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Psychological stress in relation to dementia and brain structural changes

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2012

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ISBN 978-91-628-8523-6

Printed by Kompendiet, Gothenburg, Sweden 2012

ABSTRACT

Psychological stress has been recognized as an increasing public health problem with serious consequences in both physical and mental health. Women reported a higher prevalence of psychological stress, especially in midlife. Earlier studies suggested that psychological stress may cause neuronal degeneration and brain damage by changes in endocrine, metabolic, cardiovascular, and immune systems. The aim of this thesis was to examine whether midlife psychological stress and psychosocial life stressors were associated with increased risks of dementia and brain structural changes in late-life.

The thesis is part of *the Prospective Population Study of Women* in Gothenburg, which was initiated in 1968 with an examination of a representative sample of women (n=1462, participation rate 90%) born in 1908, 1914, 1918, 1922, and 1930. Follow-ups were performed in 1974-75, 1980-81, 1992-93, 2000-02, and 2005-07. Psychological stress was reported according to a standardized question in all examinations, and 18 predefined psychosocial life stressors were rated in 1968. Dementia and subtypes of dementia were diagnosed according to DSM-III-R criteria, based on information from neuropsychiatric examinations, informant interviews, hospital records and registry data. White matter lesions (WMLs), cortical atrophy, and ventricles sizes were measured in computerized tomography (CT) scans of the brain in 2000-02.

In *Study I*, longstanding psychological stress, reported in midlife in 1968-69, 1974-75 and 1980-81, was associated with increased risk of dementia and Alzheimer's disease (AD). Women who reported stress at two or three examinations had higher risks of developing dementia than women reporting no stress or stress at only one examination. In *Study II*, midlife longstanding psychological stress was associated with late-life brain changes, including WMLs, ventricular enlargement and atrophy in temporal lobes on brain CT scans. In *Study III*, number of psychosocial life stressors in 1968-69 was associated with perceived stress in 1968-69 and all of the following examinations until 2005-07. Number of stressors in midlife was also associated with incident dementia and AD.

These studies suggested that psychological stress in midlife increased the risks of dementia and brain structural changes in late-life. Common life stressors related to work, family, marriage and socio-economy had severe and longstanding psychological and physiological consequences. Studies imply the importance of adequate intervention of stress in middle-aged women.

Keywords: Psychological stress, distress, psychosocial life stressors, dementia, Alzheimer's disease, vascular dementia, white matter lesions, brain atrophy, epidemiology, longitudinal study, risk factors.
ISBN: 978-91-628-8523-6, http://hdl.handle.net/2077/29211

SAMMANFATTNING PÅ SVENSKA

Psykologisk stress har uppmärksammats som ett växande folkhälsoproblem som kan få allvarliga fysiska och psykiska konsekvenser. Kvinnor rapporterar högre prevalens av psykologisk stress, särskilt i medelåldern. Tidigare forskning har visat att stress kan orsaka neurodegeneration och hjärnförändringar genom förändringar i endokrina, metabola, kardiovaskulära, och immunologiska system. Syftet med avhandling var att undersöka om psykologisk stress och psykosociala stressorer i medelåldern hade samband med ökad risk för demenssjukdom och strukturella hjärnförändringar senare i livet.

Avhandlingen är en del av *Kvinnoundersökningen* (KVUS) i Göteborg, vilken initierades 1968 med undersökning av ett representativt urval av kvinnor födda 1908, 1914, 1918, 1922, och 1930. Uppföljningsundersökningar genomfördes 1974-75, 1980-81, 1992-93, 2000-02, och 2005-07. Vid alla undersökningstillfällen rapporterades psykologisk stress utifrån en standardiserad frågeställning och vid undersökningen 1968-69 rapporterades 18 psykosociala stressorer. Demens diagnostiserades enligt DSM-III-R, baserat på information från neuropsykiatriska undersökningar, anhörigintervjuer, patientjournaler och sjukhusregister. Förekomst av vitsubstansförändringar, ventrikelstorlek, och kortikal hjärnatrofi gjordes med hjälp av hjärntomografi 2000-02.

I *Studie I* sågs psykologisk stress i medelåldern (1968-69, 1974-75, och 1980-81) öka risken för demens, särskilt Alzheimers sjukdom. De kvinnor som rapporterade psykologisk stress vid två eller tre undersökningar hade högre risk att insjukna i demens än de som inte rapporterat stress vid någon undersökning eller vid endast en undersökning. I *Studie II* visades att långvarig psykologisk stress i medelåldern hade samband med vitsubstansförändringar, ventrikelförstoring, och hjärnatrofi på hjärntomografi. I *Studie III* sågs ’antal psykosociala stressorer’ 1968-69 vara relaterat till upplevd psykologisk stress 1968-69 och vid samtliga följande undersökningar, ända till 2005-07. ’Antal stressorer’ var också relaterat till demens och Alzheimers sjukdom

Dessa studier hypotiserar att psykologisk stress i medelåldern ökar risken för demens och strukturella hjärnförändringar senare i livet. Vanligt förekommande stressorer, relaterade till arbete, familj, äktenskap, eller socioekonomiska förhållanden visade sig ha allvarliga och långtgående psykologiska och fysiologiska konsekvenser. Studierna visar på vikten av adekvat intervention av stress i medelålders kvinnor.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Lena Johansson, Xinxin Guo, Margda Waern, Svante Östling, Deborah Gustafson, Calle Bengtsson, Ingmar Skoog. *Midlife Psychological Stress and Risk of Dementia: A 35-Year Longitudinal Population Study.* Brain. 2010; 133:2217-24

II. Lena Johansson, Ingmar Skoog, Deborah R Gustafson, Pernille J. Olesen, Margda Waern, Calle Bengtsson, Cecilia Björkelund, Leonardo Pantoni, Michela Simoni, Lauren Lissner, Xinxin Guo. *Midlife Psychological Distress Associated With Late-Life Brain Atrophy and White Matter Lesions: A 32-Year Population Study of Women.* Psychosomatic Medicine 2012; 74:120Y125

III. Lena Johansson, Xinxin Guo, Tore Hällström, Maria C Norton, Margda Waern, Svante Östling, Calle Bengtsson, Ingmar Skoog. *Common psychosocial life stressors in relation to perceived stress and Alzheimer's disease over 38 years.* (manuscript)

CONTENTS

ABBREVIATIONS

AD	Alzheimer's disease
BMI	Body Mass Index
CHD	Coronary heart disease
CI	Confidence Interval
CSF	Cerebrospinal flow
CT	Computed Tomography
CVD	Cardiovascular diseases
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
ECG	Electrocardiogram
HPA axis	Hypothalamic-Pituitary-Adrenal axis
HR	Hazard ratio
MRI	Magnetic Resonance Imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders-Alzheimer's Diseases and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignment en Neurosciences
OR	Odds ratio
PTSD	Posttraumatic stress disorder
SD	Standard Deviation
VaD	Vascular dementia
WHO	the World Health Organization
WMLs	White matter lesions
WSQ	the Work Stress Questionnaire

1 BACKGROUND

1.1 Stress

Psychological stress and stress-related disorders have been recognized as a widespread public health problem [1-3]. According to the World Health Organization (WHO) "*Mental health problems and stress-related disorders are the biggest overall cause of early death in Europe*" [4]. Sweden have among the highest sickness absence in world of which 35% are related to mental health problems [5], and depression, stress reactions and anxiety syndromes have shown the greatest increase [6 7].

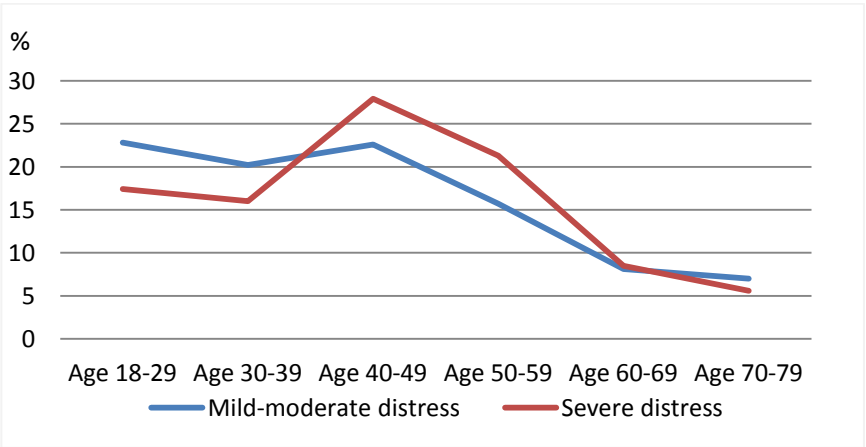
The term *stress* is etymologically a form of the Latin's *stringere* 'to draw tight', and was originally used in physics to refer to the internal distribution of a force exerted on a material body, resulting in strain. It was first in the 1920s the term also begun to be used as a reference for mental and emotional strain [8]. In medical science was stress introduced by the endocrinologist Hans Seyle who studied the effects of a variety of physical stressors (e.g. heat, cold, pain) in the human body [9]. In addition, John Mason studied the reactions of stress hormones in the body and found out that most stressors were psychological to its nature, i.e. they were induced by the interpretation of the events [10].

The concept of stress is ambiguous, with no consensus or agrees on a conceptual and operational definition. Stress can be denoted either as a *cause* (stressor) or as a *response* [11].Stress causes both biological and psychological reactions. Biological reactions include changes in endocrine, cardiovascular, metabolic, and immune system [12]. Psychological reactions are manifested as feelings of anxiety, irritability, or restlessness.

Psychological stress

There are no golden standard measurements of psychological stress and thus no easy way to get a general overview of prevalence and distribution of stress. Few population studies have measured stress within a longitudinal or prospective design. In the Prospective Population Study of Women in Gothenburg 6% of the women, aged 38 and 50 year, reported frequent stress in 1968-69, and 16% in the same ages in 2004-05 [13]. In a longitudinal population study from U.S., perceived psychological stress was increased in all ages by 10% to 30%, between 1983 and 2009 (according to *the Perceived Stress Scale)* [1 14 15]. In another U.S. study in 2004 with more than 25 million participants, 14% of the population reported severe psychological distress, and the highest amount of stress was reported by middle-aged persons in ages 45-64 years (Figure 1) [15 16]. A Canadian health survey measured general 'day-to-day stress' in 1994 and 2003, in a sample of nearly 17 000 persons. The prevalence of stress was similar and constant over the nine years of follow-up. In addition, subjects between 40 and 54 years had the highest prevalence of perceived stress in both 1994 and 2003 [17].

Figure 1. Prevalence of stress in different ages groups, in a representative population study in US (n>25 millions) [16]



In general, women report higher amount of psychological stress [1 15 18-22]. Women have also shown higher prevalence of burnout syndrome [23-25], post-traumatic stress disorder (PTSD) [26], work stress [6 7 27]. Due to this, greater stress-related physiological health-problems among women are expected.

