authors showed equal heritability across sexes (≈ 30 %), which has also been seen for major depression in other studies.[183] This suggest that genetic factors would be of similar etiologic importance for depression in men and women. However, others have suggested that men and women share some, but not all genetic factors, for the risk of major depression.[183] The heritability for late-life depression has been reported to range between 24-29 % in women, and 14-16 % in men.[114] In a Swedish twin study, the heritability for lifetime depression was shown to be higher in women (42 %) compared to men (29 %).[184] This suggested that genetic factors may play a greater role in the risk of depression for women.[185] However, this is not concluded.

Psychological factors

The sex ratio in depression may also be partly caused by cognitive or personality factors. First, women ruminate more frequently than men, while men tend to engage in more active problem solving.[126] Second, already in the 1980's, a meta-synthesis[186] showed that sex differences in neuroticism follows a similar age-trend as depression. In both neuroticism and depression, the sex ratio seems to be lowest in very young and very old persons, while higher among young and middle-aged adults. However, the sex ratio in neuroticism is greater at all ages compared to the sex differences in depression.

Social factors

Globally, suggested social factors include that women face a greater exposure to poverty, discrimination and socioeconomic disadvantages, compared to men. Physical abuse by spouse, illiteracy, financial insecurity, sexual abuse, or lack of autonomy may contribute to the vulnerability for depression across the life course, but also tend to be more common among women.[16] Further, women's subordinate social status may include stressors such as part-time employment, and attending jobs with lower status.

Gender-related factors

Gender-related factors have also been suggested to underlie the sex ratio in depression, including societal norms, gender relations, gender roles, and gender expression. First, traditional gender roles in combination with dual earning families, generate a risk that women face work-family-conflict[181] and role strain overload.[187,188] Apart from managing their own work, women are expected to have the primary responsibility of unpaid domestic work, and family duties in taking care of others. For older women, this may also include caring for spouse due to illness. Second, compared to men, older women in Sweden are more often economically strained due to having lower income-based pensions. This is, in turn, an effect by choices for and access to education and professional careers, sex-related pay gaps, and choices regarding leaving the workforce in order to take care of children, across the adult life.[189] Third, women and men may create different kinds of social relationships, which affects their social support.[189] Women tend to have larger and more intimate social networks, which can be beneficial in providing social support. However, having large and intimate networks may also be more emotionally demanding. Fourth, compared to masculinity, femininity is considered to be more connected with emotional communication about well-being and health, which can facilitate help-seeking, and partly be an explanation to why women seek help to a larger extent than men.[190,191] Further, studies have suggested that masculinity-related barriers prevent both older men and women from disclosing their low mood, in order to avoid 'looking weak'.[74,79] Fifth, older adults endorsing a masculine[192] or an androgynous[193] gender expression have been suggested to have lower rates of depressive symptoms. This will be further explored in *Paper 5*.

1.4.3 **Theoretical models explaining the sex ratio origin**

In order to understand the sex ratio in late-life depression, it is important to consider a life course perspective. Three models have been proposed aiming to explain the origin of how depression becomes more prevalent among women, compared to men, already after puberty.[194] These are shown in Table 4.

Table 4. Three hypothetical models for how depression becomes more prevalent among women (compared to men) before, during or after puberty

Model 1	**The causes of depression are the same for men and women, but become more prevalent among women during adolescence.**		
	Factor A is an important risk factor for depression, and the association between Factor A and depression is similar for men and women. The prevalence of Factor A is initially the same for men and women, but increases in women at a certain point in time (e.g. after puberty).		
	Risk factor for depression	**Prevalence of risk factor before puberty**	**Prevalence of risk factor after puberty**
Men	Factor A	1	1
Women	Factor A	1	1+x
Sex ratio*		1:1	1:1+x
Model 2	**The causes of depression are different for men and women.**		
	The risk factors for depression are different for men and women, and women's risk factor are also more prevalent. The risk factor for women are more common already in early adolescence, whereas the risk factor for men only increase slightly, or not at all.		
	Risk factor for depression	**Prevalence of risk factor before puberty**	**Prevalence of risk factor after puberty**
Men	Factor M	1	1
Women	Factor W	1+x	1+x
Sex ratio*		1:1+x	1:1+x
Model 3	**The causes of depression are the same for men and women, but are more prevalent in women already during childhood, interacting with additional challenges in early adolescence.**		
	Important risk factors are more prevalent for women than men already before puberty. These factors then interact with the challenges young persons face during early adolescence, creating different prevalence rates of depression for men and women.		
	Risk factor for depression	**Prevalence of risk factor before puberty**	**Prevalence of risk factor after puberty**
Men	Factor A	1	1+interaction with challenges
Women	Factor A	1+x	1+x+interaction with challenges
Sex ratio*		1:1+x	1:1+x^{x}

Source: Nolen-Hoeksema, et al.,[194] modified by author. *Sex ratio in the prevalence of depression. 'x': an unknown hypothetical rise in prevalence rates. ^{x} Interaction with challenges (stressors).

These models suggest that depression is more prevalent among women due to factors emerging already early in life (e.g. body dissatisfaction or rumination). Expanding from this work, the ABC-model[102] has been proposed, integrating

affective, biological and cognitive vulnerabilities in relation to negative life events (Figure 4). Adolescence is an important developmental period for sexual differentiation (the process during which sex differences develop and diverge into male or female physical and behavioral phenotypes), where differences between the sexes becomes more prominent.[177] The ABC-model propose that depression becomes more prevalent among women during adolescence due to the combination of biological vulnerabilities (e.g. pubertal timing), which affect affective vulnerabilities (e.g. temperament), which in turn affect cognitive vulnerabilities (e.g. negative cognitive style, rumination). The collection of these will then interact with negative life events, such as peer sexual harassment or body objectification.[102]

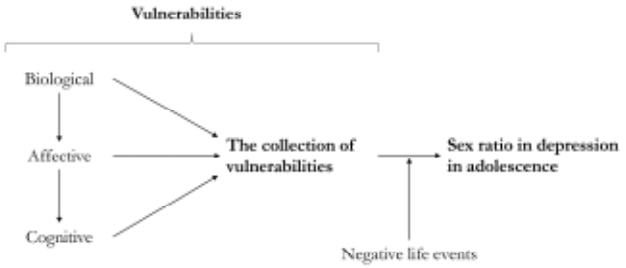


Figure 4. A simplified figure of the ABC model of the sex ratio in depression in adolescence. Source: Hyde, et al.,[102] modified by author.

Theoretically, if the incidence of depression for young women becomes higher than for young men during puberty, women would have continually higher prevalence rates across life (since there is no reported peak in incidence for men to 'even it out') solely due to the high risk of recurrence. Further, adding the layer of sociocultural factors[189] during adulthood and later life, the sex ratio is suggested to be due to an unequal exposure to risk factors for depression, as described above (*1.4.2 Factors underlying the sex ratio*). Also, men and women have been suggested to react differently when exposed to risk factors, i.e. specific risk factors may be more important for one sex or the other. Related to female and male stereotypical gender roles, this may include that female-specific stressors are connected to family or social relations (due to higher responsibility

of caring for others)[181] while male-specific may include retirement or unfulfilled work aspirations (due to masculine norms of breadwinner status).[91]

1.4.4 **Arguments questioning the sex ratio in depression**

Questioning the magnitude of the sex ratio in depression prevalence, some have suggested that methodological artefacts and gender biases may be part of the explanation. The WHO have stated that research on mental health may sometimes be skewed due to gender bias,[16] i.e. trying to explain the sex ratio primarily using a biological model (e.g. sex hormones), while not considering the role of psychosocial or lifestyle factors. This has been supported by data from the SHARE-study, suggesting that differences in the magnitude of the sex ratio among different European social contexts, may be affected by societal interventions.[26] The National Institute of Mental Health (NIMH) have also stated that while both men and women experience depression, their symptoms can vary.[195]

Further methodological difficulties have been put forward, such as biased instruments for measuring symptoms and diagnosing depression.[179,180] Among adolescents, it has been suggested that instruments tend to overestimate depressive symptoms among girls (and underestimate among boys).[196] This may be due to that instruments do not adequately consider that symptoms and experiences of depression may show different patterns for each sex. As aforementioned, among older adults with depression, women have been reported to display symptoms more related to psychomotor[8] and appetite disturbances,[9] while men display agitation[9] and suicidal ideation[8]. However, some further argue that instruments measuring depression may suffer from a 'catch 22'; they capture a female phenotype of depression, and thereby more women are diagnosed with depression than men.[191] Hence, the observed sex ratio in depression may partly be due to that parts of a potentially male phenotype of depression is not included in the current diagnostic criteria.[197] A male phenotype may include externalizing symptoms (e.g. substance use, risk-taking, and aggression), and may reflect behavioral manifestations of masculine norms in relation to depression. In Sweden, the Gotland Male Depression Scale was developed aiming towards screening for male depression.[180,198] However, whether a specific male phenotype of depression exists[197-199] or not[200,201] has been debated. Also, it is important to consider the heterogeneity of depressive symptoms, not only between men and women, but also within each sex.[202]

1.5 **Comorbidity**

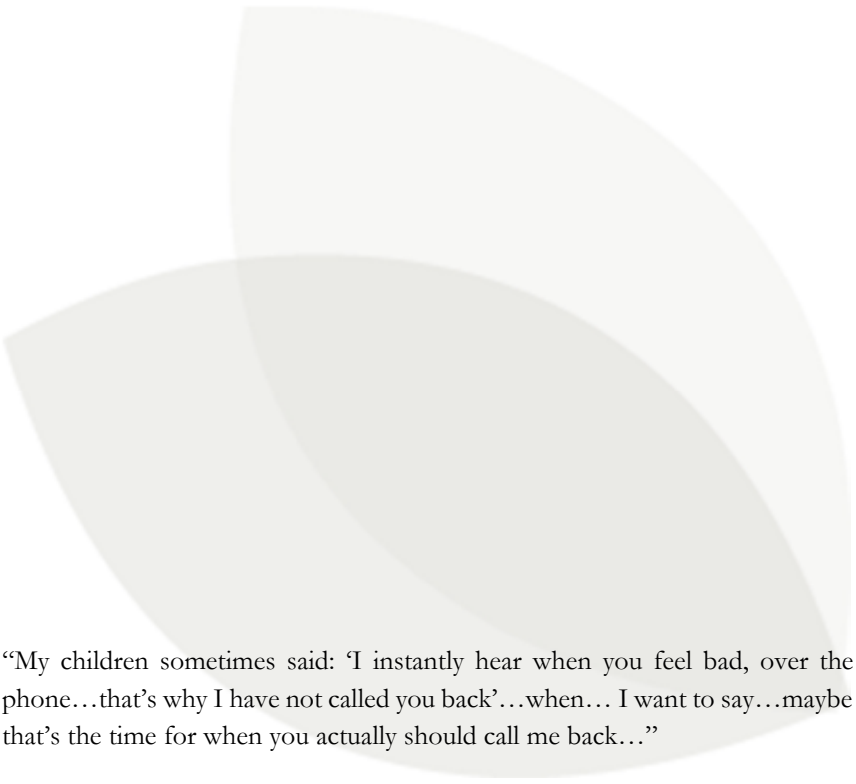
Late-life depression often occurs together with other medical illnesses.[1] A meta-analysis reported strong associations to cardiovascular disease, diabetes and stroke.[203] Suggested explanations include shared pathologies and the resulting effects on function and reduced quality of life. Anxiety disorders have been suggested to be co-existing with[204] and a risk factor for[205] late-life depression. Among older adults, the co-occurrence of depression and anxiety have been reported to increase the severity of depressive symptoms and longstanding vulnerability for recurrence.[204] There is also comorbidity between late-life depression and dementia. In relation to dementia, depression has been suggested to be a risk factor, a prodromal phase, or a common complication.[206,207] The relationship between depression and dementia is complex. Apart from sharing symptoms (e.g. concentration difficulties), studies have suggested that late-life depression and dementia may also share underlying neurobiological mechanisms, such as vascular diseases, hippocampal atrophy, inflammatory processes, and genetic predisposition (e.g. *APOE4*).[208] However, the relationship between late-life depression and dementia remains unclear.[206,208]

1.6 **Consequences of late-life depression**

Beyond personal and family suffering[6] and societal consequences,[13,14] mentioned above, depression is associated with higher risk of other medical conditions, such as cardiovascular diseases.[209] Also, among older patients treated for medical conditions (non-psychiatric disorders), depression have been reported as a risk factor for medical non-compliance.[210] Older adults with minor depression have been shown to have about five times greater risk of developing major depression after one year, compared to those not having depression at baseline.[211] Studies have shown that older adults with depression were also more likely to develop mild cognitive impairment.[212] Late-life depression may also be a risk factor for dementia,[206] also including that depression may lead to accelerated cognitive decline among those having dementia. Late-life depression is also a predominant risk factor for suicide. The link between depression and suicide have been suggested to be particularly strong among older adults, compared to those having depression earlier in life.[1] Studies have found that severity of depressive symptoms is associated with higher risk of suicide attempts among older adults with depression.[213] In addition, depression is present in about 85 % of older adults who die by suicide.[1,214]

2. **Rationale**

Little is known about the role of gender expression (femininity, masculinity, or androgyny) in relation to depression epidemiology, and its potential role for the 2:1 prevalence sex ratio. Gender expression has been suggested to be associated with various outcomes in health,[215] such as sickness absence,[216] self-reported wellbeing,[217] and physical complaints.[218] However, the impact of gender expression may be specifically important in relation to mental health. In order to meet the urgent call for further attention to both sex and gender in psychiatric research,[219] we need to be able to measure different aspects of gender. In this thesis, we devoted our specific attention to gender expression, comprising micro level aspects of femininity, masculinity and androgyny, measured with the Positive-Negative Sex-Role Inventory (PN-SRI). In 2014, PN-SRI was added into the Gothenburg H70 Birth Cohort Studies (the H70 study) battery. The H70 study comprise the research context from which this thesis was derived, described in detail in *Paper 1*. PN-SRI was tested for validity and reliability in *Paper 2*, in order to examine whether it would be relevant for our target population of older adults. Further, PN-SRI was tested in relation to depression in *Paper 5* to challenge the sex ratio in depression prevalence. As depression is heterogeneous regarding both etiology and symptom expression, it is important to stratify analyses by sex in order to reveal potential differences between men and women. Also, it is important to consider the potential differences within each sex. Utilizing PN-SRI for collecting data on gender expression makes this possible from an epidemiological standpoint. Searching for additional factors associated with depression may improve our knowledge of depression etiology. This may, in turn, lead to further developments in e.g. diagnostic assessments[219] and preventive actions.[220] In order to investigate depression later in life at a deeper level, both a quantitative and qualitative methodological approach were warranted. Therefore, *Paper 3* offers a time trend display of the point prevalence of, and sex ratio for, depression between the 1970's and 2010's. It is important to examine the potential fluctuations in order to create new hypotheses as to why potential time trends in prevalence occur. Finally, there is a need for increased understanding of how older adults from the general population experience late life depression, which would help identify potential unmet needs and knowledge gaps. This was collected by focus group discussions in *Paper 4*. The qualitative approach was important in order to enable the participants to verbalize and share their lived experiences.



"My children sometimes said: 'I instantly hear when you feel bad, over the phone…that's why I have not called you back'…when… I want to say…maybe that's the time for when you actually should call me back…"

Source: Quote from study participant during data collection in focus group discussion no.3, describing experiences from his/her latest depressive episode. Illustration made by author.

"I kind of think that depression is not something like – yesterday I did not have it, but today it's there. It is something that constantly and slowly grows, over time. You don't even notice it…

"You don't notice it yourself…"

"You get used to it."

"…you just learn to handle it somehow"

"Yes, this is how I am, and I need to accept that"

"Yes, like an Eeyore [dysterkvist]"

"…grandpa is sitting over there being an Eeyore…"

Source: Quote from study participants during data collection in focus group discussion no.4, discussing their experiences from their latest depressive episode. Eeyore (from Winnie the Pooh) here represent a person with low mood, translated from the Swedish word [dysterkvist].

3. **Aim**

The overarching aim of this thesis was to study prevalence, time trends, and subjective experiences of depression among older adults from the general population, with specific focus towards potential differences by biological sex and gender expression. The thesis comprises five papers, all of which are based on representative samples of Swedish 70-year-olds in the Gothenburg H70 Birth Cohort Study (the H70 study), with the following specific aims:

Paper 1. Describe the study procedures for the baseline examination of birth cohort 1944 in the H70 study, which was conducted 2014–16.

Paper 2. Evaluate the validity and reliability of a Swedish version of the Positive–Negative Sex-Role Inventory (PN-SRI) in the H70 study.

