Personality and risk of Alzheimer's disease: New data and meta-analysis

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Abstract

Background—We examine whether broad factors and specific facets of personality are associated with increased risk of incident Alzheimer's disease (AD) in a long-run longitudinal study and a meta-analysis of published studies.

Methods—Participants (N=1671) were followed for up to 22 years from a baseline personality assessment. The meta-analysis pooled results from up to 5 prospective studies (N=5054).

Results—Individuals with scores in the top quartile of neuroticism (HR=3.1; 95%CI=1.6–6.0) or the lowest quartile of conscientiousness (HR=3.3; 95%CI=1.4–7.4) had a three-fold increased risk of incident AD. Among the components of these traits, self-discipline and depression had the strongest associations with incident AD. The meta-analysis confirmed the associations of neuroticism (p=2*10^{-9}) and conscientiousness (p=2*10^{-6}), along with weaker effects for openness and agreeableness (p<0.05).

Conclusion—The current study and meta-analysis indicate that personality traits are associated with increased risk of AD, with effect sizes similar to those of well-established clinical and lifestyle risk factors.

Keywords

Alzheimer; dementia; observational prospective study; meta-analysis; neuroticism; anxiety; depression; conscientiousness; order; self-discipline; APOE

1. Introduction

Given the steep rise in individual and societal costs associated with Alzheimer's disease (AD), there is a need to better understand the etiology of dementia.[1] Age is clearly associated with increasing incidence of AD, and there is strong evidence that apolipoprotein E (APOE) ε4 variant is associated with higher risk of AD.[1] A number of other genetic,

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medical, psychological, and social factors have also been linked to AD.[2–4] Among the psychological factors, there has been an interest in the role of personality traits. Personality traits are enduring dispositions that underlie individuals' cognitive, emotional, and behavioral tendencies.[5] These traits are related to individuals' lifestyles and have been implicated in physical and mental health,[6–12] including risk of AD.[13–17] The present study extends the research on personality traits and risk of incident AD in two ways. First, we examine the association in one of the longest running prospective studies in the United States using a comprehensive and detailed assessment of the domain and facets of the five-factor model of personality. Second, we pooled findings from published studies and performed meta-analyses to summarize evidence for the association of personality traits with incident AD. Based on previous research, we expected that high conscientiousness (those who are organized and have more self-discipline and willpower) and low neuroticism (those who are less likely to be anxious, depressed, and vulnerable to stress) would be associated with a reduced risk of incident AD.

2. Methods

2.1. Participants

The participants (N = 1671) were part of the Baltimore Longitudinal Study of Aging (BLSA), a prospective cohort study of physical and psychological aging.[18] At entry, participants are generally in good health; extensive exclusion criteria (see ClinicalTrials.gov Identifier: NCT00233272) ensure that participants have no physical or cognitive impairments when they enter the study. Although they remain a relatively healthy group, participants develop diseases and disabilities as they age. For example, the incidence of metabolic syndrome in the BLSA is in line with data from similar samples [19] and BLSA participants tend to have similar levels of depressive symptoms to other cohorts.[20] The incidence of AD in this sample is also consistent with the rate found in other studies.[21]

At entry in the study, participants agreed to serial follow-ups with systematic physical and psychological examinations. The frequency of follow-up varied with age, with increasing frequency at older ages. Currently, participants 60 to 79 years old are tested every 2 years and participants 80 years old or older are tested approximately every year. Subjects included in the analyses were cognitively normal at time of the baseline personality assessment and had at least one follow-up evaluation. About 7% (n = 119) of participants in this study were lost to follow-up. Prior to each assessment, participants provided written informed consent. The protocol was approved by the local institutional review board.

