

Conscientiousness and the Incidence of Alzheimer Disease and Mild Cognitive Impairment

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Context: The personality trait of conscientiousness has been related to morbidity and mortality in old age, but its association with the development of Alzheimer disease is not known.

Objective: To test the hypothesis that a higher level of conscientiousness is associated with decreased risk of Alzheimer disease.

Design: Longitudinal clinicopathologic cohort study with up to 12 years of annual follow-up.

Setting: The Religious Orders Study.

Participants: A total of 997 older Catholic nuns, priests, and brothers without dementia at enrollment, recruited from more than 40 groups across the United States. At baseline, they completed a standard 12-item measure of conscientiousness. Those who died underwent a uniform neuropathologic evaluation from which previously established measures of amyloid burden, tangle density, Lewy bodies, and chronic cerebral infarction were derived.

Main Outcome Measures: Clinical diagnosis of Alzheimer

heimer disease and change in previously established measures of global cognition and specific cognitive functions.

Results: Conscientiousness scores ranged from 11 to 47 (mean, 34.0; SD, 5.0). During follow-up, 176 people developed Alzheimer disease. In a proportional hazards regression model adjusted for age, sex, and education, a high conscientiousness score (90th percentile) was associated with an 89% reduction in risk of Alzheimer disease compared with a low score (10th percentile). Results were not substantially changed by controlling for other personality traits, activity patterns, vascular conditions, or other risk factors. Conscientiousness was also associated with decreased incidence of mild cognitive impairment and reduced cognitive decline. In those who died and underwent brain autopsy, conscientiousness was unrelated to neuropathologic measures, but it modified the association of neurofibrillary pathologic changes and cerebral infarction with cognition proximate to death.

Conclusion: Level of conscientiousness is a risk factor for Alzheimer disease.

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CONSCIENTIOUSNESS REFERS to an individual's tendency to control impulses and be goal directed. This trait, also called *will*,¹ *work*,² and *dependability*,³ is a component of the 5-factor model of personality.^{4,5} In this study, we tested the hypothesis that a higher level of conscientiousness is associated with a reduced risk of developing Alzheimer disease (AD) in old age. The hypothesis is based in part on epidemiologic research showing conscientiousness to be associated with a wide range of mental and physical disorders,⁶ disability,^{6,7} and death,⁸⁻¹⁰ suggesting that the trait has some general role in health maintenance. In addition, a number of variables associated with risk of AD, including educational and occupational attainment,¹¹ physical exercise,¹² tobacco use,¹³ neuroticism,¹⁴ and depressive symptoms,¹⁵ are also associated with conscientiousness (for educational and

occupational attainment,^{16,17} for physical exercise,^{18,19} for tobacco use,^{20,21} for neuroticism,⁹ and for depressive symptoms⁷), suggesting that the trait may have a more specific link to the development of AD.

We tested the hypothesized association between conscientiousness and AD with data from the Religious Orders Study, a longitudinal clinicopathologic investigation of aging and AD in older Catholic clergy members.²² In analyses, we tested the hypothesized association of conscientiousness (assessed at baseline) with incidence of AD during up to 12 years of annual follow-up, considered possible confounding and modifying variables, and examined the relation of the trait to the rate of cognitive decline and incidence of mild cognitive impairment. In addition, among those who died and underwent brain autopsy, we tested whether conscientiousness was associated with dementia-related neuropathologic findings or modi-

fied the correlation of pathologic changes with cognition proximate to death.

METHODS

PARTICIPANTS

Subjects were participants in the Religious Orders Study, a longitudinal clinicopathologic investigation of aging and AD in older Catholic clergy members recruited from about 40 groups across the United States.²² A rolling admission was used. Eligibility required agreement to annual clinical evaluations and brain autopsy at death, and all subjects gave informed consent and signed an Anatomical Gift Act (<http://www.law.upenn.edu/bll/archives/ulc/fnact99/uaga87.htm>). Data for the present analyses were collected from 1994 to 2006. The study was approved by the institutional review board of Rush University Medical Center.

On enrollment, each person underwent a structured clinical evaluation that included a medical history, complete neurologic examination, and detailed cognitive testing. The evaluation was repeated annually thereafter with examiners blinded to previously collected data. On the basis of this evaluation and an in-person examination of the participant, an experienced clinician classified persons with respect to dementia by using the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.²³ These criteria require a history of cognitive decline and impairments in at least 2 cognitive domains and were implemented as in previous research.^{14,24} Of 1080 people who had completed the baseline evaluation at the time of these analyses, 83 met criteria for dementia; 24 of the remaining 997 people died before the first annual follow-up and 34 had been enrolled in the study less than 1 year at the time of these analyses. This left 939 eligible for follow-up, and follow-up data were available on 920 (98.0%), with a mean of 7.9 completed evaluations per individual (range, 2-13).

