

# Midlife psychological stress and risk of dementia: a 35-year longitudinal population study

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The number of people with dementia has increased dramatically with global ageing. Nevertheless, the pathogeneses of these diseases are not sufficiently understood. The present study aims to analyse the relationship between psychological stress in midlife and the development of dementia in late-life. A representative sample of females ( $n=1462$ ) aged 38–60 years were examined in 1968–69 and re-examined in 1974–75, 1980–81, 1992–93 and 2000–03. Psychological stress was rated according to a standardized question in 1968, 1974 and 1980. Dementia was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders criteria based on information from neuropsychiatric examinations, informant interviews, hospital records and registry data. During the 35-year follow-up, 161 females developed dementia (105 Alzheimer's disease, 40 vascular dementia and 16 other dementias). We found that the risk of dementia (hazard ratios, 95% confidence intervals) was increased in females reporting frequent/constant stress in 1968 (1.60, 1.10–2.34), in 1974 (1.65, 1.12–2.41) and in 1980 (1.60, 1.01–2.52). Frequent/constant stress reported in 1968 and 1974 was associated with Alzheimer's disease. Reporting stress at one, two or three examinations was related to a sequentially higher dementia risk. Compared to females reporting no stress, hazard ratios (95% confidence intervals) for incident dementia were 1.10 (0.71–1.71) for females reporting frequent/constant stress at one examination, 1.73 (1.01–2.95) for those reporting stress at two examinations and 2.51 (1.33–4.77) at three examinations. To conclude, we found an association between psychological stress in middle-aged women and development of dementia, especially Alzheimer's disease. More studies are needed to confirm our findings and to study potential neurobiological mechanisms of these associations.

**Keywords:** Alzheimer's disease; dementia; longitudinal study; stress; vascular dementia

## Introduction

Previous research has shown that psychological stress could plausibly lead to neural degeneration and development of cognitive impairment via changes in hormonal and immune system functions (Leonard, 2006). Stress may be related to cognitive decline

and dementia by its activation of the hypothalamic-pituitary-adrenal axis, and increasing levels of glucocorticoid hormones (Sapolsky, 1996; Lupien *et al.*, 1997; Peavy *et al.*, 2007), which in turn may lead to hippocampal atrophy (Bremner *et al.*, 1995; McEwen, 2000) and deposition of  $\beta$ -amyloid peptide and tau-protein in the brain (Green *et al.*, 2006), the main markers

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of Alzheimer's disease. Stress has also been associated with hypertension (Sparrenberger *et al.*, 2008) and other vascular factors (Folkow *et al.*, 1973; Pickering, 2001) that are related to both Alzheimer's disease and vascular dementia (Skoog *et al.*, 1999; Launer, 2002). Epidemiological studies report that stressful life-events or post-traumatic stress disorder increase the risk of developing cognitive decline (Amster and Krauss, 1974; Sands, 1981; Yehuda *et al.*, 2005) and dementia (Persson and Skoog, 1996), and that the stress-prone personality factor 'high neuroticism' increases the risk of developing cognitive decline (Wilson *et al.*, 2007) and Alzheimer's disease (Wilson *et al.*, 2003, 2006).

Long-term prospective studies on the impact of psychological stress on dementia are still lacking and no study has to date examined how midlife stress responses to everyday life, such as work, health and family situation, are related to the development of dementia. We therefore examined the relationship of self-reported psychological stress in midlife and the development of late-life dementia in a population-based sample of females followed for 35 years.

## Methods

### Study population

The study is part of the Prospective Population Study of Women in Gothenburg (Bengtsson *et al.*, 1973, 1978; Lissner *et al.*, 2003), which was initiated in 1968–69 with an examination of 1462 females (participation rate 90%) born in 1908, 1914, 1918, 1922 and 1930. The females were systematically sampled from the census register based on specific birth dates in order to yield a representative sample at the ages studied. Follow-ups were performed in 1974–75, 1980–81, 1992–93 and 2000–03 with participation rates (among survivors from the baseline examination) of 91, 83, 70 and 71%, respectively. In 1980–81 the sample was enriched with 47 females born in 1930, in order to ensure representation of the age strata (Bengtsson *et al.*, 1989). The Ethics Committee of Göteborg University approved the study. All subjects gave informed consent to participate, in accordance with the provisions of the Declaration of Helsinki.

