Factors related to depression in women – over the life course

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Upplevelser av depression

”Jag pendlade mellan känslomässig förlamning och skräck över hur jag faktiskt mådde”

Kvinna, 33 år

”Jag kände mig som ett fysiskt skal utan mål, utan smak, utan åsikt och utan ork, som bara existerade”

Kvinna, 34 år

”Tomhet, hopplöshet och ensamhet; det kändes som om alla människor var ensamma”

Kvinna, 33 år

”Det värsta var att jag hade så mycket roligt att se fram emot, borde varit lycklig, men jag kände mig helt tom”

Kvinna, 34 år

”Utanför mitt fönster pågick det riktiga livet, där människor har en riktning och en mening med sin dag, det livet jag inte var en del av”

Kvinna, 37 år

”Det värsta av allt var att jag totalt tappade bort mig själv i orkeslösheten och mörkret som omslöt mig”

Kvinna, 36 år

Till er,
mina älskade väninnor,
som någon gång erfarit depressionens tröstlösa mörker

ABSTRACT

Background: Depression is a serious and common disorder that is predominant in women and has an unclear etiology. To evaluate factors related to depression is of great value and the main purpose of this thesis. A life course approach and a focus on biological factors are applied.

Methods: Biological factors were investigated in relationship to depression in the Prospective Population Study of Women in Gothenburg, a multi-disciplinary longitudinal study on a representative sample of women first examined in 1968-69 (N=1462). Psychiatric examinations were performed in a subsample of women at baseline (N=800), and at four follow-ups until year 2002. Diagnoses of depression were based on DSM-III-R criteria and multiple sources of information were used. Birth-related factors were abstracted from original midwife records (n=803), and evaluated longitudinally in relationship to lifetime depression (*Paper I*). In 1992, a subsample of 84 women without dementia participated in lumbar punctures and CSF was analysed for biomarkers. Levels of biomarkers were assessed cross-sectionally in relationship to depression (*Paper II and III*).

Results: *Paper I* showed that 44.6% (n=358) of women experienced any lifetime depression. Birth weight ≤3500 gram and shorter gestational time were independently associated with a higher odds of any lifetime depression. *Paper II* showed that compared to women without depression (n=70), women with Major Depressive Disorder (MDD) (n=11), had higher levels of Amyloid beta-42 (Aβ42), and the CSF/serum albumin ratio. *Paper III* showed that women with MDD (n=11) had higher levels of Neurofilament Protein Light (NFL). A multivariate model showed that each biomarker was independently, and as a CSF biomarker profile, positively associated with MDD.

Conclusion*:* Lower than median birth weight and shorter gestational time, higher levels of CSF Aβ42 and CSF NFL, and higher CSF/serum albumin ratio, were positively associated with depression in women. These results may suggest involvement of neurodevelopmental, neurodegenerative, and vascular factors in the pathophysiology of depression, potentially supporting a stress-related hypothesis of depression.

Keywords: Depression, women, epidemiology, etiology, life course, biological factors, cerebrospinal fluid, biomarkers, birth-related, population-based, PPSW

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LIST OF PAPERS

This thesis is based on three papers, referred to in the text by their Roman numerals as follows:

I. **Depression in Swedish Women: Relationship to Factors at Birth.** Pia Gudmundsson, Susan Andersson, Deborah Gustafson, Margda Waern, Svante Östling, Tore Hällström, Sigurdur Pàlsson, Ingmar Skoog, Lena Hulthén.
European Journal of Epidemiology 2011; 26: 55-60.

II. **The relationship between cerebrospinal fluid biomarkers and depression in elderly women.** Pia Gudmundsson, Ingmar Skoog, Margda Waern, Kaj Blennow, Sigurdur Pálsson, Lars Rosengren, Deborah Gustafson.
American Journal of Geriatric Psychiatry 2007; 15: 832-838.

III. **Is there a CSF biomarker profile related to depression in elderly women?** Pia Gudmundsson, Ingmar Skoog, Margda Waern, Kaj Blennow, Henrik Zetterberg, Lars Rosengren, Deborah Gustafson.
Psychiatry Research 2010; 176: 174-178.

CONTENTS

ABBREVIATIONS

Aβ42	Amyloid beta-42
AD	Alzheimer's disease
APA	American Psychiatric Association
APP	Amyloid Precursor Protein
BBB	Blood Brain Barrier
CBT	Cognitive Behavioral Therapy
CNS	Central Nervous System
CPRS	Comprehensive Psychopathological Rating Scale
CRF	Corticotropin Releasing Factor
CSF	Cerebrospinal Fluid
CSF/S	CSF/Serum
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
GFAp	Glial Fibrillary Acidic protein
HDRS	Hamilton Depression Rating Scale
HPA	Hypothalamic-Pituitary-Adrenal
HPG	Hypothalamic-Pituitary-Gonadal
HPT	Hypothalamic-Pituitary-Thyroid
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
LP	Lumbar Puncture
MADRS	Montgomery Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
NFL	Neurofilament Light
NOS	Not Otherwise Specified

SBU	Statens Beredning för medicinsk Utvärdering
SD	Standard Deviation
T-tau	Total tau
WHO	World Health Organization

1 DEPRESSION

1.1 Depression epidemiology

Depression is a serious and common mental disorder that influences psychological, social, and somatic functions [1]. In the year 2000 depression was ranked as the fourth leading contributor to the global burden of disease, and projected to reach second place for both sexes in all ages by the year 2020 [2]. Moreover, the societal economic burden associated with depression is substantial [3, 4]. Depression is predominant among women. Occurrence of depression is reported to be at least twice as high in women compared to men. This predominance of depression among women is one of the most robust findings in psychiatric epidemiology and has been observed globally across cultures and ethnic groups [5]. Theories on the origin of this remarkable difference in occurrence of depression between women and men are many and will be discussed in the next section.

There are many factors associated with observed occurrence of depression. Reported prevalence and incidence rates vary over the life course, between urban and rural settings, between countries and cultures, and with socioeconomic status [5]. Occurrence also varies depending on the severity of the depression that is assessed (e.g. milder forms of depression are more common than severer forms) [5]. The relative influence of these associated factors is not clear due to, for example, methodological differences in the diagnosis and measurements of depression and lack of studies in the young and very old. Cultural differences in the manifestation of depression as well as in the interpretation of questions related to depressive symptoms (e.g., the expressions “feeling blue” and “loss of spirit” commonly used in western societies are not appropriate in all cultures), and may also complicate the clarification [5]. Thus, reported prevalence and incidence rates of depression vary significantly between studies. Despite this, some generalizations about prevalence of depression by age can be made. In children,

roughly 1-2.5 percent may experience depression, rising to 5-20 percent in adolescence [6-8]. Ocurrence seem to peak in late teen years and decline with age into adulthood. Reported one-year prevalence estimates range from 4-7 percent in mid adolescents [7-9] rising to 20 percent by the end of that period [8]. In adults, prevalences range from 4-10 percent [5, 10].

Depression prevalence in the elderly is a topic of debate. Some studies support a distinct drop in prevalence of depression in the elderly [11-13], while others do not [14-18]. Most studies show that roughly one person out of five will experience depression at any time during their life [5], but some report even higher lifetime prevalence estimates of 23-30 percent in men and 40-45 percent in women [15, 19, 20]. The inconsistencies in reported lifetime prevalences of depression may partly be explained by differences in study design (e.g., retrospective *vs.* prospective studies) and age groups included in the analyses. Retrospective studies and studies that do not include older adults typically report lower prevalence of lifetime depression compared to prospective studies that include this age group [21, 22].

The age of onset of clinical depression is typically young. Most individuals seem to experience their first depression between 14 and 30 years of age [10, 12, 13, 23]. Early age of onset is related to poor prognosis of depression and suicidal behaviour [24].

Depression is an episodic disorder with a serious course. At least 25 percent of individuals suffering from depression experience several relapses, chronicity or suicide [5]. Recurrence is very common and reported in 75-80 percent of individuals suffering from depression. One of every two persons has a recurrence within two years. The risk for subsequent episodes increases with number of previous episodes [10, 23], and the mean number of lifetime episodes is reported to be approximately 4-9 [25, 26]. A depressive episode lasts, on average, 6

months and the majority recover within one year. However, approximately 6-15 percent develop a chronic depression that can continue for years [10].

Depression is associated with several somatic and mental morbidities, for example, ischemic heart disease [27], stroke [28], cardiovascular disease, Type 2 diabetes mellitus [29], dementia [30], anxiety [10], and personality disorders [31]. The occurrence of multi-mental morbidities is extensive and studies show that up to 75 percent of individuals diagnosed with depression have at least one other mental disorder [10]. The most prevalent co-morbidities are anxiety disorders which are reported by 50 percent of individuals with depression [10]. Due to the cross-sectional nature of many depression studies, and the episodic nature of depression, causal conclusions related to several factors that have been associated with depression and published in the literature cannot be drawn. However, serious well-known consequences of depression include attempted suicide [32], completed suicide [33, 34], and increased overall mortality [35].

1.2 Depression in women

As stated before, women are affected by depression more often than men [5]. Women also typically experience their first depression earlier [24], report longer episodes and have a higher risk for recurrence compared to men [10]. A group with particularly high rates of depression is teenage girls who may be affected up to 4 times more often than boys [9]. Other periods in life when women experience particularly high rates of depression is during pregnancy and in the postpartum period. It is estimated that 5-16 percent of pregnant women experience depression and 10-15 percent are affected by a post-partum depression [36, 37]. As mentioned previously, some studies report that over 40 percent of women may suffer from at least one depressive episode during their life time [15, 19, 20].

The remarkably high sex ratio in depression occurrence is a topic of debate. Some researchers propose that this difference is an artefact, created by, for example, bias in the diagnostic criteria or diagnostic judgement; use of alcohol intake as a marker of depression or as a depressive equivalent in men; symptom overreporting in women and/or underreporting in men; or different help-seeking behaviours in women and men. However, these cannot alone explain the high women-to-men sex ratio observed from adolescence until midlife [38-40]. The sex ratio appears to declines with age, probably mainly due to decreasing occurrence in women [38]. As aforementioned, the underlying cause of this predominance in women is unclear and many different hypotheses have been proposed over the last centuries. Historically, biological hypotheses have been predominant. In 1860, an anatomical-physiological hypothesis was popular. This hypothesis stressed that the body, biology and patterns of illness are fundamentally different between the sexes and therefore depression rates differ. In 1880, a gynaecological model was used to explain basically all variations in the body, as well as in the psyche of women, based on their genitals. A neurological model with a focus on increased sensitivity of the nervous system in women was common in 1890, and in 1920, a psychological model with a focus on female deviations emerged. In 1940 a model focusing on sex hormones was introduced [41].

Modern models attempting to explain the high sex ratio in depression still include sex hormones [40, 42], but some models state that even though they most likely are a part of depression etiology, they cannot fully explain why women experience depression more often than men [38, 39]. If a universal biological vulnerability is the only underlying cause, sociodemographic factors, such as marital status, would not affect the ratio. However, the women-to-men sex ratio in depression is reported to be lower in single and divorced compared to married persons [38]. In addition, in socially homogeneous populations based on for

example education, sex differences in occurrence of depression is not always observed [40]. Thus, there is no consensus in the explanation for the predominance of depression in women. From a biopsychosocial perspective [43], most likely depression occurs given a combination of psychosocial, cognitive, environmental, as well as biological factors [39, 40, 42-46] (see section 1.4 *Depression etiology*). One issue that complicates this picture even more is the so-called 'gender paradox' in suicide. As previously stated, depression is a risk factor for attempted suicide [32] as well as for completed suicide [33]. However, depression and suicidal ideation, as well as attempted suicide, are predominate among women, while completed suicide is approximately twice as common in men [24, 47].

Depression may lead to great suffering, not only for the women affected, but for those around them. For example, studies show that caregivers of individuals with affective disorders experience a reduced quality of life [48], and husbands of women with depression are at higher risk of experiencing depressive symptoms [49, 50]. Thus, if nearly half of all women experience depression at least once during their lifetime, the number of people affected by this disorder is vast, and the need for research in this area cannot be overrated.

1.3 Features of depression

1.3.1 Symptoms of depression

Symptoms of depression are emotional, as well as cognitive, and somatic [1]. The most frequently reported symptoms include reduced mood, loss of interest or pleasure in ordinary activities (anhedonia), changes in appetite and weight, sleep disturbance, changes of movement, fatigue and loss of emotional energy, feelings of worthlessness or excessive or inappropriate guilt, problems with concentration and decision-making, thoughts of death, and suicidal ideation or suicide attempt

[51]. Although not included as symptoms in the official classification systems for depression used today (see next section), anxiety, sexual disturbances, and somatic symptoms often co-occur with depression [5, 52]. Two symptoms are considered the 'core symptoms' of depression; depressed mood, and loss of interest or pleasure. These core symptoms reflect the view of depression as a primary affective disorder, despite associated cognitive and somatic symptoms. The affective focus of depression is a quite recent and Western view. In the past, and in other cultures, behavioral, somatic, or other disturbances have been or are viewed as more important [1].

The symptom picture of depression may vary in different age groups. For example, studies show that in adolescents, irritability instead of reduced mood, is the most frequently reported symptom in depression [53], and increased instead of decreased sleep may also be more common [5]. Symptoms of depression in this age group may also be hard to detect [9]. Older adults may more often present aggressiveness, cognitive difficulties, and anhedonia, and often have fewer symptoms or one dominant symptom. In addition, separating symptoms of depression from consequences of physical illness may be difficult in this age group [54].

Identifying symptoms in research settings

To identify depression symptoms in research settings, various methods may be used, including diagnostic interviews, interviewer conducted- or self-administered rating scales, questionnaires, or combinations of these. Diagnostic interviews are most often structured- or semi-structured, and may be conducted by persons specialized in psychiatry or by laypeople. Example of such interviews include; the Diagnostic Interview Schedule (DIS), the Structural Clinical Interview for DSM disorders (SCID), the Composite International Diagnostics Interview (CIDI), and the Clinical Interview Schedule (CIS) [5].

Rating scales have been developed to measure the severity of depression and are often used in medical trials and in clinical practice. Individual symptoms of depression are evaluated separately using a graded scale, and the sum total of the item ratings indicates the overall severity of depression. For expert judgment, the Hamilton Depression Rating Scale (HDRS), and the Montgomery Åsberg Depression Rating Scale (MADRS) are most commonly used [5]. MADRS is based on the Comprehensive Psychopathological Rating Scale (CPRS), a 65 item scale of reported as well as observed psychiatric symptoms and signs [55]. MADRS is also available in a self-administered form, MADRS-S. Another self-administered rating scale commonly used for depression is the Beck Depression Inventory (BDI) [5].

To screen depressive symptoms in a population, specific questionnaires that identify symptoms without rating intensity, may be used. Two examples of frequently used depression questionnaires are the Center for Epidemiological Studies - Depression Scale (CES-D), and the Hospital Anxiety and Depression scale (HAD) [5].

There are several rating scales and questionnaires created for or particularly useful in specific age groups. For example, the Geriatric Depression Scale (GDS), the Center for Epidemiological Studies – Depression Scale (CES-D), and the Geriatric Mental State Schedule (GMSS) are commonly used in older populations [56].

1.3.2 Diagnosis of depression in research settings

Short historical background

The term ‘depression’ originates from the Latin words ‘de’ (‘down from’) and ‘premere’ (‘to press’), and has been used in medical terminology since the 18th century. The concept ‘melancholia’ may be viewed as a predecessor of the

concept of depression, and was described already by the ancient Greeks [57]. However, these two concepts have been used in different ways during the years, and the homology between them is debated [57, 58].

The work of Emil Kreapelin at the end of the 19th century contributed considerably to the foundation of the modern classifications of psychiatric disorders. One of his major categories was 'manic-depressive insanity', and ever since then, depression has been an essential concept in psychiatry [1, 57]. However, the term depression has been, and still is today, used to describe several different states: the natural emotion of depressed mood, the clinical symptom depressed mood, a cluster of symptoms, and a clinical diagnosis of depression [5].

The need for structured diagnostic criteria for psychiatric disorders was shown in a US-UK diagnostic study in the beginning of 1970, revealing a great difference in diagnosis of schizophrenia between American and British psychiatrists [5]. Issues regarding classification of depression subtypes, and validation of depression diagnoses without information on related known pathological mechanisms, were also raised at that time, and are still topics for debate today [59]. It was suggested that operational research criteria for depression would improve the reliability and validity of the diagnosis. In 1980, the first version of the operationalized classification system: Diagnostic and Statistical Manual of Mental disorders, 3rd version (DSM-III), was published. Thirteen years later, when DSM-IV was developing, the World Health Organization (WHO), also published diagnostic criteria to be applied in research settings: The International Classification of Mental and Behavioral Disorders. Diagnostic criteria for research, ICD-10 [2, 59]. While operationalization of psychiatric disorders, such as depression, may provide good inter-rater reliability, these criteria have limitations. When DSM-III was published, worries concerning diagnosis of subsyndromal and atypical forms of depression, as well as misclassification, were

raised. Thirty-two years and three versions of DSM later (e.g., DSM-III-R, DSM-IV, and soon, DSM-V), these issues are still discussed [59].