When the internal pressures arouse and the demands exceed the resources to cope with a stressful situation, people perceive stress. This 'psychological overload' can be expressed in various feelings of strain and pressure such as anxiety, irritability, nervousness or exhaustion. An individual's response to potentially stressful situations varies, due to e.g. personality factors and the physiological stress-response in the body. When a person gives his or her subjective assessment of stress, this is 'filtered' through the personality. The same situation may induce stress in one person, but not in another [11].

Several instruments are available for measuring perceived psychological stress. The most used in an international perspective are *the Stress Appraisal Measure* [28], *the Perceived Stress Scale* [1 15 18-20], and *the Kessler Psychological Distress Scale* [21 29]. All these three instruments are based on self-report of a variety of negative feelings and symptoms related to stress, such as nervousness, restlessness, hopelessness, anxiety, and worthlessness [28].

The word *distress* is used as a term of negative stress, i.e. when a person is unable to cope to a stressful situation and therefore shows maladaptive behaviors (e.g. aggression, passivity, or withdrawal). Opposite to distress, eustress is a positive stress which is constructive and motivating.

Psychosocial stressors

The stimulus that provokes the stress response in an individual are called *stressor*. A psychosocial stressor can either be an acute event that requires a major adjustment in a short time (e.g. event of death) [17], or it can be a more chronic strains/pressure, such as ambient circumstances related to health, marriage, or work [30]. Effects of a stressor may vary due to the severity and duration of the condition, person-related characteristics, adequate treatment, and the social environment [31], e.g. individuals have different capacities to cope with stress and thus react differently under the same stressor.

Several studies have shown that experiences of severe psychological trauma in adulthood, related to e.g. combat [32 33], natural disasters [34 35], and Holocaust [36] are related to mental and physical health decades later. Compared to such uncommon traumatic events, negative psychosocial events in relation to marriage, work, children, or socio-economy happened more frequently in daily lives and often have a longer duration although they are less intensive.

Stress and the brain

In biology, most biochemical processes strive to maintain homeostasis, a steady state that exists more as an ideal and less as an achievable condition [8]. Environmental factors, internal or external stimuli, continually disrupt homeostasis; an organism's present condition is a state in constant flux wavering about a homeostatic point that is that organism's optimal condition for living [11]. Factors causing an organism's condition to waver away from homeostasis can be interpreted as *stress*.

When an event is interpreted as being stressful, it trigs the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA)

axis [37]. The sympathetic nervous system is responsible for the rapid stress response, involving the release of catecholamines, adrenaline, and noradrenalin within seconds of the onset of the stressor; while the HPA axis is responsible for a slower stress response involving release of glucocorticoids by the adrenal cortex [38-41].

Glucocorticoids are a class of steroid hormones, and cortisol is the most important human glucocorticoid [38]. It have different effects in target systems, which aims to increase the availability of energy substrates in different parts of the body in order to optimally adapt to changing demands of the environment [8]. Cortisol regulates a variety of important cardiovascular [42], metabolic [43 44], immunologic [12 45], and homeostatic functions in brain [8]. While the activation of the HPA axis can be regarded as a basic adaptive mechanism in response to change, prolonged activation of this system presents a risk of damage to the brain.

Main targets for cortisol are the hippocampus, amygdala, and frontal lobe areas, which have high amount of cortisol receptors. Along with adrenaline, cortisol enhances the formation of memories of events associated with strong emotions [8]. It has been hypothesized that stress can lead to brain atrophy via chronic exposure to elevated levels of cortisol [46]. According to the 'glucocorticoid cascade hypothesis' can a chronic exposure to cortisol in brain lead to hippocampal neuron loss [32 47], which may result in a reduced inhibitory feedback on the HPA axis. This impaired inhibitory effect may result in hypersecretion of cortisol, which in turn, may result in further neuronal loss [12], especially in some vulnerable brain areas, e.g. in the hippocampus complex [32 48 49]. In addition, animal studies have reported that increased glucocorticoid levels and chronic stress may increase the deposition of beta-amyloid peptid and tau-protein in the brain [50-52].

1.2 Dementia

The number of individuals with dementia increases world-wide due to global aging. Few diseases have such medical and socioeconomic burden on the society today [5]. More than 24 million people live with dementia around the world [53] and the lifetime cumulative risk for developing dementia is 20% [54].

Dementia is an organic mental syndrome of global cognitive decline. According to the DSM-III-R [55] dementia is characterized by impaired short- and long-term memory, and also, impairment in one other intellectual function or personality change sufficient to interfere with a person's occupational functioning and daily life. The dementia syndrome can be caused by a number of different brain diseases, such as Alzheimer's disease (AD), Lewy-body disease, hydrocephalus, fronto-temporal lobe dementia, and a variety of cerebrovascular disorders [54].

The distinction between the neurodegenerative changes that accompany 'normal ageing' and those that characterize dementia is not clear. Unspecific vascular and neurodegenerative damage in brain are common in autopsies from older human brains, also in individuals without diagnosis of dementia. The difference between normal degenerative processes of brain and preclinical changes of dementia is a gray zone and there is no particular way to distinguish between the two. It is also not unusual that one individual have multiple dementia pathology [56].

For enable a true reduce of incident dementia it is essential to identify risk factors, especially modifiable risk factors. Although it has been intensive research in the field of dementia in recent years, little clinical progress has been made relative to how people get the dementia and what can be done to avoid it. The sporadic nature suggests that, aside from genetic factors,

environmental determinants may play a critical role in onset and progression of dementia [57].

Alzheimer's disease

AD is the most common form of dementia. It is an irreversible, progressive neurodegenerative disorder characterized by accumulation of beta-amyloid peptids and neurofibrilllary tangles in brain, resulting in neuronal death and gradual loss of cognitive abilities [57 58]. It is still unknown what trig and drives the neuropathological processes. Probably there are a complex series of events that take place in the brain over a long period of time, where multiple factors collaborate, and maybe AD refer to a group of syndromes caused by a variety of different mechanisms, rather than one 'true causal risk factor' [57]. So, even if the beta-amyloids, above all, are defined as a potential pathogenic factor they probably do not act alone, especially not in the early stages of the disease [57].

It is likely that AD is caused by a combination of both genetic, environmental, and lifestyle factors. Besides ageing, which is the most obvious risk factor for the disease, epidemiological studies have suggested several tentative associations, such as low educational, APOE e4 polymorphism, hyper-homocysteinaemia, anemia, and head injury. Several risk factors are associated with vascular disease, including hypercholesterolaemia, hypertension, atherosclerosis, coronary heart disease, smoking, obesity, and diabetes [57].

The diagnostic procedure of AD is essentially clinical, while there is no validated biomarker, beside from findings on historical examination of the brain. However, recent research have shown to be promising in the development of early diagnostic tools and a number of potential

techniques/modalities could probable be used in future diagnostic procedures, such as for example cerebrospinal fluid (CSF) biomarkers, magnetic resonance imaging (MRI), and positron emission tomography [56]. Several diagnostic criteria are available. The different versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) are the leading sets for primary degenerative dementia of the AD type, with the DSM-III-R [55] being the most frequent used criteria in epidemiological studies [59].

In research, AD is often diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [60]. These criteria specify eight cognitive domains that may be impaired in AD: memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving, and function abilities. Out of these the dementia cases are rated as; *Definite AD*: The patient meets the criteria for probable AD and has histopathologic evidence of AD via autopsy or biopsy; *Probable AD*: Dementia has been established by clinical and neuropsychological examinations. Cognitive impairments also have to be progressive and be present in two or more areas of cognition. The onset of the deficits has been between the ages of 40 and 90 years and finally there must be an absence of other diseases capable of producing a dementia syndrome; *Possible AD*: There is a dementia syndrome with an atypical onset, presentation or progression; and without a known etiology; but no co-morbid diseases capable of producing dementia are believed to be in the origin of it; or *Unlikely AD*: The patient presents a dementia syndrome with a sudden onset, focal neurological signs, or seizures or gait disturbance early in the concern of illness [61].

The progress of AD is a subtle process, where the symptoms gradually became worsens over a number of years [56]. The seeding, for the AD pathology, occurs long before the mildest symptoms appear and the disease becomes clinically manifested [62]. Pathologic biomarkers (beta-amyloids levels in CSF) have been found to be fully altered five to ten years before conversion to AD [63]. The earliest pathological signs in brain imaging are commonly seen as atrophy in the medial temporal lobe, and especially in the hippocampal area [64-66]. The implications of the hippocampus in memory processes are very well known and it is therefore coherent that this area is among the first which become affected by the pathogenic mechanisms [67]. According to the gradually progress of AD, almost all brain areas became affected. In the final stage of the disease are there often a global cortical atrophy and almost all cognitive functions are exaggerated [57].

Vascular dementia

The diagnosis of vascular dementia (VaD) is established when the dementia symptoms are specifically associated with cerebral vascular pathology, such as stroke (infarct or hemorrhagic lesions), small vessel disease, atherosclerosis, or amyloid angiopathy [68]. The diagnosis for VaD requires abrupt onset, stepwise deterioration, and history of stroke and/or focal neurological deficits.

Several specific diagnostic criteria can be used to diagnose VaD, including the DSM, and the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [69]. The NINDS-AIREN criteria specify eight cognitive domains that may be impaired in VaD: memory, orientation, attention, language, visuospatial function, executive functions, motor control,

and praxis. The deficits should be severe enough to interfere with activities of daily living, and not due to physical effects of stroke alone.

1.3 Structural brain changes in imaging

Several imaging modalities are today available as diagnostic tools to differentiate between healthy and pathological brain aging [56]. Computed tomography (CT) is still the most prevalent brain-imaging tool worldwide. A CT scan is commonly performed in diagnostic procedure of dementia in daily clinical practice. CT scans do not have optimal sensitivity for the diffuse metabolic changes associated with dementia, but may suggest or yield information relevant to other types of dementia, such as stroke or hydrocephalus [70].

Brain atrophy

Cortical brain atrophy appears as decreased brain volume and shrinkage of brain tissue, and can be visualized as ventricular dilation and/or widening of the cortical sulci in brain imaging, e.g. in CT scans [70]. The atrophy can be generalized, with neuron loss throughout the entire brain, or it can be focal, and affect only a limited brain area. Cortical atrophy is common in older persons as well as in persons with neurodegenerative disorders [71 72], and contributes to cognitive decline. Cortical atrophy may also be a marker for incipient and manifest AD type dementia [64]. Especially temporal lobe atrophy appears to be an early hallmark of AD [65 71 73].

