Midlife personality and risk of Alzheimer's disease and distress: a 38 year follow-up

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Has access to all the data and take responsibility for the data, accuracy of the data analysis, and the conduct of the research. Have the right to publish any and all data, separate and apart from the guidance of any sponsor of the research.

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ABSTRACT

Objective To study the association between midlife neuroticism and extraversion and development of late-life dementia and longstanding distress in a sample of women followed for 38 years.

Methods A population-based sample of 800 women, aged 38 to 54 years, was examined in 1968, with subsequent examinations in 1974, 1980, 1992, 2000 and 2005. Neuroticism and extraversion were assessed by the Eysenck Personality Inventory (EPI) at baseline. Distress was measured according to a standardised question at each study wave. Dementia was diagnosed according to DSM-III-R criteria based on information from neuropsychiatric examinations, informant interviews, hospital records and registry data.

Results During the 38-year follow-up 153 women developed dementia; Alzheimer's disease (AD) dementia was diagnosed in 104 of these. A higher degree of neuroticism in midlife was associated with increased risk of AD dementia and longstanding distress over 38 years. The association between neuroticism and AD dementia diminished after adjusting for longstanding distress. Extraversion was associated with a lower degree of longstanding distress, but had no impact on AD dementia. When the two personality dimensions were combined, high neuroticism/low extraversion had highest risk of AD dementia.

Conclusions Our study suggests that midlife neuroticism is associated with increased risk of AD dementia, and that distress mediates this association. Results have clinical implications; a group of women at risk for AD dementia is identified.

INTRODUCTION

The number of people with dementia disorders is expected to increase dramatically with global aging.[1] It is therefore important to identify risk and protective factors for these disorders. Most interest has been devoted to extrinsic factors, such as education, vascular risk factors and head trauma. Interest has also been devoted to intrinsic factors, mainly family history and genetic factors. Another intrinsic factor is personality. Personality is defined as "an individual's unique variation on the general evolutionary design for human nature, expressed as a developing pattern of dispositional traits, characteristic adaptations, and integrative life stories complexly and differentially situated in culture".[2] We focus here on one element of personality, dispositional traits, defined as stable patterns of behaving, thinking and feeling that influence interpersonal relations. Personality may influence the individual's risk for dementia through its effect on behavior, lifestyle, or reactions to stress. Several studies report that neuroticism is associated with cognitive decline,[3] dementia[4] and Alzheimer's disease (AD)[5-10] However, these studies were cross-sectional or had short follow-up. Thus, personality might have been affected by incipient dementia in these studies, and therefore, findings could be subject to reverse causality.

We have previously reported that longstanding distress in midlife increases the risk for dementia, AD dementia and age-related brain changes, and that psychosocial stressors in midlife were associated with increased risk for AD dementia.[11-13] In this study, we examine the relationship between midlife neuroticism and extraversion, and development of late-life dementia in a population-based sample of women with a mean age of 46 years at baseline and followed over 38 years. We also examine the relationship between personality and longstanding distress, and whether this modified the impact of personality on the risk of dementia.

METHODS

Study population

The psychiatric part of the Prospective Population Study of Women in Gothenburg, Sweden was initiated in 1968 with 800 women (participation rate 89%) born in 1914, 1918, 1922 and 1930.[13-15] The individuals were systematically sampled from the Swedish Population Register based on specific birth dates in order to yield a representative sample at the ages studied. The women were aged 38 years (n=111), 46 years (n=309), 50 years (n=290) and 54 years (n=90). Among them, 677 participated in a follow-up examinations in 1974 (response rate among survivors 85%), 629 (87%) in 1980, 371 (67%) in 1992, 363 (73%) in 2000 and 293 (74%) in 2005. Losses were mainly due to death. Four hundred and twenty-six participants died during follow-up.

Standard Protocol Approvals, Registrations and Patient Consents

The Ethics Committee for Medical Research at University of Gothenburg approved the study and informed consent was obtained from all participants, in accordance with the provisions of the Helsinki Declaration.

