Twin Research and Human Genetics (2019), **22**, 783–787
doi:10.1017/thg.2019.125

CAMBRIDGE UNIVERSITY PRESS

Article

Current Status of the Vietnam Era Twin Study of Aging (VETSA)

William S. Kremen[1,2], Carol E. Franz[1] and Michael J. Lyons[3]

[1]Department of Psychiatry and Center for Behavioral Genetics of Aging, University of California, San Diego, La Jolla, CA, USA, [2]Center of Excellence for Stress and Mental Health, VA San Diego Healthcare System, La Jolla, CA, USA and [3]Department of Psychological & Brain Science, Boston University, Boston, MA, USA

Abstract

The Vietnam Era Twin Study of Aging (VETSA) is a longitudinal behavioral genetic study with a primary focus on cognitive and brain aging in men, particularly early identification of risk for mild cognitive impairment (MCI) and Alzheimer's disease (AD). It comprises a subset of over 1600 twins from the Vietnam Era Twin Registry. Twins live all over the USA. Assessments began when participants were in their 50s. Follow-ups were conducted every 5–6 years, and wave 3 has been completed as of this writing. The age range of participants is narrow (about 10 years). An extensive neurocognitive test battery has added precision in assessing differences in middle-aged adults, and predicting progression to MCI. Young adult cognitive test data (at an average age of 20 years) provide a means of disentangling aging effects from longstanding differences. Genome wide genotyping and plasma assays of AD biomarkers from waves 1 and 3 were conducted in wave 3. These features make the VETSA ideal for studying the heterogeneity of within-individual trajectories from midlife to old age, and for early detection of risk factors for cognitive decline.

Keywords: twins; aging; longitudinal; cognition; heritability; MCI; GWAS; biomarker

(Received 3 June 2019; accepted 9 July 2019; First Published online 14 January 2020)

Here we provide an update of the Vietnam Era Twin Study of Aging (VETSA). VETSA began as a longitudinal behavioral genetic study of cognitive and brain aging, but as the participants have aged, its primary focus has shifted to early identification of risk for mild cognitive impairment (MCI) and Alzheimer's disease (AD). Descriptions of earlier waves of data collection can be found in this journal (Kremen et al., 2013; Kremen et al., 2006). Wave 3 data collection of this ongoing study was completed in late January 2019. Participants were with average age 56 (51–60) at wave 1, 62 (56–66) at wave 2 and 68 (61–70) at wave 3. VETSA participants are all part of the Vietnam Era Twin Registry, from which they were randomly selected from a large prior study that attempted to enroll all available twins (Tsuang et al., 2001). VETSA selection criteria were (1) being in one's 50s at the time of recruitment, and (2) both twins in a pair had to be willing to participate in the baseline assessment.

With the failure of drug trials focused on beta-amyloid — the hallmark pathology of AD — and recognition that the disease process begins decades prior to onset of dementia, there is a consensus that early identification of at-risk individuals is a key to preventing or slowing disease progression (Daviglus et al., 2010; Sperling et al., 2011). This calls for a focus on midlife, which is central to the VETSA study design. Hence, at the study baseline, essentially all participants were in their 50s. Moreover, the narrow age range enhances the ability to examine within-individual differences in change over time. Another key aspect of the study design was to employ an extensive neuropsychological test battery. The thinking was that batteries designed for older adults would not be sensitive enough to capture individual differences in middle-aged adults. Moreover, the extensive battery made it possible to derive latent genetic factors within each cognitive domain. Preliminary results suggest that specific cognitive abilities have much higher heritability than previously thought; average heritability of domain-specific latent factors was .75, which is much higher than heritability estimates based on individual cognitive tests.

These features also set the stage for early identification of individuals who are at elevated risk for developing MCI, that is, whether characteristics at waves 1 and 2 predict progression to MCI. Incidence of MCI should increase in the planned fourth wave of the study, and a small number of dementia cases may also begin to develop. The addition of genome wide genotyping and plasma AD biomarkers adds substantially to the prospects of achieving this goal. Indeed, AD biomarkers are required for diagnosis of preclinical AD, MCI and AD dementia in the US National Institute on Aging-Alzheimer's Association A/T/N (beta-amyloid/tau/neurodegeneration) research framework (Jack et al., 2018).

