Title: Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: a 38 year follow-up study

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Complete List of Authors:	Johansson, Lena; Institute of Neuroscience and Physiology, Sahlgrenska Academy at G&#65533;teborg University, G&#65533;teborg, Swed Guo, Xinxin; Institute of Neuroscience and Physiology, Sahlgrenska Academy at G&#65533;teborg University, G&#65533;teborg, Swed Hällström, Tore; Neuroscience and Physiology, Psychiatry Norton, Maria; Utah University, Department of Family Consumer and Human Development and Departments of Psychology Waern, Margda; Institute of Neuroscience and Physiology, Sahlgrenska Academy at G&#65533;teborg University, G&#65533;teborg, Swed Östling, Svante; Institute of Neuroscience and Physiology, Sahlgrenska Academy at G&#65533;teborg University, G&#65533;teborg, Swed Skoog, Ingmar; Institute of Neuroscience and Physiology, Sahlgrenska Academy at G&#65533;teborg University, G&#65533;teborg, Swed Bengtsson, Calle; , the Sahlgrenska Academy at University of Gothenburg,,
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Common stressors in relation to longstanding distress and Alzheimer's disease

Title page

Title: Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: a 37 year longitudinal population study

Authors´ names: Lena Johansson, Xinxin Guo, Tore Hällström, Maria C Norton, Margda Waern, Svante Östling, Calle Bengtsson, Ingmar Skoog

Address for each author: Neuropsychiatric Epidemiology Unit, Institute of Neuroscience and Physiology, Sahlgrenska Academy at Gothenburg University, Wallinsgatan 6, S-431 41 Mölndal, Sweden Lena Johansson researchers Xinxin Guo researcher, Tore Hällström professor emeritus, Margda Waern professor, Svante Östling associate professor, Ingmar Skoog professor Department of Clinical Neuroscience, Section for Psychiatry/Huddinge, Karolinska Institutet, Stockholm, Sweden Tore Hällström professor emeritus Department of Family Consumer and Human Development and Departments of Psychology, Utah State University, Logan, USA Maria Norton associate professor Sahlgrenska School of Public Health and Community Medicine, Section for Public Health Epidemiology, the Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden Calle Bengtsson professor emeritus

Correspondence to: lena.johansson@neuro.gu.se

Common stressors in relation to longstanding distress and Alzheimer's disease

Abstract

Objective To study the relation between psychosocial stressors, longstanding distress and incidence of dementia, in a sample of women followed from midlife to late-life.

Design Prospective longitudinal population study.

Setting The study is part of the Prospective Population Study of Women in Gothenburg, Sweden, which started in 1968 with subsequent follow-ups in 1974, 1980, 1992, 2000 and 2005.

Participants 800 women born in 1914, 1918, 1922 and 1930 who rated 18 psychosocial stressors (e.g. divorce, widowhood, work problems and illness in relative) at baseline 1968.

Primary and secondary outcome measures: Symptoms of distress were measured according to a standardised question at each study wave. Dementia was diagnosed according to DSM-III-R and Alzheimer's disease (AD) according to NINCD-ADRDA.

Results During the 37-years follow-up 153 women developed dementia (104 of those had AD). Number of psychosocial stressors in 1968 was associated (HR, 95% CI) with higher incidence of dementia (1.15, 1.04-1.27) and AD (1.20, 1.07-1.35) between 1968 and 2005, in multivariate Cox regressions. Number of psychosocial stressors in 1968 was also associated (OR, 95% CI) with distress in 1968 (1.48, 1.32-1.67), 1974 (1.31, 1.17-1.46), 1980 (1.27, 1.11-1.45), 2000 (1.39, 1.14-1.70) and 2005 (1.35, 1.02-1.79), in multivariate logistic regressions. Number of psychosocial stressors (HR 1.17, 95% CI 1.03-1.33) and longstanding distress (1968-1974-1980) (HR 1.58, 95% CI 1.03-2.45) were independently associated with AD.

Conclusions Our study shows that common psychosocial stressors may have severe and longstanding physiological and psychological consequences. It needs to be elucidated whether more intensive interventions such as stress management and behavioral therapy should be initiated in individuals who have experienced psychosocial stressors.

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Article summary

Article focus

To study the relation between psychosocial stressors, longstanding distress and incidence of dementia, in a sample of women followed over 37 years, from mid- to late-life.

Key messages

The study shows that the number of psychosocial stressors, measured in middle-aged women, was related to distress and incidence of AD almost four decades later.

The study also shows that the association between number of psychosocial stressors and AD was independent of longstanding perceived distress.

Strengths and limitations of this study

The strengths of this study include midlife report of psychosocial stressors occurring long before dementia onset, the long follow-up period, the representative population and that multiple sources of information were used to detect and diagnose dementia.

The rating of stressors was related to the last year for some stressors and at any time before 1968 for other stressors. Some stressors were of a short duration, while others were chronic and lasting for many years. We only have information on a limited number of psychosocial stressors in our population. Individuals have different capacities to cope with stress and thus react differently when exposed to the same stressor. We did not have an individual weighting of the included stressors.

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Introduction

Experiences of severe psychological stressors in adulthood (e.g. combat[1], natural disasters[2] and the Holocaust[3]) are known to influence mental and physical health decades later. More mild psychosocial stressors are common and could be regarded as part of normal life. The long-term consequences of these more common stressors remain unclear. Epidemiological studies in the elderly with follow-ups of less than 10 years have reported that history of early parental death,[4-6] death of spouse[7] and psychosocial risk factors in childhood[6] increase the risk of dementia or Alzheimer's disease (AD). One explanation for the associations may be that traumatic experiences give rise to longstanding chronic distress many years after the trauma. This may lead to a cumulative burden to the brain with dysregulation in neuroendocrine systems.[8-10] A study among Holocaust survivors found that higher levels of stress hormones remained decades after the traumatic experiences.[8]

We have previously reported that longstanding distress in midlife leads to long-term consequences decades later, such as increased risk of dementia, AD[11] and structural brain changes[12]. To our knowledge, no population study has examined if number of psychosocial stressors in midlife increase the risk of dementia in late-life, and whether this is modified by longstanding distress.

The aim of this study was to examine whether common psychosocial stressors in midlife were related to distress, late-life dementia and AD, in women followed over 38 years. We further aimed to examine whether experiences of psychosocial stressors mediate the previously reported association between longstanding midlife distress and AD.

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Methods

Study population

This study is part of the Prospective Population Study of Women in Gothenburg, Sweden[13 14] which was initiated in 1968 with an examination of 1462 women (participation rate 90%) born in 1908, 1914, 1918, 1922 and 1930. The individuals were systematically sampled from the Swedish Population Registry based on specific birth dates in order to yield a representative sample at the ages studied. Follow-ups were performed in 1974, 1980, 1992, 2000 and 2005 with participation rates among survivors of 91%, 83%, 70%, 71% and 70% respectively. The Ethics Committee of Gothenburg University approved the study and informed consent was obtained from all participants, in accordance with the provision of the Helsinki Declaration.

The present study included a subsample of 800 women who were systematically selected for a psychiatric examination in 1968. The women were aged 38 years (n=111), 46 years (n=309), 50 years (n=290) and 54 years (n=90). Among them, 713 participated in the follow-up examination in 1974, 639 in 1980, 472 in 1992, 368 in 2000 and 296 in 2005. Losses were mainly due to death.

Assessment of psychosocial stressors

At baseline 1968, eighteen predefined psychosocial stressors were asked and rated by a psychiatrist during the psychiatric examination. These included: divorce, widowhood, serious problem in children (e.g. physical illness, death and 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, problem related to husband's or own work (e.g. lost work) and limited social network. Some

of the 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. The others were rated as occurring at any time prior to the examination in 1968.

Assessment of distress

Symptoms of distress were rated according to a standardized question in 1968, 1974, 1980, 2000 and 2005. The question was worded identically at each examination; "Have you experienced any period of distress (one month or longer) in relation to circumstances in everyday life, such as work, health or family situation? Distress refers to feelings of irritability, tension, nervousness, fear, anxiety or sleep disturbances." Participants were asked to choose between; 0=Have never experienced any period of distress; 1=Have experienced period/s of distress more than five years ago; 2=Have experienced one period of distress during the last five years; 3=Have experienced several periods of distress during the last five years; 4=Have experienced constant distress during the last year; or 5=Have experienced constant distress during the last five years. In the present study, distress is defined as a rating of 3 to 5.

