ABSTRACT

Objective Preventing Alzheimer’s dementia (AD) fundamentally equates to delaying onset. Thus, we quantified associations of modifiable, psychosocial risk factors to years of delayed onset of dementia.

Design Two prospective cohorts (n=2860) with negative and positive psychosocial factors measured at baseline (depressive symptoms, neuroticism, cognitive activity).

Setting and participants Religious Orders Study of older priests, nuns and brothers across the USA, initiated in 1994; Rush Memory and Aging Project, of older persons in Chicago area, initiated in 1997.

Outcome measure We conducted annual neurological and neuropsychological assessments to identify AD across psychosocial risk factor groups, controlling for confounders, using accelerated failure time models.

Results We found strong relations of three or more depressive symptoms with age at AD diagnosis; estimated mean age at diagnosis was 86.9 years with significant symptoms versus 92.1 years with no symptoms (p<0.001). In addition, neuroticism was inversely related to age at AD diagnosis; estimated mean age at diagnosis was 88.8 years for the highest neuroticism tertile and 93.1 years in the lowest tertile (p<0.001). Participants with higher cognitive activity (such as reading books) had later AD diagnosis; estimated mean age at diagnosis was 89.2 years for the lowest cognitive activity group and 92.6 years for the highest activity group (p<0.001).

Conclusions Higher depressive symptoms were associated with 5-year acceleration in AD; higher neuroticism with 4-year acceleration and higher cognitive activity with a 3.5-year delay. To translate findings, prior health services research in the USA indicates delaying dementia 5 years could add 3 years of life and reduce individual costs of care >$50,000. These results provide a rigorous, easily translatable metric for communicating and evaluating the potential public health impact of psychosocial and experiential interventions.

INTRODUCTION

Approximately 50 million adults have dementia worldwide; clearly, disease prevention is a public health imperative. Indeed, many organisations have established guidelines of modifiable factors to alter risk of Alzheimer’s disease and related dementias. For example, depression is associated with a relative risk of 1.9, or 90% increase in the likelihood of developing dementia, and Lancet Commission guidelines suggest decreasing depression to reduce dementia. Yet, a 90% increase in risk is challenging to interpret for health recommendations. For common chronic diseases of ageing, prevention may be most easily communicated and understood in terms of delaying disease onset rather than increased or decreased relative risks. Indeed, in setting policies surrounding public health priorities, it is common to estimate how a delay in onset of Alzheimer’s dementia (AD) could impact health outcomes. For example, in the USA, estimates indicate that delaying onset of dementia by 5 years would result in additional...
3 years of life for those who would develop dementia, and reduce total costs of AD by 40% in the next 30 years.6 Yet, limited work has investigated the number of years by which risk factors may delay AD, rather than traditional relative risks (or HRs).

To extend research focusing on relative risks, we present a novel investigation of differences in age at AD onset across levels of potentially modifiable psychosocial risk factors, providing an easily interpretable public health metric. We considered three risk factors for dementia, representing both negative and positive health assets: depressive symptomatology, neuroticism and cognitive activity. We focused on psychological factors as they are easily measured, potentially modifiable and often receive less attention when considering dementia prevention.7 Further, all are established AD risk factors,8–10 including our own work in Religious Orders Study (ROS) and Memory and Aging Project (MAP),11–14 facilitating our goal of better translating established risk factor associations; importantly, we reviewed all the publications on depressive symptoms, neuroticism and cognitive activity in relation to dementia which were included in recent systematic reviews on these topics8–10—none calculated the differences in age at dementia onset. Thus, to characterise associations of risk factors with delays in AD onset,14 15 we applied accelerated failure time (AFT) models to data from the ROS and MAP.16

METHODS
ROS was initiated in 1994 and is ongoing with continuous recruitment through the present. The cohort includes >1495 older priests, nuns and brothers across the USA to date, free of known dementia at enrolment.16 MAP16 is also ongoing with continuous recruitment and was established in 1997 with virtually identical design/data collection; >2200 older persons from the Chicago area completed a baseline evaluation to date. Follow-up in both cohorts exceeds 90%. Both studies have considerable data collection harmonised at the item level to merge analyses.