The cellular processes, underlie age-related grey matter atrophy, include decreased synaptic density [74] and reduction of neurons [75]. Cortical atrophy can also be a consequence of deafferentation caused by loss of cortical-

subcortical connections and enlarged ventricles may be due to loss of subcortical white matter [76].

In epidemiologic studies, cortical atrophy has been found to be related to a variety of life-style and medical factors, such as hypertension [77] [78], cerebrovascular and cardiovascular disease [78], diabetes [79], smoking [77], high alcohol intake [80], and obesity [81] [82].

White matter lesions

White matter lesions (WMLs) are a radiological diagnosis obtained as rarefaction of the white matter in brain imaging. WMLs appear as low attenuation and hypodensity areas in periventricular and subcortical white matter, without regular margins or specific vascular territories [83]. The pathological findings represent areas of ischemic demyelination with arteriolosclerosis, hyalinosis and narrowing of the lumen of the small penetrating arteries in the white matter [84] [85].

White matter hyperintensities are frequently observed in old persons, and particularly among those with cardiovascular risk factors and symptomatic cerebrovascular disease [86] [87]. WMLs have been associated with dementia [88] [89], depression [90], stroke [86] [91] [92], and mortality [93] [94], in epidemiological population studies. WMLs are also present in patients with AD, especially in the temporal lobe and in the corpus callosum [88] [95].

1.4 Earlier studies

Former studies have analysed perceived stress, stressful life events, stress-prone personality, and posttraumatic stress disorder (PTSD), as possible risk

factors for pathological brain changes and dementia. Table 1 is an overview of former studies on stress in relation to dementia and cognitive decline.

Table 1. Earlier studies on stress and stressors in association to dementia and cognitive decline

First author	Study design	Stress Exposure	Outcome	Results
Archer 2009 [96]	Retrospective Case-control	Neuroticism in midlife	AD	Midlife neuroticism predicted younger age of AD onset in females but not in males
Crowe 2007 [97]	Prospective Longitudinal Case-control	Stress reactivity	Dementia	Greater stress reactivity was associated with dementia
Duberstein 2011 [98]	Longitudinal Case-control Elderly	Neuroticism	AD	Elevated neuroticism was associated with risk of AD
Grimby 1995 [99]	Longitudinal Case-control Elderly	Life-events	Cognitive tests	Losing a spouse or child was related to cognitive abilities
Norton 2009 [100]	Retrospective Population	Parental death in child-hood	Dementia	Fathers' death before subject age 5 was related with dementia
Norton 2011 [101]	Retrospective Population	Parental death in child-hood	Dementia	Mothers death in subjects adolescence was related to AD
Peavy 2009 [102]	Longitudinal Case-control Elderly	Life-events Cortisol levels	Memory tests	Higher event-based stress was associated with faster cognitive decline in subjects with MCI
Persson 1996 [103]	Population Longitudinal Elderly	Psychosocial risk factors	Dementia AD/VaD	Parents death in childhood, arduous manual work, illness in relative and number of stressors was related to dementia.
Ravona-Springer 2011 [104]	Longitudinal Case-control	Holocaust survival	Dementia	No associations with dementia

Rosnick 2007 [105]	**Population Cross-sectional Elderly**	**Perceived stress Life events Personality**	**Cognitive tests**	**Recent death of a sibling was associated with lower cognition**
Stawski 2006 [106]	Population Cross-sectional Elderly	Perceived stress Life-events	Memory test Processing speed	Self-reported stress was associated with lower working memory
Tsolaki 2010 [107]	Cross-sectional Case-control	Life-events	Dementia Cognitive tests	Stressful events were associated with cognitive decline and dementia
Wang 2009 [108]	Longitudinal Population Elderly	Neuroticism Extroversion	Dementia	Low neuroticism and high extraversion was protective to dementia
Wang 2012 [109]	Retrospective Longitudinal Population Elderly	Work stress	Dementia	Work stress was associated with dementia
Wilson 2003 [110]	Longitudinal Elderly	Distress (neurotisicm)	Dementia Cognitive tests	Distress was related to AD and episodic memory decline
Wilson 2004 [111]	Longitudinal Case-control Elderly	Distress (neuroticism)	Dementia Cognitive tests	Distress was related with lower episodic memory
Wilson 2005 [112]	Longitudinal Population Elderly	Distress (neuroticism)	Cognitive tests	Distress was related to cognitive decline
Wilson 2005 [113]	Longitudinal Population Elderly	Distress (neurotism)	Dementia	Persons with distress proneness were more likely to develop AD
Wilson 2006 [114]	Longitudinal Population Elderly	Distress (neuroticism)	Dementia Cognitive tests	Distress was related to development of AD
Wilson 2007 [115]	Population Longitudinal Elderly	Distress (neuroticism)	Dementia Cognitive decline	Distress was associated with dementia and cognition decline
Yaffe 2010 [116]	Retrospective Case-control	PTSD in war veterans	Dementia	PTSD cases were had higher risk of incident dementia
Yehuda 2005 [117]	Retrospective Case-control	PTSD in holocaust survivals Cortisol	Memory tests	High cortisol was related to lower memory in PTSD

Few former studies were based on midlife assessment of stress. Most studies had a short study follow-up or cross-sectional design. Perceived stress, stress-prone personality, and exposure of life-events was associated with cognitive decline and dementia in several studies with follow-ups ≤6 years [98 99 102 105-107 109-115 118]. Wilson et al [112] found associations between distress (neuroticism) and cognitive decline over a period over 9 years. One study had a prospective study design with measurement of stress in midlife [97]. This study found that persons with greater 'stress reactivity' had higher prevalence of dementia 30 years later.

Three studies used retrospective report of stressors. All found associations between death of parent in childhood and increase risk of dementia in late-life [100 101 103], and one study found that number of psychosocial risk factors was related to dementia [103]. Archer et al [96] used retrospective measurement of stress-prone personality, based on informant report, and found that midlife neuroticism predicted earlier onset of AD. Three studies analyzed experience of severe traumas and PTSD. Yaffe et al [116] found that persons with PTSD had increased risk of dementia, and Yehuda et al [117] found that high cortisol levels in persons with PTSD predict memory decline. However, in a large sample (n=1889) of subjects who experienced holocaust and Nazi concentration camps in World War II, Ravona-Springer et al [104] found no increased risk for dementia.

Several studies have found associations between stress and atrophy in brain, especially in the medial temporal lobe. Decreased hippocampal volume have been seen in combat-related PTSD [32 33 46 119 120 121], and in early childhood sexual abuse [122]. Studies have also found relations between PTSD and cerebrovascular insult/white matter lesion [121 123-127]. Gianaros et al [128] found

that chronic perceived stress in midlife was associated with decreased grey matter volume 20 years later.

2 AIMS

The main aims of the three studies were:

- To assess the association between perceived psychological stress in midlife and incidence of dementia in late-life.
  Study I

- To assess the effect of perceived psychological stress in midlife and occurrence of structural brain changes, WMLs and atrophy, in late-life.
  Study II

- To assess the effect of common psychosocial life stressors on perceived psychological stress and incidence of dementia.
  Study III

3 SUBJECTS AND METHODS

3.1 Study sample

All data originates from the Prospective Population Study of Women in Gothenburg, Sweden, a study initiated in 1968 and still ongoing [129-132]. The baseline study sample in 1968-69 was selected from the Revenue Office Register based on certain birth dates in order to recruit a representative sample of women at age 38, 46, 50, 56, and 60 in Gothenburg (Table 2). A total of 1622 women were invited, and 1462 (90.1%) accepted to participate.

Table 2. Selection and age in initial examination, in 1968-69

Year of birth	Date of birth	Mean age± SD (year)
1908	6	60.87±0.24
1914	6, 12	54.56±0.24
1918	6, 12, 18, 24, 30	50.55±0.20
1922	6, 12, 18, 24, 30	46.57±0.21
1930	6, 12, 18, 24, 30 [a]	38.59±0.22

[a] Of the women born on the 30th only those born in January-June were called for the examination

All surviving women were invited to participate in the follow-up examinations in 1974-75, 1980-81, 1992-93, 2000-02, and 2005-07 with participation rates of 91%, 83%, 70%, 71%, and 70% respectively (Table 3). In 1980-81 the sample was enriched with 47 women born in 1930 in order to ensure the representativeness of the age strata

Table 3. Flowchart of participants in the population study at each examination

	Examination					
	1968-69	1974-75	1980-81	1992-93	2000-02	2005-07
Born 1908, n	81	65	49	19	7	2
Born 1914, n	180	163	140	79	44	35
Born 1918, n	398	351	325	220	175	124
Born 1922, n	431	387	332	299	199	165
Born 1930, n	372	336	355	278	231	209
Total, n	1462	1302	1201	895	656	535
Participation rate [a]	90%	91%	82%	70%	71%	70%

[a] Among eligible women, i.e. surviving and living in Sweden at time for examination

Study I comprised women who had answered the question on perceived stress in 1968-69, 1974-75, and/or 1980-80, i.e. 1415 women in 1968-69 (aged 38, 46, 50, 54, and 60 years), 1301 in 1974-75 (aged 44, 52, 56, 60, and 66 years), and 1196 in 1980-81 (aged 50, 58, 62, 66, and 72 years) and were non-demented at time for the examination. The sample had complete endpoint data of death and dementia until 2003.

Study II included 344 women who had stress-data in 1968-69, 1974-75, and 1980-81, and brain CT-scan in 2000-02. Two women were born 1908; 19 born 1914; 74 born 1918; 98 born 1922; and 151 born 1930.

Study III included the 800 participants from the primary psychiatric subsample in 1968-69: 90 born 1914; 290 born 1918; 309 born 1922; and 111 born 1930. The sample had complete endpoint data of death and dementia until 2006.

The general examination

At each study wave, all participants went through a comprehensive health examination at out-patient clinic by standardized protocols including e.g.

blood and urine tests, electrocardiogram (ECG), anthropometric measurements, and blood pressure. Information on medical history, medication use, education, marital status, socio-economic status, having children, cigarette smoking, alcohol consumption, and physical activity were obtained.

For women who had difficulties to come to the out-patient clinic for examination, mainly due to high age, mental disorders, or physical impairment, home visits by research nurses were offered [132], in examination 2000-02 (n=127) and 2005-07 (n=183).

The psychiatric examination

At the baseline examination, in 1968-69, a representative subsample born in 1914, 1918, 1922, and 1930, were invited for a psychiatric examination, and 800 accepted to participate (participation rate 88.4%) (Table 4) [133]. The aim of this study was to assess the prevalence and incidence of psychiatric disorders in the population and to relate these morbidity parameters to other biosocial variables.