Another unique feature of VETSA is that general cognitive ability (GCA) scores are available when VETSA participants were, on average, 20 years of age. The same test has been readministered in all study waves. It has demonstrated excellent stability over four decades, with a phenotypic correlation of .74 and a genetic correlation that did not differ from 1.0 (Lyons et al., 2017; Lyons et al., 2009). Young adult GCA provides an important covariate for many analyses, so that longstanding differences are not misinterpreted as aging-related effects. For example, higher education is associated with reduced risk of dementia, and that

Author for correspondence: William S. Kremen, Email: wkremen@ucsd.edu

Cite this article: Kremen WS, Franz CE, and Lyons MJ. (2019) Current Status of the Vietnam Era Twin Study of Aging (VETSA). *Twin Research and Human Genetics* **22**: 783–787, https://doi.org/10.1017/thg.2019.125

Table 1. Zygosity and age range of VETSA samples

	MZ pairs	DZ pairs	MZ unpaired	DZ unpaired	Undetermined zygosity	Total individuals	Age range
VETSA 1	349	265	2	6	–	1237	
VETSA 2	333	235	34	37	–	1207	
VETSA 3	264	196	82	68	135[a]	1205	

Note: MZ = monozygotic, DZ = dizygotic.
[a]There were 135 attrition replacement participants in VETSA 3, and their zygosity has not yet been determined as of this writing.

association is often interpreted as a causal effect of education. However, we showed that the association of education with later life cognitive function is primarily explained by reverse causation (Kremen et al., 2019). GCA at age 20 accounted for about 10% of variance in specific cognitive abilities later in life. After accounting for age 20 GCA, education accounted for less than 1% of variance in those abilities.

Finally, in order to gauge practice effects, VETSA included attrition replacement participants in waves 2 and 3. Replacements were demographically matched to returnees but were taking the tests for the first time. Even though there were group mean declines, there was still evidence of practice effects in most cognitive domains after 5–6 years (Elman et al., 2018). Accounting for practice effects also meaningfully increased the number of cognitively normal individuals who were identified as progressing to MCI. VETSA MCI diagnoses have also been shown to be heritable, and higher AD polygenic risk scores are associated with significantly increased odds of having MCI in VETSA (Kremen et al., 2014; Logue et al., 2018).

VETSA Sample

Table 1 shows the number of participants and age ranges in the waves of the VETSA project. Data collection for VETSA wave 1 began in 2003 with 5- to 6-year follow-ups. Over 1200 twins participated in waves 1, 2 and 3. Over 1000 participated in both waves 1 and 2, and over 800 participated in all three waves. All VETSA participants are men and all were in some branch of military service at some time between 1965 and 1975. Approximately 80% report no combat experience. The sample is a reasonably representative, community-dwelling sample of men in their age range living throughout the entire USA based on socio-demographic and health/lifestyle characteristics (Schoeneborn & Heyman, 2009).

VETSA Measures

VETSA measures have also been described in prior special issues of *Twin Research and Human Genetics* that have described twin registries worldwide (Kremen et al., 2013; Kremen et al., 2006).

Cognition

With the primary focus of VETSA on cognitive aging, the project includes an extensive neurocognitive test battery. In addition to GCA, the neurocognitive battery covers verbal ability, abstract reasoning, executive function, working memory, episodic memory and visual-spatial ability. There are multiple measures within each cognitive domain. A novel assessment related to cognition is pupillometry (introduced at VETSA 2). Pupil dilation is a validated psychophysiological index of cognitive effort; as effort increases, dilation increases. As individuals age, they may compensate for deficiencies with more effort. Performance declines will manifest when compensatory capacity has been surpassed. Thus, if two people have the same score but one requires greater effort (indicated by greater pupil dilation during a cognitive task), the person requiring greater effort is hypothesized to be at risk for earlier decline. Thus, the pupil response could identify individuals at risk even before cognitive performance declines. In VETSA, proof of principle was demonstrated because amnestic MCI participants had greater pupil dilation than cognitively normal participants during digit span tasks, despite equivalent performance (Granholm et al., 2017). Preliminary results also indicate that pupil responses are heritable and associated with genetic risk for AD based on an AD polygenic risk score. A next step will be to examine whether pupil response in cognitively normal individuals aids in prediction of progression to MCI.

Health and Psychosocial

Because it is also important to understand how other factors affect or may be affected by the level of cognitive functioning, there are over 2 h of interviews and questionnaires assessing personality, psychosocial/lifestyle and health/medical measures.