Assessment of risk factors
At baseline, participants completed the 10-item Center for Epidemiological Studies Depression Scale (CES-D).17 Individuals were asked about 10 depressive symptoms in the past week, yielding a score from 0 to 10 symptoms. Since a score of ≥3 may be suggestive of depression,11 we examined three categories: no symptoms; mild (1–2) symptoms; significant (3+) symptoms.

We assessed neuroticism at or near baseline. Neuroticism is a classic ‘Big Five’ personality trait, and the tendency to experience negative emotions, including anxiety and distress. We measured neuroticism using 12 items from the NEO Five-Factor Inventory18; responses were summed into a score from 0 to 48; higher score represents worse neuroticism. We created tertile categories; intervals were ≤12 in the bottom, 13–17 in the middle and ≥18 in the top tertile.

For cognitive activity, participants were asked at baseline about frequency over the past year of seven mentally stimulating activities, chosen for being easily accessible. Although previous work by our group has examined cognitive activity only in the MAP cohort,13 14 we were able to leverage the full sample of both cohorts here by focusing on four common activities queried in both ROS and MAP cohorts (reading newspapers, reading magazines, reading books and playing games such as board games, cards and crossword) using a Likert scale: 1=everyday, 2=several times/week, 3=several times/month, 4=several times/year, 5=once/year or less. All scores were averaged and reverse coded so higher scores indicated more activity. We created tertile categories of cognitive activity; intervals were 1–3.5 in the lowest group, 3.6–4.0 in the ‘moderate’ group and >4.0 in the highest activity group.

Assessment of covariates
We collected key covariates at baseline, including sex and years of education. Physical activity was determined using questions adapted from the 1985 National Health Interview Survey. Participants were asked if they engaged in any of five activities (walking for exercise, gardening, callisthenics, bicycle riding, swimming) within the past 2 weeks, the number of occasions and average minutes. Time in each activity was combined and expressed as hours/week. Finally, we calculated the number of comorbidities among seven self-reported conditions: hypertension, type 2 diabetes, heart disease, cancer, thyroid disease, head injury with loss of consciousness, stroke.

Assessment of AD
Participants had annual uniform clinical evaluations including structured medical history, detailed cognitive testing and neurological examination. An experienced clinician diagnosed AD, according to criteria of the working group of the Department of Health and Human Services Task Force on Alzheimer’s Disease. Generally, diagnosis required impairment in >2 cognitive domains; participants were classified with AD if they met the criteria established by the working group, as previously reported.19 Since most dementia in these cohorts (>90%) is diagnosed as Alzheimer’s, we did not separately consider all-cause dementia here. We also note that currently the term ‘Alzheimer’s disease’ is used to denote pathological diagnosis,20 thus we refer to clinical disease here as ‘Alzheimer’s dementia’.

Population
Across ROSMAP, 3686 women and men with no known dementia completed a baseline examination; 3285 had complete data on the three risk factors. We excluded 151 who were determined to have dementia at baseline pursuant to clinical examination, and 169 who did not have any follow-up. Since few participants were <65 years, limiting estimation of AD onset at younger ages, we...
excluded 105 participants <65 years. Our analytical population included 2860 participants.

Statistical analysis
To estimate age at diagnosis of incident AD across baseline levels of the three risk factors, we used Kaplan-Meier survival curves and extended AFT models, with age as the time scale. In analyses, participants enter the risk set at the age they completed their baseline examination, given they survived to this age with no dementia. Such left truncation may underestimate risks (the analytical population excludes those who did not survive or developed dementia prior to recruitment). We estimated survival curves taking into consideration left truncation (and right censoring) Follow-up was censored at diagnosis of dementia, death or loss to follow-up, whichever came first. For statistical comparison of survival curves, we used log-rank tests to compare risk factor levels.

