Cognitive and brain aging and the influence of amyloid-β

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Submitted in total fulfilment of the requirements for the degree of Doctor of Philosophy

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April 2020

“It is not the critic who counts; not the man who points out how the strong man stumbles, or where the doer of deeds could have done them better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs, who comes short again and again, because there is no effort without error and shortcoming; but who does actually strive to do the deeds; who knows great enthusiasms, the great devotions; who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement, and who at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who neither know victory nor defeat.”

– Teddy Roosevelt

Abstract

Models of cognitive and brain aging suggest that some cognitive decline and cortical volume loss is normal in aging beyond age 60; however, these models have failed to account for the presence of Alzheimer's disease (AD) neuropathological markers such as amyloid-β (Aβ). The inadvertent inclusion of older adults who later progress from being cognitively normal (CN) to mild cognitive impairment (MCI) or dementia, or who have elevated levels of cerebral Aβ (Aβ+) may lead to inflated estimates of cognitive decline or cortical volume loss that may not be entirely due to the process of aging. The overarching aim of this thesis was to characterize the cognitive and brain morphological changes associated with normal aging, defined as the cognitive and neurobiological changes that occur with the passage of time independent of neuropathological processes. Changes in cognition and brain morphology were examined in up to 599 CN older adults from the Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing who underwent repeated clinical, neuropsychological and neuroimaging (MRI and Aβ PET) assessments over up to 8 years. The presence of Aβ+ in otherwise CN older adults was associated with greater risk of future clinical disease progression to MCI or dementia, and faster rates of cognitive decline and cortical volume loss compared to those who were Aβ-. These results remained consistent when examined with respect to the SuperAging construct, and suggest that trajectories of cognitive and brain morphological changes in Aβ+ are not reflective of normal aging processes. This thesis challenges widely-accepted models of cognitive and brain aging by showing that aging is characterized by preserved cognitive function and minimal cortical volume loss, and concludes that cognitive decline is not inevitable in aging.

Declaration

This is to certify that

- The thesis comprises only my original work towards the PhD unless otherwise indicated in the preface.
- Due acknowledgment has been made in the text to all other material used.
- This thesis contains no material published elsewhere, or extracted in whole or in part from a thesis by which I have qualified for or have been awarded another degree or diploma.
- The thesis is fewer than 100 000 words in length, exclusive of tables, maps, bibliographies, and appendices.

_____

Christa Dang

April 2020

Preface

This thesis was conducted with the Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing. AIBL is a large study that has required the support of many people to run. As such, a number of people have made contributions to the data and materials presented in this thesis – not least of all the participants who have volunteered their time to AIBL, without whom none of this work would be possible. Below are the individuals who made a direct contribution to the data and materials presented in this thesis and are thus listed as co-authors on any published work.

Dr David Ames and Dr Joanne Robertson oversaw the neuropsychological assessment and clinical classification of all AIBL participants. Dr Kathryn Ellis was the study coordinator from inception until 2012. Prof Chris Rowe, Prof Victor Villemagne, Dr Olivier Salvado, Dr Pierrick Bourgeat, Dr Jurgen Fripp and Dr Ying Xia oversaw the acquisition and processing of neuroimaging (PET and MRI) data. A/Prof Simon Laws oversaw the genotyping. Dr James Doecke and Dr Robert Pietrzak provided statistical advice for Chapters 5 and 6, respectively. Dr Karra Harrington conducted the exploratory factor analysis to identify the four cognitive domains and the neuropsychological tests that loaded onto those domains to generate cognitive composite scores. The cognitive composite scores were calculated by me using the framework that she developed to maintain consistency in the measures used between our studies. In addition to the above contributions, all co-authors for each published chapter provided critical revisions and approved the final version of the manuscript for submission for publication.

I am the primary author for all chapters and articles presented in the thesis, having performed all statistical analyses, written all articles and made revisions in response to

feedback from co-authors and reviewers. Chapters 1-2 and 5-7 contain unpublished material not submitted for publication.

Acknowledgments

My deepest gratitude goes out to each and every person who has walked alongside me for all or part of this journey: thank you for the time you have shared, whether it was some seconds or many years. Thank you, also, to the people who have yet to enter my life and to everyone who will be a part of the journeys to come.

To Martha Hickey: thank you for your support and for having been there from the very beginning of this journey right through to the end; that, in itself, says more than words can ever say. To Paul Maruff: thank you endlessly for the time you have dedicated to overseeing the planning, development and writing of these thesis chapters – at any and all hours of the day and night – and the many enlightening philosophical chats (wax on, wax off). To Yen Ying Lim: you have shown me what it truly means to be an academic/scientist and the hard work and resilience it necessitates to be a good one, and what it means to care for the people you mentor and supervise – thank you for being the quintessential example for me in this way. To Nawaf Yassi: thank you for always taking the time to help when needed, for all of your assistance with the neuroimaging, and for the time you spent rating infarcts. To David Ames: thank you for your kind support, and for the time you have spent looking over AIBL participant files and this thesis in minute detail. Words cannot do justice to the contribution you all have made to this journey and the invaluable learnings that have come from everyone involved.

Many thanks to Jane Girling and Harry Georgiou for both doing a fantastic job as postgraduate coordinator and for your support as my committee chairs, and to Rebecca Whitsed for all of your help. Thank you to Lex Doyle and Andrea Maier for your assistance as part of my thesis committee. Thank you, also, to Jo Robertson and Chris Fowler for your

support and assistance with all things AIBL and beyond. Thank you to Karra, Jenalle, Tia, Lisa, Alex, Matt, David, Tyra and Jean for your friendship and all the laughs, food and fun. It is my great pleasure to have met you all along the way!

Thank you to my family for their endless support and patience, and their understanding that what has kept me so far away from home these past few years are the multitude of wonderful opportunities for growth and learning that it has been my great fortune to have. My parents have sacrificed a lot for us to live better lives – it is a perfect outcome to now be in a position where it is possible to help countless people age well and live better lives, themselves.

Last, but certainly not least: thank you always to my dearest friends, with very special appreciation to the people who have made Melbourne home.

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List of abbreviations

Aβ	Amyloid-beta
AIBL	Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing
AD	Alzheimer's Disease
APOE ε4	Apolipoprotein E epsilon 4 allele
ANOVA	Analysis of variance
BMI	Body mass index
CN	Cognitively normal
CNFA	Cognitively normal for their age
CVLT-II	California Verbal Learning Test, second edition
GM	Grey matter
HADS	Hospital Anxiety and Depression Scale
LMM	Linear mixed model
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
PET	Positron emission tomography
SD	Standard deviation
SE	Standard error
SUVR	Standardised uptake value ratio
WM	White matter
WMH	White matter hyperintensity
WMS	Wechsler Memory Scale

Peer-reviewed publications and presentations

Published work arising from thesis

1. **Dang, C.**, Yassi, N., Harrington, K., Xia, Y., Lim, Y. Y., Ames, D., Laws, S., Hickey, M., Rainey-Smith, S., Sohrabi, H. R., Doecke, J. D., Fripp, J., Salvado, O., Weinborn, M., Villemagne, V., Rowe, C. C., Masters, C. L., & Maruff, P., for the AIBL Research Group. (2019). Rates of age- and amyloid β-associated cortical atrophy in older adults with superior memory performance. *Alzheimer's & Dementia: Diagnosis, Assessment and Disease Monitoring, 11,* 566-575. https://doi.org/10.1016/j.dadm.2019.05.005
2. **Dang, C.**, Harrington, K., Lim, Y. Y., Ames, D., Hassenstab, J., Laws, S., Yassi, N., Hickey, M., Rainey-Smith, S., Robertson, J., Sohrabi, H. R., Salvado, O., Weinborn, M., Villemagne, V., Rowe, C. C., Masters, C. L., & Maruff, P., for the AIBL Research Group. (2018). Superior memory reduces 8-year risk of mild cognitive impairment and dementia but not amyloid β-associated cognitive decline in older adults. *Archives of Clinical Neuropsychology.* https://doi.org/10.1093/arclin/acy078
3. **Dang, C.**, Harrington, K., Lim, Y. Y., Ames, D., Hassenstab, J., Laws, S., Yassi, N., Hickey, M., Rainey-Smith, S., Robertson, J., Sohrabi, H. R., Salvado, O., Weinborn, M., Villemagne, V., Rowe, C., Masters, C., & Maruff, P., for the AIBL Research Group. (2018). Relationship between amyloid-β positivity and progression to mild cognitive impairment or dementia over 8 years in cognitively normal older adults. *Journal of Alzheimer's Disease, 65*(4), 1313–1325. https://doi.org/10.3233/JAD-180507

Additional work published during candidature

1. **Dang, C.** & Maruff, P. (2019). SuperAging: Current findings yield future challenges. A response to Rogalski and Goldberg. *Alzheimer's & Dementia: Diagnosis, Assessment and Disease Monitoring, 11,* 562-563. https://doi.org/10.1016/j.dadm.2019.05.004
2. Sadeh, T., **Dang, C.**, Gat-Lazer, S., Moscovitch, M. (2019). Recalling the firedog: Individual differences in associative-memory for unitized and non-unitized associations among older adults. *Hippocampus, 1–13.* https://doi.org/10.1002/hipo.23142
3. Harrington, K. D., **Dang, C.**, Lim, Y. Y., Ames, D., Laws, S. M., Pietrzak, R. H., Rainey-Smith, S., Robertson, J., Rowe, C. C., Salvado, O., Villemagne, V. L., Masters, C. L., Maruff, P., for the AIBL Research Group. (2018). The effect of preclinical Alzheimer's

disease on age-related changes in intelligence in cognitively normal older adults. *Intelligence, 70,* 22–29. https://doi.org/10.1016/j.intell.2018.07.004

4. Harrington, K. D., Schembri, A., Lim, Y. Y., **Dang, C.**, Ames, D., Hassenstab, J., Laws, S. M., Rainey-Smith, S., Robertson, J., Rowe, C. C., Sohrabi, H. R., Salvado, O., Weinborn, M., Villemagne, V. L., Masters, C. L., Maruff, P., for the AIBL Research Group. (2018). Estimates of cognitive aging are inflated by unrecognized Alzheimer's disease. *Neurobiology of Aging, 70,* 170–179. https://doi.org/10.1016/j.neurobiolaging.2018.06.005
5. Bone, M. B., St-Laurent, M., **Dang, C.**, McQuiggan, D. A., Ryan, J. D., Buchsbaum, B. R. (2018). Eye-movement reinstatement and neural reactivation during mental imagery. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhy014
6. Szoeke, C., **Dang, C.**, Lehert, P., Hickey, M., Morris, M. E., Dennerstein, L., Campbell, S. (2017). Unhealthy habits persist: The ongoing presence of modifiable risk factors for disease in women. *PLOS ONE, 12*(4), e0173603. https://doi.org/10.1371/journal.pone.0173603

Conference presentations during candidature

1. **Dang, C.**, Harrington, K. D., Lim, Y. Y., Yassi, N., Hickey, M., Ames, D., Rowe, C., Villemagne, V., Masters, C. L., & Maruff, P., for the AIBL Research Group. (2018). *Examining resilience to cognitive decline and neurodegeneration due to age and beta-amyloid in SuperAgers.* Oral presentation given at the 17th National Conference of Emerging Researchers in Ageing, Melbourne.
2. **Dang, C.**, Harrington, K. D., Lim, Y. Y., Yassi, N., Hickey, M., Ames, D., Rowe, C., Villemagne, V., Masters, C. L., & Maruff, P., for the AIBL Research Group. (2018). *Examining resilience to cognitive decline and neurodegeneration due to age and beta-amyloid in SuperAgers.* Oral presentation given at the 1st Organization for Human Brain Mapping – Australian Chapter Symposium, Melbourne.
3. **Dang, C.**, Harrington, K. D., Lim, Y. Y., Yassi, N., Hickey, M., Ames, D., Rowe, C., Villemagne, V., Masters, C. L., & Maruff, P., for the AIBL Research Group. (2018). *Differential risk factors for progression to MCI/dementia by amyloid-beta status.* Oral presentation given at the Alzheimer's Association International Conference, Chicago. https://doi.org/10.1016/j.jalz.2018.06.2726
4. **Dang, C.**, Lim,Y. Y., Harrington, K. D., Yassi, N., Hickey, M., Ames, D., Rowe, C., Villemagne, V., Masters, C. L., & Maruff, P., for the AIBL Research Group. (2018). *Examining the resilience of SuperAgers: Risk of clinical progression and Aβ-associated memory decline over 8 years.* Poster presented at the Alzheimer's Association International Conference, Chicago. https://doi.org/10.1016/j.jalz.2018.06.007 *(Student poster competition finalist)*
5. **Dang, C.** (2017). *Memory performance over time is mediated by subjective memory complaint and APOE-ε4 carriage.* Oral presentation given at the Alzheimer's

Association International Conference, London. http://doi.org/10.1016/j.jalz.2017.07.338

6. **Dang, C.**, Szoeke, C., Hickey, M. (2017). *Different normative distributions of cognitive performance between healthy olders and cognitively impaired olders – but what about the grey area?* Poster presented at the 13th International Conference on Alzheimer's & Parkinson's Diseases, Vienna.

Awards and honours

Melbourne Research Scholarship, University of Melbourne	2016–2019
Donor Award for High Achieving Female Early Career Researcher	2019
Alzheimer's Association International Conference Travel Fellowship	2017, 2019
Emerging Researchers in Ageing Bursary	2018
AAIC Student Poster Competition Finalist	2018
Postgraduate Student Conference Support Grant, University of Melbourne	2017
Henry and Rachel Ackman Travelling Scholarship	2016–2017

Thesis presentation

This thesis is submitted as a series of five empirical articles, each representing an independent study. The first three articles have been published in international peer-reviewed scientific journals, and the published articles are reprinted in Appendix A. For consistency, all thesis chapters have been reformatted such that references are presented using the Vancouver reference style and all tables and figures are placed in the body of the text.

The empirical studies in this thesis (Chapters 3-7) were conducted using data from the prospective Australian, Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing. The AIBL protocols and inclusion/exclusion criteria are summarized in each empirical chapter, and have been published in detail elsewhere. More specific selection criteria have been applied in accordance to the specific aims of each study; therefore, while participants are all drawn from the same pool of cognitively normal AIBL participants, the number of participants included for analysis will vary between studies (see Chapter 2).