Paper 3. Explore birth cohort differences in burden of depressive symptoms, prevalence of depression and neuroticism in 1976–77, 1992–93, 2000–02, and 2014–16, and whether time trends differed by sex.

Paper 4. Explore subjective experiences of depression in early late life.

Paper 5. Test if sex and gender expression (femininity, masculinity, and androgyny) had independent associations with depression and burden of depressive symptoms.

4. **Materials and Methods**

4.1 **Study populations**

The population-based representative samples in this thesis were derived from the Gothenburg H70 Birth Cohort Studies (the H70 studies). All men and women were, at the time of their first examination, 70 years of age and registered residents in Gothenburg, Sweden (according to the Swedish Tax Agency).

The H70 studies are multidisciplinary epidemiological studies examining representative birth cohorts of older populations in Gothenburg, Sweden. The first study started in 1971. So far, six birth cohorts with baseline examination at age 70 have been followed longitudinally. Study procedures for birth cohorts 1901-02, 1906-07 and 1911-12 have been described elsewhere,[221,222] study procedures for birth cohort 1930 is an ongoing paper conducted by my research colleagues, and study procedures for birth cohort 1944 has been published[223] and is included in the thesis as *Paper 1*. Figure 5 displays an overview of birth cohorts and examination years included in the H70 studies. The main focus for this thesis were 70-year-olds born 1944, examined in 2014-16. In addition, the cross-sectional examinations of 70-year-olds examined in 1976-77, 1992-93, and 2000-02 were included for birth cohort comparisons in *Paper 3*.

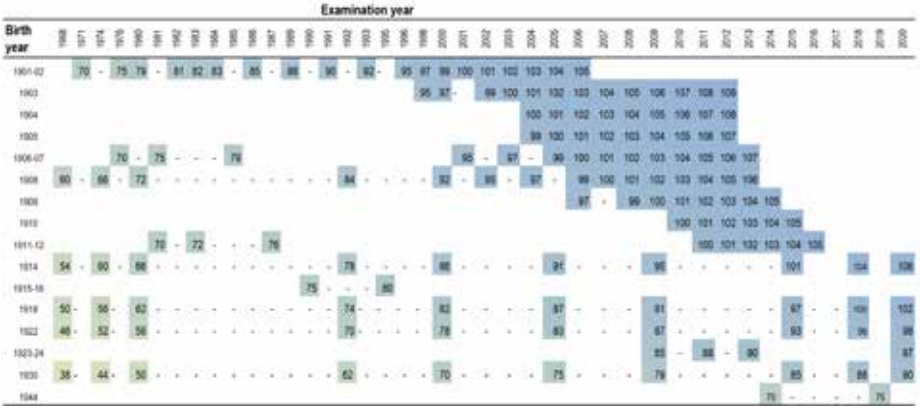


Figure 5. Overview of birth cohorts and examination years included in the Gothenburg H70 Birth Cohort Studies (the H70 studies). Source: Original picture created by Thomas Marlow (former statistician in the H70 studies), modified and published by Mellqvist Fässberg & Vanealst et al.,[224] and further modified by author.

4.1.1 **Examination 1976-77 (birth cohort 1906-07)**

In 1976-77,[225] all 70-year-olds living in Gothenburg and born between July 1st, 1906 and June 30th 1907 on birth dates ending with 2, 5 or 8 were invited to participate (n=1 281; 567 men, 714 women). A total of 1 049 participated (476 men, 573 women). All participants were numbered from 1 to 5. Those with number 1 or 2 were invited to take part in a psychiatric examination (n=513; 214 men, 299 women). Out of these, 404 participated (response rate 78.8 %); 177 men, 227 women). The participants and non-participants were similar regarding in-patient psychiatric care during the past two years according to the National Patient Register, and they had similar 3-year mortality rates (as previously described[225,226]). There was no difference in response rate by sex (x^2; p=0.06). Out of 404 participants, 48 (11.9 %) died within five years after the examination. The five-year mortality rate was 15.3 % (n=27) among men, and 9.3 % (n=21) among women. The mortality rate did not differ by sex (x^2; p=0.07). Information on dates of death was obtained from the Swedish Tax Agency.

4.1.2 **Examination 1992-93 (birth cohort 1922)**

The 1922 cohort comprise a merged sample deriving from the H70 study, and the Prospective Population study of Women in Gothenburg (PPSW).[221,227] PPSW is a longitudinal multi-disciplinary study with over 50 years of follow-up, which is now partly included under the H70 study umbrella. PPSW started in 1968 including 1 467 women. Out of 1 467, a systematic subsample (n=800) also participated in psychiatric examinations in 1968 and in the subsequent follow-ups. In 1992-93, all 70-year-old women living in Gothenburg and born during 1922 on birth dates 6, 12, 18, 24 or 30 were invited to participate (n=473) in order to include a representative sample (not only follow-up examinations). A total of 299 participated (response rate 63.2 %).[228,229] Out of these, 236 women took part in the psychiatric examination (n=183 women had participated in the psychiatric examination also in 1968). The participants and non-participants were similar regarding in-patient psychiatric care during the past two years, according to the National Patient Register, and they had similar 3-year mortality rates (as previously described[226]). Out of 236 participants, 19 (8.1 %) died within five years after the examination. Information on dates of death was obtained from the Swedish Tax Agency.

4.1.3 **Examination 2000-02 (birth cohort 1930)**

In 2000-02,[226] all 70-year-olds living in Gothenburg and born during 1930 on birth dates: 3, 6, 12, 18, 21, 24, or 30 were invited to participate (n=753; 363 men, 390 women). A total of 524 participated (response rate 70%; 243 men, 281 women). Out of these, 499 (229 men, 270 women) took part in the psychiatric examination. The participants and non-participants were similar regarding in-patient psychiatric care during the past two years, according to the National Patient Register, and they had similar 3-year mortality rates (as previously described[226]). There was no difference in response rate by sex (x^2; p=0.13). Out of 499 participants, 25 (5.0 %) died within five years after the examination. The five-year mortality rate was 8.3 % (n=19) among men, and 2.6 % (n=7) among women. The mortality rate was higher among men (p=0.004). Information on dates of death was obtained from the Swedish Tax Agency.

4.1.4 **Examination 2014-16 (birth cohort 1944)**

In 2014-16,[223] all 70-year-olds living in Gothenburg and born during 1944 on birth dates ending with 0, 2, 5 or 8 were invited to participate (n=1 667; 773 men, 894 women). A total of 1 203 participated (response rate 72.2 %; 559 men, 644 women). Out of 1 203, 1 194 (555 men, 639 women) took part in the psychiatric examination, and 1 138 (526 men, 612 women) answered the Positive Negative Sex-Role Inventory (PN-SRI). Table 5 display characteristics for the H70 study sample (n=1 203), and for 70-year-olds born 1944 from the general population in Gothenburg and in Sweden. No data was collected for non-participants.

Table 5. Characteristics for 70-year-olds in the H70 study sample, 70-year-olds in Gothenburg and 70-year-olds in Sweden, in 2014

	H70 study 2014 n=1 203		**Gothenburg 2014** n=4 658		**Sweden 2014** n=115 197	
% (n)	♀	♂	♀	♂	♀	♂
70-year-olds born 1944	**53.5** (644)	**46.5** (559)	**52.3** (2 434)	**47.7** (2 224)	**50.5** (58 208)	**49.5** (56 989)
Mood disorders [a]	**0.5** (3)	**0.9** (5)	**1.8** (43)	**1.0** (22)	**1.3** (772)	**0.9** (530)
Depressive episode[b]	**0.3** (2)	**0.7** (4)	**0.8** (20)	**0.5** (12)	**0.5** (317)	**0.4** (231)
Born in Sweden	**86.5** (552/638)	**82.2** (458/557)	**81.9** (1 994)	**79.0** (1 757)	**89.2** (51 900)	**89.3** (50 864)
Married [c]	**50.5** (322/638)	**65.1** (363/558)	**47.5** (1 156)	**58.0** (1 291)	**56.0** (32 577)	**64.5** (36 775)
Primary education ≤ 9 y[d]	**12.8** (82/640)	**16.9** (94/556)	**24.5** (597)	**25.8** (573)	**27.4** (15 923)	**31.5** (17 957)
Secondary education [e]	**58.6** (375/640)	**46.2** (257/556)	**38.7** (942)	**39.4** (876)	**43.5** (25 304)	**41.4** (23 580)
Higher education [f]	**28.6** (183/640)	**36.9** (205/556)	**34.8** (848)	**32.9** (732)	**27.9** (16 249)	**25.9** (14 734)

[a] Diagnostic codes F30-F39 (ICD-10[230]) and [b] Diagnostic code F32 (ICD-10[230]); Source: The National Patient Registry administered by the National Board of Health and Welfare [Socialstyrelsen]; % and number of persons born 1944 that received either in-patient or out-patient care during 2014. [c] Married does not include having cohabiting or non-cohabiting partner. Data on education from the H70-study (n=1 196) includes [d] Primary education [folkskola] and/or [grundskola] 1-10 years; [e] Secondary education [realskola], [läroverk], [gymnasium] and/or [yrkesutbildning]; and [f] having studied 3 or more years at the university (or [högskola]) or having university degree. Source from Gothenburg and Sweden: Statistics Sweden [Statistiska centralbyrån].

A few differences (x^2; $p<0.05$) were observed when comparing the H70 study participants (reference group for all comparisons) to 70-year-olds in Gothenburg, and 70-year-olds in Sweden. There was no difference in the proportion of women between the H70 study and 70-year-olds in Gothenburg. However, the proportion of women was higher compared to 70-year-olds in Sweden. No differences were observed regarding mood disorders or depressive episodes, except that the proportion of mood disorders among women in the H70 study was lower compared to women in Gothenburg. Of those born in Sweden, the proportion of women in the H70 study sample was higher compared to the population in Gothenburg, but lower compared to the population in Sweden. For men, the proportion in the H70 study was similar compared to Gothenburg, but lower compared to Sweden. There were more married women in the H70 study compared to married women in Sweden, and more married men compared to married men in Gothenburg. Over all, the H70 study participants had higher education (lower rates had only primary education, and higher rates had secondary education) compared to Gothenburg and Sweden. However, women in the H70 study had lower rate of university

studies compared to women in Gothenburg, while men in the H70 study had higher rates compared to men in Sweden. There was no difference in response rate by sex (x^2; p=0.89). Out of 1 203 participants, 56 (4.7 %) died within five years after the examination. All 56 had taken part in the psychiatric examination. The five-year mortality rate was 5.9 % (n=33) among men, and 3.6 % (n=23) among women. The mortality rate did not differ by sex (x^2; p=0.06). Information on dates of death was obtained from the Swedish Tax Agency.

4.1.5 **Focus group sub-sample (birth cohort 1944)**

Derived from the H70 study total sample (n=1 203), the focus group sample was strategically selected. The basis for recruitment comprised self-reported information on having experienced at least one depressive episode between 60 to 70 years of age. Research journals of eligible participants (n=208; 63 men, 145 women) were audited, and a prior depression diagnosis was confirmed or refuted by a psychiatrist according to DSM-5.[231] Information on the following exclusion criteria were obtained from the H70 study 2014-16: home visits, Mini-Mental State Examination (MMSE)[232] score < 25, lack of information in research journal notes (not possible to confirm/refute depression), or that depression was secondary to severe alcohol disorder, severe anxiety disorder, post-traumatic stress disorder, or severe physical illness. Out of 208, 41 (10 men, 31 women) were invited to the study. They were first contacted by mail, followed by a telephone call, during which information of the study's aim and procedure were given. Out of 41, 16 (4 men, 12 women) accepted participation. Table 6 display characteristics for the focus group sub-sample, non-participants and to those not included.

Table 6. Characteristics for the focus group sub-sample compared to non-participants, and those not included in the focus group study

	Focus group sub-sample n=16		**Non-participants** n=25		**Participants not included** n=1 162	
% (n)	♀	♂	♀	♂	♀	♂
70-year-olds born 1944	**75.0** (12)	**25.0** (4)	**76.0** (19)	**24.0** (6)	**53.2** (613)	**47.6** (549)
Born in Sweden	**75.0** (9)	**100.0** (4)	**94.7** (18)	**100.0** (6)	**85.6** (525)	**81.6** (448)
Married [c]	**83.3** (10)	**75.0** (3)	**52.6** (10)	**66.7** (4)	**62.3** (382)	**82.9** (455)
Primary education [d]	**0.0** (0)	**25.0** (1)	**0.0** (0)	**16.7** (1)	**13.4** (82)	**16.8** (92)
Secondary education [e]	**50.0** (6)	**25.0** (1)	**78.9** (15)	**50.0** (3)	**50.6** (310)	**43.5** (239)
Higher education [f]	**50.0** (6)	**50.0** (2)	**21.1** (4)	**33.3** (2)	**35.4** (217)	**39.2** (215)

Source: *Paper 4*, modified by author by adding information on non-participants and those not included in the study. Focus group sample (n=16). Non-participants (n=25). Hence, out of the 1 203 who participated in the H70 2014-16 study, 1 162 were not included. [c] Includes having cohabiting or non-cohabiting partner. [d] Primary education [folkskola] and/or [grundskola] 1-10 years; [e] Secondary education [realskola], [läroverk], [gymnasium] and/or [yrkesutbildning]; and [f] having studied ≥ 1 year at the university (or [högskola]) or having university degree.

Due to the small number (n=16) of participants in the focus group sub-sample, the analyses for comparisons were not stratified by sex. Still, no differences (x^2; $p<0.05$) were observed when comparing the focus group sub-sample (reference group for all comparisons) to non-participants and to those not included.

4.2 **Sample flowchart**

All samples included in *Paper 1* to *5* are displayed in Figure 6.

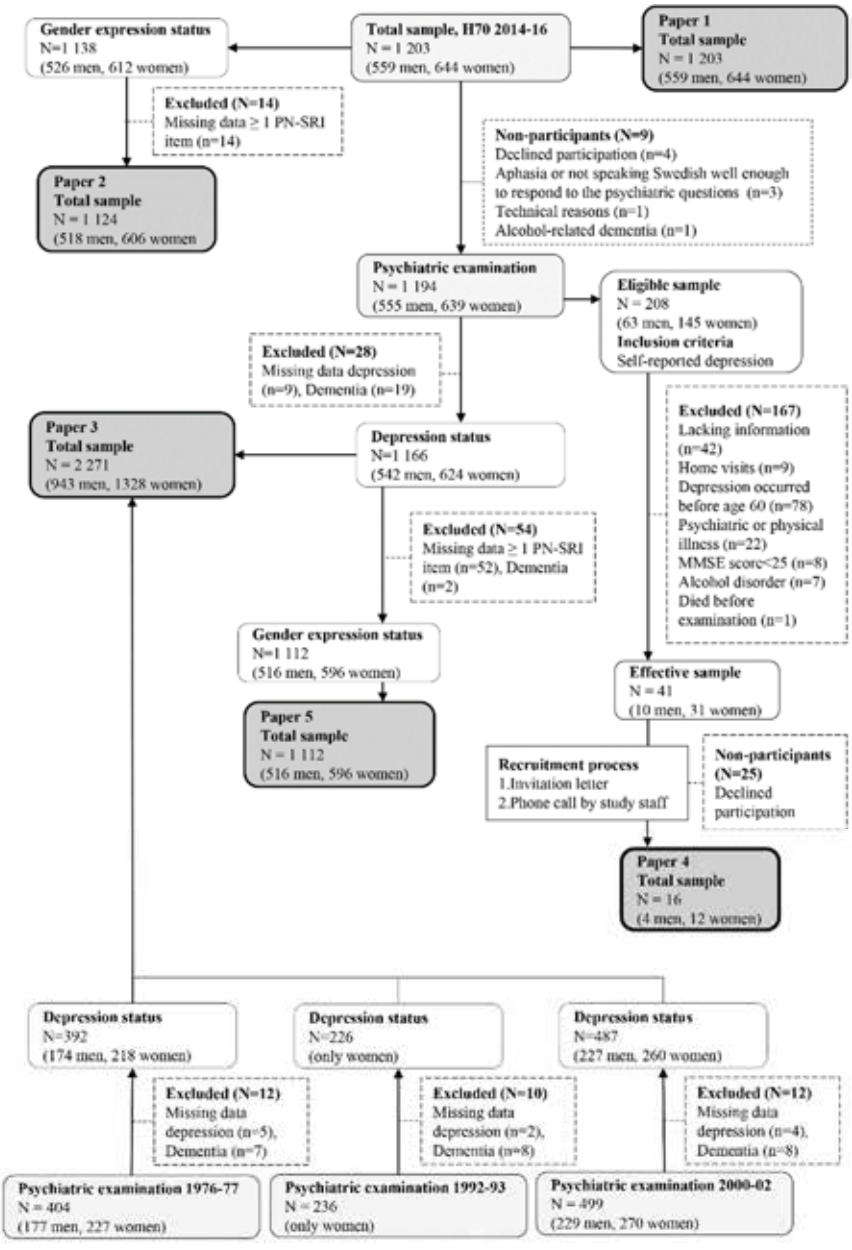


Figure 6. Sample flowchart for all five thesis papers combined. Source: Made by author.