In addition, we used extended AFT models to calculate adjusted mean ages at AD diagnosis across groups. The extended AFT model takes the form

\[ \log T_i = \beta_i + \sigma_i \times \log (T_0), \]

where \( T_i \) is age at onset for the \( i \)-th participant; \( \beta_i \) and \( \sigma_i \) are respectively the mean and scale parameters of the \( i \)-th participant; \( T_0 \) is a standard baseline distribution. This model extends the classic AFT model by introducing a person-specific scale term \( \sigma_i \), which fit the data better than the classic model. To examine the effects of covariates on the mean and scale parameters, we assume \( \beta_i = \beta^T X_i \), and \( \sigma_i = \exp \left( \gamma_0 + \gamma^T X_i \right) \), where \( X_i \) is the vector of covariates. A positive entry in the vector \( \beta \) indicates, for example, that increasing the corresponding variable postpones mean age of AD onset. Based on goodness-of-fit testing, we used a generalised gamma distribution for \( T_0 \), which includes Weibull, log-normal and gamma distributions as special cases.

In addressing potential confounding, we controlled for years of education, sex, physical activity, number of comorbidities and cohort. We also tested an interaction term for sex by each of the three risk factors. We conducted secondary analyses which (1) included both depressive symptoms and neuroticism in models, and (2) controlled for depressive symptomatology when examining cognitive activity.

Finally, to compare the results from AFT models with traditional metrics, we estimated HRs of AD, and 95% CIs, by levels of depressive symptoms, neuroticism and cognitive activity. We used Cox proportional hazards models, with age as the time scale. All analytical criteria were parallel to those above.

Participant and public involvement
The ROS and the Rush MAP actively incorporate community groups, and community education as part of research, starting from initial recruitment. Investigators and staff regularly visit study recruitment sites and community groups to discuss research, participation and findings (including dissemination of findings), and solicit input regarding study-related issues. Participants and the public were not directly involved in the development of study measures or study design.

RESULTS
At baseline (table 1), participants’ mean age was 78 years (SD 7.0). Approximately one-quarter were male, >90% were white and, on average, participants completed nearly 17 years (SD 3.7) of education. Mean follow-up was 9.2 (SD 5.9) years. At baseline, over half of participants had a CES-D score of 0, while about 15% scored ≥3, suggesting

| Table 1 | Baseline characteristics of participants, Religious Orders Study and Memory and Aging Project (n=2860) |
|---------|---------------------------------------------------------------------------------------------------|
| **Characteristic** | **Mean (SD) or n (%)** |
| **Demographic factors** |  |
| Mean age (years) | 78.2 (7.0) |
| Mean education (years) | 16.6 (3.7) |
| Male | 747 (26%) |
| Race—white | 2689 (94%) |
| Cohort |  |
| Religious Orders Study | 1270 (44%) |
| Memory and Aging Project | 1590 (56%) |
| Mean follow-up (years) | 9.2 (5.9) |
| **Depressive symptoms, neuroticism, cognitive activity** |  |
| Mean depressive symptoms | 1.0 (1.5) |
| 0 symptom | 1580 (55) |
| 1–2 symptoms | 887 (31) |
| 3+ symptoms | 393 (14) |
| Mean neuroticism score | 15.6 (6.6) |
| Mean cognitive activity | 3.7 (0.8) |
| **Health-related factors** |  |
| Mean number comorbidities | 1.4 (1.1) |
| Mean physical activity (hours/week) | 3.2 (3.8) |
| Number of deaths | 1576 (55%) |
| **Diagnosis of Alzheimer’s dementia** |  |
| Incident cases of Alzheimer’s dementia during follow-up | 785 (27%) |
| Mean age at diagnosis of Alzheimer’s dementia (years) | 87.6 (6.6) |
| Mean time from baseline to diagnosis of Alzheimer’s dementia (years) | 7.8 (5.6) |

*Depressive symptoms measured using the Center for Epidemiological Studies Depression Scale, with a range of 0–10 symptoms. Neuroticism score was derived from 12 items of the NEO Five-Factor Inventory, with a range of 0–48 points, where higher score indicates worse neuroticism. Cognitive activity is the average frequency across four activities on a scale from 1 (once/year or less) to 5 (daily).
depression. Mean neuroticism score was approximately 16 (SD 6.6). Participants reported a mean of 1.4 comorbidities, and approximately 3 hours of physical activity per week. Overall, 1576 participants died during follow-up. Finally, during follow-up, we identified 785 incident AD cases, with mean age at diagnosis of nearly 88 years (SD 6.6).