2.2 Clinical and Neuropsychological Evaluations

At enrollment, each participant was evaluated for history of cerebrovascular disease, focal neurological abnormalities, and impairment of cognitive or behavioral functioning. Follow-up evaluations included a neuropsychological battery, neurological examination, medication review, and informant/subject structured interview. The latter was based on the Clinical Dementia Rating (CDR)[22] scale after 1998 and the Dementia Questionnaire[23] before 1998. All subjects were reviewed at a diagnostic consensus conference if their Blessed Information Memory Concentration score[24] was 4 or above, if their informant or subject CDR score was 0.5 or above, or if their Dementia Questionnaire was abnormal. All neuropsychological diagnostic tests and clinical data were available for review at the diagnostic conference. Diagnosis of dementia was based on DSM-III-R criteria and diagnosis of AD was based on the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[25]

2.3 Personality Assessment

Participants completed the self-report version of the Revised NEO Personality Inventory (NEO-PI-R).[5] The NEO-PI-R is a 240-item questionnaire that assesses 30 facets, six for each of the five major dimensions of personality – neuroticism (the tendency to experience negative emotions, such as anxiety, anger, and sadness), extraversion (an inclination toward being sociable, assertive, enthusiastic, and energetic), openness (the tendency to be imaginative, unconventional, curious, emotionally and artistically sensitive), agreeableness (an interpersonal dimension defined by altruism, trust, modesty and cooperativeness), and conscientiousness (the tendency to be organized, strong-willed, persistent, reliable and a follower of rules and ethical principles). Raw scores were standardized using combined-sex norms reported in the manual.[5] In the BLSA sample, the NEO-PI-R factor structure shows high congruence with the normative structure (Tucker's *phi*s = .97 to .99), the internal consistencies for the five dimensions ranged from 0.87 to 0.92, and the test-retest correlations for the five dimensions ranged from 0.78 to 0.85 over an average interval of 10 years.[26]

2.4 Data Analysis

To test whether personality traits conferred risk of AD, we used proportional hazards regression models, controlling for age of personality assessment, sex, ethnicity (white vs. others), and education (years of schooling). The analyses were conducted separately for each of the five personality domains and each of the facets. Personality scores were standardized so that one unit corresponded to a 1 SD difference. In addition to the continuous scores, domain scores were recoded to provide a statistical and graphical comparison of the top and bottom quartiles of the distribution. We also tested a model that included all five factors simultaneously. The time end point was the year of onset of AD-type clinical dementia. Participants who did not develop AD were censored at the time of their last clinical evaluation. Because of differences in the pathophysiologic processes among dementia subtypes, we excluded 44 participants who developed non-AD dementia (e.g., vascular, Lewy body, Parkinson disease). The results were similar if we included these 44 participants censored at time of onset of non-AD dementia.

We estimated the population attributable risk (PAR) based on the hazards ratio (HR) of incident AD associated with the top or bottom quartile of the distribution on a personality trait vs. the rest of the sample (adjusted for the demographic covariates). We used the formula $PAR = P_{RF}*((HR-1)/HR)$,[27] where P_{RF} is the prevalence of the risk factor (i.e., 25%). The PAR estimates are calculated for comparisons with established risk factors. PAR estimates, however, are generally based on clinically recognized cut-points (e.g., blood pressure values that define hypertension), whereas we used statistical thresholds for the personality traits. In addition, in calculating the PAR, we are not necessarily assuming a direct causal link between the risk factor and the outcome.

Secondary analyses with APOE genotype (presence vs. absence of ε4 allele) as a covariate or moderator of the association between personality and incident AD were performed for the subset of 1472 participants with available APOE genotype. We also repeated the analyses excluding individuals younger than 50 years at initial examination, or those who developed AD within two years after the initial personality assessment. Finally, we tested whether sex moderated the association between personality traits and incident AD. The analyses were conducted using SPSS statistical software.

2.5 Meta-analysis

To identify studies for inclusion in the meta-analysis, we searched the PubMed and Scopus databases up to February 2012 and screened the reference lists of relevant articles for

additional studies. We focused on prospective cohort studies, with five-factor model personality traits assessed at baseline in cognitively healthy participants who were evaluated at follow-up for incident AD. In cases with multiple publications from the same sample, we considered one effect for each trait from each sample. To reduce variability across studies, we generally chose the risk estimates from the main model, with age, sex, education, and ethnicity as covariates. The logHR and SE were scaled in each study to correspond to the effect associated with 1 SD difference on the trait. We performed random-effect model meta-analyses. Heterogeneity was evaluated using the Q statistic, and publication bias was evaluated statistically with the Kendall's tau and Egger test. The meta-analyses were conducted using the "Comprehensive Meta-Analysis" software package.