Psychiatric examinations

The psychiatric examinations were performed in 1968, 1974, 1980 and 1992 by psychiatrists and in 2000 and 2005 by experienced psychiatric research nurses. The examinations were semi-structured and included a comprehensive neuropsychiatric examination and an extensive battery of neuropsychiatric tests.[15] Close informant interviews were performed in 1992, 2000 and 2005. These included questions about changes in behaviour and intellectual functions and, in cases of dementia, age of onset and disease course.[15] Medical records were collected

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

Diagnosis of dementia

The diagnosis of dementia 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.[15] Dementia diagnosis at each examination was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) based on the combined information from the psychiatric examination and the close informant interview. Dementia diagnoses for individuals lost to follow-up were based on information from medical records evaluated by geriatric psychiatrists in consensus conferences, and information from the Swedish Hospital Discharge Registry.[16]

AD 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 (NINCDS-ADRDA).[17] The criteria for vascular dementia (VaD) were similar to the criteria proposed by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherce et l´Enseignement en Neurosciences (NINDS-AIREN).[18] VaD was thus 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. Other dementias were diagnosed when other causes were likely to have caused the dementia. 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; or (d) December 31, 2006 for surviving drop-outs.

Potential confounders and mediators

Information on education, socioeconomic status, marital status, work status, blood pressure, antihypertensive medication use, coronary heart disease (CHD), diabetes mellitus, stroke, waist and hip circumferences, cigarette smoking and wine consumption was obtained at the examination in 1968. Education was dichotomised as compulsory (6 years for those born 1914-1922 and 7 years for those born 1930) versus more than compulsory education. Socioeconomic status was based on husband's occupation for married women, and own occupation for unmarried women and was defined as higher middle, lower middle, skilled workers and unskilled workers.[19] Marital status was classified as married and/or co-habiting versus single. Work status was measured as full-time work and/or part-time work versus no work outside home. Hypertension was defined as systolic blood pressure of 160 mmHg or more, and/or diastolic blood pressure 95 mmHg or more and/or taking antihypertensive medication. CHD was defined as fulfilling one or more of the following criteria: angina pectoris according to the Rose criteria,[20] 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.[21] Diabetes mellitus was defined as a diagnosis told by a doctor, death certificates, being on anti-diabetes drugs or having two fasting blood glucose values of 7.0 mmol/l or more. Stroke was diagnosed based on information from the examinations and the Swedish Hospital Discharge Registry. Waist-to-hip ratio was calculated as the ratio of waist and hip circumferences, measured to the nearest 0.5 cm. Cigarette smoking was defined as never, former or current smoker. Wine consumption was classified as none, less than once weekly and once weekly or more.

Statistical analyses

Logistic regressions were used to analyse the associations between number of psychosocial stressors in 1968 and report of distress in 1968, 1974, 1980, 2000 and 2005. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs) in two separate models. The first model adjusts for age only. The second model adjusts for age, education, socioeconomic status, marital status, work status, hypertension, CHD, stroke, diabetes mellitus, waist-to-hip ratio, smoking and wine consumption.

Cox regressions were used to study the association between number of psychosocial stressors and incidence of dementia and dementia subtypes. Associations are presented as hazard ratios (HRs) and 95% CIs, adjusting for the same covariates as listed above. A third model was added which also included longstanding midlife distress (i.e. distress in all examinations 1968-1974-1980) as a covariate.

We also examined the associations between psychosocial stressors and dementia onset before and after age 75. The association between stressors and dementia was further studied in a subsample excluding women whose parents had mental illness to minimize the influence of psychiatric heredity.

Results

Baseline characteristics of the 800 participants are given in Table 1. The proportion of women who reported specific life stressors in 1968 are shown in Table 2. Twenty-five percent of the women reported one psychosocial stressor, 23% reported two stressors, 20% three stressors and 16% four or more stressors. The most frequently reported psychosocial stressor was mental illness in first degree relative (mother 27 %, father 19% and sibling 32%).

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Four hundred and twenty five participants died during follow-up (mean age 79 years). From 1968 to 2006, 153 (19.1%) women developed dementia during 25,131 person-years of follow-up, including 104 with AD, 35 with VaD and 14 with other dementias. The mean time from the baseline examination in 1968 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 years).

Number of psychosocial stressors in 1968 was associated with distress in 1968, 1974, 1980, 2000 and 2005, after adjustment for potential confounders (Table 3). ORs were similar through all five examinations. Number of psychosocial stressors in 1968 was associated with longstanding midlife distress (i.e. distress in 1968-1974-1980) both in later born cohorts, born 1922 and 1930, (multiadjusted OR 1.32, 95% CI 1.14-1.52) and earlier born cohorts, born 1914 and 1918 (multiadjusted OR 1.58, 95% CI 1.30-1.94).

Number of psychosocial stressors in 1968 was associated with higher incidence of AD (HR 1.20, 95% CI 1.07-1.35) and all-type dementia (HR 1.15, 95% CI 1.04-1.27) after adjustment for multiple confounders (Table 4). The associations remained after further adjustment for longstanding distress (i.e. distress in 1968-1974-1980). In the final model, longstanding distress (HR 1.58, 95% CI 1.01-2.46) and number of psychosocial stressors (HR 1.17, 95% CI 1.02-1.33) were independently associated with AD. The association between number of psychosocial stressors and incidence of AD were similar in those with early onset AD (aged <75 years) (multiadjusted HR 1.25, 95% CI 1.02-1.54) and late onset AD (aged ≥75 years) (multiadjusted HR 1.19, 95% CI 1.03-1.38). The association between number of psychosocial stressors and incidence of dementia remained when excluding women whose parents had

mental illness (multiadjusted HR 1.14, 95% CI 1.01-1.28). Finally, there were no associations between number of psychosocial stressors and VaD in any of the models.

Discussion

We found that number of common psychosocial stressors in midlife was associated with incidence of late-life dementia, especially AD, in a population-based sample of women followed for 38 years. The associations remained when controlling for longstanding distress. We also found that number of psychosocial stressors in 1968 was related to increased level of distress at every examination conducted between 1968 and 2005.

We have previously reported that longstanding distress in midlife increase risk of AD[11] and structural brain changes.[12] These findings are now extended by showing that number of psychosocial stressors and report of distress independently predicted AD, i.e. increased distress could not completely explain the association between midlife stressors and dementia. One reason for this is that individuals respond differently to psychosocial stressors. Thus, biological responses may develop in connection with psychosocial stressors also in individuals who do not experience or report increased distress in association to the stressor.

There may be several biological explanations for the association between psychosocial stressors in midlife and dementia. One is related to the stress hypothesis. Stress may cause a number of physiological reactions in the central nervous, endocrine, immune and cardiovascular systems.[10] Thus, psychological stress has been reported to increase the activity of the hypothalamic-pituitary-adrenal axis and the levels of glucocorticoid hormones,[22] cause structural and functional damage to the hippocampus,[22] influence learning and memory processes,[23] increase the production of pro-inflammatory cytokines in the brain,[10] increase the

deposition of β-amyloid peptid and tau-protein in the brain [24-26]and to increase the frequency of cardiovascular disease[27 28], and hypertension.[29] All these factors have been linked to dementia.[30]

The associations between psychosocial stressors reported in midlife and perceived distress later in life was consistent through all follow-up years, as indicated by ORs of similar magnitude. Thus, even common psychosocial stressors (related to work and family) can cause distress over several decades. Our finding is supported by studies reporting that stress-hormones may remain elevated many years after traumatic events.[8] Another explanation is that experiences of psychosocial traumas might make an individual more vulnerable to future stressors due to biological changes and dysfunctional stress coping mechanisms.[31 32]

Strengths and weaknesses of the study

The strengths of this study include midlife report of psychosocial stressors occurring long before dementia onset, the long follow-up period, the representative population and that multiple sources of information were used to detect and diagnose dementia. Some methodological issues need to be considered. First, the rating of stressors was related to the last year for some stressors and at any time before 1968 for other stressors. However, both these were related to the outcome in a similar way (data not shown). Second, some stressors were of a short duration, while others were chronic and lasting for many years. In addition, some stressors were severe and others more trivial. This might give an unbalanced weight among the factors studied. Third, we only have information on a limited number of psychosocial stressors in our population. Some events were not included, e.g. physical abuse and own severe physical illness. The relationships might thus have been confounded by unmeasured factors. However, it is not likely that this had any major influence on our

findings. Fourth, individuals have different capacities to cope with stress and thus react differently when exposed to the same stressor. We did not have an individual weighting of the included stressors. If anything, this might have decreased the strengths of associations. Fifth, some stressors are interrelated, for example mental illness and alcohol abuse in spouse. However these stressors independently increased stress reactions (data not shown). We therefore decided not to merge them. Sixth, 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 women detected in the different age groups is what could be expected from other incidence studies.[33] Finally, 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. Furthermore, cerebrovascular disease may influence the presence and severity of clinical symptoms of AD, and vice versa.[34] 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, and mixed types are probably common.