### Survival curves for remaining free of AD, according to depressive symptoms, neuroticism and cognitive activity

When we examined survival curves according to level of depressive symptoms (figure 1), the probability of remaining free of dementia was similar comparing participants with mild (1–2) versus no symptoms at baseline (p=0.1). However, we found substantially lower probability of remaining dementia free for those with significant depressive symptoms (CES-D>3) versus none (p=0.001). For example, in those with significant symptoms, median age by which dementia was diagnosed was approximately 5 years earlier: medians were 88.5 years (95% CI 84.5 to 92.9) in those with 3+ symptoms, but 93.4 years (95% CI 92.5 to 94.1) with no symptoms (these findings represent age at which likelihood of remaining free of dementia was 50%).

Comparing survival without AD across tertiles of neuroticism (figure 2), probabilities of remaining AD free were lower with higher neuroticism (p<0.001 and p=0.003, respectively, for highest and middle tertiles of neuroticism vs lowest tertile). For example, median age at diagnosis was approximately 4 years earlier with higher neuroticism: medians were 90.4 years (95% CI 89.6 to 92.2) for those with highest neuroticism, 92.0 years (95% CI 90.7 to 93.4) with moderate levels and 94.1 years (95% CI 93.7 to 95.4) for the lowest level of neuroticism.

When we considered cognitive activity (figure 3), likelihood of remaining free of dementia was lower for the second and the highest tertiles of cognitive activity than for the lowest tertile (p=0.04 and p<0.001, respectively, compared with bottom tertile). For example, median age at dementia diagnosis was approximately 4 years later with the highest cognitive activity: median was 91.0 years (95% CI 89.8 to 92.4) among those with least activity, while it was 92.4 years (95% CI 90.6 to 93.7) in the ‘moderate’ group and 94.0 years (95% CI 83.1 to 95.1) in the highest level of cognitive activity.

### Multivariable-adjusted relations of depressive symptoms, neuroticism and cognitive activity to age at onset of AD

Next, we controlled for covariates using AFT models, and estimated mean ages at AD diagnosis (table 2). We found no association of mild depressive symptoms with age at AD diagnosis (p=0.1). However, there was a strong relation of significant depressive symptoms with age at dementia onset (p=0.001); estimated mean age at diagnosis was 86.9 years with 3+ symptoms versus 92.1 years with none—more than 5 years earlier onset of dementia with significant depressive symptoms at baseline.
There were also significant associations of mean age at AD diagnosis with higher levels of neuroticism (third vs lowest tertile, p<0.001; middle vs lowest tertile, p=0.03). For example, estimated mean age at dementia diagnosis was 88.8 years in the worst tertile of neuroticism, 90.5 years with moderate levels, but 93.1 years in the lowest tertile. Thus, while HRs are broadly consistent (as expected) with relations identified in AFT models, findings for each risk factor remained consistent with those reported above. Additionally, results for cognitive activity were similar controlling for depressive symptomatology. We found no interactions of the three risk factors with sex in relation to age at diagnosis.

**DISCUSSION**

In these older persons, we found that depressive symptoms were strongly related to age at AD onset— with 5-year earlier diagnosis among those with significant versus no symptoms. Further, higher levels of neuroticism appeared to advance dementia by approximately 4 years. In contrast, greater cognitive activity was related to as much as 3.5 years’ later onset of AD. Given the rapid ageing of our population, the public and individual health implications of these results are simple and striking.

Specifically, previous health services research estimated how delays in dementia onset could influence health and financial outcomes. In terms of ‘translating’ our findings for significant depressive symptoms, these estimates indicate that a 5-year delay in AD onset would yield almost three additional years of life in those who eventually develop AD, and yield >$60,000 of savings/person in formal and informal healthcare costs. To consider the value of interventions for reducing depression, approximately one in five older adults have depression or significant depressive symptoms, further, some estimates suggest that >50% of late-life depression may be preventable. Depression in older persons can be successfully treated, although approximately one-third of those with depression in the USA do not receive treatment.