Table 4. Flowchart of participants from the baseline psychiatric examination and psychiatric follow-ups

	Examination					
	1968-69	1974-75	1980-81	1992-93	2000-02	2005-07
Born 1914, n	89	79	71	70	21	16
Born 1918, n	291	248	233	215	120	82
Born 1922, n	309	264	230	286	145	120
Born 1930, n	111	86	95	-	77	75
Total, n	800	677	629	571	363	293

Psychiatric examinations were made by psychiatrists in 1968-69, 1974-75, 1980-81, and 1992-93 and by experienced psychiatric nurses in 2000-02 and 2005-07. The nurses were supervised and trained by psychiatrists. The psychiatric examinations included clinical interviews, observations of psychiatric signs, neuropsychiatric tests, and self-rated questionnaires [134]. In the last three examinations, in 1992-93, 2000-02, and 2005-07, have a more extensive rating of dementia symptoms/signs been made, with rating of language, memory, orientation, gait and motor difficulties, intellectual ability, for time, place, person and situation, and knowledge of general information [134].

Close informant interviews

Close informant interviews were performed in 1992-93, 2000-02, and 2005-07 by psychiatric nurses. The interviews were done over telephone, they were semi-structured, and comprised questions about changes in behaviour and intellectual function, changes in personality, psychiatric symptoms, performances in activities of daily living, and, in cases of dementia, age of onset and disease course [134].

Medical records and hospital discharge registry

Medical records were collected from all inpatient and outpatient departments and general practitioners' offices in Gothenburg for all women. The Swedish Hospital Discharge Registry provided diagnostic information for all individuals discharged from hospitals on a nationwide basis since 1978.

3.2 Perceived psychological stress

A question on perceived stress was asked by a physician in 1968-69, 1974-75, 1980-81, 2000-02, and 2005-07. The question was identical at each examination, and was as following: *"Have you experienced any period of*

stress (one month or longer) in relation to circumstances in everyday life, such as work, health, or family situation? Stress referred to feelings of irritability, tension, nervousness, fear, anxiety or sleep disturbances."

The alternative answers were:

0: Have never experienced any period of stress

1: Have experienced period/s of stress more than five years ago

2: Have experienced one period of stress during the last five years

3: Have experienced several periods of stress during the last five years

4: Have experienced constant stress during the last year

5: Have experienced constant stress during the last five years

Alternatives 3-5 were defined as 'frequent/constant stress' in *Study I* and *Study II*, and as 'perceived stress' in *Study III*.

3.3 Psychosocial stressors

In the 1968-69 examination, eighteen predefined life stressors were collected in the psychiatric subsample (n=800). These stressors included: divorce, widowhood, serious problem in children (e.g. physical illness, death, abuse), extramarital childbirth, mental illness in spouse or first degree relative, alcohol abuse in spouse or first degree relative, physical illness or social problems related to husband, receiving help from social-security, problems related to husband's or own work (e.g. lost work or removal), and limited social network. Some of the life stressors (physical illness, mental illness and alcohol abuse in spouse; serious problem and mental illness in child; work related problems; and limited social network) were rated in the last year before examination in 1968-69. The others were rated as occurring sometimes before the examination in 1968-69.

3.4 Dementia and subtypes of dementia

Dementia diagnosis for participants at each examination was based on the combined information from the psychiatric examinations and the close informant interview according to the Diagnostic and Statistic Manual of Mental Disorders (DSM-III-R) [55], as described previously [134]. Dementia diagnoses for individuals lost to follow-up were based on information from medical records evaluated by geriatric psychiatrists in consensus conferences, and the Swedish Hospital Discharge Registry [134]. The diagnoses had to be compatible with DSM-III-R criteria. The duration had to be at least six month.

Dementia subtypes were determined by geriatric psychiatrists. Probable or possible AD was diagnosed according to the criteria of the NINCDS-ADRDA [60], and VaD was diagnosed according to the criteria of the NINDS-AIREN [69]. VaD was diagnosed when there was a temporal relationship (within 1 year) between a history of acute focal neurological symptoms and signs (hemiparesis or motor aphasia) and the first symptoms of dementia. Further, due to the recognized difficulties to determine the relative importance of cerebrovascular disease in the etiology of dementia, various ways of defining dementia subtypes was explored. In *Study I* the AD group was divided into AD with or without cerebrovascular disease. There was also a group ´dementia with cerebrovascular disease´ which included individuals with dementia and stroke without considering the temporal relationship between the occurrence of dementia and stroke. In practice, this group included pure VaD and AD with cerebrovascular disease. Other dementias were diagnosed when other causes were likely to have caused the dementia [134 135].

3.5 Computed tomography of the brain

In 2000-02, all participating women (n=684) were invited for a brain CT scan. The scans were performed without contrast enhancement and with 8-mm continuous slices on a Picker 6000 [70 136], and were evaluated by a neurologist experienced in visual CT and MRI rating scales of WMLs and other brain lesions. The rater was blinded to the participants' clinical characteristics. The rating procedures were carried out separately for WMLs and brain atrophy.

Measurement of brain atrophy

Cortical atrophy of temporal, parietal, frontal, and occipital lobes was categorized according to the anatomical subdivision [70]. The severity of atrophy was scored as normal, mild, and moderate-severe, according to the extent of sulcal widening. Ventricular sizes and sylvian fissure sizes were measured using a transparent metric ruler as described by de Leon and colleagues [70 137]. The following linear distances were measured: (i) the bifrontal span of the lateral ventricles, (ii) the width of the lateral ventricles at the head of the caudate nucleus, (iii) the minimum width of the bodies of the lateral ventricles at the waist, (iv) the greatest width of the third ventricle, and (v) the sum of the greatest width of the left and right sylvian fissures. Ratios for (i), (ii), (iii), and (v) were determined by dividing the obtained values by the internal diameter of the skull at the level of the measurement, giving the following ratios: bifrontal ratio, bicaudate ratio, cella media ratio, and sylvian fissure ratio.

Measurement of white matter lesions

WMLs were defined as low-density areas in periventricular and subcortical white matter [70 138]. Decreased density was rated as no, mild, moderate, and

severe in relation to the attenuation of normal white matter. The Gothenburg scale was used [138]. This scale is a 0–3 point scale that takes into accounts the severity of the attenuation of WML, being 0: absence of any attenuation, 1: mild signal attenuation, 2: moderate signal attenuation, 3: severe signal attenuation.

3.6 Potential confounders

Information on a number of potential confounders was obtained at the examinations in 1968-69, 1974-75, and 1980-81. Education was dichotomized as compulsory (6 years for those born in 1908-1922, and 7 years for those born in 1930), or more. Socio-economic status was based on husband's occupation for married women and own occupation for unmarried women and was defined as high, medium and low [139]. Work status was measured as full-time work and/or part-time work versus no work outside home. Cigarette smoking was defined as never, former and current smoker. Wine consumption was classified as none, < once weekly, and ≥ once weekly. Physical activities during leisure time were rated as low (< 4 hour/week) and medium/high (≥4 hour/week). Hypertension was defined as systolic blood pressure ≥160mmHg (≥140mmHg in *Study II*) and/or diastolic blood pressure ≥95mmHg (≥90 mmHg in *Study II*), and/or taking antihypertensive medications. Coronary heart disease (CHD) was defined as meeting one or more of the following criteria: angina pectoris according to the Rose criteria [140]; documented history of myocardial infarction; ECG-evidence of ischemia, i.e. complete left bundle branch block or major Q-waves; pronounced ST-depression and/or negative T-waves [141]. Waist-to-hip ratio was calculated as the ratio of waist and hip circumferences, measured to the nearest 0.5 cm. Blood samples were taken after an overnight fast, and serum cholesterol concentrations were measured. Diabetes mellitus was

defined as a diagnosis by a doctor, being on anti-diabetes therapy, having two fasting blood glucose values ≥7.0 mmol/l, or according to death certificates. History of myocardial infarction was based on medical charts and death certificates. Stroke was diagnosed based on information from psychiatric examinations and the Swedish Hospital Discharge Registry.

3.7 Statistical analyses

Study I

Cox regressions were used to study the association between psychological stress at each examination and incidence of dementia and dementia subtypes. The associations are presented as hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted for age, education, marital status, socio-economic status, having children, smoking, wine consumption, physical activity, coronary heart disease, hypertension, and waist-to-hip ratio. Person-years were calculated from the date of the baseline examination to (a) time of dementia onset; (b) the date of death; (c) the date of the last follow-up examination for participants in 2000-03; or (d) December 31 2001 for surviving drop-outs. We further examined whether number of examinations with stress report influenced dementia risk by using Cox regression models. The study sample was classified as: never reporting frequent/constant stress at any of the examinations and frequent/constant stress at one, two, or three examinations. Adjustments were based on data from 1980-81.

As individuals might have experienced increased stress because of incipient dementia, we reanalysed the data after excluding women with dementia onset before 1992. Finally the influence of stress on dementia with onset before and after age 70 was analysed.

Study II

Independent sample *t* tests or χ^2 tests were used to compare CT-participants and non CT-participants. Logistic regression analyses were applied to estimate associations between psychological stress and cortical atrophy (no-mild versus moderate-severe) and between psychological stress and WMLs (no-mild versus moderate-severe). The associations are presented as odds ratios (ORs) and 95% CI. Linear regression models were used to assess associations between psychological stress and bifrontal ratio, bicaudate ratio, cella media ratio, third ventricle width, and sylvian fissure ratio. The regression models were adjusted for potential confounders (collected in 1980-81) i.e. age, hypertension, current smoking, serum cholesterol, waist-hip-ratio, diabetes mellitus, and myocardial infarction. As number of reports of constant/frequent stress at each examination was too small to make further analyses, we combined the stress-data from the three examinations in 1968-69, 1974-75, and 1980-81. Those with no stress in any of the three examinations were compared to those who reported frequent/constant stress in at least one examination.

We also analyzed the association between stress and moderate-severe WMLs after excluding women with moderate-severe temporal lobe atrophy, and the association between stress and moderate-severe temporal lobe atrophy after excluding women with moderate-severe WMLs. Finally, we made analyses after excluding women with dementia, and after age stratification in younger (born 1930 and 1922) and older cohorts (born 1918, 1914, and 1908).

Study III

Logistic regressions were used to analyse the associations between number of life stressors in 1968-69 and perceived stress in 1968-69, 1974-75, 1980-81, 2000-02, and 2005-07. The associations are presented as ORs and 95% CIs in two separate models. The first model adjusts for age only. The second model adjust for age, education, socio-economic status, marital status, work status, wine consumption, hypertension, CHD, smoking, stroke, diabetes, and waist-to-hip ratio. Person-years were calculated from the date of the baseline examination to (a) the time of dementia onset; (b) the date of death; (c) the date of the last follow-up examination for participants in 2005-07; or (d) December 31, 2006 for surviving drop-outs.

Cox regression analyses were used to study the association between number of life stressors and incidence of dementia, and subtypes of dementia. The associations are presented as HRs and 95% CIs, and adjust for the same covariates as the logistic regression analyses. A third model was added which also included longstanding perceived stress as a covariate.