Genotyping and Zygosity

Whole genome genetic variation was assessed at deCODE (Reykjavik, Iceland), with genotyping performed on Illumina HumanOmniExpress-24 v1.0A (Illumina, San Diego, CA, USA). These data are primarily used to create polygenic scores based on the results of large-scale, independent genome wide association studies. DNA for VETSA participants has been banked under the auspices of the Vietnam Era Twin Registry at the Puget Sound VA Healthcare System, Seattle, WA, USA (Nicholas L. Smith, PhD, Director).

For approximately 96% of the participants, zygosity was determined on the basis of genome wide genotyping and/or 25 microsatellite markers. For the small number of remaining participants, zygosity was determined by a combination of questionnaire and blood group methods (Eisen et al., 1989). In this sample, 95% of the questionnaire-based zygosity classifications were in agreement with the DNA-based classifications. The zygosity breakdown of participants is shown in Table 1.

AD Biomarkers

Plasma AD biomarkers were assessed from samples taken at VETSA 1 and 3 (not available for VETSA 2). The focus is on three A/T/N biomarkers: beta-amyloid, tau and neurofilament light (NfL). Beta-amyloid and tau are well known as the hallmark pathologies of AD (Blennow & Zetterberg, 2018; Gisslen et al., 2016;

https://doi.org/10.1017/thg.2019.125 Published online by Cambridge University Press

Petzold, 2005; Preische et al., 2019). NfL is a sensitive marker of axonal damage that is associated with cortical atrophy and cognitive decline (Mattsson et al., 2019). This information will make it possible to longitudinally track biomarker accumulation. Cutoffs for pathological levels of beta-amyloid and tau have been established for assays derived from cerebrospinal fluid and positron emission tomography, but plasma-based cutoffs have not yet been established. When plasma-based cutoffs are determined, it will then be possible to determine A/T/N classifications for VETSA participants (i.e., whether someone is A+, T+ or N+).

Magnetic Resonance Imaging

Over 500 VETSA twins have undergone Magnetic Resonance Imaging (MRI), which began midway into wave 1. MRI assessments include 3D structural MRIs to measure brain structure (cortical and subcortical volumes and cortical thickness and surface area) based on FreeSurfer and diffusion tensor imaging (DTI), which indexed white matter integrity. Beginning at VETSA 2, all MRI participants also underwent assessment of abnormal white matter (white matter hyperintensities).

At wave 2 only, a subset of participants underwent a resting-state functional MRI protocol to assess the default mode network and arterial spin labeling (ASL) to measure cerebral blood flow or perfusion. There is evidence that the correlation between regions in the default mode network is reduced in AD (Buckner et al., 2008; Greicius et al., 2004), but a meta-analysis suggests that results are not consistent enough for it to be used as a biomarker for MCI (Eyler et al., 2019). ASL may be important for understanding cognitive and brain aging because there are age-related changes in perfusion and they may reflect important vascular changes (Bangen et al., 2009).

VETSA MRI data have been used to show the heritability of the size of individual cortical and subcortical regions of interest (Eyler, Prom-Wormley, Fennema-Notestine et al., 2011; Eyler, Prom-Wormley, Panizzon et al., 2011; Kremen, Prom-Wormley et al., 2010), the genetic associations among continuously measured cortical regions (Chen et al., 2013; Chen et al., 2011; Eyler et al., 2012; Rimol et al., 2010) and the genetic distinction between cortical thickness and cortical surface area (Panizzon et al., 2009). In addition, they have been used to create a novel brain atlas of cortical regions defined entirely on the basis of genetically informative data (Chen et al., 2012). This atlas may be useful for genetic association studies because the brain phenotypes are defined by genetic rather than structural or functional information. They have also been used to model genetic associations between cortex and cognition (Vuoksimaa et al., 2015; Vuoksimaa et al., 2016).

Neuroendocrine Data

In wave 1 of VETSA, neuroendocrine data from saliva samples were collected from 795 participants. A total of 17 samples per person were collected: 5 on each of 2 days at home and 7 on the in-lab day. The schedule for sampling was designed primarily for the assessment of the stress hormone cortisol. Cortisol follows a diurnal variation in which the peak typically occurs shortly after awakening and levels then decline throughout the day. Samples were thus collected at awakening, 30 min after awakening, 10 h, 15 h and bedtime. Two additional samples were collected just before and just after lunch on the day of testing. In addition to cortisol, the saliva samples were also used to measure testosterone and dehydroepiandrosterone sulfate (DHEA-S). Because cortisol is important in the hypothalamic–pituitary–adrenal axis stress response system, it may be a mediator or moderator of age-related changes. Testosterone levels decline steadily with age, making it a potentially important factor in male aging. Studies based on VETSA data have shown the heritability of these hormones (Franz et al., 2010; Prom-Wormley et al., 2011) and their relationship to cognition and brain (Franz et al., 2011; Kremen, O'Brien et al., 2010; Panizzon et al., 2010; Panizzon et al., 2014; Panizzon et al., 2012; Panizzon et al., 2018).