### Psychological stress

A question about psychological stress was asked by a physician and answered by 1415 non-demented females in 1968–69 (aged 38, 46, 50, 54 and 60 years), by 1301 in 1974–75 (aged 44, 52, 56, 60 and 66 years) and by 1196 in 1980–81 (aged 50, 58, 62, 66 and 72 years). The question was identical at each examination and was as follows: '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'. Participants were asked to choose '0: have never experienced any period of stress'; 1: 'have experienced period/s of stress more than 5 years ago'; 2: 'have experienced one period of stress during the last 5 years'; 3: 'have experienced several periods of stress during the last 5 years'; 4: 'have experienced constant stress during the last year'; or 5: 'have experienced constant stress during the last 5 years'. According to their answers, the participants were classified into four groups: no stress (response 0), previous stress (response 1), occasional stress (response 2) and frequent/constant stress (response 3–5).

## Diagnosis of dementia

Dementia diagnosis was based on information from psychiatric examinations, close informant interviews, medical record examinations and the Swedish Hospital Discharge Registry. The diagnostic procedures have been described in detail previously (Guo *et al.*, 2007). The neuropsychiatric examinations were performed in 1968–69, 1974–75, 1980–81 and 1992–93 by psychiatrists and in 2000–03 by experienced psychiatric nurses. The examinations were semi-structured and included a comprehensive psychiatric interview, observations of mental symptoms and an extensive battery of neuropsychiatric tests (Guo *et al.*, 2007). Close informant interviews were performed in 1992–93 and in 2000–03 by psychiatric nurses. The interviews were semi-structured and comprised questions regarding changes in behaviour and intellectual function, psychiatric symptoms, activities of daily living and, in cases of dementia, age of onset and disease course (Skoog *et al.*, 1993). Medical records were collected from all inpatient and outpatient departments and general practitioners' offices in Gothenburg for all participants. The Swedish Hospital Discharge Registry provided diagnostic information for all individuals discharged from hospitals on a nationwide basis since 1978.

Dementia diagnosis for participants at each examination was based on the combined information from the neuropsychiatric examinations and the close informant interview according to the Diagnostic and Statistical Manual of Mental Disorders (1987) as described previously (Skoog *et al.*, 1993). 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 (Guo *et al.*, 2007). The diagnoses had to be compatible with Diagnostic and Statistical Manual of Mental Disorders criteria. Altogether, 117 cases of dementia were diagnosed from psychiatric examinations/close informant interviews and 91 cases were diagnosed from medical records or the Swedish Hospital Discharge Registry.

Dementia subtypes were determined by geriatric psychiatrists. Probable or possible Alzheimer's disease was 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 (1985). The criteria for vascular dementia were similar to the criteria proposed by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (Roman *et al.*, 1993). Vascular dementia 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. Due to the recognized difficulties in determining the relative importance of cerebrovascular disease in the aetiology of dementia, we explored various ways of defining dementia subtypes. The Alzheimer's disease group was divided into Alzheimer's disease with or without cerebrovascular disease. We also created 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 vascular dementia and Alzheimer's disease with cerebrovascular disease. Other dementias were diagnosed when other causes were likely to have caused the dementia.

## Potential confounders

Information on education, marital status, socioeconomic status, having children, cigarette smoking, wine consumption, physical activity, coronary heart disease, blood pressure, antihypertensive medication

use and waist and hip circumferences were obtained with identical protocols 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. Socioeconomic status was based on the husband's occupation for married women and own occupation for unmarried women, and was defined as high, medium or low (Carlsson, 1958). Cigarette smoking was defined as never, former or current smoker. Wine consumption was classified as none, < once weekly or  $\geq$  once weekly. Physical activities during leisure time were rated as low (<4 h/week) or medium/high ( $\geq$ 4 h/week). Hypertension was defined as systolic blood pressure  $\geq$ 160 mmHg and/or diastolic blood pressure  $\geq$ 95 mmHg and/or taking antihypertensive medications. Coronary heart disease was defined as meeting one or more of the following criteria: angina pectoris according to the Rose criteria (Rose, 1962), documented history of myocardial infarction; ECG-evidence of ischaemia i.e. complete left bundle branch block or major Q waves; pronounced ST depression and/or negative T waves (Rinder *et al.*, 1975). Waist-to-hip ratio was calculated as the ratio of waist and hip circumferences, measured to the nearest 0.5 cm.