Conclusion

To conclude, psychosocial stressors in midlife were associated with incidence of AD and longstanding distress, over several decades. This suggests that common psychosocial stressors may have severe and longstanding physiological and psychological consequences. It needs to be elucidated whether more intensive interventions such as stress management and behavioral

therapy should be initiated in individuals who have experienced several negative psychosocial stressors.

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Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and

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Contributors All authors participating in the interpretation of data, writing and critically reviewing the paper. LJ, XG and IS designing the study, generate the hypothesis, and wrote the draft. LJ did the analyses. All authors had full access to the data. LJ is guarantor.

Ethical approval The Ethics Committee of Gothenburg University approved the study and informed consent was obtained from all participants, in accordance with the provision of the Helsinki Declaration.

Data sharing Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the dataset.

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Tables

Table 1 Characteristics of the study sample in 1968 (N=800)

	n	%
Birth year (age)		
1914 (54 year)	89	11.1
1918 (50 year)	291	36.4
1922 (46 year)	309	38.6
1930 (38 year)	111	13.9
Education		
Compulsory	600	75.0
More than compulsory	200	25.0
Socioeconomic status		
Upper middle	161	20.2
Lower middle	267	33.4
Skilled workers	209	26.1
Unskilled workers	163	20.4
Marital status		
Married	638	79.8
Co-habited (not married)	94	11.7
Living alone (not married)	68	8.5
Work status		
Full-time work	270	33.8
Part-time work	258	32.3
No work outside home	272	34.0
Hypertension	138	17.4
CHD	67	8.4
Diabetes mellitus	86	10.8
Stroke	68	8.5
Smoking	320	40.0
Wine consumption		
None	390	48.8
< once weekly	249	31.1
≥ once weekly	155	19.4
	Mean	SD
Waist-to-hip ratio	0.74	0.05

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Table 2 Prevalence of psychosocial stressors in women in 1968 (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
Number of psychosocial stressors		
0 psychosocial stressor	149	18.6
1 psychosocial stressor	197	24.6
2 psychosocial stressors	184	23.0
3 psychosocial stressors	143	19.9
4 psychosocial stressors	69	8.6
≥5 psychosocial stressors	58	7.2

Table 3 Number of psychosocial stressors in 1968 in relations to report of distress in 1968, 1974, 1980, 2000 and 2005

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

Logistic regression analyses presented as ORs with 95% CIs. [a]Adjusted for age. [b] Adjusted for age, education, socioeconomic status, marital status, work status, hypertension, CHD, stroke, diabetes mellitus, waist-to-hip ratio, smoking and wine consumption in 1968.

Table 4 Number of psychosocial stressors in 1968 in relation to incidence of dementia over 38 years

	Cases, n (%)	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
All-type dementia	153 (19.1)	1.15 (1.05-1.27)	1.15 (1.04-1.27)	1.13 (1.01-1.26)
Vascular dementia	35 (4.4)	0.94 (0.75-1.19)	0.92 (0.72-1.18)	0.93 (0.71-1.22)
Alzheimer's disease	104 (13.0)	1.21 (1.08-1.36)	1.20 (1.07-1.35)	1.17 (1.02-1.33)

Cox regression analyses presented as HRs with 95% CIs. [a]Adjusted for age. [b]Adjusted for age, education, socioeconomic status, marital status, work status, hypertension, CHD, stroke, diabetes mellitus, waist-to-hip ratio, smoking, and wine consumption in 1968. [c] Adjusted for age, education, socioeconomic status, marital status, work status, hypertension, CHD, stroke, diabetes mellitus, waist-to-hip ratio, smoking and wine consumption in 1968, and longstanding distress (i.e. in 1968, 1974 and 1980).

The original protocol for the study

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Contributors All authors participating in the interpretation of data, writing and critically reviewing the paper. LJ, XG and IS designing the study, generate the hypothesis, and wrote the draft. LJ did the analyses. All authors had full access to the data. LJ is guarantor.

STROBE checklist

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	7-8

		group	
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9-10
		(*d*) If applicable, explain how loss to follow-up was addressed	9-10
		(*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	20
		(b) Indicate number of participants with missing data for each variable of interest	20
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	11

		interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

Ethical approval The Ethics Committee of Gothenburg University approved the study and informed consent was obtained from all participants, in accordance with the provision of the Helsinki Declaration.

Data sharing Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the dataset.

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Complete List of Authors:	Johansson, Lena; Institute of Neuroscience and Physiology, Sahlgrenska Academy at G&#65533;teborg University, G&#65533;teborg, Swed Guo, Xinxin; Institute of Neuroscience and Physiology, Sahlgrenska Academy at G&#65533;teborg University, G&#65533;teborg, Swed Hällström, Tore; Neuroscience and Physiology, Psychiatry Norton, Maria; Utah University, Department of Family Consumer and Human Development and Departments of Psychology Waern, Margda; Institute of Neuroscience and Physiology, Sahlgrenska Academy at G&#65533;teborg University, G&#65533;teborg, Swed Östling, Svante; Institute of Neuroscience and Physiology, Sahlgrenska Academy at G&#65533;teborg University, G&#65533;teborg, Swed Skoog, Ingmar; Institute of Neuroscience and Physiology, Sahlgrenska Academy at G&#65533;teborg University, G&#65533;teborg, Swed Bengtsson, Calle; , the Sahlgrenska Academy at University of Gothenburg,,
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Common stressors in relation to longstanding distress and Alzheimer's disease

Title page

Title: Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: a 38 year longitudinal population study

Authors´ names: Lena Johansson, Xinxin Guo, Tore Hällström, Maria C Norton, Margda Waern, Svante Östling, Calle Bengtsson, Ingmar Skoog

Address for each author: Neuropsychiatric Epidemiology Unit, Institute of Neuroscience and Physiology, Sahlgrenska Academy at Gothenburg University, Wallinsgatan 6, S-431 41 Mölndal, Sweden Lena Johansson researchers Xinxin Guo researcher, Tore Hällström professor emeritus, Margda Waern professor, Svante Östling associate professor, Ingmar Skoog professor Department of Clinical Neuroscience, Section for Psychiatry/Huddinge, Karolinska Institutet, Stockholm, Sweden Tore Hällström professor emeritus Department of Family Consumer and Human Development and Departments of Psychology, Utah State University, Logan, USA Maria Norton associate professor Sahlgrenska School of Public Health and Community Medicine, Section for Public Health Epidemiology, the Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden Calle Bengtsson professor emeritus

Correspondence to: lena.johansson@neuro.gu.se

Common stressors in relation to longstanding distress and Alzheimer's disease

Abstract

Objective To study the relation between psychosocial stressors, longstanding distress and incidence of dementia, in a sample of women followed from midlife to late-life.

Design Prospective longitudinal population study.

Setting and Participants The study is part of the Prospective Population Study of Women in Gothenburg, Sweden, which started in 1968 with subsequent follow-ups in 1974, 1980, 1992, 2000 and 2005. At baseline, 800 women aged 38-54 years (born in 1914, 1918, 1922 and 1930), rated 18 psychosocial stressors (e.g. divorce, widowhood, work problems and illness in relative).

Primary and secondary outcome measures: Symptoms of distress were measured according to a standardised question at each study wave. Dementia was diagnosed according to DSM-III-R and Alzheimer's disease (AD) according to NINCD-ADRDA.