Assessment of personality

At baseline 1968, the Eysenck Personality Inventory (EPI) was used to measure the personality dimensions neuroticism-stability and extraversion-introversion, each including 24 dichotomous items.[16] The neuroticism scale assesses emotional reactivity, anxiety and psychosomatic concerns, ego-strength and guilt proneness. The extraversion scale assesses sociability and positive affect.[17] Comparisons between the EPI dimensions of neuroticism and extraversion and the corresponding dimensions within the five-factory model of personality show that the two different systems match well.[18]

Assessment and diagnosis of dementia

Neuropsychiatric examinations were performed in 1968, 1974, 1980 and 1992 by psychiatrists and in 2000 and 2005 by experienced psychiatric nurses. The examinations were semi-structured and included comprehensive psychiatric interviews, observations of mental symptoms and an extensive battery of neuropsychiatric tests.[19,20] *Close informant interviews* were performed in 1992, 2000 and 2005. The interviews were semi-structured and comprised questions about changes in behaviour and intellectual function, psychiatric symptoms, activities of daily living and, in cases of dementia, age of onset and disease course.[19, 20] *Medical records* were collected from all inpatient and outpatient departments and general practitioners' offices in Gothenburg for all women. *The Swedish Hospital Discharge Registry* provided diagnostic information for all individuals discharged from hospitals on a nationwide basis since 1978.

The diagnosis of dementia at each examination was based on the combined information from the neuropsychiatric examinations and the close informant interview according to the Diagnostic and Statistic Manual of Mental Disorders (DSM-III-R criteria).[21] For individuals lost to follow-up, the diagnosis was based on information from medical records evaluated by geriatric psychiatrists in consensus conferences, and the Swedish Hospital Discharge Registry.[19] The diagnoses had to be compatible with the DSM-III-R criteria. Dementia subtypes were determined by geriatric psychiatrists. Probable or possible AD dementia 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).[22] The criteria for vascular dementia were similar to the criteria proposed by the National Institute of Neurological Disorders and Stroke and the

Association Internationale pour la Recherce et l´Enseignement en Neurosciences (NINDS-AIREN).[23] Vascular dementia was diagnosed when there was a temporal relationship (within 1 year) between a history of acute focal neurological symptoms and signs (hemiparesis or motor aphasia) and the first symptoms of dementia. 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) time of dementia onset; (b) the date of death according to the Swedish Population Register; (c) the date of the last follow-up examination for participants in 2005; or (d) December 31, 2006 for surviving drop-outs. The diagnostic procedures have been described in detail previously.[20]

Assessment of distress

Self-reported distress was assessed at the examinations in 1968, 1974, 1980, 2000 and 2005. The question was; "Have you experienced any period of stress (one month or longer) in relation to circumstances in everyday life, such as work, health, or family situation? Stress referred to feelings of irritability, tension, nervousness, fear, anxiety or sleep disturbances." Participants were asked to choose; "0: Have never experienced any period of stress; 1: Have experienced period/s of stress more than five years ago; 2: Have experienced one period of stress during the last five years; 3: Have experienced several periods of stress during the last five years; 4: Have experienced constant stress during the last year; or 5: Have experienced constant stress during the last five years". For the purpose of this study, women who acknowledged responses 3, 4 or 5 were considered to have distress.

Assessment of potential confounders

Information on education, blood pressure, antihypertensive medication use, myocardial infarction, angina pectoris, cigarette smoking, waist and hip circumferences, and depression

were obtained at baseline in 1968. Education was dichotomized as compulsory (6 years for those born in 1908-1922, and 7 years for those born in 1930) vs. education beyond compulsory level. Hypertension was defined as systolic blood pressure ≥160mmHg and/or diastolic blood pressure ≥95mmHg and/or taking antihypertensive medications. Coronary heart disease (CHD) was defined as fulfilling one or more of the following criteria: angina pectoris according to the Rose criteria,[24] 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.[25] Cigarette smoking was defined as never vs. former and current smoker. Body mass index (BMI) was calculated by using the formula kg/m2. Diagnoses of depression were diagnosed according to DSM-III criteria for major depressive disorders.[26] In addition, Apolipoprotein E (ApoE) allele status has been measured in a sub-sample of women with genotype data. ApoE genotype was dichotomized into E4 allele present or absent.

Statistical analyses

Mean value, standard deviation (SD), median and skewness were determined for the neuroticism and extraversion scales. Spearman coefficient tested the correlation between neuroticism and extraversion. Logistic regression models were used to study the association between personality in 1968 and distress in 1968, 1974, 1980, 2000 and 2005. The associations are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The 1st model adjusted for age only and the 2nd model adjusted for age, education, hypertension, CHD, smoking and BMI. The Log-minus-log test analyzed the distribution of dementia cases over the study period. Cox regression analyses were used to test the relationship between neuroticism/extraversion at baseline and incidence of dementia. The associations are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) in three separate models.