## Statistical methods

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 and 95% confidence intervals (CIs), adjusted for age, education, marital status, socioeconomic 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 (i) time of dementia onset; (ii) the date of death; (iii) the date of the last follow-up examination for participants in 2000–03; or (iv) 31 December 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.

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

## Results

Characteristics of the study sample in 1968–69, 1974–75 and 1980–81 are shown in Table 1. Frequent/constant psychological stress within the last 5 years was reported by 277 (20%) females in 1968, 305 (23%) in 1974 and 183 (15%) in 1980. Among those who participated in all three examinations ( $n=1096$ ), 265 (24%) 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.

Among 1415 non-demented females who answered the stress question in 1968, 161 developed dementia during 35 years of follow-up (40 089 person-years). These included 105 with Alzheimer's disease (73 without cerebrovascular disease and 32

with cerebrovascular disease), 40 with vascular dementia and 16 with 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 and 80 years, and 57 after age 80 years).

Frequent/constant stress reported in 1968, 1974 and 1980 was related to increased risk of developing dementia (Table 2). The associations were consistent and similar across all three examinations. Adjustment for multiple potential confounders did not change the associations. 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. Frequent/constant stress in 1968 and 1974 was associated with higher risks of Alzheimer's disease. Frequent/constant stress was not related to pure vascular dementia at any examinations. Frequent/constant stress in 1980 was associated with 'dementia with cerebrovascular disease' (Table 3). Neither occasional stress nor previous stress was associated with development of any subtype dementia.

Among women who participated in all three examinations ( $n=1096$ ), risk of dementia increased with numbers of examinations when stress was reported (Table 4). Compared to females never reporting frequent/constant stress, hazard ratios (95% CIs) for incident dementia were 1.10 (0.71–1.71) for females 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. Participants who reported frequent/constant stress at two or three occasions were at higher risk of developing Alzheimer's disease, both 'Alzheimer's disease with cerebrovascular disease' and 'Alzheimer's disease without cerebrovascular disease', and 'dementia with cerebrovascular disease'. There was no increased risk of developing pure vascular dementia (Table 5).

To minimize the influence of incipient dementia on the association between stress and dementia, we re-analysed the data excluding females with dementia onset before 1992. This did not change the association between stress and incidence of dementia (data not shown). The associations between stress and dementia were also similar in participants with dementia onset before and after age 70 years (data not shown).

## Discussion

In a large population-based sample of women followed for 35 years, we found that frequent/constant stress reported in midlife was associated with an increased risk for dementia. To the best of our knowledge, this is the first study to examine the association between midlife psychological stress and development of dementia. The association was consistent over three examinations and remained after adjustment for multiple potential confounders. In addition, women reporting stress at two or three examinations had higher risks of developing dementia than women reporting no stress or stress at only one examination. Furthermore, stress was related to both early onset dementia (<70 years old) and late onset dementia ( $\geq$ 70 years old) and

**Table 1** Characteristics of women without dementia in 1968, 1974 and 1980

	Participants 1968 (n = 1415)	Participants 1974 (n = 1301)	Participants 1980 (n = 1196)
Age (years) (mean $\pm$ SD)	47 $\pm$ 6	53 $\pm$ 6	58 $\pm$ 6
Birth year 1908, n (%)	81 (6)	65 (5)	49 (4)
Birth year 1914, n (%)	180 (12)	163 (12)	138 (12)
Birth year 1918, n (%)	380 (27)	351 (27)	323 (27)
Birth year 1922, n (%)	421 (30)	386 (30)	331 (27)
Birth year 1930, n (%)	353 (25)	336 (26)	355 (30)
Psychological stress, n (%)			
No stress	758 (54)	736 (57)	758 (62)
Previous stress	176 (12)	81 (6)	141 (12)
Occasional stress	204 (14)	179 (14)	114 (10)
Frequent/constant stress	277 (20)	305 (23)	183 (16)
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)
Socioeconomic 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)
Less than once weekly	452 (32)	494 (38)	533 (45)
More than or equal to 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 $\pm$ SD)	0.74 $\pm$ 0.05	0.79 $\pm$ 0.07	0.81 $\pm$ 0.07

the associations remained when individuals with dementia onset before 1992 were excluded.