3. Results

3.1 Association results from the BLSA sample

Participants were followed for up to 22 years (M = 12, SD = 6, range 1–22). The onset of clinical AD was diagnosed in 90 individuals within an average of 8 years (SD = 4, range 1–18) from the baseline personality assessment. Table 1 presents the initial demographic characteristics of the overall sample and separately for the group of participants who developed AD and those who did not. The incident dementia group was significantly older and more likely to be white. This effect of ethnicity was due partly to the younger age of the minority group (54.8 vs. 57.2, p = 0.005), because they were recruited later in the study. There were no significant differences between the groups on education or sex.

Table 2 presents the results of the survival analyses, with the hazard ratios of AD (adjusted for age, sex, education, and ethnicity) and the 95% confidence intervals associated with each factor and facet. For each SD increase in neuroticism, the risk of incident AD increased by more than 30% (HR = 1.37; 95%CI =1.09–1.73). We contrasted groups with high and low scores on neuroticism and found that the risk of incident AD was threefold higher for the group in the highest quartile compared to the lowest quartile of neuroticism (HR = 3.13; 95%CI = 1.62–6.04; see Figure 1). The absolute risk, which does not account for covariates or censoring, was 7% and 3% for the highest and lowest quartiles of neuroticism. Further, we calculated that over 10% of the AD cases in the population could be attributed to high neuroticism (top quartile vs. others; HR = 2.02; PAR = 13%). A similar effect was observed for conscientiousness (HR = 0.69; 95%CI =0.55–0.87), and as illustrated in Figure 1, the risk of incident AD was threefold higher for the group in the lowest compared to the highest quartile of conscientiousness (HR = 3.26; 95%CI = 1.43–7.40; absolute risk 8% and 2% for the lowest and highest quartiles). Similar to neuroticism, the proportion of AD cases that could be attributed to low conscientiousness (bottom quartile vs. others; HR = 1.74) was about 10% (PAR = 11%).

Additional analyses supported the robustness of these associations. Because Neuroticism and Conscientiousness are moderately correlated, we tested whether these were independent effects. When we repeated the analyses with all five factors entered in the regression model simultaneously, scoring in the top quartile of neuroticism (HR = 2.53; 95%CI = 1.23–5.23) or the bottom quartile of conscientiousness (HR = 2.63; 95%CI =1.10–6.26) was still associated with increased risk of AD. We further tested whether the combination of high neuroticism and low conscientiousness increased vulnerability to AD beyond the main effects, but we found no significant interaction. The results remained essentially the same when we excluded individuals younger than age 50 at baseline or those who developed AD within 2 years of the baseline personality assessment (p's < 0.05 for both neuroticism and conscientiousness). In the full sample, we also tested whether the association of the five major factors with incident AD was different for men and women, but we found no significant interactions.

Separate analyses with the APOE ε4 allele as an additional covariate confirmed that an increased risk of incident AD was associated with scoring in the top quartile of neuroticism (HR = 3.82; 95%CI =1.85–7.89) or the bottom quartile of conscientiousness (HR = 3.40; 95%CI =1.39–8.28). We also tested for interactions between each of the five factors and the APOE ε4 risk variant. We found significant interactions between APOE genotype and openness (interaction term: HR = 0.58; 95%CI =0.34–0.98) and agreeableness (interaction term: HR = 1.87; 95%CI =1.10–3.16), such that high openness was protective among the APOE ε4 carriers, whereas high agreeableness was protective among the non-carriers.

At the facet level (Table 2), the anxiety, angry hostility, and depression aspects of neuroticism increased risk of incident AD by more than 30%; there was a trend for vulnerability (p = 0.05). Among the facets of conscientiousness, self-discipline had the strongest association, followed by competence, order, and dutifulness: risk of incident AD was reduced by over 30% for each SD higher score on any of these facets. Finally, one facet of Openness, Openness to Ideas, was associated significantly with an approximately 25% reduced risk of AD for each SD higher score.