Summary

The VETSA projects constitute a rich scientific resource, with assessments of twins in multiple domains beginning in the sixth decade of life. Wave 3, when participants averaged 68 years of age, has been completed, and wave 4, when participants will average 74 years of age, is planned. Not surprisingly, the number of participants with MCI is expected to increase in these later study waves, making the study increasingly valuable for elucidating genetic and environmental risk and protective factors for progression along the AD continuum. VETSA is also a partner contributing to several international consortia: CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology); ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis); PGC (Psychiatric Genomics Consortium); CODATwins (Cohort Description of Collaborative Project of Development of Anthropometrical Measures in Twins); and IGEMS (Interplay of Genes and Environment Across Multiple Studies).

Acknowledgments. This work was supported by National Institute on Aging grants R01 AG050595 (to William S. Kremen, Michael J. Lyons and Carol E. Franz), AG022381 and AG022982 (to William S. Kremen). It was also, in part, the result of work supported with resources of the VA San Diego Center of Excellence for Stress and Mental Health. The Cooperative Studies Program of the Office of Research & Development of the United States Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin (VET) Registry. All statements, opinions or views are solely of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government, the NIA or the NIH. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution this research would not have been possible.

References

Bangen, K. J., Restom, K., Liu, T. T., Jak, A. J., Wierenga, C. E., Salmon, D. P., & Bondi, M. W. (2009). Differential age effects on cerebral blood flow and BOLD response to encoding: Associations with cognition and stroke risk. *Neurobiology of Aging*, *30*, 1276–1287.

Blennow, K., & Zetterberg, H. (2018). The past and the future of Alzheimer's disease fluid biomarkers. *Journal of Alzheimer's Disease*, *62*, 1125–1140.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, *1124*, 1–38.

Chen, C. H., Fiecas, M., Gutierrez, E. D., Panizzon, M. S., Eyler, L. T., Vuoksimaa, E., … Kremen, W. S. (2013). Genetic topography of brain morphology. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 17089–17094.

Chen, C. H., Gutierrez, E. D., Thompson, W., Panizzon, M. S., Jernigan, T. L., Eyler, L. T., … Dale, A. M. (2012). Hierarchical genetic organization of human cortical surface area. *Science*, *335*, 1634–1636.

Chen, C. H., Panizzon, M. S., Eyler, L. T., Jernigan, T. L., Thompson, W., Fennema-Notestine, C., … Dale, A. M. (2011). Genetic influences on cortical regionalization in the human brain. *Neuron*, *72*, 537–544.

https://doi.org/10.1017/thg.2019.125 Published online by Cambridge University Press

Daviglus, M. L., Bell, C. C., Berrettini, W., Bowen, P. E., Connolly, E. S., Cox, N. J., ... Trevisan, M. (2010). National Institutes of Health State-of-the-Science Conference statement: Preventing Alzheimer's disease and cognitive decline. *NIH Consensus Statement Science Statements*, *27*, 1–27.

Eisen, S., Neuman, R., Goldberg, J., & Rice, T. (1989). Determining zygosity in the Vietnam Era Twin Registry: An approach using questionnaires. *Clinical Genetics*, *35*, 423–432.

Elman, J. A., Jak, A. J., Panizzon, M. S., Tu, X. M., Chen, T., Reynolds, C. A., ... Kremen, W. S. (2018). Underdiagnosis of mild cognitive impairment: A consequence of ignoring practice effects. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *10*, 372–381.

Eyler, L. T., Chen, C. H., Panizzon, M. S., Fennema-Notestine, C., Neale, M. C., Jak, A., ... Kremen, W. S. (2012). A comparison of heritability maps of cortical surface area and thickness and the influence of adjustment for whole brain measures: A magnetic resonance imaging twin study. *Twin Research and Human Genetics*, *15*, 304–314.

Eyler, L. T., Elman, J. A., Hatton, S. N., Gough, S., Mischel, A. K., Hagler, D. J., Jr., ... Kremen, W. S. (2019). Resting state abnormalities of the default mode network in mild cognitive impairment: A systematic review and meta-analysis. *Journal of Alzheimer's Disease*, *70*, 107–120.