Further, as noted earlier, scientific evidence is convincing regarding associations of depressive symptomatology to AD. While there has been concern that depressive symptoms may be an initial sign or consequence of dementia rather than a predisposing factor, studies consistently find depressive symptoms are associated with dementia when assessed many years prior to dementia diagnosis; further, in prior analysis of our cohorts, there was no marked escalation in depressive symptoms in the years before AD was identified. Thus,
reducing depression has potential to profoundly impact the burden of dementia, besides other health benefits.

For neuroticism, we found that higher levels were associated with 3–4 years of earlier onset of AD. Estimates indicate that a 3-year delay in dementia onset could lead to nearly 2 years of added life, and savings of >$50 000/person combining formal and informal costs of care, in those who will develop AD.6 Regarding interventions, while personality traits such as neuroticism were once considered immutable, it is now appreciated that neuroticism levels can change, and are only moderately stable over long periods.27 In particular, neuroticism can be modified in response to pharmacological and non-pharmacological interventions, and there is growing interest in population-level approaches for reducing neuroticism.28 Interestingly, later life appears to be particularly amenable to changing neuroticism.28

While neuroticism has received somewhat less attention as a risk factor for dementia than depressive symptomatology, a recent meta-analysis found highly significant relations of neuroticism to dementia.8 Across 12 prospective studies,8 each SD increase in neuroticism score was associated with an incremental increase in dementia risk (pooled HR=1.24, 95% CI 1.15 to 1.33). Similar to depressive symptoms, reverse causation is possible, such that the pathology underlying dementia could lead to personality changes, rather than personality leading to higher risk of developing dementia.8 However, in the meta-analysis,8 length of follow-up did not influence the extent of relation between neuroticism and dementia (whereas reverse causation should result in stronger associations with shorter follow-up). In addition, a long-term study tracking changes in neuroticism found no evidence of varying trajectories of neuroticism for those who did and did not develop dementia.29

We also found that engagement in cognitive activities was associated with as much as 3.5-year delayed onset of dementia. As a health intervention, cognitive activity is believed to increase cognitive reserve,30 31 defined as the ability to tolerate neuropathology without manifesting clinical cognitive symptoms.32 Neuropathology is ubiquitous in older persons,33 and there is no known treatment. Thus, targeting enhanced cognitive reserve may be a highly feasible path to dementia prevention. Notably, community-based programmes for older persons, such as Experience Corps (a volunteer programme), have already been demonstrated to increase cognitive activity.34

In a systematic review of 10 prospective studies of cognitive activity and dementia,35 most reported higher cognitive activity was associated with lower dementia risk. In this review,35 quantitative bias analyses indicated that observed inverse associations were robust to potential

| Status at baseline* | Incident Alzheimer’s dementia (n) | Estimated mean age at diagnosis of Alzheimer’s dementia† (years) | P value‡ |
|---------------------|----------------------------------|-------------------------------------------------------------|----------|
| **Depressive symptoms** |                                  |                                                             |          |
| No depressive symptoms (n=1293) | 328 | 92.1 | Reference |
| Mild depressive symptoms (n=654) | 185 | 89.5 | 0.1 |
| Significant depressive symptoms (n=914) | 272 | 86.9 | 0.001 |
| **Neuroticism** |                                  |                                                             |          |
| Lowest tertile/least neuroticism (n=923) | 193 | 93.1 | Reference |
| Second tertile (n=958) | 288 | 90.5 | 0.03 |
| Highest tertile/most neuroticism (n=979) | 304 | 88.8 | <0.001 |
| **Cognitive activity** |                                  |                                                             |          |
| Lowest tertile/least activity (n=1198) | 347 | 89.2 | Reference |
| Second tertile (n=803) | 216 | 90.8 | 0.02 |
| Highest tertile/most activity (n=859) | 222 | 92.6 | <0.001 |

*Depressive symptoms measured using the 10-item Center for Epidemiological Studies Depression Scale. No symptoms were defined as a score of 0; mild symptoms as a score of 1–2; and significant symptoms as a score of 3–10. Neuroticism measured using the NEO Five-Factor Inventory (range, 0–48 points). The bottom tertile included scores <12; the second tertile 13–17; top tertile ≥18. Cognitive activity included self-reported frequency over the past year of four activities: reading the newspaper, reading magazines, reading books, playing games. Responses for each activity were averaged to create a score from 1 (once a year or less) to 5 (every day/almost every day). The tertiles were defined by scores of ≤3.5; 3.6–4.0; >4.0.