ASSESSMENT OF PERSONALITY TRAITS

At baseline, we administered the NEO Five-Factor Inventory²⁵ to quantify conscientiousness and 4 other traits that make up a widely accepted 5-trait model of personality.^{4,5,25} The inventory has 60 items, 12 for each trait. Persons rated agreement with each item on a 5-point scale. Item scores ranged from 0 to 4 and were summed to yield a total score for each trait that ranged from 0 to 48, with higher scores indicating more of the trait. Conscientiousness (eg, "I am a productive person who always gets the job done") refers to a tendency to be self-disciplined, scrupulous, and purposeful. Neuroticism (eg, "I often feel inferior to others") indicates proneness to experience psychological distress. Extraversion (eg, "I laugh easily") is the tendency to be sociable, active, and optimistic. Openness (eg, "I often try new and foreign foods") refers to intellectual curiosity and independence of judgment. Agreeableness (eg, "I would rather cooperate with others than compete with them") indicates the tendency to be altruistic and helpful. The Cronbach coefficient α , an indicator of internal consistency reliability, was 0.81 for conscientiousness, 0.80 for neuroticism, 0.78 for extraversion, 0.68 for openness, and 0.66 for agreeableness. These values are comparable to those reported in the normative cohort²⁵ and indicate adequate levels of internal consistency.

ASSESSMENT OF COGNITIVE FUNCTION

A set of 20 cognitive performance tests was administered annually in an approximately 1-hour session. One test, the Mini-Mental State Examination, was used for descriptive but not ana-

lytic purposes. The remaining 19 tests included 7 measures of episodic memory: Word List Memory, Word List Recall, and Word List Recognition plus immediate and delayed recall of the East Boston Story and Story A of the Wechsler Memory Scale-Revised. Semantic memory was assessed with Verbal Fluency, a 20-item version of the Boston Naming Test, a 20-item version of the National Adult Reading Test, and a 15-item form of Extended Range Vocabulary. Working memory measures consisted of Digit Span Forward, Digit Span Backward, Digit Ordering, and Alpha Span. The oral version of the Symbol Digit Modalities Test and Number Comparison were used to assess perceptual speed, and a 15-item form of Judgment of Line Orientation and a 17-item form of Standard Progressive Matrices were used to assess visuospatial ability.

To minimize floor and ceiling artifacts and other forms of measurement error, we used composites of 2 or more individual cognitive tests in analyses. We constructed measures of global cognition (based on all 19 tests), episodic memory (7 tests), semantic memory (4 tests), working memory (4 tests), perceptual speed (2 tests), and visuospatial ability (2 tests). In each case, raw scores on individual tests were converted to z scores, by means of the baseline mean and SD in the entire cohort, and then z scores on component tests were averaged to yield the composite score. Detailed information on the individual tests and on the derivation and correlates of the composite measures is contained in previous publications.^{14,22,24,26}

DIAGNOSIS OF MILD COGNITIVE IMPAIRMENT

Clinical classification of mild cognitive impairment was based on previously published criteria that have been clinically²⁷ and pathologically²⁸ validated in this cohort. The criteria require cognitive impairment in the absence of dementia.²³ The determination of cognitive impairment was made by a neuropsychologist, after reviewing results of cognitive tests, 11 of which have educationally adjusted cutoff scores and an algorithm for rating impairment in 5 cognitive domains, as previously described.^{22,27}

ASSESSMENT OF OTHER COVARIATES

Frequency of participation in cognitively stimulating activities was quantified with a previously established scale.²⁶ People rated how often they had participated in each of 7 cognitive activities (eg, reading a newspaper) in the past year on a 5-point scale. The mean score for the 7 activities has been associated with cognitive decline and AD in this²⁴ and other^{29,30} cohorts. Physical activity was assessed with questions adapted³¹ from the 1985 Health Interview Survey.³² For each of 5 physical activities (eg, walking for exercise), we asked people whether they had participated in the past 2 weeks and, if so, how many times and the duration of each. These data were combined across activities to provide an index of hours of physical activity per week, as previously reported.²⁴ We used standard questions³³ to quantify social network size as the number of friends and family members seen at least once per month, as described elsewhere.³⁴

We constructed composite measures of vascular burden by means of the baseline medical history and clinical evaluation.³⁵ *Vascular risk factors* was the number of 3 factors present (ie, hypertension, diabetes mellitus, and cigarette smoking), and *vascular conditions* was the number of 3 conditions present (ie, heart attack, stroke, and claudication).

To assess depressive symptoms, we used a 10-item form³⁶ of the Center for Epidemiological Studies Depression scale.³⁷ After each item (eg, "I felt that people disliked me") was read, participants were asked whether they had felt that way much of the time during the past week. The number of symptoms endorsed has been associated with risk of cognitive decline and AD in this³⁸ and other³⁹ cohorts.