4.3 **Data collection**

4.3.1 **The H70 study protocol**

The full extension of the study protocol for the H70 study 2014-16 examining birth cohort 1944, can be seen in *Paper I*. A brief flowchart of included examinations is displayed in Figure 7.

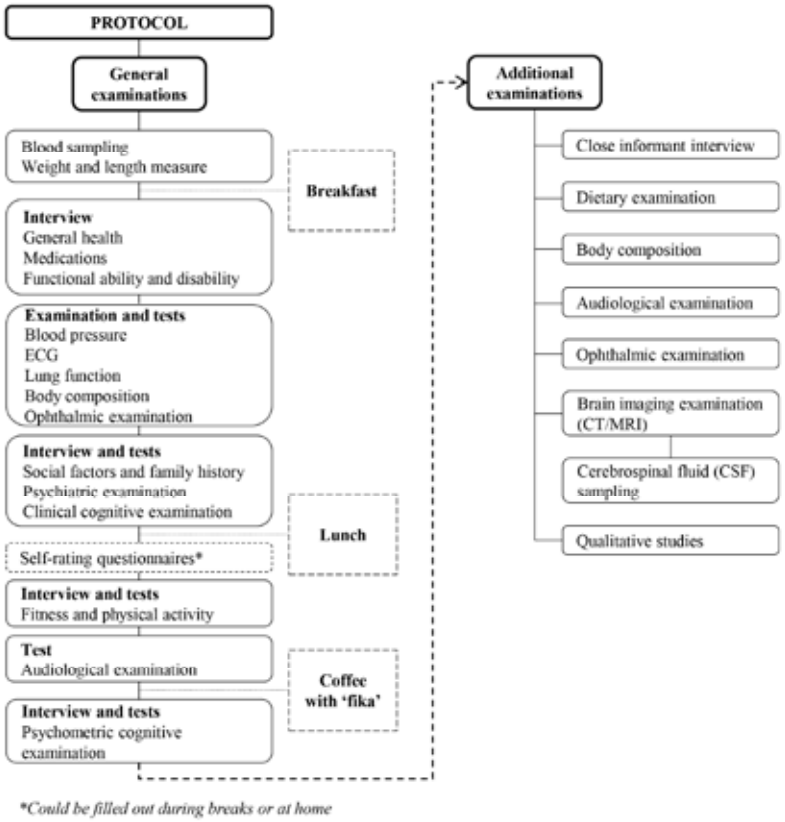


Figure 7. Flowchart of included examinations in the H70 study 2014-16. Source: *Paper 1*.

In short, the study participant visited the outpatient department for 8 hours (including lunch and coffee breaks), or divided the 8 hours between two different days, alternatively were examined during home visits. First, a physical examination was conducted. Second, interviews were performed regarding social factors, mental health, sexual habits, sleeping habits, suicidal behavior, medical history and present medical condition. Some of the questions were

answered through self-rating forms. The self-rating forms could be filled out during the day of examination, or be sent back after answering the questions at home. Third, the study participant underwent tests for cognition, memory, physical abilities and hearing. Fourth, after the day of basic examination the study participant were asked to take part in further examinations: dietary examination, computed tomography (CT-scan), magnetic resonance imaging (MRI), ophthalmological examination (only a sub sample), audiological examination (only a sub sample), lumbar puncture and/or body composition examination. Examinations have been virtually identical between the H70 studies in 1976-77, 1992-93, 2000-02 and 2014-16, although new and modern types of assessments have been added over time.

4.3.2 Psychiatric examination

The psychiatric examination consisted of a semi-structured interview and comprised the following questions: circumstances during early life, history of previous mental disorders, psychiatric symptoms during the month preceding the interview, thoughts about death and suicide, feelings of loneliness, phobias, cognitive symptoms during the month preceding the interview, and sleep patterns. In addition, the participants were asked for permission regarding interview of a close informant. Psychiatric symptoms and signs were rated in accordance with the Comprehensive Psychopathological Rating Scale (CPRS),[233] which has good reliability among older persons.[234] The diagnostic procedures regarding major and minor depression are presented below, together with ratings of burden of depressive symptoms.

4.3.3 Depression diagnosis

After the psychiatric examination, items representing depressive symptoms in CPRS were selected (see Table 7, further specified in Appendix 2). The diagnostic procedure for depression followed the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria as closely as possible, including reported symptoms during the month preceding the interview. Depression diagnoses were established using computerized symptom algorithms based on the CPRS, retrospectively applied to the responses from the psychiatric interviews at all examinations, in accordance with previous analyses from the H70 studies. This enables comparison of prevalence across the borders of

different examinations through time. The assessment was further supported by psychiatrist's clinical judgment.

Table 7. Included Comprehensive Psychopathological Rating Scale (CPRS) items, with respective cut-offs, used for diagnosing major [a] and minor [b] depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria

Depressive symptoms DSM	CPRS items (no. in parenthesis) [c]	Cut-off
1. Depressed mood	(1.) sadness	2-6
	(41.) apparent sadness (observed)	4-6
2. Diminished interest/pleasure	(5.) inability to feel	2-6
3. Change in weight or appetite	(18.) reduced appetite	2-6
4. Insomnia/hypersomnia	(19.) reduced sleep	3-6
	(20.) increased sleep	4-6
5. Psychomotor agitation /retardation	(54.) reduced speech (observed)	2-6
	(60.) slowness of movement (observed)	3-6
	(61.) agitation (observed)	3-6
6. Fatigue or loss of energy	(15.) fatiguability	3-6
	(14.) lassitude	3-6
7. Feelings of worthlessness or guilt	(6.) pessimistic thoughts	3-6
8. Diminished ability to think /concentrate or indecisiveness	(16.) concentration difficulties	4-6
	(13.) indecision	3-6
	(48.) distractibility (observed)	4-6
9. Recurrent thoughts of death or suicidal ideation	(7.) suicidal thoughts	2-6

[a] DSM-5[231]. [b] DSM-IV-TR[235]. In order for major or minor depression diagnosis to occur, either '**1.** depressed mood' or '**2.** diminished interest/pleasure' needs to be present, together with a combination of DSM symptom no. 3 to 9; [c] The listed CPRS items are included in the computerized symptom algorithm. Where several CPRS items are listed for the same DSM symptom, only one needs to be present in order to fulfil the DSM symptom criteria.

Major depression was diagnosed according to DSM-5,[231] and required the presence of at least 5 out of 9 pre-specified depressive symptom clusters of which one needed to be the cardinal symptoms depressed mood or diminished interest/pleasure. Minor depression was diagnosed according to DSM-IV-TR[235] research criteria and required the presence of 2–4 of the same pre-specified symptoms as for major depression. For the purpose of this thesis, the term "any depression" was used to denote those fulfilling criteria for either major or minor depression. The DSM diagnostic criteria are displayed in Appendix 1.

4.3.4 **Burden of depressive symptoms**

Depressive symptoms were also rated according to the Montgomery-Åsberg Depression Rating Scale (MADRS)[236] to assess the overall burden of depressive symptoms. MADRS is a subscale of CPRS and include 10 items for the rating

of depressive symptom burden (see Table 8). MADRS was created in the 1970's. CPRS ratings was performed in English and Swedish patient samples, identifying the most common symptoms for those having depression. The aim was to create a depression scale sensitive to change in order to follow symptom trajectory over time. Further, MADRS has been validated among older adults.[237]

Table 8. Depressive symptoms included in the Montgomery Åsberg Depression Rating Scale (MADRS)

Depressive symptoms MADRS	Included in DSM [a]	CPRS items (no. in parenthesis) [b]
1. Apparent sadness	Yes	(41.) apparent sadness (observed)
2. Sadness	Yes	(1.) sadness
3. Inner tension	*No*	(3.) inner tension
4. Reduced sleep	Yes	(19.) reduced sleep
5. Reduced appetite	Yes	(18.) reduced appetite
6. Concentration difficulties	Yes	(16.) concentration difficulties
7. Lassitude	Yes	(14.) lassitude
8. Reduced emotional engagement	Yes	(5.) inability to feel
9. Pessimistic thoughts	Yes	(6.) pessimistic thoughts
10. Suicidal thoughts	Yes	(7.) suicidal thoughts

[a] Status yes/no for whether the MADRS symptom also is included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for depression diagnosis. [b] the Comprehensive Psychopathological Rating Scale.

In this thesis, individual items were rated from 0 (no symptoms) to 6 (severe symptoms), generating a MADRS-score ranging between 0-60. Previous studies have used a cut-off including >9[238,239] or >21[237] for having depression. However, as MADRS score have been utilized as a measure for symptom burden in this thesis, no cut-off has been used.

4.3.5 **Gender expression**

The Positive–Negative Sex-Role Inventory (PN-SRI) assesses gender expression and was originally developed, tested and published in Germany in 2013.[159] In the H70 study 2014-16, PN-SRI was added into the data collection battery as the first instrument measuring gender expression. The validity and reliability testing of PN-SRI, utilizing the H70 study sample, are described in detail in *Paper 2*. PN-SRI comprises 24 gender-coded personality traits (see Table 9). The items are coded as masculine or feminine, and contain dimensions of social desirability (marked by: desirable '+' or undesirable '–'). As of data collection, all items are self-reported on a seven-step scale, ranging from one point (never or almost never true) to seven points (always or almost always

true). The item coding of femininity, masculinity and social desirability are not disclosed to the study participants.

Table 9. The 24 gender-coded personality traits in the Positive-Negative Sex-Role Inventory (PN-SRI), divided into the masculinity scales and the femininity scales

Masculinity		**Femininity**	
MAS+ items	**MAS- items**	**FEM+ items**	**FEM- items**
Analytical	Arrogant	Emotional	Anxious
Logical	Boastful	Empathic	Disoriented
Objective	Harsh	Loving	Naïve
Practical	Inconsiderate	Passionate	Overcautious
Rational	Ostentatious	Sensitive	Oversensitive
Solution-focused	Power-hungry	Tender	Self-doubting

Source: Krahé & Berger,[159] modified by author. Abbreviations: PN-SRI= Positive-Negative Sex-Role Inventory; FEM(+)=Feminine personality traits (desirable); FEM(-)=Feminine personality traits (undesirable); MAS(+)= Masculine personality traits (desirable); MAS(-)=Masculine personality traits (undesirable).

Original development of PN-SRI

The original development of PN-SRI was described in detail in its original publication.[159] In summary, the original creators of PN-SRI[159] aimed to construct an instrument comprising both socially desirable and undesirable traits, as previous measures of gender expression had mainly focused on including desirable traits.[158,240-242] The two most widely used instruments measuring femininity and masculinity are the Personal Attribute Questionnaire (PAQ)[241] and the Bem Sex-Role Inventory (BSRI),[158] both created during the 1970's. PN-SRI was created based on two arguments: (1) some items in e.g. BSRI are no longer valid in distinguishing between femininity and masculinity as gender-related norms have changed over time; and (2) socially undesirable aspects of gender expression make unique contributions in understanding gender-related differences in health. The steps taken towards creating PN-SRI are summarized in Table 10.

Table 10. A summary of how the Positive-Negative Sex-Role Inventory (PN-SRI) was created

Step	Aim	Method and Result
1. Item pool	Generate pool of socially desirable and undesirable attributes, either stereotypically more common for each sex	*Sample*: n=197 (82 men, 115 women), mean age 29.2. *Data collection*: All participants were asked to list ≤ 7 desirable and undesirable attributes respectively, which they considered were more typical for either sex. *Inclusion criteria* for item selection: (1) it had been listed by at least 2 % of the sample; and (2) it had been nominated by both men and women as typical for one sex, but not for the other sex. *Exclusion criteria*: Synonyms and antonyms. *Result*: 127 items were selected.
2. Reduce item pool	Select a reduced set of attributes for the final scales	*Sample*: A new sample were selected, comprising three groups: (1) n=277 (133 men, and 144 women), mean age 23; (2) n=1 212 (582 men, and 630 women); and (3) n=1 687 (574 men, and 1113 women), mean age 22.8. *Data collection*: Group (1): rate the desirability for all items. Group (2): rate the item typicality by sex. Group (3): rate themselves according to all items (not knowing the present coding). *Analysis*: ANOVAs. *Inclusion criteria*: (1) desirable items rated above scale midpoint, undesirable items below scale midpoint, by both sexes; (2) consensus in desirability ratings by sex; (3) typicality ratings above scale midpoint for each gender group; (4) typicality ratings different between gender groups; and (5) difference in self-ratings by sex. *Result*: 24 items were selected.
3. Testing	Test the reliability and validity of the femininity and masculinity scales	*Sample*: n=800 (272 men, and 528 women), mean age 23. *Analysis*: ANOVA, factor analysis, Pearson correlation. *Result*: Internal consistency (α = .73 to .88). Item correlation > 0.3. Men scored higher on masculine items, women scored higher on feminine items. Retest reliability (α = .61 to .86). Four factor model, acceptable model fit ($\chi 2/df=2.25$, CFI = 0.96, RMSEA=0.04).

Source: Krahé & Berger,[159] summarized by author. Abbreviations: CFI=comparative fit index; RMSEA=root-mean-square error of approximation.

Femininity, masculinity and androgyny scores

The 24 items generate a femininity scale (12 items) and a masculinity scale (12 items), ranging between 12 and 84 points. Higher scores indicate higher level of femininity/masculinity. Based on the classification of social desirability, the femininity and masculinity scales comprise two sub-scales each (as seen in Table 9 above). FEM+ reflects desirable feminine traits, FEM- reflects undesirable feminine traits, MAS+ reflects desirable masculine traits, and MAS- reflects undesirable masculine traits. Each sub-scale ranges from 6 to 42 points. For the purpose of this thesis, both an androgyny t score and androgyny difference score are used in order to increase comparability to previous studies. The androgyny scores indicate that both feminine and masculine traits are present, without femininity or masculinity being dominant. The calculations are made in accordance to previous studies.[158] An androgyny t score was calculated as the ratio (Student's t ratio) between masculine and feminine items (ratio=masculinity/femininity), reflecting the relative amount of masculinity and femininity ($[t] \geq 2.09$; $df=22$; $p<0.05$). An androgyny difference score was calculated as the difference between the masculinity score and the femininity

score (difference=masculinity – femininity). A value closer to 0 (for both the t score and the difference score) indicates an androgynous gender expression where both masculine and feminine personality traits are endorsed, while the opposite indicates a gender-typed expression where either masculine or feminine personality traits are dominant.

4.3.6 **Focus group discussions**

Qualitative methods, such as focus group methodology, have specific focus on the participants collective understanding of a phenomenon based on personal descriptions and stories.[243,244] Focus group discussion is a form of group interview where people meet and are asked to discuss a specific topic. This discussion captures a collective understanding of participants' shared phenomena,[245] in this case having experienced early late-life depression. The focus group discussions were conducted at the same outpatient clinic as the main examinations within the H70 study. The participants were divided into 4 focus groups, with 3-5 participants in each. Each focus group lasted for approximately 1.5 hours. The moderator began the session by clarifying that they (the participants) were the experts in this context, and that we (as researchers) could learn from their experiences. The moderator recalled the aim of the study and introduced the first discussion topic. The topic guide included open ended discussion points about overall experience of depression, gender norms in relation to depression, coping, and depression treatment. The participants were encouraged to discuss openly, although only to disclose as much information as they felt comfortable with. During the discussion, the moderator posed questions in order to deepen the discussions and ensured that all participants were given the chance to speak. All focus group discussions were audio-recorded.