Eyler, L. T., Prom-Wormley, E., Fennema-Notestine, C., Panizzon, M. S., Neale, M. C., Jernigan, T. L., ... Kremen, W. S. (2011). Genetic patterns of correlation among subcortical volumes in humans: Results from a magnetic resonance imaging twin study. *Human Brain Mapping*, *32*, 641–653.

Eyler, L. T., Prom-Wormley, E., Panizzon, M. S., Kaup, A. R., Fennema-Notestine, C., Neale, M. C., ... Kremen, W. S. (2011). Genetic and environmental contributions to regional cortical surface area in humans: A magnetic resonance imaging twin study. *Cerebral Cortex*, *21*, 2313–2321.

Franz, C. E., O'Brien, R. C., Hauger, R. L., Mendoza, S. P., Panizzon, M. S., Prom-Wormley, E., ... Kremen, W. S. (2011). Cross-sectional and 35-year longitudinal assessment of salivary cortisol and cognitive functioning: The Vietnam Era Twin Study of Aging. *Psychoneuroendocrinology*, *36*, 1040–1052.

Franz, C. E., York, T. P., Eaves, L. J., Mendoza, S. P., Hauger, R. L., Hellhammer, D. H., ... Kremen, W. S. (2010). Genetic and environmental influences on cortisol regulation across days and contexts in middle-aged men. *Behavior Genetics*, *40*, 467–479.

Gisslen, M., Price, R. W., Andreasson, U., Norgren, N., Nilsson, S., Hagberg, L., ... Zetterberg, H. (2016). Plasma concentration of the neurofilament light protein (NFL) is a biomarker of CNS injury in HIV infection: A cross-sectional study. *EBioMedicine*, *3*, 135–140.

Granholm, E. L., Panizzon, M. S., Elman, J. A., Jak, A. J., Hauger, R. L., Bondi, M. W., ... Kremen, W. S. (2017). Pupillary responses as a biomarker of early risk for Alzheimer's disease. *Journal of Alzheimer's Disease*, *56*, 1419–1428.

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 4637–4642.

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., ... Contributors. (2018). NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*, *14*, 535–562.

Kremen, W. S., Beck, A., Elman, J. A., Gustavson, D. E., Reynolds, C. A., Tu, X. M., ... Franz, C. E. (2019). Influence of young adult cognitive ability and additional education on later-life cognition. *Proceedings of the National Academy of Sciences of the United States of America*, *116*, 2021–2026.

Kremen, W. S., Franz, C. E., & Lyons, M. J. (2013). VETSA: The Vietnam Era Twin Study of Aging. *Twin Research and Human Genetics*, *16*, 399–402.

Kremen, W. S., Jak, A. J., Panizzon, M. S., Spoon, K. M., Franz, C. E., Thompson, W. K., ... Lyons, M. J. (2014). Early identification and heritability of mild cognitive impairment. *International Journal of Epidemiology*, *43*, 600–610.

Kremen, W. S., O'Brien, R. C., Panizzon, M. S., Prom-Wormley, E., Eaves, L. J., Eisen, S. A., ... Franz, C. E. (2010). Salivary cortisol and prefrontal cortical thickness in middle-aged men: A twin study. *Neuroimage*, *53*, 1093–1102.

Kremen, W. S., Prom-Wormley, E., Panizzon, M. S., Eyler, L. T., Fischl, B., Neale, M. C., ... Fennema-Notestine, C. (2010). Genetic and environmental influences on the size of specific brain regions in midlife: The VETSA MRI study. *Neuroimage*, *49*, 1213–1223.

Kremen, W. S., Thompson-Brenner, H., Leung, Y. M., Grant, M. D., Franz, C. E., Eisen, S. A., ... Lyons, M. J. (2006). Genes, environment, and time: The Vietnam Era Twin Study of Aging (VETSA). *Twin Research and Human Genetics*, *9*, 1009–1022.

Logue, M. W., Panizzon, M. S., Elman, J. A., Gillespie, N. A., Hatton, S. N., Gustavson, D. E., Kremen, W. S. (2018). Use of an Alzheimer's disease polygenic risk score to identify mild cognitive impairment in adults in their 50s. *Molecular Psychiatry*, *24*, 421–430.

Lyons, M. J., Panizzon, M. S., Liu, W., McKenzie, R., Bluestone, N. J., Grant, M. D., ... Xian, H. (2017). A longitudinal twin study of general cognitive ability over four decades. *Dev Psychol*, *53*, 1170–1177.