Table 1. Descriptive Information on Persons Who Developed AD and Those Who Did Not

Baseline Characteristic	Unaffected Persons (n = 728) ^a	Incident AD (n = 176) ^a	P Value
Age, y	73.5 (6.5)	80.0 (6.5)	<.001
Education, y	18.2 (3.3)	17.8 (3.4)	.17
Sex, % F	68.0	71.0	.47
MMSE score	28.8 (1.3)	27.5 (2.2)	<.001
Conscientiousness score	34.3 (4.8)	32.8 (5.5)	.001
Neuroticism score	16.3 (5.6)	17.4 (5.4)	.02
Extraversion score	28.2 (5.7)	27.1 (5.2)	.02
Openness score	26.6 (5.3)	25.3 (4.5)	.001
Agreeableness score	34.4 (3.7)	33.5 (3.8)	.004
Cognitive activity ^b	3.6 (0.5)	3.5 (0.6)	.11
Physical activity, h/wk	2.9 (3.9)	2.9 (4.7)	.35
Social network ^c	8.0 (10.0)	10.2 (13.3)	.25
Vascular risk factors ^d	0.8 (0.8)	0.8 (0.7)	.73
Vascular conditions ^d	0.2 (0.5)	0.3 (0.5)	.08
CES-D score	0.9 (1.4)	1.3 (1.7)	.001
ApoE ε4 allele, %	22.2	34.6	.002
MCI, %	18.6	49.4	<.001

Abbreviations: AD, Alzheimer disease; ApoE, apolipoprotein E; CES-D, Center for Epidemiologic Studies Depression Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

^aData are mean (SD) unless otherwise specified.

^bMean frequency rating, on a 1 to 5 scale.

^cMean number of people seen at least monthly.

^dMean number present at baseline, of a maximum of 3.

Apolipoprotein E genotyping was done with blinding to all clinical data by methods adapted from Hixson and Vernier.⁴⁰ For analyses, we divided people into those with and without at least one ε4 allele.

NEUROPATHOLOGIC EVALUATION

A standard protocol was followed for brain removal at predetermined sites, sectioning and preserving tissue, and quantifying pathologic findings, as reported in more detail elsewhere.^{28,41} All neuropathologic data collection was done by a neuropathologist (J.A.S.) or trained technician blinded to all clinical data. We used immunohistochemistry and computer-assisted sampling to quantify the percentage area occupied by amyloid-β-immunoreactive plaques and the density of τ-immunoreactive neurofibrillary tangles in 6 brain regions (entorhinal cortex, CA1/subiculum, dorsolateral prefrontal cortex, inferotemporal cortex, angular/supramarginal gyrus cortex, and calcarine cortex). Composite measures of amyloid load and tangle density were formed by averaging standard scores in each region. Lewy bodies were identified in these same regions with antibodies to α-synuclein and treated as present or absent in analyses. Chronic cortical and subcortical infarctions were quantified, as previously described,⁴² and persons without infarctions were contrasted with subgroups with 1 and more than 1 infarction.

DATA ANALYSIS

All analyses controlled for age, sex, and education. We used proportional hazards regression models⁴³ to test the association of conscientiousness with incidence of AD. The core model included a term for conscientiousness. We repeated this model with terms added for other personality traits, activity patterns, vascular conditions, and other risk factors in separate models and then with all covariates in a single model. We also tested for interactions of conscientiousness with neuroticism and demo-

graphic variables. A similar approach was used to test the relation of conscientiousness to mild cognitive impairment.

We used mixed-effects models⁴⁴ to characterize individual paths of change in cognitive function and to assess the relation of conscientiousness to rate of cognitive decline while controlling for baseline level of cognition. Each analysis included terms for time (in years since baseline) and time squared to allow for nonlinear change in cognitive decline, and for conscientiousness and its interaction with time to assess the association of the trait with initial level of and linear change in cognition. Further information on the application of these models to longitudinal cognitive data is provided elsewhere.⁴⁵

Linear regression was used to test whether neuropathologic findings were related to conscientiousness, controlling for time from baseline (when conscientiousness was assessed) to death. We also regressed global cognitive score most proximate to death on pathologic measures and conscientiousness and then repeated the analysis with a term for the interaction of conscientiousness with pathologic features.

Programming was done with SAS statistical software.⁴⁶ Models were validated graphically and analytically.

RESULTS

CONSCIENTIOUSNESS AND INCIDENCE OF AD

The level of conscientiousness in the cohort (mean, 34.0; SD, 5.0) was similar to published normative data.²³ Scores had an approximately normal distribution (skew, -0.5) and ranged from 11 to 47, with higher values indicating a higher level of the trait. Conscientiousness was higher in women than men ($t_{476}=3.9$, $P<.001$) and was not related to age (Pearson $r=-0.06$, $P=.09$) or education ($r=0.06$, $P=.08$). It also had selected associations with other personality traits (neuroticism, $r=-0.29$, $P<.001$; extraversion, $r=0.27$, $P<.001$; openness, $r=0.06$, $P=.07$; and agreeableness, $r=0.27$, $P<.001$), activity patterns (physical activity, Spearman $\rho=0.08$, $P=.02$; cognitive activity, $r=0.08$, $P=.02$; and social network size, $\rho=0.02$, $P=.55$), vascular burden (summary index of vascular risk factors, $\rho=-0.11$, $P=.001$; summary index of vascular conditions, $\rho=-0.09$, $P=.007$), and other risk factors (depressive symptoms, $r=-0.17$, $P<.001$; possession of apolipoprotein E ε4 allele, $t_{274}=1.3$, $P=.19$; and mild cognitive impairment, $t_{916}=1.2$, $P=.23$).