3.2 Meta-Analysis

Including the present BLSA sample, we identified five samples with data on neuroticism (total N = 5054; incident AD, N = 607) and three samples with data for each of the other four factors (N = 3342; incident AD, N = 382). We did not conduct meta-analyses for the facets because we found only one study that examined the facets of neuroticism aside from the current BLSA sample. Table 3 presents the characteristics of the studies included in the meta-analyses. All traits were measured with some variation of the NEO-PI-R instrument, and all studies included at least age, sex, and education as covariates. The HRs from each study and the pooled association are presented in Table 4. The meta-analysis confirmed a highly significant effect for neuroticism (p = $2*10^{-9}$): for every SD increase in this trait, the risk of AD increased by more than 30% (HR = 1.33; 95%CI =1.21–1.45). The association was highly consistent across studies (Q = 2.6; degrees of freedom (df) = 4; p = 0.63), and in this set of studies we observed no statistical evidence of publication bias (Kendall's z-tau = 1.22; p = 0.22; and Egger's regression intercept test: t = 1.87; df = 3; p = 0.16). The meta-analysis also indicated that lower scores on conscientiousness were associated with higher risk of incident AD (HR = 0.77; 95%CI =0.69–0.86; p = $2*10^{-6}$); again there was no evidence of heterogeneity (p = 0.55) or publication bias (p > 0.05). By pooling the results from the three studies, we also found significant associations for Openness (HR = 0.86; 95%CI =0.77–0.96; p = 0.008; heterogeneity: p = 0.91; publication bias p > 0.05) and Agreeableness (HR = 0.88; 95%CI =0.79–0.98; p = 0.019; heterogeneity: p = 0.51; publication bias p > 0.05), such that open and agreeable people were at lower risk of AD. There was no significant association with Extraversion (HR = 0.96; 95%CI =0.86–1.07; p = 0.53).

4. Discussion

In a large sample followed for up to 22 years, we found those in the highest quartile of neuroticism (vs. the lowest quartile) or those in the lowest quartile of conscientiousness (vs. the highest quartile) were at a three-fold increased risk of incident AD. We further estimated that neuroticism and conscientiousness could account for 13% and 11% of the AD cases in the population, respectively. These effect sizes and PAR estimates are comparable to those reported for recognized clinical and lifestyle risk factors for AD, such as diabetes (RR = 1.39, 1.17–1.66; PAR = 3%), lower education (RR = 1.59, 1.35–1.86; PAR = 7%), smoking (RR = 1.59, 1.15–2.20; PAR = 11%), midlife obesity (RR = 1.60; 1.34–1.92; PAR = 7%), midlife hypertension (RR = 1.61; 1.16–2.24; PAR = 8%), physical inactivity (RR = 1.82; 1.19–2.78; PAR = 21%), or depression (RR = 1.90; 1.55–2.33; PAR = 15%).[2] These

findings indicate that personality traits may help identify individuals at greater risk of AD, and potentially aid in the early detection of AD.

In addition to effect sizes that are similar to other major risk factors for AD, the meta-analyses indicated a high degree of consistency across studies; all strongly supported the association of neuroticism and conscientiousness with risk of AD. This lack of heterogeneity is a notable finding, given the differences in demographic characteristics of the samples, study design, and length of the follow-up. Furthermore, the greater statistical power afforded by combining multiple samples suggested a significant association for the openness factor, which was significant in only one of the primary studies,[16] and for agreeableness. There was no significant association for extraversion.

These associations might be explained, in part, by the links between personality and health-related behaviors, lifestyle factors, and clinical conditions. Low conscientiousness and high neuroticism are associated with cigarette smoking,[7] physical inactivity,[28] and obesity,[9] which in turn are risk factors for dementia.[2] Neuroticism is a strong vulnerability factor for major depression,[6] which is also associated with AD.[2, 29, 30] Personality traits are related to coping skills, and chronic stress over the lifespan might contribute to the inability to cope with the neurodegenerative process underlying AD. Direct physiological pathways are another plausible mechanism, given that low conscientiousness and high neuroticism are related to inflammatory markers such as IL6, CRP, and WBC counts.[8, 31] Neuroticism is also related to level of brain derived neurotrophic factors (BDNF),[32] which is thought to play an important role in neurodegenerative disorders. Another possibility is shared genetic liability. For example, in a large founder population[33] but not in other samples,[34] variants in the *DYRK1A* gene were associated with conscientiousness. The gene *DYRK1A* maps in the Down syndrome critical region on chromosome 21, its activity is up-regulated by Aβ, and it is involved in tau phosphorylation.[35] We also found suggestive evidence that personality traits may interact with the APOE genotype, such that openness and agreeableness were protective factors depending on the ε4 carrier status in the BLSA sample.