Our findings are supported by a few comparable epidemiological studies reporting that stressful life-events, post-traumatic stress disorder (Amster and Krauss, 1974; Sands, 1981; Persson and Skoog, 1996; Yehuda *et al.*, 2005) or having the stress-prone personality factor 'high neuroticism' (Wilson *et al.*, 2003, 2006, 2007) are associated with development of cognitive decline (Amster and Krauss, 1974; Sands, 1981; Yehuda *et al.*, 2005; Wilson *et al.*, 2007), dementia (Persson and Skoog, 1996) and Alzheimer's disease (Wilson *et al.*, 2003, 2006). Our findings were mainly driven by Alzheimer's disease type dementia. The physiological mechanism of stress and its possible relation to Alzheimer's disease is complex. There are several possible biological explanations. The main hypotheses are related to the hypothalamic-pituitary-adrenal axis and the effects of

glucocorticoids on the brain. Psychological stress increases the activity of the hypothalamic-pituitary-adrenal axis and thus the level of glucocorticoid hormones (Sapolsky, 1996; Lupien *et al.*, 1999; Peavy *et al.*, 2007). Stress may cause structural and functional damage to the hippocampus (Sheline *et al.*, 1996; Gould and Tanapat, 1999; Bremner, 2006) and influence learning and memory processes (Lupien *et al.*, 1997; Csernansky *et al.*, 2006; Payne *et al.*, 2007). Animal studies have reported that increased glucocorticoid levels and chronic stress may increase the deposition of  $\beta$ -amyloid peptide and tau-protein in the brain (Dong *et al.*, 2004; Green *et al.*, 2006; Kang *et al.*, 2007). Glucocorticoids may also decrease the clearance of  $\beta$ -amyloid peptide from the brain (Harris-White *et al.*, 2001). Another theory is linked to the possible role of stress on inflammatory processes. Stress increases the production of pro-inflammatory cytokines (Kiecolt-Glaser *et al.*, 2002), which are suggested to give rise to Alzheimer's disease

**Table 2** Hazard ratios for incidence of dementia, in participants reporting psychological stress compared to those reporting no stress, in a population sample of females followed from 1968 to 2003

	No stress	Previous stress	Occasional stress in the last 5 years	Frequent/constant stress in the last 5 years
Examination 1968				
No. of persons = 1415/No. of cases = 161				
Hazard ratio (95% CI) <sup>a</sup>	1.0 (ref.)	0.86 (0.51–1.45)	0.94 (0.58–1.53)	1.74 (1.20–2.51)
Hazard ratio (95% CI) <sup>b</sup>	1.0 (ref.)	0.87 (0.51–1.47)	0.89 (0.55–1.46)	1.60 (1.10–2.34)
Examination 1974				
No. of persons = 1301/No. of cases = 148				
Hazard ratio (95% CI) <sup>a</sup>	1.0 (ref.)	1.03 (0.51–2.05)	1.07 (0.64–1.79)	1.65 (1.14–2.39)
Hazard ratio (95% CI) <sup>b</sup>	1.0 (ref.)	1.03 (0.51–2.07)	1.13 (0.67–1.90)	1.65 (1.12–2.41)
Examination 1980				
No. of persons = 1196/No. of cases = 137				
Hazard ratio (95% CI) <sup>a</sup>	1.0 (ref.)	1.35 (0.82–2.22)	1.53 (0.91–2.56)	1.73 (1.10–2.71)
Hazard ratio (95% CI) <sup>b</sup>	1.0 (ref.)	1.33 (0.80–2.23)	1.62 (0.96–2.73)	1.60 (1.01–2.52)

a Hazard ratio adjusted for age.

b Hazard ratio adjusted for age, education, marital status, socioeconomic status, having children, smoking, wine consumption, physical activity, coronary heart disease, hypertension and waist-to-hip ratio, at each examination.