The 1st model adjusted for age only. The 2nd model adjusted for age, education, hypertension, CHD, smoking, BMI and depression. The 3rd model adjusted for all variables in the second model and for longstanding distress (i.e. report of distress in one or more examination 1968, 1974 and 1980). In sub-analyses; we stratified by early onset and late onset AD dementia (i.e. onset before vs. after age 75); excluded cases diagnosed with AD dementia before 1992; controlled for ApoE4 allele status; and stratified by experience of longstanding distress. We also examined relationships between neuroticism score quartiles and AD dementia in regression models. Finally, the combined effect of neuroticism and extraversion in risk of AD dementia were tested. The lowest and highest quartiles in the personality scales were then combined into four groups: (1) Low neuroticism/high extraversion, (2) Low neuroticism/low extraversion, (3) High neuroticism/high extraversion and (4) High neuroticism/low extraversion.

RESULTS

Characteristics of the 800 participants are presented in Table 1. From 1968 to 2006, 153 (19%) women developed dementia during 25,131 person-years of follow-up, including 104 with AD, 35 with vascular dementia 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). Log-minus-log test showed a linear distribution of dementia over the study period.

The mean value of neuroticism was 8.1 ± SD 4.6 (median 8, skewness 0.55) and the mean of extraversion was 11.3 ± SD 3.3 (median 11, skewness 0.07). Neuroticism and extraversion scores were significantly correlated (r_s-0.24; *p* 0.001). Perceived distress was reported by 19%

of the women in 1968, 23% in 1974, 14% in 1980, 18% in 2000 and 12% in 2005. Table 2 shows that higher neuroticism in 1968 was associated with distress in 1968, 1974, 1980, 2000 and 2005, and that extraversion was associated with lower distress in 1968, 1974, 1980 and 2000.

Table 3 shows that higher scores of neuroticism were associated with increased risk of AD dementia (multi adjusted HR per point increase in score: 1.04, 95% CI 1.00-1.08, *p* 0.046), but not with all-type dementias or vascular dementia (model 1 and 2). The associations between neuroticism and AD dementia were essentially similar in those with early and late onset AD dementia and when cases diagnosed with AD dementia before 1992 were excluded (data not shown). Findings also remained after controlling for ApoE4 allele status in a sub-sample of 306 women with genotyping (data not shown). When we contrasted groups with high and low scores on neuroticism, it was found that the risk of AD dementia was twofold higher for the highest quartile compared with the lowest quartile (HR 1.99, 95% CI 1.00-4.00, *p* 0.050), while the second/third quartiles were not significantly associated (HR 1.59, 95% CI 0.86-2.94, *p* 0.140).

In model 3 (Table 3), where longstanding distress in 1968-80 was added, the association between neuroticism and AD dementia was attenuated and no longer significant. However, longstanding distress was significantly associated with increased risk of AD dementia in this model. When stratified by presence of longstanding distress, the interaction *neuroticism*longstanding distress* was not significant (*p* 0.626), meaning that the association between neuroticism and AD dementia was similar in the group with longstanding distress (HR 1.03; 95% CI 0.97-1.09) and in the group without distress (HR 1.00; 95% CI 0.93-1.09). Extraversion was not associated with any risk of developing dementia (Table 3).

Table 4 shows the combined effect of neuroticism and extraversion on risk of AD dementia. Women with high neuroticism/low extraversion had increased risk of developing AD dementia, compared to women with low neuroticism/high extraversion, in the age adjusted model (model 1). After further adjustment for social and medical covariates in model 2 the association where no longer significant. Individuals with high neuroticism/high extraversion or low neuroticism/low extraversion had no increased risk of AD dementia, in any of the models.

DISCUSSION

We found that a higher degree of neuroticism in midlife was associated with higher incidence of late-life AD. The association between neuroticism and AD dementia diminished after adjusting for longstanding distress, suggesting that the association between AD dementia and neuroticism is at least partially mediated by a life-long increased proneness to experience everyday life stressors as well as stressor-related distress.[27] It is possible that neuroticism makes the individual more vulnerable to stressors and distress, which leads to later development of dementia. In this study was neuroticism associated with higher degree of distress and extraversion with lower levels of distress, of many years. Our results should be seen in light of previous findings, that midlife distress and number of psychosocial stressors increases the risk of AD dementia.[11, 13]