Results During the 37-years follow-up 153 women developed dementia (104 of those had AD). Number of psychosocial stressors in 1968 was associated (HR, 95% CI) with higher incidence of dementia (1.15, 1.04-1.27) and AD (1.20, 1.07-1.35) between 1968 and 2005, in multivariate Cox regressions. Number of psychosocial stressors in 1968 was also associated (OR, 95% CI) with distress in 1968 (1.48, 1.32-1.67), 1974 (1.31, 1.17-1.46), 1980 (1.27, 1.11-1.45), 2000 (1.39, 1.14-1.70) and 2005 (1.35, 1.02-1.79), in multivariate logistic regressions. Number of psychosocial stressors (HR 1.17, 95% CI 1.03-1.33) and longstanding distress (1968-1974-1980) (HR 1.58, 95% CI 1.03-2.45) were independently associated with AD.

Conclusions Our study shows that common psychosocial stressors may have severe and longstanding physiological and psychological consequences. However, more studies are needed to confirm these results and investigate whether more interventions such as stress

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management and behavioral therapy should be initiated in individuals who have experienced psychosocial stressors.

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Article summary

Article focus

To study the relation between psychosocial stressors, longstanding distress and incidence of dementia, in a sample of women followed over 38 years, from mid- to late-life.

Key messages

The study shows that the number of psychosocial stressors, measured in middle-aged women, was related to distress and incidence of AD almost four decades later.

The study also shows that the association between number of psychosocial stressors and AD was independent of longstanding perceived distress.

Strengths and limitations of this study

The strengths of this study include midlife report of psychosocial stressors occurring long before dementia onset, the long follow-up period, the representative population and that multiple sources of information were used to detect and diagnose dementia.

The rating of stressors was related to the last year for some stressors and at any time before 1968 for other stressors. Some stressors were of a short duration, while others were chronic and lasting for many years. We only have information on a limited number of psychosocial stressors in our population. Individuals have different capacities to cope with stress and thus react differently when exposed to the same stressor. We did not have an individual weighting of the included stressors.

Common stressors in relation to longstanding distress and Alzheimer's disease

Introduction

Experiences of severe psychological stressors in adulthood (e.g. combat[1], natural disasters[2] and the Holocaust[3]) are known to influence mental and physical health decades later. More mild psychosocial stressors are common and could be regarded as part of normal life. The long-term consequences of these more common stressors remain unclear. Epidemiological studies in the elderly with follow-ups of less than 10 years have reported that history of early parental death,[4-6] death of spouse[7] and psychosocial risk factors in childhood[6] increase the risk of dementia or Alzheimer's disease (AD). One explanation for the associations may be that traumatic experiences give rise to longstanding chronic distress many years after the trauma. This may lead to a cumulative burden to the brain with dysregulation in neuroendocrine systems.[8-10] A study among Holocaust survivors found that higher levels of stress hormones remained decades after the traumatic experiences.[8]

We have previously reported that longstanding distress in midlife leads to long-term consequences decades later, such as increased risk of dementia, AD[11] and structural brain changes[12]. To our knowledge, no population study has examined if number of psychosocial stressors in midlife increase the risk of dementia in late-life, and whether this is modified by longstanding distress.

The aim of this study was to examine whether common psychosocial stressors in midlife were related to distress, late-life dementia and AD, in women followed over 38 years. We further aimed to examine whether experiences of psychosocial stressors modify the previously reported association between longstanding midlife distress and AD.

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Methods

Study population

This study is part of the Prospective Population Study of Women in Gothenburg, Sweden[13 14] which was initiated in 1968 with an examination of 1462 women (participation rate 90%) born in 1908, 1914, 1918, 1922 and 1930. The individuals were systematically sampled from the Swedish Population Registry based on specific birth dates in order to yield a representative sample at the ages studied. Follow-ups were performed in 1974, 1980, 1992, 2000 and 2005 with participation rates among survivors of 91%, 83%, 70%, 71% and 70% respectively. The Ethics Committee of Gothenburg University approved the study and informed consent was obtained from all participants, in accordance with the provision of the Helsinki Declaration.

The present study included a subsample of 800 women who were systematically selected for a psychiatric examination in 1968. The women were aged 38 years (n=111), 46 years (n=309), 50 years (n=290) and 54 years (n=90). Among them, 713 participated in the follow-up examination in 1974, 639 in 1980, 472 in 1992, 368 in 2000 and 296 in 2005. Losses were mainly due to death.

Assessment of psychosocial stressors

At baseline 1968, eighteen predefined psychosocial stressors were asked and rated by a psychiatrist during the psychiatric examination. These included: divorce, widowhood, serious problem in children (e.g. physical illness, death and 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, problem related to husband's or own work (e.g. lost work) and limited social network. Some

of the 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. The others were rated as occurring at any time prior to the examination in 1968.

Assessment of distress

Symptoms of distress were rated according to a standardized question in 1968, 1974, 1980, 2000 and 2005. The question was worded identically at each examination; "Have you experienced any period of distress (one month or longer) in relation to circumstances in everyday life, such as work, health or family situation? Distress refers to feelings of irritability, tension, nervousness, fear, anxiety or sleep disturbances." Participants were asked to choose between; 0=Have never experienced any period of distress; 1=Have experienced period/s of distress more than five years ago; 2=Have experienced one period of distress during the last five years; 3=Have experienced several periods of distress during the last five years; 4=Have experienced constant distress during the last year; or 5=Have experienced constant distress during the last five years. In the present study, distress is defined as a rating of 3 to 5.

Psychiatric examinations

The psychiatric examinations were performed in 1968, 1974, 1980 and 1992 by psychiatrists and in 2000 and 2005 by experienced psychiatric research nurses. The examinations were semi-structured and included a comprehensive neuropsychiatric examination and an extensive battery of neuropsychiatric tests.[15] Close informant interviews were performed in 1992, 2000 and 2005. These included questions about changes in behaviour and intellectual functions and, in cases of dementia, age of onset and disease course.[15] Medical records were collected

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

Diagnosis of dementia

The diagnosis of dementia 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.[15] Dementia diagnosis at each examination was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) based on the combined information from the psychiatric examination and the close informant interview. Dementia diagnoses for individuals lost to follow-up were based on information from medical records evaluated by geriatric psychiatrists in consensus conferences, and information from the Swedish Hospital Discharge Registry.[16]

AD 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 (NINCDS-ADRDA).[17] The criteria for vascular dementia (VaD) were similar to the criteria proposed by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherce et l´Enseignement en Neurosciences (NINDS-AIREN).[18] VaD was thus 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. Other dementias were diagnosed when other causes were likely to have caused the dementia. 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; or (d) December 31, 2006 for surviving drop-outs.

Potential confounders and mediators

Information on education, socioeconomic status, marital status and work status was obtained at the examination in 1968, and information on blood pressure, antihypertensive medication use, coronary heart disease (CHD), diabetes mellitus, stroke, waist and hip circumferences, cigarette smoking and wine consumption was obtained at the examinations in 1968, 1974 and 1980. Education was dichotomised as compulsory (6 years for those born 1914-1922 and 7 years for those born 1930) versus more than compulsory education. Socioeconomic status was based on husband's occupation for married women, and own occupation for unmarried women and was defined as higher middle, lower middle, skilled workers and unskilled workers.[19] Marital status was classified as married and/or co-habiting versus single. Work status was measured as full-time work and/or part-time work versus no work outside home. Hypertension was defined as systolic blood pressure of 160 mmHg or more, and/or diastolic blood pressure 95 mmHg or more and/or taking antihypertensive medication. CHD was defined as angina pectoris according to the Rose criteria[20] or documented history of myocardial infarction. Diabetes mellitus was defined as a diagnosis told by a doctor, death certificates, being on anti-diabetes drugs or having two fasting blood glucose values of 7.0 mmol/l or more. Stroke was diagnosed based on information from the examinations and the Swedish Hospital Discharge Registry. High waist-to-hip ratio was defined as a ratio of waist and hip circumferences over 0.85. Cigarette smoking was defined as never, former or current smoker. Wine consumption was classified as none, less than once weekly and once weekly or more.

Statistical analyses

Logistic regressions were used to analyse the associations between number of psychosocial stressors in 1968 and report of distress in 1968, 1974, 1980, 2000 and 2005. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs) in three separate models. The 1st model adjusts for age only. The 2nd model adjusts for age, education, socioeconomic status, marital status, work status, hypertension, CHD, stroke, diabetes mellitus, waist-to-hip ratio, smoking and wine consumption. The 3rd model adjusts for age and psychiatric family history, i.e. mental illness in mother, father and/or sibling. (These three variables were then not counted as psychosocial stressors).