During up to 12 years of annual follow-up evaluations, 176 people developed AD; the diagnosis was made a mean of 4.2 years after baseline (SD, 3.1 years; range, 0.4-11.5 years). The rates of incidence were 0.005 for ages younger than 75 years (10 cases per 2135.3 person-years), 0.028 for ages 75 to 84 years (80 cases per 2900.3 person-years), and 0.083 for ages older than 84 years (86 cases per 1036.5 person-years). Sixteen individuals who developed another form of dementia were excluded from analyses of incident AD. At baseline, those who developed AD were older and more cognitively impaired and apt to have an ε4 allele than unaffected persons were, and they differed in personality, affect, and activity patterns (**Table 1**).

We constructed a proportional hazards model to test the hypothesized association of conscientiousness with incidence of AD. This and all subsequent analyses controlled for age, sex, and education. In the initial model, hazard of AD decreased by more than 5% for each addi-

tional point on the conscientiousness scale (hazard ratio [HR], 0.949; 95% confidence interval [CI], 0.921-0.977). As shown in **Figure 1**, which is based on this analysis, hazard of AD was reduced by about 89% in a person with a high level of conscientiousness compared with a person low in conscientiousness.

Neuroticism has been associated with risk of AD in this¹⁴ and other^{47,48} cohorts. Therefore, we repeated the analysis with a term to control for the effect of neuroticism (HR, 1.033; 95% CI, 1.005-1.063), and conscientiousness continued to be associated with reduced risk (HR, 0.958; 95% CI, 0.929-0.988). When we repeated the analysis with all 5 personality traits in the same model, both conscientiousness (HR, 0.959; 95% CI, 0.929-0.990) and neuroticism (HR, 1.032; 95% CI, 1.001-1.063) were associated with risk, and no effects were observed for extraversion (HR, 1.016; 95% CI, 0.984-1.050), openness (HR, 0.981; 95% CI, 0.948-1.015), or agreeableness (HR, 0.972; 95% CI, 0.931-1.016). In a subsequent analysis, there was no evidence of an interaction between conscientiousness and neuroticism (data not shown).

Because selected activity patterns have been associated with conscientiousness²⁰ and AD,¹² we added terms for frequency of physical activity, frequency of cognitive activity, and size of social network. There was no change in the association of conscientiousness with AD risk in this analysis (HR, 0.947; 95% CI, 0.919-0.976).

Conscientiousness has been related to behaviors associated with cardiovascular health, such as smoking and exercise.²⁰ To see whether vascular factors could account for the relation of conscientiousness to AD, we repeated the original model controlling for summary indexes of vascular risk factors and vascular disease. The association of conscientiousness with risk of AD was not substantially changed (HR, 0.949; 95% CI, 0.921-0.978).

In previous analyses of data from this cohort, level of depressive symptoms,³⁸ possession of a copy of the apolipoprotein E $\epsilon 4$ allele,⁴⁹ and presence of mild cognitive impairment²⁷ have been related to risk of AD. In separate models that controlled for depressive symptoms (HR for conscientiousness, 0.955; 95% CI, 0.926-0.984), the $\epsilon 4$ allele (HR for conscientiousness, 0.956; 95% CI, 0.927-0.986), or mild cognitive impairment (HR for conscientiousness, 0.947; 95% CI, 0.920-0.974), the association of conscientiousness with risk of AD persisted.

We conducted a final model that included all of the covariates from the preceding analyses. In this fully adjusted model, conscientiousness continued to be associated with risk of AD (HR, 0.965; 95% CI, 0.934-0.997).

Women reported higher levels of conscientiousness than men. To see whether the relation of conscientiousness to AD varied by sex, we repeated the original model with a term for the interaction of conscientiousness and sex. There was no evidence of an interaction of conscientiousness with sex in this model or with age or education in separate subsequent analyses (data not shown).

CONSCIENTIOUSNESS AND INCIDENCE OF MILD COGNITIVE IMPAIRMENT

Because mild cognitive impairment is increasingly viewed as a prodromal state that precedes clinically evident de-

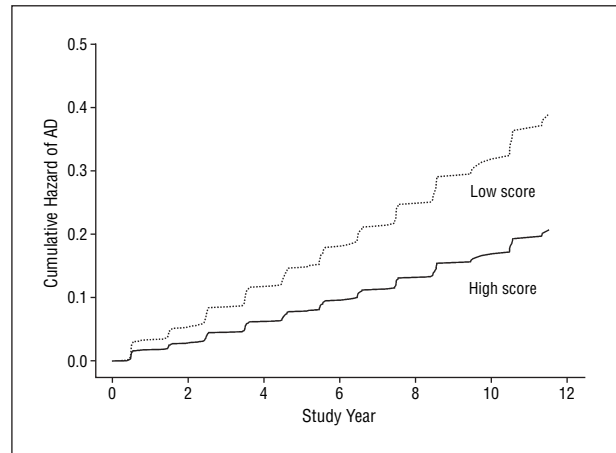


Figure 1. Cumulative hazard of developing incident Alzheimer disease (AD) associated with low (score, 28; 10th percentile) and high (score, 40; 90th percentile) conscientiousness, adjusted for age, sex, and education.