4.3.7 **Additional factors**

Dementia and cognitive impairment

Each examination included a psychiatric interview, observations of psychiatric symptoms and an extensive battery of cognitive tests. Also, close informant interviews were performed via telephone including questions about changes in behavior and intellectual function, psychiatric symptoms, activities of daily living and, in cases of dementia, age of onset and disease course. Diagnoses of dementia were established combining information from the psychiatric- and

close informant interviews based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R),[246] which previously has been described in detail.[247] We were not able to diagnose dementia according to DSM criteria in 1976–77. To enable the time trend analysis in *Paper 3*, dementia was instead diagnosed according to criteria described by Kay et al.[248] for all included examinations (1976-77, 1992-93, 2000-02, and 2014-16). These criteria required the presence of severe disorientation in time or place or severe memory impairment as assessed during the psychiatric examination. In 2000–02, we were able to diagnose dementia according to both the criteria described by Kay et al. and DSM-III-R. The observed agreement between the two was high (K = 0.81).[249] In *Paper 3* and *5*, participants having dementia were excluded from the analyses, due to the difficulty of diagnosing depression when dementia is present (e.g. due to a difficulty in answering questions when cognitively impaired). In *Paper 2*, data collection using the additional survey (regarding face validity) (n=406) did not include those having dementia. However, dementia was not an exclusion criterion for the further psychometric evaluation using the total sample that had completed PN-SRI during their participation in the H70 study (n=1 124). Out of 1 124, ten participants were diagnosed with dementia. This is not considered to have negatively affected the results. In *Paper 4*, data collection using focus groups was performed short after the H70 study had ended, and before dementia diagnoses had been thoroughly evaluated. Instead, we used the Mini-mental State Examination (MMSE)[232] score < 25 as exclusion criteria.

Demographics and co-variates

All factors presented below were based on self-reported information. Regulations for mandatory years in Swedish primary education ([folkskola] and/or [grundskola]), have changed several times during the 20th century. Changes in number of years for, as well as type of, secondary education have also occurred ([realskola], [läroverk], [gymnasium] and/or [yrkesutbildning]). In *Paper 3*, this generated different cut-off points for **educational level**. In order to compare over time, we were only able to use a dichotomized education variable (≤ primary education vs. > primary education). Primary education was defined as ≤6 years in 1976-77 and 1992-93 (cohort born 1906–07 and 1922), ≤7 years in 2000-02 (cohort born 1930), and ≤9 years in 2014-16 (cohort born 1944). In *Paper 5*, since only using the 2014-16 examination (cohort born 1944),

we were able to define highest level of education (irrespective of number of years) as 'primary' ([folkskola] and/or [grundskola]), 'secondary' ([realskola], [läroverk], [gymnasium] and/or [yrkesutbildning]) and 'higher' (i.e. university studies or [högskola] with or without degree). **Neuroticism** was measured with the Eysenck Personality Inventory (EPI).[250,251] The neuroticism score ranges from 0 to 24, where high scores represent emotional overreaction combined with low ego-strength, guilt proneness, anxiety, and psychosomatic concerns. **Country of birth** was dichotomized as Sweden versus other in *Paper 5*, while *Paper 1* also reported the categories Nordic or European countries. **Type of residence** was categorized as 'ordinary' (e.g. private household) vs. 'special housing' (e.g. sheltered living). We also asked if the participant was living alone or not. **Having partner** included married, and having non-cohabiting or cohabiting partner. We further asked **if the relationship was happy** or not, and if the partner received **informal care** from the participant. All participants were asked if they had **children**, at least one **confidant**, if they had **lost their partner** during the past five years due to death or divorce, if they **felt lonely**, and their status for **current employment**. Having **contact with health care** was defined as contact with medical doctor or nurse during the past 3 or 12 months. **Self-rated health**, measured with SF-36,[252] was defined as 'good' (including 'good, very good and excellent') or not. **Smoking** was dichotomized as current smoker vs nonsmoker and past smoker. Also, we asked all to report their medications, doses and indications for treatment. **Antidepressants** (N06A) were classified according to the Anatomical Therapeutic Chemical (ATC) classification system recommended by the WHO.[253] **High alcohol consumption** was defined as ≥100 g per week (guidelines by the National Institute on Alcohol Abuse and Alcoholism (NIAAA)), previously described in detail.[254] We also asked if the participant was experiencing **back or joint pain** (joint pain also included stiff or swollen joints).

4.4 **Data analyses**

In *Paper 1, 2, 3* and *5*, statistical tests were two-tailed and p-values < 0.05 were considered statistically significant. The analyses were carried out using IBM SPSS STATISTICS 22 or R program for data transformation and computation (version 3.6.0 package DPLYR for data wrangling or Lavaan package). In *Paper 4*, qualitative focus-group method was used to analyze the material.

Paper 1. Frequencies and proportions were extracted using descriptive statistics. Comparative statistics for sample characteristics were added under Main Results of this thesis. Differences in proportions were compared using Pearson's Chisquare, differences in mean were analyzed using independent samples t-test, and differences in median were analyzed using Mann-Whitney U Test.

Paper 2. Kolmogorov-Smirnov test was used to test scale distribution. Cronbach's alpha was used to test internal consistency. Fisher's exact test was used to test differences in proportions. Pearson's correlation test was used to test scale item correlations. Exploratory and confirmatory factor analyses were conducted in order to test construct validity.

Paper 3. Fisher's exact test was used to test differences in proportions. ANOVA (analysis of variance) and independent samples t-tests were used in order to compare mean values of MADRS score and neuroticism between birth cohorts. Logistic regression was used in order to compare prevalence rates of depression between birth cohorts. GLM (Generalized Linear Model) and logistic regression were used in order to test for possible effect modifications of sex or neuroticism.

Paper 4. Digital recordings were transcribed verbatim and reviewed for accuracy in transcription. The analysis was conducted in Swedish as far as possible in order to be close to the raw material, and followed the analytical steps described by Krueger and Casey.[244] First, the audio recordings were listened to several times to get an overall sense of the data. Second, the transcriptions were carefully read independently by each author conducting the analysis. Third, guided by the study aim, relevant themes were identified into which the material was sorted. Specific attention was paid to gender-related discussions. Fourth, sub-themes emerging from our review were defined within each theme. Descriptive statements synthesizing, abstracting, and conceptualizing the data were extracted from the raw material. Finally, the categorized material was summarized and interpreted in order to provide an overall understanding. The analysis was conducted using NVivo 12 software.

Paper 5. Pearson's Chi-square was used to test differences in proportions. Independent samples t-test was used to test differences in means. Linear regression was used to test associations between gender expression and MADRS score (Model 1), with sex as covariate in Model 2. Binary logistic regression was used to test sex differences in the prevalence of depression (crude odds ratios with 95 % confidence intervals), and associations between

gender expression and any depression (Model 1), adding sex as covariate in Model 2. To select covariates for the fully adjusted Model 3, linear regression was first used to test the association of each potential confounder in relation to MADRS, femininity, masculinity, and androgyny scores. Only covariates that were associated with both depression and gender expression were included. In order to check for potential effect modification by sex, the interaction terms sex*(femininity, masculinity, androgyny) was added in regressions models. All sensitivity analyses were performed using linear regression models.

4.4.1 **Missing data**

No imputation for missing data was performed. In *Paper 1*, sample sizes for each examination were reported, although not considering whether the participation was made in part or in full. In *Paper 2*, out of those included in the psychometric testing (n=1 124), we excluded those with missing data on PN-SRI items > 1 (n=14; 1.1 %). Out of those included in the sub-sample providing the test for face validity (n=406), we did not exclude those with missing data (n=28; 6.9 %) for the 48 validation items (confirming or refuting gender norms, and social desirability norms). Out of the 28 persons having missing data, nine had missing data on 1 item, ten had missing data on < 10 items, and nine had missing data on < 24. Table 11 shows the pattern of missing responses.

Table 11. Number of missing datapoints for each PN-SRI item regarding face validity (gender-related and social desirability norms), provided by the sub-sample

Missing data face validity							
		♥	☿			♥	☿
MAS+, %(n)	Analytical	**1.0** (4)	**1.7** (7)	**FEM+**, %(n)	Emotional	**1.2** (5)	**1.7** (7)
	Logical	**0.7** (3)	**2.7** (11)		Empathic	**0.7** (3)	**1.7** (7)
	Objective	**1.0** (4)	**2.9** (12)		Loving	**0.7** (3)	**2.2** (9)
	Practical	**0.7** (3)	**2.2** (9)		Passionate	**1.0** (4)	**2.2** (9)
	Rational	**0.7** (3)	**1.7** (7)		Sensitive	**0.7** (3)	**1.9** (8)
	Solution-foc.	**0.7** (3)	**1.5** (6)		Tender	**0.7** (3)	**1.9** (8)
MAS–, %(n)	Arrogant	**0.7** (3)	**2.7** (11)	**FEM–**, %(n)	Anxious	**0.7** (3)	**2.2** (9)
	Boastful	**0.7** (3)	**2.7** (11)		Disoriented	**0.7** (3)	**2.7** (11)
	Harsh	**1.0** (4)	**1.9** (8)		Naïve	**1.0** (4)	**3.2** (13)
	Inconsiderate	**0.7** (3)	**2.2** (9)		Overcautious	**0.7** (3)	**1.7** (7)
	Ostentatious	**1.9** (8)	**3.2** (13)		Oversensitive	**0.7** (3)	**2.2** (9)
	Power-hungry	**0.7** (3)	**1.9** (8)		Self-doubting	**1.0** (4)	**1.9** (8)

N=406. ♥Social desirability. ☿ Gender stereotypic femininity or masculinity. Abbreviations: MAS(+)= Masculine attributes (socially desirable); MAS(-)=Masculine attributes (socially undesirable); FEM(+)=Feminine attributes (socially desirable); FEM(-)=Feminine attributes (socially undesirable).

In *Paper 3* and *5*, participants for whom depression diagnosis could not be established due to missing data on depressive symptoms were excluded from the analyses. Out of those participating in the psychiatric examination, the following numbers of participants were excluded from the analyses due to missing data on depression in 1976-77: (n=5; 1.2 %); in 1992-93: (n=2; 0.8 %); in 2000-02: (n=4; 0.8 %); and in 2014-16: (n=9; 0.7 %). In *Paper 5*, after excluding those with missing data on depression (n=9) and those having dementia (n=22), we also excluded those with missing data on PN-SRI items > 1 (n=52; 4.5 %).

4.5 Ethical considerations

The H70 studies were approved by the Ethics Committee for Medical Research at the University of Gothenburg 1976–2000 (approval number 52/76: 1976-03-22; approval number 179-92: 1992-05-19; and approval number S227-00: 2000-08-24) and by the Regional Ethical Review Board in 2014 (approval number 869-13: 2013-11-21). All examinations were conducted according to the Helsinki Declaration. All study participants provided written informed consent prior to the general and additional examinations. Consent [samråd] was obtained from a relative if the participant was unable to provide own consent. Travel checks for local transportation were offered upon request. Taxis were booked and pre-paid by the study for participants in need of assisted transportation. All participants examined at the Neuropsychiatric outpatient department were offered complimentary breakfast, lunch and afternoon snack. No other financial compensation was given. The focus group study was approved by the Regional Ethical Review Board (approval number 959-15: 2016-02-03). Informed consent was obtained from all participants. No financial compensation was offered.

The H70 study contain a large variety of interviews and tests. The magnitude of the study may be perceived as demanding for participants, especially for those having a high burden of disease. Most participants have taken part in most examinations, and have returned to follow-up examinations over several decades generating high response rates. In addition, participants could opt to take the examination over several days, and home visits were also offered as an alternative. In addition, when adding newly developed instruments in the H70 study research setting (as the gender scale PN-SRI) we considered it to be

important to test its psychometric properties in order to evaluate the suitability within the target population (in this case older adults).

4.5.1 **Participation experience**

Following the baseline examination for birth cohort 1944 in 2014-16, participants were invited to additional focus group discussions.[255] These discussions aimed to explore the participant's motives, understandings and experiences of their study participation. After nine conducted focus group discussions, the overall theme "It was well worth the effort" emerged, summarizing the participant's experiences. Despite expressing mixed views concerning various aspects of the H70 study content, their participation was described as being worthwhile, overall. They expressed that the study had been an intense event, both regarding their time and efforts, but also regarding the risk of receiving unexpected results of their physical and mental health status. One of the key reasons for accepting the invitation to participate in the H70 study was for the benefit of oneself and others. They expressed gratitude towards getting a free and thorough health check-up as a 'receipt' for being healthy or for being informed whether or not they were in need of health-care treatments. They also expressed trust towards health research and the researcher, which was an important element in the tendency of sharing their thoughts, feelings, prior and current diagnoses or symptoms of illness, testing for memory function, giving blood samples etc., but also the trust that the results from our research gain their own children and grandchildren and future generations of older persons.

5. **Main Results**

The main results for each of the five individual papers included in the thesis are presented below. For complete results sections, please see the re-printed publications and manuscripts at the end of the thesis.

Illustration: Original by author, graphically illustrated by Jonathan Sterner.

5.1 **Paper 1**

Rydberg Sterner T & Ahlner F, et al. *The Gothenburg H70 Birth Cohort Study 2014-16: design, methods and study population.* Eur J Epidemiol 2019:34(2):191-209

Paper 1 gives a methodological description of the baseline examination of birth cohort 1944 which is part of the Gothenburg H70 Birth Cohort Studies (the H70 studies). As all papers in this thesis are based on this examination, *Paper 1* introduces the data framework. A total of 1 203 (response rate 72.2%; 559 men and 644 women; mean age 70.5 years) agreed to participate. Sample characteristics is shown in Table 12. An overview of response rates is shown in Figure 8.

Table 12. Sample characteristics of 70-year-olds born 1944, participating in the H70-study 2014-16

	N (♂/♀)	All	♂	♀	*p* [c]
Marital status, % (n)					
Having partner [a]	1 196 (558/638)	**70.7** (845)	**80.5** (449)	**62.1** (396)	***
Education [b], **%** (n)					
≤ Primary education	1 196 (556/640)	**14.7** (176)	**16.9** (94)	**12.8** (82)	0.05
Secondary education	1 196 (556/640)	**48.0** (574)	**43.7** (243)	**51.7** (331)	**
Tertiary education	1 196 (556/640)	**8.4** (101)	**7.2** (40)	**9.5** (61)	0.15
University degree	1 196 (556/640)	**26.5** (317)	**28.6** (159)	**24.7** (158)	0.13
Doctoral degree	1 196 (556/640)	**2.3** (28)	**3.6** (20)	**1.3** (8)	**
Country of birth, % (n)					
Sweden	1 195 (557/638)	**84.5** (1010)	**82.2** (458)	**86.5** (552)	**
Nordic countries	1 195 (557/638)	**5.3** (63)	**5.2** (29)	**5.3** (34)	0.93
European countries	1 195 (557/638)	**6.7** (80)	**7.5** (42)	**6.0** (38)	0.27
Other	1 195 (557/638)	**3.5** (42)	**5.0** (28)	**2.2** (14)	**
Net income/month, *mean*					
Individual income [c]	949 (448/501)	16 618	19 862	13 718	***
Individual pension [d]	740 (322/418)	15 109	17 783	13 047	***
Net income/month, *median*					
Individual income [c]	949 (448/501)	14 000	16 500	12 000	***
Individual pension [d]	740 (322/418)	13 225	15 000	12 000	***
Paid labor, **%** (n)					
Working part-time/periods	1 195 (557/638)	**19.0** (227)	**23.5** (131)	**15.0** (96)	***
Working full-time	1 195 (557/638)	**2.6** (31)	**4.8** (27)	**0.6** (4)	***
Housing, **%** (n)					
Sheltered living	1 188 (557/631)	**2.1** (25)	**2.3** (13)	**1.9** (12)	0.61

Source: *Paper 1 (Table 2)*, modified by author. Total sample n=1 203 (559 men and 644 women). [a] Including living with partner, living apart from partner, and married. [b] Highest level of education (data has been updated during 2019); ≤ Primary education (elementary school) include the Swedish [folkskola] and [grundskola] 1-10 years; Secondary education [realskola], [läroverk], [gymnasium] and/or [yrkesutbildning]; Tertiary education include studies at the university (or [högskola]) without a university degree; University degree include bachelor's and/or master's degree from university (or [högskola]); Doctoral degree from PhD studies. [c] Including paid labour and pensions (SEK). [d] Including only those not working and having pension as only income (SEK). [c]Differences in proportions were compared using Pearson's Chisquare, differences in mean were analyzed using independent samples t-test, differences in median were analyzed using Mann-Whitney U Test. ** $p<0.05$; *** $p<0.01$.