Cox regressions were used to study the associations between number of psychosocial stressors and incidence of dementia and dementia subtypes. Associations are presented as hazard ratios (HRs) and 95% CIs, and model 1-3 adjust for the same covariates as listed above. The 4th model adjusts for age and longstanding midlife distress (i.e. distress in all examinations 1968-1974-1980). Two interaction models were also added; (1) number of stressors*psychiatric family in relation to AD and (2) number of stressors*longstanding distress in relation to AD. Finally, we examined the associations between longstanding midlife distress and psychosocial stressors in relation to AD before and after age 75.

Results

Characteristics of the 800 participants are given in Table 1. The proportion of women who reported specific life stressors in 1968 are shown in Table 2. Twenty-five percent of the women reported one psychosocial stressor, 23% reported two stressors, 20% three stressors and 16% four or more stressors. The most frequently reported psychosocial stressor was mental illness in first degree relative (mother 27 %, father 19% and sibling 32%).

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Four hundred and twenty five participants died during follow-up (mean age 79 years). From 1968 to 2006, 153 (19.1%) women developed dementia during 25,131 person-years of follow-up, including 104 with AD, 35 with VaD and 14 with other dementias. The mean time from the baseline examination in 1968 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 years).

Number of psychosocial stressors in 1968 was associated with distress in 1968, 1974, 1980, 2000 and 2005, after adjustment for potential confounders (Table 3). ORs were similar after further adjustment for psychiatric family history in model 3. Number of psychosocial stressors was associated with longstanding midlife distress (i.e. distress in 1968-1974-1980) both in later born cohorts, born 1922 and 1930, (multiadjusted OR 1.32, 95% CI 1.14-1.52) and earlier born cohorts, born 1914 and 1918 (multiadjusted OR 1.58, 95% CI 1.30-1.94).

Number of psychosocial stressors in 1968 was associated with higher incidence of AD (HR 1.21, 95% CI 1.08-1.36) and all-type dementia (HR 1.15, 95% CI 1.05-1.27) (Table 4). The associations remained after adjusting for multiple confounders in model 2, psychiatric family history in model 3 and longstanding distress (i.e. distress in 1968-1974-1980) in model 4. In the 4th model, longstanding distress (HR 1.58, 95% CI 1.01-2.46) and number of psychosocial stressors (HR 1.17, 95% CI 1.02-1.33) were independently associated with AD. There were no interactions between number of stressors and psychiatric family history in relation to AD (age adjusted HR 1.05, 95% CI 0.75-1.45, p=0.79) or between number of stressors and longstanding distress in relation to AD (age adjusted HR 1.04, 95% CI 0.77-1.40, p=0.82). The association between number of psychosocial stressors and incidence of AD were similar

in those with early onset AD (aged <75 years) (multiadjusted HR 1.25, 95% CI 1.02-1.54) and late onset AD (aged ≥75 years) (multiadjusted HR 1.19, 95% CI 1.03-1.38). There were no visible associations between number of psychosocial stressors and VaD in any of the models.

Discussion

We found that number of common psychosocial stressors in midlife was associated with incidence of late-life dementia, especially AD, in a population-based sample of women followed for 38 years. The associations remained when controlling for longstanding distress. We also found that number of psychosocial stressors in 1968 was related to increased level of distress at every examination conducted between 1968 and 2005.

We have previously reported that longstanding distress in midlife increase risk of AD[11] and structural brain changes.[12] These findings are now extended by showing that number of psychosocial stressors and report of distress independently predicted AD, i.e. increased distress could not completely explain the association between midlife stressors and dementia. One reason for this is that individuals respond differently to psychosocial stressors. Thus, biological responses may develop in connection with psychosocial stressors also in individuals who do not experience or report increased distress in association to the stressor.

There may be several biological explanations for the association between psychosocial stressors in midlife and dementia. One is related to the stress hypothesis. Stress may cause a number of physiological reactions in the central nervous, endocrine, immune and cardiovascular systems.[10 21] Thus, psychological stress has been reported to increase the activity of the hypothalamic-pituitary-adrenal axis and the levels of glucocorticoid

hormones,[22] cause structural and functional damage to the hippocampus,[22] influence learning and memory processes,[23] increase the production of pro-inflammatory cytokines in the brain,[10] increase the deposition of β-amyloid peptid and tau-protein in the brain [24-26]and to increase the frequency of cardiovascular disease[27 28], and hypertension.[29] All these factors have been linked to dementia.[30]

The associations between psychosocial stressors reported in midlife and perceived distress later in life was consistent through all follow-up years, as indicated by ORs of similar magnitude. Thus, even common psychosocial stressors (related to work and family) can cause distress over several decades. Our finding is supported by studies reporting that stress-hormones may remain elevated many years after traumatic events.[8] Another explanation is that experiences of psychosocial traumas might make an individual more vulnerable to future stressors due to biological changes and dysfunctional stress coping mechanisms.[31 32]

Strengths and weaknesses of the study

The strengths of this study include midlife report of psychosocial stressors occurring long before dementia onset, the long follow-up period, the representative population and that multiple sources of information were used to detect and diagnose dementia. Some methodological issues need to be considered. First, the rating of stressors was related to the last year for some stressors and at any time before 1968 for other stressors. However, both these were related to the outcome in a similar way (data not shown). Second, some stressors were of a short duration, while others were chronic and lasting for many years. In addition, some stressors were severe and others more trivial. This might give an unbalanced weight among the factors studied. Third, we only have information on a limited number of psychosocial stressors in our population. Some events were not included, e.g. physical abuse

and own severe physical illness. The relationships might thus have been confounded by unmeasured factors. However, it is not likely that this had any major influence on our findings. Fourth, individuals have different capacities to cope with stress and thus react differently when exposed to the same stressor. We did not have an individual weighting of the included stressors. If anything, this might have decreased the strengths of associations. Fifth, some stressors are interrelated, for example mental illness and alcohol abuse in spouse. However these stressors independently increased stress reactions (data not shown). We therefore decided not to merge them. Sixth, distress in our study was based on self-report and we did not include an objective measure of stress reactions. However, most epidemiological studies use subjective report to assess stress or distress. Seventh, there are a number of risk factors occurring between baseline and development of dementia and these might potentially modify the association between common psychosocial stressors in midlife and dementia. However, these risk factors would most likely decrease the possibility to find associations in a study with long follow-up, as may exert competing risk, and controlling for future factors might lead to an over-adjustment. Eight, psychiatric family history may have an impact on the predisposition to distress and dementia. However, after adjust for psychiatric family history (i.e. mental illness in mother, father and/or sibling) the associations between number of stressors was still associated with both longstanding distress, AD and all-type dementia. Ninth, 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 women detected in the different age groups is what

could be expected from other incidence studies.[33] Finally, 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. Furthermore, cerebrovascular disease may influence the presence and severity of clinical symptoms of AD, and vice versa.[34] 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, and mixed types are probably common.

Conclusion

To conclude, psychosocial stressors in midlife were associated with incidence of AD and longstanding distress, over several decades. This suggests that common psychosocial stressors may have severe and longstanding physiological and psychological consequences. However, more studies are needed to confirm these results and investigate whether more interventions such as stress management and behavioral therapy should be initiated in individuals who have experienced psychosocial stressors.