Thesis outline

Chapter 1: General Introduction

The opening chapter presents a general introduction and literature review to provide a foundation for the empirical studies (Chapters 3-7). Overviews of dementia, Alzheimer's disease (AD), aging and successful aging are given. For clarity, this chapter outlines the definition of aging used in this thesis. The argument is made that estimates of age-associated cognitive decline and cortical atrophy have been negatively biased by inadvertent inclusion of individuals with preclinical dementia or preclinical AD; therefore, cognitive and brain morphological changes in aging must be distinguished from that which are reflective of underlying neuropathological processes. Relevant successful aging and SuperAging literature is also reviewed. Whether these individuals are uniquely protected from age-associated changes in cognition and brain morphology must be assessed with reference to a sample of normal aging older adults. Following this, the aims of the thesis are outlined.

Chapter 2: Methods

Assessment and measurement procedures for the neuropsychological, neuroimaging and blood data from the Australian Imaging, Biomarkers and Lifestyle (AIBL) flagship study of ageing are presented in this chapter. Classification criteria for Aβ+, SuperAging and mild cognitive impairment (MCI) or dementia are shown. Sample selection and statistical methods for each empirical chapter are outlined, and overall limitations of the methodology are discussed.

Chapter 3: Relationship between amyloid-β positivity and progression to mild cognitive impairment or dementia over 8 years in cognitively normal older adults

This study aimed to examine the risk and incidence of amyloid-β (Aβ)-associated progression to MCI/dementia among cognitively normal (CN) older adults, and to identify any demographic and clinical characteristics that increased or decreased that risk. The results showed that Aβ+ is an important prognostic marker for progression from CN to MCI/dementia in older adults, and that *APOE* ε4 carriage, older age, and relatively higher levels of Aβ increased risk further in the presence of Aβ+. Age was the only risk factor for progression to MCI/dementia in Aβ-. These data suggest that Aβ-associated clinical progression is consistent with clinical-pathological models of AD, whereas progression in the absence of elevated Aβ deposition may be the result of neuropathological processes other than AD.

Chapter 4: Superior memory reduces 8-year risk of mild cognitive impairment and dementia but not amyloid β-associated cognitive decline in older adults

This study aimed to examine the risk of progression to MCI/dementia for older adults classified as SuperAgers compared to those who were cognitively normal for their age (CNFA), and to determine the extent to which SuperAgers were resilient to the negative effects of Aβ+ on cognition. SuperAgers displayed resilience against clinical progression to MCI/dementia compared to CNFA despite equivalent risk for AD; however, SuperAgers had no greater protection from the deleterious effects of Aβ+ on cognition than did CNFA. Thus,

superior cognitive performance reflected by SuperAger classification does not reflect resistance against the neuropathological processes associated with AD, and the observed resilience to clinical disease progression for SuperAgers may instead reflect neuropsychological criteria for cognitive impairment.

Chapter 5: Rates of age- and amyloid β-associated cortical atrophy in older adults with superior memory performance

This study aimed to examine whether SuperAgers are resistant to age- and Aβ-associated neurodegeneration compared to CNFA older adults. This study also explored differences between SuperAgers and CNFA in white matter hyperintensity (WMH) volume and accumulation over time, and whether this was mediated by Aβ. No differences between SuperAgers and CNFA were observed for rates of Aβ-associated atrophy. There were also no differences between SuperAgers and CNFA in baseline WMH volume nor rate of accumulation, and neither were influenced by Aβ status. Therefore, defining SuperAging on the basis of neuropsychological criteria alone has limited ability to identify individuals who are uniquely protected from the effects of age or neuropathological changes. The results of this study suggest that the most advantageous characteristic for attenuated brain volume loss in older adults was to have reached old age without elevated Aβ deposition.

Chapter 6: Examining the moderating effect of amyloid-β on associations between cortical volume loss and cognitive change in cognitively normal older adults

The results from the last two chapters revealed a dissociation where cognition was improving or remaining stable for Aβ- older adults despite some observable cortical volume

loss, while both cognition and cortical volume declined for the Aβ+ group. Therefore, this study aimed to examine relationships between concurrent changes in cortical volume and cognition in CN older adults with and without evidence of AD neuropathological changes (i.e. Aβ- and Aβ+). It was first necessary to confirm that rates of cortical volume and cognitive change were different between the Aβ- and Aβ+ groups in the present sample. The results from this study extended previous findings and confirmed that studies of aging can overestimate rates of age-associated cortical volume loss and cognitive decline due to inadvertent inclusion of participants with preclinical AD in otherwise CN samples. The relationship between grey matter (GM) volume loss and decline in cognitive function was moderated by whether participants were classified Aβ- or Aβ+. For the Aβ- group, GM volume loss was not associated with change in either verbal memory or executive function, but strong associations were observed for the Aβ+ group. Taken together, the results suggest that cortical volume loss associated with AD neuropathological changes may give rise to declines in cognitive function; however, age-associated cortical volume loss in the absence of Aβ+ may not affect cognitive ability in aging. It is, therefore, possible that cognitive decline is not a normal part of aging.

Chapter 7: Examining the moderating effect of *APOE*-ε4 carriage on associations between cortical volume loss and cognitive change in a robust sample of aging older adults

This study aimed to examine the effects of *APOE* ε4 carriage on trajectories of cortical volume and cognitive changes in a robust sample of older adults who remained CN and Aβ- throughout the study period. Following from the results of Chapter 6, we explored the association between *APOE* ε4 carriage and trajectories of GM volume loss and decline in

verbal memory or executive function. Further exploratory analyses then examined whether relationships between concurrent changes in cortical GM volume and cognition were moderated by *APOE* ε4 carrier status. Initial results showed no effect of *APOE* ε4 carriage on rates of cortical atrophy or cognitive change. However, further exploratory analyses found that faster GM volume loss may be associated with greater verbal memory decline in *APOE* ε4 carriers. This suggests that inclusion of *APOE* ε4 carriers may bias results of studies aiming to examine the process of aging in the absence of preclinical neurodegenerative processes.

Chapter 8: General Discussion

A summary of the research findings is presented in three main sections: 1) the detrimental effects of Aβ+, 2) the limited utility of neuropsychologically-defined SuperAging, and 3) estimates of cognitive and brain aging are negatively biased by Aβ+. Following this summary, the implications of the research findings for current models of cognitive and brain aging, and successful aging are considered. The overall limitations of the studies presented in this thesis and future directions are also discussed.

Chapter 1: General Introduction

1 General Introduction

1.1 Dementia

The word “dementia” is derived from the Latin *demens*, where *de* means “away from, down from, out of” and *mens* means “thought, mind, intellect, reasoning”. In translation, the concept refers to an individual who is “out of [their] mind”. In order to reduce the stigma associated with diagnoses of dementia, the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 replaced the term “dementia” with “major neurocognitive disorder” [1,2]; however, “dementia” remains widely used in research. Today, dementia refers to the loss of mental faculties that impairs an individual’s ability to function normally in their everyday life. Dementia is a syndrome: a collection of symptoms with several underlying mechanisms, some of which are neurodegenerative diseases [3]. The most common cause is Alzheimer’s disease (AD), which accounts for 60–80% of all dementia cases [4]. Although risk and prevalence of dementia increases with older age [4,5], aging without dementia is achievable and dementia is, therefore, not a normal part of aging [6].

Whilst some of the factors leading to an increased risk of dementia have been identified, it is currently not possible to predict the likelihood of sporadic dementia on an individual basis. Dementia and AD have recently become the second leading cause of death in Australia (the first leading cause for women and third for men) [7]: approximately 9% of Australians aged over 65 years have been diagnosed with dementia, and the prevalence increases to 30% of Australians aged 85 and over [8]. Global prevalence of dementia has more than doubled between 1990-2016 [9], and it is expected that the number of people worldwide living with dementia will double every 20 years [10,11] or triple between 2015 to 2050 [12] as the population ages. However, around one-third of dementia risk factors may

be modifiable [13]. This is supported by reports that incidence of dementia may be declining in high-income countries [14] while increasing in middle- and low-income countries such as China [15]. The reasons behind observations of declining incidence are not entirely known, but may be due in part to population-wide changes in levels of education in the USA, for example [14,16]. Regardless, the prevalence of dementia still remains unacceptably high due to its associated emotional, social and economic costs. Primary prevention initiatives targeting modifiable risk factors of dementia and improving health in old age can help further reduce incidence of dementia. For example, dementia prevalence is estimated to increase in the USA if rising rates of obesity and resultant poor health in mid-life were to continue as projected [17,18]. Reducing the prevalence of dementia requires interventions or treatments to prevent or halt the progression of dementia. Further work to understand and characterize the process of aging without dementia may provide some insight into risk and protective factors for dementia to ultimately minimize or eliminate its prevalence.

1.2 Alzheimer's disease (AD)

Dr Alois Alzheimer first identified the hallmarks of what came to be known as AD in 1906, when his histopathological assessment of Auguste Deter's brain revealed the presence of amyloid plaques and neurofibrillary tangles [19]. Amyloid plaques are toxic, insoluble aggregations of amyloid-β (Aβ) that accumulate in the intercellular space between neurons and disrupt neuronal communication. The sequential cleavage of amyloid precursor protein (APP) by the proteases β-secretase and γ-secretase results in the protein fragment, Aβ, which is released outside of the neuron. Neurofibrillary tangles consist of hyperphosphorylated tau protein, and accumulate within neurons. The hyperphosphorylation of tau protein results in the disintegration of cellular microtubules

and ultimately causes the internal transport network of the neuron to collapse. Together, amyloid plaques and neurofibrillary tangles are associated with death of neurons, which results in the disproportionate atrophy observed in medial temporal lobe structures such as the hippocampus and entorhinal cortex [20,21]. The presence of AD neuropathological changes can be detected up to 30 years prior to the manifestation of clinical symptoms [21–23], the first of which to appear are cognitive: impairments in abstract reasoning, executive function and memory have been detected up to 10 years in advance of AD diagnosis [24–26]. No disease-modifying therapies currently exist to treat AD; the available treatments can alleviate symptoms but do not change the overall course of disease [3,4]. Given the lengthy prodromal stage of this disease, research has endeavoured to develop methods of early detection and intervention in order to prevent or delay its onset. This has included the development of preclinical diagnostic concepts such as preclinical AD and mild cognitive impairment (MCI).

1.2.1 Diagnosis of Alzheimer's disease

The first criteria for the diagnosis of AD were established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, now known as the Alzheimer's Association) work groups, which required *post-mortem* evidence of AD neuropathology for a definite diagnosis of AD [27]. Without neuropathologic evidence, only a diagnosis of probable AD could be made on the basis of clinical presentation. These criteria were widely used until 2011, when they were updated by the National Institute on Aging and Alzheimer's Association (NIA-AA) to incorporate new scientific findings and technologies, such as biomarker testing for Aβ deposition, hyperphosphorylated tau protein, and disproportionate atrophy for use in the context of research [28]. At this time, the NIA-AA

proposed diagnostic criteria for preclinical AD [29] and MCI (also considered prodromal AD in the presence of AD pathological changes) [30] in order to capture the continuum of cognitive function from CN to dementia. These recommendations also made clear a distinction between AD pathophysiology and AD clinical symptoms [31]. More recently, the NIA-AA has proposed a research framework defining AD as a biological construct that relies on the primary use of biomarkers to identify AD *in vivo,* with cognitive impairment considered as secondary to AD neuropathological changes [32].

1.2.2 Biological staging of Alzheimer's disease

1.2.2.1 *Amyloid hypothesis*

The amyloid cascade hypothesis was initially proposed in 1992, suggesting that Aβ deposition is the initial cause of AD that then triggers the hyperphosphorylation of tau and formation of neurofibrillary tangles, neuronal death and ultimately dementia [33]. It has since been refined to suggest that AD pathogenesis begins with abnormal production or clearance of Aβ [34,35]. The amyloid hypothesis remains the most widely accepted theory of AD pathogenesis [36,37] and informs the development for the majority of AD therapeutics being clinically trialled [38,39]. While it is generally accepted that Aβ accumulation and aggregation is a key feature of AD, whether it is the causative factor remains controversial: some experts have recently called for reconsideration of alternative theories due to lack of clinical efficacy in Aβ-targeted therapeutics [40–46], while others argue that these clinical failures do not reflect failure of the amyloid hypothesis and suggest that clinical trials must instead target individuals in earlier disease stages [47–49].

1.2.2.2 *Alzheimer's disease continuum*

Measuring Aβ burden *in vivo* enables detection of AD neuropathological changes prior to development of clinical symptoms. Positron emission tomography (PET) neuroimaging uses

radiotracers that bind to Aβ fibrils and not to soluble Aβ. The four most commonly used tracers are: ^{11}C-PiB (PiB), ^{18}F-AV-45 (Florbetapir), ^{18}F-AV-1 (Florbetaben) and ^{18}F (Flutemetamol). Through a lumbar puncture, decreased levels of cerebrospinal fluid (CSF) Aβ are associated with increased levels of insoluble Aβ burden in the brain.

Older adults with evidence of abnormally elevated Aβ burden are considered to be in the AD continuum or are classified as preclinical AD in the absence of cognitive impairment; the specific disease stage will depend on the presence of other AD biomarkers such as hyperphosphorylated tau or markers of neurodegeneration or neuronal injury (i.e. hippocampal atrophy on structural magnetic resonance imaging (MRI), elevated total tau protein in CSF, or reduced glucose metabolism on ^{18}FDG (Fludeoxyglucose) PET), and whether cognitive impairment is evident [29,32]. Elevated Aβ burden, or Aβ positivity (Aβ+), is determined by levels of Aβ measured to be beyond a threshold for normalcy that varies depending on the specific method of measurement (above the threshold for PET measurements, below the threshold for CSF measurements). Cut-off values are identified by the value that best discriminates CN from AD participants based on measured Aβ load [50]; therefore, CN individuals classified as Aβ+ exhibit Aβ burden similar to that of individuals with AD, while Aβ- reflects clinically non-significant levels of Aβ. A limitation to this approach is that quantification of Aβ burden in the subthreshold range (i.e. Aβ-) cannot be reliably differentiated from sources of noise such as non-specific radiotracer binding when measured using PET [51]. Furthermore, it is unclear whether a universal cut-off value for Aβ+ is appropriate because there remains some inter-individual variability in the amount of AD neuropathological changes each individual can sustain before downstream consequences such as increased cortical atrophy and cognitive impairment become evident [52]. The dichotomization of Aβ status into Aβ- and Aβ+ is adequate to identify individuals

on opposite ends of the AD continuum; however, ambiguous cases of individuals with equivocal Aβ load have been observed and suggest that Aβ status may best be represented as categorical stages [53,54].