mentia in AD,^{28,50} we conducted additional analyses to test whether conscientiousness was associated with incidence of mild cognitive impairment. At baseline, 688 people had no evidence of cognitive impairment. During follow-up, 317 (46.1%) developed mild cognitive impairment. The rates of incidence were 0.037 for those younger than 75 years old (64 cases per 1729.3 person-years), 0.102 for ages 75 to 84 years (180 cases per 1770.5 person-years), and 0.181 for ages older than 84 years (73 cases per 404.4 person-years). Higher level of conscientiousness was associated with reduced risk of mild cognitive impairment (HR, 0.977; 95% CI, 0.956-0.999). This association remained in subsequent analyses that controlled for physical, cognitive, and social activity or for cardiovascular health, but it was no longer significant in analyses that controlled for other personality traits, depressive symptoms, or the $\epsilon 4$ allele (data not shown).

CONSCIENTIOUSNESS AND COGNITIVE DECLINE

We examined the relation of conscientiousness to cognitive decline, the principal clinical manifestation of AD, to ensure that results were not due to diagnostic bias or imprecision. To make use of all cognitive data, we began with the composite measure of global cognition (mean, 0.10; SD, 0.51). We constructed a series of mixed-effects models that allowed us to estimate the association of conscientiousness with rate of change in cognition while controlling for baseline level of cognition. In the initial analysis, conscientiousness was not related to global cognition at baseline but was associated with rate of global cognitive decline (**Table 2**). **Figure 2** depicts this result: individuals with high levels of conscientiousness began the study at about the same level of cognition as those low in conscientiousness but declined substantially less during follow-up.

Because cross-sectional research suggests that conscientiousness may be related to some cognitive domains but not others,^{51,52} we repeated the original mixed-effects model with measures of specific cognitive domains in place of the global measure. In these analyses (**Table 2** and **Figure 3**), conscientiousness was associated with better baseline per-

Table 2. Relation of Conscientiousness to Decline in Different Cognitive Systems

Cognitive Outcome	Model Term	Estimate (SE) ^a	P Value ^a
Global cognition	Time	0.001 (0.005)	.83
	Time squared	-0.008 (<0.001)	<.001
	Conscientiousness	0.002 (0.003)	.53
	Conscientiousness × time	0.003 (0.001)	<.001
Episodic memory	Time	0.015 (0.008)	.05
	Time squared	-0.009 (0.001)	<.001
	Conscientiousness	0.000 (0.004)	.94
	Conscientiousness × time	0.004 (0.001)	<.001
Semantic memory	Time	-0.010 (0.006)	.09
	Time squared	-0.006 (<0.001)	<.001
	Conscientiousness	-0.005 (0.004)	.22
	Conscientiousness × time	0.003 (0.001)	<.001
Working memory	Time	-0.001 (0.005)	.80
	Time squared	-0.005 (0.001)	<.001
	Conscientiousness	0.002 (0.004)	.62
	Conscientiousness × time	0.001 (0.001)	.04
Perceptual speed	Time	-0.038 (0.007)	<.001
	Time squared	-0.006 (0.001)	<.001
	Conscientiousness	0.016 (0.005)	<.001
	Conscientiousness × time	0.003 (0.001)	.003
Visuospatial ability	Time	-0.004 (0.006)	.50
	Time squared	-0.004 (0.001)	<.001
	Conscientiousness	0.004 (0.004)	.38
	Conscientiousness × time	0.001 (0.001)	.06

^aFrom mixed-effects models adjusted for age, sex, and education.

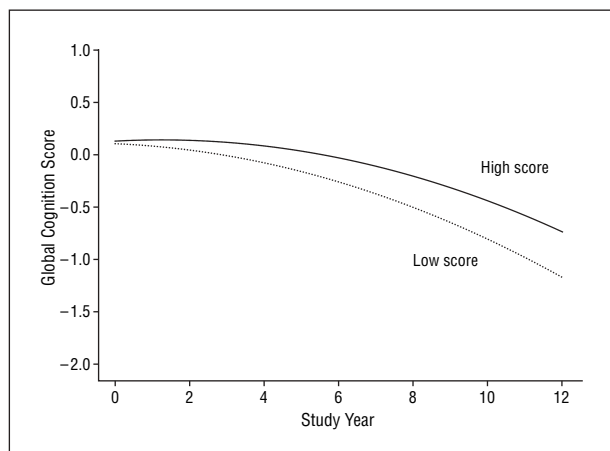


Figure 2. Predicted paths of global cognitive decline associated with low (score, 28; 10th percentile) and high (score, 40; 90th percentile) conscientiousness, adjusted for age, sex, and education.

formance in perceptual speed but not in other domains. By contrast, higher level of conscientiousness was associated with reduced rates of decline in episodic memory, semantic memory, working memory, and perceptual speed. The association was especially robust for episodic memory and nearly significant for visuospatial ability.

