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Modifiable psychosocial risk factors and delayed onset of dementia in older populations: analysis of two prospective US cohorts

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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 >$60,000. 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 could impact health outcomes. For example, in the USA, estimates indicate that delaying onset of dementia by 5 years would result in additional

Strengths and limitations of this study

► A strength of this research is our formal quantification of risk factor associations according to the number of years by which each appears to delay/accelerate onset of dementia, which provides substantial benefits in terms of interpretability, compared with typical epidemiological measures.

► These cohorts are particularly well suited to quantifying associations of risk factors to the number of years of delayed onset due to the rigorous, annual clinical evaluations of dementia, which reduce misclassification regarding timing of onset compared with most cohorts, which evaluate dementia less frequently.

► A limitation is the select cohort of participants in the Religious Orders Study and Memory and Aging Project who are primarily white and have high education.

► An additional limitation is the relatively low levels of depressive symptoms or neuroticism, potentially leading to underestimates of their associations with delayed onset of dementia.
3 years of life for those who would develop dementia, and reduce total costs of AD by 40% in the next 30 years. 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. Further, all are established AD risk factors, including our own work in Religious Orders Study (ROS) and Memory and Aging Project (MAP), 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 topics—none calculated the differences in age at dementia onset. Thus, to characterise associations of risk factors with delays in AD onset, we applied accelerated failure time (AFT) models to data from the ROS and MAP.

**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. MAP 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). 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, 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 Inventory; 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, 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 crosswords) using a Likert scale: 1=everyday, 2=several times/month, 3=several times/week, 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. 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, 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...
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 of neuroticism—suggesting up to 4-year earlier onset of dementia with worse neuroticism.

Finally, after adjusting for covariates, we found strong relations of later age at AD diagnosis with more cognitive activity at baseline (p<0.001 for highest tertile, p=0.03 for the ‘moderate’ group, vs lowest tertile). For example, those with the highest cognitive activity had mean age at AD diagnosis of 92.6 years, with mean of 90.8 years for the moderate group and 89.2 years in the group with least cognitive activity. That is, there appeared to be approximately a 3.5-year delay in AD onset with frequent cognitive activity.

In secondary analyses (data not shown in tables) simultaneously including depressive symptoms and neuroticism in 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.

Multivariable-adjusted HRs for relations of depressive symptoms, neuroticism and cognitive activity to incidence of AD
To contrast the findings with traditional effect estimates, we calculated the HRs for each factor (data not shown in tables). For significant depressive symptoms compared with no symptoms, the HR was 1.47 (95% CI 1.20 to 1.81), controlling for covariates. The highest tertile of neuroticism was associated with nearly 50% increased AD risk (HR=1.48, 95% CI 1.23 to 1.79), with approximately 25% increase (HR=1.27, 95% CI 1.05 to 1.53) for the middle versus lowest tertile. For cognitive activity, the HR was 0.65 (95% CI 0.55 to 0.77) for the highest tertile, and 0.82 (95% CI 0.69 to 0.97) for the moderate group, versus the lowest tertile. Thus, while HRs are broadly consistent (as expected) with reports identified in AFT models, there is no direct link of the HR (eg, 1.47 for the relation of significant depressive symptoms to risk of AD) and the estimated difference in age at AD onset (eg, 5 years earlier for those with depression).

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 relations 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,
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. Across 12 prospective studies, 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. However, in the meta-analysis 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.

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, defined as the ability to tolerate neuropathology without manifesting clinical cognitive symptoms. Neuropathology is ubiquitous in older persons 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.

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. 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. 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. Interestingly, later life appears to be particularly amenable to changing neuroticism.

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

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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 L6121802). 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.

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REFERENCES

25. Center for Behavioral Health Statistics and Quality. 2017 national survey on drug use and health: methodological summary and