Aβ+ has been reported to precede the onset of dementia by up to 30 years [22,23]. Approximately 16-44% of cognitively normal (CN) older adults aged 60-90 are Aβ+ [22]. The prevalence of Aβ+ increases with age, starting with approximately 3-15% of older adults above 50 years of age and increasing to about 40% of adults above age 80 [22,55]. Despite showing no signs of cognitive impairment, CN Aβ+ older adults are at increased risk of developing dementia due to AD [55–59] and display faster rates of cognitive decline [60–62] and cortical atrophy [63–68] compared to older adults with subthreshold or normal levels of Aβ (i.e. Aβ-). Rates of cognitive decline and cortical volume loss are further pronounced when Aβ+ occurs in conjunction with evidence of elevated hyperphosphorylated tau and/or neurodegeneration [59,62,69–74].

Aβ- individuals with no evidence of either elevated hyperphosphorylated tau or neurodegeneration are considered to have normal AD biomarkers. Aβ- in the presence of either markers of hyperphosphorylated tau or neurodegeneration are considered to show non-AD pathologic changes due to the absence of Aβ+, and are therefore not in the AD continuum [32]. This thesis will focus on examining differences between Aβ- and Aβ+ older adults, effectively assessing differences between individuals who either are or are not in the AD continuum.

1.2.3 Cognitive staging of Alzheimer's disease

Independently of biomarker profiles, research studies can classify participants into one of three categories on the basis of cognitive function [32]. CN participants display cognitive

performance within the normative range for their respective age and education groups. This also includes participants reporting subjective concerns about their cognitive abilities, but who display no cognitive impairment upon formal testing. MCI was introduced as an intermediate stage between normal aging and dementia where the degree of cognitive impairment observed is greater than expected for age-associated cognitive decline, but is not yet severe enough to interfere with an individual's daily functioning [30,75]. Individuals are classified as MCI based on neuropsychological performance below their expected range with some evidence or report of declining cognitive performance over time. MCI may or may not be due to AD disease processes (i.e. prodromal AD); this determination can be made on the basis of biomarker information, if available. Finally, participants with dementia display substantial and progressive cognitive impairment that impedes performance of everyday functional tasks such that they are no longer fully independent [28].

The etiology of dementia was previously inferred from the presented profile of cognitive impairment but can now be determined with biomarker testing whether individuals with dementia are in the AD continuum or if other causes are responsible [32]. The majority of dementia cases may be due to more than one cause according to studies reporting evidence of mixed pathologies (such as Aβ, cerebrovascular disease, Lewy bodies, hippocampal sclerosis, etc.), indicating that these pathologies are not mutually exclusive but synergistically interact to influence development of dementia [76,77].

1.2.4 Risk factors for Alzheimer's disease

Although no definitive causes of late-onset, or sporadic, AD are known, it is understood that a multitude of factors contribute to the disease risk and etiology [78]. Therefore, many factors have been studied that can influence cognitive decline and increase the risk of developing AD [13,79]. Studies of risk factors allow researchers and clinicians to target

groups at risk of future decline for early intervention initiatives. However, results reported in the literature can be inconsistent due to the extensive range of possible methodologies for conducting such studies, and results contrary to widely accepted findings continue to be disseminated. For example, results from cross-sectional or longitudinal studies may vary. Because studies of risk factors do not necessarily investigate causation, their conclusions may vary depending on the study population and measurements used. While some potentially modifiable risk factors have been identified [13], the greatest risk factors for AD are age and genetics.

The likelihood of developing AD increases with older age beyond 65 years; however, old age is not a causative factor [4], as cases of cognitively healthy centenarians [80–83] and very old adults [84] have been reported. Carriage of the ε4 allele of the apolipoprotein E (*APOE*) gene on chromosome 19 is the strongest genetic risk factor for late-onset AD [85,86]. Risk of AD conferred by *APOE* ε4 increases in a gene dose-dependent manner with the greatest risk and youngest age of onset observed for homozygotes compared to heterozygotes [87–89]. *APOE* ε4 carriage is understood to increase AD risk primarily through its effect on Aβ: while the exact mechanisms are unclear, the ApoE4 isoform encoded by the *APOE* ε4 allele has been associated with increased Aβ aggregation and impaired Aβ clearance through multiple pathways compared to the other two isoforms (ApoE2 and ApoE3), ultimately increasing cortical Aβ burden [88,90–92]. Levels of Aβ deposition and prevalence of Aβ+ are higher for carriers of the *APOE* ε4 allele regardless of disease status [93,94]. *APOE* ε4 carriers have also been shown to accumulate Aβ at a faster rate compared to non-carriers; however, this effect is observed only in Aβ- older adults [95]. Furthermore, *APOE* ε4 carriage reduces age of onset for Aβ+, cognitive decline and dementia [73,96,97]. While meta-analyses of the relationship between *APOE* ε4 and cognition in healthy adults

report significantly lower cognitive performance in *APOE* ε4 carriers, the effect sizes are small and based only on cross-sectional results, and the presence or absence of Aβ+ remains a confounding factor [98,99]. Studies taking into account both *APOE* ε4 carriage and Aβ status report that *APOE* ε4 carriage is associated with increased cognitive decline only in the presence of Aβ+ [100–102]. This suggests that the effect of *APOE* ε4 carriage on cognitive decline is driven by the association between *APOE* ε4 carriage and increased Aβ deposition; however, little work has investigated the effect of *APOE* ε4 specifically in Aβ- older adults, and thus any Aβ-independent effects of *APOE* ε4 are not well known.

1.3 Aging

Aging is a complex process that requires integrative understanding across multiple areas of science [103]. While the causes of aging may not be entirely understood, researchers can endeavour to describe its characteristics. There is no universally accepted definition for aging; however, it will be defined in this thesis as the passage of time and its effect on biological systems independent of any incipient or overt disease processes that may also act over time. Older age has been associated with increased risk of dementia and neurodegenerative disease [4,5], multimorbidity [104], and other age-associated diseases or geriatric syndromes such as frailty [105]. Historically, old age was even considered to be a disease in itself [105]. However, increased risk and prevalence of age-associated diseases does not mean that these clinical outcomes are associated with aging; instead, these may reflect disease processes interacting with the passage of time and may not be considered "normal" in the process of aging. It is now known that trajectories in aging can vary from one person to the next and that it is possible to remain in good physical and cognitive health well into old age [6,106–108]. Substantial heterogeneity is observed in aging, such that one

individual aged 85 may present completely differently to another individual of the same age with regard to their health, functional status and cognitive ability [109]. Individual outcomes in older age may reflect a multitude of factors including lifetime exposures to biological stresses or injuries, genetics, environmental influences and so on [105,110].

1.3.1 Cognitive aging

Cognitive aging is typically defined as longitudinal changes in cognitive ability observed in CN individuals as they get older; however, the present thesis conceptualizes cognitive aging as changes in cognitive ability over time in the absence of any underlying neurodegenerative disease processes. It is necessary to first understand the nature and magnitude of cognitive change normally associated with aging without dementia in order to adequately identify signs of abnormal cognitive decline. Cross-sectional studies compare the cognitive performance of participants across a wide range of ages at a single time point as a way to describe how cognition changes across the lifespan. Such studies have found that, on average, older people do not perform as well on cognitive testing as their younger counterparts [111–113], displaying poorer performance in memory, processing speed and executive function [114,115]. These group-level results can be interpreted to mean that any individual person may display a similar pattern of declining cognition with increasing age; however, claims about intra-individual changes in cognition over time cannot be made with cross-sectional assessment. Thus, longitudinal assessment of the same individuals over time is necessary to adequately describe trajectories of cognitive change in aging. Prospective studies of cognitive change in CN older adults have reported general declines in cognitive functioning over time, which have led to the understanding that cognitive decline is a normal part of the aging process [112,116–119]. However, cognitive decline may not be universal nor inevitable [81,111,115] – this is exemplified by the existence of centenarians

who remain CN [80–84]. Cognitive aging is a highly variable process, with inter- and intra-individual variability increasing in older age ranges [111,114,120–122]; therefore, a profile of "normal" cognitive aging is difficult to discern without first taking into consideration some of the sources of variability in cognitive aging estimates.

1.3.1.1 *Rates of age-associated cognitive decline may be overestimated by preclinical disease*

Cognitive performance at a single timepoint is considered normal if diagnostic criteria for MCI or dementia are not met based on age- and education-specific normative data [122]. However, most normative data are based on cross-sectional assessment and may be derived from study samples that include individuals with preclinical dementia whose impairments are not yet severe enough to be detected based on clinical presentation [123]. Normative samples typically exclude individuals with incipient dementia at the time of assessment [124], but individuals with preclinical dementia are often undetected because their cognitive performance continues to fall within normal limits until further disease progression. Subtle cognitive decline due to dementia may be observable more than a decade prior to diagnosis [24,125,126] and neuropathological changes associated with AD begin even earlier [21–23,127,128]. Therefore, so-called conventional normative samples including individuals with preclinical dementia would underestimate mean performance, overestimate variance and overestimate the effect of age on cognitive measures [123]. Robust normative samples either conduct longitudinal assessments and retrospectively remove individuals who later receive dementia diagnoses, or use predictive screening models to identify those who may go on to develop dementia based on data collected at a single time point [123,129]. The aim of this sampling method is to make normative samples more representative of normal cognitive aging and to improve the ability of these normative data to identify cognitive impairment at earlier stages [26,123,130–133].

Robust sampling methods may be valuable for studies of cognitive aging. Inclusion criteria for prospective studies of cognitive aging require that participants are CN with no known neurological conditions. Participants are assessed for their eligibility (i.e. screened) on the basis of clinical presentation at study entry. Typical CN samples may therefore include older adults who live in the community and either: report no prior diagnosis of dementia or other psychiatric or neurological conditions, perform within normative ranges on cognitive testing, are classified CN by a consensus clinical panel, function independently with minimal impairment, or achieve scores above a certain cut-point on global screening measures such as the Mini-Mental State Examination (MMSE) [119,134–137]. The same limitations of conventional normative samples discussed above may also apply to studies of cognitive aging: relying on the above screening methods may result in overestimated rates of cognitive decline associated with age due to inadvertent inclusion of participants with preclinical dementia or preclinical AD. An early neuropathological study estimated that 20-40% of people over the age of 65 may be in the preclinical stage of AD due to the presence of AD neuropathological markers despite no cognitive impairment prior to death [138]. After the introduction of preclinical AD as a diagnostic construct in 2011 [29], biomarker studies have supported these estimates and report similar prevalence of preclinical AD (defined by Aβ+) in samples of CN older adults [22,55]. These reports confirm that AD neuropathological changes begin decades prior to clinically-defined cognitive impairment, while individuals are CN. The trajectories of cognitive change for these individuals would then be attributed to incipient disease processes rather than the normal process of aging. Therefore, it is likely that studies of cognitive aging include participants with preclinical dementia or preclinical AD, and that estimates of age-associated cognitive decline have been overestimated by their inclusion.

Cognitive changes in normal aging must be distinguished from those that are reflective of underlying neuropathological processes. *Post-mortem* evidence of neuropathology has been associated with cognitive decline, with studies suggesting that cognitive decline in old age is the result of neuropathological changes rather than of age [139–141]. Now that preclinical AD can be detected *in vivo,* it is possible for Aβ+ to be taken into consideration when examining cognitive aging. For example, one prospective study of 494 CN older adults observed age-associated cognitive decline (0.01-0.06 SD/year) comparable to other prospective cognitive aging studies (follow-up = 4-9 years, n = 1012-11391, reported cognitive decline = 0.01-0.09 SD/year) [142–144] when examining cognitive trajectories without consideration to Aβ status [145]. However, statistically controlling for Aβ+ and clinical progression to MCI or dementia during the study period revealed no association between age and memory decline in older adults over up to 6 years [145]. Another study reported no effect of age on episodic memory and executive function change after adjusting for clinical diagnosis, baseline and changes in cortical volumes and baseline levels of AD biomarkers (Aβ and tau) [142]. Up to 80% of the age-associated variance in cognitive changes has been attributed to a combination of brain markers that include grey matter volume and thickness, white matter lesions, white matter integrity, functional connectivity, and PET markers of Aβ and glucose metabolism [146]. These findings support the possibility that reported cognitive changes in aging are driven by non-age-associated processes such as the presence of AD neuropathological markers and neurodegeneration. Studies of brain and cognitive aging may assume that any observed changes in cognition or brain morphology are the result of aging processes, but this assumption may be inaccurate if sample screening criteria are not stringent enough to isolate samples of older adults with no underlying neuropathological changes. Therefore, estimated rates of cognitive decline in

aging may be attenuated when examined in samples with no or minimal evidence of AD neuropathological changes. This is supported by studies examining Aβ-associated differences in cognitive trajectories, which have reported little-to-no decline in memory and executive function for Aβ- older adults over periods of 5-10 years [66,71,147]. Taken together, these findings indicate that studies aiming to assess age-associated changes in cognition would benefit from including only participants who are not in the AD continuum (i.e. Aβ-) and who do not later progress to MCI or dementia (i.e. a robust sample). This may reduce both inter- and intra-individual variability in cognitive aging estimates, and the results from such a sample may more closely approximate changes expected in normal cognitive aging. As methods to identify the presence of other neuropathological or neurodegenerative changes become more available, studies can further refine these aging samples to yield even more representative estimates of normal cognitive aging without the influence of underlying neurobiological processes on cognitive change. Preliminary evidence suggests that declining memory or executive function may not be characteristic of normal cognitive aging; however, it must be noted that the widely-used cognitive assessment tools have been designed primarily to identify incipient disease and thus may not be adequate for fine-grained assessment of non-disease processes.

1.3.2 Brain aging

Aging studies typically characterize brain aging as morphological changes that occur in CN individuals as they get older. This thesis further defines brain aging as changes observed in brain morphology over time in the absence of any markers of neurodegenerative disease. Cortical volume loss in total white matter (WM) and grey matter (GM) have been consistently observed in CN older adults [148–150], indicating an average 0.50% whole brain volume loss per year [151–157]. Burden of white matter hyperintensities (WMH) also

increases with age [158,159]. Individuals with MCI or AD display increased rates of cortical atrophy compared to those who are CN [160], and older adults who are Aβ+ display faster rates of cortical and medial temporal lobe volume loss compared to those who are Aβ- [63–68]. Therefore, it is likely that, similar to rates of age-associated cognitive change, rates of age-associated cortical atrophy have been overestimated due to studies inadvertently including older adults who are in the AD continuum. This is supported by one report of 0.35% annual whole brain atrophy for Aβ- older adults [63], which suggests that previously reported rates were overestimated by inclusion of both Aβ- and Aβ+ participants. While Aβ- older adults display substantially reduced rates of cortical volume loss compared to Aβ+, some volume loss is still observed [63–68]. This raises the possibility that some cortical volume loss is expected in the process of aging. While increased rates of cortical volume loss may reflect some AD neuropathological processes for Aβ+ older adults, atrophy observed in the absence of Aβ+ indicates that some morphological changes do occur in normal brain aging, albeit at an attenuated rate.