3.8 Ethics

The Ethics Committee for Medical Research at the University of Gothenburg approved the study. In accordance with the provisions of the Helsinki Declaration, informed consent was obtained from participants and/or their relatives.

4 RESULTS

4.1 Psychological stress in midlife

Prevalence of psychological stress in 1968-69, 1974-75, and 1980-81 are presented in Table 5. The five years of retrospective answers gave stress-data from 1963 to 1981, i.e. in a period of more than 15 years. One woman with dementia onset before 1974-75 and five women with dementia onset before 1980-81 were excluded. A majority of the participants reported no period of stress. Frequent/constant stress (alternatives 3, 4, and 5) was reported by 20% in 1968-69, 23% in 1974-75, and 16% in 1980-81.

Table 5. Prevalence of psychological stress

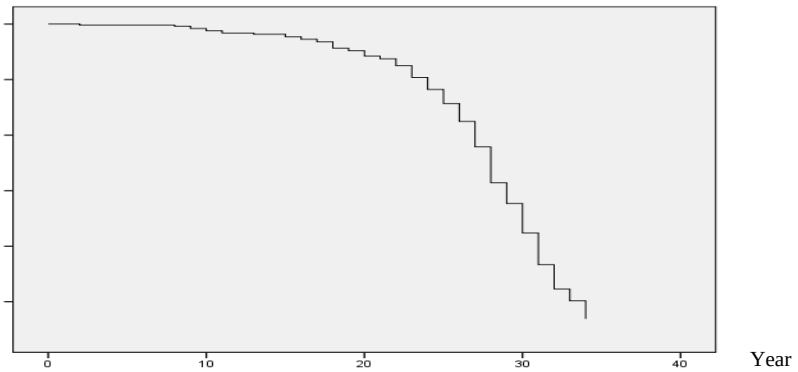
Psychological stress	Examination 1968-69 n=1415	Examination 1974-75 n=1301	Examination 1980-81 n=1196
0. Never experienced any period of stress, n (%)	758 (54)	737 (57)	758 (50)
1. Experienced period/s of stress more than 5 years ago, n (%)	176 (12)	81 (6)	141 (9)
2. Experienced one period of stress during the last 5 years, n (%)	204 (14)	179 (14)	114 (8)
3. Experienced several periods of stress during the last 5 years, n (%)	184 (13)	211 (16)	102 (7)
4. Experienced constant stress during the last year, n (%)	42 (3)	52 (4)	42 (3)
5. Experienced constant stress during the last 5 years, n (%)	51 (4)	42 (3)	39 (3)
Frequent/constant stress, n (%) [a]	277 (20)	305 (23)	183 (16)

[a] Answer alternatives 3-5.

4.2 Incidence of dementia

Among the 1415 non-demented women who answered the stress question in 1968-69, 161 (11%) developed dementia during 35 years of follow-up (40,089 person-years). These included 105 with AD (73 without cerebrovascular disease and 32 with cerebrovascular disease), 40 VaD, and 16 other dementias. The mean time from the baseline examination to dementia onset was 25 years (8 had dementia onset before 1980, 32 between 1980 and 1992, and 121 after 1992). Mean age of dementia onset was 76 years. (32 had dementia onset before age 70 years, 72 between ages 70 to 80, and 57 after age 80).

Figure 2. The cumulative risk of dementia in the Prospective Population Study of Women in Gothenburg 1968 to 2006



Among the 800 women in the psychiatric sub-sample in 1968-69, 153 (19%) developed dementia between 1968 and 2006, during 25,131 person-years of follow-up. These included 104 with AD, 35 with VaD, and 14 with other dementias. The mean time from the baseline examination in 1968-69 to dementia onset was 29 years (26 had dementia onset before 1992, 73 between 1992 and 2000, and 54 after 2000). Mean age of dementia onset was 78 years, 45 had dementia onset before age 75 years and 108 after age 75.

4.3 Study I

Characteristics of non-demented participants in 1968-69, 1974-75, and 1980-81 are shown in Table 6.

Table 6. Characteristics of women in 1968-69, 1974-75, and 1980-81

	Participants 1968-69 n=1415	Participants 1974-75 n=1301	Participants 1980-81 n=1196
Education level, n (%)			
Compulsory	984 (70)	901 (69)	817 (69)
More than compulsory	426 (30)	396 (31)	375 (31)
Marital status, n (%)			
Never married	121 (9)	97 (8)	88 (7)
Married	1121 (79)	988 (76)	830 (70)
Widowed	60 (4)	93 (7)	131 (11)
Divorced	113 (8)	123 (9)	147 (12)
Socio-economic status, n (%)			
High	191 (14)	173 (13)	152 (13)
Medium	721 (52)	678 (53)	625 (53)
Low	468 (34)	430 (34)	391 (34)
Having children, n (%)	1153 (82)	1074 (83)	975 (82)
Smoking, n (%)			
Never	734 (52)	684 (53)	655 (55)
Former	106 (7)	129 (10)	158 (13)
Current	574 (41)	486 (37)	383 (32)
Wine consumption, n (%)			
None	691 (49)	538 (41)	444 (37)
< once weekly	452 (32)	494 (38)	533 (45)
≥ once weekly	270 (19)	269 (21)	219 (18)
Physical activity, n (%)			
Low	260 (18)	295 (23)	353 (29)
Medium/high	1154 (82)	1006 (77)	842 (71)
Coronary heart disease, n (%)	29 (2)	82 (6)	116 (10)
Hypertension, n (%)	299 (21)	371 (28)	499 (44)
Waist-to-hip ratio (mean ± SD)	0.74 ± 0.05	0.79 ± 0.07	0.81 ± 0.07
Depression, n (%) [a]	55 (6.9)	-	-

[a] In the subsample of women with psychiatric data in 1968-69 (n=800)

Frequent/constant stress in 1968-69 was associated with divorce ($p<0.001$) and former/current smoker ($p<0.01$) in 1968-69. No other covariates were associated with stress at baseline.

Among the 795 women with psychiatric data from 1968-69, 55 had depression (according to DSM-III-R criteria) at time for the examination (Table 7). In age-adjusted logistic regression model, frequent/constant stress in 1968-69 was associated with depression in 1968-69 (OR 5.87, 95% CI 3.38-10.18).

Table 7. Prevalence of depression among the stress-groups in 1968-69

	Depression n=55	No depression n=740
No stress, n (%)	9 (16.4)	420 (56.8)
Previous stress, n (%)	6 (10.9)	89 (12.0)
Occasional stress, n (%)	9 (16.4)	114 (15.4)
Frequent/constant stress, n (%)	31 (56.4)	117 (15.8)

Midlife stress and incidence of dementia

Frequent/constant stress reported in 1968-69, 1974-75, and 1980-81 were related to increased risk of incident dementia until 2002 (Table 8). The associations were consistent and similar across all three examinations, and remained after adjustment for multiple potential confounders. Neither occasional stress (only one period in last 5 years) nor stress in the more distant past was associated with increased risk of developing dementia.

Table 8. HRs (95% CIs) [a] between stress in 1968-69, 1974-75, and 1980-81, and incidence of dementia until 2002

	Examination 1968-69	Examination 1974-75	Examination 1980-81
No stress, n (%)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Previous stress, n (%)	0.87 (0.51-1.47)	1.03 (0.51-2.07)	1.33 (0.80-2.23)
Occasional stress, n (%)	1.89 (0.55-1.46)	1.13 (0.67-1.90)	1.62 (0.96-2.73)
Frequent/constant stress, n (%)	1.60 (1.10-2.34)	1.65 (1.12-2.41)	1.60 (1.01-2.52)

[a] Adjusted for age, education, marital status, socio-economic status, having children, smoking, wine consumption, physical activity, coronary heart disease, hypertension, and waist-to-hip ratio, at each examination.

To minimize the influence of incipient dementia on the association between stress and dementia, we re-analysed the data excluding women with dementia onset before 1992. This did not change the association between stress and incidence of dementia. The associations between stress and dementia were also similar in women with dementia onset before and after age 70. Frequent/constant stress in 1968-69 was associated with incident of dementia, also after further adjustments for depression in 1968-69.

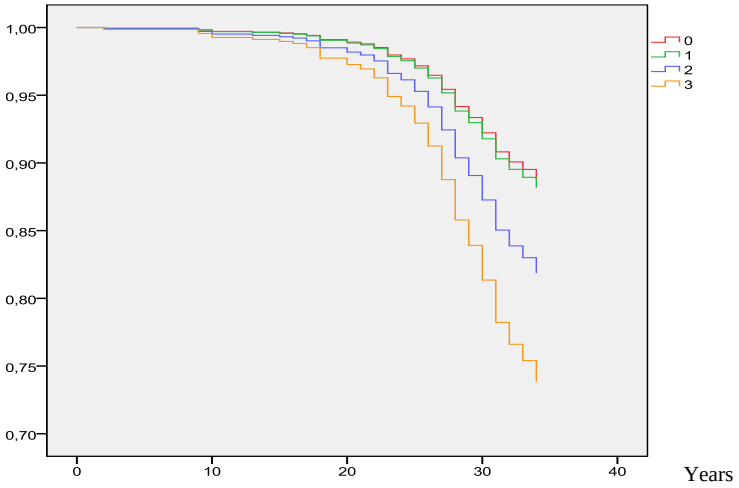
Longstanding perceived stress and risk for dementia

A total of 1096 women had stress-data in all of the three midlife examinations, i.e. in 1968-69, in 1974-74, and 1980-81. Two hundred and sixty-five (24%) of those reported frequent/constant stress at one examination, 105 (10%) at two examinations, 53 (5%) at all three examinations, and 673 (61%) never reported frequent/constant stress.

The risk of dementia increased with numbers of examinations when frequent/constant stress was reported (Figure 3). Compared to women never reported stress, HRs (95% CI) for incident dementia were 1.10 (0.71-1.71) for women reporting frequent/constant stress at one examination, 1.73 (1.01-

2.95) reporting stress at two examinations, and 2.51 (1.33-4.77) at three examinations.

Figure 3. Proportional hazard plot, with separate lines for numbers of examinations when stress was reported and dementia until 2002



(0) Frequent/constant stress reported in no examination
(1) Frequent/constant stress reported in one examination
(2) Frequent/constant stress reported in two examinations
(3) Frequent/constant stress reported in three examinations

Midlife stress and sub-types of dementia

Frequent/constant stress in 1968-69 and 1974-75 were associated with higher risks of AD (Table 9). Frequent/constant stress was not related to pure vascular dementia at any examinations. Frequent/constant stress in 1980-81 was associated with ´dementia with cerebrovascular disease´. Neither occasional stress nor previous stress was associated with development of any subtype dementia.