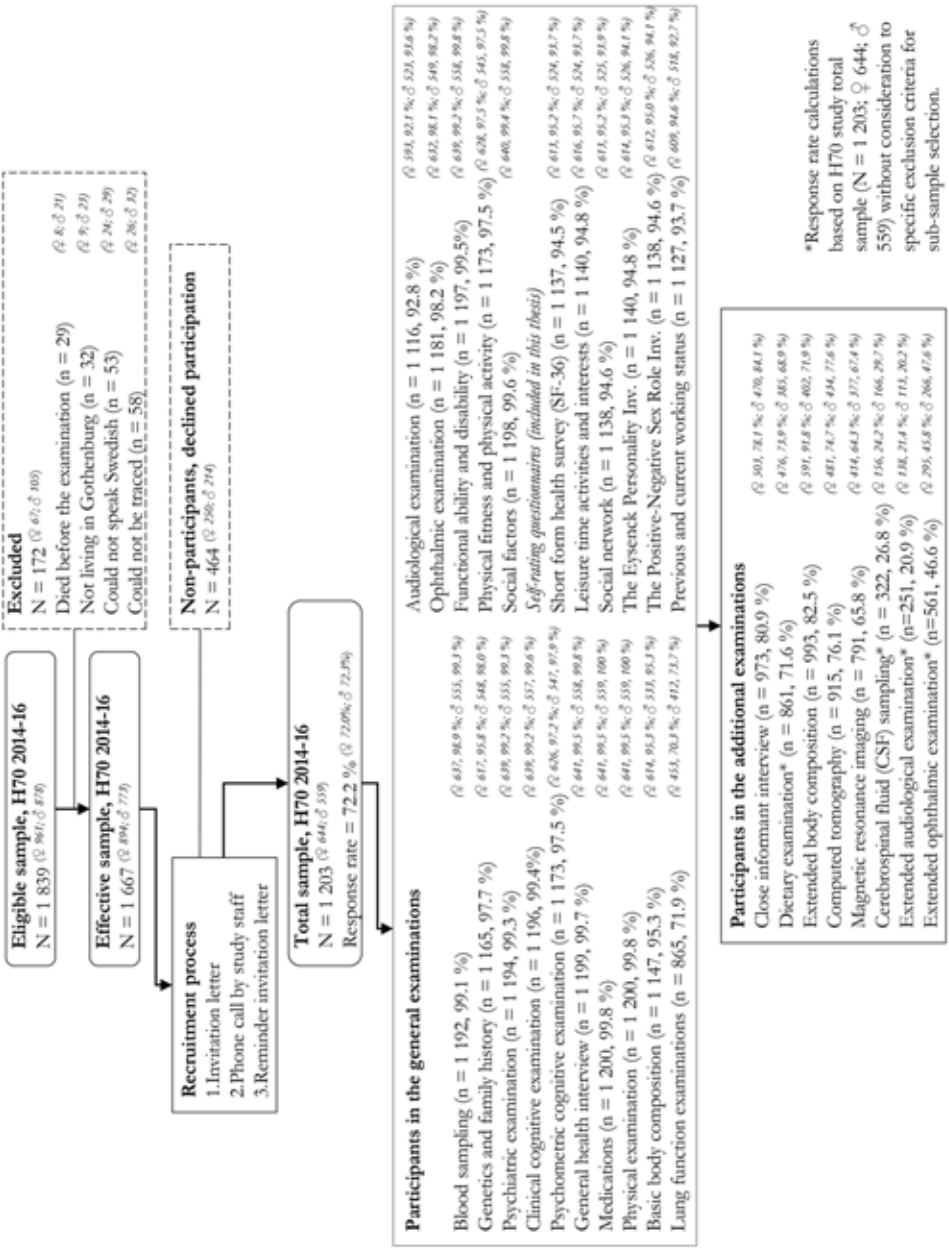


Figure 8. Sample flow chart with no. of participants and response rates by sex. Source: *Paper 1 (Figure 3)*, modified by author.

5.2 **Paper 2**

Rydberg Sterner T, et al. *A Psychometric Evaluation of a Swedish version of the Positive–Negative Sex-Role Inventory (PN-SRI) –Results from the H70-study*. Societies 2018:8(13)

In summary, the Positive-Negative Sex-Role Inventory (PN-SRI) was applicable in the H70 study, which may be generalizable to other research settings among older adults. Table 13 show scale and item distributions. Overall, we found sex differences for all but seven of the 24 attributes.

Table 13. The Positive-Negative Sex-Role Inventory score distribution

		Mean		Median	SD	Min-Max	t	df	*p*
Scales	All	♂	♀						
Masculinity	43.8	45.4	42.5	44.00	7.9	16-81	6.2	1050	**
Femininity	47.5	45.4	49.3	47.00	9.1	19-80	-7.3	1117	**
MAS+	31.0	31.6	30.5	31.00	5.5	9-42	3.5	1117	**
MAS-	12.8	13.8	12.0	12.00	5.1	6-40	6.0	1119	**
FEM+	29.8	28.4	31.0	30.00	5.5	8-42	-7.9	1118	**
FEM-	17.7	17.0	18.4	17.00	6.2	6-42	-3.7	1118	**
Attributes									
Analytical	4.9	5.1	4.7	5.00	1.4	1-7	4.9	1120	**
Empathic	5.5	5.0	5.9	6.00	1.4	1-7	-10.7	1031	**
Rational	5.3	5.3	5.3	5.00	1.2	1-7	0.6	1120	n.s.
Naïve	3.0	3.1	3.0	3.00	1.6	1-7	0.7	1120	n.s.
Sensitive	5.0	4.7	5.2	5.00	1.4	1-7	-5.1	1121	**
Arrogant	2.1	2.4	1.9	2.00	1.3	1-7	5.7	1032	**
Anxious	3.4	3.1	3.6	3.00	1.7	1-7	-4.8	1108	**
Ostentatious	2.4	2.6	2.3	2.00	1.4	1-7	3.6	1120	**
Objective	4.8	4.9	4.7	5.00	1.2	1-7	3.7	1117	**
Harsh	2.9	3.0	2.8	3.00	1.5	1-7	2.0	1119	n.s.
Oversensitive	2.8	2.6	2.9	2.00	1.7	1-7	-3.9	1118	**
Logical	5.2	5.4	5.1	5.00	1.2	1-7	4.7	1120	**
Passionate	4.3	4.3	4.2	4.00	1.4	1-7	1.6	1120	n.s.
Emotional	4.6	4.3	4.7	5.00	1.4	1-7	-5.1	1119	**
Boastful	2.2	2.4	1.9	2.00	1.2	1-7	6.7	1036	**
Practical	5.5	5.4	5.6	6.00	1.5	1-7	-2.4	1021	**
Disoriented	2.2	2.1	2.3	2.00	1.5	1-7	-1.6	1111	n.s.
Tender	5.1	4.8	5.4	5.00	1.3	1-7	-7.9	1119	**
Inconsiderate	1.6	1.7	1.6	1.00	1.1	1-7	1.9	1119	n.s.
Power-hungry	1.7	1.8	1.6	1.00	1.2	1-7	3.9	1055	**
Overcautious	3.2	3.2	3.2	3.00	1.7	1-7	-0.1	1114	n.s.
Loving	5.4	5.1	5.6	6.00	1.2	1-7	-6.3	1119	**
Self-doubting	3.2	3.0	3.4	3.00	1.6	1-7	-4.2	1112	**
Solution-focused	5.3	5.4	5.2	6.00	1.4	1-7	3.2	1113	**

Source: *Paper 2 (Table 3)*, modified by author. N=1 124. Abbreviations: PN-SRI=Positive-Negative Sex-Role Inventory; MAS(+)=Masculine attributes (socially desirable); MAS(-)=Masculine attributes (socially undesirable); FEM(+)=Feminine attributes (socially desirable); FEM(-)=Feminine attributes (socially undesirable). $^{**}p<.05$; $^{n.s.}$ $p>.05$.

Reliability tests were performed using Cronbach's α. The Cronbach's α coefficient was 0.734 (masculinity scale), 0.747 (femininity scale), 0.775 (MAS+), 0.748 (MAS-), 0.785 (FEM+), and 0.710 (FEM-), indicating a satisfactory level of internal consistency. **Validity tests** were performed using a face validity test (Table 14) among a subsample of study participants (n = 406), and factor analyses using data from the psychometric testing (n = 1 124). In summary, the four-factor model (Model 2) fitted the data at an acceptable level (root mean-square error of approximation, RMSEA = 0.068, standardized root-mean-square residual, SRMR = 0.07).

Table 14. Proportion of participants agreeing with the original classification of the 24 PN-SRI items regarding social desirability♥ and gender stereotypes☿

	Agreeableness	<50 %	>50 %	>60 %	> 70 %	>80 %	>90 %
		Subsample (n=406)		**Men** (n=187)		**Women** (n=219)	
		♥	☿	♥	☿	♥	☿
MAS+, n(%)	Analytical	367 (91.3)	313 (78.4)	170 (91.8)	150 (81.5)	196 (90.7)	162 (75.7)
	Logical	387 (96.0)	285 (72.2)	176 (95.1)	146 (80.2)	210 (96.8)	139 (65.6)
	Objective	381 (94.8)	275 (69.8)	176 (95.1)	134 (74.0)	204 (94.4)	140 (66.0)
	Practical	399 (99.0)	244 (61.5)	182 (98.4)	152 (83.1)	216 (99.5)	92 (43.2)
	Rational	386 (95.8)	272 (68.2)	178 (96.2)	147 (79.9)	207 (95.3)	125 (58.4)
	Solution-foc.	376 (93.3)	341 (85.3)	174 (94.1)	166 (90.2)	201 (92.6)	174 (80.9)
MAS–, n(%)	Arrogant	381 (94.5)	381 (96.5)	174 (94.0)	176 (96.7)	206 (94.9)	204 (96.2)
	Boastful	384 (95.3)	368 (93.2)	175 (94.6)	174 (95.6)	208 (95.9)	193 (91.0)
	Harsh	357 (88.8)	376 (94.5)	166 (90.2)	177 (96.7)	190 (87.5)	198 (92.5)
	Inconsiderate	391 (97.0)	388 (97.7)	179 (96.8)	179 (97.8)	211 (97.2)	208 (97.7)
	Ostentatious	300 (75.4)	242 (61.6)	139 (75.9)	121 (66.9)	160 (74.7)	120 (56.9)
	Power-hungry	385 (95.5)	391 (98.2)	179 (96.8)	180 (98.4)	205 (94.5)	210 (98.1)
FEM+, n(%)	Emotional	304 (75.8)	381 (95.5)	144 (77.8)	174 (95.1)	159 (73.9)	206 (95.8)
	Empathic	381 (94.5)	387 (97.0)	175 (94.5)	173 (94.0)	205 (94.4)	213 (99.5)
	Loving	386 (95.8)	385 (97.0)	177 (95.7)	174 (94.6)	208 (95.9)	210 (99.1)
	Passionate	330 (82.1)	331 (83.4)	155 (83.7)	145 (79.2)	174 (80.5)	186 (87.3)
	Sensitive	236 (58.6)	381 (95.7)	117 (63.2)	171 (93.4)	118 (54.3)	209 (97.7)
	Tender	381 (94.5)	385 (96.7)	177 (95.7)	174 (94.6)	203 (93.5)	210 (98.6)
FEM–, n(%)	Anxious	369 (91.6)	370 (93.2)	163 (88.1)	162 (89.0)	206 (94.9)	207 (96.7)
	Disoriented	394 (97.8)	328 (83.0)	180 (97.3)	141 (77.5)	213 (98.2)	186 (87.7)
	Naïve	370 (92.0)	317 (80.7)	169 (91.3)	136 (74.7)	200 (92.5)	180 (85.7)
	Overcautious	359 (89.1)	376 (94.2)	159 (85.9)	165 (90.2)	199 (91.7)	210 (97.7)
	Oversensitive	380 (94.3)	377 (95.0)	171 (92.4)	171 (93.4)	209 (96.3)	205 (96.2)
	Self-doubting	378 (94.0)	355 (89.2)	173 (93.5)	149 (81.4)	205 (94.9)	205 (95.8)

Source: *Paper 2 (Table 4)*, modified by author. Missing data is seen in Table 11 (*4.4.1 Missing data*). ♥Classification of socially desirable or undesirable attributes (yes/no). ☿ Classification of gender stereotypic feminine or masculine attributes (yes/no). Original classifications of the 24 PN-SRI items: MAS(+)= Masculine attributes (socially desirable); MAS(-)=Masculine attributes (socially undesirable); FEM(+)=Feminine attributes (socially desirable); FEM(-)=Feminine attributes (socially undesirable).

5.3 **Paper 3**

Rydberg Sterner T, et al. *Depression and neuroticism decrease among women but not among men between 1976-2016 in Swedish septuagenarians*. Acta Psych Scand 2019:139(4):381-394

We found that depressive symptom burden (MADRS) and neuroticism decreased among women but not among men between 1976 and 2016 among a population-based sample of 70-year-olds (Table 15).

Table 15. Burden of depressive symptoms and neuroticism score by sex and examination year/birth cohort

Examination year	1976-77	1992-93	2000-02	2014-16
Birth cohort	1906-07	1922	1930	1944
MADRS score‡, mean(sd)				
N (men/women)	(174/218)	(†/226)	(227/260)	(542/624)
All	4.8 (5.8)¶	†	4.6 (5.5)¶	4.0 (5.1)
Men	3.6 (4.4)	†	3.9 (4.7)	3.6 (4.6)
Women	5.8 (6.5)¶	6.1 (7.3)¶	5.4 (6.1)	4.4 (5.4)
Neuroticism, mean(sd)				
N (men/women)	(151/178)	(†/194)	†	(520/602)
All	7.8 (4.9)¶	†	†	6.1 (3.9)
Men	6.1 (4.1)	†	†	5.5 (3.8)
Women	9.2 (5.0)§¶	7.7 (4.1)¶	†	6.6 (3.9)

Source: *Paper 3 (Table 2)*, modified by author. † Data not available for this birth cohort. ‡ Montgomery Åsberg Depression Rating Scale (MADRS). § Difference compared to 1992-93 ($p<0.05$). Difference compared to 2014-16 ($p<0.05$).

Time trends for the diagnoses of major, minor, and any depression were less clear (Figure 9). In the total sample, the lowest prevalence for minor and any depression was noted in 2014–16, while that of major depression remained stable. Odds ratios for each birth cohort comparison (in Figure 9), is shown in Table 16.

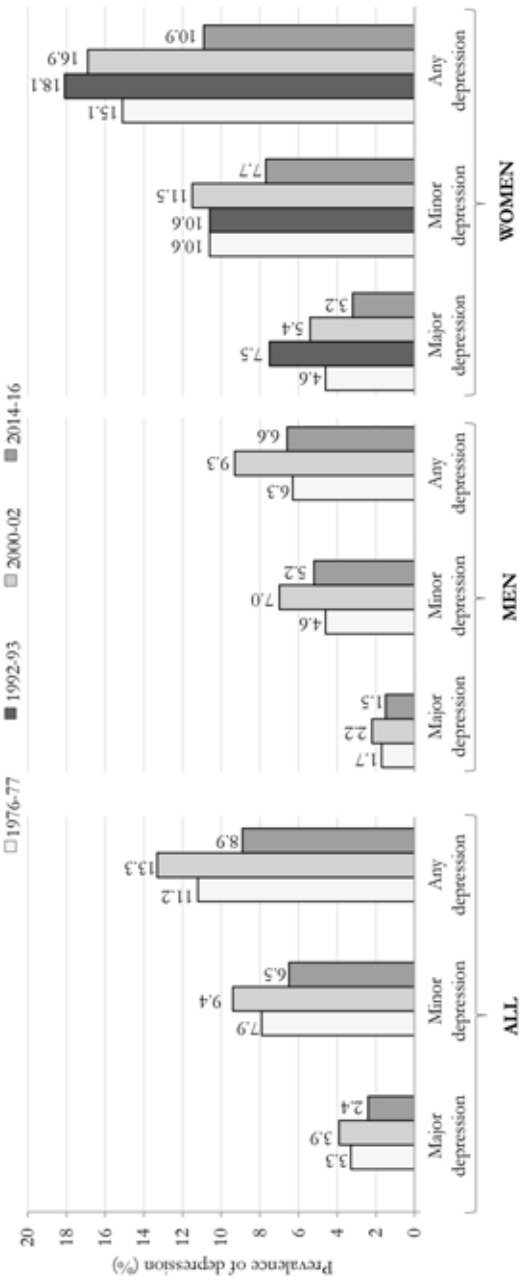


Figure 9. Prevalence of major, minor and any depression by sex and examination year. Source: *Paper 3 (Figure 1)*, modified by author.