The meta-analysis supported an inverse association between openness and risk of AD. Open individuals prefer variety, are attentive to inner feelings, are sensitive to art and beauty, and are intellectually engaged, curious, and imaginative. Open individuals tend to perform well on cognitive measures, such as executive functions and working memory tasks,[36–38] and on measures of academic achievement.[39] The higher intellectual engagement of these individuals is consistent with other evidence that relates cognitive activity with risk of AD.[40, 41] Openness, especially its Ideas facet, is correlated with aspects of intelligence and education, which are associated with greater cognitive reserve and decreased risk for AD.[40] It should be noted that openness was associated with risk of AD even with education as a covariate, suggesting that the effects of openness on AD might thus have been underestimated in our analyses.

A novel finding from our meta-analysis was that agreeable people have a reduced risk of AD. We interpret this finding with caution, since none of the individual studies show a significant association, and therefore replication in additional samples is particularly warranted. Still, it is worth considering that agreeableness measures interpersonal tendencies, and an inclination to be altruistic and cooperative might facilitate the formation of interpersonal connections and the stability of social networks.[42] Extraversion, however, the other major personality dimension that shapes interpersonal tendencies, was not associated with risk of AD. Another possibility is that individuals who score low on Agreeableness tend to be aggressive, competitive, and antagonistic, which increase risk of cardiovascular disease.[43, 44] Thus, the greater cardiovascular burden carried by antagonistic individuals may contribute to their risk of AD.

Among the strengths of this study was the use of a psychometrically robust and detailed personality assessment administered over a relatively long follow-up interval. The facet-level analyses allowed us to examine which aspects of the heterogeneous domains were most strongly related to AD. For neuroticism, we found the strongest effects for the depression, anxiety, and angry-hostility facets, and a trend for vulnerability. Given the large literature documenting the role of depression in dementia[2, 30, 45, 46] it was not surprising to find an association between this facet and risk of AD. Comparatively less is known about the role of anxiety as a risk factor of AD, but some studies have found similar associations.[47, 48] The association of angry-hostility supports the above hypothesis for agreeableness (i.e., hostility increases risk), and the effect of vulnerability supports the role of stress vulnerability in dementia.[48, 49] Turning to conscientiousness, most of the facets were associated with reduced risk of AD. The strongest effect was observed for self-discipline, a measure of motivation, persistence, and ability to achieve a goal despite distractions, boredom, or difficulties. This impulsivity-related trait plays an important role in health-risk behaviors and outcomes,[8, 9] and might be related to AD through a number of the direct and indirect pathways discussed above.

Among the limitations of this study is the observational design of the BLSA and most studies included in the meta-analyses. The BLSA is also not a representative sample of the US population. However, as the meta-analysis supports, the BLSA results were similar to those obtained in other samples, and we found no evidence of heterogeneity in the published studies. The number of studies that measured the five factors is still relatively small, but for neuroticism the meta-analysis included a total 5054 individuals, with 607 cases of incident AD. Additional studies are needed to increase these numbers and to test the potential mechanisms underlying the association between personality traits and incident AD. Given the strength of the association between personality traits and risk of AD, the consistency of these associations across the published studies, and the clinical value of identifying factors that may promote resilience to AD neuropathology,[50] personality traits should be further evaluated as important risk factors of AD.

Research in Context

Systematic review – We reviewed the literature using PubMed and Scopus, and examined the reference list of identified articles. Numerous studies have examined personality traits in Alzheimer's disease (AD) patients, but few have prospective measures of personality traits to test as predictors of incident dementia, and most used a brief personality measure within 3 to 6 years from the onset of dementia.

Interpretation – We found consistent evidence that personality traits predict incident AD; effect sizes were comparable to those of more established risk factors. The BLSA findings further contribute to current knowledge by (a) testing this association over a significantly longer follow-up period (M = 12 years), and (b) examining the association with a more comprehensive and detailed measure of personality.