1.3.3 Successful aging

The concept of healthy or successful aging has become widely used in academic literature and in health policy. However, a universally-accepted definition and methods of measurement have yet to be established [161–167]. The wide range of possible definitions, outcome measures and cohort characteristics leads to varied results; studies have reported that between 3% to 80% of their populations were “healthy agers” [165].

Rowe and Kahn’s model of successful aging is one of the most well-known. It differentiates successful aging from usual aging by the presence of three main components: avoiding disease and disability, high cognitive and physical function, and engagement with life [106,168]. According to their model, a cross-sectional study of aging may indicate poorer

cognitive or physiological outcomes with older age but there may be some older adults with better than expected measures for their age. Those individuals may be considered to have successfully aged, while the remainder of the study sample may be reflective of usual aging in the absence of disability or disease. Rowe and Kahn emphasize the role and importance of personal agency in successful aging, suggesting that aging trajectories may be modified by individual choices or environmental changes [106].

A study of the successful aging literature found two distinct concepts of successful aging: one approach defines successful aging using objective measures defined by researchers (i.e. observed successful aging), and the other explores successful aging from the perspective of older adults (i.e. experienced successful aging) [169]. Furthermore, studies of observed successful aging are largely split between those of overall successful aging, which considers overall health and well-being, and successful cognitive aging, which considers only cognitive function in older age. This thesis will focus on observed successful cognitive aging; however, it is important to note that cognitive function in aging does not exist in a vacuum. Successful cognitive aging is not necessarily independent of overall health and well-being because systemic illnesses [170,171], depressive or anxious symptomology [172–174] or perceived stress [175], for example, have each been associated with increased rates of cognitive decline.

1.3.3.1 *Successful cognitive aging*

While there are some broad similarities across all studies in the way that successful cognitive aging is characterized, no consensus definition currently exists due to considerable heterogeneity in the execution of these definitions [167,176]. Overall, successful cognitive aging has been characterized as superior performance on neuropsychological tests in old age – predominately of verbal episodic memory – either in reference to a younger sample,

or relative to the study group itself. Successful cognitive aging has been studied across 9 different cohorts and the identified subsamples have been given numerous names, including successful cognitive agers [177–179], successful agers [180], resilient-agers [181], cognitively elite [182], supernormals [183], optimal memory performers [184], and SuperAgers [185]. Studies identifying the features and characteristics of successful cognitive aging may be able to inform guidelines to increase future prevalence of successful cognitive aging and thereby reduce the incidence of dementia [186].

1.3.3.2 *SuperAging*

The term "SuperAging" was coined by researchers from the Northwestern Super Aging Study to identify older adults whose verbal memory performance was comparable or better than that of individuals decades younger [185]. Specifically, SuperAgers were defined as individuals aged 80 and above who perform at or above normative values for individuals aged 50-60 on the Rey Auditory Verbal Learning Test long delay (i.e. ≥ 9), and within 1 SD of average range for their age and education on non-memory measures. Therefore, SuperAgers are said to have maintained "youthful" memory performance into old age [187]. Typical agers were of similar age to the SuperAgers and defined as individuals who perform within 1 SD of average range for their age and education on all measures [185]. Early studies of cognitive and brain morphological changes in SuperAging suggest the possibility that youthful memory performance may reflect some unique protection against cognitive changes or cortical atrophy typically associated with aging.

Prospective studies of cognition report that SuperAgers display less cognitive decline compared to typical agers over periods of 18 months [188] and an average of five years [180]. Cross-sectional comparisons of brain morphology between SuperAgers and elderly controls report larger measurements on cortical volume and thickness for SuperAgers

compared to controls [180,185,189,190] and lower burden of WMH [180]. These cross-sectional reports suggest that SuperAgers are protected from age-associated cortical volume loss; however, findings from longitudinal analyses have been mixed. SuperAgers displayed reduced rates of cortical atrophy compared to typical agers over 18 months [191] but no group differences were observed in a 5-year study [180]. However, the reported differences between SuperAgers and typical agers may be due to lower prevalence of Aβ+ in SuperAgers because a small neuropathological study reported lower frequency of amyloid plaques and neurofibrillary tangles in this group [190].

To date, only one small study has included *in vivo* Aβ burden in their analyses. While no group differences in Aβ burden were observed between successful agers (n=19) and typical older adults (n=70), Aβ-associated decline in episodic memory was observed for the typical older adults but not for the successful agers [180]. These findings provide early support for the possibility that SuperAgers, defined on the basis of superior neuropsychological performance, may be protected from the deleterious effects of Aβ on cognitive decline and cortical atrophy; however, larger studies are needed to examine this further. If this is the case, examining the characteristics associated with SuperAging and the mechanisms conferring this unique protection from age- and Aβ-associated cognitive decline and cortical atrophy may provide valuable insight into ways in which aging without dementia can be achieved.

1.4 Conclusion

The superlative of “successful” or “super” used in the context of aging suggests that these constructs reflect something above or beyond normal aging; however, the processes of normal cognitive and brain aging must first be understood in order to appropriately

evaluate what is then "successful" or "super" relative to normal. Approximately 30% of CN older adults are in the AD continuum (i.e. Aβ+), and Aβ+ is associated with faster rates of cognitive decline and cortical atrophy. However, rates of age-associated changes in cognition and brain morphology are estimated from samples of CN older adults without screening for the presence of Aβ+. It is, therefore, possible that rates of cognitive and brain aging have been overestimated due to inadvertent inclusion of older adults with preclinical AD. Studies seeking to elucidate the nature of age-associated changes must endeavour to control for sources of non-age-associated variability such as the presence of neuropathological changes in older adults. The criteria for SuperAging and whether these individuals are uniquely protected from age- and Aβ-associated changes in cognition and brain morphology must also be assessed with reference to a sample of normal aging older adults.

Taken together, typical models of cognitive and brain aging suggest that some cognitive decline and cortical volume loss is normal in aging; however, recent evidence suggests it is now necessary to consider a more precise definition of "aging". In most studies, "aging" refers to average age-associated changes observed in CN older adults, but this non-specific definition does not preclude the presence of preclinical AD or other neurodegenerative diseases. Therefore, this thesis conceptualizes aging as the cognitive and neurobiological changes that occur with the passage of time independent of neuropathological processes such as Aβ+. By isolating the effects of aging from the effects of AD neuropathological changes and characterizing the neurocognitive changes that occur in normal aging, deviations from normality can be identified as early as possible.

The overarching aim of this thesis was to characterize the cognitive and brain morphological changes associated with normal aging. Thus, this body of work investigated the possibility

that risk profiles and trajectories of cognitive and brain aging for CN Aβ+ older adults may not be reflective of normal aging processes. Whether classification of older adults as SuperAgers on the basis of neuropsychological performance is reflective of a unique phenotype of aging that is above and beyond normal was also examined with consideration to how models of normal cognitive aging and SuperAging may be consolidated into a single model. The first aim was to examine the risk and incidence of Aβ-associated progression to MCI/dementia among CN older adults over 8 years, and to identify any demographic or clinical characteristics that increased or decreased that risk [Chapter 3]. The second aim was to evaluate trajectories of cognitive and brain aging for older adults classified as SuperAgers, and whether they displayed any unique resistance or resilience to Aβ+ compared to those classified as cognitively normal for their age (CNFA) [Chapters 4-5]. The final aim was to investigate relationships between concurrent changes in cortical volume and cognitive function, and whether these relationships were moderated by the presence of Aβ+ [Chapter 6] or *APOE* ε4 in older adults who remained CN Aβ- [Chapter 7]. These findings may support the identification of "robust" samples for studies of aging to isolate the effects of aging from that of preclinical neurodegenerative conditions. The results from this body of work challenges previously well-established models of aging and provides evidence that cognitive decline is not inevitable with age.

Chapter 2: Methods

2 Methods

The studies in this thesis used longitudinal data collected over up to 8 years from the Australian Imaging, Biomarker and Lifestyle (AIBL) Flagship Study of Ageing. Chapter 3 employed survival analysis methods to estimate the risk of progression from cognitively normal (CN) to mild cognitive impairment (MCI) or dementia during the study period due to amyloid-β (Aβ) status, and the extent to which risk was influenced by other demographic, genetic and clinical characteristics. Chapters 4 and 5 investigated trajectories of cognitive and brain morphological changes and whether these were different between groups based on Aβ status and SuperAger classification. Chapters 6 and 7 examined relationships between concurrent changes in cortical volume and cognition, and whether these relationships were moderated by Aβ status and *APOE* ε4 carriage.

2.1 Participants

Participants were enrolled in the AIBL study, which is a prospective cohort study of aging that began in November 2006. The study was initiated by the Commonwealth Scientific and Industrial Research Organisation (CSIRO) as a joint collaboration between the University of Melbourne, Edith Cowan University, Neurosciences Australia, the Mental Health Research Institute of Victoria, the National Ageing Research Institute and CSIRO. The institutional ethics committees of Austin Health, St Vincent's Health, Hollywood Private Hospital and Edith Cowan University approved the AIBL study, and all volunteers gave written informed consent before participating in the study and again at each subsequent study visit (every 18 months). The AIBL study aimed to improve the understanding of the causes, development and diagnosis of Alzheimer's disease (AD), and to identify risk or protective factors for AD. It is now one of the largest and longest-running studies of AD in the world. Participants

continue to be recruited and followed up, and data up to the fifth assessment (September 2016) were available for inclusion in this thesis.

2.1.1 Recruitment and screening

The full study protocol has been reported in detail elsewhere [192]. AIBL participants were recruited through media appeal and referrals from medical practitioners. Potential participants were screened either over telephone or in person to assess their eligibility for the AIBL study. Minimum age for entry was 60 years. Participants were also recruited in two waves, the original inception cohort (8 years available follow-up data) and an enrichment cohort (4.5 years available follow-up data). The enrichment cohort were, on average, one year younger than the inception cohort with no other demographic or clinical differences. General exclusion criteria were: diagnosis of non-AD dementia, history of schizophrenia or bipolar disorder, current depression (Geriatric Depression Scale (GDS) score >5), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, obstructive sleep apnea, past head injury with >1 hour of post-traumatic amnesia, or current regular alcohol intake above recommended limits [193]. Due to the stringent exclusion criteria, the AIBL participants had no, or medically well-controlled, systemic illnesses at study entry.

2.1.2 Sample selection

While the AIBL study includes participants in three main diagnostic groups (CN, MCI and AD), this thesis only examined data from participants who were classified CN at their baseline assessment. There were 1171 CN participants in the AIBL study by the fifth assessment. All studies included in this thesis required that participants had attended at least 2 study visits during which neuropsychological assessment was completed, and had at least one positron emission tomography (PET) scan such that their Aβ status was known.

Participants whose Aβ status fluctuated around the classification threshold on multiple PET scans could not be accurately classified as either Aβ- or Aβ+ and were therefore excluded from all analyses. Finally, participants whose clinical classification fluctuated from CN to MCI and back to CN over the study period were excluded from all analyses because the clinical trajectory for these individuals was unclear. Further selection criteria varied for each chapter in this thesis in accordance to the specific aims of each study; therefore, the number of participants included for analysis was different between studies (see below). Sample selection figures are also displayed in each chapter.

Brief analyses were conducted to examine whether any significant differences were observed between the participants who were included in the study samples below and those who did not meet the inclusion criteria. No demographic or clinical differences were observed between the included and excluded participants for any study other than the one described in Chapter 3.

2.1.2.1 *Chapter 3 – Relationship between amyloid-β positivity and progression to mild cognitive impairment or dementia over 8 years in cognitively normal older adults*

This study included 599 participants (333 Aβ- and 266 Aβ+) who had undergone Aβ PET neuroimaging, who had attended at least 2 study visits, and who did not have history of serious head injury at baseline. A slightly greater proportion of men met the inclusion criteria compared to those who did not (44.4% and 38.2%, p=0.03, OR: 0.77, 95% CI: 0.61-0.98). Participants who had reported a history of stroke or transient ischaemic attack (TIA) at baseline were included in this study because history of stroke or TIA at any time before or during the study period was examined as a potential risk factor for future progression to MCI or dementia. All subsequent studies in this thesis excluded participants with baseline history of stroke or TIA.

2.1.2.2 *Chapter 4 – Superior memory reduces 8-year risk of mild cognitive impairment and dementia but not amyloid β-associated cognitive decline in older adults*

Additional inclusion criteria for this study and all subsequent studies were that participants needed to be aged over 60 with a baseline Mini-Mental State Examination (MMSE) score greater than 24. CN participants were classified as either SuperAgers or cognitively normal for their age (CNFA) based on neuropsychological performance. The 179 identified SuperAgers were then case-matched with CNFA on age, sex, education and follow-up time in order to ensure that any observed group differences were due to classification and no other demographic or follow-up factors. CNFA participants who were not matched with SuperAgers were excluded. Thus, this study included 358 participants in total.

2.1.2.3 *Chapter 5 – Rates of age- and amyloid β-associated cortical atrophy in older adults with superior memory performance*

In addition to the selection criteria listed for Chapter 4, this study required that participants had also undergone magnetic resonance imaging (MRI) scans in order to examine trajectories of cortical volume change. Of the 179 SuperAgers identified in Chapter 4, 172 also had MRI data available. These participants were then case-matched with CNFA on age, sex, education, follow-up time and number of serial MRI scans. The total number of participants included in this study was 344.

2.1.2.4 *Chapter 6 – Examining the moderating effect of amyloid-β on associations between cortical volume loss and cognitive change in cognitively normal older adults*

The sample selection criteria was further restricted to participants who had completed at least 3 neuropsychological assessments and at least 3 serial MRI scans, regardless of SuperAger classification status. This was done because slopes of cortical volume and cognitive change were calculated for each participant and used in the analyses, and having at least 3 time points of data instead of 2 enables more accurate estimations of individual trajectories of change in cortical volume and cognition. This study included 141 participants (78 Aβ- and 63 Aβ+).

2.1.2.5 *Chapter 7 – Examining the moderating effect of APOE ε4 carriage on associations between cortical volume loss and cognitive change in a robust sample of aging older adults*

This study included a sub-sample of the participants included in Chapter 6. Only participants who were classified as Aβ- and CN at all assessments were included in the study, constituting a robust sample, in order to examine relationships between cortical volume loss and cognitive change in the absence of AD neuropathological changes or clinical disease progression. The final sample included a total of 70 participants (54 *APOE* ε4- and 16 *APOE* ε4+). The reader is asked to bear in mind that the sample size for this study is small and that all statistical results are interpreted with due consideration of this fact.