Diagnosis of depression in epidemiological studies

The ICD-10 and DSM-IV diagnostic criteria for depression are basically the same, however, in epidemiological studies the DSM criteria are most commonly used [10]. According to the DSM classification system depression is defined as a syndrome, characterized by a cluster of symptoms and signs occurring together and potentially reflecting a common pathophysiology [1]. The etiology of depression is not well defined (see section 1.4 *Depression etiology*), and most likely, etiologies vary by depression case. Thus depression is not considered a disease based on common medical definitions, where disease denotes a condition that is more uniformly diagnosed over time due to a recognized etiologic agent (cause), identifiable group of signs and symptoms, and consistent anatomic alterations. [1].

According to DSM-III-R criteria, the two main types of depression are Major Depressive Disorder (MDD) and dysthymia, but several subgroups of MDD are also presented [52, 60]. Dysthymia has less severe symptoms than MDD, but is more prolonged and may be associated with the individual's personality [60]. While DSM-III-R criteria are used for the papers in this thesis, it is important to note that these criteria were updated in DSM-IV. Currently, and more commonly used, are Major and Minor Depression diagnoses.

Five of nine listed symptoms are required for a DSM diagnosis of MDD, of which one has to be either depressed mood, or loss of interest or pleasure (i.e., the core symptoms). Thus, two individuals can fulfill the criteria for MDD without sharing a single symptom, thus the heterogeneity between individuals suffering from depression is substantial [52]. In addition to a certain number of symptoms

required, several inclusion as well as exclusion criteria should be applied in the diagnosis of depression based on DSM criteria. For example, duration of symptoms should be at least two weeks, and an associated functional impairment should be present. Exclusion criteria include underlying organic factors, medical conditions or substance use, delusions, hallucinations, and bereavement [51]. Despite inclusion and exclusion criteria, the level of symptom burden is often not empirically determined. Instead it is based on subjective consensus of one or more physicians. Thus, distinctions between depressed and non-depressed individuals in the population are not clear [5]. Furthermore, research studies show little empirical support for some of the depression criteria in DSM-III-R or DSM-IV, including number of required symptoms, the two weeks duration criteria, the criterion of functional impairment [61]. The relevance of bereavement as an exclusion criterion is also debated [62-64].

Epidemiological studies may investigate depression severity, based on, for example MADRS (see previous section), or a clinical depression based on DSM criteria [10]. However, in epidemiological studies not focusing on mental health, or using short depression screening tools or questionnaires, it may not be possible to make a DSM-based depression diagnosis due to insufficient data. For example, information on duration, functional impairment, certain symptoms (e.g. suicidal thoughts) organic disorders, hallucinations, and so on, may not be available. More thorough diagnostic interviews, rating scales, or questionnaires of various kinds are used to identify symptoms of depression (see previous section). DSM criteria may then be applied to results obtained from these investigations, with or without the use of algorithms to actually make the diagnosis [5].

1.4 Depression etiology

The etiology of depression is unclear and most likely consists of complex interactions between multiple risk- and protective factors over the life course [65, 66] including those that are biological, environmental, behavioural, psychosocial, and cognitive [42, 45, 65, 66]. The diathesis-stress model, first described in schizophrenia research by Zubin and Spring in 1977 [67], is often used as an explanatory model for the interactions of factors in depression. This model proposes that one's biological predisposition (genetic or acquired) interacts with external or internal stressors in the etiology of depression [66-69]. A multifactorial model for depression and depression vulnerability over the life course is shown in *Figure 1.*

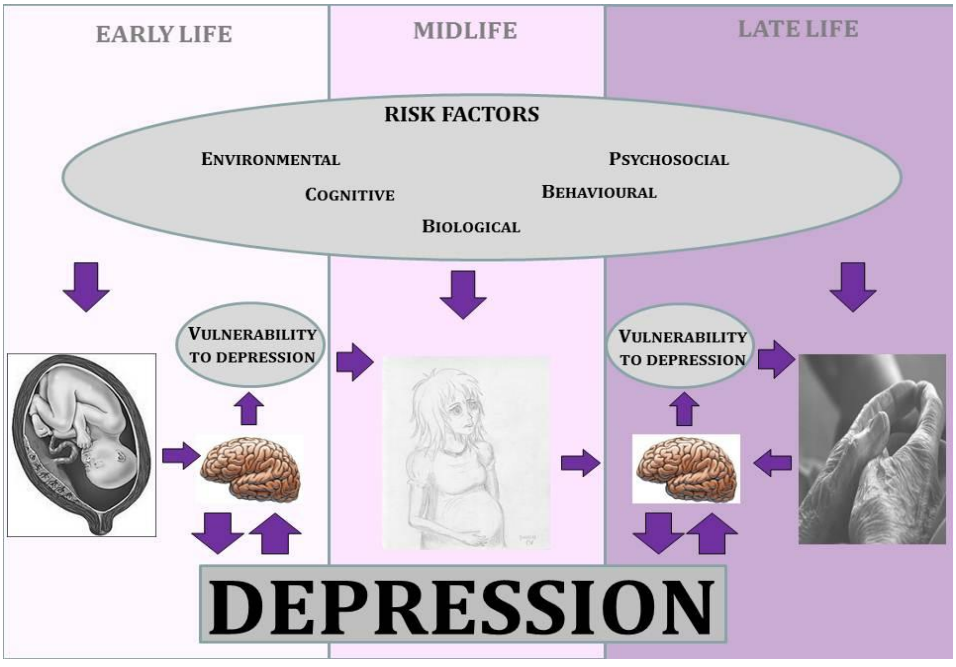


Figure 1. *A potential multifactorial hypothesis for depression and depression vulnerability over the life course* (By Pia Gudmundsson and Caroline Sturman)

In *Figure 2*, factors potentially related to depression are clustered under separate useful themes or categories. However, since pathways between and among various factors and depression are most likely multidirectional, as well as related to both risk and protection, individual factors within a general category may be linked to multiple factors and categories For example, physical and mental illnesses may lead to depression through pathways that are biological, environmental, psychosocial, behavioral and cognitive. In addition, biological factors such as disturbances in regulatory axes may be caused by psychosocial or environmental stressors. Thus, this separation is both illustrative as well as necessary for development of research models to better understand the role of individual factors and subsequently their interaction and overlap with other factors. Furthermore, the direction of potentially causal relationships between depression and many of these factors is not clear.

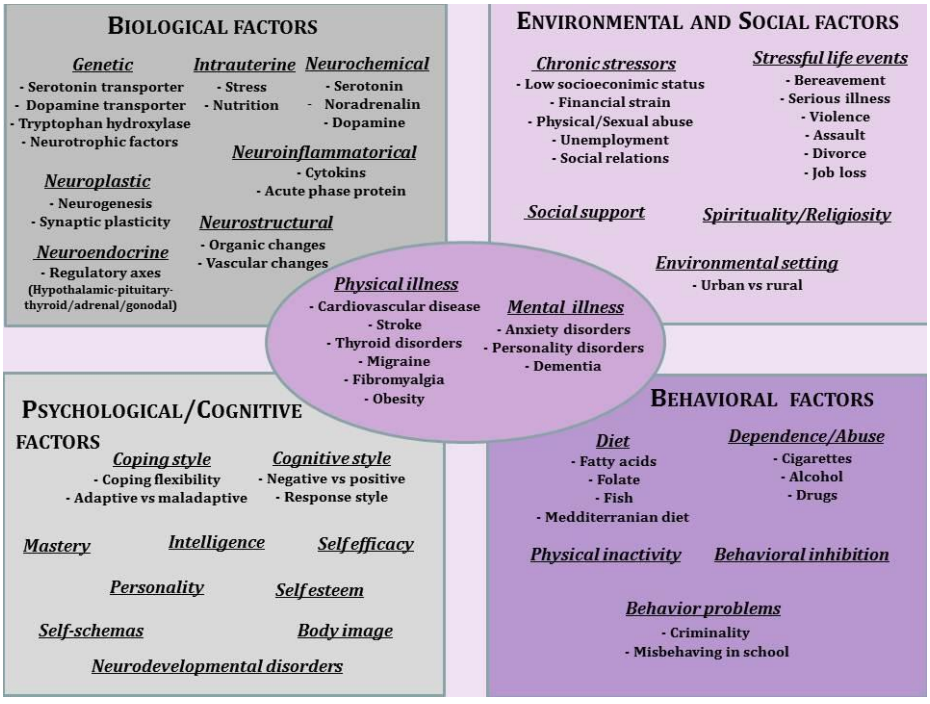


Figure 2. Factors potentially related to depression [7, 10, 31, 45, 66, 68-91] (By Pia Gudmundsson)

On the individual level, there is a large heterogeneity in factors related to depression. One might even suggest that every depressive episode has its own etiology, unique for a specific individual, in a specific context and at a specific point in time. However, to clarify the etiology of depression on an aggregate level, it is important to continue the identification of potential risk- and protective factors in different populations and different groups. For this purpose, epidemiological, population-based studies such as The Prospective Population study of Women in Gothenburg (PPSW), from which all results presented in this thesis originate, are invaluable.

The relative influence of factors related to depression may be equally important across different fields, however, biological factors are the focus of this thesis, and will be discussed more thoroughly below.

1.5 Biological factors related to depression

Over the last 60 years of biological research on depression, the theory about dysfunction of the serotonin, noradrenaline and dopamine systems in the brain (the monoamine hypothesis) has dominated the area [92]. The monoaminergic systems are responsible for the regulation of several fundamental behavioral functions that are impaired in depression including mood, concentration, motivation, energy, sleep, psychomotor activity, appetite, and sexual activity [83]. In addition, a large number of studies show reduced monoamine availability in blood, urine, cerebrospinal fluid and post-mortem brain tissues in persons suffering from depression [83]. The reduced availability of neurotransmitters could be due to depletion of precursors (i.e. tryptophan and tyrosine), down regulation of enzymes responsible for synthesis of neurotransmitters, and activity of re-uptake transporter proteins [83, 93]. Related hypotheses focus on changes in neurotransmitter receptor functions or regulation of second messengers which alter the transmission of monoamines in the synaptic cleft and reduce the effect of

monoamines in the brain [83]. Thus, dysfunction in the monoaminergic systems in the brain is shown to be involved in processes related to depression, and evidence is accumulating for the involvement of additional neurotransmitters in the pathophysiology of depression, including glutamate [94], and nitric oxide (NO) [83]. However, this hypothesis cannot explain some fundamental issues in the pathophysiology of depression such as the delayed clinical effect of antidepressants in relationship to the direct biochemical action generated by these medicines, the function of some antidepressants that acts in ways that do not fit this hypothesis, and the fact that antidepressants may be effective for other disorders [83]. The Network hypothesis suggests that disturbances in the complex interactions of neurons in neural networks, and not merely in monoaminergic systems, may be related to the etiology of depression [95].

Several additional biological approaches to depression over the life course have been investigated. Early in life, depression is considered to have a genetic component that influences the vulnerability to develop the disease [69]; reported heritability ranges from 31 to 42 percent. Over 30 candidate genes have been considered, for example genes related to regulation of monoamines and neurotrophic factors [91]. Already in the uterus factors appear to influence depression vulnerability and studies show relationships between birth-related factors and depression [96-102]. Birth-related factors were evaluated in relationship to lifetime depression in *Paper I* of this thesis and will be described in more detail in section 1.5.1. *Birth-related factors*.

Over the last decade evidence has accumulated for a stress-related hypothesis of depression and depression vulnerability [69]. Biological effects of childhood, adolescent, and adult stressful life events and prolonged exposure to stress include hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis. This dysfunction is related to elevated levels of glucocorticoids (cortisol) which are

reported in persons suffering from depression [83, 92]. The cascade of biological responses initiated by a stressful stimulus begins in the hypothalamus with an elevated release of Corticotropin Releasing Factor (CRF) resulting in the release of cortisol from the adrenal glands. The overactivity of the HPA axis in depression may be caused by elevated central CRF levels and/or an impaired feed-back mechanism in the hippocampus. [83, 92]. CRF appears to be involved in the regulation of noradrenaline synthesis and may constitute a potential link between the monoamine and endocrine systems in relationship to depression [92].

Many studies report a reduction in hippocampal volume in depression [83], and dysfunctions in neuroplasticity may be involved in this process. One of the leading biological hypotheses; the neurotrophic hypothesis, proposes that factors important for neuroplasticity such as Brain Derived Neurotropic Factor (BDNF), are of great importance in the pathogenesis of depression [83, 103]. This hypothesis is supported by post mortem studies in humans and studies using animal models of depression showing lower levels of BDNF in depression and elevated expression of this neurotrophic factor after treatment with antidepressant medication and Electro Convulsive Shock (ECS) therapy [103]. Neurogenesis in the hippocampus is related to cognitive function; impairment of this process could thus contribute to the cognitive symptoms seen in depression [104].

Influence of Hypothalamic-Pituitary-Gonadal (HPG) axis hormones on mood is well documented [105, 106]. In men, testosterone has been related to depressive symptoms, and women frequently report depressive symptoms or depression in the premenstrual- and post-partum periods which are characterized by low levels of estrogens [105]. Studies on depressive symptoms in the menopause, another period of low estrogen levels, are inconclusive [105, 107, 108], however, use of Hormone Replacement Therapy (HRT) during this period has shown antidepressant effects [105, 106]. The mood disturbance related to estrogen levels

does not seem to be caused by abnormalities in the HPG system, but may instead be present in a subgroup of women sensitive to fluctuations of gonadal hormones [106]. The relationship between gonadal hormones and depression may be mediated through several different processes potentially involved in the pathophysiology of depression. Estrogen is involved in brain metabolism of neurotransmitters, genetic expression of serotonin receptors, and neurogenesis [106, 109].

Another regulatory axis that appears to be involved in depression pathophysiology is the Hypothalamic-Pituitary-Thyroid (HPT) axis. An association between thyroid function and mood disorders was already described 200 years ago and is still evaluated [110]. Both hypo- and hyperthyroidism are related to depression, probably reflecting a dysfunction in the HPT axis and not a response to actual levels of thyroid hormones. Most persons with depression have normal thyroid function, and although advances in the area have provided some new insights, the underlying mechanisms explaining the association between thyroid function and depression needs further clarification [110].

Various structural brain changes have been reported in depression. For example, enlarged third and lateral ventricles, and atrophy of hippocampus, amygdala, prefrontal-, and temporal cortices has been observed, as well as vascular and white matter lesions [111-114]. Some of these changes may be more related to late life depression, and it is thought that late life depression may differ from depression occurring earlier in life [115]. There are three predominant biological paradigms for the etiology of late life, or geriatric depression (i.e., the 'Degenerative' paradigm, the 'Vascular depression' hypothesis, and the 'Inflammatory' paradigm) [115], and two of them include structural brain changes. In the degenerative paradigm, geriatric depression is thought to be a precursor of cognitive decline and dementia caused by neurodegenerative

processes in the brain, and the vascular depression hypothesis states that depression is caused by vascular lesions in the brain [112]. These hypotheses are supported by studies showing relationships between brain atrophy or elevated levels of cerebrospinal fluid (CSF) biomarkers of neurodegeneration *vs* vascular disease in the brain and geriatric depression [112, 114, 116]. CSF biomarkers of neurodegeneration and vascular perturbations were evaluated in relationship to depression in *Paper II* and *Paper III* of this thesis and will be described in more detail in section 1.5.2. *Cerebrospinal fluid biomarkers*.

The third etiological paradigm for geriatric depression: the inflammatory paradigm, is based on findings of elevated levels of inflammatory markers in the brain of elderly patients with depression [115]. However, inflammatory processes may be involved in the pathophysiology of depression at all ages and the evidence for an inflammatory or cytokine hypothesis is accumulating [104]. Cytokines are proteins that function as signal molecules in the immune system but can also influence, be synthesized and secreted by other cells [83]. Cytokines are released by immune cells in response to a peripheral immune activation caused by for example a local infection, wounding or psychosocial stress. These molecules are too large to freely pass the blood brain barrier, but probably reach the brain through several different pathways [85]. Evidence for involvement of inflammatory processes in the etiology of depression is broad. Interaction by cytokines seems to be present in a large number of the pathophysiological processes in the brain potentially related to depression, for example in processes related to monoamine metabolism, neuroplasticity and endocrine pathways [83, 85]. In addition, studies indicate that antidepressant treatment may reduce inflammatory processes and that anti-inflammatory drugs may have an antidepressant effect [85, 117].