Lyons, M. J., York, T. P., Franz, C. E., Grant, M. D., Eaves, L. J., Jacobson, K. C., ... Kremen, W. S. (2009). Genes determine stability and the environment determines change in cognitive ability during 35 years of adulthood. *Psychological Science*, *20*, 1146–1152.

Mattsson, N., Cullen, N. C., Andreasson, U., Zetterberg, H., & Blennow, K. (2019). Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. *JAMA Neurology*, *76*, 791–799.

Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T., Jernigan, T. L., Prom-Wormley, E., Neale, M. C., ... Kremen, W. S. (2009). Distinct genetic influences on cortical surface area and cortical thickness. *Cerebral Cortex*, *19*, 2728–2735.

Panizzon, M. S., Hauger, R., Dale, A. M., Eaves, L. J., Eyler, L. T., Fischl, B., ... Kremen, W. S. (2010). Testosterone modifies the effect of APOE genotype on hippocampal volume in middle-aged men. *Neurology*, *75*, 874–880.

Panizzon, M. S., Hauger, R. L., Eaves, L. J., Chen, C. H., Dale, A. M., Eyler, L. T., ... Kremen, W. S. (2012). Genetic influences on hippocampal volume differ as a function of testosterone level in middle-aged men. *Neuroimage*, *59*, 1123–1131.

Panizzon, M. S., Hauger, R. L., Xian, H., Jacobson, K., Lyons, M. J., Franz, C. E., & Kremen, W. S. (2018). Interactive effects of testosterone and cortisol on hippocampal volume and episodic memory in middle-aged men. *Psychoneuroendocrinology*, *91*, 115–122.

Panizzon, M. S., Hauger, R., Xian, H., Vuoksimaa, E., Spoon, K. M., Mendoza, S. P., ... Franz, C. E. (2014). Interaction of APOE genotype and testosterone on episodic memory in middle-aged men. *Neurobiology of Aging*, *35*, e1771–1778.

Petzold, A. (2005). Neurofilament phosphoforms: Surrogate markers for axonal injury, degeneration and loss. *Journal of the Neurological Sciences*, *233*, 183–198.

Preische, O., Schultz, S. A., Apel, A., Kuhle, J., Kaeser, S. A., Barro, C., ... Dominantly Inherited Alzheimer Network. (2019). Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. *Nature Medicine*, *25*, 277–283.

Prom-Wormley, E. C., York, T. P., Jacobson, K. C., Eaves, L. J., Mendoza, S. P., Hellhammer, D., ... Kremen, W. S. (2011). Genetic and environmental effects on diurnal dehydroepiandrosterone sulfate concentrations in middle-aged men. *Psychoneuroendocrinology*, *36*, 1441–1452.

Rimol, L. M., Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T., Fischl, B., Franz, C. E., ... Dale, A. M. (2010). Cortical thickness is influenced by regionally specific genetic factors. *Biological Psychiatry*, *67*, 493–499.

Schoeneborn, C. A., & Heyman, K. M. (2009). Health characteristics of adults aged 55 years and over: United States, 2004–2007. *National Health Statistics Reports*, (16), 1–31. Hyattsville, MD: National Center for Health Statistics.

https://doi.org/10.1017/thg.2019.125 Published online by Cambridge University Press

Sperling, R. A., Jack, C. R., Jr., & Aisen, P. S. (2011). Testing the right target and right drug at the right stage. *Science Translational Medicine*, *3*, 111–133.

Tsuang, M. T., Bar, J. L., Harley, R. M., & Lyons, M. J. (2001). The Harvard Twin Study of Substance Abuse: What we have learned. *Harvard Review of Psychiatry*, *9*, 267–279.

Vuoksimaa, E., Panizzon, M. S., Chen, C. H., Fiecas, M., Eyler, L. T., Fennema-Notestine, C., ... Kremen, W. S. (2015). The genetic association between neocortical volume and general cognitive ability is driven by global surface area rather than thickness. *Cerebral Cortex*, *25*, 2127–2137.

Vuoksimaa, E., Panizzon, M. S., Chen, C. H., Fiecas, M., Eyler, L. T., Fennema-Notestine, C., ... Kremen, W. S. (2016). Is bigger always better? The importance of cortical configuration with respect to cognitive ability. *Neuroimage*, *129*, 356–366.

https://doi.org/10.1017/thg.2019.125 Published online by Cambridge University Press