2.2 Measures

2.2.1 Assessment

Participants were assessed every 18 months for up to 90 months. Once informed consent was given, fasting blood samples were drawn and participants were provided with breakfast. During breakfast, participants were asked to fill out a questionnaire package that included demographics, self-reported medical history and mood questionnaires. Some questionnaires were mailed to participants prior to the assessment date and the completed questionnaires were given to researchers on the day. The neuropsychological assessment was then conducted. Finally, measurement of vital signs were taken at the conclusion of the study visit (height, weight, waist circumference, and blood pressure using an electric sphygmomanometer). The candidate conducted assessments for the AIBL cohort on a weekly basis for one year during her PhD candidature.

2.2.2 Neuropsychological tests

A full neuropsychological battery was administered by trained staff at each 18-month assessment. This took approximately 2 hours to complete. Two cognitive screening tools

were administered to assess overall cognitive and functional capacity: the MMSE [194] and the clinical dementia rating (CDR) scale [195]. The test battery included the following measures: California Verbal Learning Test – Second edition (CVLT-II) [196], Wechsler Memory Scale (WMS) Logical Memory Story A only [197], Weschler Test of Adult Reading (WTAR) [198], D-KEFS verbal fluency (i.e. category fluency) [199], 30-item Boston Naming Test [200], Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) Digit Span and Digit Symbol Substitution Test [201], letter fluency (FAS) [202], Victoria Stroop test [202], and the Rey Complex Figure Test (RCFT). Estimated IQ was determined from performance on the WTAR, and was included as a covariate in Chapter 4.

Participants also completed a computerized cognitive test battery called the Cogstate battery, which took approximately 30 minutes [203]. The Cogstate battery includes 5 tasks using digital playing cards, and the final task was a Continuous Paired Associate Learning task.

Individual tests were not used in examination of cognitive outcomes; instead, cognitive composites representing particular cognitive domains were calculated in order to reduce the number of neuropsychological variables and improve the parsimony of conclusions drawn from the results. The neuropsychological tests included in these composites are described in more detail below.

2.2.3 Cognitive composites

Four composite domain scores were derived via exploratory factor analysis, as previously reported [145]. The neuropsychological test measures included in the factor analyses were tests identified to be optimal for assessing the effects of age on cognition in the AIBL study [204]. Composite measures were calculated for verbal memory, executive function, working memory and processing speed. The verbal memory composite included CVLT-II Immediate

Recall Trials 1-5, CVLT-II Long Delay Free Recall, and Logical Memory II. The executive function composite included category fluency (total animals and male names, and total fruit and furniture), letter fluency (sum of FAS), Victoria Stroop Test (words trial), and Digit Symbol Substitution Test. Working memory included two Cogstate tasks (One Card Learning, One Back). Finally, processing speed included the Cogstate Identification and Detection tasks. Composite scores were calculated for each participant visit by averaging z-scores for each cognitive domain relative to the full CN AIBL sample at baseline.

2.2.3.1 *Verbal memory composite score*

CVLT-II: Participants are asked to free-recall a list of 16 words (in which there are 4 semantic categories) for 5 immediate learning trials. Participants are then asked to free-recall these words again after a short and a long delay (up to 20 minutes). The total number of words recalled across the 5 immediate learning trials and the number of words recalled at the long delay trial were included in the composite measure.

Logical Memory II: Participants are read aloud a short story and asked to recall the details of the story immediately (Logical Memory I) and after a 25-35 minute delay (Logical Memory II). The number of details recalled is scored out of 25. The composite measure included only the delayed recall score.

2.2.3.2 *Executive function composite score*

Category fluency: In one minute, participants are asked to name as many things as they can that are 1) animals and 2) male names. A third task involved naming all the fruit and all the furniture they could, but switching between the categories as they went (i.e. fruit, furniture, fruit, etc.). A switching score can also be derived from this task. The composite measure included the total number of animals and male names combined, and the total number of fruit and furniture combined.

Letter fluency: Participants are given one minute to list as many words as they can that start with each of the following letters: F, A and S. The total number of words generated over the three-minute task was included in this composite score.

Victoria Stroop Test: This timed task assesses participants' ability to accurately process information in the face of interference from competing stimuli. All stimuli are either red, blue, green or yellow and presented in a 4 x 6 array. Participants are asked to respond as quickly as possible. The first trial (dots) required participants to identify the colour of each presented circle. The second trial (words) required participants to identify the colour of the text for neutral words. The final trial (colours) was an interference task, where participants were again asked to identify the colour of the presented text, but the text were of incongruous colours. For example, the word "red" written in blue ink (**RED**). The time taken to complete the words trial was included in the composite measure.

Digit Symbol Substitution Test: Participants are shown a key of numbers (1-9) each corresponding to a symbol. They are asked to write the corresponding symbol in the blank space below each provided number and to complete as many as possible in 2 minutes. The total score is determined by the number of correct symbols completed in the given time.

2.2.3.3 *Working memory composite score*

Cogstate One Card Learning: This is a continuous recognition task. Participants are shown face-up playing cards, one at a time, and are asked to determine if they had seen that card before in this task. Participants are instructed to press the "yes" and "no" buttons as appropriate. There are 6 cards that are repeated throughout the task, interspersed with non-repeating cards (i.e. distractors). Accuracy, measured as the proportion of correct answers in the task, was included in the composite measure.

Cogstate One Back: Participants are shown playing cards one at a time on the screen and asked to determine if the current card is the same as the one shown immediately before it. If yes, participants were instructed to press "yes" and "no" otherwise. Accuracy was included in the composite measure.

2.2.3.4 *Processing speed composite score*

Cogstate Detection: A face-down deck of cards is displayed on the screen, and participants are instructed to press "yes" as soon as a card is turned face-up. Mean reaction time in milliseconds is recorded at the end of the task and was included in the composite measure.

Cogstate Identification: As soon as a card is turned over, participants must decide whether the presented card is red or not (i.e. is black) and press either the "yes" or "no" button. Mean reaction time in milliseconds was included in the composite measure.

2.2.4 Clinical classification

Monthly expert clinical panels reviewed all available neuropsychological and psychiatric information for participants at each visit based on neuropsychologist referral. The panel was blinded to information about Aβ and *APOE* ε4 status, and consensus classifications were made using standard clinical criteria for MCI [205] and AD [27]. All participants with a classification of MCI or AD were reviewed by the panel after each assessment. CN participants were referred to the panel to review their clinical classification if any of the following were observed during the neuropsychological assessment: MMSE score <28, CDR score of 0.5 or higher, performance below the education-adjusted cut-off scores for Logical Memory II, or performance below -1.5 SD on published age- and education-adjusted normative data on at least two neuropsychological tests. Other potential reasons for referring CN participants for review included self-reported or informant reported memory difficulties, evidence of significant mood symptomology on either the GDS or the Hospital

Anxiety and Depression Scale (HADS), or any medical condition or medication/substance use that may affect cognition.

2.2.5 SuperAger classification

Individuals were classified as SuperAgers at baseline using neuropsychological criteria adapted from the Northwestern SuperAging Study criteria [185,206]; however, a greater number of non-memory tests were included in the classification criteria for this study compared to that used in the Northwestern SuperAging Study to increase classification specificity. SuperAger classification required performance above the sex-adjusted normative average for 30-44 year olds on the CVLT-II Long Delay Free Recall trial (≥13 for women, ≥12 for men) [196], and above -1 SD using published normative data for all non-memory tests identified to be optimal for the study of cognitive aging, including the Digit Symbol Substitution Test, the Victoria Stroop Test (words trial), Digit Span, letter fluency (FAS), and category fluency (total animals and male names, and fruit and furniture) (as per [204]).

2.2.6 Mood symptomology

The AIBL study included two self-administered mood questionnaires, the Geriatric Depression Scale (GDS) and the Hospital Anxiety and Depression Scale (HADS). This thesis used only data from the HADS in order to assess specific contributions of anxious or depressive symptomology. The GDS was not included in the following analyses due to the high correlation between the two measures. The HADS is a 15-item questionnaire of anxiety and depression [207] that yields a score for anxious symptomology (HADS-A) and a score for depressive symptomology (HADS-D) based on the respondent's experiences within the last week. A score greater than 11 on either the HADS-A or HADS-D is considered clinically

elevated or potentially diagnosable with further clinical assessment [208]. Participants with scores above 8 were referred to the AIBL clinical panel for review.

2.2.7 Subjective memory complaint

The Memory Assessment Clinics Questionnaire (MAC-Q) is a self-administered memory complaint questionnaire [209]. It is a brief 6-item questionnaire that asks respondents to assess their memory ability for different tasks (e.g. names, phone numbers) now compared to what it was in their late teens or early twenties. The maximum total score is 35, with increasing score representative of greater memory complaints.

2.2.8 Blood analysis

Fasting blood samples were collected from participants (80 mL) and extensive testing was conducted. Only the lipid panel (total cholesterol, tryglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL)) and genotyping data are presented in this thesis.

2.2.8.1 *APOE genotype*

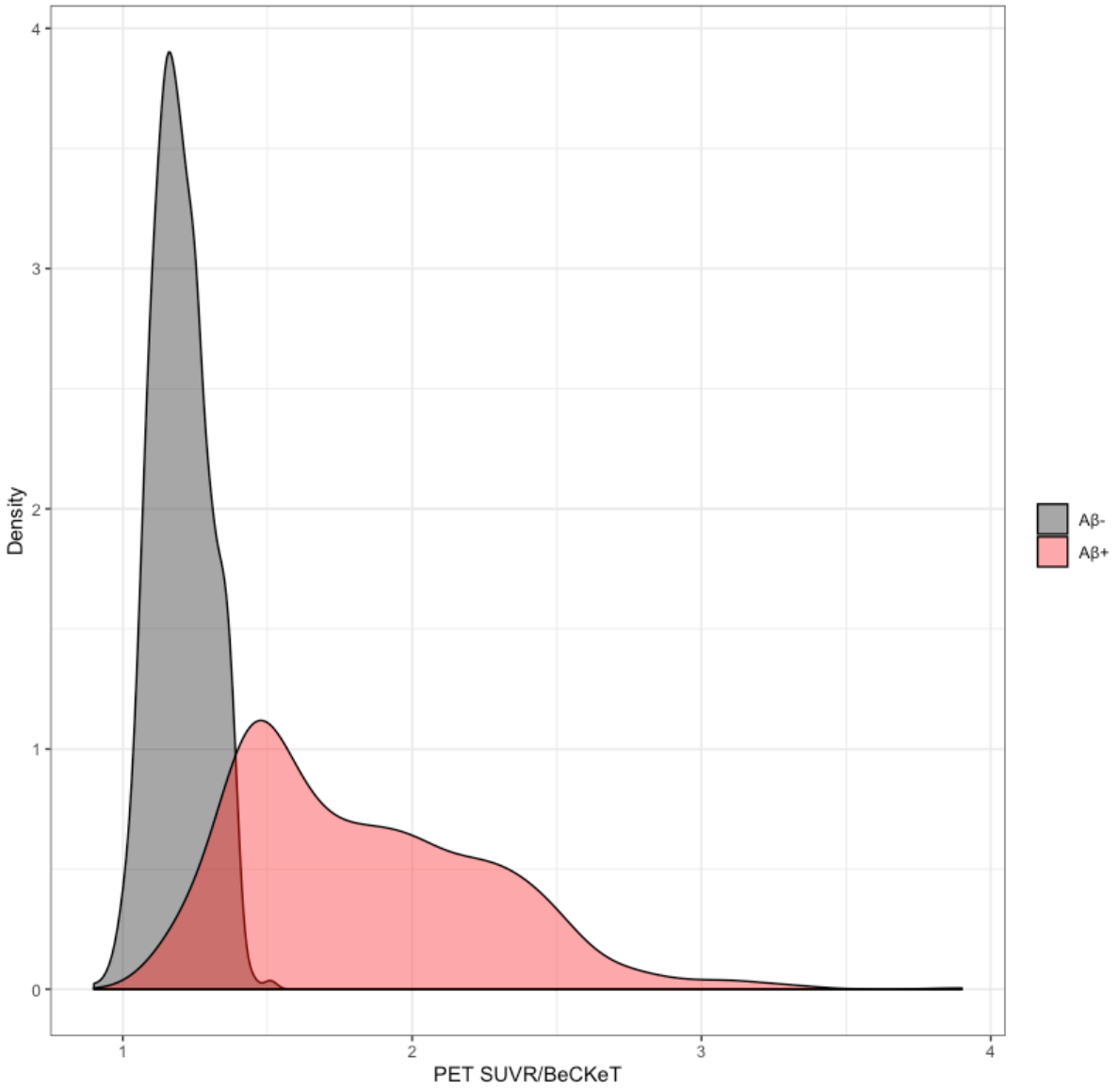
One 5 mL tube of whole blood was used for *APOE* genotyping. DNA extraction was performed using QIAmp DNA Blood Maxi Kits (Quiagen, Hilden, Germany), and TaqMan® genotyping assays were used to determine *APOE* genotypes. More detail on these procedures has been published elsewhere [210]. Participants were classified as either *APOE* ε4 non-carriers or carriers, and this was coded as a dichotomous variable (*APOE* ε4- and *APOE* ε4+).

2.2.9 Measurement of Aβ

All participants included for analysis in this thesis were required to have received at least one Aβ PET scan. PET neuroimaging was conducted using one of the following Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB), ^{18}F-NAV4694 (NAV), ^{18}F-Florbetapir (FBP), or ^{18}F-Flutemetamol (FLUTE). PET methods and procedures have been reported previously in

detail [211,212]. Briefly, PET acquisitions were performed up to 90 minutes following tracer injection. Standardized uptake value (SUV) data were summed and normalized to a reference region (the cerebellar cortex for PiB and NAV, the whole cerebellum for FBP, and the pons for FLUTE) to generate a SUV ratio (SUVR). Threshold values for elevated Aβ deposition vary by radiotracer, therefore, a linear regression transformation was applied to the FBP and FLUTE SUVR to create a "PiB-like" SUVR unit called Before the Centiloid Kernel Transformation (BeCKeT) [34]. All participants with SUVR/BeCKeT$\geq$1.40 at their most recent PET scan were classified Aβ+ and those below the threshold were classified Aβ-. Participants whose SUVR/BeCKeT fluctuated around the threshold on multiple PET scans could not be accurately classified and were therefore excluded from all analyses. This thesis primarily treated Aβ as a dichotomous variable (Aβ- and Aβ+) due to the binomial distribution observed when treated as a continuous variable across the full study sample. The SUVR/BeCKeT distributions across the Aβ- and Aβ+ groups are shown in Figure 2-1, where SUVR/BeCKeT is normally distributed within the Aβ- group but negatively skewed within the Aβ+ group. Chapter 3 included some post-hoc analyses within the Aβ- and Aβ+ groups separately that included continuous SUVR/BeCKeT; otherwise, SUVR/BeCKeT was only used as a continuous variable for descriptive purposes in this thesis.