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Common stressors in relation to longstanding distress and Alzheimer's disease

Table 1 Characteristics of the study sample (N=800)

	N	%
Birth year (age)		
1914 (54 year)	89	11.1
1918 (50 year)	291	36.4
1922 (46 year)	309	38.6
1930 (38 year)	111	13.9
Education[a]		
Compulsory	600	75.0
More than compulsory	200	25.0
Socioeconomic status[a]		
Upper middle	161	20.2
Lower middle	267	33.4
Skilled workers	209	26.1
Unskilled workers	163	20.4
Marital status[a]		
Married	638	79.8
Co-habited (not married)	94	11.7
Living alone (not married)	68	8.5
Work status[a]		
Full-time work	270	33.8
Part-time work	258	32.3
No work outside home	272	34.0
Hypertension[b]	144	18.0
Coronary heart disease[b]	74	9.3
Diabetes mellitus[b]	24	3.0
Stroke[b]	5	0.5
Smoking[b]	341	42.6
Wine consumption[b]	246	30.8
High waist-to-hip ratio[b]	210	26.3

[a]Measured in 1968, [b]Measured in 1968, 1974 and 1980

Common stressors in relation to longstanding distress and Alzheimer's disease

Table 2 Prevalence of psychosocial stressors in women in 1968 (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
Number of psychosocial stressors		
0 psychosocial stressor	149	18.6
1 psychosocial stressor	197	24.6
2 psychosocial stressors	184	23.0
3 psychosocial stressors	143	19.9
4 psychosocial stressors	69	8.6
≥5 psychosocial stressors	58	7.2

Table 3 Number of psychosocial stressors in 1968 in relations to report of distress in 1968, 1974, 1980, 2000 and 2005

	Cases, n (%)	Model 1	Model 2	Model 3
Distress in 1968	148 (18.5)	1.46 (1.30-1.63)	1.49 (1.31-1.70)	1.61 (1.22-2.13)
Distress in 1974	161 (20.1)	1.31 (1.18-1.46)	1.33 (1.17-1.50)	1.23 (1.05-1.44)
Distress in 1980	88 (11.0)	1.26 (1.10-1.43)	1.26 (1.08-1.47)	1.22 (1.00-1.50)
Distress in 2000	49 (6.1)	1.41 (1.17-1.72)	1.40 (1.13-1.74)	1.24 (0.95-1.64)
Distress in 2005	39 (2.6)	1.37 (1.05-1.80)	1.35 (1.00-1.85)	1.50 (1.05-2.20)

Logistic regression analyses presented as ORs with 95% CIs; Model 1 adjust for age, and: Model 2 adjust for age, education, socioeconomic status, marital status, work status at baseline (in 1968), and hypertension, CHD, stroke, diabetes mellitus, high waist-to-hip ratio, smoking and wine consumption (in 1968-80), and Model 3 adjust for age and psychiatric family history (mental illness in mother, father and/or sibling is not included in number psychosocial stressors).

Table 4 Number of psychosocial stressors in 1968 in relation to incidence of dementia over 38 years

	Cases n (%)	Model 1	Model 2	Model 3	Model 4
All-type dementia	153 (19.1)	1.15 (1.05-1.27)	1.16 (1.04-1.30)	1.10 (1.00-1.25)	1.13 (1.01-1.26)
Vascular dementia	35 (4.4)	0.94 (0.75-1.19)	0.97 (0.75-1.26)	0.79 (0.57-1.10)	0.93 (0.71-1.22)
Alzheimer's disease	104 (13.0)	1.21 (1.08-1.36)	1.21 (1.06-1.38)	1.16 (1.00-1.35)	1.17 (1.02-1.33)

Cox regression analyses presented as HRs with 95% CIs; Model 1 adjust for age; Model 2 adjust for age, education, socioeconomic status, marital status, work status at baseline (in 1968), and hypertension, CHD, stroke, diabetes mellitus, high waist-to-hip ratio, smoking, and wine consumption (in 1968-80); Model 3 adjust for age and psychiatric family history (mental illness in mother, father and/or sibling is not included in number psychosocial stressors), and; Model 4 adjust for age and longstanding distress (in 1968-80).

Common stressors in relation to longstanding distress and Alzheimer's disease

Title page

Title: Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: a 38 year longitudinal population study

Authors´ names: Lena Johansson, Xinxin Guo, Tore Hällström, Maria C Norton, Margda Waern, Svante Östling, Calle Bengtsson, Ingmar Skoog

Address for each author: Neuropsychiatric Epidemiology Unit, Institute of Neuroscience and Physiology, Sahlgrenska Academy at Gothenburg University, Wallinsgatan 6, S-431 41 Mölndal, Sweden Lena Johansson researchers Xinxin Guo researcher, Tore Hällström professor emeritus, Margda Waern professor, Svante Östling associate professor, Ingmar Skoog professor Department of Clinical Neuroscience, Section for Psychiatry/Huddinge, Karolinska Institutet, Stockholm, Sweden Tore Hällström professor emeritus Department of Family Consumer and Human Development and Departments of Psychology, Utah State University, Logan, USA Maria Norton associate professor Sahlgrenska School of Public Health and Community Medicine, Section for Public Health Epidemiology, the Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden Calle Bengtsson professor emeritus

Correspondence to: lena.johansson@neuro.gu.se

Common stressors in relation to longstanding distress and Alzheimer's disease

Abstract

Objective To study the relation between psychosocial stressors, longstanding distress and incidence of dementia, in a sample of women followed from midlife to late-life.

Design Prospective longitudinal population study.

Setting and Participants The study is part of the Prospective Population Study of Women in Gothenburg, Sweden, which started in 1968 with subsequent follow-ups in 1974, 1980, 1992, 2000 and 2005. At baseline, 800 women aged 38-54 years (born in 1914, 1918, 1922 and 1930), rated 18 psychosocial stressors (e.g. divorce, widowhood, work problems and illness in relative).

Primary and secondary outcome measures: Symptoms of distress were measured according to a standardised question at each study wave. Dementia was diagnosed according to DSM-III-R and Alzheimer's disease (AD) according to NINCD-ADRDA.

Results During the 37-years follow-up 153 women developed dementia (104 of those had AD). Number of psychosocial stressors in 1968 was associated (HR, 95% CI) with higher incidence of dementia (1.15, 1.04-1.27) and AD (1.20, 1.07-1.35) between 1968 and 2005, in multivariate Cox regressions. Number of psychosocial stressors in 1968 was also associated (OR, 95% CI) with distress in 1968 (1.48, 1.32-1.67), 1974 (1.31, 1.17-1.46), 1980 (1.27, 1.11-1.45), 2000 (1.39, 1.14-1.70) and 2005 (1.35, 1.02-1.79), in multivariate logistic regressions. Number of psychosocial stressors (HR 1.17, 95% CI 1.03-1.33) and longstanding distress (1968-1974-1980) (HR 1.58, 95% CI 1.03-2.45) were independently associated with AD.

Conclusions Our study shows that common psychosocial stressors may have severe and longstanding physiological and psychological consequences. However, more studies are needed to confirm these results and investigate whether more interventions such as stress

management and behavioral therapy should be initiated in individuals who have experienced psychosocial stressors.

Common stressors in relation to longstanding distress and Alzheimer's disease

Article summary

Article focus

To study the relation between psychosocial stressors, longstanding distress and incidence of dementia, in a sample of women followed over 38 years, from mid- to late-life.

Key messages

The study shows that the number of psychosocial stressors, measured in middle-aged women, was related to distress and incidence of AD almost four decades later.

The study also shows that the association between number of psychosocial stressors and AD was independent of longstanding perceived distress.

Strengths and limitations of this study

The strengths of this study include midlife report of psychosocial stressors occurring long before dementia onset, the long follow-up period, the representative population and that multiple sources of information were used to detect and diagnose dementia.

The rating of stressors was related to the last year for some stressors and at any time before 1968 for other stressors. Some stressors were of a short duration, while others were chronic and lasting for many years. We only have information on a limited number of psychosocial stressors in our population. Individuals have different capacities to cope with stress and thus react differently when exposed to the same stressor. We did not have an individual weighting of the included stressors.

Common stressors in relation to longstanding distress and Alzheimer's disease

Introduction

Experiences of severe psychological stressors in adulthood (e.g. combat[1], natural disasters[2] and the Holocaust[3]) are known to influence mental and physical health decades later. More mild psychosocial stressors are common and could be regarded as part of normal life. The long-term consequences of these more common stressors remain unclear. Epidemiological studies in the elderly with follow-ups of less than 10 years have reported that history of early parental death,[4-6] death of spouse[7] and psychosocial risk factors in childhood[6] increase the risk of dementia or Alzheimer's disease (AD). One explanation for the associations may be that traumatic experiences give rise to longstanding chronic distress many years after the trauma. This may lead to a cumulative burden to the brain with dysregulation in neuroendocrine systems.[8-10] A study among Holocaust survivors found that higher levels of stress hormones remained decades after the traumatic experiences.[8]

We have previously reported that longstanding distress in midlife leads to long-term consequences decades later, such as increased risk of dementia, AD[11] and structural brain changes[12]. To our knowledge, no population study has examined if number of psychosocial stressors in midlife increase the risk of dementia in late-life, and whether this is modified by longstanding distress.

The aim of this study was to examine whether common psychosocial stressors in midlife were related to distress, late-life dementia and AD, in women followed over 38 years. We further aimed to examine whether experiences of psychosocial stressors modify the previously reported association between longstanding midlife distress and AD.