Table 16. Odds ratios for each birth cohort comparison in depression prevalence by sex

		Odds Ratio, (95 % CI)		
		Major depression	Minor depression	Any depression
All				
	2000-02 *vs.* 1976-77	1.2 (0.61-2.56)	1.3 (0.80-2.10)	1.3 (0.86-1.94)
	2014-16 *vs.* 2000-02	0.6 (0.32-1.06)	**0.7** (0.46-0.98)***	**0.6** (0.45-0.87)***
	2014-16 *vs.* 1976-77	0.7 (0.37-1.42)	0.9 (0.55-1.32)	0.8 (0.56-1.17)
Men				
	2000-02 *vs.* 1976-77	1.3 (0.31-5.54)	1.6 (0.67-3.83)	1.5 (0.72-3.28)
	2014-16 *vs.* 2000-02	0.7 (0.21-2.05)	0.7 (0.36-1.30)	0.7 (0.38-1.19)
	2014-16 *vs.* 1976-77	0.9 (0.23-3.30)	1.1 (0.49-2.48)	1.0 (0.52-2.09)
Women				
	1992-93 *vs.* 1976-77	1.8 (0.82-4.11)	1.1 (0.60-2.01)	1.4 (0.83-2.25)
	2000-02 *vs.* 1976-77	1.3 (0.56-2.94)	1.2 (0.68-2.14)	1.2 (0.76-2.04)
	2000-02 *vs.* 1992-93	0.7 (0.34-1.45)	1.1 (0.62-1.93)	0.9 (0.57-1.46)
	2014-16 *vs.* 1976-77	0.7 (0.32-1.54)	0.8 (0.47-1.32)	0.7 (0.48-1.17)
	2014-16 *vs.* 1992-93	**0.4** (0.20-0.75)***	0.7 (0.43-1.19)	**0.5** (0.36-0.84)***
	2014-16 *vs.* 2000-02	0.6 (0.27-1.12)	0.7 (0.40-1.05)	**0.6** (0.40-0.90)***

Source: Based on unpublished data from *Paper 3*. 1976-77 (n=174 men, 218 women), 1992-93 (n=226 women), 2000-02 (n=227 men, 260 women), 2014-16 (n=542 men, 624 women). *** $p < 0.05$

Women had higher prevalence of any depression compared with men at all examinations (Table 17). The sex ratio seems to have decreased across the study period (however, overlapping confidence intervals). There were no sex differences in burden of depressive symptoms (MADRS score) among those having depression.

Table 17. Sex differences in depression in 70-year-olds by examination year/birth cohort

Examination year	1976-77		2000-02		2014-16	
Birth cohort	1906-07		1930		1944	
	♀ **vs** ♂	*p*	♀ **vs** ♂	*p*	♀ **vs** ♂	*p*
Total sample						
MADRS score (mean)	5.8/3.6	***	5.4/3.9	***	4.4/3.6	***
Participants without depression						
MADRS score (mean)	3.8/2.8	***	3.4/2.8	*0.05*	3.0/2.8	*0.20*
Participants with major depression						
No. of cases with major depression	(10/3)		(14/5)		(20/8)	
OR, *(95 % CI)*	2.7 (0.7-10.1)	*0.13*	2.5 (0.9-7.1)	*0.08*	2.2 (1.0-5.1)	*0.06*
MADRS score (mean)	26.9/19.3	*0.12*	21.6/20.2	*0.65*	23.8/26.6	*0.17*
Participants with minor depression						
No. of cases with minor depression	(23/8)		(30/16)		(48/28)	
OR, *(95 % CI)*	2.5 (1.1-5.7)	***	1.7 (0.9-3.2)	*0.09*	1.5 (0.9-2.5)	*0.08*
MADRS score (mean)	12.8/12.9	*0.97*	12.6/12.4	*0.91*	12.4/11.2	*0.23*
Participants with any depression						
No. of cases with any depression	(33/11)		(44/21)		(68/36)	
OR, *(95 % CI)*	2.6 (1.3-5.4)	***	2.0 (1.1-3.5)	***	1.7 (1.1-2.6)	***
MADRS score (mean)	17.1/14.6	*0.41*	15.5/14.3	*0.50*	15.8/14.6	*0.44*

Source: *Paper 3 (Table 3)*, modified by author. 1976-77 (n=174 men, 218 women), 2000-02 (n=227 men, 260 women), 2014-16 (n=542 men, 624 women). *** $p < 0.05$

5.4 **Paper 4**

Rydberg Sterner T, et al. *"I wanted to talk about it, but I couldn't". A focus group study about experiencing late life depression - results from the H70 study (submitted)*

As *Paper 4* includes unpublished results, the following summary of main results is downsized. In total, 16 participants (derived from the H70 study) accepted to take part in the study. Four focus group discussions were conducted. The overall theme that emerged from the focus group analysis was 'I wanted to talk about it, but I couldn't', which summarizes the participants´ discussions about experiencing depression later in life. The participants expressed feelings of grief towards losing their old normal, more colorful, selves due to having had depression. They further expressed unmet needs of communication with their close ones and with healthcare staff, and a lack of trust towards psychiatric healthcare. They felt frustrated over not knowing possible causes and effects of depression, available treatment options, and how to avoid recurrence. Thoughts of death and suicide were experienced in solitude and could generate a feeling of comfort and control knowing that there was an escape. Our findings highlight that younger-old adults want to talk about how they feel and what they experience during and after their late-life depression.

5.5 **Paper 5**

Rydberg Sterner T, et al. *Depression in relation to sex and gender expression among Swedish septuagenarians – results from the H70 study* (*submitted*)

As *Paper 5* includes unpublished results, the following summary of main results is downsized. In summary, a total of 1 112 participants from the H70 study 2014-16 had answered questions about both depression and gender expression, and was included in our cross-sectional analyses. We found that sex and gender expression were independently related to depression diagnosis and burden of depressive symptoms. Irrespective of biological sex, femininity (especially traits with low social desirability, FEM-) were associated with a greater burden of depressive symptoms. The inverse was observed for androgyny and masculine traits with high social desirability. Further, we found no interactions between sex and gender expression in relation to any depression or MADRS score, indicating that the association between gender expression and depression were similar for men and women.

Source: Quote from study participant during data collection in focus group discussion no.3, answering the question "What was the hardest experience during your latest depressive episode?". Illustration made by author.

"I started to plan my own funeral. I wrote it down on paper; the music, the flowers, and what my children might say…my wishes for the type of flowers on my coffin…so horrible. I cried and cried…When I woke up the next day and saw the notes, I felt terrible. I tore them into a thousand pieces and threw them away, and I remember thinking: '…how sick are you…?'"

"[…]…some can move on, and I have thought about it [*suicide*] when I felt sad and kind of thought: 'why live?'…it takes courage to live as well."

"Mm, it is a bit cowardly to give up…"

"Yes, to take my own life…I guess one just have to hang on and…try to be brave while thinking about it, and still be able to try to manage with today. Because there is no doubt that these pains and worries…I have to live with them."

Source: Quote from study participants during data collection in focus group discussion no.3, discussing their thoughts about death and suicide during their latest depressive episode.

6. **Discussion**

6.1 **Strengths**

Among the strengths of this thesis is the utilization of both quantitative and qualitative methodologies. The research perspectives of depression thus span from examining time trends in depression prevalence to subjective descriptions of experiencing depression during early late life. All thesis papers use data from the Gothenburg H70 Birth Cohort Study (the H70 study). *Paper 1* gives a full display of the study protocol, generating an overview of the research context within which this thesis was derived. The H70 study comprise representative samples from the general population with high response rates. This increase the possibility to generalize our results from *Paper 2, 3* and *5*. The H70 study comprises comprehensive personal examinations, during which the interview regarding psychiatric symptoms and signs were conducted by well-trained mental health professionals (psychiatrists, psychiatric nurses, psychologist or medical doctors). The semi-structured face-to-face interviews were conducted according to CPRS, which has shown to have good reliability and validity among older adults.[234] The depression diagnoses were based on past month symptoms, which reduces recall bias.[49] In addition, data collection method regarding depression was identical over time where the diagnostic criteria followed the DSM as closely as possible. Also, by retrospectively applying symptom-based algorithms (for the diagnostic criteria), the possible effects of altering diagnostic criteria over time was diminished. The consistency over time was also supported by the high inter-rater reliability for depressive symptoms reported in *Paper 3*. The PN-SRI was tested for its psychometric properties in the H70 study (*Paper 2*), using the same target population as in *Paper 5,* when testing its association with depression. Our results from *Paper 2* showed that PN-SRI had acceptable levels of reliability and validity. In *Paper 4*, the first author both moderated the focus group discussions and was the leading researcher during the analysis. This has been proposed as an advantage within focus group methodology.[244,245] The analysis was further interpreted together with two other co-authors.

6.2 **Limitations**

Paper 1 did not include any comparisons between participants and non-participants. This was due to stricter ethical regulations regarding data collection from those who have declined participation. However, data from the general population in Gothenburg and Sweden were added in the method section of this thesis. Further, representativeness is discussed in more detail below. The additional survey provided by the sub-sample in *Paper 2*, only included a binary choice of answers for all questions. It could have benefitted from having had a seven-step scale, as in PN-SRI. As for the factor analysis, all standardized factor loadings for the indicators, specified to measure their respective factor, did not reach the level of > 0.50. This suggested only a mediocre level of convergent validity when considering a strict goodness-of-fit criteria.[256] In addition, the CFI did not reach > 0.9. The PN-SRI comprise a fixed set of 24 self-reported personality traits. This may not fully capture the gender expression complexity. In addition, due to stigma as well as political awareness, the gender coded personality traits are potentially at risk for social desirability bias. Although the diagnosis of depression followed the DSM-5 criteria as closely as possible, the duration criteria of at least two weeks could not be applied, leaving the diagnoses of depression based on symptoms occurring during the preceding month. Also, data for whether the symptoms represented a change in function was lacking. However, the chosen cut-off values for each CPRS item were selected based on severity, corresponding to DSM criteria of functional change. In *Paper 3*, the potential explanations of the time trend for the prevalence of depression, or the association between gender expression and depression, are merely suggestive and speculative. We were not able to differentiate between birth cohort and time period effects in *Paper 3*. The cross-sectional design of *Paper 5* made it impossible to elucidate temporality. For *Paper 3* and *5*, some subgroups in our analyses (e.g., those having major depression) were small. This may have limited the statistical power, generating false-negative results. Further in *Paper 3*, the cohort born 1922 only included women. This limited our ability to investigate time trends in men to the same extent. There may be a risk of recall bias in *Paper 4*, due to the inclusion criteria of having had depression during past 10 years. We also conducted a limited number of focus group discussions, which may negatively have affected data saturation and transferability of results. However, four to five focus groups have been reported to be enough when working with specific target groups,[245] as is the case in *Paper 4*.

6.3 **Methodological considerations**

Apart from the strengths and limitations described above, some methodological considerations need to be discussed.

6.3.1 **Sex, gender and the 'conceptual drift'**

The conceptual distinction between sex and gender in this thesis include the awareness that they are interrelated and difficult to disentangle. The definitions of sex and gender, and whether the two are considered distinctive concepts or not, differ among research fields. Within medical research, 'gender' is still often used as a synonym for 'sex', e.g. when examining differences between men and women. Suggested reason for this includes that gender is considered being a more politically correct way of saying sex,[257] and that the concepts sometimes are used interchangeably. It may also be due to the hardship of distinguishing the two, and disentangling whether the factor(s) under study are related to biological aspects of sex, psychosocial (or cultural) aspects of gender, or both.

In an article published in the Swedish medical journal 'Läkartidningen' in 2000,[258] the phenomenon of this conceptual drift [begreppsglidning] was highlighted as problematic. Today, 20 years later, this is still an unresolved issue within medical research. Not only does this conceptual drift add to concept confusion and gender blindness[259] in studies, it indirectly becomes biologically deterministic (i.e. that biological factors are the only explanation for health outcomes). Further, it diminishes the extent to what a gender perspective can add when also analyzing gender-related factors in relation to sex differences in health. However, in fields such as medicine and public health, the distinction needs to be clear, as we cannot ignore biology any more than we can ignore the psychosocial and cultural factors that influence health. Following this discussion, the scientific medical journal 'The Lancet' have added the following statement to their author guidelines: "…*For all study types, we encourage correct use of the terms sex (when reporting biological factors) and gender (when reporting identity, psychosocial, or cultural factors). Where possible, report the sex and/or gender of study participants, and describe the methods used to determine sex and gender*…".[260] As stated in the Introduction of this thesis, there is also an ongoing discussion whether femininity, masculinity and androgyny should be called 'gender identity', 'gender role (orientation)', 'sex role' or 'gender expression', creating a discrepancy among studies. However, as gender expression was launched[170] the field will probably gain by making a distinction between the interrelated terms gender expression (femininity, masculinity, androgyny) and gender roles. This

as gender roles may be a wider concept, also including socially constructed roles in relation to family, partner or friends, life style activities and behavior.

6.3.2 **To measure (or not to measure) gender expression**

Apart from utilizing PN-SRI when measuring gender expression, inventories such as PAQ[241] and BSRI[158] have previously been used for data collection. However, since both were created during the 1970's, others have questioned their conformity to current societal norms about gender.[159,261] Others suggest measuring gender expression by asking study participants to self-categorize themselves as being more or less feminine and masculine.[262] However, this may be affected by social desirability bias, which is somewhat reduced using PN-SRI as the 24 included traits does not disclose the gender coding to the study participants. In *Paper 2*, we argue that when including measures of gender expression in research, results must be interpreted with caution. Reducing gender expression to a fixed set of attributes, as in PN-SRI, requires serious consideration of the ways it is used to structure differences and similarities between individuals. Also, there is always a risk of conforming gender stereotypes when put in focus. A clear distinction is made between feminine and masculine attributes. However, these are not based on antonyms on the same continuum, but rather constitute two different entities. In epidemiology it is crucial to clearly define and classify all studied phenomena in order to facilitate the collection of statistical data.[263] If not properly measured, results may be biased and lead to incorrect interpretations. One can still argue that this is not a good enough reason to risk the potential negative effects following a potential confirmation of gender stereotypes. However, with or without a gender expression measurement, gender norms and preconceptions about stereotypical male and female behavior will still be present in our everyday life, affecting our health. With this in mind, the pros of studying gender expression may outweigh the cons, as including gender expression can give a unique contribution of knowledge when studying sex differences in health (as seen in *Paper 5*). Still, one may argue that the results in this thesis are generated from heteronormative assumptions, as *Paper 1-5* does not include aspects of intersectionality.[264] Intersectionality, within which sex and gender only plays a part, lies beyond the scope of this thesis. However, it is worth mentioning that future studies investigating the sex ratio in depression may benefit from also including power relations by adding aspects of e.g. ethnicity, functional abilities, social class, sexuality, and religious beliefs, in order to further problematize the

sex ratio in depression prevalence and burden of depressive symptoms. In relation to defining biological sex by the Swedish personal identity number, it could be worth also asking study participants to categorize their self-defined identity.[265] However, having a third option (e.g. man/woman, or non-binary, transgender, other) may include limitations such as: (1) non-binary excludes further categories (e.g. genderfluid, agender); (2) the false implication that all transgender persons identify as trans; (3) or that the researcher will not know what 'other' represent to those participants choosing this option.[265]

6.3.3 **External validity**

In quantitative research, external validity[266] means to what extent we are able to make unbiased interpretations about study results, generalizing them beyond the specific study population. In qualitative research, external validity (trustworthiness of results) may refer to the concept of transferability.[267] As data are collected from smaller samples, findings cannot be generalized to a larger population (neither is that the purpose). However, findings may be transferable to another setting. As availability of data comparing H70 study participants to non-participants and the general population differed among birth cohorts, primary focus will further be directed towards the H70 study 2014-16, as this sample is included in all thesis papers.

Quantitative results

Apart from scientific knowledge and insight regarding the phenomena under study, one key component of external validity within epidemiology is whether the samples are representative or not in relation to the target population. Since the beginning of the H70 studies in 1971, the sampling has comprised a strive towards including representative population-based samples in Gothenburg, Sweden. The willingness to participate in epidemiological studies has decreased during the last decades.[268] Although still fairly high, a fluctuating trend may be seen also for the examinations of 70-year-olds included in this thesis (78.8 % in 1976-77, 63.2 % in 1992-93, 70.0 % in 2000-02, and 72.2 % in 2014-16). There was no difference in response rate by sex at any of the examinations. The systematic selection of study participants helped minimize selection bias related to recruitment. However, as the 1992-93 examination only includes women, there is an over-representation of women for the time trend analyses in *Paper 3*. Therefore, the ability to examine the male time trend of depression was limited

in comparison. In 2014-16, the proportion of women did not differ between the study sample and 70-year-olds in Gothenburg. This adds to the generalizability of our results in *Paper 2 and 5*.

