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AU1) Please provide a footnote for the designator “a” in table 2.
Midlife personality and risk of Alzheimer disease and distress
A 38-year follow-up

ABSTRACT

Objective: To study the association between midlife neuroticism and extraversion and development of late-life dementia and long-standing 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 using the Eysenck Personality Inventory at baseline. Distress was measured according to a standardized 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 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 long-standing distress over 38 years. The association between neuroticism and AD dementia diminished after adjusting for long-standing distress. Extraversion was associated with a lower degree of long-standing distress, but had no impact on AD dementia. When the 2 personality dimensions were combined, high neuroticism/low extraversion showed the 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. The results have clinical implications because a group of women at risk of AD dementia is identified.

GLOSSARY

AD – Alzheimer disease; BMI – body mass index; CI – confidence interval; DSM-III-R – Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised; HR – hazard ratio.

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 of 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 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 long-standing distress in midlife increases the risk of dementia, AD dementia, and age-related brain changes, and that psychosocial stressors in midlife were associated with increased risk of AD dementia.11–13 In this study, we examined
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 examined the relationship between personality and long-standing 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 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 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 twenty-six participants died during follow-up.

**Standard protocol approvals, registrations, and patient consents.** The Ethics Committee for Medical Research at the 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 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 Eysenck Personality Inventory dimensions of neuroticism and extraversion and the corresponding dimensions within the 5-factor model of personality show that the 2 different systems match well.18

**Assessment and diagnosis of dementia.** Details of the diagnostic procedures of dementia have previously been published.13-15,19,20 Briefly, the diagnoses of dementia were based on information from neuropsychiatric examinations, close informant interviews, medical records, and the Swedish Hospital Discharge Register, and were compatible with the *DSM-III-R* criteria.21 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,22 and the diagnosis of vascular dementia was similar to the criteria proposed by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences.23 The diagnoses were performed in consensus conferences of geriatric psychiatrists. Person-years were calculated from the date of the baseline examination to (1) time of dementia onset, (2) the date of death according to the Swedish Population Register, (3) the date of the last follow-up examination for participants in 2005, or (4) December 31, 2006 for surviving dropouts.

**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 (1 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 the following: 0 = have never experienced any period of stress; 1 = have experienced a period(s) of stress more than 5 years ago; 2 = have experienced one period of stress during the last 5 years; 3 = have experienced several periods of stress during the last 5 years; 4 = have experienced constant stress during the last year; or 5 = have experienced constant stress during the last 5 years.11-13 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 potential confounders was obtained at baseline. The following confounders were included: education (compulsory vs beyond compulsory); hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥95 mm Hg and/or taking antihypertensive medications); coronary heart disease (documented history of myocardial infarction and/or ECG evidence of ischemia),12,14 and/or angina pectoris according to the Rose criteria); cigarette smoking (never vs former/current smoker); body mass index (BMI) (kg/m²); and depression (DSM-III criteria for major depressive disorders). In a subsample of women with genotype data, *APOE* genotype was dichotomized into ε4 allele present or absent.