**Table 3** Hazard ratios for incidence of dementia and dementia subtypes, in participants reporting frequent/constant stress compared with those reporting no stress, in a population sample of females, followed from 1968 to 2003

	Examination 1968 (n = 1035)	Examination 1974 (n = 1041)	Examination 1980 (n = 941)
All Alzheimer's disease			
No. of cases	81	81	68
Hazard ratio (95% CI) <sup>a</sup>	2.23 (1.44–3.47)	1.84 (1.18–2.87)	1.68 (0.97–2.91)
Hazard ratio (95% CI) <sup>b</sup>	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
Hazard ratio (95% CI) <sup>a</sup>	2.14 (1.25–3.66)	1.67 (0.97–2.82)	1.30 (0.65–2.60)
Hazard ratio (95% CI) <sup>b</sup>	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
Hazard ratio (95% CI) <sup>a</sup>	2.80 (1.29–6.07)	2.69 (1.18–6.14)	2.93 (1.15–7.46)
Hazard ratio (95% CI) <sup>b</sup>	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
Hazard ratio (95% CI) <sup>a</sup>	0.86 (0.35–2.12)	0.99 (0.42–2.35)	2.32 (0.99–5.44)
Hazard ratio (95% CI) <sup>b</sup>	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
Hazard ratio (95% CI) <sup>a</sup>	1.59 (0.91–2.80)	1.60 (0.89–2.85)	2.51 (1.34–4.72)
Hazard ratio (95% CI) <sup>b</sup>	1.41 (0.78–2.53)	1.57 (0.86–2.88)	1.94 (1.01–3.73)

a Hazard ratio adjusted for age.

b Hazard ratio adjusted for age, education, marital status, socioeconomic status, having children, smoking, wine consumption, physical activity, coronary heart disease, hypertension and waist-to-hip ratio, at each examination.

changes in the brain (Papassotiropoulos *et al.*, 2001; Mrak and Griffin, 2005). Psychological stress has also been associated with cardiovascular disease (Folkow *et al.*, 1973; Pickering, 2001), hypertension (Sparrenberger *et al.*, 2008) and central adiposity (Brydon *et al.*, 2008), which has been linked to dementia (Skoog *et al.*, 1999; Whitmer *et al.*, 2008). One reason for the absence of association between stress and pure vascular dementia may be earlier mortality due to cardiovascular disease among

individuals with stress. This may thus underestimate the relationship between stress and risk of vascular dementia (Gustafson, 2009). Absence of association may also be due to a smaller number of participants with pure vascular dementia.

It is also possible that a heightened stress response is a predictor or early marker for dementia rather than a causal factor. It has been suggested that Alzheimer's disease changes in the brain already appear 20–30 years before the clinical manifestations of the

**Table 4** Hazard ratios for dementia, in relation to numbers of examinations when participants reported frequent/constant stress, in a population sample of females followed from 1968 to 2003 (*n* = 1096)

Number of examinations with stress	No. of persons	No. of cases	Hazard ratio (95% CI) <sup>a</sup>	Hazard ratio (95% CI) <sup>b</sup>
Never frequent/constant stress	673	70	1.0 (ref.)	1.0 (ref.)
Frequent/constant stress in one examination	265	29	1.09 (0.71–1.69)	1.10 (0.71–1.71)
Frequent/constant stress in two examinations	105	17	1.82 (1.07–3.09)	1.73 (1.01–2.95)
Frequent/constant stress in three examinations	53	12	2.83 (1.53–5.23)	2.51 (1.33–4.77)

a Hazard ratio adjusted for age.

b Hazard ratio adjusted for age, education, marital status, socioeconomic status, having children, smoking, wine consumption, physical activity, coronary heart disease, hypertension and waist-to-hip ratio, at examination in 1980.

**Table 5** Hazard ratios for dementia subtypes, in participants reporting frequent/constant stress at two or three examinations in a population sample of females followed from 1968 to 2003 (*n* = 1096)

Dementia and subtypes of dementia	No. of cases	Hazard ratio (95% CI) <sup>a</sup>	Hazard ratio (95% CI) <sup>b</sup>
Total dementia	128	2.08 (1.37–3.15)	1.92 (1.25–2.94)
All Alzheimer's disease	86	2.50 (1.53–4.06)	2.33 (1.41–3.85)
Alzheimer's disease without cerebrovascular disease	60	2.10 (1.13–3.89)	2.02 (1.07–3.80)
Alzheimer's disease with cerebrovascular disease	26	4.07 (1.80–9.20)	3.28 (1.40–7.71)
Pure vascular dementia	32	1.45 (0.55–3.79)	1.20 (0.45–3.23)
Dementia with cerebrovascular disease	58	2.40 (1.31–4.40)	1.95 (1.04–3.65)

a Hazard ratio adjusted for age.