Inflammatory processes may also lead to depression through the action of free radicals [83]. The formation of free radicals is increased by the action of cytokines, and oxidative stress is suggested to be involved in depression etiology through several different pathways [83].

Psychological stress is reported to induce inflammatory responses and may be involved in the potential relationship between inflammatory processes and depression [83]. Another factor that may be involved in the pathway of inflammatory processes and depression is obesity. Obesity is a potential risk factor for depression [80], and cytokines may be released from adipose tissue. Furthermore, leptin, a peptide produced by adipocytes and important in the regulation of dietary intake, is involved in cytokine metabolism [85]. Leptin receptors are also present in brain regions potentially involved in depression pathology including the hypothalamus, the hippocampus and the amygdala [118], thus obesity may lead to depression through several different pathways.

As stated in the previous section, biological systems and processes that appear to be involved in depression do not act independently, but are interconnected in different known (and most likely unknown) ways, and it is difficult to draw conclusions about cause and effect. Although research in this area has made great progress in the last decades, there is still much work left to be done.

1.5.1 Birth-related factors

Factors associated with depression may be present as early as during foetal development. Several studies show an association between birth-related factors and later depression. In particular, lower birth weight [96-100] and shorter gestational time [101, 102] have been related to later depression.

The idea that adult disease may have an origin in foetal development was first described by Barker and Osmond in the 'foetal origins' or Barker hypothesis in

1986 [119]. This model was based on findings from a geographical analysis in England and Wales showing a relationship between high adult rates of ischemic heart disease and high infant mortality rates fifty years earlier [119]. The foetal origins hypothesis proposes that somatic diseases occurring during adult life such as coronary heart disease, type 2 diabetes mellitus, stroke and hypertension, are responses to undernutrition during fetal life and infancy [120]. Several studies support this hypothesis showing long term health effects of fetal undernutrition including impaired glucose tolerance, higher levels of obesity, coronary heart disease, and schizophrenia [121, 122].

The biological basis for foetal origins of adult disease appears to include developmental plasticity and compensatory growth. Developmental plasticity is the ability to adapt to different environments early in life. During *in utero* development many organs and systems of the body have critical periods or 'windows' for this plasticity, and when this period is over some structures and functions are permanently fixed [120]. In response to low birth weight, compensatory or catch-up growth refers to a rapid weight gain in early childhood caused by improved nutrition compared to that received during intrauterine growth. This phenomenon is shown to reduce the life span in animals, and seems to increase the risk of disease related to low birth and infancy weight in humans [123]. Thus, biological functions developed in response to one environment may not be optimal in another [124].

Related to developmental plasticity is the concept of 'programming' that refers to "the idea that stimuli or insults during critical or sensitive periods in early life can have lifetime consequences" [125]. Early nutrition and intrauterine stress are environmental stimuli that can programme lifetime metabolism, growth, and neurodevelopment that may lead to illness later on [125, 126]. For example, alterations in programming of the hypothalamic-pituitary-adrenal (HPA) and

other regulatory axes may potentially cause increased susceptibility to depression later in life [66, 126].

Birth factors including birth weight, birth length, and head circumference are commonly used as indirect markers of the adequacy of foetal somatic and brain development. Birth weight and/or birth length have been related to various adverse health outcomes including hypertension, coronary heart disease, type 2 diabetes mellitus and cancer [123, 127, 128], and head circumference at birth has been related to later neuropsychological outcomes [129]. Size at birth is influenced by several factors such as maternal genotype, body size, health, parity and lifestyle, paternal and foetal genotype, placental function, rate of foetal growth, environmental availability of nutrients, and gestational time [129-131]. Small size at birth can reflect both intrauterine growth retardation and preterm birth, and a measure of gestational time is required to separate these two conditions [130]. A short gestational time represents preterm birth and is associated with long- term neurological morbidities such as cerebral palsy, hearing loss, epilepsy, cognitive disabilities, developmental delay, and behavioural problems [132].

A potential link between birth weight, gestational time, and depression is related to adipose tissue. After 30 weeks of gestation, accumulation of fat tissue exceeds that of the nonfat components, and from this point on, birth weight represents accumulation of adipose tissue during foetal development [133]. The importance of foetal fat accumulation for neurodevelopment is illustrated by the observation that premature babies are at higher risk of smaller brain volume and later neurocognitive impairment [133, 134]. In addition, leptin, a hormone produced mainly by adipose tissue, has been shown to have effects in the brain that may protect against mood disorders [135].

Relationships between birth factors and depression have been reported, but some studies do not support this finding [136, 137]. In addition, studies are few and varying measurement methods have been used to assess birth factor data and depression status. In *Paper I* of this thesis, birth factor data including birth weight, birth length, head circumference, and gestational time, collected from original midwife records were investigated in relationship to lifetime depression in women using several different sources of information.

1.5.2 Cerebrospinal fluid biomarkers

One of the challenges in evaluating the etiology of depression is the relative lack of appropriate biomarkers. One definition of a biomarker is "cellular, biochemical or molecular alterations that are measurable in biological media such as human tissue, cells or fluids" [138].

Brain tissue metabolism may be involved in depression etiology and can be studied indirectly using CSF biomarkers. The central nervous system (CNS) is surrounded by three protective membranes, the meninges. The two innermost meninges are separated by the subarachnoid space which is filled with CSF, a colorless liquid that also runs in the ventricular system of the brain [139] (*Figure 3).* In humans, the total volume of CSF is about 160 ml and the mean rate of CSF production is approximately 0.35 ml/minute. The main source of CSF is the choroid plexus in the ventricles, but about 20 percent originates from the extracellular space of the brain [139]. Since the extracellular space of the brain is in direct contact with the CSF, this fluid may reflect biochemical changes in the brain. Due to the protective barriers of the CNS, the protein content in CSF is approximately 1/200 of that in serum. CSF gives the brain a mechanical shelter and functions as a selective transporter of metabolically active substances and by-products [139].

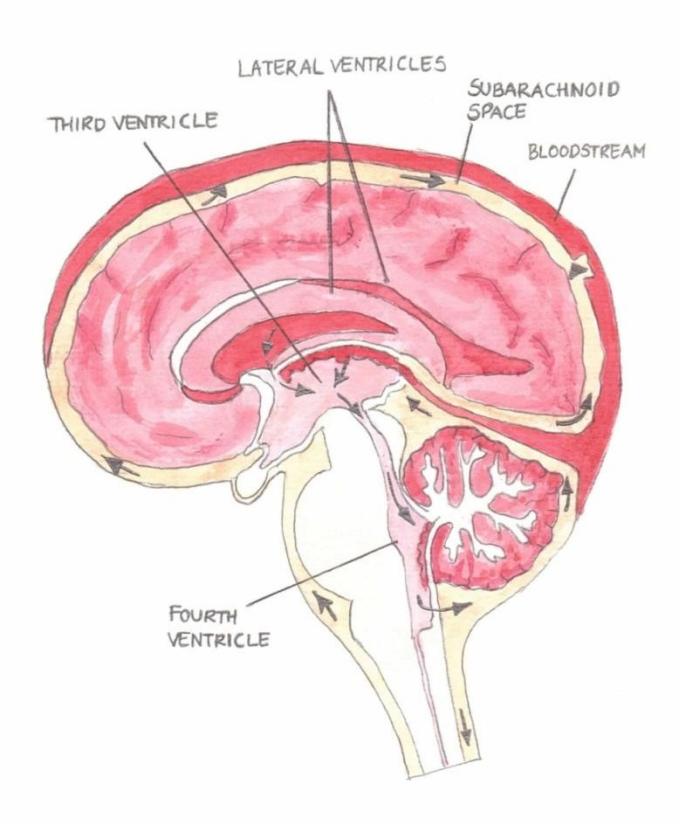


Figure 3. CSF flow (By Emma Eliasson)

Practically, CSF samples are taken from the subarachnoid space by lumbar puncture. Cell counts and total protein are routinely measured in the examination. As a complement, cytological examination and analysis of certain proteins can also be done. CSF analyses are used routinely in clinical neurology research centers to measure levels of proteins such as Amyloid beta-42 (Aβ42), Total tau-protein (T-tau), Neurofilament Light chain (NFL), and Glial fibrillary acidic protein (GFAp) [140-142]. In addition, integrity of the Blood-Brain Barrier (BBB) is measured using the CSF/serum albumin ratio (CSF/S albumin ratio) [143]. Measurements of CSF levels of Aβ42 and tau-protein can help discriminate the diagnosis of Alzheimer's disease (AD) from geriatric depression [142].

In the evaluation of depressive disorders and suicidal behavior, CSF measurements of for example monoamine metabolites (i.e., homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and methoxy-4hydroxyphenylglycole (MHPG)); neuropeptides (i.e., orexin, cocaine and amphetamine regulated transcript (CART), and cholecystokinin (CCK)); hormones (i.e., Corticotropin-Releasing Hormone (CRH) and leptin), and inflammatory cytokines may be valuable [144-151].

Neurodegeneration and vascular perturbations may potentially be involved in the pathophysiology of depression, and are evaluated using CSF biomarkers including CSF/S albumin ratio, Aβ42, T-tau, NFL, and GFAp. Few studies have investigated these CSF biomarkers in relationship to depression, and population data are lacking. In *Paper II* and *Paper III* of this thesis, these five CSF biomarkers were evaluated in a cross-sectional population-based sample of older women, and will be overviewed in the following sections.

Blood brain barrier

There are three protective barriers of the CNS that restrict and control molecular exchange between the blood and the neural tissue or CSF: 1) the BBB between blood and brain interstitial fluid, 2) the choroid plexus epithelium between blood and ventricular CSF, and 3) the arachnoid epithelium between blood and subarachnoid CSF. Since individual neurons are closer to brain capillaries than to the choroid plexus- and arachnoid epithelium, the BBB is the barrier in most control over the direct microenvironment in the brain [152]. Except for some small dispersed areas, the parenchyma of the entire CNS has a barrier and it protects the brain from toxic polar substances in blood and provides a careful stabilization of the CSF [139]. The brain capillary system and the general capillary system differ from each other in several ways. For example, general capillaries have clefts between individual endothelial cells through which small

molecules are able to diffuse, while brain capillary endothelial cells are fused to each other by tight junctions. The general capillary system also has permeability mechanisms called fenestra and pinocytosis. The brain capillaries lack these mechanisms and possess highly selective permeability to solutes [139].
Materials that are sufficiently hydrophobic may penetrate the endothelial cell membrane almost everywhere while hydrophilic substances, such as glucose, must be transported via special carrier proteins. Common drugs directly affecting the brain such as ethanol, caffeine, amphetamine and nicotine are all sufficiently hydrophobic to immediately penetrate the BBB [139]. Many neurotransmitters cannot enter the brain because they are polar (hydrophilic) substances that lack carriers, but their precursors have carrier systems that take them across the BBB. This is an economical and advantageous system for the brain because it traps the neurotransmitters and keeps them outside of brain before they are needed [152].

Albumin is a protein that is synthesized in the liver, thus the albumin present in CSF originates from serum and has crossed the blood-CSF barriers. One way to examine the function of the brain barriers is to calculate the ratio of the albumin concentration in CSF to that in serum (CSF/S albumin ratio). CSF/S albumin ratio is a measure of the blood-CSF-barrier, but since the interstitial fluid is in direct contact with CSF, this is also a measure of BBB integrity [152]. If the CSF/S albumin ratio is high, a BBB disturbance can be suspected. The BBB permeability is increased in healthy aging and the reference value for the CSF/serum albumin ratio for healthy persons over 45 years of age is estimated at <10 (mg/l)/(g/l) [153]. Anything greater may denote severe disease.

Several neurological diseases are associated with BBB disturbance, for example stroke, multiple sclerosis, Human Immunodeficiency Virus (HIV), AD, Parkinson's disease, and head trauma. Since the integrity of the BBB is also

disturbed in relation to infectious- or inflammatory processes in the brain, this may denote common underlying mechanisms among brain diseases [152].

According to the vascular hypothesis of depression [112], disturbance of the BBB may be part of depression etiology. Studies indicate that the BBB may be involved in the regulation of monoamines in the brain [154], and estrogen is involved in the regulation of BBB permeability [155]. In addition, the inflammatory hypothesis of depression may also suggest the involvement of BBB disturbance, since a disrupted BBB enable cytokines into the CNS [156]. However, few studies are available on BBB integrity and depression, but two have suggested BBB disturbance in MDD [116], and suicidal behavior [157].

Amyloid beta-42

Aβ42 is a variant of beta-amyloid (Aβ), which is a cleavage product of Amyloid Precursor Protein (APP). APP is a transmembrane protein that is encoded by a gene on chromosome 21. The C-terminus is cytoplasmic, is shorter than the N-terminus and has one single transmembrane domain. The first 28 extracellular amino acids and 12-14 transmembrane amino acids form the Aβ part of APP, which is cleaved by two proteases β- and γ- secretase [142].

The formation of Aβ peptide from APP is called *the amyloidogenic pathway*. However, this is not the principal proteolytic cleavage of APP. In the main APP processing - *the non-amyloidogenic pathway* - the protease α-secretase is responsible for the first step in proteolysis and consequently no formation of Aβ occurs [142]. Activation of Protein Kinase C (PKC) or inhibition of certain protein phosphatases seem to favor the non-amyloidogenic pathway, thus reducing Aβ formation [158]. A mutation in the APP gene increases protein levels of Aβ and other genes may also influence the processing of APP [159].

Aβ is a protein that, in many patients with AD accumulates as extracellular non-fibrillary Aβ deposits called diffuse plaques. These plaques are probably the first step in the formation of Senile Plaques (SP) seen in later AD [160]. Aβ42 is the longer of two C-terminal variants of Aβ that has been implicated in AD. Aβ42 has a higher aggregation rate than the other dominant variant in AD, Aβ40, and is also the main component in diffuse plaques and SP [142].

It is known that Aβ exerts a neurotoxic effect, but the mechanism behind it is unclear. One hypothesis is that the Aβ peptide generates free radicals by increasing the cellular production of peroxides like hydrogen peroxide. Aβ may also cause perturbations in mitochondrial activity. These processes may lead to neurodegeneration and synaptic degradation [158, 159].
Aβ42 deposition is found in different types of dementia, Down´s syndrome, and in normal aging [142, 159]. The reference value for CSF Aβ42 in healthy individuals is >500 ng/l [161].

Aβ pathology may be involved in the etiology of depression through various pathways. Studies report a relationship between activation of serotonin receptors and the processing of APP [162-164], and glucocorticoids are reported to increase Aβ formation [165]. A relationship between Aβ42 and sex hormones has also been found; estradiol levels seem to be correlated with increased CSF levels or increased deposition of Aβ42 in both women [166, 167], and men [168]. Furthermore, Aβ accumulation is associated with inflammatory responses [169].
Few studies have examined CSF Aβ42 levels in depression. Most studies done have compared CSF values of Aβ42 in depression, AD, and healthy controls, and the results are mixed [170-175]. Several studies found no difference in levels of CSF Aβ42 between persons with depression and healthy controls [171, 173], while other studies found both higher [170], and lower [176] levels of CSF Aβ42 in depression.

Tau protein

Tau protein is expressed mainly in small-caliber axons of cortical nerve cells [177], but has also been found in other cells types [178]. Tau is involved in microtubule assembly and stabilization by forming bridges between the microtubules so they run parallel to each other. If this structure is disrupted, the normal axonal transport between the cell body and the synapse in the neuron is disrupted, potentially causing synaptic degradation and oxidative stress [159].
Tau is a phosphoprotein and six isoforms are expressed in the brains of human adults [179]. Tau is highly phosphorylated during embryonic development, but after that tau normally appears in a relatively unphosphorylated form [159]. After embryonic development, hyperphosphorylated or abnormally phosphorylated tau (P-tau) can cause neurofibrillary lesions which prevent normal tau from binding to microtubules. The tau gene has been identified, and mutations in this gene are thought to reduce the ability of tau to bind to microtubules. As a result, Neurofibrillary Tangels (NFTs) are formed in nerve cell bodies and apical dendrites which also will causes neuronal death [179].

Axonal and neuronal degeneration or injury of nerve cells as indicated by elevated CSF values of T-tau and/or (P-tau) are found in for example AD, Down syndrome, Pick´s disease, and after head trauma occurring in sports such as boxing [180, 181]. Neurofibrillary degeneration is also seen in normal aging [179], and reference values for healthy persons 71-93 years old is <500 ng/l [182].

The cause of the disturbed phosphorylation of tau protein that generates neurofibrillary lesions is not clear. However, in AD, changes in CSF Aβ levels are observed before changes in CSF tau, thus Aβ pathology may be involved [159]. According to the degenerative- as well as the inflammatory hypotheses of depression [115], tau pathology may be involved in depression etiology. Studies indicate that tau pathology is both induced by, and may induce, inflammatory

processes [169]. Furthermore, tau accumulation is reported to be influenced by glucocorticoids [165], and hyperphosphorylation of tau is reduced by estrogen [183], pointing to further potential links between tau pathology and depression. However, studies on CSF tau (T-tau and/or P-tau) in relationship to depression are few and the ones available compare levels of tau in depression, AD and, in some cases, healthy controls. In general, those with depression show lower levels of CSF tau compared to those with AD but no difference compared to healthy controls [141, 174, 176, 184].