Figure 2-1: Density plot of PET SUVR/BeCKeT values across the whole AIBL CN cohort



2.2.10 Brain morphological measures

A subsample of the CN AIBL participants underwent a 3D T1-weighted (T1W) magnetization-prepared rapid gradient-echo (MPRAGE) MRI sequence using the following acquisition parameters: in-plane resolution 1×1 mm, slice thickness 1.2 mm, repetition time (TR)/echo time (TE)/inversion time (TI)=2300/2.98/900, flip angle 9°, and field of view (FOV) 240×256. Some participants declined to receive MRI scans, while others were excluded for safety reasons. Image processing was done using a fully automated pipeline called CurAIBL [213],

which employs a longitudinal segmentation and parcellation scheme. T1W images for all participants at each timepoint were segmented into white matter (WM), grey matter (GM) and cerebrospinal fluid using an implementation of the expectation maximization algorithm [214]. The resulting tissue masks are then used to skull-strip the T1W images. The skull-stripped images are used to build an unbiased within-subject template with a procedure similar to that used by FreeSurfer [215]. The tissue probability maps from the original segmentations are propagated to the mean within-subject template space, and averaged across all timepoints to generate subject-specific priors. Each image is then re-segmented in the mean space using the subject-specific priors to generate the final tissue segmentations. The within-subject templates are parcellated by multi-atlas segmentation propagation using the MIRORR package [216] for the affine registration and the NiftyReg package [217] for the non-rigid registration. The atlas selection is based on the LEAP method [218]. Each timepoint is parcellated with the same set of atlases selected for the within-subject template, initializing the non-rigid registration with the deformation fields computed from the within-subject template. Using this first whole brain parcellation, a region of interest (ROI) was defined around the hippocampus and the procedure was reiterated within the ROI to obtain the final hippocampus parcellation. The final parcellations were masked using the GM segmentation. The anatomical definition of the hippocampus for the template was based on the Harmonized Hippocampus Protocol [219].

A subset of the participants who received MRI scans also underwent a 3D fluid attenuation inversion recovery (FLAIR) sequence to determine white matter hyperintensity (WMH) burden. Three different sets of FLAIR acquisition parameters were used across the different scanning sites: 1) in-plane resolution 0.98×0.98 mm, slice thickness 0.9 mm, TR/TE/TI=6000/420/2100, flip angle 120°, FOV 240×256, and 176 slices; 2) in-plane

resolution 0.5×0.5 mm, slice thickness 1.0 mm, TR/TE/TI=5000/355/1800, flip angle 120°, FOV 512×512, and 160 slices; 3) in-plane resolution 1.0×1.0 mm, slice thickness 1.0 mm, TR/TE/TI=5000/391/1800, flip angle 120°, FOV 256×256, and 192 slices. WMH were automatically segmented using the HyperIntensity Segmentation Tool based on an ensemble of pre-trained neural network classifiers [220,221] and quantified from the segmented lesion masks in the common Montreal Neurological Institute space.

All measures (WM, GM, hippocampal and WMH volume) were corrected for scanner and total intracranial volume.

2.3 Statistical analysis

All chapters conducted between-group comparisons for baseline measures. All continuous variables were assessed for normality by visual inspection of Q-Q plots. Between-group comparisons for Aβ status were conducted using a one-way analysis of variance (ANOVA) for normally distributed variables. Kruskal-Wallis one-way ANOVAs were used for non-normally distributed variables. Fisher's exact tests were used for dichotomous variables. Effect sizes (Cohen's *d)* were calculated for all comparisons.

2.3.1 Chapter 3 – Relationship between amyloid-β positivity and progression to mild cognitive impairment or dementia over 8 years in cognitively normal older adults

The aim for this chapter was to estimate the risk of progression from CN to MCI or dementia during the study period due to Aβ status, and the extent to which risk was influenced by other demographic, genetic and clinical characteristics.

Survival analysis using Fine-Gray subdistribution hazards models examined risk of clinical disease progression in the presence of competing risks. Progression to

MCI/dementia were coded as events, and time to event or censoring was entered in months from the baseline visit. Death or withdrawal from the study due to illness were coded as competing risks because the deceased have no risk of clinical progression and those who withdraw due to illness may have higher risk [222]. These survival analyses were conducted in 5 stages. Model 1 included characteristics that differed between Aβ groups at baseline (age, hypertension, and BMI). Model 2 added Aβ status, and Model 3 added *APOE* ε4 status. To examine the effects of health factors proposed to influence disease progression, diabetes and stroke/TIA were added in Model 4. Finally, Model 5 included an Aβ status by *APOE* ε4 interaction to compare the hazard of progression between participants who had both Aβ+ and *APOE* ε4 against all other participants.

Post-hoc analyses repeated Model 4 within the Aβ+ and Aβ- groups separately to examine differences in risk of clinical disease progression associated with Aβ status. These analyses used continuous PET SUVR/BeCKeT to assess the relative effect of Aβ deposition on progression within the pre-defined ranges for the Aβ- and Aβ+ groups.

2.3.2 Chapter 4 – Superior memory reduces 8-year risk of mild cognitive impairment and dementia but not amyloid β-associated cognitive decline in older adults

This study aimed to prospectively examine eight-year risk of clinical disease progression to MCI/dementia in older adults aged ≥60 classified as SuperAgers compared to those who were cognitively normal for their age (CNFA). The second aim was to determine the extent to which SuperAgers were resilient to the negative effects of Aβ+ on cognition compared to CNFA.

Fine-Gray subdistribution hazard modelling was used to estimate the risk of progression to MCI/dementia while accounting for the presence of competing risks (i.e.

death, withdrawal from study due to illness unrelated to dementia). Hierarchical models included the following predictors to assess risk: SuperAger status (i.e. CNFA/SuperAger), estimated IQ, baseline age, sex, *APOE* ε4 carriage, and Aβ status (+/-).

To examine trajectories of cognitive change in SuperAgers and CNFA with consideration to Aβ status, multiple linear mixed models (LMMs) were conducted with each of the four cognitive domain composite scores as continuous dependent measures (verbal memory, executive function, working memory, processing speed). Fixed factors were SuperAger status, Aβ status, time from baseline assessment in years, and their interactions. Participant was entered as a random factor with random slopes for time. Covariates were baseline age, progression status, estimated IQ, and *APOE* ε4 status.

2.3.3 Chapter 5 – Rates of age- and amyloid β-associated cortical atrophy in older adults with superior memory performance

Following from Chapter 4, this study aimed to whether SuperAgers were resistant to age- and Aβ-associated neurodegeneration compared to CNFA older adults.

Separate LMMs were run with each of the neuroimaging measures (WM, GM, hippocampal volume) as dependent measures. Fixed factors were SuperAger classification, Aβ status, time (years from baseline scan), and their interactions. Random intercepts and slopes were calculated for each participant. Covariates were baseline age and progression status; *APOE* ε4 status and number of serial MRI scans did not significantly contribute to the models and were therefore removed.

Exploratory analyses were also conducted to examine differences between SuperAgers and CNFA in white matter hyperintensity (WMH) volume and accumulation over time, and whether this was mediated by Aβ. This was explored using a gamma generalized linear mixed model fitted with a log link function using the same fixed and random factors

included in the LMMs. Covariates were baseline age, *APOE* ε4 status and self-reported hypertension.

2.3.4 Chapter 6 – Examining the moderating effect of amyloid-β on associations between cortical volume loss and cognitive change in cognitively normal older adults

This study aimed to examined relationships between concurrent changes in cortical volume (WM, GM and hippocampus) and cognition (verbal memory and executive function) in CN Aβ- and CN Aβ+ older adults. LMMs for all cortical volume and cognitive measures were conducted first to confirm that rates of cortical volume and cognitive change were different between the Aβ- and Aβ+ groups in the present sample. Time (years from baseline neuropsychological assessment or MRI scan) and Aβ status (-/+) were entered as fixed factors, as well as the interaction between time and Aβ status. Participant was entered as a random factor with random intercepts and slopes. Covariates were baseline age and progression status. *APOE* ε4 carrier status did not contribute significantly to the models and was therefore removed. Separate LMMs were then conducted to derive unadjusted individual slopes for each measure with only time as a fixed factor and no other covariates.

A series of multiple regression analyses examined relationships between concurrent changes in cortical volume and cognition. In each regression analysis, the cognitive slope was regressed onto the corresponding baseline cognitive measure and the three baseline cortical volume measures (WM, GM, hippocampal volume). The slope of cognitive change was then regressed with the three cortical volume slopes to identify the presence of any associations between cortical volume and cognitive changes. The three cortical volume measures were included simultaneously in each regression analysis to ensure that

significant associations between any cortical volume measure and cognitive composite reflected specific associations independent of general changes in cortical volume. These analyses were first conducted in the full sample, then with Aβ status included as a dichotomous moderator variable. The models were then run separately within each of the Aβ- and Aβ+ groups to examine any Aβ-associated differences in the relationships between cortical volume change and cognitive change.

2.3.5 Chapter 7 – Examining the moderating effect of *APOE* ε4 carriage on associations between cortical volume loss and cognitive change in a robust sample of aging older adults

This study aimed to examine the effects of *APOE* ε4 carriage on trajectories of cortical volume and cognitive changes in a robust sample of CN Aβ- older adults. Following from the results of Chapter 6, we explored the association between *APOE* ε4 carriage and trajectories of GM volume loss and decline in verbal memory or executive function. This was conducted using LMMs that included *APOE* ε4 status (-/+), time (years from baseline neuropsychological assessment or MRI scan) and their interaction as fixed factors, while covarying for age and treating participant as a random factor. Further exploratory analyses then examined whether relationships between concurrent changes in cortical GM volume and cognition in aging were moderated by *APOE* ε4 carrier status using multiple regression analyses similar to that described for Chapter 6 above, except Aβ status was replaced with *APOE* ε4 carrier status.

2.4 Limitations

Because AIBL is a large prospective cohort study for which data collection began years before this PhD candidature, the analyses conducted in this thesis can be considered

secondary analyses of existing data. The measures administered and data to be collected were determined at the inception of the study, and the research team endeavour to consistently maintain this protocol for each participant follow-up visit. Thus, a key limitation of this approach is that research questions and subsequent analyses are constrained by the available data and sample size. For this reason, power analyses have not been conducted in this thesis because the number of participants for each study was based on the number of participants who met the sample selection criteria for each study; there was no opportunity to identify the number of participants optimal for each study question and to subsequently test that many participants, and post-hoc power analyses have limited value [223]. Therefore, where the sample sizes are particularly small (as in Chapter 7), these analyses are treated as exploratory and the results are interpreted with due consideration to the limited sample size available. Finally, while previous studies have reported that anticholinergic drug exposure can increase risk of dementia [224,225], complete medication data were not available for the sample and it was therefore not possible to examine or control for the effects of medication exposure on clinical outcomes or aging trajectories.

Chapter 3: Relationship between amyloid-β positivity and progression to mild cognitive impairment or dementia over 8 years in cognitively normal older adults

This study has been published in *Journal of Alzheimer's Disease* and is reproduced here. The published manuscript is included in Appendix A. Preliminary results were also presented during an oral session at the Alzheimer's Association International Conference in July 2018.

3 Relationship between amyloid-β positivity and progression to mild cognitive impairment or dementia over 8 years in cognitively normal older adults

3.1 Abstract

BACKGROUND: Preclinical Alzheimer's disease (AD) is defined by cerebral amyloid-β positivity (Aβ+) in cognitively normal (CN) older adults.

OBJECTIVE: To estimate the risk of progression to the symptomatic stages of AD due to PET Aβ+ and the extent that progression was influenced by other demographic, genetic and clinical characteristics in a large prospective study.

METHODS: Fine-Gray subdistribution modelling was used to examine the risk of progression from CN to MCI/dementia due to Aβ+, *APOE* ε4 carriage, and their interaction in the Australian Imaging, Biomarkers and Lifestyle (AIBL) flagship study of aging CN cohort (n=599) over 8 years.

RESULTS: 17.7% Aβ+ and 8.1% Aβ- progressed over 8 years (OR: 2.43). Risk of progression for Aβ+ was 65-104% greater than Aβ-. Aβ+ *APOE* ε4 carriers were at 348% greater risk than all other participants. Significant risk factors of progression in Aβ+ were age (HR: 1.05), PET SUVR (HR: 2.49) and *APOE* ε4 carriage (HR: 2.63); only age was a significant risk factor in Aβ- (HR: 1.09). Aβ- progressors were not near the threshold for Aβ+. These relationships were not moderated by hypertension, diabetes, obesity, or stroke/TIA.

CONCLUSION: Aβ+ is an important prognostic marker for progression from CN to MCI/dementia in older adults and *APOE* ε4 carriage provides further predictive value in the presence of Aβ+. These data suggest that Aβ-associated clinical progression is consistent with clinical-pathological models of AD, whereas progression in the absence of elevated Aβ deposition may be the result of neuropathological processes other than AD that accumulate with age.

3.2 Introduction

Clinical-pathological models propose that Alzheimer's disease (AD) begins with accumulation of amyloid-β (Aβ) followed by aggregation of tau, which result in cortical atrophy, cognitive decline and, ultimately, dementia [29,226]. Biomarker studies using positron emission tomography (PET) neuroimaging or cerebrospinal fluid (CSF) sampling show that Aβ accumulation begins up to 20 years prior to the onset of dementia [22]. According to these models, cognitively normal (CN) older adults with elevated levels of Aβ (Aβ+) are in the preclinical stages of AD [29,32]. Even though CN Aβ+ individuals are clinically asymptomatic, preclinical AD is characterized by subtle progressive cognitive decline, primarily in episodic memory [61], which may reflect insidious loss of cortical brain volume due to Aβ+ [23,68,227]. Prospective studies in both experimental and epidemiological cohorts have indicated that CN Aβ+ adults have higher risk of progression to clinical classification of mild cognitive impairment (MCI) or dementia compared to those without elevated Aβ (i.e. Aβ-) [55,228]. Clinical trials of Aβ-lowering drugs have endeavored to recruit CN Aβ+ older adults based on their increased risk for incident MCI/dementia in an attempt to slow cognitive decline and prevent onset of symptomatic AD (e.g. Clinical Trials NCT02569398 and NCT02008357) [49]. Furthermore, recently proposed guidance from the US Food and Drug Administration (FDA) acknowledges the centrality of biomarkers such as Aβ+ for recruitment of participants for early AD clinical trials, where Stage 0 includes individuals who are asymptomatic but have evidence of AD pathophysiologic changes [229]. Understanding the risk of progression to MCI/dementia associated with Aβ+ over the long time periods characteristic of preclinical AD is therefore necessary to inform models of

disease etiology and guide recruitment and outcome expectations in clinical trials or clinical studies of preclinical AD and AD.