b Hazard ratio adjusted for education, marital status, socioeconomic status, having children, smoking, wine consumption, physical inactivity, hypertension, coronary heart disease and waist-to-hip ratio, at examination in 1980.

disease (Mann, 1989; Lemere *et al.*, 1996). We cannot exclude the possibility that these brain changes may give rise to an increased vulnerability to stress. Decreased stress tolerance may thus reflect early symptoms of dementia. 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 or may not be due to incipient Alzheimer's disease changes in the brain. Furthermore, 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.

The strengths of this study include a representative population, long follow-up and multiple sources of information to detect and diagnose dementia. Some methodological issues need to be considered. First, individuals can differ in their capacity to adapt to different situations, or in their evaluation of stress. Second, psychological stress was based on a subjective personal response to a single question, which may better capture stress than objective measures of stress load (e.g. life event scales). Furthermore, a single question can possibly make the interpretation of results more distinct than a conglomerate of combined items/questions. Our question on stress has been used in several previous studies and found to be related to indicated increased risk for hypertension (Eriksson *et al.*, 1989), myocardial infarction (Bengtsson, 1973), cancer (Helgesson *et al.*, 2003) and psychosomatic diseases

(Hange *et al.*, 2007). Third, we cannot evaluate the potential influence of levels of stress severity, as our stress question gave information only on duration of stress. Fourth, 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 receive their hospital treatment within the public health care system 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 (Fratiglioni *et al.*, 2000). Fifth, it is difficult to diagnose dementia subtypes on clinical grounds alone. Individuals with Alzheimer's disease often have cerebrovascular disease and individuals with vascular dementia often have concomitant Alzheimer's disease pathology; and cerebrovascular disease may influence the presence and severity of clinical symptoms of Alzheimer's disease (Snowdon *et al.*, 1997). It is thus often difficult to make a clear distinction between Alzheimer's disease and vascular dementia 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. 'Alzheimer's disease with and without cerebrovascular disease', 'dementia with cerebrovascular disease'). Sixth, semi-structured examinations were performed by experienced psychiatrists in 1974–75, 1980–81 and 1992–93 and by

experienced psychiatric nurses in 2000–03. The instruments used were identical across examinations, and inter-rater reliability between psychiatrists and nurses regarding the symptoms assessed was satisfactory (Wancata *et al.*, 2007). It is therefore not likely that the use of different professionals could have influenced the main results of this study. Finally, only females were examined in this study. We can therefore not generalize our findings to males, or make any statements about potential sex differences in the relation between stress and dementia.

In summary, our results suggest an association between long-standing psychological stress in middle-aged females and development of dementia later in life. More studies are needed to confirm our findings and to study potential neurobiological mechanisms of these associations.