Neurofilament Light chain

Neurofilaments are major components of the neuronal cytoskeleton. They are particularly abundant in large myelinated axons of the central- and peripheral nervous systems, and play a central role in maturation of regenerating myelinated axons [185] and growth of dendrites [186]. Most importantly, they control axonal caliber [185, 187, 188], and are therefore essential for morphological integrity and conduction of nerve impulses [189]. The neurofilaments are composed of a triplet protein, of which the neurofilament light chain (NFL) is the subunit with the lowest molecular mass [190], and is the essential component of the neurofilament core [141].

NFL is a marker of subcortical axonal and neuronal degeneration or injury [190, 191], and CSF NFL levels are elevated in several human cerebral disorders such as cerebral infarction, multiple sclerosis [189, 192], late onset AD [141, 189], vascular dementia [141, 189, 192], and in acute brain trauma, after for example boxing [180, 181]. NFL is also reported to be a marker of white matter lesions [193, 194].

According to both neurodegenerative, as well as the vascular, hypotheses of depression, CSF NFL may be elevated in depression. Animal studies suggest

involvement of NFL in the morphological changes seen in the hippocampus that are associated with depression [195]. Elevated levels of glucocorticoids are also associated with higher levels of CSF NFL, [190], potentially supporting a stress-related hypothesis of depression. However, only one study has evaluated CSF NFL levels in relationship to depression, and showed elevated levels of this biomarker in depression [116].

Glial fibrillary acidic protein

GFAp is a monomeric intermediate filament protein that is mostly abundant in astrocytes, but also found in a variety of other cells [196]. GFAp is a key component of the cytoskeleton in mature astrocytes, important for maintaining mechanical strength and shape of the cells. During the last two decades, evidence for functions of astrocytes apart from cell support has emerged, including regulation of the BBB, protection of neurons through clearance of neurotransmitters, coordination of neural activity, and promotion of synaptic plasticity. Astrocytes also serve as stem cells in the adult human brain [196].

Several studies have investigated the function of GFAp in astrocytes, and *Figure 4* shows a schematic overview of processes that may involve GFAp [196].

GFAp was first purified from plaques in brains of patients with multiple sclerosis, and is traditionally used as a marker of brain damage and neuronal degeneration [197]. In humans, the GFAp gene is found on chromosome 17, and 76 mutations have been reported. GFAp expression is induced by for example brain damage and various diseases [196].

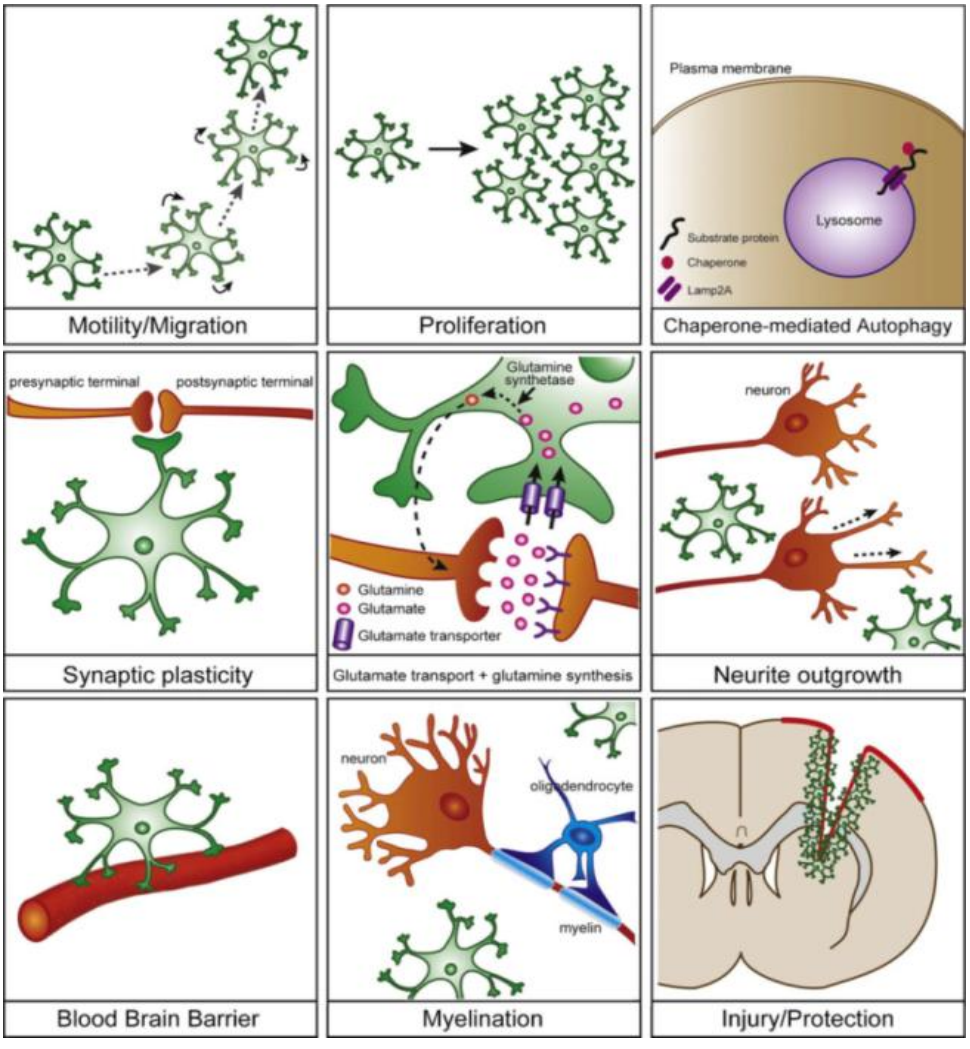


Figure 4. Cellular processes in the brain potentially involving GFAp[196]
(Reprinted with kind permission of Elsevier)

Astroglial injury as indicated by elevated values of CSF GFAp, have been demonstrated in central nervous system (CNS) injury [197, 198], after head trauma following boxing [180, 181], in chronic disorders with astrogliosis [140, 199, 200], and in dementia [201].

GFAp may potentially be involved in the etiology of depression through some of the processes showed in *Figure 5*, including those associated with neuronal plasticity [83], glutamate metabolism [94], and BBB permeability [116].

Alterations in expression of GFAp have been observed post-mortem in MDD patients [202-208], as well as in studies using animal models of depression [209]. However, no studies are available on CSF GFAp and depression.

Summary of CSF biomarkers

In general, all CSF markers discussed in this section are general markers of brain injury, while Aβ42 is more specifically associated with AD. While the role of these CSF markers has not been evaluated to any great extent in geriatric depression, we had the opportunity to do this in a population sample of Swedish women (*Paper II and Paper III*).

2 THE PROSPECTIVE POPULATION STUDY OF WOMEN IN GOTHENBURG

2.1 Historical background

All results presented in this thesis are based on data from the Prospective Population Study of Women in Gothenburg (PPSW). PPSW is a longitudinal multi-disciplinary study that contains epidemiological, clinical, and biological data related to psychiatric disorders in women. The initiative for starting a population study on women came from Leif Hallberg, professor at the Department of medicine (the present Sahlgrenska University hospital) in Gothenburg. In June 1967, Leif Hallberg asked Calle Bengtsson, at that time working at the same department, later on professor of primary health care at the University of Gothenburg, to plan, organise and perform a population study of women in Gothenburg. This was successfully done by Mr. Bengtsson, mainly assisted by Elisabeth Tibblin, a laboratory doctor. A few years earlier, in 1963, another population- based study of women had been performed. However, due to a small number of women from every birth cohort, analysis of data was limited, and no follow-up was performed. Experiences from this study, together with the study of the "Men of 1913" [210], also performed in 1963, formed the basis for the planning of a new health study of women. In the end of September 1967, Mr. Bengtsson had the first proposal of the design of the new "Women´s health study" in his hands. During 15th May to 5th of June, a first group of women were examined, in what was considered a pilot study. However, everything worked out as planned, and no essential changes had to be done before the 'real' study started on September the 2nd. Thus, women from the pilot study (who were representative and recruited in the same manner as all future women), came to be a part of the baseline sample. The baseline examination took approximately 12 months, and totally 1462 women participated [211].

The two overall primary themes of the study were blood/iron deficiency and the menopause. These themes together with a wish to compare women with the 50- and 54-year old men from the "Men of 1913" study, were the determining factors influencing the choice of birth cohorts included. Thus, women living in Gothenburg and born on specific dates (see section 4.1.1 *Participants*) in 1908, 1914, 1918, 1922, and 1930, were invited to the study. Since the primary purpose was to examine blood/iron deficiency and women around the menopausal period, it was decided that more women were to be invited from the birth cohorts of 1918, 1922, and 1930, and less from the two oldest cohorts. After the women were identified from the Swedish Revenue Office Register, written invitation letters were sent out with some basic information. The letter also came with a preparation note saying that they would be called up in a few days. When an appointment was set up, two questionnaires were sent out, and women were asked to come to the clinic fasting [212].

When arriving to the clinic, the women met a nurse who took care of urine samples and gave them dresses to put on for the examinations (these dresses were homemade by Elisabeth Tibblin and Calle Bengtsson´s wife, and washed and carried back in a backpack every day by Mr. Bengtsson). Ms. Tibblin also guided participants through the remaining 9 different stations and gave women in different subgroups appointments for other examinations. Every station was completed in 15 minutes, thus each woman was at the clinic for 2.5 hours. 12 women were invited to the clinic every day, but on average, 10-11 women were examined every day [213]. The clinical stations included general examinations, dental examination, blood samples, gynaecological examination, Electrocardiography (ECG), and a dietary interview. Various questionnaires were filled in at the different stations, including questions about diseases, health problems, smoking- and dietary habits, use of alcohol, dental health, psychological stress, physical activity, and menopausal- and gynaecological

issues. One station was a coffee break, with buns, homemade mainly by Mr. Bengtsson and his wife (and transported every morning in the back pack together with the dresses). The examiners often shared the coffee break with the women, something that was highly appreciated. There was an official slogan applied in the Women´s health study that said "to give more than to take", which was reflected in the dresses, the homemade buns, and the kind and respectful treatment towards the women. This is probably a strong reason for the high response rates in future follow-ups of the study [211].

Subgroups of women were invited to various additional examinations and tests, including measurements of iron absorption, assessment of body composition, breast examination, sternal puncture, working test with ECG registration, and psychiatric examination. [211]. Women born on specific dates in 1914, 1918, 1922, and 1930 were invited to a psychiatric examination performed by Psychiatrist Tore Hällström. The suggestion to include a psychiatric examination came from Mr. Hällström himself when he heard about the planning of a new health study of women, and he was the one performing all 800 interviews [107]. At every upcoming follow-up of the study, psychiatric examinations have been performed by clinical experienced psychiatrists or psychiatric nurses.

The women received results from several of the tests performed in the study by mail, and these results were also sent to their physician if they wished. If abnormalities were found at any test or examination, the women got a new appointment or a remittance was sent for verification in another medical setting. In addition, in 1999, all women were invited to a presentation of aggregated data generated from the study by Calle Bengtsson at the Concert Hall in Gothenburg in connection with his retirement. Approximately 500 women attended [211].

Follow-up examinations of the PPSW have been performed in 1974-75, 1980-81, 1992-93, 2000-02, 2005-06, and 2009-10. The latest follow-up is in 2012.

Various samples were frozen for future analyses at all follow-ups. Examinations, tests and questionnaires have been basically the same at all follow-ups, for the purposes of adequate comparisons over time. However, some examinations, tests and questionnaires have been added, removed, or changed slightly over the years. Women participating in earlier examinations were invited to the next follow-up [211, 214].

Calle Bengtsson was in charge of the four first follow-ups of the PPSW, but several other persons have been involved in the study at different times. To name some, Cecilia Björkelund, Lauren Lissner, Margda Waern, and Ingmar Skoog are important persons in the performance of PPSW.

In 1968, plans for new follow ups after 4, 8, and 12 years existed, but at that time, no one could probably imagine a follow-up period of over 40 years. PPSW has resulted in a large amount of scientific articles and approximately 30 theses's (the first and second written by Tore Hällström and Calle Bengtsson) [211].

The large amount of data, the high response rates and careful identification of non-responders, the clinical psychiatric experienced interviewers, and the over 40 years long follow-up period, make PPSW one of the most prominent population-based studies in the world.

3 OBJECTIVES

To evaluate factors associated with depression is of great value and the main purpose of this thesis. A life course approach and a focus on biological factors in relationship to depression in women are applied (*Figure 5)*. The specific aims are to:

1. Examine potential relationships between birth-related factors and lifetime depression (*Paper I)*
2. Investigate potential cerebrospinal fluid biomarkers in relationship to depression (*Paper II* and *Paper III*)
3. Explore a potential cerebrospinal fluid biomarker profile related to depression (*Paper III*)

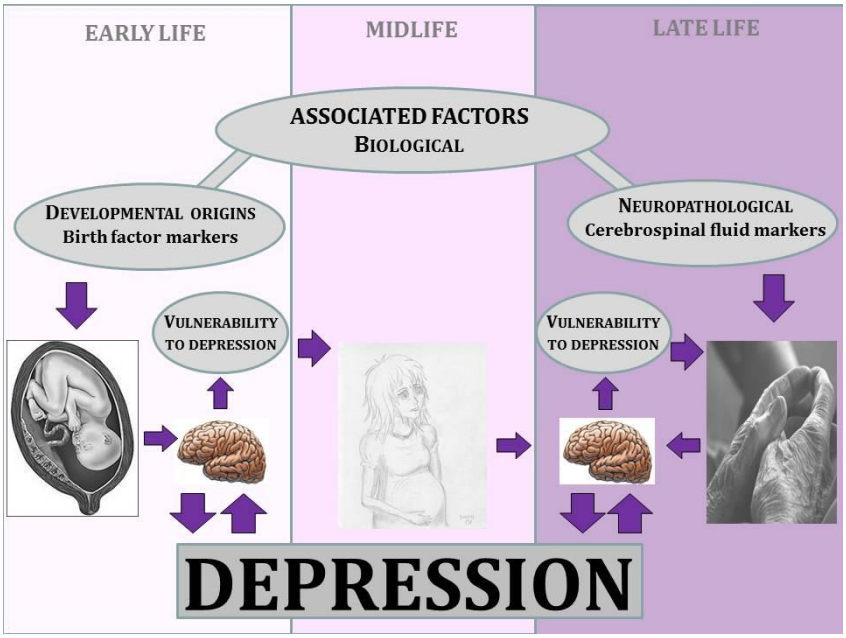


Figure 5. Factors evaluated in relationship to depression in this thesis
(By Pia Gudmundsson and Caroline Sturman)

4 METHODS

4.1 Baseline sample

4.1.1 Participants

PPSW is a multi-disciplinary longitudinal study on a representative sample of women living in Gothenburg (for historical background, see section 2.1 *Historical background)*. In 1968, women born on specific dates in 1908, 1914, 1918, 1922, and 1930, were identified from the Swedish Revenue Office Register, and invited to take part of the study. Of the 1622 invited women, 90.1 percent (N=1462) participated [212] (*Table 1*).

Table 1. Baseline sample of women in 1968 [212]

Mean baseline age (SD)	***Birth dates***	***n***
60.87 (0.24)	6	81
54.56 (0.24)	6, 12	180
50.55 (0.20)	6, 12, 18, 24, 30*	398
46.59 (0.21)	6, 12, 18, 24, 30*	451
38.59 (0.22)	6, 12, 18, 24, 30	372

*Only women born on this date in January-June were invited

At the baseline examination, all women were healthy sufficiently to come to the clinic, however, at follow-up examinations home visits were offered, and both persons living in private households and in institutions were included. Women who participated in the baseline examination, were alive and effective and living

in Sweden at the time, were invited for follow-up examinations in 1974-75 (91 % response rate), 1980-81 (83 % response rate), 1992-93 (70 % response rate), and 2000-2002 (71 % response rate). [215]. Response rates represent the proportion of women participating in relation to the number of women alive and eligible to take part at the time of the follow-up study. In 1980-81 and in 1992-93, the sample was extended [216]. More recent follow-ups have been performed in 2005-2006, 2009-2010, and currently on-going in 2012.

For each cohort, the main samples have been found to be representative of the population base with regard to sex, marital status, income, and community rent allowance, rate of inpatient and outpatient care in psychiatric hospitals, clinics and municipal out-patient departments and rates of registration with the Temperance Board. Those who died, refused to take part, or participated in a cohort that had a shorter length of follow-up, have been traced via records of inpatient and outpatient departments in hospitals and clinics, municipal outpatient departments in Gothenburg, the hospital-linkage system, the Swedish National Cancer Registry, and death certificates [216].