CONSCIENTIOUSNESS AND NEUROPATHOLOGIC FINDINGS

Alzheimer disease has been reported to reduce conscientiousness.^{53,54} Therefore, we considered the possibil-

ity that reduced conscientiousness might be a subtle early sign of the neuropathologic changes associated with dementia. At the time of these analyses, 383 individuals had died, of whom 358 (93.5%) underwent brain autopsy, the results of which were available in 324 at the time of these analysis (mean age, 86.1 years [SD, 7.0 years]; mean postmortem interval, 8.1 hours [SD, 8.0 hours]). In separate linear regression models that were controlled for age at death, sex, education, and time since baseline, conscientiousness was not related to density of τ -immunoreactive tangles (composite measure available in 281 subjects; mean, 7.1; SD, 8.8; estimate, -0.02; SE, 0.04; $P = .53$), burden of amyloid- β -immunoreactive plaques (composite measure available in 244 subjects; mean, 2.0; SD, 2.1; estimate, -0.18; SE, -0.15; $P = .22$), cerebral infarction (data available in 320 subjects; 1 infarct: estimate, 0.76; SE, 0.77; $P = .32$; > 1 infarct: estimate, -0.01; SE, 0.75; $P = .99$), or Lewy bodies (data available in 246 subjects; estimate, -1.98; SE, 1.93; $P = .31$).

We conducted a final series of linear regression models to test whether conscientiousness modified the association of neuropathologic findings with cognition. In the initial analyses (**Table 3**, model A), each of the 4 forms of neuropathologic changes showed the expected inverse association with level of global cognition proximate to death, and, consistent with analyses in the entire cohort, conscientiousness was not related to level of global cognition. In subsequent analyses (Table 3, model B), conscientiousness did not interact with amyloid or Lewy bodies but did with tangles and multiple infarctions. **Figure 4** shows these effects. In A, the negative correlation of tangles with global cognition is stronger at high than low levels of conscientiousness. In B, the negative impact of multiple infarctions on cognition is stronger in those high in conscientiousness than those low in the trait.

COMMENT

In a group of nearly 1000 older persons studied annually for up to 12 years, we examined the relation of the personality trait of conscientiousness to incidence of AD. We found that a higher level of the trait was associated with reduced risk of developing clinical AD, even after controlling for other personality traits and risk factors for AD. The results suggest that conscientiousness is inversely associated with risk of developing an AD-like dementia syndrome in old age.

Previous research on conscientiousness and AD has primarily focused on change in the trait as a consequence of the disease. Persons with clinically diagnosed AD are described by others as being less conscientious than they were before dementia onset,⁵³ with further decline in conscientiousness occurring as the disease progresses.⁵⁴ These observations suggest that level of conscientiousness might be a subtle early indicator of the underlying disease or a reaction to its earliest behavioral manifestations, ie, a consequence of AD rather than a true risk factor. A reverse causality hypothesis can account for the association of conscientiousness with loss of cognition as well as a risk factor hypothesis can, but it is not easily reconciled with other data. Thus, conscientious-