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## References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, revised (DSM-III-R). 3rd edn., Washington, DC: American Psychiatric Association; 1987.
- Amster LE, Krauss HH. The relationship between life crises and mental deterioration in old age. *Int J Aging Hum Dev* 1974; 5: 51–5.
- Bengtsson C. Ischaemic heart disease in women. A study based on a randomized population sample of women and women with myocardial infarction in Göteborg, Sweden. *Acta Med Scand Suppl* 1973; 549: 1–128.
- Bengtsson C, Blohme G, Hallberg L, Hallstrom T, Isaksson B, Korsan-Bengtson K, et al. The study of women in Gothenburg 1968-1969—a population study. General design, purpose and sampling results. *Acta Med Scand* 1973; 193: 311–8.
- Bengtsson C, Gredmark T, Hallberg L, Hallstrom T, Isaksson B, Lapidus L, et al. The population study of women in Gothenburg 1980-81—the third phase of a longitudinal study. Comparison between participants and non-participants. *Scand J Soc Med* 1989; 17: 141–5.
- Bengtsson C, Hallberg L, Hallstrom T, Hultborn A, Isaksson B, Lennartsson J, et al. The population study of women in Göteborg 1974-1975—the second phase of a longitudinal study. General design, purpose and sampling results. *Scand J Soc Med* 1978; 6: 49–54.
- Bremner JD. Stress and brain atrophy. *CNS Neurol Disord Drug Targets* 2006; 5: 503–12.
- Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, et al. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry* 1995; 152: 973–81.
- Brydon L, Wright CE, O'Donnell K, Zachary I, Wardle J, Steptoe A. Stress-induced cytokine responses and central adiposity in young women. *Int J Obes (Lond)* 2008; 32: 443–50.
- Carlsson G. Socialgruppering. Social mobility and class structure. University of Lund, Sweden: GWK Gleerup; 1958.
- Criteria for the clinical diagnosis of Alzheimer's disease. Excerpts from the NINCDS-ADRDA Work Group report. *J Am Geriatr Soc* 1985; 33: 2–3.
- Csernansky JG, Dong H, Fagan AM, Wang L, Xiong C, Holtzman DM, et al. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. *Am J Psychiatry* 2006; 163: 2164–9.
- Dong H, Goico B, Martin M, Csernansky CA, Bertchume A, Csernansky JG. Modulation of hippocampal cell proliferation, memory, and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress. *Neuroscience* 2004; 127: 601–9.
- Eriksson H, Svardsudd K, Larsson B, Ohlson LO, Tibblin G, Welin L, et al. Risk factors for heart failure in the general population: the study of men born in 1913. *Eur Heart J* 1989; 10: 647–56.
- Folkow B, Hallback M, Weiss L. Cardiovascular responses to acute mental “stress” in spontaneously hypertensive rats. *Clin Sci Mol Med Suppl* 1973; 45 (Suppl 1): 131s–3s.
- Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, et al. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000; 54: S10–5.
- Gould E, Tanapat P. Stress and hippocampal neurogenesis. *Biol Psychiatry* 1999; 46: 1472–9.
- Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J Neurosci* 2006; 26: 9047–56.
- Guo X, Waern M, Sjogren K, Lissner L, Bengtsson C, Bjorkelund C, et al. Midlife respiratory function and incidence of Alzheimer's disease: a 29-year longitudinal study in women. *Neurobiol Aging* 2007; 28: 343–50.
- Gustafson DR, Bäckman K, Waern M, Östling S, Guo X, Zandi P, et al. Adiposity indicators and dementia over 32 years in Sweden. *Neurology* 2009; 73: 1559–66.
- Hange D, Bengtsson C, Sundh V, Bjorkelund C. The natural history of psychosomatic symptoms and their association with psychological symptoms: observations from the Population Study of Women in Gothenburg. *Eur J Gen Pract* 2007; 13: 60–6.
- Harris-White ME, Chu T, Miller SA, Simmons M, Teter B, Nash D, et al. Estrogen (E2) and glucocorticoid (Gc) effects on microglia and A beta clearance in vitro and in vivo. *Neurochem Int* 2001; 39: 435–48.
- Helgesson O, Cabrera C, Lapidus L, Bengtsson C, Lissner L. Self-reported stress levels predict subsequent breast cancer in a cohort of Swedish women. *Eur J Cancer Prev* 2003; 12: 377–81.
- Kang JE, Cirrito JR, Dong H, Csernansky JG, Holtzman DM. Acute stress increases interstitial fluid amyloid-beta via corticotropin-releasing factor and neuronal activity. *Proc Natl Acad Sci USA* 2007; 104: 10673–8.
- Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Psychoneuroimmunology and psychosomatic medicine: back to the future. *Psychosom Med* 2002; 64: 15–28.
- Launer LJ. Demonstrating the case that AD is a vascular disease: epidemiologic evidence. *Ageing Res Rev* 2002; 1: 61–77.
- Lemere CA, Blusztajn JK, Yamaguchi H, Wisniewski T, Saido TC, Selkoe DJ. Sequence of deposition of heterogeneous amyloid beta-peptides and APO E in Down syndrome: implications for initial events in amyloid plaque formation. *Neurobiol Dis* 1996; 3: 16–32.