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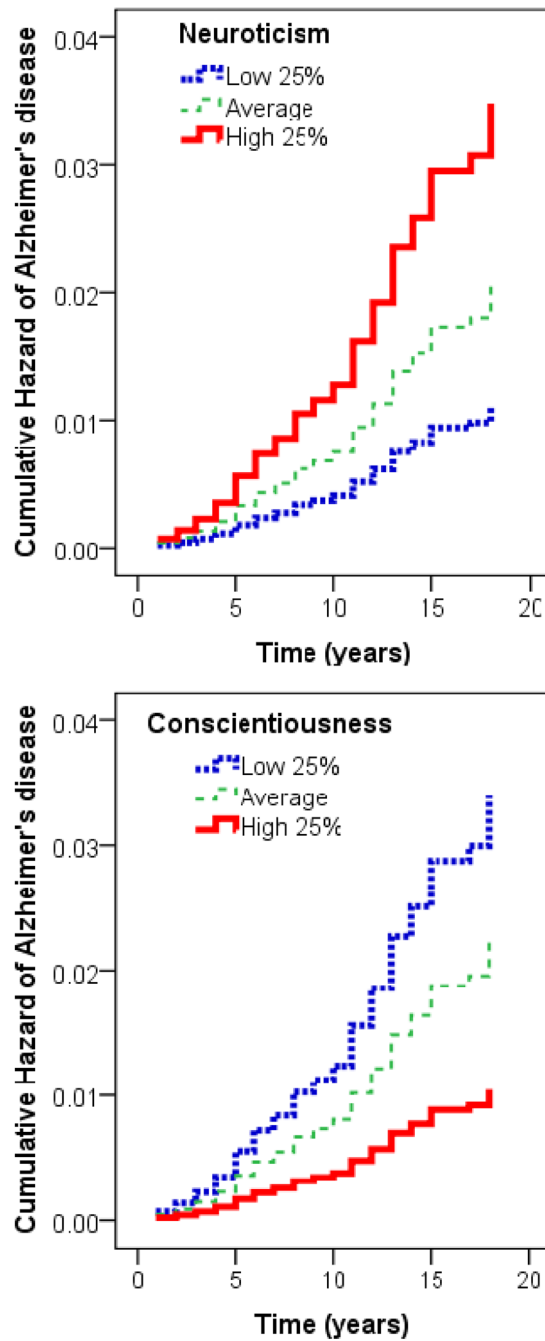
Figure 1.
Cumulative hazard of incident AD clinical dementia associated with the low 25% and high 25% on neuroticism and conscientiousness, adjusted for age, sex, ethnicity, and education. The group with average scores (25% to 75%) were included in the analyses but are not shown in the figure. For neuroticism, the low 25% N = 405, the high 25% N = 436. For conscientiousness, the low 25% N = 422, the high 25% N = 393.

Table 1

Baseline descriptive statistics for the overall sample and by dementia status

	Overall (n=1671)	**No AD (n=1581)**	**Incident AD (n=90)**	**P**
Age, years	56.5 (16.0)	55.4 (15.7)	75.7 (7.6)	<0.001
Education, years	16.7 (2.5)	16.7 (2.5)	16.4 (3.0)	0.29
Female, %	49.4	49.5	46.7	0.6
Minority, %	29.3	30.5	7.8	<0.001

Table 2

Results from separate Cox regression with personality factors and facets as predictors of incident AD.