**Statistical analyses.** Mean value, SD, median, and skewness were determined for the neuroticism and extraversion scales. Spearman coefficient was used to test 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 and 95% confidence intervals (CIs). The first model adjusted for age only and the second model adjusted for age, education, hypertension, coronary heart disease, 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% CIs in 3 separate models. The first model adjusted for age only. The second model adjusted for age, education, hypertension, coronary heart disease, smoking, BMI, and depression. The third model adjusted for all variables in the second model and for long-standing distress (i.e., report of distress in one or more examinations in 1968, 1974, and 1980). In subanalyses, we stratified by early-onset and late-onset AD dementia (i.e., onset before vs after age 75 years), excluded cases diagnosed with AD dementia before 1992, controlled for *APOE* ε4 allele status, and stratified by experience of long-standing 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 was tested. The lowest and highest quartiles in the personality scales were then combined into 4 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 participants are presented in table 1. As previously described,13 the 800 study participants were followed from 1968 to 2006; 153 women (19%) developed dementia during 25,131 person-years of follow-up, including 104 with AD, 35 with vascular dementia, and 14 with
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 ($r = -0.24, p = 0.001$). 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 (models 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 $APOE$ $e4$ allele status in a subsample 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 2-fold 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 long-standing distress in 1968–1980 was added, the association between neuroticism and AD dementia was attenuated and no longer significant. However, long-standing distress was significantly associated with increased risk of AD dementia in this model. When stratified by presence of long-standing distress, the interaction of neuroticism × long-standing distress was not significant ($p = 0.626$), meaning that the association between neuroticism and AD dementia was similar in the group with long-standing distress (HR 1.03, 95% CI 0.72–1.46).
Table 4 shows the combined effect of neuroticism score. HR1 adjusted for age; HR2 adjusted for age, education, hypertension, coronary heart disease, smoking, body mass index, and depression; HR3 adjusted for all variables in HR2 and for long-standing distress 1968-1980. Adjusting for long-standing distress, suggesting that the association between AD dementia and neuroticism is at least partially mediated by a lifelong 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, neuroticism was associated with a higher degree of distress and extraversion with lower levels of distress, of many years. Our results should be seen in light of the previous findings that midlife distress and number of psychosocial stressors increase 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 vs 12 years for the Baltimore Study10 and ≤6 years for other studies4-7) and our lower age at baseline (46 vs 57 years for the Baltimore Study10 and older than 70 years for other studies4-9). Only our study and the Kungsholmen Study4 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 individual’s risk of dementia through its effect on behavior and lifestyle; e.g., individuals with low neuroticism more often have 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 an 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 have a role in neurodegenerative diseases.31 Finally, both neuroticism and extraversion have been found to moderate the relationship between APO E4 genotype and AD dementia.32

Abbreviations: CI = confidence interval; HR = hazard ratio.
Cox regression analyses, presented as HRs with 95% CIs, and 1-unit increase per scale score. HR3 adjusted for all variables in HR2 and for long-standing distress 1968-1980.

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

<table>
<thead>
<tr>
<th>Neuroticism</th>
<th>Extraversion</th>
<th>AD Dementia</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No. of cases (%)</td>
<td>HR1 (95% CI)</td>
</tr>
<tr>
<td>Low*</td>
<td>Highb</td>
<td>8/64 (12.5)</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>3/16 (18.8)</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>4/31 (12.9)</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>16/63 (25.4)</td>
</tr>
</tbody>
</table>

Abbreviations: AD = Alzheimer disease; CI = confidence interval; HR = hazard ratio; ref. = reference. HR3 adjusted for all variables in HR2 and for long-standing distress 1968-1980.

*Low = the lowest quartile.

bHigh = the highest quartile.

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

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 was 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.
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, because neuroticism has been associated with cardiovascular disease. 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. 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 attributable to the small number with pure vascular dementia. Furthermore, results regarding subtypes should be taken cautiously because 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. 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%, 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 methodologic issues need to be considered. First, distress was evaluated by a 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 was found to be related to increased risk of hypertension, myocardial infarction, cancer, dementia, and psychosomatic symptoms. Second, there is a tendency in long-term follow-up studies for participants to be 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 because a group of women at risk of AD dementia is identified. Future studies should examine the etiologic 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 lifestyle changes.

AUTHOR CONTRIBUTIONS
Lena Johansson, PhD: has access to all the data and takes responsibility for the data, accuracy of the data analysis, and the conduct of the research, has the right to publish any and all data, separate and apart from the guidance of any sponsor of the research, drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, obtaining funding. Xin Xin Gao, MD, PhD: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, acquisition of data, obtaining funding. Paul R. Dubenstein, PhD: drafting/revising the manuscript for content, including medical writing for content. Tore Hallström, MD, PhD: drafting/revising the manuscript for content, including medical writing for content, analysis or interpretation of data, acquisition of data, obtaining funding. Svante Östling, MD, PhD: drafting/revising the manuscript for content, including medical writing for content, analysis or interpretation of data, acquisition of data, obtaining funding. Ingmar Skoog, MD, PhD: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, acquisition of data, study supervision or coordination, obtaining funding.

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DISCLOSURE
The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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