Table 9. Incidence of dementia and dementia subtypes, in women reporting frequent/constant stress compared to women reporting no stress

	Examination 1968-69 n= 1035	Examination 1974-75 n= 1041	Examination 1980-81 n=941
All Alzheimer's disease			
No. of cases	81	81	68
HR_1 (95% CI)[a]	2.23 (1.44-3.47)	1.84 (1.18-2.87)	1.68 (0.97-2.91)
HR_2 (95% CI)[b]	2.14 (1.36-3.38)	1.74 (1.09-2.78)	1.58 (0.90-2.77)
Alzheimer's disease without cerebrovascular disease			
No. of cases	55	58	49
HR_1 (95% CI)	2.14 (1.25-3.66)	1.67 (0.97-2.82)	1.30 (0.65-2.60)
HR_2 (95% CI)	2.03 (1.16-3.54)	1.54 (0.87-2.67)	1.30 (0.64-2.64)
Alzheimer's disease with cerebrovascular disease			
No. of cases	26	23	19
HR_1 (95% CI)	2.80 (1.29-6.07)	2.69 (1.18-6.14)	2.93 (1.15-7.46)
HR_2 (95% CI)	2.79 (1.25-6.25)	2.70 (1.13-6.45)	2.35 (0.88-6.27)
Pure vascular dementia			
No. of cases	29	29	25
HR_1 (95% CI)	0.86 (0.35-2.12)	0.99 (0.42-2.35)	2.32 (0.99-5.44)
HR_2 (95% CI)	0.67 (0.27-1.73)	1.01 (0.41-2.46)	1.79 (0.74-4.30)
Dementia with cerebrovascular disease			
No. of cases	55	52	44
HR_1 (95% CI)	1.59 (0.91-2.80)	1.60 (0.89-2.85)	2.51 (1.34-4.72)
HR_2 (95% CI)	1.41 (0.78-2.53)	1.57 (0.86-2.88)	1.94 (1.01-3.73)

[a] HR_1 adjusted for age. [b] HR_2 adjusted for age, education, marital status, socio-economic status, having children, smoking, wine consumption, physical activity, coronary heart disease, hypertension, and waist-to-hip ratio, at each examination.

4.4 Study II

Characteristics of the study sample are given in Table 10.

Table 10. Description of the study sample (n=344)

Age, mean±S.D, years	
Mean age 1968-69	44±6
Mean age 1974-75	50±6
Mean age 1980-81	56±6
Mean age 2000-02	76±6
Education level, n (%)	
Compulsory	222 (64.5)
More than compulsory	122 (35.5)
Marital status, n (%)[a]	
Never married	24 (7.0)
Married	254 (74.7)
Widowed	26 (7.6)
Divorced	37 (10.8)
Hypertension, n (%)[a]	210 (61.0)
Cholesterol, mean±S.D, mmol/l [a]	6.80±1.25
Smoking, n (%)[a]	
Never	210 (61.0)
Former	52 (15.1)
Current	82 (23.8)
Cardiovascular disease, n (%)[a]	5 (1.5)
Waist-hip-ratio, mean±S.D, cm[a]	0.80±0.07
Physical activity, n (%)[a]	
Low	88 (25.6)
Medium/high	256 (74.4)
Wine consumption, n (%)[a]	
None	107 (31.1)
< once weekly	161 (46.8)
≥ once weekly	76 (22.1)

[a] Measured in 1980-81

Among the 344 participants, 134 (39%) reported frequent/constant stress in one or more examination 1968-69, 1974-75, and 1980-81, 71 (21%) reported occasional stress (i.e. some period of stress in one or more examination in 1968-80), and 139 (40%) reported no stress in all examinations in 1968-80. Prevalence of WMLs and brain atrophy are presented in Table 11.

Table 11. Presence of white matter lesions and cortical atrophy (n=344)

	n	%
Moderate-severe white matter lesions	58	16.9
Moderate-severe temporal lobe atrophy	34	9.9
Moderate-severe parietal lobe atrophy	9	2.6
Moderate-severe frontal lobe atrophy	36	10.5
Moderate-severe occipital lobe atrophy	7	2.0
	mean	SD
Bifrontal ratio	33.18	4.02
Bicaudate ratio	15.16	3.21
Cella media ratio	23.63	3.96
Third ventricle width	0.27	0.10
Sylvian fissure ratio	9.89	4.20

The inter-observer agreement between the rating neurologist and a neuroradiologist were examined in 130 CT scans. The intra-class correlation coefficient was 0.57 for presence and severity of WMLs (55% concordance), 0.49 for temporal lobe atrophy (68% concordance), 0.39 for parietal lobe atrophy (68% concordance), 0.38 for frontal lobe atrophy (67% concordance), 0.32 for occipital lobe atrophy (68% concordance), 0.64 for bifrontal ratio (p <0.001), 0.57 for bicaudate ratio (p <0.001), 0.51 for cella media ratio (p <0.001), 0.67 for width of the third ventricle (p <0.001), and 0.26 for sylvian fissure ratio (p=0.001).

Midlife stress in relation to late-life WMLs

Compared to individuals without stress, women reporting frequent/constant stress in one or more examination (1968-69, 1974-75, and 1980-81) were more disposed for moderate-severe WMLs on CT scans in 2000-02 (Table 12).

Table 12. Psychological stress 1968-80, in relation to moderate-severe white matter lesions in 2000-02 (n=344)

	No of cases	OR (95% CI) [a]
No stress, (n=139)	16	1.0 (ref.)
Occasional stress, (n=71)	12	1.62 (0.68-3.86)
Frequent/constant stress, (n=134)	30	2.39 (1.16-4.92)

[a] Adjusted for age, hypertension, smoking, cholesterol, waist-hip-ratio, physical activity, and wine consumption.

Midlife stress in relation to late-life brain atrophy

In logistic regression analyses, women with frequent/constant stress had more often moderate-severe temporal lobe atrophy compared to women without stress (Table 13). However, there were no associations between frequent/constant stress and atrophy in parietal, frontal, or occipital lobes.

In linear regression analyses, frequent/constant stress in 1968-80 was associated with a higher bicaudate ratio ($p<0.05$), a higher cella media ratio ($p<0.01$), and a wider third ventricle ($p<0.05$) in 2000-02, after multiple adjustment. There were no associations with bifrontal ratio or Sylvian fissure ratio.

Table 13. Perceived psychological stress 1968-80 in relation to moderate-severe cortical atrophy in brain CT-scans 2000-02 (n=344)

	No stress (n=139)	Occasional stress (n=71)	Frequent/constant stress (n=134)
Temporal lobe atrophy, n	10	7	17
OR_1 (95% CI) [a]	1.00 (ref.)	1.43 (0.51-4.05)	2.32 (0.99-5.42)
OR_2 (95% CI) [b]	1.00 (ref.)	1.50 (0.52-4.35)	2.51 (1.04-6.05)
Frontal lobe atrophy, n	13	8	15
OR_1 (95% CI) [a]	1.00 (ref.)	1.28 (0.48-3.21)	1.46 (0.65-3.29)
OR_2 (95% CI) [b]	1.00 (ref.)	1.30 (0.50-3.40)	1.46 (0.63-3.38)
Occipital lobe atrophy, n	1	1	5
OR_1 (95% CI) [a]	1.00 (ref.)	1.98 (0.12-32.16)	6.49 (0.73-57.55)
OR_2 (95% CI) [b]	1.00 (ref.)	1.99 (0.12-33.67)	6.21 (0.66-58.41)
Parietal lobe atrophy, n	4	1	4
OR_1 (95% CI) [a]	1.00 (ref.)	0.48 (0.05-4.40)	1.32 (0.31-5.59)
OR_2 (95% CI) [b]	1.00 (ref.)	0.56 (0.06-5.19)	1.31 (0.30-5.67)

[a] OR_1 adjusted for age, [b] OR_2 adjusted for age, hypertension, smoking, cholesterol, waist-hip-ratio, physical activity, and wine consumption.

Influence of dementia and stroke

When women with dementia (n=15) where excluded from the analyses, frequent/constant stress 1968-80 was still associated with moderate-severe WMLs (multi adjusted OR 2.14; CI 95% 1.01-4.55) and central brain atrophy (i.e. bicaudate ratio, cella media ratio, and third ventricle width), and there was a tendency in the same direction for moderate-severe temporal lobe atrophy (multi adjusted OR 2.34; CI 95% 0.91-6.01). After excluding women with history of stroke (n=25), frequent/constant stress 1968-80 was still associated with moderate-severe WMLs (multi adjusted OR 3.27; CI 95% 1.46-7.49), moderate-severe temporal lobe atrophy (multi adjusted OR 4.08; CI 95% 1.41-11.81), and central brain atrophy (i.e. higher bicaudate ratio, higher cella media ratio, and wider third ventricle width).

Comorbidity of WMLs and temporal lobe atrophy

When participants with moderate-severe temporal lobe atrophy were excluded, the associations between frequent/constant stress in one or more examination and moderate-severe WMLs remained (multi adjusted OR 3.23; CI 95% 1.35-7.73). Similar, when excluding participants with moderate-severe WMLs from the sample, the associations between frequent/constant stress in one or more examination and moderate-severe temporal lobe atrophy remained (multi adjusted OR 5.87; CI 95% 1.45-23.69).

Age stratified analyses

The associations between frequent/constant stress in one or more examination and CT findings (i.e. moderate-severe WMLs, moderate-severe temporal lobe atrophy, and central atrophy) were similar in younger (born 1930 and 1922) and older cohorts (born 1918, 1914, and 1908).

4.5 Study III

Table 14 report characteristics of the study sample in *Study III*, from the primary psychiatric sample in 1968-69 (n=800).