- Leonard BE. HPA and immune axes in stress: involvement of the serotonergic system. *Neuroimmunomodulation* 2006; 13: 268–76.
- Lissner L, Skoog I, Andersson K, Beckman N, Sundh V, Waern M, et al. Participation bias in longitudinal studies: experience from the Population Study of Women in Gothenburg, Sweden. *Scand J Prim Health Care* 2003; 21: 242–7.
- Lupien SJ, Gaudreau S, Tchiteya BM, Maheu F, Sharma S, Nair NP, et al. Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. *J Clin Endocrinol Metab* 1997; 82: 2070–5.
- Lupien SJ, Nair NP, Briere S, Maheu F, Tu MT, Lemay M, et al. Increased cortisol levels and impaired cognition in human aging: implication for depression and dementia in later life. *Rev Neurosci* 1999; 10: 117–39.
- Mann DM. Cerebral amyloidosis, ageing and Alzheimer's disease; a contribution from studies on Down's syndrome. *Neurobiol Aging* 1989; 10: 397–9; discussion 412–4.
- McEwen BS. The neurobiology of stress: from serendipity to clinical relevance. *Brain Res* 2000; 886: 172–189.
- Mrak RE, Griffin WS. Potential inflammatory biomarkers in Alzheimer's disease. *J Alzheimers Dis* 2005; 8: 369–75.
- Papassotiropoulos A, Hock C, Nitsch RM. Genetics of interleukin 6: implications for Alzheimer's disease. *Neurobiol Aging* 2001; 22: 863–71.
- Payne JD, Jackson ED, Hoscheidt S, Ryan L, Jacobs WJ, Nadel L. Stress administered prior to encoding impairs neutral but enhances emotional long-term episodic memories. *Learn Mem* 2007; 14: 861–8.
- Peavy GM, Lange KL, Salmon DP, Patterson TL, Goldman S, Gamst AC, et al. The effects of prolonged stress and APOE genotype on memory and cortisol in older adults. *Biol Psychiatry* 2007; 62: 472–8.
- Persson G, Skoog I. A prospective population study of psychosocial risk factors for late onset dementia. *Int J Geriatr Psych* 1996; 11: 15–22.
- Pickering TG. Mental stress as a causal factor in the development of hypertension and cardiovascular disease. *Curr Hypertens Rep* 2001; 3: 249–54.
- Rinder L, Roupe S, Steen B, Svanborg A. Seventy-year-old people in Gothenburg. A population study in an industrialized Swedish city. *Acta Med Scand* 1975; 198: 397–407.
- Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993; 43: 250–60.
- Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 1962; 27: 645–58.
- Sands JD. The relationship of stressful life events to intellectual functioning in women over 65. *Int J Aging Hum Dev* 1981; 14: 11–22.
- Sapolsky RM. Why stress is bad for your brain. *Science* 1996; 273: 749–50.
- Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 1996; 93: 3908–13.
- Skoog I, Kalaria RN, Breteler MM. Vascular factors and Alzheimer disease. *Alzheimer Dis Assoc Disord* 1999; 13 (Suppl 3): S106–14.
- Skoog I, Nilsson L, Palmertz B, Andreasson LA, Svanborg A. A population-based study of dementia in 85-year-olds. *N Engl J Med* 1993; 328: 153–8.
- Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA* 1997; 277: 813–7.
- Sparrenberger F, Cicheler FT, Ascoli AM, Fonseca FP, Weiss G, Berwanger O, et al. Does psychosocial stress cause hypertension? A systematic review of observational studies. *J Hum Hypertens* 2008; 23: 12–19.
- Wancata J, Borjesson-Hanson A, Ostling S, Sjogren K, Skoog I. Diagnostic criteria influence dementia prevalence. *Am J Geriatr Psychiatry* 2007; 15: 1034–45.
- Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology* 2008; 71: 1057–64.
- Wilson RS, Arnold SE, Schneider JA, Kelly JF, Tang Y, Bennett DA. Chronic psychological distress and risk of Alzheimer's disease in old age. *Neuroepidemiology* 2006; 27: 143–53.
- Wilson RS, Evans DA, Bienias JL, Mendes de Leon CF, Schneider JA, Bennett DA. Proneness to psychological distress is associated with risk of Alzheimer's disease. *Neurology* 2003; 61: 1479–85.
- Wilson RS, Schneider JA, Boyle PA, Arnold SE, Tang Y, Bennett DA. Chronic distress and incidence of mild cognitive impairment. *Neurology* 2007; 68: 2085–92.
- Yehuda R, Golier JA, Harvey PD, Stavitsky K, Kaufman S, Grossman RA, et al. Relationship between cortisol and age-related memory impairments in Holocaust survivors with PTSD. *Psychoneuroendocrinology* 2005; 30: 678–87.