Analyses of non-participants have been done at each follow-up, and some differences between participants and nonparticipants were observed. Unmarried women, divorced women, and widows, were overrepresented among nonparticipants [217]. Furthermore, nonparticipants had higher systolic and diastolic blood pressure, higher waist/hip ratio, and higher mortality. In addition, smokers were overrepresented among nonparticipants [216, 218].

4.1.2 General investigation

Throughout the years, examinations, tests and surveys have been basically identical. An introductory letter was sent to all women, followed by a call from a nurse to set up an appointment. A questionnaire concerning physical illness was

sent out to fill up before the examination [107]. In the general investigation, clinical examinations including vision and hearing tests, electrocardiogram (ECG), gynecological and dental examinations, were performed. Furthermore, measurement of a variety of parameters, such as height and weight, blood pressure, and Peak Expiratory Flow (PEF), was performed. Blood and urine samples were also taken. Surveys assessing factors such as education, physical activity, smoking habits, socioeconomic status, alcohol intake, medication use, and reproductive and medical history, were also included [212]. Some additional examinations and tests have been performed in the whole sample or in subsamples of women over the years, such as psychiatric examination, measurement of iron absorption, assessment of body composition, breast examination, sternal puncture, working test with ECG registration, chest x-ray, neuropsychological examination, computerized tomography (CT), and lumbar puncture (LP) [15]. Case record studies on all women examined since 1968 took place between 2002 and 2004 [214].

4.1.3 Ethical approvals

At the time for the examinations in1968 and 1974, there was no ethics committee handling studies of this kind, thus ethical approval was not applied for. However, the concept of "to give more than to take" was consistent throughout the study [213], thus, basic ethical considerations were applied. From the 1980 examination and on, informed consent has been obtained from all participants and/or their relatives or others, and the study has been approved by the Ethics Committee for Medical Research of University of Gothenburg.

4.2 Psychiatric sample

4.2.1 Participants

A subsample of women born in 1914, 1918, 1922, and 1930, on specific dates, was identified from the Swedish Revenue Office Register and invited to take part of a psychiatric examination. Of the 956 selected women, 57 were part of a pilot study and not included in the baseline sample, thus 899 were invited to take part in the examination. Between selection and examination, 7 women died, 8 women moved from Gothenburg, and 3 women could not be reached. Of the remaining 881, 89 percent (N=800) participated [212] (*Table 2*).

Table 2. Baseline psychiatric sample of women in 1968 [107]

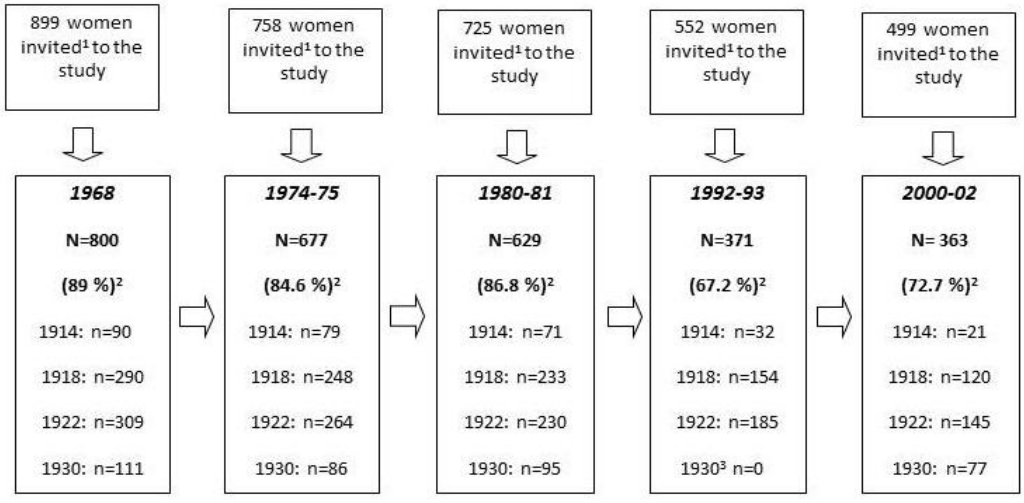
Mean baseline age (SD)	***Birth dates***	***n***
54.62 (0.20)	12	90
50.58 (0.19)	12, 18, 24, 30	290
46.62 (0.28)	12, 18, 24, 30	309
38.62 (0.22)	12, 18*	111

*Only women born on this date in January-June were invited

Case record data were collected from psychiatric institutions and clinics, as supplementary to self-reported information and for dropout analyses. Women who had died or moved were traced via the Health Insurance Office in Gothenburg [107]. Analyses of non-participants (n=99) concerning demographic variables and psychiatric morbidity have been performed [107]. No difference in social

grouping was observed between nonparticipants and participants in the psychiatric examination. Being a single woman or a widow, and being born in 1914 were more common in nonparticipants. Furthermore, living in Gothenburg for a shorter period of time, and unemployment, was slightly over-represented in nonparticipants. It was more common to have a psychiatric diagnosis in the non-participant group. However, number of sickness periods was higher among participants. Nonparticipants had more inpatient visits to psychiatric clinics than participants; however, number of periods did not differ between the groups. Taken together, nonparticipants differed from participants in the psychiatric examination on a number of variables, but most differences were small. However, caution must be taken before drawing conclusions about single women and widows, since these groups are under-represented in the examination group [107].

The psychiatric sample has been followed up in the same manner as the baseline sample (see section 4.1.1 *Participants* and *Figure 6).*



[1] Participants in 1968 who were alive and eligible at the time for the baseline PPSW follow-up
[2] Response rate is calculated as the number of women participating divided by the number of women invited
[3] The cohort of 1930 was not invited to participate in the study

Figure 6. Flow chart of the psychiatric sample from 1968 to 2000

4.2.2 Psychiatric examinations

In 1968-1969, one to four weeks after the somatic examination took place; face-to-face psychiatric interviews were performed by a psychiatrist. These interviews took one to two hours, and five women were invited each day. The interview consisted of structured questions in combination with oriented semi-structured conversations. The questionnaire included both questions for the participant, as well as subjective observations by the interviewer. During the interview, 16 different subjects were covered [107] (see *Table 3*).

Table 3. Contents of the psychiatric interview in 1986 [107]

• Personality traits • Current psychic disturbance • Autonomous functions and psychological drives • Interests • Early home environment • Mental illness in the amily • School life • Work	• Marriage • Other social conditions • Nervous troubles during childhood • Previous nervous trouble • Mental health during pregnancy • Mental health post-partum • Sexual history • Details of menstruation

In the baseline psychiatric examination of 1968, diagnoses of depression were based on the Hamilton Rating Scale (HRS), and a global rating based on a five-degree scale, subjectively performed by the interviewer [107]. At each follow-up, interviews have been performed exclusively by psychiatrists, or psychiatric nurses. The content of the psychiatric interviews has remained essentially the same over the years. However, some new assessments were introduced over 32 years of follow-up. In 1974-75, a working version of the Comprehensive Psychopathological Rating Scale (CPRS) [219] was introduced to rate psychiatric symptoms and signs during the preceding month. In 1980, a self-administered CPRS-based questionnaire regarding symptoms in the previous week, "auto-

CPRS", was sent via post to the participants. In the follow-up examinations of 1992-93 and 2000-02, CPRS [55] (see *Appendix I*) was used in semi-structured face-to- face interviews, to rate psychiatric symptoms and signs during the preceding month [220].

Neuropsychological examinations including various psychometric tests, for example, The Mini-Mental State Examination (MMSE), was conducted on all psychiatric participants in 1992-93 and 2000-02 [221].

4.2.3 Close informant interview

In 1992-93 and 2000-02, interviews of close informants were conducted. After permission from each participant, a close informant was contacted for a phone interview. The interviews were semi-structured and focused on changes in behaviour and intellectual function, as previously described [221].

4.2.4 Diagnostic procedures

At all examinations, diagnosis of depression during the last month was made as closely as possible according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised (DSM-III-R) criteria [222]. In the examinations of 1968-69, 1974-75 and 1980-81, diagnoses were based on the judgment of psychiatrists, and retrospective applications of DSM-III-R have been made [220, 223]. In 1992-93 and 2000-02, computerized algorithms were applied to CPRS responses to identify cases fulfilling symptom criteria for depression (see *Appendix II*) [224]. Due to lack of information, the two-week DSM-III-R time criterion was not applied, and dysthymia was considered a mild form of depression. While participants were not specifically asked whether there had been a change from previous functioning, algorithm cut-offs for each CPRS symptom were selected based on a level of severity corresponding to the DSM-III-R criteria regarding functional change [220]. Bereavement, underlying organic

factors (other than dementia), medical conditions, or use of substances were not considered as exclusion criteria in the diagnosis of depression. In accordance with the DSM-II-R criteria, diagnoses of schizophrenia/schizophreniform disorders and dementia precluded the diagnosis of depression [220]. Depression diagnoses included Major Depressive Disorder (MDD), dysthymia, and depression Not Otherwise Specified (NOS) [222].

History of depression before 1968, and depression between examinations, was based on self-reported information evaluated by psychiatrists [107, 220]. Medical records and the Swedish Hospital Discharge Registry were used as supplementary sources of information. Medical records were collected from hospitals and outpatient departments including psychiatric and primary care in Gothenburg. The Swedish Hospital Discharge Registry provided diagnostic information for all individuals in Sweden discharged from hospitals since 1987 [225].

Diagnoses of dementia were made by geriatric psychiatrists at consensus conferences, based on the psychiatric and close informant interviews, medical records and the Swedish Hospital Discharge Registry as previously described [226].

4.2.5 Measurement of depression symptom burden

The MADRS was used to measure the severity of depression within the past month, and to evaluate specific symptoms of depression including reported and observed depressed mood, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. MADRS includes 10 symptoms rated from 0 (no symptoms) to 6 (severe symptoms), with a total possible score of 60 [227]. Based on total MADRS score, depression severity categories were created using the clinical cut-

points of 0-12 for no depression, 13-19 for mild depression, 20-34 for moderate depression, and >34 for severe depression.

4.3 Birth factor sample (Paper I)

4.3.1 Participants

Of all participants who took part in the study between 1968 and 2002, 1140 women born in 1914, 1918, 1922, or 1930, participated in at least one psychiatric examination. For 803 of them birth factor information, retrieved from original midwife records was available. From the birth cohort of 1914 and later, birth factors were recorded from both home births and hospital deliveries. In 1908, birth factors were not recorded for home births which made up nearly 80 % of all births at that time (*Figure 7*).

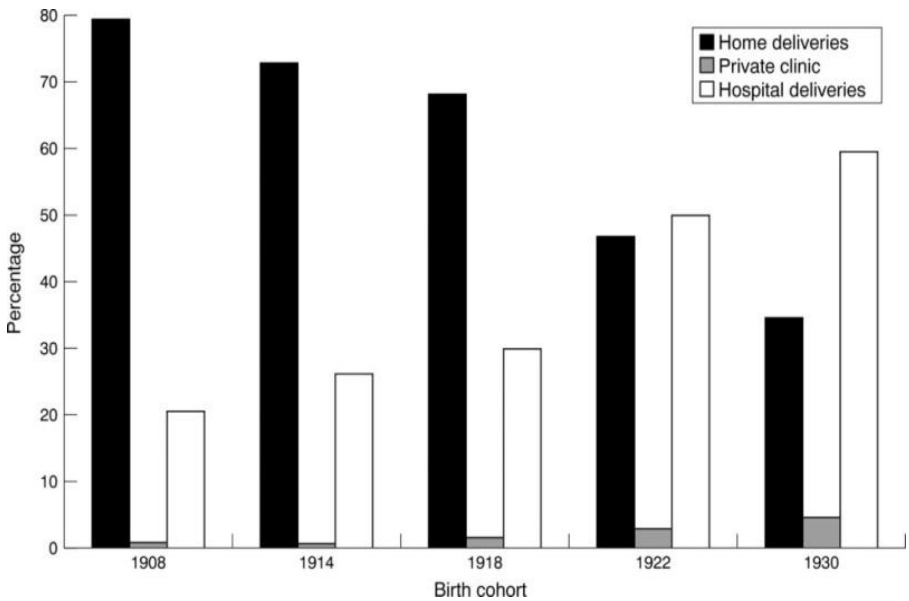


Figure 7. Distribution of delivery place by cohort [130]
(Reprinted with kind permission of Susan Andersson)

Due to lack of representative birth factor data in 1908, this cohort was excluded from all analyses. Number of women included from each cohort is shown in *Table 4.*

Table 4. Birth cohort distribution in 803 participants with available birth factor information

Birth Cohort	n (%)
1914	89 (11.1)
1918	200 (24.9)
1922	257 (32.0)
1930	257 (32.0)

Comparisons of participants with versus without birth factor information in the 1968 baseline sample have been performed. Participants with birth factor information had slightly younger mothers, were from lower socioeconomic groups [130], and were younger compared to those without birth factor information. However there was no difference in maternal age, maternal parity, marital status [130], or level of education obtained in adult life. A comparison between birth weights in full term singleton participants born 1914-1930, and full term singleton women born in 1991-1995, showed similar distributions [130].

4.3.2 Collection of birth-related factors

Birth-related factors were abstracted from original midwife records and hospital records as previously described [127]. Church records were traced for all women, and used for confirmation of delivery records based on age of the mother, place of residence, and number of previous births [127]. Recorded biological birth-related

factors included birth weight, gestational time, birth length, and head circumference**.** While information on birth weight and gestational time were routinely recorded for all birth cohorts studied, birth length was first recorded in Swedish midwife records in 1917, and head circumference in 1926. Additional information was collected when available, including parental social group (categorized in five class levels based on occupation of the father, or if missing or no father, on the mother), maternal age, maternal parity and the participant's birth location (i.e., home vs. hospital) and twin status [130].

4.3.3 Lifetime diagnosis of depression

Diagnosis of lifetime depression was based on multiple sources of information, including history of depression before 1968 as evaluated by a clinical psychiatrist [228], self-reported depression between examinations, current depression evaluated at each examination in 1968-69, 1974-75, 1980-81, 1992-93, and 2000-02, and information from Medical records and the Swedish Hospital Discharge Registry (see section 4.2.4 *Diagnostic procedures)*.

4.3.4 Ethical approval

In addition to basic ethical approvals for the PPSW (see section 4.1.3 *Ethical approval*), identification and analyses of original birth data in participants was approved by the Ethics Committee for Medical Research of University of Gothenburg in 1994.

4.3.5 Statistical analyses

While birth weights were available for all 803 participants, birth record information was incomplete for other birth-related factors. Thus, varying sample sizes are included across analyses. Gestational time was available for 750, birth length for 648, and head circumference for 444 women. All values for birth

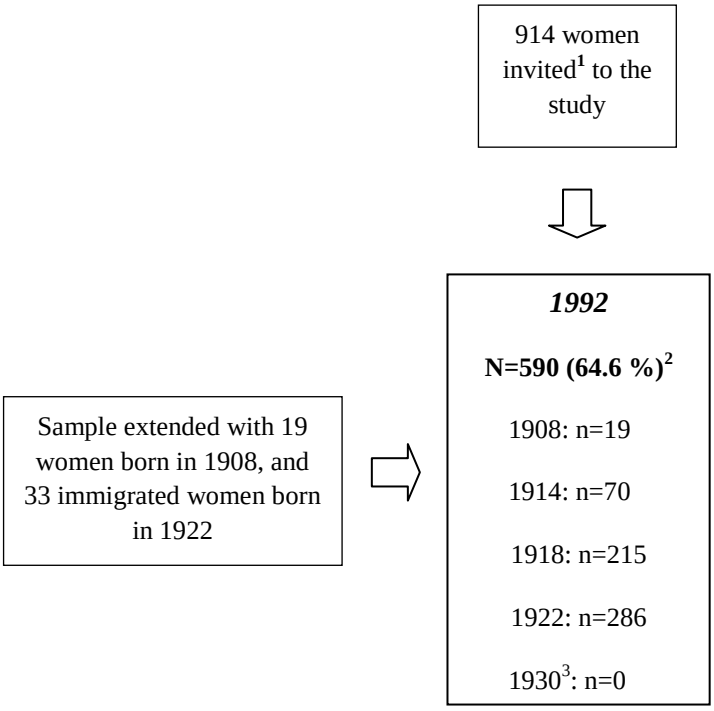
weight, birth length, and head circumference were within acceptable ranges. However, due to some extreme outliers for gestational time, only individuals with gestational times ranging 1.5 standard deviations from the mean of 40 weeks (between 35.2 – 44.9 weeks) (n=715) were included in analyses with gestational time. All birth factors were normally distributed.