Table 14. Characteristics of the study sample in 1968-69

	n	%
Education		
Compulsory	600	75.0
More than compulsory	200	25.0
Socio-economic status		
Upper middle	161	20.2
Lower middle	267	33.4
Skilled workers	209	26.1
Unskilled workers	163	20.4
Work status		
Full-time work	270	33.8
Part-time work	258	32.3
No work outside home	272	34.0
Marital status		
Married and/or co-habited	638	79.8
Co-habited, not married	94	11.7
Living alone, not married	68	8.5
Wine consumption		
None	390	48.8
< once weekly	249	31.1
≥ once weekly	155	19.4
Hypertension	138	17.4
Myocardial infarction	67	8.4
Smoking	320	40.0
Diabetes	86	10.8
Stroke	68	8.5
	Mean	SD
Waist-to-hip ratio	0.74	0.05

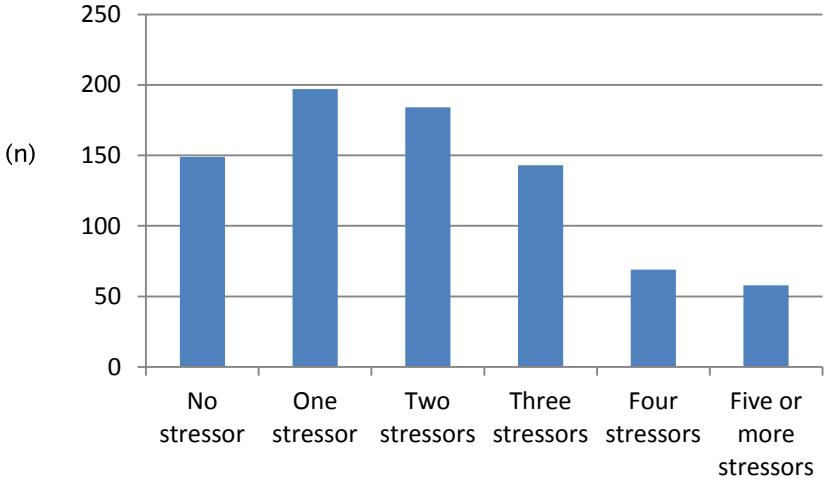
Number of participants who reported life stressors are presented in Table 15. The most frequently reported life stressors were mental illness in first degree relative (mother 27 %, father 32%, and sibling 19%).

Table 15. Life stressors in 1968-69 (n=800)

	n	%
Physical illness in spouse	62	7.8
Mental illness in spouse	98	12.3
Alcohol abuse in spouse	55	6.9
Social problem in spouse	81	10.1
Work related problems in spouse	32	4.0
Serious problem in children	70	8.8
Mental illness in child	139	17.4
Mental illness in father	151	18.9
Alcohol abuse in father	100	12.5
Mental illness in mother	212	26.5
Mental illness in sibling	255	31.9
Alcohol abuse in sibling	79	9.9
Divorced	65	8.1
Widowed	34	4.3
Limited social contacts	53	6.6
Work related problems	19	2.4
Received help from social security	10	1.3
Extramarital childbirth	84	10.5

Among the 800 participants reported 197 (25%) one life stressor, 184 (23%) two life stressors, 143 (20%) three life stressors, 69 (9%) four life stressors, and 58 (7%) five or more life stressors (Figure 4).

Figure 4. Number of life stressors in 1968-69 (n=800)



Life stressors in relation to perceived stress

In multi-adjusted logistic regressions, number of life stressors in 1968-69 was associated with perceived stress in 1968-69, 1974-75, 1980-81, 2000-02, and 2005-07 (Table 16). ORs were similar at all examinations indicating that the strength of associations between life stressors and perceived stress was consistent through all follow-up years.

Table 16. Number of psychosocial life stressors in 1968-69 in relations to perceived stress

	Cases, n (%)	OR (95% CI) [a]	OR (95% CI) [b]
Perceived stress 1968-69	148 (18.5)	1.46 (1.30-1.63)	1.48 (1.32-1.67)
Perceived stress 1974-75	161 (20.1)	1.31 (1.18-1.46)	1.31 (1.17-1.46)
Perceived stress 1980-81	88 (11.0)	1.26 (1.10-1.43)	1.27 (1.11-1.45)
Perceived stress 2000-02	49 (6.1)	1.41 (1.17-1.72)	1.39 (1.14-1.70)
Perceived stress 2005-07	39 (2.6)	1.37 (1.05-1.80)	1.35 (1.02-1.79)

[a]Adjusted for age. [b]Adjusted for age, education, socio-economic status, work status, marital status, wine consumption, hypertension, CHD, stroke, diabetes, smoking, and waist-to-hip ratio in 1968-69

HRs (95% CI) for the association between number of life stressors and 'longstanding stress' were 1.58 (1.30-1.94) in earlier born cohorts (born 1914 and 1918), and 1.32 (1.14-1.52) in later born cohorts (born 1922 and 1930).

Life stressors in relation to dementia

In multi-adjusted Cox regressions, number of life stressors in 1968-69 was associated with incidence of AD and all-type dementia (until 2006) (Table 17). There were no associations with VaD.

Table 17. Number of life stressors in 1968-69 in relations to incidence of dementia over 38 years (n=800)

	Cases, n (%)	HR (95% CI)
Alzheimer's disease	104 (13.0)	1.20 (1.07-1.35)
Vascular dementia	35 (4.4)	0.92 (0.72-1.18)
All-type dementia	153 (19.1)	1.15 (1.04-1.27)

HR adjusted for age, education, socio-economic status, work status, marital status, wine consumption, hypertension, CHD, stroke, diabetes, smoking, and waist-to-hip ratio in 1968-69.

The associations were similar in those with early onset dementia (<75 years old) (multi adjusted HR 1.25, 95% CI 1.02-1.54) and late onset dementia (≥75 years old) (multi adjusted HR 1.19, 95% CI 1.03-1.38). The association remained when those whose parents had mental illness were excluded (multi adjusted HR 1.14, 95% CI 1.01-1.28).

Life stressors, perceived stress and AD

Number of life stressors was dose-response related to both longstanding stress and incident AD (Table 18). In Cox regression model, longstanding stress (i.e. frequent/constant stress in 1968-69, 1974-75, and 1980-81) (HR 1.58, 95% CI 1.01-2.46) and number of life stressor (HR 1.17, 95% CI 1.02-1.33) were independently associated with AD.

Table 18. Life stressors in relation to longstanding perceived stress and AD

	Number of life stressors n=800	Longstanding stress 1968-80[a] n=224	Alzheimer's disease [b] n=104
0 life stressor, n (%)	149	27 (21.6)	13 (9.4)
1 life stressor, n (%)	197	38 (24.8)	24 (12.7)
2 life stressors, n (%)	184	59 (37.3)	25 (14.6)
3 life stressors, n (%)	143	52 (49.5)	19 (14.7)
4 life stressors, n (%)	69	23 (47.9)	11 (16.7)
≥5 life stressors, n (%)	58	25 (59.5)	12 (21.4)

[a] Perceived stress in one or more examination 1968-80, [b]AD between 1968 and 2006

5 DISCUSSION

5.1 Study design

All three studies had a prospective design with long follow-up duration. Psychological stress was measured repeatedly during midlife, many years before clinically manifested dementia. The prevalence of severe structural changes in brain, like brain atrophy and WMLs, were also probably low in midlife. This longitudinal study design was thus suitable to identify potential risk factors of dementia and structural changes in brain.

Our studies include only women. Numerous epidemiological studies report a skewed gender distribution regarding the prevalence of psychological stress, with higher prevalence in women [24]. Earlier studies found that the prevalence of dementia and structural changes in brain were also higher in women than in men [54 142]. We thus cannot generalize our findings to men.

5.2 Study sample

The participants in the Prospective Population Study of Women were systematically selected from a general female population at the ages studied in Gothenburg, Sweden [129]. Participation rate in baseline study as well as follow-up studies were high.

The subsample in the psychiatric examination in 1968-69 was also systematically selected based on certain birth dates. It is therefore a representative sample of the general female population at the aged studied.

The subsample in CT study represented a healthier population with 55% participation rate. Compared to non CT-participants, the CT-participants were younger, had less often dementia, and had a lower mortality rate (from the examination in 2000-02 to five years after the examination). This positive selection bias might underestimate the association between psychological stress and brain atrophy and WML.

5.3 Methods

Psychological stress question

Perceived psychological stress was based on a single-item question. In addition, this question only gives information on duration of stress, not intensity of stress.

The question was first used in another population study in Gothenburg, 'the Study of Men Born in 1913', from 1963 [143]. The question has not been extensively validated against a more extensive scale, such as *the Perceived Stress Scale.* However, in 2004-05 a sample of women aged 38 and 50 years in the Prospective Population Study of Women answered both the stress-question and *the Work Stress Questionnaire* (WSQ) [144]. It showed that all 6 categories in WSQ were associated with higher levels of perceived psychological stress [145]. In addition, the question has been used in several former studies and have found to be associated with hypertension [146], myocardial infarction [147], coronary artery disease [148], cancer [149 150], sleeping problems [151], obstructive symptoms [152], and work stress [145].

Psychosocial life stressors

The 18 included life stressors in our study are assumed to give rise to stress in most people. However, the effects of these stressors can vary greatly

depending on the severity and duration of the condition, person-related characteristics, and social circumstances. In addition, the rating of life stressors was related only to the last year for some factors, and any time before 1968 for other factors. This might have given an unbalanced weight between stressors.

We had only information on a limited number of life stressors in our population. Some stressful events were not included, e.g. physical abuse and severe physical illness. Unmeasured stressful events may thus have inflated our findings. It is not likely that this had any major influence on our finding, that number of life stressors was associated with longstanding perceived stress and risks of AD.

Some of the life stressors are interrelated, for example mental illness and alcohol abuse in spouse. However, both these stressors may independently increase stress-reactions for individuals and therefore it was not appropriate to merge them.

Diagnostic of dementia

Cumulative attrition is a problem in long-term follow-up studies. While this problem was, to some extent, alleviated by using medical records and the hospital registry data to diagnose dementia in those lost to follow-up, these sources probably underestimate the number of dementia cases. It should be noted, however, that almost all people in Sweden received their hospital treatment within the public health care system (during the time of the study), and that the Swedish Hospital Discharge Register covers the entire country. Furthermore, the number of demented detected in the different age groups is what could be expected from other incidence studies [54].

It is difficult to diagnose dementia subtypes on clinical grounds alone. Individuals with AD often have cerebrovascular disease and individuals with VaD often have concomitant AD pathology; and cerebrovascular disease may influence the presence and severity of clinical symptoms of AD [153]. It is thus often difficult to make a clear distinction between AD and VaD in patients with a history of stroke or cerebrovascular disease, both on clinical grounds and at autopsy. Furthermore, mixed types are probably common. We therefore explored various ways of defining dementia subtypes, e.g. 'AD disease with and without cerebrovascular disease' and 'dementia with cerebrovascular disease'.

Semi-structured examinations were performed by experienced psychiatrists in 1974–75, 1980–81 and 1992–93 and by experienced psychiatric nurses in 2000–02 and 2005-07. The instruments used were identical across examinations, and inter-rater reliability between psychiatrists and nurses regarding the symptoms assessed was satisfactory [154]. It is therefore not likely that the use of different professionals could have influenced the main results of this study.

Measurement of brain CT scans

Visual rating of severity of WMLs and brain atrophy on CT is a rather crude method. CT scans are less sensitive than magnetic resonance imaging (MRI) in detecting brain structural changes, especially in regions of the temporal lobe [155]. However, it has been reported that WMLs on CT better predict later development of cerebrovascular disorders than WMLs noted on MRI, supporting the view that CT may be more specific [156]. CT is still the most commonly used brain-imaging modality world-wide, and more suitable for the older persons, as it is less sensitive to motion artefacts than for example MRI [90].