Our results expand on the findings of several previous studies reporting associations between neuroticism and dementia. [4-10] Differences between those studies and our own include our longer follow-up period (38 years vs. 12 years for the Baltimore Study[10] and ≤6 years for other studies[4-9]) and our lower age at baseline (46 years vs. 57 years for the Baltimore Study[10]

and >70 years for other studies[4-9]). Only our study and the Kungsholmen Study[4] were population-based. One of the above-cited studies was a clinical study that focused on patients with AD dementia. Personality was evaluated retrospectively by information from close relatives.[9]

The finding that a combination of low extraversion/high neuroticism had the highest risk of AD dementia is partly supported by the Kungsholmen Study,[4] which found that persons with low neuroticism/high extraversion had a *decreased* risk of dementia. In that study, neuroticism was not a risk factor for dementia in the presence of high extraversion, which is in line with our findings.

There are several possible explanations for the relationship between neuroticism and AD dementia. First, personality may influence the individuals risk for dementia through its effect on behavior and lifestyle, e.g. individuals with low neuroticism have more often a lifestyle with healthier metabolic, cardiovascular and inflammatory risk profiles.[27] Second, both neuroticism and stress have been associated with functional and structural changes in the hippocampus.[28] One reason may be that these factors increase levels of glucocorticoid hormones in the brain. Functional damage to the hippocampus affects learning, cognition and memory.[29] Third, neuroticism has been associated with increased amount of neurofibrillary tangles in brain.[30] Fourth, low neuroticism has been associated with higher levels of serum brain derived neurotrophic factor, a key protein in synaptic neurogenesis thought to play a role in neurodegenerative diseases.[31] Finally, both neuroticism and extraversion have been found to moderate the relationship between ApoE4 genotype and AD dementia.[32]

It must be mentioned that among the elderly, clinically diagnosed dementia presumed to be due to AD is often multi-factorial. The most common other factor is silent cerebrovascular disease, e.g. silent infarcts or ischemic white matter lesions. This might also be a reason for our finding of an association between neuroticism and AD, as neuroticism has been associated with cardiovascular disease.[27] In contrast, we did not find any relation between personality factors and vascular dementia. Those diagnosed with vascular dementia probably have a more severe cardiovascular disease, and are thus subject to earlier mortality.[33] Earlier mortality may be even higher in individuals with both cardiovascular disease and stress, which may contribute to the observed absence of associations. Negative findings may also be due to the small number with pure vascular dementia. Furthermore, results regarding subtypes should be taken cautiously as it is difficult to diagnose dementia subtypes on clinical grounds alone. Individuals with AD dementia often have cerebrovascular disease and individuals with vascular dementia often have concomitant AD pathology, and cerebrovascular disease may influence the presence and severity of clinical symptoms of AD dementia.[34] Others have reported that the specificity for possible vascular dementia according to the criteria used in this study is 84%, while sensitivity is only 55%,[35] further suggesting that some cases of AD dementia probably had concomitant cerebrovascular disease.

The strengths of this study include a representative population, long follow-up, measurement of distress and personality already in midlife and multiple sources of information and assessment to detect and diagnose dementia. Some methodological issues need to be considered. First, distress was evaluated by one single question. We have no information on situations that may evoke the distress or intensity of distress. However, our question on distress has been used in several previous studies, and found to be related to increased risk for hypertension,[36] myocardial infarction,[37] cancer,[38] dementia[11] and psychosomatic

symptoms.[39] Second, there is a tendency in long-term follow-up studies that participants are lost over time. This problem was partly mitigated by also using medical records and hospital discharge registry data to diagnose dementia in those lost to follow-up. However, these sources often miss dementia cases. On the other hand, almost all people in Sweden receive their hospital treatment within the public health care system and the Swedish Hospital Discharge Register covers the entire country. Third, some of the subgroups were small. Lack of power might therefore explain some of our negative findings. Finally, the study was only conducted in women. Thus, our results cannot be generalized to men.

The results have practical implications as a group of women at risk for AD dementia is identified. Future studies should examine the etiological pathways for the associations and test whether this group responds well to interventions. It remains to be seen whether neuroticism could be modified e.g. by medical treatment or through life style changes.