Means and standard deviations were calculated for all continuous variables, and t-tests were used to assess mean differences by depression status. Continuous measures of birth factors were used in all initial analyses, and further analyses were conducted considering birth weight, birth length, and head circumference in quintiles and as dichotomous variables using median values as cut-offs. Birth weight was considered as a continuous variable in 500 gram increments. Pearson correlation coefficients were calculated for all continuous variables. Partial correlation coefficients were calculated after adjustment for birth cohort. Linear trends in means of birth factors across level of social group were also tested. Due to inaccuracies in estimating date of depression onset, logistic regression analyses were used to estimate the odds of lifetime depression by birth-related factors, both biological and social. Cohort-adjusted birth-related factors that were significant at a level of $p < 0.05$, were subsequently included in multivariate models. Cox proportional hazards analyses were run to estimate the relationship between birth factors and overall mortality. Results were statistically significant at $p < 0.05$ using two-tailed tests. SPSS, version 15.0, was used to analyse study data.

4.4 Lumbar puncture sample (Paper II & III)

4.4.1 Participants

In 1992-93, 837 surviving women born in 1908, 1914, 1918 and 1922 (mean age 70.9 years), were invited to take part in the study (*Figure 8)*. Of those, 590 agreed to take part in a psychiatric examination. Of these 590 women, 86 consented to undergo LP. Two of these women were diagnosed with dementia according to DSM-III-R [222] in 1992-93, and were excluded from these analyses. *Table 5* shows number of participants from each cohort in the lumbar puncture sample.



[1] Participants in 1968 who were alive and eligible at the time for the baseline PPSW follow-up
[2] Response rate is calculated as the number of women participating divided by the number of women invited
[3] The cohort of 1930 was not invited to participate in the study

Figure 8. Number of women participating from each cohort in 1992

Table 5. Birth cohort distribution in 84 women without dementia who participated in lumbar puncture in 1992-93

Birth Cohort	n (%)
1908	2 (2.4)
1914	7 (8.3)
1918	33 (39.3)
1922	42 (50.0)

There were no differences between women who participated in the lumbar puncture (n=86) and those who participated in the rest of the psychiatric examination (n=590) with regard to a large number of factors, including age; psychiatric illnesses, including depression symptoms; smoking status; alcohol intake; physical activity level (work and leisure time); body mass index; blood levels of cholesterol, high density lipoprotein, and triglycerides; systolic and diastolic blood pressures; age of menopause; history of angina pectoris, myocardial infarction and diabetes; mean total MADRS score, and use of a variety of medications including lipid-lowering agents, anti-hypertensive agents, hormone replacement therapy, and neuroleptics.

4.4.2 LPs and CSF analyses

LPs were generally carried out through the L3/L4 interspace. If macroscopically stained, the initial 0.5-1 ml CSF was discarded and the following 12 ml was collected in one polypropylene vials and gently mixed to avoid gradient effects [229]. Serum samples were taken at the same time. To eliminate cells and other insoluble material, the samples were centrifuged at 2000*g* for 10 minutes and then stored in polypropylene vials at -80 degrees Celsius in 1ml aliquots until analyses. Freeze chains were unbroken until biomarker analyses were done within 5 years after LP [153].

CSF Aβ42 was determined using a sandwich ELISA (Innotestβ-amyloid$_{1-42}$; Innogenetics) constructed to specifically measure Aβ1-42 [230, 231]. To measure levels of CSF T-tau, sandwich ELISA (InnotesthTAU-Ag; Innogenetics, Ghent, Belgium) constructed to measure total T-tau (both normal and phosphorylated tau) was used [232]. The CSF/S albumin ratio was calculated as CSF-albumin (mg/L)/S-albumin (g/L)] [233]. Quantitative determination of albumin in serum and CSF was performed by nephelometry with the Behring Nephelometer Analyzer (Behringwerke AG). CSF NFL and GFAp were determined using a sandwich ELISA as described in detail elsewhere [192, 200]. The limit of detection for NFL was 125 ng/L, thus levels below this detection limit were set to 125 ng/L. Limits of detection for all other biomarkers were sufficiently low to detect all values in the sample.

4.4.3 Cross-sectional diagnoses of depression

At the examination of 1992-93, diagnoses were based on DSM-III-R (APA, 1987) criteria as described in section 4.2.4 *Diagnostic procedures*. The MADRS [227] was used to measure the severity of depression within the past month, and to evaluate specific symptoms of depression.

4.4.4 Ethical approval

In addition to basic ethical approvals for the study (see section 4.1.3 *Ethical approvals*), lumbar punctures in a subsample of women was approved by the Ethics Committee for Medical Research of University of Gothenburg in 1992.

4.4.5 Statistical analyses

As depression status and severity are measured in an ordinal scale, non-parametric tests of correlation were used to test linear associations between levels of depression, quintiles of biomarkers, and age group. A Monte Carlo approximation of the exact permutation test of association, based on 10,000 samples, was used to

assess linear by linear trends in the SPSS crosstab procedure. Logistic regression analyses were used to estimate the odds of depression or depression subtype by biomarker quintiles with consideration for age and, in *Paper II*, future occurrence of dementia. Two women were diagnosed with dementia according to DSM-III-R [222] in 1992-93, and were excluded from all analyses. In *Paper III*, 6 women who became demented within 10 years of the lumbar punctures were also excluded. Total MADRS scores were summed for all participants based on their responses to 10 symptoms rated from 0 (no symptoms) to 6 (severe symptoms), with a total possible score of 60. Based on total MADRS score, depression severity categories were created using the clinical cut-points of 0-12 for no depression, 13-19 for mild depression, 20-34 for moderate depression, and >34 for severe depression.

As CSF biomarkers are continuous measures, some parametric analyses were also performed. Before doing so, tests of normality were conducted using Q-Q-plots in SPSS. T-tau, NFL, and the CSF/serum albumin ratio were natural log (ln) transformed to improve normality. Means and standard deviations were calculated for continuous variables. T-tests were then used to compare mean biomarker levels by depression status, and linear regression models to adjust means comparisons for age. Pearson correlation coefficients were used to assess relationships between CSF biomarkers, with and without age adjustment. Purposeful selection of variables were used in logistic regression analyses to explore independent and combined effects of CSF biomarkers, NFL, Aβ42, and the CSF/S albumin ratio, and age, in relationship to depression. In this thesis, additional likelihood ratio tests were performed to further evaluate these effects. Results were statistically significant at $p < 0.05$ using two-tailed tests. SPSS, version 15.0, was used to analyse study data.

5 RESULTS

5.1 Paper I

In this sample of women age 72-88 years, 44.6% experienced depression at any time during their life. Their average birth parameters are shown in *Table 6*. Evaluating interrelationships among birth-related factors showed that birth weight was associated with a variety of other factors. A higher birth weight was related to a higher maternal age, and maternal parity, an increasing level of parental social group, and home births. Lower birth weight was related to being one of a twin pair, and having a shorter gestational time.

Table 6. Birth related factors in 803 women from the PPSW.

Birth-related Factors[1]	Mean (SD)	Range
Weight, grams	3511.5 (559.6)	1600.0-5500.0
Gestational time, weeks[2]	40.1 (1.7)	35.3-44.9
Length, cm	50.2 (2.7)	35.0-64.0
Head circumference, cm	34.8 (1.7)	24.0-40.0

[1] *n*=803 with information on birth weight, 715 with gestational time, 648 with length, and 444 with head circumference
[2] Only gestational times within 1.5 SDs were included (35.2-44.9 weeks)

Women with any lifetime depression had a lower mean birth weight compared to women without depression (3460.9 (561.0) *vs.* (3552.2 (555.7) gram, t=2.3, df=801, *p*=0.021). Gestational time was also shorter in women with any lifetime depression compared to those women with no depression (39.9 (1.8) *vs.* 40.3 (1.6) weeks, t=2.9, df=713, *p*=0.004). There were no differences between women with

and without lifetime depression regarding other biological birth-related factors. Further analyses showed that birth weights of 3500 grams or less (3500 grams was the median and approximate mean of the sample), and shorter gestational time were independently associated with higher odds of any lifetime depression. No other birth-related factors, biological, nor social, were associated with lifetime depression (*Table 7).*

Table 7. Odds of any lifetime depression by birth-related factors in women

Birth-Related Factors	OR (95% CI)	Age-adjusted *p-value*
Univariate Models		
Biological Factors[1]		
Birth weight ≤ 3500, grams	1.72 (1.29-2.28)	<0.001
Shorter gestational time, weeks	1.13 (1.04-1.24)	0.005
Birth length, cm	0.97 (0.92-1.03)	0.353
Head circumference, cm	0.96 (0.86-1.08)	0.518
Being a twin	1.74 (0.65-4.66)	0.268
Social Factors[2]		
Maternal age, years	0.99 (0.97-1.02)	0.568
Maternal parity, number of live births	0.98 (0.93-1.04)	0.565
Increasing parental social group	0.97 (0.86-1.09)	0.570
Birth location, home *versus* hospital	0.96 (0.72-1.28)	0.779
Multivariate Model[3]		
Birth weight ≤ 3500, grams	1.63 (1.20-2.22)	0.002
Gestational time, weeks	1.11 (1.01-1.22)	0.018

[1] *n*=803 with information on birth weight, 715 with gestational time, 648 with length, 444 with head circumference, and 803 with twin status
[2] *n*=802 with information on maternal age, 803 with maternal parity, 797 with parental social group, and 803 with birth location
[3] Multivariate logistic model based on factors significant at $P<0.05$, birth weight and gestational time, in age-adjusted analyses, *n*=715

As expected, individuals below the median birth weight had shorter mean gestational time compared to those with birth weight above the median (39.9 (1.8) vs 40.4 (1.6) weeks, $p < 0.001$). The direction of the relationship between gestational time and lifetime depression did not differ by median birth weight strata. Among those with a birth weight greater than the median, shorter gestational time was related to lifetime depression (OR 1.23, 95% CI 1.06-1.43, $p = 0.006$). However, there was no evidence of an interaction between birth weight and gestational time in a logistic regression model.

5.2 Paper II & Paper III

Mean age, levels of biomarkers, and depression status in women who participated in a lumbar puncture in 1992 are shown in *Table 8*. In *Paper II* (*Sample 1*), women with prevalent dementia were excluded from all analyses, and adjustment for future dementia up to ten years after LP was performed in all analyses. In *Paper III* (*Sample 2*, i.e., a subset of *Sample 1* with two additional CSF biomarkers*)*, women with prevalent and future dementia up to ten years after LP were excluded. Mean levels of CSF biomarkers were within suggested reference ranges.

Higher levels of Aβ42, NFL, and a higher CSF/ S albumin ratio, were related to MDD (*Table 9*). Boxplots illustrating levels of Aβ42, NFL and the CSF/ S albumin ratio by prevalent MDD are shown in *Figure 9-11*. The CSF/ S albumin ratio was also elevated in women with any depression (6.7 + 2.6 versus 5.4 + 1.7, p=0.018). No relationships were observed between levels of T-tau, or GFAp.

Table 8. Characteristics of women who participated in lumbar puncture in 1992-93

Characteristics	***Sample 1*[3] *(n=84)***	***Sample 2*[4] *(n=78)***
	Mean (SD)	**Mean (SD)**
Age, years	72.6 (3.1)	73.9 (3.2)
CSF biomarkers[1]		
Aβ42, ng/L	813.3 (234.7)	826.6 (236.6)
Tau, ng/L	329.2 (191.2)	309.3 (152.2)
NFL, ng/L	-	298.0 (212.0)
GFAp, ng/L	-	889.0 (293.0)
CSF/S albumin ratio, (mg/L)/(g/L)	5.6 (1.9)	5.5 (1.9)
Depression status[2]	**n (%)**	**n (%)**
Any Depression	14 (16.7)	13 (16.7)
MDD	11 (13.1)	11 (14.1)
Dysthymia	3 (3.5)	2 (2.6)
Depression NOS	0 (0)	0 (0)

[1]CSF: Cerebrospinal Fluid; Aβ42: Amyloid beta-42; T-Tau, Total tau; NFL: Neurofilament Light; GFAp: Glial Fibrillary Acidic protein; CSF/S: CSF/Serum
[2] MDD: Major Depressive Disorder; NOS: Not Otherwise Specified
[3] Prevalent cases of dementia were excluded
[4] Prevalent and future (up to 10 years after LPs) cases of dementia were excluded

Table 9. Comparisons of biomarker levels in women with and without MDD

	No depression		**MDD**		***t-test***[4]	***Age-adjusted***[5]	
	n	**Mean (SD)**	**n**	**Mean (SD)**		***OR***[6] ***(95% CI)***	***p-value***
Sample 1 (n=81)[1]							
CSF biomarkers[2]							
Aβ42 (ng/L)	70	794.0 (234.4)	11	973.3 (184.1)	***p***=0.018 **t**=-2.418 **df**=79	1.88[6] (1.02-3.48)	0.045
CSF/S albumin ratio (mg/L)/(g/L)	70	5.4 (1.7)	11	7.1 (2.8)	***p***=0.015 **t**=-2.477 **df**=79	1.80 (1.06-3.06)	0.029
Sample 2 (n=76)[3]							
CSF biomarkers[2]							
NFL (ng/L)	65	277.0 (186.0)	11	427.0 (318.0)	***p***=0.064 **t**=-1.514 **df**=74	3.27 (1.05-10.07)	0.041

[1] Prevalent cases of dementia and dysthymia were excluded. Analyses were adjusted for future dementia (up to ten years after LP)
[2] CSF: Cerebrospinal Fluid; Aβ42: Amyloid beta 42; CSF/S: CSF/Serum; NFL: Neurofilament light
[3] Prevalent cases of dysthymia and current and future (up to 10 years after LP) cases of dementia were excluded
[4] Two-tailed Student's t-tests were used for mean comparisons between women without depression and women with MDD after CSF/S albumin ratio and NFL were natural log transformed
[5] Age-adjustment accomplished using logistic regression analyses predicting depression status and age group by CSF biomarker level
[6] Odds of depression are presented per quintile Aβ42 and NFL (ng/L)

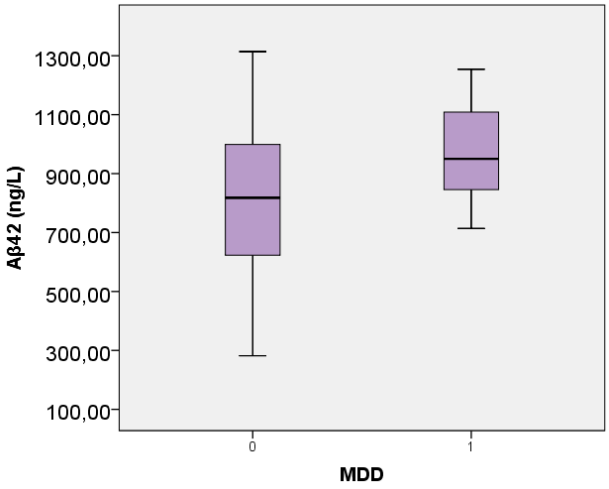


Figure 9. Box plot illustrating CSF levels of Aβ42 by prevalent MDD*

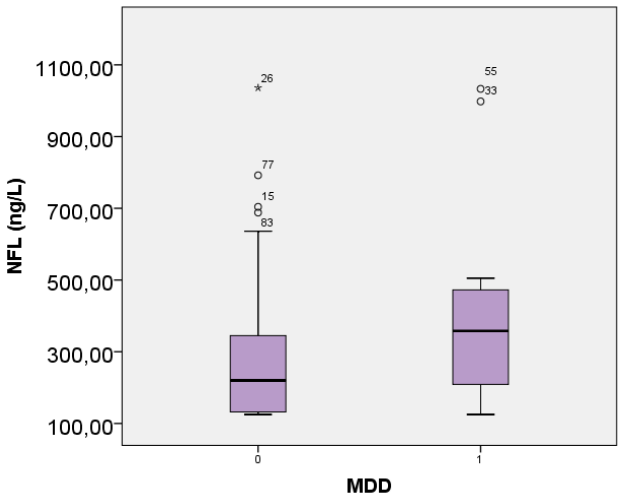


Figure 10. Box plot illustrating CSF levels of NFL by prevalent MDD*

*Shaded boxes include the interquartile range of CSF biomarker values where the median is indicated by a horizontal line dividing the shaded box. The smallest and largest values that are not outliers are connected to the box by a 'whisker', and open circles indicate outliers.