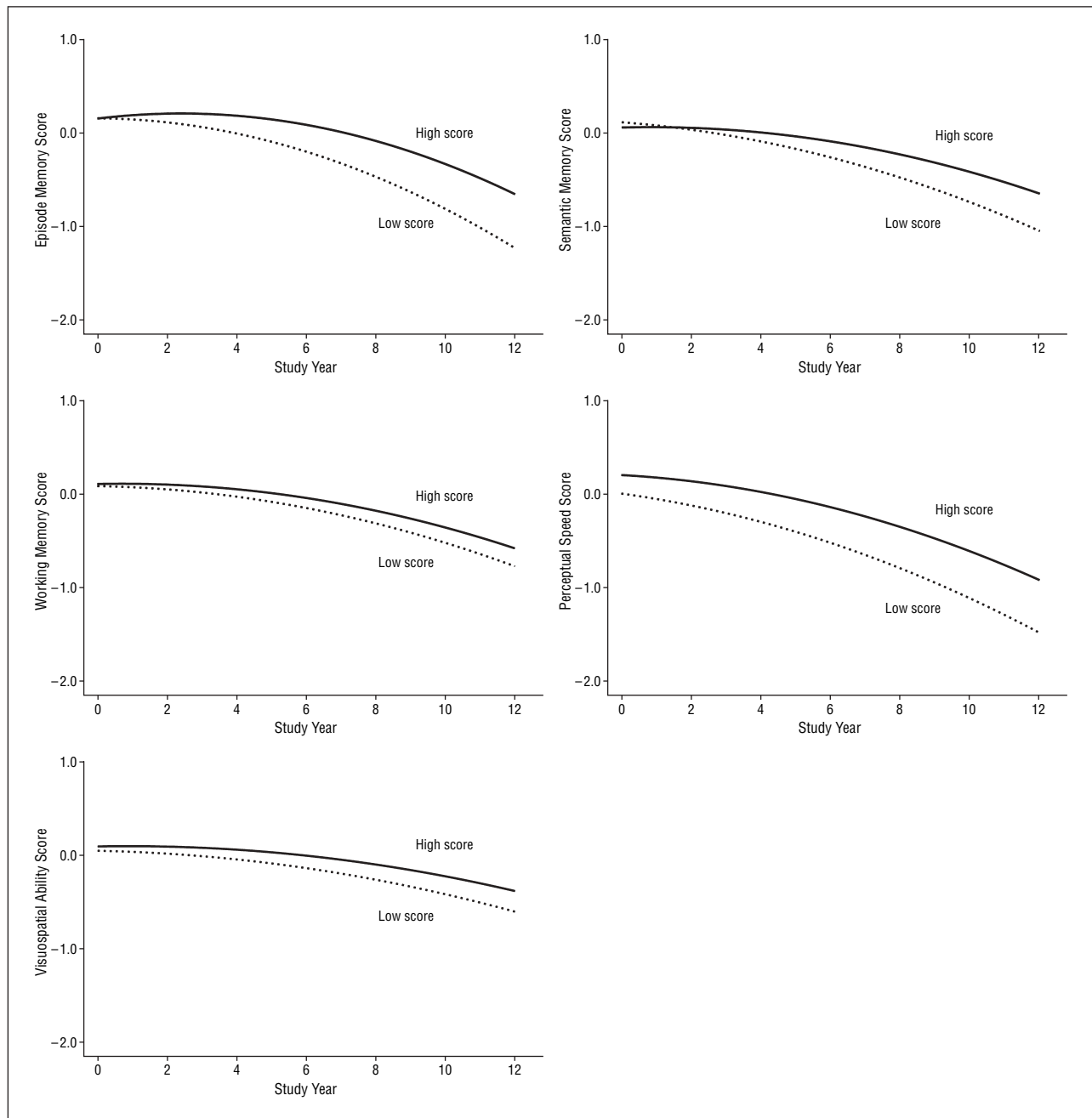


Figure 3. Predicted paths of decline in different cognitive domains associated with low (score, 28; 10th percentile) and high (score, 40; 90th percentile) conscientiousness, adjusted for age, sex, and education.

ness was not related to level of global cognition or the presence of mild cognitive impairment at baseline, robust early indicators of AD, or to composite measures of its neuropathologic features or to other pathologic lesions associated with dementia; and conscientiousness tends to slightly increase in old age.⁵⁵ By contrast, other signs that predict AD, such as olfactory dysfunction, parkinsonian gait, and reduced body mass, are related to cognition⁵⁶⁻⁵⁸ and AD pathologic changes⁵⁹⁻⁶¹ and worsen in old age.^{57,58,62}

Factors that predict the development of AD may do so through associations with level of cognitive function, rate of cognitive decline, or both. In this study, conscientiousness was not associated with level of cognitive

function at baseline, a finding generally consistent with previous research,^{51,52,63} except for a positive association with perceptual speed, which has been previously observed in both young⁵¹ and old⁵² persons, suggesting that it may reflect an association between the conscientiousness trait complex and clerical skill that develops before old age.⁵¹ By contrast, conscientiousness was robustly related to rate of decline in multiple domains of cognition, with less decline in those with higher levels of the trait. Moreover, among those without evidence of cognitive impairment at baseline, conscientiousness was related to incidence of mild cognitive impairment, with a higher level of the trait being associated with reduced risk. Thus, conscientiousness was associated with the emer-

Table 3. Level of Global Cognitive Function Proximate to Death as a Function of Neuropathologic Features, Conscientiousness, and Their Interaction^a

Model Terms	Model A		Model B	
	Estimate (SE)	P Value	Estimate (SE)	P Value
Amyloid load	-0.152 (0.033)	<.001	-0.154 (0.035)	<.001
Conscientiousness	0.020 (0.015)	.17	0.023 (0.020)	.25
Conscientiousness × amyloid	-0.001 (0.007)	.83
Tangle density	-0.067 (0.007)	<.001	-0.071 (0.007)	<.001
Conscientiousness	0.012 (0.012)	.33	0.035 (0.016)	.03
Conscientiousness × tangles	-0.004 (0.002)	.02
1 Infarct	0.086 (0.183)	.64	0.071 (0.183)	.70
Multiple infarcts	-0.492 (0.177)	.006	-0.552 (0.179)	.002
Conscientiousness	0.013 (0.013)	.32	0.024 (0.014)	.10
Conscientiousness × 1 infarct	-0.019 (0.043)	.66
Conscientiousness × infarcts	-0.083 (0.040)	.04
Lewy bodies	-1.921 (0.449)	<.001	-1.771 (0.507)	<.001
Conscientiousness	0.009 (0.014)	.52	0.006 (0.015)	.70
Conscientiousness × Lewy bodies	0.054 (0.083)	.52

Abbreviation: Ellipses, not applicable.

^aFrom separate linear regression models with terms for a given neuropathologic feature and conscientiousness (model A column) or for the neuropathologic feature, conscientiousness, and their interaction (model B column). All models were adjusted for age at death, sex, education, and time from baseline to death.