5.4 Results

Midlife perceived stress and risk for dementia (Study I)

Frequent/constant stress, reported in midlife, was associated with increased risk for late-life dementia, in a study over 35 years. The associations were consistent over three examinations, and remained after adjustment for multiple potential confounders. Women who reported stress at two or three examinations had higher risks of developing dementia than women reporting no stress or stress at only one examination. Our findings remained after excluding individuals with dementia onset before 1992, giving a time-span of more than 24 years between stress and dementia onset, suggesting that our results may not be due to incipient AD disease changes in the brain.

The biological mechanisms by which psychological stress increase the risk of dementia is probably complex. There are several possible explanations. Our findings were mainly driven by AD type of dementia. The theory behind this is mainly based on neurodegenerative pathological hypotheses. Increased levels of circulating blood cortisol and dysfunctional HPA axis circuits are early pathological signs in AD [67], together with atrophy in the medial temporal lobe, and especially in the hippocampus area [64-66], and deficient hippocampal cognition, such as decreased learning and memory [157 158].

In animal studies, glucocorticoids and stress have been associated with increased amyloid precustor protein [159 160] and beta-amyloid [50-52 161] in brain, the main biomarkers in AD. An increased activation of the HPA axis may also lead to suppressed immune functions, which in a chronic state can be considered harmful for the brain, and contribute to the AD progress [12 162].

In addition, stress may lead to dementia through cerebrovascular processes. Stress have been extensively associated with a variety of pathological vascular disorders, such as hypertension [163], diabetes [164], metabolic syndrome [43], and other vascular factors [165], which in turn have been related to both AD and VaD [166-169]. However, we found no association between perceived stress and VaD. One reason for the absence of association between stress and pure VaD may be earlier mortality due to cardiovascular disease among individuals with stress. This may thus underestimate the relationship between stress and risk of VaD [170]. Absence of association may also be due to a smaller number of participants with VaD.

Vulnerability to stress may be both a cause and a consequence of different life style factors, such as socioeconomic status, nutritional status, smoking, hypertension, central adiposity and physical activity, which may partly mediate the association between stress and dementia. However, our findings remained after adjusting for numerous life style factors.

At baseline, clinical depression was assessed in a sub-sample of women (n=800). When we included depression as a covariate, in analyses between stress and dementia, it did not influence the results. However, depression and perceived stress had a considerable over-lap. Among women with frequent/constant stress, 51% had a clinical diagnose of depression. The two variables share several symptoms, but the inclusion criteria also differ. Depression refers to feelings of lower mood, loss of energy, worthlessness, guilt, and recurrent thoughts of death. Symptoms which are not included in the question on perceived stress. Also, the studied time-period, the duration, of symptoms differs. Perceived stress was assessed in a period of five years, while depression was assessed only in the last month before the examination.

Finally, depression was only registered in a smaller subsample, which yielding low statistical power in analyses.

To the best of our knowledge, this was the first study to examine the association between midlife psychological stress and development of dementia. Several cross-sectional studies have shown associations between perceived psychological stress and low cognitive performance [106 171 39 172] in older persons. However, due to the cross-sectional design, these findings may potential be due to incipient dementia.

Number of life stressors and risk for dementia (Study III)

Number of life stressors in midlife was associated with incidence of dementia over 38 years, especially AD. This supported the findings in *Study I.*

Longstanding psychological stress (1968-80) and number of life stressor were independently associated with AD. The interpretation of this can be that some individuals do not perceive stress even after a number of events, but that the biological response still occurs. The rating of life stressors was related only to the last year for some factors, and any time before 1968 for other factors. This might give an unbalanced weight between factors, and can be one reason why life stressors and perceived stress were independently related to AD.

Our findings supports by studies showing higher risk for cognitive decline and dementia in persons with PTSD [116 117], lost of parent in childhood [100 101 103], and number of psychosocial risk factors [103]. However, studies on more common and less severe stressors are still lacking.

Midlife perceived stress and structural brain changes (Study II)

In the 32 years of study follow-up, frequent/constant psychological stress in midlife was associated with late-life brain changes, including WMLs, atrophy in the temporal lobe, and ventricular enlargements. These findings supported *Study I*, by pointing to intermediating links between stress and dementia, as these brain changes are strongly associated with dementia diseases [69 173].

WMLs represent areas of ischemic demyelination with arteriolosclerosis, hyalinosis and narrowing of the lumen of the small penetrating arteries in the white matter, while cortical atrophy is related to neurodegeneration in the grey matter [70]. Our findings that psychological stress was related to WMLs and temporal lobe atrophy independently of each other suggest that longstanding stress can be an underlying mechanism for both subcortical vascular pathology and neurodegeneration.

Stress induced changes in memory are related to alterations in hippocampal structure[174], in part related to glucocorticoid elevations[175 176]. Although originally conceived as a cognition oriented structure, the hippocampus may play a greater role in behavior than we previously thought. It has long been known that the hippocampus mediates emotional responses to the context of a situation [177].

Numerous studies have found associations between atrophy in medial temporal lobe, and especially in the hippocampus area, in cases with clinical syndroms such as PTSD [32 33 46 119-122] and depression [178 179]. However, it is still unknown whether chronic stress is associated with decreased hippocampal volume in those without a clinical syndrome. Only one former study has been found. In a small sample of women (n=48), Gianaros et al [128] shown that

chronic perceived stress measured in midlife was associated hippocampus atrophy 20 years later. Several former studies have also studied PTSD as a predictor for white matter lesion [121 123-127].

Midlife stressors and perceived stress (Study III)

Number of psychosocial life stressors in 1968-69 was associated with perceived stress in 1968-69 and all of the following examinations until 2005-07. The strength of association was consistent through all follow-up years as indicated by similar ORs.

Explanations for this are several. First, biological studies have found that increased stress-hormone levels many years after severe traumatic events, pointing to long-term effects of stressors [117]. Second, measured life stressors occurred before, or at time for, the examination in 1968-69, but they might have last over years, such as e.g. mental illness or alcohol abuse in relative. Third, experiences of earlier stressors may also make an individual more vulnerable to future traumas due to biological changes and dysfunctional stress coping [180].

6 CONCLUSION OF THE STUDY FINDINGS

1. Psychological stress is common in middle-aged women. In our studies conducted in 1968-69, 1974-75 and 1980-81, around 20% of middle-aged women reported that they perceived constant or several periods of stress during the last five years.

2. Stress in midlife increased risks of development of dementia in women.

- Women who perceived longstanding stress in midlife had higher risks of development of dementia and AD in late-life. In addition, the longer periods of psychological stress, the higher risks of development of dementia.
- Women who perceived longstanding stress in midlife had higher risks of development of brain structural changes, including WMLs, ventricular enlargement, and atrophy in temporal lobes on brain CT scans.
- Women who experienced more number of psychosocial stressors in midlife had higher risks of development of dementia and AD.

3. Common psychosocial stressors that related to family, work, marriage, and socio-economy had severe and longstanding psychological and physiological consequences. Besides association with incident dementia, psychosocial stressors reported in midlife were related to perceived stress in midlife and even 38 years later.

7 IMPLICATIONS OF THE STUDY FINDINGS

Our study findings have both clinical and public health implications. Psychological stress is an increasing public health problem with severe consequences in both physical and mental health. Psychological stress is potentially modifiable. Our study findings imply the importance to promptly and adequately treat, manage and reduce stress load in women, especially in midlife. Intensive interventions such as stress management and behavioral therapy should be conducted in individuals who have experienced a number of negative life stressors in order to reduce stress.

Our study findings have also implications for further research. First, more prospectively longitudinal studies in both men and women are needed to confirm our findings. Second, it needs to develop better methods of studying stress, both self-reported psychological stress and stress biomarkers. Third, more studies are needed to investigate the underlying mechanisms of stress and brain damage. Finally, psychological stress in early, mid- and late-life may have different impact on cognitive function, which is also need to be studied.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to all who have contributed to this thesis, especially;

The study participants and their relatives, without you this study would not have been possible.

Xinxin Guo, my supervisor, for all the time and effort you spend on advising me during work with this thesis. I am deeply thankful to you!

Ingmar Skoog, co-supervisor and head of the Unit, thank for scientific advice, support, inspiration, and great generosity!

Valter Sundh for all help with statistical analyses.

Co-authors; Calle Bengtsson, Cecilia Björkelund, Deborah Gustafson, Margda Waern, Lauren Lissner, Leonardo Pantoni, Maria Norton, Michela Simoni, Pernille Olesen, Svante Östling, and Tore Hällström, who all have been a great support in the writing process.

A special thank to Calle Bengtsson, how initiated the Prospective Population Study of Women, and who always are so supportive.

All wonderful persons in our group; Anne Börjesson Hansson, Birgitta Tengelin Widepalm, Björn Karlsson, Cecilia Mellqvist, Erik Joas, Eva Billstedt, Hanna Falk, Helen Liden, Helena Hörder, Isak Frendén Klenfeldt, Johan Nilsson, Johan Skoog, Jürgen Kern, Kerstin Frändin, Kristoffer Bäckman, Linnea Sjöberg, Lena Larsson, Lova Eklöf, Madeleine Mellqvist,

Margareta Lewander, Maria Larsson, Maria Staaf, Nils Beckman, Pia Gudmundsson, Robert Sigström, Silke Kern, Simona Sacuiu, Stefan Wiktorsson, Svante Östling, Tom Marlow, Thorsteinn Gislason, Tina Jacobsson, and Tore Hällström.

Anna Wikman, Carina Alklid, Cecilia Wallmark Nilsson, Maria Staaf, Nils Beckman, for giving me such a joyful start in this group.

Sonja Klingén, Åsa Dahlén and other staff at the Neuropsychiatric Clinic at Sahlgrenska, for all support during years.

My warmest thanks go to my dearest friends; Carin, Cristina, Christina, Emine, Jeanette, Helena, Maria, Mia, Thommy, and Veronica. Love you! I also want to thanks my childhood friends Charlotte, Fia, Sara, and Agnetha, who followed me through years.

Finally, my love go to my family, my mother Brita, my father Ingvar, my brother Mats, his wife Camilla, and my dear nephews Nils and Olle.

This thesis was supported by the Swedish Research Council; the Swedish Council for Working Life and Social Research; The Alzheimer's Association Zenith Award; The National Institutes of Health/National Institutes on Aging; the Alzheimer's Association Stephanie B. Overstreet Scholars; The Bank of Sweden Tercentenary Foundation, Swedish Brain Power; Stiftelsen Söderström-Königska Sjukhemmet; Stiftelsen för Gamla Tjänarinnor; Handlanden Hjalmar Svenssons Forskningsfond; and Stiftelsen Professor Bror Gadelius' Minnesfond, and the Sahlgrenska Academy, University of Gothenburg.

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