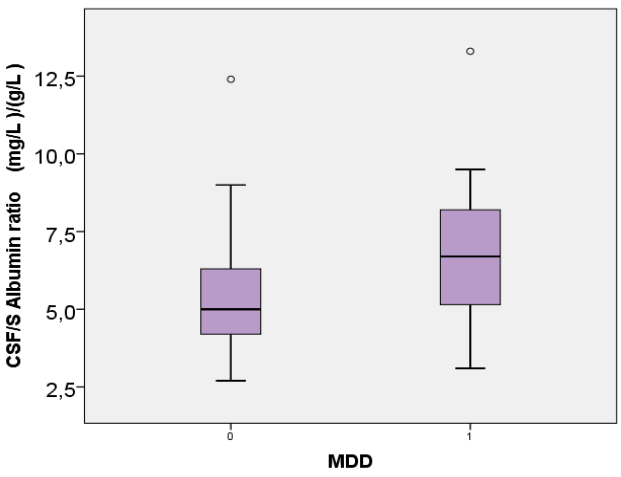


Figure 11. Box plot illustrating values of the CSF/S albumin ratio by prevalent MDD*

*Shaded boxes include the interquartile range of CSF/S albumin ratio values where the median is indicated by a horizontal line dividing the shaded box. The smallest and largest values that are not outliers are connected to the box by a 'whisker', and open circles indicate outliers.

As expected, the mean total MADRS score differed between those with any depression versus those without depression (21.5 ± 7.6 versus 3.9 ± 4.0, $p<0.001$, range 0-34) *(Paper II).* However, there were no associations between CSF levels of biomarkers and MADRS score, categories, or specific symptoms of depression.

When findings from *Paper II* (i.e., higher CSF levels of Aβ42 and higher CSF/S albumin ratio in women with prevalent MDD) were combined in multivariate regression models with findings from *Paper III* (i.e., higher CSF levels of NFL in women with prevalent MDD), each biomarker was independently associated with MDD. The combination of CSF NFL, Aβ42, and the CSF/S albumin ratio provided better model fit than any single biomarker or other combination of biomarkers as indicated by the increase in pseudo R2 (range of pseudo R2= 0.128-0.285) and confirmed by additional likelihood ratio tests (data not shown).

6 DISCUSSION

In this thesis, factors potentially related to depression in women are evaluated. There are several issues associated with the investigation of factors in the relationship to depression. As stated, depression is a multifactorial syndrome that may appear in different forms and various severities [5], thus, many different etiologies and pathophysiological pathways may be involved. In addition, depression is episodic [5], and may be hard to detect, especially in adolescents and in older adults [9, 54].

The next step after an identification of potential factors associated with depression is to clarify if they are potential causes or effects of depression. In cross-sectional studies, such as those in *Paper II* and *Paper III* of this thesis, temporality cannot be clarified, since factors and outcome (i.e., CSF biomarkers and depression) are measured at the same point in time. Temporality may be better understood in longitudinal designs, such described in *Paper I* of this thesis. Specifically, temporality may be demonstrated if the outcome is influenced by changes in that specific factor [234]. Epidemiologic studies such as the PPSW, are excellent first steps towards identifying potential risk factors for depression.

In *Paper I*, birth factors collected from original midwife records were evaluated in relationship to lifetime occurrence of depression, based on multiple sources of information in 72-88 year old women. Lower birth weight and shorter gestational time were independently associated with lifetime depression, a result that is supported by other studies [96-102]. In contrast, one previous study reported a relationship between *higher* birth weight and depression [235], while others found no relationships between birth-related factors and depression [136, 137]. Most studies reported sex-adjusted relationships between birth factors and depression in women and men [96, 100, 101], while other studies have investigated this

relationship solely in men [97], or women [102]. Thus, sex-related differences related to birth factors are not clear and cannot be excluded. Furthermore, diagnosis of depression have varied as well, to include psychiatric register data only [136] or self-reported information only [137]. Definition of a 'lifetime' has varied, and in the latter study, was defined up to age 39, a relatively young age, compared to *Paper I* [137]. The study reporting higher birth weight in women and men related to depression, used self-reported data, and measured depression occurrence until the age of 31 [235].

According to a recently published systematic review and meta-analysis, the overall support for a relationship between low birth weight and depression is weak, or after correction for publishing bias, even non-significant [236]. However, the methodological quality of the 26 studies included in the systematic review (including *Paper I* of this thesis) varied [236]. First, most studies reported depression measured at one point in time, and the sensitivity of depression ascertainment may not have been sufficient to detect potential effects of birth weight [236]. Second, diagnoses of depression were made in different ways, and most studies used only one source of information. Third, most studies did not adjust for gestational time [236], thus lower birth weight may reflect pre-term birth as opposed to intrauterine growth retardation [130]. Fourth, the risk of residual confounding in estimating this relationship is obvious, as only one third of all studies considered other potential confounders [236]. Fifth, only 50 percent of studies used non-selective, population-based samples, thus, half of all studies could not be considered representative. Although non-selective sampling strategies were used in *Paper I* of this thesis, it was considered selective in the meta-analysis, since only women were included (and thus, this study was not included in the meta-analysis forming the bases for the non-significant result). Sixth, several studies had small sample sizes and/or low response rates [236]. Finally, almost 90 percent of studies included participants that were younger than

35 years of age, and no other study included lifetime diagnoses of depression based on multiple sources of information and DSM criteria covering at least seven decades of participants lives [236]. Thus, additional studies with high methodological quality must be done in this area before conclusions can be drawn concerning the relationship between birth weight and depression.

If there is a relationship between birth factors and depression, several different pathways may be considered. The relationship between birth weight, shorter gestational time, and depression may support a stress-related hypothesis of depression. Maternal psychosocial stress has been associated with low birth weight [237]. Furthermore, glucocorticoids play a central role for the timing of delivery, and high glucocorticoid levels in the maternal blood stream may be associated with psychosocial stress [238]. Lower birth weight may be related to depression through glucocorticoid-induced programming of the hypothalamic-pituitary-adrenal (HPA) axis. For example, glucocorticoid levels in the foetus are controlled by the placental enzyme, Type 2 11β–Hydroxysteroid Dehydrogenase (11βHSD2), and lower birth weights are related to decreased expression of this enzyme [239]. In addition, low birth weight (i.e., < 2500 grams) has been associated with higher plasma cortisol concentrations in adults [240], and elevated cortisol has been related to depression in adults [241]. Early programming of other hypothalamic–pituitary–end organ axes, such as the hypothalamic–pituitary–thyroid (HPT), and –gonadal (HPG) axes, may also be involved in the relationship between birth weight, gestational time, and depression [242, 243]. An association between thyroid function and depression is reported [110], and the potential role of estrogen in mood disorders is well documented [105, 106, 109].

Another potential link between birth weight, gestational time, and depression is related to adipose tissue. Foetal fat accumulation is shown to be important for neurodevelopment [133], and adipose tissue is an important energy source, a

source of bioactive free fatty acids, and the largest endocrine organ in the human body [133, 134]. Furthermore, leptin, a hormone produced mainly by adipose tissue, has lately been shown to have effects in the brain that may protect against mood disorders [135]. However, results presented in this thesis show birth weights of or below the median of 3500 grams in relationship to depression. Thus, a pathway including foetal fat accumulation may not be involved here, since these babies probably gained sufficiently adipose tissue during development.

One may suspect that the serious outcomes associated with lower birth weights are related to severe intrauterine growth retardation and pathologically low birth weight. However, as stated previously , the results of *Paper I*, show a relationship between birth weights of 3500 grams or less and depression, a finding in line with two other studies [96, 98]. Processes associated with pathologically low birth weights and preterm births occur over a continuum, and thus variation within the normal range may confer some degree of susceptibility to developing depression later in life. Lower birth weight and shorter gestational time, although not pathological, could cause less neuroplasticity [244] from birth in these women**,** and thus may be markers of a higher susceptibility for depression.

The lifetime prevalence of depression of 44.6 percent reported in *Paper I* is high compared to many other studies [5]. However, most of these studies are retrospective and do not include older populations [21, 22]. Other studies support a lifetime prevalence of 40-45 percent in women [15, 19, 20].

As previously stated, no causal conclusions can be drawn due to the cross-sectional designs of *Paper II* and *III*. Since these studies evaluate unknown relationships between biomarkers and depression, no specific hypotheses are tested, and they are considered hypothesis generating. Thus, elevated levels of Aβ42, NFL, and a higher albumin ratio, may be either cause or consequence of

depression. Few studies have evaluated these CSF biomarkers in depression, most studies have been performed in clinical dementia settings, and no other population-based studies are available. Several studies show higher levels of CSF Aβ42 in depression as compared to AD [167, 171, 175]. One study supports higher levels of CSF Aβ42 in persons with depression compared to healthy persons without depression [170]. However, this study also reported higher levels of CSF Aβ42 in those with AD, a finding that is contrary to other studies [182, 245]. Other studies found no relationship between CSF Aβ42 and depression [171, 173].

One previous study showed *lower* levels of CSF Aβ42 in depression [176]. However, similar to *Paper I* in this thesis, this study is very small (n=47). In addition, exclusion of cases with dementia does not seem to have been done in a structured manner, and there were no adjustments for future dementia. Depression has been an observed prodromal feature of dementia, thus, the lower levels of Aβ42 may reflect a prodromal state of dementia. The authors of that paper [176] suggest that one reason for discrepancy between their results and the result of *Paper I* is that included cases of depression might differ. They speculate that persons with depression in *Paper I* may be suffering from a more acute form of depression, and state that this is not uncommon in population-based studies [176]. However, this is not the case. Persons with acute depression are more likely to reject study invitations, and thus are less likely to be represented in population-based studies. Furthermore, the authors suggest that the elevated levels of CSF Aβ42 presented in *Paper I* may reflect an elevation in soluble CSF Aβ42 that is seen before the formation of senile plaques [176]. Conversely, this is not likely to be the case in these women. Adjustment for future dementias up to ten years after the lumbar puncture was performed, and studies show that significant lower levels of CSF Aβ42 is seen already 5-10 years before the clinical onset of AD [246]. An alternative explanation for the different findings of the two studies may be

suggested. The reported lower levels of CSF Aβ42 may, as the authors suggest, [176] reflect depression cases that are prodromal states of dementia with ongoing formation of plaques, while reported levels of higher CSF Aβ42 (*Paper I*) may reflect a pathophysiology of geriatric depression that is not related to dementia. However, to be able to draw any conclusion about this relationship, evaluations in larger population-based samples including adjustment for future dementia are needed. Unfortunately, lumbar puncture is seldom performed in population-based studies, and the PPSW is fairly unique in having these data.

If in fact higher levels of CSF Aβ42 are associated with depression, as mentioned previously, the question is whether this represents a cause or consequence of depression. In any case, there are several pathophysiological pathways potentially related to this relationship, involving for example serotonin [162-164], and estrogen [167, 168]. Aβ42 may also be associated with processes related to glucocorticoids [165], and inflammatory responses [169], thus potentially supporting stress-related, and inflammatory hypotheses of depression [92, 115] . Related to specific symptoms of depression, levels of Aβ in the brain interstitial fluid has been reported to increase during acute sleep deprivation [247]. In addition, one previous animal study showed that the process of Long-Term Potentiation (LTP), related to memory, was impaired by intracellular injections of Aβ in the hippocampus [248]. However, no association between CSF levels of Aβ42 and specific symptoms of depression were observed in *Paper II* of this thesis. Several issues concerning metabolism, pathology and processes associated with Aβ42 are still unknown [249], thus additional research within this field is needed.

BBB disturbance, as indicated by a higher CSF/S albumin ratio, was associated with depression in *Paper I*. This relationship has not been studied in great detail, and further research is required. However, two studies have suggested BBB

disturbance in MDD [116], and suicidal behavior [157]. These observations may support vascular, inflammatory, as well as stress-related hypotheses of depression [83, 112, 169]. A disrupted BBB may enable cytokines to enter the CNS, which may alter the excretion and turnover of neurotransmitters such as dopamine and serotonin [92, 156]. Other processes that may be involved in a potential relationship between BBB disturbance and depression include disrupted regulation of monoamines in the brain [154], and estrogen-regulation of BBB permeability [155].

In *Paper II*, higher levels of CSF NFL were observed, a finding that is supported by one other study [116]. In addition, decreased immunostaining of NFL in the hippocampus has been observed in animal models of depression [195], and this may provide a basis for elevated CSF levels of NFL.

Increased levels of CSF NFL suggest structural damage of subcortical axons in myelin rich tissue in the brain, i.e. white matter [190, 191], and may support neurodegenerative and vascular hypotheses of depression. In relationship to depression, it may be suggested that structural damage of axons potentially disturb the transport of monoamines in subcortical pathways, such as serotonin [250]. Furthermore, animal models suggest that glucocorticoids may decrease NFL in hippocampus, pointing to potential NFL degradation [190]. Thus, as for other biomarkers associated with depression in *Paper II* (i.e., CSF Aβ42, and the CSF/S albumin ratio) stress-related processes may be involved in the potential relationship between NFL and depression.

Paper II also suggested that a biomarker profile including CSF Aβ42, NFL and the CSF/S albumin ratio, describes more variation in the model related to depression compared to individual biomarkers or other combination of biomarkers. If findings from *Paper II* and *Paper III* were replicated in other, larger studies and associations between these biomarkers and depression could be

confirmed, the question regarding what role they might play in the pathophysiology of depression still remains. In addition, how these biomarkers may interact in the etiology or manifestation of depression is unclear. According to the network hypothesis, depression may be caused by disturbances in neural networks [95], and adverse processes related to Aβ42, NFL, and BBB disturbance may effect these interactions. In addition, as mentioned before, all three biomarkers may be related to depression through processes related to stress.

No relationships with depression were observed for other biomarkers; CSF T-tau and CSF GFAp. The non-finding related to CSF T-tau is supported by other studies [141, 174, 176, 184]. CSF T-tau and CSF NFL are both markers of neurodegeneration, but are abundant in different types of axons. Tau protein is a marker of degradation of small-caliber axons of cortical nerve cells, while NFL, as previously mentioned, represents structural damage of subcortical axons in myelin rich tissue [143]. Thus, depression-related neurodegeneration may be limited to this latter form of axons. *Paper II* seems to be the only study evaluating CSF GFAp in depression. However, there are several processes through which Tau and GFAp may potentially be related to depression [165, 169, 183, 196] (see section 1.5.2 *Cerebrospinal fluid markers*), and the non-finding related to these biomarkers and depression reported in *Paper II* and *Paper III* may be due to limitation in sample sizes.

In summary, there are several processes potentially involved in all the reported relationships to depression in this thesis. However, birth factors, Aβ42 pathology, and neurodegeneration and vascular perturbations as indicated by higher levels of CSF NFL and a higher CSF/S albumin ratio, may all be associated with depression through stress-related processes. Birth factors may represent stress-related intrauterine programming potentially altering the susceptibility for depression over the life course, while Aβ42 pathology, neurodegeneration, and

BBB disturbance may be associated with depression through psychosocial stress occurring later in life.

6.1 Methodological strengths and considerations

There are some methodological strengths related to all three papers included in this thesis. First of all, PPSW was thoroughly planned before set up. In addition, the slogan pervading the PPSW from the beginning; "to give more than to take" is probably a strong reason for the high response rates in future follow-ups of the study. Second, PPSW includes a systematically selected and well-characterized population sample of women. Third, PPSW is a multi-disciplinary longitudinal study including seven extensive follow-ups during more than 40 years. Fourth, the data included are broad and extensive, and examinations, tests and surveys have been basically identical throughout the years, making it suitable for the longitudinal design. Fifth, various tests that are not common in population-based studies, such as lumbar puncture, have been performed in subsamples of women. Sixth, the careful identification of non-responders has made it possible to evaluate the representativeness of the sample. Finally, diagnoses of depression obtained from examinations were based on semi-structured psychiatric interviews performed by experienced clinical psychiatrists or psychiatric nurses, and multiple sources have been used in the diagnosis of mental disorders. Thus, the validity of the psychiatric data is high. Furthermore, diagnoses at each examination were based on DSM-III-R criteria; rigorous standardized criteria for diagnosing clinical psychiatric disorders.

However, all studies, no matter how well planned and performed, have methodological considerations that need to be evaluated and be considered limitations. Some tests and surveys included in the beginning of the study may not be optimal today. However, as mentioned in the previous section, to be able to

analyse data longitudinally, all surveys and tests have been kept basically identical throughout the years. New, more modern surveys and tests have also been added in recent examinations. This increase of data collection in later follow-ups may have negatively affected response rates.

Related to diagnoses of depression, data regarding change in function were lacking. However, algorithm cut-offs for each CPRS symptom were selected based on severity corresponding to the DSM-III-R criteria regarding functional change (see *Appendix 2*). As for bereavement, the criterion of functional change may not be optimal to include in epidemiological studies searching for risk factors for depression [214]. The duration criterion of at least two weeks could not be applied, and diagnoses of depression are based on symptoms during the previous month. Thus, dysthymia was considered a milder form of depression [226]. It is important to remember that criteria included in DSM are based on consensus, and there seems to be little empirical support for both the two week duration criterion and the criteria concerning clinical functional impairment [61]. Finally, diagnoses of depression were based mainly on self-reported depressive symptoms in the previous month, thus recall bias must be considered.