†Age at diagnosis was estimated using the mean parameters from an extended accelerated failure time model, with a covariate for years of education; education was set as median years of education (16) in the population. This simplified model with education and no other covariates yielded results within approximately 10% of the estimates in the full model with all covariates.

‡P value is from the coefficient comparing each risk factor group to its reference group within a single extended accelerated failure time model controlled for sex, education, cohort, physical activity and number of comorbidities. Separate models were created for depressive symptoms, neuroticism and cognitive activity.
unmeasured confounding, and that relations of cognitive activity to dementia were not likely fully explained by reverse causation. Therefore, substantial evidence has established both that cognitive activity can be modified in populations, and that activity is related to reduced likelihood of dementia.

Limitations should be considered. In these cohorts, few participants reported high numbers of depressive symptoms. Thus, our findings may underestimate associations of depression to age at AD diagnosis. Similarly, few persons had very high neuroticism scores, and we likely somewhat underestimate relations of higher neuroticism with AD. Another limitation is the homogeneity of ROSMAP in terms of education, as well as factors such as profession (ROS), geographic region (MAP is based in the Chicago area) and race (>90% white race). In particular, since dementia onset differs across racial/ethnic groups,35 our findings may not be generalisable to diverse populations; research should be extended to diverse racial and ethnic groups.

There are important strengths of this research. ROSMAP participants receive annual neurological examinations. Thus, we uniformly identify AD at its earliest clinical manifestation, greatly reducing misclassification of age at onset. Further, loss to follow-up was low, limiting bias in describing associations. Most importantly, our results are unique in providing rigorous estimates of the number of years by which modifiable psychosocial and experience risk factors may delay onset of dementia; such information has the potential to meaningfully advance dementia prevention efforts and risk communication in communities.

Contributors FG, TW, SL, RSW and DAB conceptualised and designed the study. FG and SL contributed to data analysis. FG wrote the first draft of the manuscript. TW conducted the data analysis and visualisation. FG and SL verified the underlying data. SL, RSW and DAB supported the data collection. SL and DAB provided project administration and supervision. TW, SL, RSW and DAB were involved in data interpretation and revision of the manuscript. FG is the guarantor and accepts full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish.

Funding This study was supported by grants from the National Institute on Aging in the US National Institutes of Health (grant numbers P30AG10161, P30AG72975, R01AG15819, R01AG17917).

Disclaimer The funding agency had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by Rush University Medical Center IRB (Protocol LB6121802). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data used for this research are available from the Religious Orders Study and Rush Memory and Aging Project and can be requested at https://www.radc.rush.edu.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

ORCID iDs
Francine Grodstein http://orcid.org/0000-0002-2699-7051
Tianhao Wang http://orcid.org/0000-0002-1831-8266