Common stressors in relation to longstanding distress and Alzheimer's disease

Methods

Study population

This study is part of the Prospective Population Study of Women in Gothenburg, Sweden[13 14] which was initiated in 1968 with an examination of 1462 women (participation rate 90%) born in 1908, 1914, 1918, 1922 and 1930. The individuals were systematically sampled from the Swedish Population Registry based on specific birth dates in order to yield a representative sample at the ages studied. Follow-ups were performed in 1974, 1980, 1992, 2000 and 2005 with participation rates among survivors of 91%, 83%, 70%, 71% and 70% respectively. The Ethics Committee of Gothenburg University approved the study and informed consent was obtained from all participants, in accordance with the provision of the Helsinki Declaration.

The present study included a subsample of 800 women who were systematically selected for a psychiatric examination in 1968. The women were aged 38 years (n=111), 46 years (n=309), 50 years (n=290) and 54 years (n=90). Among them, 713 participated in the follow-up examination in 1974, 639 in 1980, 472 in 1992, 368 in 2000 and 296 in 2005. Losses were mainly due to death.

Assessment of psychosocial stressors

At baseline 1968, eighteen predefined psychosocial stressors were asked and rated by a psychiatrist during the psychiatric examination. These included: divorce, widowhood, serious problem in children (e.g. physical illness, death and 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, problem related to husband's or own work (e.g. lost work) and limited social network. Some

of the 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. The others were rated as occurring at any time prior to the examination in 1968.

Assessment of distress

Symptoms of distress were rated according to a standardized question in 1968, 1974, 1980, 2000 and 2005. The question was worded identically at each examination; "Have you experienced any period of distress (one month or longer) in relation to circumstances in everyday life, such as work, health or family situation? Distress refers to feelings of irritability, tension, nervousness, fear, anxiety or sleep disturbances." Participants were asked to choose between; 0=Have never experienced any period of distress; 1=Have experienced period/s of distress more than five years ago; 2=Have experienced one period of distress during the last five years; 3=Have experienced several periods of distress during the last five years; 4=Have experienced constant distress during the last year; or 5=Have experienced constant distress during the last five years. In the present study, distress is defined as a rating of 3 to 5.

Psychiatric examinations

The psychiatric examinations were performed in 1968, 1974, 1980 and 1992 by psychiatrists and in 2000 and 2005 by experienced psychiatric research nurses. The examinations were semi-structured and included a comprehensive neuropsychiatric examination and an extensive battery of neuropsychiatric tests.[15] Close informant interviews were performed in 1992, 2000 and 2005. These included questions about changes in behaviour and intellectual functions and, in cases of dementia, age of onset and disease course.[15] Medical records were collected

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

Diagnosis of dementia

The diagnosis of dementia 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.[15] Dementia diagnosis at each examination was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) based on the combined information from the psychiatric examination and the close informant interview. Dementia diagnoses for individuals lost to follow-up were based on information from medical records evaluated by geriatric psychiatrists in consensus conferences, and information from the Swedish Hospital Discharge Registry.[16]

AD 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 (NINCDS-ADRDA).[17] The criteria for vascular dementia (VaD) were similar to the criteria proposed by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherce et l´Enseignement en Neurosciences (NINDS-AIREN).[18] VaD was thus 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. Other dementias were diagnosed when other causes were likely to have caused the dementia. 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; or (d) December 31, 2006 for surviving drop-outs.

Potential confounders and mediators

Information on education, socioeconomic status, marital status and work status was obtained at the examination in 1968, and information on blood pressure, antihypertensive medication use, coronary heart disease (CHD), diabetes mellitus, stroke, waist and hip circumferences, cigarette smoking and wine consumption was obtained at the examinations in 1968, 1974 and 1980. Education was dichotomised as compulsory (6 years for those born 1914-1922 and 7 years for those born 1930) versus more than compulsory education. Socioeconomic status was based on husband's occupation for married women, and own occupation for unmarried women and was defined as higher middle, lower middle, skilled workers and unskilled workers.[19] Marital status was classified as married and/or co-habiting versus single. Work status was measured as full-time work and/or part-time work versus no work outside home. Hypertension was defined as systolic blood pressure of 160 mmHg or more, and/or diastolic blood pressure 95 mmHg or more and/or taking antihypertensive medication. CHD was defined as angina pectoris according to the Rose criteria[20] or documented history of myocardial infarction. Diabetes mellitus was defined as a diagnosis told by a doctor, death certificates, being on anti-diabetes drugs or having two fasting blood glucose values of 7.0 mmol/l or more. Stroke was diagnosed based on information from the examinations and the Swedish Hospital Discharge Registry. High waist-to-hip ratio was defined as a ratio of waist and hip circumferences over 0.85. Cigarette smoking was defined as never, former or current smoker. Wine consumption was classified as none, less than once weekly and once weekly or more.

Statistical analyses

Logistic regressions were used to analyse the associations between number of psychosocial stressors in 1968 and report of distress in 1968, 1974, 1980, 2000 and 2005. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs) in three separate models. The 1st model adjusts for age only. The 2nd model adjusts for age, education, socioeconomic status, marital status, work status, hypertension, CHD, stroke, diabetes mellitus, waist-to-hip ratio, smoking and wine consumption. The 3rd model adjusts for age and psychiatric family history, i.e. mental illness in mother, father and/or sibling. (These three variables were then not counted as psychosocial stressors).

Cox regressions were used to study the associations between number of psychosocial stressors and incidence of dementia and dementia subtypes. Associations are presented as hazard ratios (HRs) and 95% CIs, and model 1-3 adjust for the same covariates as listed above. The 4th model adjusts for age and longstanding midlife distress (i.e. distress in all examinations 1968-1974-1980). Two interaction models were also added; (1) number of stressors*psychiatric family in relation to AD and (2) number of stressors*longstanding distress in relation to AD. Finally, we examined the associations between longstanding midlife distress and psychosocial stressors in relation to AD before and after age 75.

Results

Characteristics of the 800 participants are given in Table 1. The proportion of women who reported specific life stressors in 1968 are shown in Table 2. Twenty-five percent of the women reported one psychosocial stressor, 23% reported two stressors, 20% three stressors and 16% four or more stressors. The most frequently reported psychosocial stressor was mental illness in first degree relative (mother 27 %, father 19% and sibling 32%).

Common stressors in relation to longstanding distress and Alzheimer's disease

Four hundred and twenty five participants died during follow-up (mean age 79 years). From 1968 to 2006, 153 (19.1%) women developed dementia during 25,131 person-years of follow-up, including 104 with AD, 35 with VaD and 14 with other dementias. The mean time from the baseline examination in 1968 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 years).

Number of psychosocial stressors in 1968 was associated with distress in 1968, 1974, 1980, 2000 and 2005, after adjustment for potential confounders (Table 3). ORs were similar after further adjustment for psychiatric family history in model 3. Number of psychosocial stressors was associated with longstanding midlife distress (i.e. distress in 1968-1974-1980) both in later born cohorts, born 1922 and 1930, (multiadjusted OR 1.32, 95% CI 1.14-1.52) and earlier born cohorts, born 1914 and 1918 (multiadjusted OR 1.58, 95% CI 1.30-1.94).

Number of psychosocial stressors in 1968 was associated with higher incidence of AD (HR 1.21, 95% CI 1.08-1.36) and all-type dementia (HR 1.15, 95% CI 1.05-1.27) (Table 4). The associations remained after adjusting for multiple confounders in model 2, psychiatric family history in model 3 and longstanding distress (i.e. distress in 1968-1974-1980) in model 4. In the 4th model, longstanding distress (HR 1.58, 95% CI 1.01-2.46) and number of psychosocial stressors (HR 1.17, 95% CI 1.02-1.33) were independently associated with AD. There were no interactions between number of stressors and psychiatric family history in relation to AD (age adjusted HR 1.05, 95% CI 0.75-1.45, p=0.79) or between number of stressors and longstanding distress in relation to AD (age adjusted HR 1.04, 95% CI 0.77-1.40, p=0.82). The association between number of psychosocial stressors and incidence of AD were similar

in those with early onset AD (aged <75 years) (multiadjusted HR 1.25, 95% CI 1.02-1.54) and late onset AD (aged ≥75 years) (multiadjusted HR 1.19, 95% CI 1.03-1.38). There were no visible associations between number of psychosocial stressors and VaD in any of the models.