Incidence of progression to MCI/dementia in large samples of Aβ+ CN adults ranges from 17.7% over an average of 3.7 years in the Mayo Clinic Study of Aging (MCSA, mean age 76) [55], 26.4% over 5 years in the Knight Alzheimer's Disease Research Center study (Knight ADRC, mean age 72) [230], 19% over 6 years in the Australian Imaging, Biomarkers and Lifestyle study (AIBL, mean age 73) [231], to 32.2% over an average of 4 years in the Alzheimer's Disease Neuroimaging Initiative (ADNI, mean age 74) [58]. In all studies, the incidence of progression was at least two times greater in Aβ+ compared to Aβ-. Together, these studies show that Aβ+ increases risk for clinical disease progression in CN adults, although the error associated with some risk estimates is increased by the small sample sizes at the longer follow-up intervals [232]. For example, in ADNI, data beyond 4 years were available for 16% of the initial Aβ+ sample [58]. Similarly, estimates of progression at 5 years were based on 25% of the baseline MCSA sample [55], and 35% of the Knight ADRC data were available beyond 5 years [233]. These small samples limit the use of complex analyses to examine the influence of other characteristics proposed to hasten progression to symptomatic disease (e.g. age, interactions between apolipoprotein E (*APOE*) ε4 carriage and Aβ status) [102]. *APOE* ε4 carriage is associated with increased risk of both Aβ+ and dementia in CN older adults [234,235], and neuropsychological studies show that Aβ+ *APOE* ε4 carriers experience greater cognitive decline than Aβ+ *APOE* ε4 non-carriers [100,102,236]; therefore, the prognostic value of Aβ and *APOE* ε4 may be increased by examining their effects combined. Finally, although there is evidence that vascular and metabolic conditions increase risk of cognitive impairment and dementia in CN adults [237,238], few studies have sought to account for their influence on estimates of Aβ-

associated clinical progression. Although the prevalence of vascular disease in the population-based MCSA is higher than that found in controlled experimental samples [239], it was reported that adjustment for vascular diseases did not change their progression risk estimates [55]. Whether this remains the case in a large experimental cohort is yet to be seen.

The first aim of this study was to examine the incidence of Aβ-associated progression to MCI/dementia among CN older adults. The second aim was to identify demographic and clinical characteristics that moderate the relationship between Aβ status and progression. The first hypothesis was that Aβ+ would be associated with greater risk of clinical disease progression over 8 years. The second hypothesis was that Aβ-associated progression to MCI/dementia would be increased further by *APOE* ε4 carriage. Post-hoc analyses explored how demographic and clinical risk factors influenced clinical disease progression in Aβ+ and Aβ- CN adults.

3.3 Method

3.3.1 Participants

Participants were enrolled in the Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing, details of which have been described elsewhere [192]. Briefly, volunteers were excluded from entry if they had any of the following: non-AD dementia, history of schizophrenia or bipolar disorder, current depression (Geriatric Depression Scale score >5), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, obstructive sleep apnea, past head injury with >1 hour of post-traumatic amnesia, or current regular alcohol intake above recommended limits [193]. Health status at each study visit was determined from clinical

assessment comprising measurement of vital signs (height, weight, waist circumference, and blood pressure using an electric sphygmomanometer) and self-reported medical history. Blood pathology for all participants was assessed at baseline. All included participants were identified to have no, or medically well-controlled systemic illnesses at baseline. Ethics approval for the AIBL study was granted by St Vincent's Health, Austin Health, and Edith Cowan University, and written informed consent was collected from all participants prior to clinical and neuropsychological assessment at every 18-month interval.

Currently, the AIBL study includes 787 CN adults aged above 60 years who have undergone Aβ PET neuroimaging. Participants were recruited in two waves: an inception cohort (n=444) followed for up to 8 years, and an enrichment cohort (n=343) followed for up to 4.5 years. Of the initial cohort, 70.5% have remained active in the study for all visits up to 8 years. This study sample was restricted to those who attended at least two visits over the 8-year period (n=621). Data for 19 participants with inconsistent clinical classification (n=16) or Aβ status (n=3) during the study period were excluded from all analyses. Twenty participants had incomplete covariate data, which were imputed based on information contained in their clinical visit notes where possible. One participant who met exclusion criteria but was inadvertently included in the AIBL study was also excluded. Thus, the total sample for this study consisted of 599 older adults (Figure 3-1).

3.3.2 Clinical classification of cognitive status

An expert clinical panel reviewed all available neuropsychological and psychiatric information for participants at each visit based on neuropsychologist referral. They were blinded to information about Aβ and *APOE* ε4 status, and consensus classifications were made using standard clinical criteria for MCI [205] and AD [27]. Participants classified with

MCI/dementia during the follow-up period were coded as “progressors”; participants who did not meet those criteria were classified CN.

3.3.3 Measures

Self-reported history of stroke/TIA at any time before or during the study period and current hypertension or diabetes was recorded. *APOE* ε4 carriage was determined from whole blood extracted DNA [210], and fasting glucose and lipid concentrations were measured. Body mass index (BMI) was calculated using height and weight (kg/m^2). Education was coded as ≤12 years or >12 years. Baseline mood was assessed using the Hospital Anxiety and Depression Scale (HADS) [207], and the Memory Complaint Questionnaire (MAC-Q) [209] was used to assess subjective memory complaint.

3.3.4 Amyloid PET neuroimaging

PET neuroimaging was conducted using one of the following Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB, n=216), ^{18}F-NAV4694 (NAV, n=56), ^{18}F-Florbetapir (FBP, n=158), or ^{18}F-Flutemetamol (FLUTE, n=169). PET methods and procedures have been reported previously [211,212]. Briefly, PET acquisitions were performed up to 90 minutes following tracer injection. Standardized uptake value (SUV) data were summed and normalized to a reference region (the cerebellar cortex for PiB and NAV, the whole cerebellum for FBP, and the pons for FLUTE) to generate a SUV ratio (SUVR). Threshold values for elevated Aβ deposition vary by radiotracer, so a linear regression transformation was applied to the FBP and FLUTE SUVR to create a “PiB-like” SUVR unit called Before the Centiloid Kernel Transformation (BeCKeT) [34]. All participants with SUVR/BeCKeT≥1.40 at their most recent PET scan were classified Aβ+ and those below the threshold were classified Aβ-; however,

participants whose SUVR/BeCKeT fluctuated around the threshold on multiple PET scans could not be accurately classified and were therefore excluded from all analyses.

3.3.5 Statistical analyses

3.3.5.1 *Baseline group differences*

All continuous variables were assessed for normality by visual inspection of Q-Q plots. Between-group comparisons for Aβ status were conducted using a one-way analysis of variance (ANOVA) for normally distributed variables. Kruskal-Wallis one-way ANOVAs were used for non-normally distributed variables. Fisher's exact tests were used for dichotomous variables. Effect sizes (Cohen's *d)* were calculated for all comparisons reaching statistical significance.

3.3.5.2 *Survival analysis*

Fine-Gray subdistribution hazards models were fit to examine risk of clinical disease progression in the presence of competing risks. Progression to MCI/dementia were coded as events, and time to event or censoring was entered in months from the baseline visit. Death or withdrawal from the study due to illness were coded as competing risks because the deceased have no risk of clinical progression and those who withdraw due to illness may have higher risk [222]. Schoenfeld residuals tests indicated that the proportional hazards assumption was met. No outliers were detected.

Survival models evaluated the main hypotheses in 5 stages. Model 1 included characteristics that differed between Aβ groups at baseline (age, hypertension, and BMI). Model 2 added Aβ status, and Model 3 added *APOE* ε4 status. To examine the effects of health factors proposed to influence disease progression, diabetes and stroke/TIA were added in Model 4. Finally, Model 5 included an Aβ status by *APOE* ε4 interaction to compare the hazard of progression between participants who had both Aβ+ and *APOE* ε4 against all

other participants. Sex and education were not included in these models because no baseline differences were observed between Aβ groups on these factors. Hazard ratios with 95% confidence intervals were calculated, and the cumulative hazard functions were plotted. All statistical analyses were performed using R version 3.4.3 and SPSS 23, with statistical significance at $p<0.05$. Results were interpreted on the basis of the hazard ratios and confidence intervals; therefore, no adjustments were made for multiple comparisons.

3.3.5.3 *Post-hoc analyses*

Model 4 was repeated within the Aβ+ and Aβ- groups separately to examine differences in risk of clinical disease progression associated with Aβ status. These analyses used continuous PET SUVR/BeCKeT to assess the relative effect of Aβ deposition on progression within the pre-defined ranges for the Aβ- and Aβ+ groups.

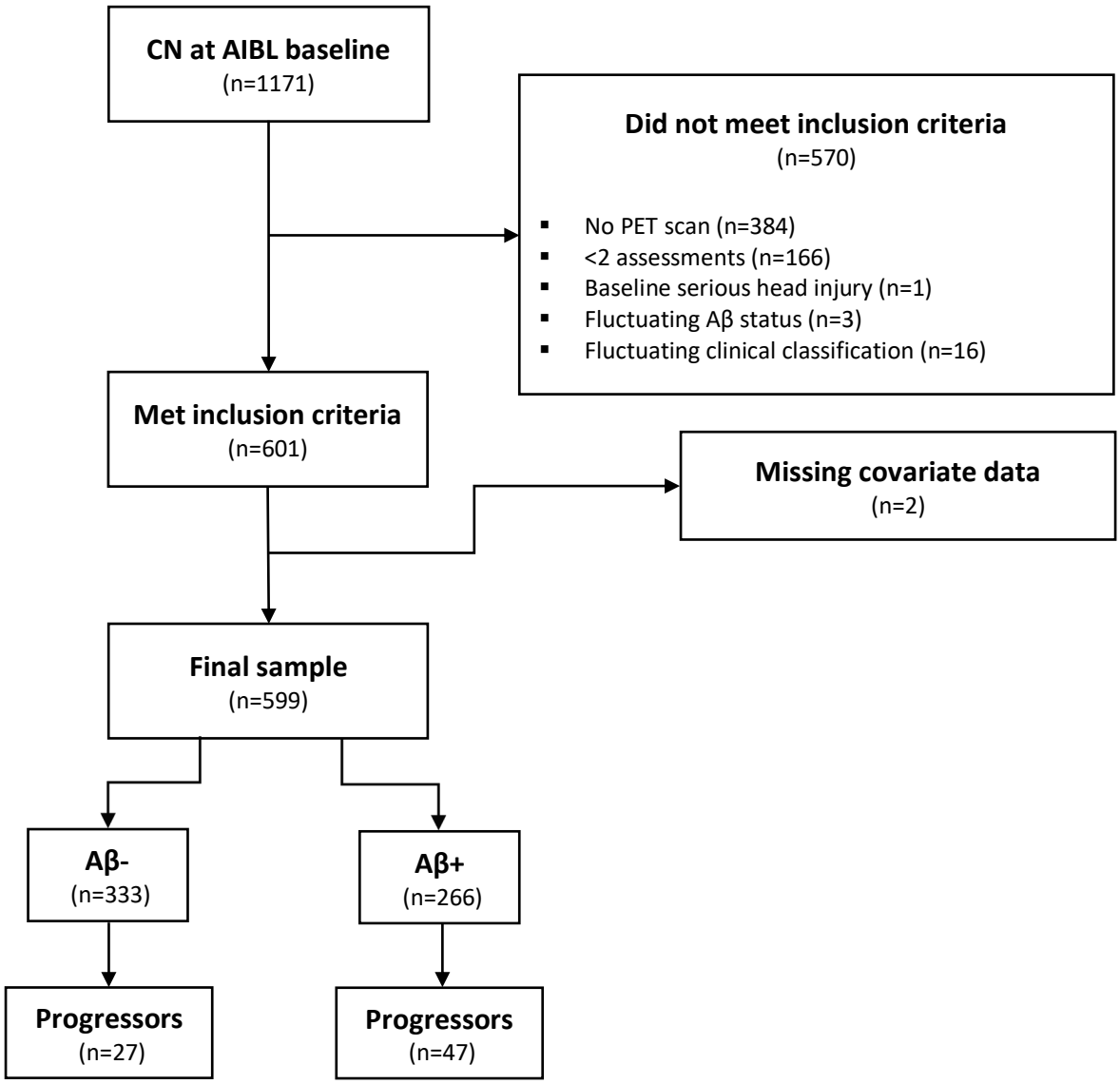
3.4 Results

3.4.1 Sample characteristics and attrition

Details of the study sample are shown in Figure 3-1. Of the 599 included participants, 74 progressed to MCI or dementia over the 8-year period (CN->MCI->dementia=7, CN->MCI=58, CN->dementia=9; median time to progression: 36.5 months, ranging from 16-94 months). Non-AD causes were identified for only two of the people who progressed to dementia (dementia not otherwise specified and Parkinson's disease dementia). During the study period, 15 participants died, 20 withdrew due to ill health (3 of whom did so after progressing), 50 withdrew formally from the study and 4 were not contactable for follow-up. The median follow-up time was 88 months (interquartile range 54).

Average age of participants was 70 (range 60-90), and 55.8% had >12 years of education. Demographic and clinical characteristics, and prevalence of vascular and metabolic risk factors are shown in Table 3-1.

Figure 3-1: Sample selection



Selection criteria and final sample sizes for the present study.