It is a well-known phenomenon that those agreeing to participate in studies tend to be of better health than those declining, i.e. healthy respondent effect.[268] In addition, it has been suggested that older persons having depression are more prone to decline study participation than those not having depression.[269,270] However most likely true, those studies suffered from low participation rate in general (24 %[269] and 52 %[270]), which is not comparable to the examinations included in this thesis. In the H70 study 2014-16, there were no differences in the prevalence of depression (registry data) when comparing the H70 study sample to 70-year-olds in Gothenburg and to 70-year-olds in Sweden. However, since there was no possibility to compare participants and non-participants, a difference in depression rates between the two cannot be ruled out.

Further, it is important to be aware of potential survival bias, where those whom have survived until 70 years of age may be more resilient or 'robust' compared to those who did not. For those who participated at age 70, the five-year mortality rate seems to have declined over time; 11.9 % in birth cohort 1906-07, 8.1 % in birth cohort 1922, 5.0 % in birth cohort 1930, and 4.7 % in birth cohort 1944. However, this potential time trend has not been statistically tested.

All examinations comprised samples of older Swedish adults. One inclusion criterion was that the participants needed to be able to speak Swedish. Thus, our findings may not be generalized to non-Swedish-speaking persons. Since the 1970s, the demographics in Sweden has shifted. For all ages, the proportion of those born outside of Sweden (registered citizens) has increased from 6.7 % in the 1970's, to 9.2 % in the 1990's, to 11.3 % in the 2000's, to 14.7 % in the 2010's.[271] Compared to Sweden in general, Gothenburg has a larger proportion of citizens born in other countries. Among people ≥ 65 years of age living in the Gothenburg Metropolitan Area [Stor-Göteborg], the proportion of those born outside Sweden (same time interval as above) has changed from 0.7 %, 2.0 %, 3.3 %, to 3.6 %.[272] Being born outside of Sweden does not predict the ability to speak Swedish at 70 years of age per se. However, if the proportion of those born outside of Sweden is lower in the study sample compared to the general population, it is important to consider that a potentially vulnerable

group may be missing. Data regarding country of birth is lacking for the H70 examinations in 1976-77, 1992-93 and 2000-02. The proportion born outside Sweden in the H70 examination 2014-16 (15.5 %) was lower than among 70-year-olds in Gothenburg (19.5 %) (x^2; p=0.002), was similar to 70-year-olds in the Gothenburg Metropolitan Area [Stor-Göteborg] (13.9 %) (x^2; p=0.14), and was higher than among 70-year-olds in Sweden (12.1 %) (x^2; p<0.01).

Qualitative results

Qualitative research is about attempting to represent the reality of the study participants, rather than to attain statistically significant results. In order to achieve trustworthiness,[267] qualitative research should be evaluated in relation to the utilized methods of data collection and analysis. Focus group methodology considers participant interactions which can empower and engage persons with limited influence,[245] in *Paper 4*, persons having had early late-life depression. This was the main reason for the choice of focus group methodology, rather than in-depth individual interviews. The focus groups enabled the participants to verbalize and share their lived experiences, generating an in-depth understanding of subjective experiences from having early late-life depression. This essence could not have been collected using quantitative methods. No relevant data was excluded during the analysis. In order to increase dependability, data collection was conducted during 2.5 months, during which the focus group discussion guide did not alter.

In order to enhance the credibility of the findings and to show sensitivity to the ways in which the authors and the research process shaped the findings, prior assumptions about late-life depression were made clear in the outset of *Paper 4*. Also, elements in the data that seemed to contradict the emerging explanations was discussed by the authors, and these discussions refined the analysis. The relevance of a study depends, to a certain extent, on whether findings can be generalized beyond the setting in which they were generated. In *Paper 4*, the sample was derived from the H70 study, and the eligible sample (persons reporting to have had depression at age 60-70) was confined. Both men and women participated in the focus group discussions. In addition, sufficient detail about the sample is provided in the study so that readers, themselves, will be able to judge if the findings can be applied in other similar settings. However, due to the small effective sample, together with an acceptance rate of about 40 %, the number of conducted focus groups was limited to four. As stated above,

this may negatively have affected transferability of results to other settings comprising young-old adults having depression. However, some suggest that four to five focus groups are enough when working with specific target groups,[245] as was the case in *Paper 4*.

6.4 **General discussion**

Apart from the strengths, limitations and further methodological considerations discussed above, a general discussion of a few selected topics earns our attention.

6.4.1 **The association between gender expression and depression**

Explanations for the association between gender and the sex ratio in depression are complex. In *Paper 5*, Table 1, we showed that men were currently working to a higher extent compared to women, while women were predominantly family caregivers. In the main results for *Paper 1* (Table 12), we also showed that men had a higher income (both wage and pension) than women. This may indicate that the female disadvantaged social status may be present also beyond retirement age. In both *Paper 3* and *5*, we found a sex ratio in depression prevalence, however not always statistically significant, (probably partly due to small samples limiting the power). However, interestingly in *Paper 5*, the association between sex and depression did not remain when the feminine subscale FEM– was added in the model. Instead, we found an association between FEM– and depression for both men and women, also in fully adjusted models. Our findings suggest that feminine traits may be important to consider regarding the sex ratio in depression. In terms of risk and protective factors for depression, the possible interpretations may be multifaceted. Before further disentanglement of the association and its temporality, femininity should not merely be considered as being a potential risk factor, nor should masculinity be considered as being merely a potential protective factor. Based on previous studies,[192,193,273-279] together with the theoretical framework of this thesis, four possible explanations are suggested. These suggestions are speculative, but aims to inspire for new hypothesis in future studies:

(1) Masculine coping strategies. Those endorsing a masculine gender expression, irrespective of biological sex, may be more prone to have greater coping skills regarding problem solving (one of the masculine items in PN-SRI).

Studies have shown that women ruminate more frequently than men, while men tend to engage in more active problem solving,[126] which has been suggested to affect the risk of depression. Also, older persons have disclosed experiencing a reduced ability to solve problems in daily life while having depression.[83]

(2) Communication about low mood. Those endorsing a feminine gender expression, irrespective of biological sex, may be more prone to verbally express their low mood to others. Compared to masculinity, femininity is more connected with emotional communication about well-being. First, communicating about low mood with friends or family may generate increased emotional support, reducing the risk for depression.[145,146] Emotional support may, in turn, prevent feeling lonely which is a risk factor for depression.[141] Second, the association between femininity and communication may partly be an explanation to why women seek help to a larger extent than men,[187,191] and hence, showing greater prevalence rates of depression. Studies have suggested that masculinity-related norms become barriers for disclosing low mood, in order to avoid 'looking weak'.[74,79]

(3) The 'catch 22'. Those endorsing a masculine gender expression, irrespective of biological sex, may be less prone to be diagnosed with depression. Measurement and diagnostic instruments have been suggested to suffer from a 'catch 22'; capturing a female phenotype of depression,[191] and thereby underestimating depression among those expressing male phenotype symptoms, as these symptoms are not included in the diagnostic criteria.[197] A male phenotype may include externalizing symptoms (e.g. substance use, risk-taking, and aggression), and may reflect behavioral manifestations of masculine norms in relation to depression.[180,198]

(4) The androgyny model. Those endorsing an androgynous gender expression, irrespective of biological sex, may have lower prevalence of depression.[193] It has been proposed that androgynous persons (endorsing both feminine and masculine traits) are more flexible in their behavioral and psychological adaptability, compared to masculine males and feminine females (sex-typed individuals) who are more restricted by gender-related norms for how men and women are expected to act.[280] This adaptive flexibility has been suggested to be beneficial in terms of mental health.[280,281] This has been further supported by studies showing that gender-role stress (i.e. stress from not

upholding gender norms) may be a mediator in the association between stressful life events and depression in men.[282]

6.4.2 **Time trends in depression and gender equality**

Within the epidemiological framework of this thesis, the fluctuating prevalence of depression may be problematized by considering that the balance between risk and protective factors may alter during the life course and differ between societal, geographical and historical contexts. This gives rise to time-varying elements, such as age, birth cohort and time period effects.[63] Our Swedish society has undergone major changes during the last century.[283,284] Period effects of dietary habits, industrialization, access and quality of education and health care, technological and infrastructural development, as well as economic growth improved population health and living situation during this time period, and paved the way for Sweden's demographic transition. Thus, the cohort effects and life course patterns may differ among the five birth cohorts included in this study,[283,285] which partly could explain the decrease in the prevalence of depression seen in *Paper 3*. A simplified overview is displayed in Figure 10. Since all of our study participants are 70 years of age, a possible age effect is ruled out.

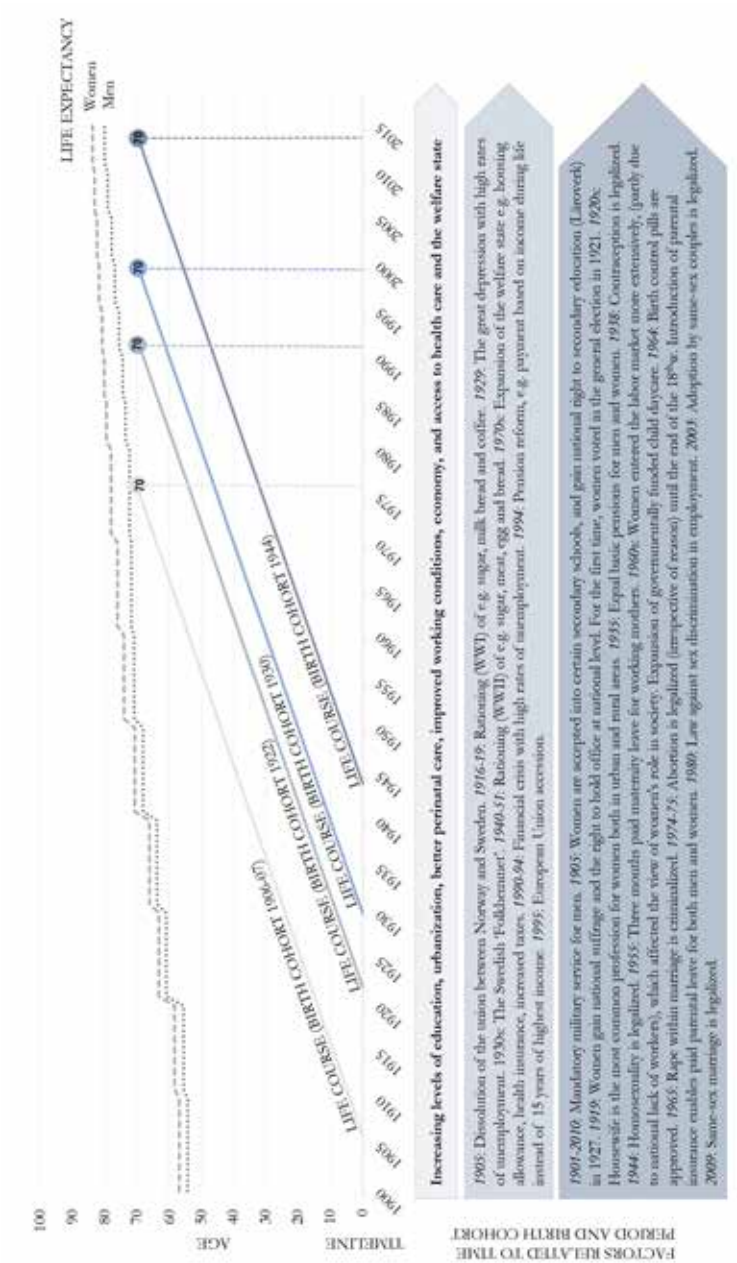


Figure 10. A simplified contextual overview of the life courses for 70-year-olds born in 1906-07, 1922, 1930 and 1944. This include examples of national laws and regulations, with specific focus on gender-related events. No distinctions are made between period or cohort-related factors. Source: Originally adapted from Skoog,[285] modified and published in *Paper 3*, and further modified by author for this thesis. Additional sources: Statistics Sweden,[286,287] Hirdman et al.,[288] Andersson et al.[289]

Period effect

When comparing time trend results among studies, examination year is important to consider. This may include both timing (historical time period) and number of years (as longer study periods have a greater chance of capturing possible prevalence fluctuations). In *Paper 3*, we found a tendency towards a higher prevalence of depression in 1992-93 and 2000-02 compared to 1976-77 and 2014. The peak in the 1990s could partly be due to Sweden having an economic recession, affecting all Swedish residents, or that the cohort born 1922 (examined in 1992-93) was strongly affected by the recession. Our first examination was conducted in 1976 and the last in 2016, generating a 40-year-long study period. Other studies examining time trends in depression for older adults had their last examination during the 1970's,[50,59] 1980's,[55,57,58] 1990's,[54,60] 2000's,[24,51,56,61,62] and during the 2010's[28,52,53] (in 2013 at the latest). Their study periods ranged between 4-15 years,[28,51-53,55-57] 20-30 years,[50,58-61] and only one had a 40-year-long study period[54] (apart from our study). The Stirling County Study in Canada, conducted in 1952, 1970 and 1992, reported a stable prevalence of depression over time.[60] A stable prevalence of depression was also found in our study between 1976-77 and 1992-93.

Cohort effect

Several birth cohort effects may have affected our results in *Paper 3*. The cohort born in 1906-07 started life during times of poverty, cramped housing accommodations and poor perinatal care, and had reached about 40 years of age when penicillin was first discovered. Women from the 1922 cohort were born a year after women´s suffrage became a lawful right in Sweden, spent their early childhood during the great economic depression and were teenagers when World War II started in 1939. When the 1930's cohort was born, primary care facilities for maternal and perinatal care with governmental funding were initiated, decreasing risk factors during pregnancies related to the child's birth weight. Previous research has suggested that lower birthweight (< 3 500 grams) may be associated with an increased risk of having depression at some point during life.[290] The 1930´s cohort could also access treatment for hypertension as adults, and store their food in freezers when moving to own households in their twenties after its market introduction in the 1950´s. During the 1944 cohort's early childhood, the public food service in school was nationally further developed in order to improve the children's dietary intake. These circumstances may have generated that vulnerability factors for health varied

among the birth cohorts included in this thesis. It is also important to consider that life expectancy has increased for the later born cohorts compared to those born in the beginning of the 20th century.[287] Not only do the later born cohorts survive to higher ages, they may also have a greater possibility for healthier aging.

Gender equality

Our findings in *Paper 3* may be related to the increasing gender equality,[291] of which dramatic shifts occurred during the 20th century.[292] Compared to those born 1906-07, 1922, and 1930, the women born in 1944 have to a larger extent benefitted from societal improvements, such as women's emancipation during the 20th century, the expansion of governmentally funded child day care in the 1940s, the sexual revolution in the 1960s, high quality of obstetric and antenatal care, high standard and accessibility of health care, easier to get divorced due to increased social and economic autonomy, and access to university education. On the other hand, due to cultural gender norms in Western societies, women face a 'role strain' overload,[190] expected to manage primary household responsibility, care for children and relatives, and full-time employment, sometimes beyond the age of retirement. This overload has been shown to have an association with depressive symptoms for women,[188] and might partly explain the higher prevalence of depression and higher MADRS score in women compared to men across the 40-year study period in *Paper 3*. A comparison of gender stereotypes between 1983 and 2014 showed that in spite of societal changes and changes in attitudes towards male and female roles, the perception of stereotypical gender attributes and behavior were rather constant during this time period. However, arguments were made for the possibility that changes in attitudes and stereotypes in regards to gender might have reached a plateau during the 1980's, following more active turns.[293]

However, a meta-analysis[96] on cross-national comparisons of the sex ratio in depression, showed larger sex ratios in major depression among countries with greater gender equality. This was not found regarding burden of depressive symptoms[(a,b)]. Suggested explanations for these findings included that gender equality measures were missing for some of the included nations, that depression may manifest differently due to cultural differences, and that higher national gender equality leads to more inter-group-comparisons (i.e. women and men are more free to interact more and hence compare themselves more

to the opposite sex).[96] Perfect gender equality has not yet been obtained in any of our world nations. Therefore, one hypothesis may be that populations in nations with higher gender equality (compared to lower) may have a higher awareness about the existing gender *in*equalities. This may be important to consider when conducting cross-national comparisons, in order to avoid interpretations including that gender equality in itself would be negative for health.