In this thesis, factors in relationship to depression are evaluated in women only. Thus, these results may not be generalizable to men, and potential sex-related differences should be mentioned. As stated before, regarding sex-related differences in the relationship between birth factors and depression (*Paper I*), available data is inconclusive and these differences cannot be excluded. However, there seem to be no biological reasons to believe that this specific relationship should not consider both women and men. Regarding results in *Paper II* and *Paper III*, one might speculate that higher levels of Aβ42 and a higher CSF/S albumin ratio may be found in women only, considering the reported connections between decreased levels of estrogen and release of Aβ42 [167] and estrogen-

regulation of BBB permeability [155]. However, men are also influenced by estrogen [168]. For other biomarkers, no obvious biological factors supporting an association in women only seem to be present.

Women participating in PPSW are all white and are living in Gothenburg, a large city of Sweden, and thus ethnical, environmental and cultural generalizability is limited. Finally, women investigated in this thesis are born in the first half of the 20th century, and may differ from later cohorts in respect to exposure of factors related to birth factors, levels of CSF biomarkers, and depression. In that case, generalizability of results may be limited to these early cohorts. In addition, results may only be generalized to the older population (*Paper I and Paper II*). However, birth weights of this sample of women (*Paper I*) are comparable to women born in the end of the 20th century [130]. In addition, most studies reporting a relationship between birth factors and depression have investigated persons from cohorts after 1960, and although these persons are younger than the persons included in this thesis, this potential association does not seem to reflect secular trends.

6.1.1 Specific strengths and considerations in Paper I

As reported previously, *Paper I* is the only study to report birth factors related to lifetime diagnoses of depression based on multiple sources of information and DSM criteria covering at least seven decades of participants lives [236]. In addition, this present study have birth factor data collected from original midwife records, which is not common in population-based samples of these age cohorts. Original data from midwife records is reported to be more accurate than self-report [251]. Birth weight was adjusted for gestational time, thus excluding the possibility that low birth weight was due to pre-term birth [130]. Furthermore, consideration for several potential confounding factors including maternal age, maternal parity, parental social group, birth location, and twin status were taken.

Regarding psychiatric interviews, to evaluate the reliability of psychiatric data at baseline, 100 interviews were tape-recorded and data was rated by another psychiatrist. Inter-rater reliability was found to be high [107]. Over the years, inter-rater reliability has been frequently evaluated and found satisfactory [214]. In addition, at each follow-up, psychiatric nurses have rated random interviews together with psychiatrists, to ensure high quality of the data.

Specific methodological considerations of *Paper I* are listed below. First, the sample was small compared to other developmental origins studies. Second, although a vast amount of research shows relationships between birth weight and later disease [120], one has to keep in mind that birth weight is a very crude measure of foetal environment, and the use of this marker in developmental origins research has been questioned [252, 253]. Third, measure of gestational time was estimated based on date of last menstrual period, and this parameter may have been imprecise. However this is one of the methods still used today; and only women with gestational times ranging 1.5 SDs from the mean was included. Fourth, depression is an episodic disorder, thus, despite the use of case records, registry data and retrospective information to complement depression diagnoses via psychiatric examinations, there are most likely cases of depression in the non-depressed group. Fifth, history of previous depression prior to the baseline examination in 1968 based on retrospective self-reported data may be subject to recall bias, and was not ascertained in the structured fashion as at later follow-ups. However, diagnoses were based on the judgment of a clinical experienced psychiatrist, and case records were also considered. Furthermore, an ongoing reevaluation of this data from 1968 concerning depression earlier in life, performed by four psychiatrists with long clinical experience, suggests that prevalence of depression before 1968 may even be underestimated [214]. Sixth, in 1980, diagnoses of depression were based on self-administered surveys instead of psychiatric examinations. However, a subsample of 75 women who completed the

questionnaire, were interviewed for analyses of reliability, and based on these analyses, reliability of the self-administered question forms was considered high [254]. Seventh, maternal factors during pregnancy may be related to lower birth weight, shorter gestational time, and depression symptoms in the offspring, and the risk of residual confounding is obvious. The most important maternal factors include external stress, smoking, psychiatric illness, preeclampsia, SES, and maternal birth weight [118, 130]. Some of these factors, such as smoking, were not available in this sample. However, smoking was not common in the beginning of the 20th century, especially not among women [127]. Other factors are available, but due to limitation in power, could not be evaluated.

6.1.2 Specific strengths and considerations in Paper II and Paper III

Paper II and *Paper III* are the first studies to focus on CSF biomarkers in a population-based sample of older women and their relationship to a clinical diagnosis of depression using DSM–III–R criteria. The ability to evaluate CSF in a population-based sample of elderly who are healthy and without dementia is a rare opportunity, and at present, the PPSW seems to be fairly unique in the availability of these data. In addition, exclusions and adjustments for current and future dementias (including AD) were performed, which are important strengths in the evaluation of biomarker traditionally related to AD. Both studies are cross-sectional and small, and considered hypotheses generating. However, these kinds of studies are important for the generation of new ideas, and this is especially important in the study of disorders with unclear etiologies, such as depression.

In addition to the small sample sizes and the cross-sectional designs, some other limitations concerning *Paper II* and Paper *III* should be mentioned. First, related to the small sample sizes, non-findings may be due to limitation in power.

Second, although women in the lumbar puncture sample did not differ from the total psychiatric sample on a large amount of variables, the possibility that these women, especially the ones diagnosed with MDD, may differ in some essential way from other women, cannot be excluded and results may be sample specific. Third, depression is an episodic disorder, and women without depression as evaluated in 1992, may have experienced depression previously. Fourth, some classes of medications were used very infrequently by women in these samples, thereby creating difficulty in evaluating their influence.

6.2 Ethical issues

The PPSW has been approved by the Ethics Committee for Medical Research of University of Gothenburg since the follow-up of 1980. Before this Ethics committee was established, ethical principals were applied to the study through the concept of "to give more than to take" (see section 2 *The Prospective Population Study of Women in Gothenburg*). Regarding the papers comprising this thesis, some ethical issues may be addressed. Research performed on highly vulnerable persons that cannot give informed consent, such as women with dementia, may be questioned. On the other hand, to be able to understand this serious disorder and identify potential cures, research is required. In this thesis, diagnoses of dementia were used as exclusion criteria for depression. In addition, exclusions and adjustments for current and future dementias were performed in *Paper II* and *Paper III*, which are important strengths in the evaluation of biomarker traditionally related to AD. The performance of LP, especially in women with dementia, is also an ethical issue. However, complications with this procedure in the elderly are very rare [143], CSF levels of Aβ42 and T-tau are often used to confirm a diagnosis of Alzheimer's Disease and the potential findings generated from CSF analyses in relationship to mental disorders may outweigh these complications.

7 CONCLUSION

Depression is a very serious disorder associated with severe consequences for the affected individual, those in her surroundings, and society. Depression may affect nearly half of all women at some time during their lives. The etiology of depression is unclear, and evaluating related factors is associated with several issues. However, epidemiological population-based studies are of great value in the first step to identify potential risk or protective factors for depression.

In this thesis, results from the PPSW indicate that birth weight, gestational time, BBB disturbance, and pathology associated with CSF biomarkers Aβ42 and NFL, may be related to depression. Some of these results are supported by several other studies (i.e., results regarding birth factors), while other results are hypothesis-generating and require replication in larger samples (i.e. results regarding CSF biomarkers). Individual relationships may be related to various potential pathophysiological pathways in depression etiology, however, all results presented in this thesis may be linked to stress related hypotheses of depression.

Every potential clue for even one of the countless pieces in the puzzle of depression etiology could save many individuals from unnecessary suffering in the future, thus, research in this area must continue to advance.

8 FUTURE PERSPECTIVES

8.1 Research

The need for research regarding factors related to depression is vast. In this section, selected projects planned for the future are presented. However, this is a fractions of what may be evaluated in the population-based longitudinal studies in Gothenburg.

The results of *Paper II* and *Paper III* in this thesis merit replication, and this may be done in other population-based studies in Gothenburg (i.e., the H70 and H85 studies), in which lumbar punctures also have been performed. These studies include both women and men, making it possible to evaluate sex-related differences in the relationship between CSF biomarkers and depression.

As stated several times in this thesis, depression is a multifactorial disorder, and it is important to evaluate related factors from different fields. In the behavioural field, physical activity has been evaluated in relationship to depression and depressive symptoms. Studies show an inverse relationship between depressive symptoms and physical activity [255-257], and several longitudinal studies report physical activity as a potential protective factor for depression or depressive symptoms [258-261]. However, additional longitudinal studies are required in this area. Furthermore, since studies show that reduced physical activity may also be a consequence of depression [261, 262], studies evaluating both these pathways are needed. In PPSW, questions about physical activity were included from the beginning of the study, and relationships between physical activity and depressive symptomology will soon be investigated.

8.2 Prevention of depression

It is always better to prevent than to cure. Depression is no exception, and identification of potential factors related to depression, as done in this thesis, is one step in that direction. Research shows that education about depression is protective against depressive episodes - both new and recurring ones [7, 8, 65, 263]. Education via knowledge dissemination is a priority for me and the work in depression prevention I hope to accomplish in the future.

More specific, regarding prevention of depression in adolescents, studies show that a school-based combination of education about depression and Cognitive Behavioral Therapy (CBT) strategies is a promising approach [8]. Furthermore, CBT strategies alone, interpersonal approaches or family-based prevention strategies including information on depression seem to be very helpful [7, 263]. Studies on prevention of post-partum depression show promising results for screening of depressive symptoms in pregnant women, as well as classroom based CBT interventions [263]. Finally, in older adults, several potential prevention strategies have been reported including for example educational interventions [65].

9 SAMMANFATTNING PÅ SVENSKA

Bakgrund: Depression är en allvarlig och vanlig sjukdom som är associerad med många svåra konsekvenser både för den drabbade, för anhöriga och för samhället. Ungefär dubbelt så många kvinnor jämfört med män drabbas. Etiologin bakom depression är oklar och kan vara svår att utreda då sjukdomen är episodisk och visar sig i olika svårighetsgrader. Troligen är förklaringen multifaktoriell och man har funnit samband mellan depression och biologiska, psykosociala, kognitiva, miljö- och beteendefaktorer. Det är viktigt att försöka klargöra etiologin bakom depression för att kunna minska risken för insjuknande och därmed bespara mycket lidande.

Metod: Syftet med detta avhandlingsarbete är att undersöka faktorer i relation till depression hos kvinnor över livsspannet. Dessa faktorer har studerats i en populationsbaserad svensk longitudinell studie, Kvinnoundersökningen (KVUS), som startade 1968 (N=1462) och har följts upp 7 gånger under mer än 40 år. KVUS innehåller epidemiologisk, klinisk och biologisk data relaterad till psykiatriska sjukdomar hos äldre. Psykiatriska undersökningar gjordes i en subgrupp av kvinnor vid basundersökningen (N=800), och vid fyra uppföljningar till och med år 2000. Diagnoser av depression över livsspannet baseras på flera olika informationskällor och DSM-III-R-kriterier. Födelsedata hämtad från barnmorskeböcker och sjukhusdata i original fanns tillgänglig för 803 kvinnor som deltagit vid någon psykiatrisk undersökning mellan 1968 och 2000. Dessa faktorer utvärderades i relation till livstids depression i *Artikel I*. 1992 togs ryggmärgsvätskeprov (likvor) på en subgrupp av 84 kvinnor utan demens. Nivåer av biomarkörer utvärderades i tvärsnittsstudier i relation till depression i *Artikel II och Artikel III*.

Resultat: 44.6% (n=358) av kvinnorna i *Artikel I* fick diagnosen livstids depression. Födelsevikt $\leq$3500 gram och kortare graviditetslängd var oberoende associerade med livstids depression. *Artikel I och II* visade högre nivåer av Amyloid beta-42 (Aβ42), Neurofilament protein Light (NFL), och en högre Albuminkvot vid svår depression. I *Artikel II* var en profil av biomarkörer relaterade till svår depression.

Konklusion*:* Födelsevikt samt graviditetslängd, högre nivåer av Aβ42 och NFL i likvor och högre Albuminkvot var associerade med depression hos kvinnor. Dessa resultat kan möjligtvis stödja en stressrelaterad hypotes för depression.

10 REFERENCES

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11 APPENDICES

11.1 Appendix 1

CPRS items used for diagnoses of depression

(Åsberg et al, 1978)

All reported items refer to the previous month

1 Reported sadness

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.

5 Inability to feel

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.

6 Pessimistic thoughts

0-1 No pessimistic thoughts.
2-3 Persistent self-accusations, or definite but still rational ideas of guilt or sin.
4-5 Fluctuating ideas of failure, self-reproach or self-depreciation. Increasingly pessimistic about the future.
6 Delusions of ruin, remorse and unredeemable sin. Absurd self-accusations.

7 Suicidal thoughts

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.

13 Indecision

0-1 No indecisiveness.

2-3 Some vacillation but can still make a decision 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.

14 Lassitude

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 Complete inertia. Unable to start activity without help.

15 Fatiguability

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 wearied. Frequently forced to pause and rest.

6 Exhaustion interrupts almost all activities or even makes them impossible

16 Concentration difficulties

0-1 No difficulties in concentrating.
2-3 Incapacitating lack of concentration.
4-5 Occasional difficulties in collecting one's thoughts.
6 Difficulties in concentrating and sustaining thought which interfere with reading or concentration.

18 Reduced appetite

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 forced to eat. Food refusal.

19 Reduced sleep

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.

20 Increased sleep

0-1 No extra sleep.
2-3 Several hours extra sleep.
4-5 Sleeps deeper or longer than usual.
6 Spends a great part of the day asleep in spite of normal or increased sleep at night.

41 Apparent sadness (observed)

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.

48 Distractability (observed)

0-1 Adequately sustained attention.
2-3 Attention occasionally distracted by irrelevant stimuli (such as background noises).
4-5 Easily distracted.
6 Continually distracted by incidental events and objects which makes interviewing difficult or impossible.

54 Reduced speech (observed)

0-1 Ordinary speech without undue pauses.
2-3 Takes time to produce brief answers.
4 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.

60 Slowness of movement (observed)

0-1 Ordinary change between rest and activity.
2-3 Minimal gestures and facial movements.
4-5 Almost no spontaneous motor activity. Slow and laboured movement.
6 Has to be led to the interview. No spontaneous movements. Immobile face. Stupor

61 Agitation (observed)

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.

For further details, see *Åsberg, M., et al., A comprehensive psychopathological rating scale. Acta Psychiatr Scand Suppl, 1978(271): p. 5-27.*

11.2 Appendix 2

DSM-III-R based algorithms applied on CPRS items

(Skoog et al, 1993)

Algorithm for Major Depressive Disorder

At least five of the following symptoms and at least one should be (1) or (2)

(1) depressed mood:

sadness = 2-6 **or** apparent sadness (observed) = 4-6

(2) markedly diminished interest or pleasure:

inability to feel = 2-6

(3) significant weight loss or weight gain or decrease or increase in appetite:

reduced appetite = 2-6

(4) insomnia or hypersomnia nearly every day:

reduced sleep = 3-6 **or** increased sleep = 4-6

(5) psychomotor agitation or retardation:

agitation (observed) = 3-6
or slowness of movement (observed) = 3-6
or reduced speech (observed) = 2-6

(6) fatigue or loss of energy:

fatiguability = 3-6 **or** lassitude = 3-6

(7) feelings of worthlessness or excessive or inappropriate guilt:

pessimistic thoughts =3-6

(8) diminished ability to think or concentrate, or indecisiveness:

concentration difficulties = 4-6 **or** indecision = 3-6
or distractability = 4-6

(9) recurrent thoughts of death, recurrent suicidal ideation:

suicidal thoughts = 2-6

Algorithm for Dystymia

(1) and at least two other

(1) depressed mood:
sadness = 2-6 **or** apparent sadness (observed) = 4-6

(2) poor appetite or overeating:
reduced appetite = 2-6

(3) insomnia or hypersomnia:
reduced sleep = 3-6 **or** increased sleep = 4-6

(4) low energy or fatigue:
fatiguability = 3-6 **or** lassitude = 3-6

(5) low self-esteem:
pessimistic thoughts =3-6

(6) poor concentration or difficulty making decisions:
concentration difficulties = 4-6
or
indecision = 3-6
or
distractability = 4-6

(7) feelings of hopelessness:
pessimistic thoughts =5-6

Algorithm for Depression Not Otherwise Specified (NOS)

Features that do not meet criteria for MDD or Dysthymia

sadness = 4-6
or
apparent sadness (observed) = 6
or
inability to feel = 4-6

For further details, see *Skoog, I., Nilsson, L., Landahl, S., Steen, B., Mental disorders and the use of psychotropic drugs in an 85-year-old urban population. Int Psychogeriatr, 1993. 5(1): p. 33-48.*

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