REFERENCES
1. Patterson C. World Alzheimer report. London: Alzheimer’s Disease International, 2018.
2. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413–46.
3. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer’s disease prevalence and incidence. Alzheimers Dement 2011;10:819–29.
4. Naik G, Ahmed H, Edwards AGK. Communicating risk to patients and the public. Br J Gen Pract 2012;62:213–6.
5. Brookmeyer R, Abdalla N, Kawas CH, et al. Forecasting the prevalence of preclinical and clinical Alzheimer’s disease in the United States. Alzheimers Dement 2018;14:121–9.
6. Zissimopoulos J, Crimmins E, St Clair P. The value of delaying Alzheimer’s disease onset. Forum Health Econ Policy 2014;18:25–39.
7. Dafsan JF, Jessen F. Depression—an underrecognized target for prevention of dementia in Alzheimer’s disease. Transl Psychiatry 2020;10:160.
8. Aschwanden D, Strickhouser JE, Luchetti M, et al. Is personality associated with dementia risk? A meta-analytic investigation. Ageing Res Rev 2021;67:101269.
9. Cherbuin N, Kim S, Anstey KJ. Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis. BMJ Open 2015;5:e008853.
10. Sajev G, Weuve J, Jackson DW. Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons. Epidemiology 2016;27:732–42.
11. Wilson RS, Schneider JA, Bienias JL, et al. Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons. Neurology 2003;61:1102–7.
12. Wilson RS, Arnold SE, Schneider JA, et al. Chronic psychological distress and risk of Alzheimer’s disease in old age. Neuroepidemiology 2006;27:143–53.
13. Wilson RS, Scherr PA, Schneider JA, et al. Relation of cognitive activity to risk of developing Alzheimer disease. Neurology 2007;69:1911–20.
14. Wilson RS, Wang T, Yu L, et al. Cognitive activity and onset age of incident Alzheimer disease dementia. Neurology 2021;97:e922–9.
15. Boyle PA, Wang T, Yu L, et al. Purpose in life may delay adverse health outcomes in old age. Am J Geriatr Psychiatry 2022;30:00322–5.
16. Bennett DA, Buchman AS, Boyle PA, et al. Religious orders study and rush memory and aging project. JAD 2018;64:5161–89.
17. Kohout FJ, Berkman LF, Evans DA, et al. Two shorter forms of the CES-D depression symptoms index. J Aging Health 1993;5:179–93.
18. Costa PTJ, McCrae RR. Revised NEO personality inventory (NEO-PI-R) and NEO five-factor inventory (NEO-FFI) manual. Psychological Assessment Resources, Odessa, FL, 1992.
19. Bennett DA, Schneider JA, Aggarwal NT, et al. Decision rules guiding the clinical diagnosis of Alzheimer’s disease in two community-based cohort studies compared to standard practice in a clinic-based cohort study. Neuroepidemiology 2006;27:169–76.
20. Jack CR, Bennett DA, Blennow K. NIA-AA research framework: toward a biological definition of Alzheimer’s disease. Alzheimer’s Dementia 2018;14:535–62.
21. Kalbfleisch JD, Lawless JF. Some useful statistical methods for truncated data. J Qual Technol 1992;24:45–52.
22. Volkert J, Schulz H, Härtler M, et al. The prevalence of mental disorders in older people in Western countries – a meta-analysis. Ageing Res Rev 2013;12:339–53.
23. Chang S-C, Pan A, Kawachi I, et al. Risk factors for late-life depression: a prospective cohort study among older women. Prev Med 2016;91:144–51.
24. Kok RM, Reynolds CF. Management of depression in older adults: a review. JAMA 2017;317:2114–22.
25. Center for Behavioral Health Statistics and Quality. 2017 national survey on drug use and health: methodological summary and
definitions. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018.

26 Wilson R, Bennett D. How does psychosocial behavior contribute to cognitive health in old age? Brain Sci 2017;7:56.

27 Wilson RS, Arnold SE, Beck TL, et al. Change in depressive symptoms during the prodromal phase of Alzheimer disease. Arch Gen Psychiatry 2008;65:439–45.

28 Bleidorn W, Hill PL, Back MD, et al. The policy relevance of personality traits. Am Psychol 2019;74:1056–67.

29 Terracciano A, An Y, Sutin AR, et al. Personality change in the preclinical phase of Alzheimer disease. JAMA Psychiatry 2017;74:1259–65.

30 Scarmeas N, Zarahn E, Anderson KE, et al. Association of life activities with cerebral blood flow in Alzheimer disease: implications for the cognitive reserve hypothesis. Arch Neurol 2003;60:359–63.

31 Rajan KB, Barnes LL, Skarupski KA, et al. Physical and cognitive activities as deterrents of cognitive decline in a biracial population sample. Am J Geriatr Psychiatry 2015;23:1225–33.

32 James BD, Bennett DA. Causes and patterns of dementia: an update in the era of redefining Alzheimer’s disease. Annu Rev Public Health 2019;40:65–84.

33 Boyle PA, Yu L, Wilson RS, et al. Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol 2018;83:74–83.

34 Parisi JM, Kuo J, Rebok GW, et al. Increases in lifestyle activities as a result of experience Corps® participation. J Urban Health 2015;92:55–66.

35 Brewster P, Barnes L, Haan M. Progress and future challenges in aging and diversity research in the United States. Alzheimer’s Dementia 2019;15:995–1003.