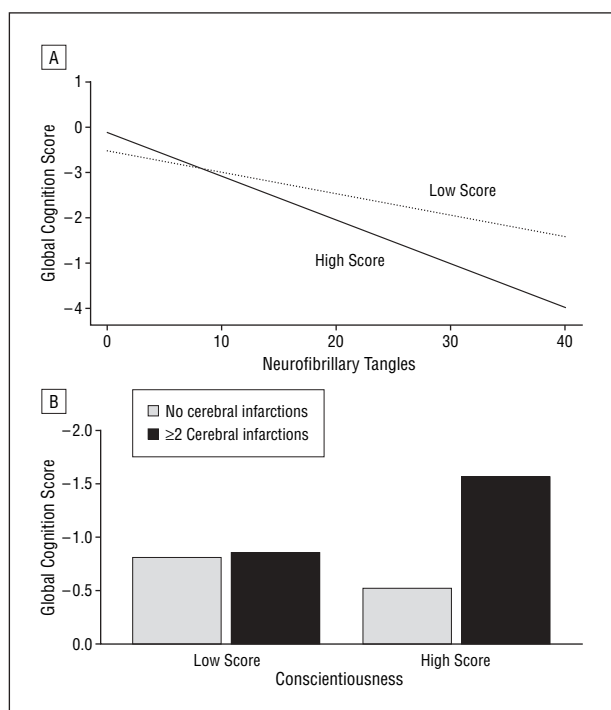


Figure 4. A, Predicted association of tangles with global cognition proximate to death at low (score, 28; 10th percentile) and high (score, 40; 90th percentile) levels of conscientiousness. B, Predicted levels of global cognition proximate to death with no cerebral infarctions vs multiple cerebral infarctions at low vs high levels of conscientiousness.

gence of the earliest signs of cognitive dysfunction in old age, in contrast to its lack of association with cognitive decline once dementia is clinically evident.⁶⁴

How might conscientiousness contribute to loss of cognition? We considered the possibility that cardiovascular health or lifestyle activity patterns might be mediat-

ing the association of conscientiousness with risk of AD.²⁰ Controlling for these variables, however, did not substantially affect findings.

Another consideration is that conscientiousness is a consistent predictor of academic and occupational performance.^{16,17} Both level of educational and occupational attainment¹¹ and the nature of occupational experiences⁶⁵ have been associated with risk of AD. Highly conscientious people may have a more intensive exposure to these educational and occupational experiences than less conscientious individuals and thereby derive additional benefit. Also, meta-analyses suggest that conscientiousness shows systematic growth in young adulthood and old age,⁵⁵ perhaps partly in reaction to life experiences in the workplace and the home environment. Thus, level of conscientiousness in old age might be an indicator of successful experiences in social and occupational roles.

Conscientiousness is associated with a higher level of resilience^{66,67} and greater reliance on task-oriented coping.⁶⁸ These factors might lessen the adverse consequences of negative life events and chronic psychological distress, which have been associated with risk of dementia in old age.^{14,47,48,69} In this cohort, controlling for neuroticism, an indicator of chronic distress, reduced the association of conscientiousness with AD by about one-fifth, partly consistent with this idea.

An unexpected finding was that 2 pathologic lesions, tangles and infarctions, had stronger negative correlations with cognition proximate to death among those high in conscientiousness compared with those low in the trait. Because conscientiousness was associated with reduced cognitive decline in the cohort, this finding probably does not mean that conscientious people are less able to tolerate these lesions. We suggest another possibility. That conscientiousness is associated with risk of dementia but not with its traditional pathologic features suggests that

it may be related to some other neurodeteriorative changes that do not leave currently recognized pathologic footprints. In that case, the brains of highly conscientious people would be more pathologically homogeneous (ie, relatively confined to amyloid, tangles, infarction, and Lewy bodies) than the brains of people low in the trait, and this pathologic homogeneity would be expected to result in stronger correlations of traditional pathologic features with clinical function. Further research will be needed to test this and other possibilities.

This study has some notable strengths. Clinical classification of AD and mild cognitive impairment was based on a uniform evaluation and previously established criteria²³ implemented by an experienced clinician, minimizing the likelihood of diagnostic error. Cognitive function was assessed at evenly spaced intervals with psychometrically sound composite scales for up to 12 years with high rates of follow-up participation, enhancing our ability to reliably characterize individual paths of cognitive decline. We assessed conscientiousness and other traits with a standard scale. More than 90% of those who died underwent a brain autopsy, allowing us to directly test whether conscientiousness proximate to death was related to age-related neuropathologic changes.

The main limitation of the study is that the data were based on a selected group of people who differ from the general population of older persons in education and lifestyle. It will therefore be important to replicate these findings in more representative cohorts. In addition, conscientiousness is a somewhat heterogeneous trait complex, but the brief measure used in this study precluded investigation of its subcomponents.

In conclusion, level of conscientiousness is associated with incidence of mild cognitive impairment and AD but not with the pathologic hallmarks of these conditions. Understanding the mechanisms linking conscientiousness to maintenance of cognition in old age may suggest novel strategies for delaying the symptoms of AD.

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