Table 1 Characteristics of the study sample

Birth year, age at baseline, n (%)	
1914, age 54 year	90 (11.3)
1918, age 50 year	290 (36.3)
1922, age 46 year	309 (38.6)
1930, age 38 year	111 (13.9)
Neuroticism, mean (SD)	8.1 (4.6)
Extraversion, mean (SD)	11.3 (3.3)
Self-perceived distress, n (%)	
Distress in 1968	148 (18.6)
Distress in 1974	161 (22.6)
Distress in 1980	88 (13.8)
Distress in 2000	49 (17.9)
Distress in 2005	39 (12.0)
Longstanding distress (1968-80)	224 (35.5)
Education, n (%)	
Compulsory	600 (75.0)
More than compulsory	200 (25.0)
Medical and lifestyle factors at baseline	
Hypertension, n (%)	138 (17.3)
Coronary heart disease, n (%)	20 (2.5)
Smoking, n (%)	320 (40.0)
BMI, mean (SD)	24.2 (3.7)
Depression, n (%)	60 (7.5)
ApoE4 allele (one or two),[a] n (%)	90 (11.3)

[a] In a sub-sample of 306 women with genotyping

Table 2 Midlife neuroticism and extraversion in 1968 in relation to distress over 38 years presented as odds ratios with 95% confidence intervals

	Distress 1968 n=148	Distress 1974 n=161	Distress 1980 n=88	Distress 2000 n=49	Distress 2005 n=39
Neuroticism					
OR_1 (95% CI)	1.26 (1.20-1.32)	1.19 (1.14-1.24)	1.20 (1.14-1.27)	1.21 (1.12-1.30)	1.13 (1.02-1.25)
OR_2(95% CI)	1.26 (1.21-1.32)	1.18 (1.13-1.23)	1.20 (1.14-1.27)	1.21 (1.12-1.31)	1.12 (1.01-1.25)
Extraversion					
OR_1 (95% CI)[a]	0.93 (0.87-0.98)	0.93 (0.88-0.99)	0.93 (0.86-0.99)	0.89 (0.81-0.98)	1.06 (0.93-1.22)
OR_2 (95% CI)	0.93 (0.87-0.98)	0.93 (0.88-0.98)	0.92 (0.86-0.99)	0.89 (0.81-0.96)	1.06 (0.92-1.21)

Logistic regression analyses, presented as odds ratios with 95% confidence interval, and one unit increase per scale-score; OR_1 adjusted for age; OR_2 adjusted for age, education, hypertension, coronary heart disease, smoking and BMI.

Table 3 Neuroticism and extraversion in 1968 in relation to dementia and subtypes of dementia over 38 years presented as hazard ratios with 95% confidence intervals

	All-type dementia n=153	AD dementia n=104	Vascular dementia n=35
Neuroticism			
HR_1 (95% CI)	1.02 (0.99-1.06)	1.04 (1.00-1.08)	0.95 (0.88-1.03)
HR_2 (95% CI)	1.02 (0.98-1.06)	1.04 (1.00-1.08)	0.95 (0.88-1.04)
HR_3 (95% CI)	1.00 (0.96-1.04)	1.02 (0.97-1.07)	0.94 (0.86-1.03)
Extraversion			
HR_1 (95% CI)	0.98 (0.93-1.03)	0.96 (0.90-1.01)	1.02 (0.92-1.13)
HR_2 (95% CI)	0.98 (0.94-1.03)	0.96 (0.90-1.02)	1.03 (0.92-1.14)
HR_3 (95% CI)	0.98 (0.93-1.04)	0.95 (0.90-1.02)	1.04 (0.93-1.16)

Cox regression analyses, presented as hazard ratios with 95% confidence interval, and one unit increase per scale-score; HR_1 adjusted for age; HR_2 adjusted for age, education, hypertension, coronary heart disease, smoking, BMI and depression; HR_3 adjusted for all variables in HR_2 and for longstanding distress 1968-80.

Table 4 The combined effect of neuroticism and extraversion in relation to AD dementia

		AD dementia		
Neuroticism	Extraversion	n of cases (%)	HR_1 (95% CI)	HR_2 (95% CI)
Low[a]	High[b]	8/64 (12.5)	1.00 (ref.)	1.00 (ref.)
Low	Low	3/16 (18.8)	1.35 (0.36-5.11)	1.16 (0.22-6.23)
High	High	4/31 (12.9)	1.48 (0.44-4.96)	1.53 (0.41-5.66)
High	Low	16/63 (25.4)	2.50 (1.07-5.86)	1.98 (0.65-6.06)

[a] Low= the lowest quartile; [b] High= the highest quartile; HR_1 adjusted for age; HR_2 adjusted for age, education, hypertension, coronary heart disease, smoking, BMI, depression and longstanding distress 1968-80

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