	Hazard Ratios	95% Confidence Interval
Neuroticism	1.371**	1.085–1.733
Extraversion	0.86	0.687–1.077
Openness	0.889	0.707–1.116
Agreeableness	0.858	0.679–1.082
Conscientiousness	0.692**	0.549–0.873
N1: Anxiety	1.336**	1.078–1.657
N2: Angry Hostility	1.331**	1.076–1.649
N3: Depression	1.349*	1.070–1.701
N4: Self-consciousness	1.114	0.888–1.398
N5: Impulsiveness	1.065	0.833–1.363
N6: Vulnerability	1.251	0.996–1.571
E1: Warmth	0.864	0.685–1.090
E2: Gregariousness	0.959	0.774–1.188
E3: Assertiveness	0.947	0.759–1.182
E4: Activity	0.834	0.665–1.045
E5: Excitement-Seeking	0.822	0.642–1.052
E6: Positive Emotions	0.968	0.770–1.216
O1: Fantasy	1.039	0.831–1.301
O2: Aesthetics	0.996	0.794–1.250
O3: Feelings	0.901	0.722–1.125
O4: Actions	0.89	0.720–1.100
O5: Ideas	0.764*	0.605–0.984
O6: Values	0.968	0.784–1.195
A1: Trust	0.886	0.689–1.139
A2: Straightforwardness	0.942	0.743–1.194
A3: Altruism	0.88	0.698–1.110
A4: Compliance	0.963	0.787–1.179
A5: Modesty	0.86	0.689–1.074
A6: Tender-mindedness	0.91	0.725–1.141
C1: Competence	0.707**	0.582–0.904
C2: Order	0.746**	0.610–0.944
C3: Dutifulness	0.758*	0.588–0.978
C4: Achievement Striving	1.008	0.798–1.274
C5: Self-Discipline	0.681***	0.555–0.834
C6: Deliberation	0.838	0.673–1.043

Note. Total N = 1671, incident AD cases N = 90. Cox regressions controlling for age, sex, education, and ethnicity.

Table 3

. Baseline characteristics of the samples included in the meta-analyses

Sample	N	AD-N	Max Follow-up	Average follow-up	Age	Females%	Education	Minority
Rush Biracial[13]	1064	170	6	†	74 (9.6)	62%	12.9(6.3)	50%
Rush MAP[14]	648	55	7	3	81 (6.9)	74%	14.6(2.9)	2%
ROS[15]	904	176	12	†	74–80 (6.5)	68%–71%	18 (3.3)	8%
GEM[16]	767	116	7	6	79 (3.1)	42%	†	8%
BLSA	1671	90	22	12	57 (16.0)	49%	16.7 (2.5)	29%

Rush MAP = Rush Memory and Aging Project; ROS= Religious Order Study; GEM = Ginkgo Evaluation of Memory study; BLSA=Baltimore Longitudinal Study of Aging.

† See original study

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Table 4

Risk of incident AD associated with personality traits reported in each study, meta-analytic effect sizes and heterogeneity.

Sample	Neuroticism	Extraversion	Openness	Agreeableness	Conscientiousness
Rush Biracial[13]	1.338 (1.065–1.682)				
Rush MAP[14]	1.480 (1.143–1.918)				
ROS[15]	1.191 (1.008–1.408)	1.093 (0.911–1.311)	0.906 (0.760–1.080)	0.900 (0.765–1.059)	0.809 (0.692–0.947)
GEM[16]	1.390 (1.158–1.668)	0.900 (0.745–1.087)	0.780 (0.640–0.950)	0.860 (0.711–1.041)	0.760 (0.626–0.923)
BLSA	1.371 (1.085–1.733)	0.86 (0.687–1.077)	0.889 (0.708–1.117)	0.858 (0.680–1.083)	0.692 (0.549–0.873)
Meta-Analyses (random model)	1.326 (1.210–1.454)	0.954 (0.824–1.105)	0.858 (0.766–0.961)	0.877 (0.786–0.979)	0.767 (0.689–0.855)
Heterogeneity Q (p)	2.6 (0.63)	3.3 (0.19)	0.2 (0.91)	1.4 (0.51)	1.2 (0.55)

Rush MAP = Rush Memory and Aging Project; ROS= Religious Order Study; GEM = Ginkgo Evaluation of Memory study; BLSA=Baltimore Longitudinal Study of Aging

All studies controlled for age, sex, and education. Ethnicity was an additional covariate in the Rush Biracial, GEM and BLSA. The Rush Biracial further adjusted for the presence of APOE-ε4 allele. The HRs from the ROS are from a model that included all five factors. The logHR and SE were scaled in the ROS, Rush Biracial, and Rush MAP study to correspond to the effect associated with 1 SD difference on the trait. For neuroticism (k=5, total N = 5054; incident AD, N = 607) and for each of the other 4 factors (k = 3, total N = 3342; incident AD, N = 382).