Discussion

We found that number of common psychosocial stressors in midlife was associated with incidence of late-life dementia, especially AD, in a population-based sample of women followed for 38 years. The associations remained when controlling for longstanding distress. We also found that number of psychosocial stressors in 1968 was related to increased level of distress at every examination conducted between 1968 and 2005.

We have previously reported that longstanding distress in midlife increase risk of AD[11] and structural brain changes.[12] These findings are now extended by showing that number of psychosocial stressors and report of distress independently predicted AD, i.e. increased distress could not completely explain the association between midlife stressors and dementia. One reason for this is that individuals respond differently to psychosocial stressors. Thus, biological responses may develop in connection with psychosocial stressors also in individuals who do not experience or report increased distress in association to the stressor.

There may be several biological explanations for the association between psychosocial stressors in midlife and dementia. One is related to the stress hypothesis. Stress may cause a number of physiological reactions in the central nervous, endocrine, immune and cardiovascular systems.[10 21] Thus, psychological stress has been reported to increase the activity of the hypothalamic-pituitary-adrenal axis and the levels of glucocorticoid

hormones,[22] cause structural and functional damage to the hippocampus,[22] influence learning and memory processes,[23] increase the production of pro-inflammatory cytokines in the brain,[10] increase the deposition of β-amyloid peptid and tau-protein in the brain [24-26]and to increase the frequency of cardiovascular disease[27 28], and hypertension.[29] All these factors have been linked to dementia.[30]

The associations between psychosocial stressors reported in midlife and perceived distress later in life was consistent through all follow-up years, as indicated by ORs of similar magnitude. Thus, even common psychosocial stressors (related to work and family) can cause distress over several decades. Our finding is supported by studies reporting that stress-hormones may remain elevated many years after traumatic events.[8] Another explanation is that experiences of psychosocial traumas might make an individual more vulnerable to future stressors due to biological changes and dysfunctional stress coping mechanisms.[31 32]

Strengths and weaknesses of the study

The strengths of this study include midlife report of psychosocial stressors occurring long before dementia onset, the long follow-up period, the representative population and that multiple sources of information were used to detect and diagnose dementia. Some methodological issues need to be considered. First, the rating of stressors was related to the last year for some stressors and at any time before 1968 for other stressors. However, both these were related to the outcome in a similar way (data not shown). Second, some stressors were of a short duration, while others were chronic and lasting for many years. In addition, some stressors were severe and others more trivial. This might give an unbalanced weight among the factors studied. Third, we only have information on a limited number of psychosocial stressors in our population. Some events were not included, e.g. physical abuse

and own severe physical illness. The relationships might thus have been confounded by unmeasured factors. However, it is not likely that this had any major influence on our findings. Fourth, individuals have different capacities to cope with stress and thus react differently when exposed to the same stressor. We did not have an individual weighting of the included stressors. If anything, this might have decreased the strengths of associations. Fifth, some stressors are interrelated, for example mental illness and alcohol abuse in spouse. However these stressors independently increased stress reactions (data not shown). We therefore decided not to merge them. Sixth, distress in our study was based on self-report and we did not include an objective measure of stress reactions. However, most epidemiological studies use subjective report to assess stress or distress. Seventh, there are a number of risk factors occurring between baseline and development of dementia and these might potentially modify the association between common psychosocial stressors in midlife and dementia. However, these risk factors would most likely decrease the possibility to find associations in a study with long follow-up, as may exert competing risk, and controlling for future factors might lead to an over-adjustment. Eight, psychiatric family history may have an impact on the predisposition to distress and dementia. However, after adjust for psychiatric family history (i.e. mental illness in mother, father and/or sibling) the associations between number of stressors was still associated with both longstanding distress, AD and all-type dementia. Ninth, 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 women detected in the different age groups is what

could be expected from other incidence studies.[33] Finally, 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. Furthermore, cerebrovascular disease may influence the presence and severity of clinical symptoms of AD, and vice versa.[34] 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, and mixed types are probably common.

Conclusion

To conclude, psychosocial stressors in midlife were associated with incidence of AD and longstanding distress, over several decades. This suggests that common psychosocial stressors may have severe and longstanding physiological and psychological consequences. However, more studies are needed to confirm these results and investigate whether more interventions such as stress management and behavioral therapy should be initiated in individuals who have experienced psychosocial stressors.

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Table 1 Characteristics of the study sample (N=800)

	N	%
Birth year (age)		
1914 (54 year)	89	11.1
1918 (50 year)	291	36.4
1922 (46 year)	309	38.6
1930 (38 year)	111	13.9
Education[a]		
Compulsory	600	75.0
More than compulsory	200	25.0
Socioeconomic status[a]		
Upper middle	161	20.2
Lower middle	267	33.4
Skilled workers	209	26.1
Unskilled workers	163	20.4
Marital status[a]		
Married	638	79.8
Co-habited (not married)	94	11.7
Living alone (not married)	68	8.5
Work status[a]		
Full-time work	270	33.8
Part-time work	258	32.3
No work outside home	272	34.0
Hypertension[b]	144	18.0
Coronary heart disease[b]	74	9.3
Diabetes mellitus[b]	24	3.0
Stroke[b]	5	0.5
Smoking[b]	341	42.6
Wine consumption[b]	246	30.8
High waist-to-hip ratio[b]	210	26.3

[a]Measured in 1968, [b]Measured in 1968, 1974 and 1980

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Table 2 Prevalence of psychosocial stressors in women in 1968 (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
Number of psychosocial stressors		
0 psychosocial stressor	149	18.6
1 psychosocial stressor	197	24.6
2 psychosocial stressors	184	23.0
3 psychosocial stressors	143	19.9
4 psychosocial stressors	69	8.6
≥5 psychosocial stressors	58	7.2

Table 3 Number of psychosocial stressors in 1968 in relations to report of distress in 1968, 1974, 1980, 2000 and 2005

	Cases, n (%)	Model 1	Model 2	Model 3
Distress in 1968	148 (18.5)	1.46 (1.30-1.63)	1.49 (1.31-1.70)	1.61 (1.22-2.13)
Distress in 1974	161 (20.1)	1.31 (1.18-1.46)	1.33 (1.17-1.50)	1.23 (1.05-1.44)
Distress in 1980	88 (11.0)	1.26 (1.10-1.43)	1.26 (1.08-1.47)	1.22 (1.00-1.50)
Distress in 2000	49 (6.1)	1.41 (1.17-1.72)	1.40 (1.13-1.74)	1.24 (0.95-1.64)
Distress in 2005	39 (2.6)	1.37 (1.05-1.80)	1.35 (1.00-1.85)	1.50 (1.05-2.20)

Logistic regression analyses presented as ORs with 95% CIs; Model 1 adjust for age, and: Model 2 adjust for age, education, socioeconomic status, marital status, work status at baseline (in 1968), and hypertension, CHD, stroke, diabetes mellitus, high waist-to-hip ratio, smoking and wine consumption (in 1968-80), and Model 3 adjust for age and psychiatric family history (mental illness in mother, father and/or sibling is not included in number psychosocial stressors).

Table 4 Number of psychosocial stressors in 1968 in relation to incidence of dementia over 38 years

	Cases n (%)	Model 1	Model 2	Model 3	Model 4
All-type dementia	153 (19.1)	1.15 (1.05-1.27)	1.16 (1.04-1.30)	1.10 (1.00-1.25)	1.13 (1.01-1.26)
Vascular dementia	35 (4.4)	0.94 (0.75-1.19)	0.97 (0.75-1.26)	0.79 (0.57-1.10)	0.93 (0.71-1.22)
Alzheimer's disease	104 (13.0)	1.21 (1.08-1.36)	1.21 (1.06-1.38)	1.16 (1.00-1.35)	1.17 (1.02-1.33)

Cox regression analyses presented as HRs with 95% CIs; Model 1 adjust for age; Model 2 adjust for age, education, socioeconomic status, marital status, work status at baseline (in 1968), and hypertension, CHD, stroke, diabetes mellitus, high waist-to-hip ratio, smoking, and wine consumption (in 1968-80); Model 3 adjust for age and psychiatric family history (mental illness in mother, father and/or sibling is not included in number psychosocial stressors), and; Model 4 adjust for age and longstanding distress (in 1968-80).