We only had data on gender expression for those born 1944. Therefore, we were not able to examine its possible time trends. Interestingly however, a meta-analysis[294] including studies on gender expression between 1973 and 1993 in the United States (age 18-24) showed that women had higher masculinity scores in the later conducted studies compared to those conducted earlier. Also, the sex difference in masculinity and femininity scores decreased over time. This trend is suggested to be explained by cultural change. The older generations (born during the 1950's) grew up during the "Father knows best" era accompanied by conservative gender roles, while younger generations (born during the 1970's) grew up during the feminist movement accompanied with more gender-permissive roles, and an increase in women working outside of the home. Following this work, a meta-analysis[295] including studies between 1993 and 2012 in the same setting, showed that women's femininity scores had decreased over time (masculinity scores remained stable), while no time trends in gender expression were observed for men. In the H70 study, data collection regarding gender expression will be included at follow-up examinations of those born 1944, as well as up-coming newly added birth cohorts. Future studies may therefore have the possibility to examine time trends in gender expression in regards to age, period and cohort effects.

[a] Gender equality included national economic and gender-related factors: (1) income categories low-middle-high; (2) the United Nations GINI index, (3) contraceptive prevalence among women age 15-49; (4) percentage of executive positions held by women; (5) literacy ratio among adults; (6) intimate partner violence against women; and (7) sexism ideals measured by the question "when jobs are scarce, men should have more right to a job than women, using the following sources: Human Development Report 2005, United Nations 2010 Report (The Worlds Women, for the years 2000-2006), and The World Values Survey 2014 (years 1999-2004). [b] Data for major depression (12-month prevalence, DSM/ICD criteria) was collected covering 1991-2014, while depressive symptoms covered 1978-2014.

Studying time trends of depression - challenges

Studying time trends in depression is related to a number of methodological challenges. There are several potential explanations for contrasting time trend reports on depression prevalence, when comparing studies. A number of methodological approaches should be considered, such as study design (e.g. population-based, register data), geographical setting, and diagnostic criteria (e.g. DSM or ICD).[18,296]

First, as discussed in *Paper 3*, in order to capture potential changes in the prevalence of depression in a population, studies should include representative samples, be of longitudinal design, and utilize the same data-collection methods at each follow-up. However, these studies demand an extensive amount of time, monetary resources and well-trained staff in order to obtain a high inter-rater reliability over time. While register-based studies (such as health care registers or prescription data) is an alternative that demands less resources, register-data may be influenced by changes in awareness of depression among clinicians and patients. In addition, register studies only captures those seeking help at health care facilities. Hence, only using register-based data will be a biased measure of studying the time trend of the point prevalence of depression in a population. In addition, when comparing the prevalence of depression cross-nationally, studies have suggested that differences in rates may partly be due to cultural influences.[30] These may include different patterns regarding risk and protective factors for depression, or cultural differences in the expression of depressive symptoms.

Second, it is important to consider whether the prevalence of depression is comparable across diagnostic criteria or symptom scales. Among female twins, the genetic correlation between liability to major depression and liability to depressive symptoms has been shown to be high (+0.70).[297] This would suggest that symptom scales may be a useful screening tool to detect depression. However, in a population-based sample of older adults, the prevalence of depression varied when using different diagnostic criteria.[238] The prevalence of depression (including all severity grades) was 4.2 % for the International Statistical Classification of Diseases and Related Health Problems (ICD-10),[230] 9.3 % for DSM-IV-TR,[235] 9.2-10.6 % for rating scales (Geriatric Depression Scale, GDS-15[298] and MADRS[236]), and 9.1 % for self-reported information. These findings are useful when comparing depression prevalence across

studies, and over time, considering that depression prevalence was relatively stable between symptom scales and DSM-criteria, while ICD-10 generated much lower figures. In *Paper 3*, we used DSM-5 criteria (retrospectively applied with algorithm-based diagnoses) at all examinations, which minimized the potential effects of altered diagnostic boundaries over time.

Third, previous studies suggest that contrasting time trend between major and minor depression (including depressive symptoms) may partly be explained by different etiological background for these entities. Major depression in late life is suggested to be a chronic mood disturbance, based on long-standing vulnerability factors, such as genetic and neurobiological factors, while minor depression is more affected by environmental circumstances.[299] This may partly be the reason for why we found larger fluctuations for minor depression and symptom burden, compared to major depression, in *Paper 3*.

7. **Concluding remarks**

Perspectives of gender have an important place within mental health research, which is highlighted in this thesis. If not considering gender-related factors when studying the sex ratio in depression, the generated results may be incomplete or simply incorrect; we risk not only doing harm (e.g. interpreting the sex ratio in depression as being only biologically determined), but also missing critical opportunities to improve health (e.g. not detecting differences and similarities regarding risk factors or symptom patterns in subgroups). We found a decreasing time trend in the prevalence of late-life depression among women, but not among men. The sex ratio in depression is complex, partly linked to gender-related factors such as gender expression. Older adults have expressed limited trust towards healthcare providers in seeking medical help for depression. Also, they have expressed a need for more communication and health knowledge about depression. Specific concluding remarks for each paper are given below.

Paper 1: A contribution to understanding the thesis data framework. When conducting longitudinal population-based studies it is important to keep examinations as similar as possible over time to enhance possibilities of comparisons between birth cohorts and examination years. This paper will be used as documentation of the H70 study 2014-16, as reference material for future projects based on H70 study data, and will also be used as a foundation for planning and carrying through the future follow-up examinations at ages 75 up to ages above 95 years of the 1944 birth cohort.

Paper 2: When adding the newly developed PN-SRI instruments into the H70 study research setting, it was important to test its psychometric properties in order to evaluate its suitability for the target population. This cross-cultural adaptation of the PN-SRI indicated that it was applicable in a Swedish research setting comprising older adults. Adding the PN-SRI to epidemiological studies will contribute to provide a nuanced way of analyzing differences and similarities among men and women in relation to depression, as well as to various health outcomes.

Paper 3: The prevalence of depression has decreased among 70-year-old women, but not among 70-year-old men. Our results were not affected by age

effects or changing diagnostic criteria over time. However, it may have been affected by both period and cohort effects, as well as an improvement in the general health among successive birth cohorts. These time trends provide a dynamic view of population mental health over time. Our results may generate hypotheses for future research of depression, but also be utilized during psychiatric healthcare need assessments, preventive actions, service planning or policy development.

Paper 4: The results of this study may have important implications for clinicians and researchers who work with older adults with late-life depression (between 60 to 70 years of age). We found a lack of trust towards healthcare providers in seeking medical help for depression. The participants wanted to talk about their experiences from having depression, and expressed a need for more knowledge about available treatments, potential side effects, and how to avoid recurrence. Care providers need to be aware there is a need for an existential dialogue about death. This study contributes with new empirical knowledge of how older adults from the general population experience late-life depression.

Paper 5: This paper challenges the current knowledge regarding the sex ratio in depression, and this is the first examination of sex and gender expression in relation to depression among older adults in a Swedish context. We found that irrespective of biological sex, feminine traits with low social desirability were associated with higher prevalence of depression and greater burden of depressive symptoms. The inverse was observed for androgyny and masculine traits with high social desirability. Our results point to the importance of including gender expression when studying sex differences in depression. Having a gender perspective in the health care of persons with depression could nuance preconceptions about sex differences in the occurrence, etiology and symptom expression, and be valuable for detection, prevention, and evaluation of treatment effects.

7.1 **Future directions**

Future research should utilize a longitudinal design to validate temporality for the association between gender expression and depression. Studies also needs to be conducted among various societal settings in order to further investigate the generalizability of our results. Due to differences in norms and attitudes

across cultural contexts and historical time periods, the gender-coding in PN-SRI may need to be revisited in the future. Studies including multi-level factors (at macro, meso, micro levels) when studying the sex ratio in depression in relation to gender is warranted. This would help us understand the time trends in depression prevalence in the general population. Beyond the scope of this thesis lies the theoretical concept of intersectionality,[264] in which gender only plays a part. It is worth mentioning that future studies investigating the sex ratio in depression may benefit from also including further aspects of e.g. ethnicity, functional abilities, social class, sexuality, and religiosity.

The suggested heterogeneity of depressive symptoms between men and women may be an object for future epidemiological studies in older populations. Also, it is important to consider the heterogeneity of depressive symptom patterns, not only between men and women, but also within each sex and possibly in combination with different gender expressions. As well as aiding clinicians in their diagnostic assessment, this may lead to further improvements in diagnostic criteria and knowledge about potential patterns of symptom expression.

Finally, increased knowledge about risk and protective factors for depression will also increase the possibility for testing and planning preventive actions. As stated in a World Psychiatry letter to editor in 2019,[300] prevention of depression will succeed if structurally embedded in society, targeting big determinants. Prevention, one of the corner stones in public health science, may in this context include preventing first incidence of depression by targeting risk factors (primary prevention), and prevent depression to recur or managing depression after diagnosis to stop symptom progression (secondary prevention). As seen in *Paper 4*, there is a strong thirst for knowledge about preventive methods also among older adults that has suffered from depression. As a research community, we need to keep searching for answers.

Source: Quote from a study participant during data collection in focus group discussion no.3, fearing that the rest of his/her life would include having depression. Illustration made by author.

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Appendix 1

Diagnostic criteria for depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) are presented below.

Major depression (DSM-5)
A. Five (or more) of the following symptoms have been present during the same 2-veek period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad, empty, hopeless) or observation made by others (e.g. appears tearful) (note: in children or adolescents, can be irritable mood).
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5 % of body weight in a month), or decrease or increase in appetite nearly every day (note: in children, consider failure to make expected weight gain).
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or another medical condition. Note: Criteria A-C represent a major depressive episode. Note: Responses to significant loss (e.g. bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgement based on the individual's history and the cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode. Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Minor depression (DSM IV-TR research criteria)
A. At least two (but less than five) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful). Note: In children and adolescents, can be irritable mood.

2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5 % of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.

D. The symptoms are not better accounted for by bereavement (i.e. normal reaction to the death of a loved one).

E. There has never been a major depressive disorder, and criteria are not met for dysthymic disorder. There has never been a manic episode, a mixed episode, or a hypomanic episode. The mood disturbance does not occur exclusively during schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, psychotic disorder not otherwise specified.

Appendix 2

DSM [a]	CPRS items (no. in parenthesis) and rating options [b]	Cut-off
1. Depressed mood	**(1.) Sadness*** Representing subjectively experienced mood, regardless of whether it is reflected in appearance or not. Includes depressed mood, low spirits, despondency, and the feeling of being beyond help and without hope. Elated mood is scored zero on this item. *0-1* Occasional sadness may occur in the circumstances. *2-3* Predominant feelings of sadness, but brighter moments occur. *4-5* Pervasive feelings of sadness or gloominess. The mood is hardly influenced by external circumstances. *6* Continuous experience of misery or extreme despondency.	2-6
	(41.) Apparent sadness (observed)* Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up. *0-1* No sadness *2-3* Looks dispirited but brightens up occasionally. *4-5* Appears sad and unhappy all of the time. *6* Extreme and continuous gloom and despondency.	4-6
2. Diminished interest /pleasure	**(5.) Inability to feel*** Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced. *0-1* Normal interest in the surroundings and in other people. *2-3* Reduced ability to enjoy usual interests. Reduced ability to feel anger. *4-5* Loss of interest in the surroundings. Loss of feelings for friends and acquaintances. *6* The experience of being emotionally paralyzed, inability to feel anger or grief, and a complete or even painful failure to feel for close relatives and friends.	2-6
3. Change in weight or appetite	**(18.) Reduced appetite*** Representing the feeling of a loss of appetite compared with when well. *0-1* Normal or increased appetite. *2-3* Slightly reduced appetite. *4-5* No appetite. Food is tasteless. Need to force oneself to eat. *6* Must be forces to eat. Food refusal.	2-6
4. Insomnia /hyper-insomnia	**(19.) Reduced sleep*** Representing a subjective experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well. *0-1* Sleeps as usual. *2-3* Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep. *4-5* Sleep reduced or broken by at least 2 hours. *6* Less than two- or three-hours sleep.	3-6
	(20.) Increased sleep Representing a subjective experience of increased duration or depth of sleep, compared to the subject's own normal pattern when well. *0-1* No extra sleep. *2-3* Sleeps deeper or longer than usual. *4-5* Several hours extra sleep. *6* Spends a great part of the day asleep in spite of normal or increased sleep at night.	4-6

5. Psycho-motor agitation /retardation	**(54.) Reduced speech (observed)** Representing reticent or slowed speech with long delays or pauses. Pressure of speech is scored zero on this item. *0-1* Ordinary speech without undue pauses. *2-3* Takes time to produce brief answers. *4-5* Extremely brief monosyllabic answers with long delays. Hardly any spontaneous comments and when they occur they are slow. *6* Monosyllabic answers are only produced with great effort. Almost or completely mute.	2-6
	(60.) Slowness of movement (observed) Representing a decrease in frequency and extent of voluntary movements. Facial movements, gait, accompanying movements and gestures retarded and sluggish. *0-1* Ordinary change between rest and activity. *2-3* Minimal gestures and facial movements. *4-5* Almost no spontaneous motor activity. Slow and labored movement. *6* Has to be led to the interview. No spontaneous movements. Immobile face.	3-6
	(61.) Agitation (observed) Representing "purposeless" motor activity such as hand-wringing, picking at objects and clothes, inability to sit still. *0-1* No agitation. *2-3* Difficult to keep hands still. Changes position several times during the interview. Fiddles with objects. *4-5* Obviously restless. Vacant and obtrusive picking at objects. Half-rises occasionally. *6* Cannot be persuaded to sit except for brief periods. Incessant purposeless wandering.	3-6
6. Fatigue or loss of energy	**(15.) Fatiguability** Representing the experience of tiring more easily than usual. *0-1* Ordinary staying power. Not easily fatigued. *2-3* Tires easily but does not have to take a break more often than usual. *4-5* Easily tired. Frequently forced to pause and rest. *6* Exhaustion interrupts almost all activities or even make them impossible.	3-6
	(14.) Lassitude* Representing a difficulty getting started or slowness initiating and performing everyday activities. *0-1* Hardly any difficulty in getting started. No sluggishness. *2-3* Difficulties in starting activities. *4-5* Difficulties in starting simple routine activities which are carried out only with effort. *6* Unable to start activity without help.	3-6
7. Feelings of worthlessness or guilt	**(6.) Pessimistic thoughts*** Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin. *0-1* No pessimistic thoughts. *2-3* Fluctuating ideas of failure, self-reproach or self-depreciation. *4-5* Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future. *6* Delusions of ruin, remorse, and unredeemable sin. Absurd self-accusations.	3-6
8. Diminished ability to think /concentrate or indecisiveness	**(16.) Concentration difficulties*** Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced. *0-1* No difficulties in concentrating. *2-3* Occasional difficulties in collecting one's thoughts. *4-5* Difficulties in concentrating and sustaining thought which interfere with reading or conversation. *6* Incapacitating lack of concentration.	4-6

	(13.) Indecision Representing vacillation and difficulty in choosing between simple alternatives. *0-1* No indecisiveness. *2-3* Some vacillation but can still decide when necessary. *4-5* Indecisiveness or vacillation which restricts or prevents action, makes it difficult to answer simple questions or make simple choices. *6* Extreme indecisiveness even in situations where conscious deliberation is not normally required, such as whether to sit or stand, enter or stay outside.	3-6
	(48.) Distractibility (observed) Representing attention easily diverted by irrelevant external stimuli. *0-1* Adequately sustained attention. *2-3* Attention occasionally distracted by irrelevant stimuli (such as background noices). *4-5* Easily distracted. *6* Continually distracted by incidental events and objects which makes interviewing difficult or impossible.	4-6
9. Recurrent thoughts of death or suicidal ideation	**(7.) Suicidal thoughts*** Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating. *0-1* Enjoys life or takes it as it comes. *2-3* Weary of life. Only fleeting suicidal thoughts. *4-5* Much better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention. *6* Explicit plans for suicide when there is an opportunity. Active preparations for suicide.	2-6
-	**(3.) Inner tension*** Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to panic, dread and anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for. *0-1* Placid. Only fleeting inner tension. *2-3* Occasional feelings of edginess and ill-defined discomfort. *4-5* Continuous feelings of inner tension, or intermittent panic which the patient can only master with some difficulty. *6* Unrelenting dread or anguish. Overwhelming panic.	-

[a] Symptoms listed in the Diagnostic and Statistical Manual of Mental Disorders [b] The Comprehensive Psychopathological Rating Scale. Original rating for every item is 0 to 3. However, the H70-studies utilize ratings 0 to 6, following the ratings in the Montgomery Åsberg Depression Rating Scale (MADRS): 0=*0-1*; 1=*2-3*; 2=*4-5*; 3=*6*. * Item included also in the Montgomery Åsberg Depression Rating Scale (MADRS). Item no. 3 is only included in MADRS, not in the symptom criteria for depression diagnosis.