Table 3-1: Baseline sample characteristics

Measure	Full sample	Aβ-	Aβ+	*p*	*d*
n	599	333	266		
Aβ+, %	44.4	0	100		
APOE ε4 carrier, %	28.4	17.4	42.1	**<0.0005**	0.68
Age at baseline (years)	70.21, 70 (10)	68.99, 68 (9)	71.77, 72 (10)	**<0.0005**	0.47
Female, %	55.6	57.4	53.4	0.36	
Education >12 years, %	55.8	56.2	55.3	0.87	
HADS A	4.36, 4 (4)	4.44, 4 (5)	4.25, 4 (4)	0.37	
HADS D	2.69, 2 (3)	2.74, 2 (3)	2.63, 2 (3)	0.39	
MAC-Q	25.61, 25 (5)	25.50, 26 (5)	25.74, 25 (6)	0.82	
Stroke/TIA, %	8.7	8.7	8.6	1.00	
Hypertension, %	50.8	46.5	56.0	**0.02**	0.21
Systolic BP	138.00, 137 (22)	136.67, 135 (22)	139.67, 140 (20)	**0.03**	0.19
Diastolic BP	79.22, 80 (13)	79.03, 80 (13)	79.46, 80 (16)	0.82	
Diabetes, %	9.8	8.4	11.7	0.22	
Fasting glucose	5.12, 5 (0.70)	5.08, 5 (0.70)	5.17, 5 (0.70)	0.45	
Total cholesterol	5.51, 5.50 (1.40)	5.53, 5.50 (1.45)	5.49, 5.50 (1.40)	0.60	
Triglycerides	1.29, 1.10 (0.70)	1.33, 1.10 (0.80)	1.23, 1.10 (0.70)	0.09	
HDL	1.64, 1.58 (0.59)	1.63, 1.56 (0.61)	1.65, 1.62 (0.57)	0.44	
LDL	3.28, 3.30 (1.40)	3.28, 3.30 (1.35)	3.27, 3.30 (1.40)	0.71	
Waist circumference	93.00, 92 (17.50)	93.53, 92 (17)	92.32, 92 (18)	0.28	
BMI	26.55, 25.86 (5.59)	26.87, 26.30 (5.50)	26.14, 25.60 (5.35)	**0.02**	0.19
Current smoker, %	10.2	9.8	10.7	0.88	
Attended all 6 study visits, %	49.4	52.9	45.1	0.07	
Length of follow-up (months)	66.90, 88.50 (53)	68.62, 89 (53)	64.73, 75 (54)	0.10	

All descriptive statistics for continuous variables reported as mean, median (IQR); categorical variables reported as percentages. *P*-values and Cohen's *d* shown for comparisons between Aβ groups.

Abbreviations used: Aβ+ = elevated cerebral amyloid-β; *APOE* ε4 = apolipoprotein epsilon 4 allele carriage; HADS A = Hospital Anxiety and Depression Scale – Anxiety; HADS D = Hospital Anxiety and Depression Scale – Depression; MAC-Q = Memory Complaint Questionnaire; TIA = transient ischemic attack; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; BMI = body mass index.

3.4.2 Baseline group differences

Table 3-1 summarizes the differences between Aβ groups at baseline. Aβ+ participants were 3 years older on average and more likely to be *APOE* ε4 carriers (odds ratio (OR): 3.45, 95% confidence interval (CI): 2.37-5.01) than were Aβ- participants. Hypertension was more frequent in the Aβ+ group (OR: 1.46, 95% CI: 1.06-2.02), who also had higher systolic blood pressure (3mmHg) and lower BMI (0.7kg/m^2) than the Aβ- group. *APOE* ε4 carriage in Aβ+ was associated with higher PET SUVR/BeCKeT [$F(1,264)=19.79$, $p<0.0005$; $d=0.56$], but not in the Aβ- group [$F(1,331)=0.45$, $p=0.50$; $d=0.10$].

3.4.3 Risk of progression to MCI or dementia

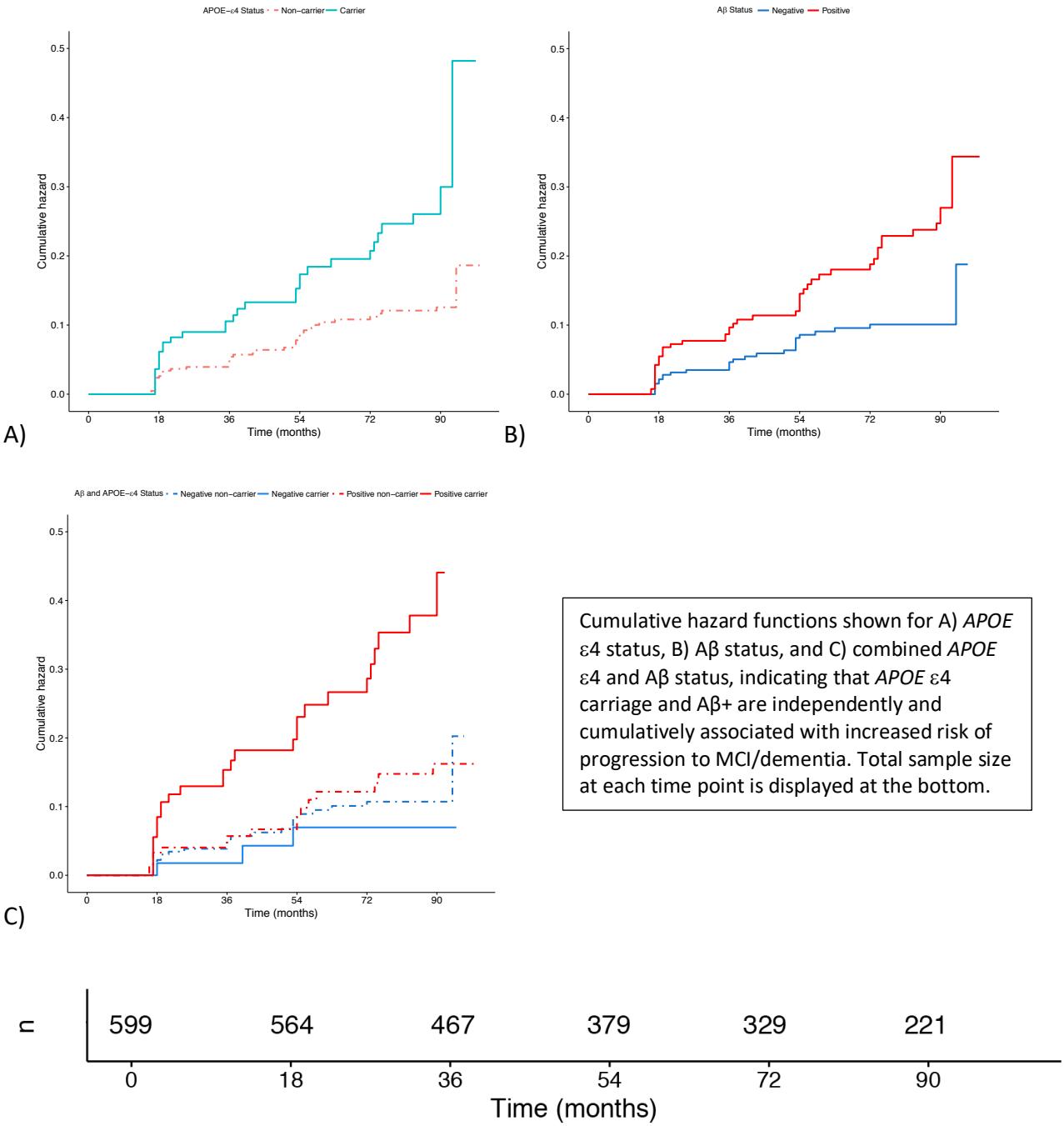
Aβ+ participants were significantly more likely to progress to MCI/dementia than Aβ- (17.7% vs 8.1%, OR: 2.43, 95% CI: 1.47-4.03). In all 5 survival models, every additional year of age at baseline conferred greater risk (7%) of progressing over the 8-year period for all participants (Table 3-2). In Model 2, Aβ+ status increased the risk of progression by 104% (Figure 3-2A). In Model 3, *APOE* ε4 carriers had 114% greater risk than non-carriers (Figure 3-2B). The risk conferred by Aβ+ was mediated by the addition of *APOE* ε4 into the model. Model 4 showed that the health factors had no influence on risk of progression, nor did they mediate risk due to Aβ+; no interactions were observed in post-hoc analyses. In Model 5, the Aβ and *APOE* ε4 interaction was significant: Aβ+ *APOE* ε4 carriers had 348% greater risk of progressing to MCI/dementia compared to all other participants. Further analysis showed that progression risk in Aβ+ *APOE* ε4 non-carriers (hazard ratio (HR): 1.08, 95% CI: 0.56-2.07) and Aβ- *APOE* ε4 carriers (HR: 0.72, 95% CI: 0.21-2.45) was not significantly greater than in Aβ- *APOE* ε4 non-carriers (Figure 3-2C); therefore, it was appropriate to combine these three groups in the interaction analysis.

Table 3-2: Fine-Gray subdistribution models for the full study sample

MODEL 1	*p*-value	HR	95% CI	
Age	**<0.0005**	**1.07**	**1.04**	**1.10**
Hypertension	0.70	0.91	0.56	1.47
BMI	0.30	1.03	0.97	1.09
MODEL 2	*p*-value	HR	95% CI	
Age	**<0.0005**	**1.06**	**1.03**	**1.09**
Hypertension	0.61	0.88	0.55	1.42
BMI	0.20	1.04	0.98	1.09
Aβ status	**0.004**	**2.04**	**1.25**	**3.33**
MODEL 3	*p*-value	HR	95% CI	
Age	**<0.0005**	**1.07**	**1.04**	**1.10**
Hypertension	0.78	0.94	0.58	1.50
BMI	0.19	1.04	0.98	1.09
Aβ status	**0.04**	**1.65**	**1.02**	**2.65**
APOE ε4	**0.001**	**2.14**	**1.36**	**3.36**
MODEL 4	*p*-value	HR	95% CI	
Age	**<0.0005**	**1.07**	**1.03**	**1.10**
Hypertension	0.77	0.93	0.58	1.49
BMI	0.17	1.04	0.98	1.10
Aβ status	**0.04**	**1.65**	**1.03**	**2.66**
APOE ε4	**0.001**	**2.10**	**1.34**	**3.28**
Diabetes	0.62	0.82	0.37	1.80
Stroke/TIA	0.30	1.36	0.76	2.44
MODEL 5	*p*-value	HR	95% CI	
Age	**<0.0005**	**1.07**	**1.04**	**1.10**
Hypertension	0.88	0.97	0.60	1.55
BMI	0.23	1.03	0.98	1.09
Aβ status	0.88	1.05	0.55	2.02
APOE ε4	0.57	0.71	0.21	2.36
Diabetes	0.80	0.90	0.41	2.00
Stroke/TIA	0.50	1.23	0.68	2.24
Aβ+ and *APOE* ε4+	**0.03**	4.48	1.14	17.60

Abbreviations used: Aβ = amyloid-β; *APOE* ε4 = apolipoprotein epsilon 4 allele carriage; BMI = body mass index; CI = confidence interval; HR = hazard ratio; TIA = transient ischemic attack.

Figure 3-2: Cumulative hazard functions for APOE *ε4 status and Aβ status*



Cumulative hazard functions shown for A) *APOE* ε4 status, B) Aβ status, and C) combined *APOE* ε4 and Aβ status, indicating that *APOE* ε4 carriage and Aβ+ are independently and cumulatively associated with increased risk of progression to MCI/dementia. Total sample size at each time point is displayed at the bottom.

3.4.4 Clinical disease progression within Aβ+ and Aβ- groups

Examination of risk factors within the Aβ+ group showed that higher age, higher PET SUVR/BeCKeT, and *APOE* ε4 carriage increased risk of progression (Table 3-3). Risk increased by 5% for each additional year of age at baseline, and by 149% for every whole PET SUVR/BeCKeT unit increase. Lastly, risk of progression was 163% greater with *APOE* ε4

carriage. Within the Aβ- group, the only risk factor for progression to MCI/dementia was higher age (9%). Overlap in 95% confidence intervals were observed for all predictor variables between Aβ+ and Aβ- groups, although these overlaps were smallest for *APOE* ε4 carriage and PET SUVR/BeCKeT. The degree of overlap suggests that *APOE* ε4 carriage and greater Aβ deposition increased risk of progression for the Aβ+ group but not for the Aβ- group, and that this difference was significant [240].

Table 3-3: Fine-Gray subdistribution models within the Aβ- and Aβ+ groups

	Aβ-				**Aβ+**			
	p-value	HR	95% CI		*p*-value	HR	95% CI	
Age	**0.01**	**1.09**	**1.02**	**1.16**	**0.01**	**1.05**	**1.01**	**1.08**
Hypertension	0.57	0.78	0.33	1.84	0.63	1.15	0.65	2.06
BMI	0.35	1.05	0.95	1.16	0.56	1.02	0.95	1.09
Aβ (PET SUVR)	0.10	0.02	0.00	2.00	**<0.0005**	**2.49**	**1.60**	**3.88**
APOE ε4	0.61	0.73	0.22	2.46	**0.004**	**2.63**	**1.37**	**5.03**
Diabetes	0.63	0.72	0.19	2.74	0.98	1.01	0.37	2.78
Stroke/TIA	0.96	0.97	0.30	3.17	0.57	1.22	0.62	2.39

Abbreviations used: Aβ = amyloid-β; *APOE* ε4 = apolipoprotein epsilon 4 allele carriage; BMI = body mass index; CI = confidence interval; HR = hazard ratio; PET SUVR = positron emission tomography standardized uptake value ratio; TIA = transient ischemic attack.

3.5 Discussion

Rates of Aβ+ progression from CN to MCI/dementia in the AIBL sample and the associated risk factors for both Aβ- and Aβ+ progression over 8 years are reported for the first time. The results supported the first hypothesis that Aβ+ would be associated with greater risk of progression to MCI/dementia. Eight-year risk of progression to MCI/dementia in CN Aβ+ adults from the AIBL study was increased by 65-104% compared to Aβ- (Table 3-2). This indicates that Aβ+ is an important prognostic marker for progression to MCI/dementia in CN older adults. The second hypothesis, that Aβ-associated risk for progression to

MCI/dementia would be increased further by *APOE* ε4 carriage, was also supported. The large sample studied here allowed the risk of progression conferred by concurrent Aβ+ and *APOE* ε4 carriage to be estimated, taking into account health factors posited to influence progression to MCI/dementia as well as competing risks such as death or withdrawal due to illness. Risk of progression to MCI/dementia was 348% greater in Aβ+ *APOE* ε4 carriers compared to all other participants (Table 3-2). Similar findings were observed in the MCSA, although their risk estimate was reported relative to Aβ- *APOE* ε4 non-carriers (190%) [66]. In this study, no difference in risk was observed between Aβ- *APOE* ε4 non-carriers, Aβ- *APOE* ε4 carriers and Aβ+ *APOE* ε4 non-carriers, suggesting an additive effect between Aβ+ and *APOE* ε4 carriage that is greater than the sum of their individual contributions. This is consistent with results of neuropsychological studies showing that CN Aβ+ *APOE* ε4 carriers experience greater cognitive decline over time with earlier onset [100,102,236,241]. In agreement with a recent report that episodic memory performance remains stable in Aβ- regardless of *APOE* ε4 status, *APOE* ε4 carriage did not increase the risk of clinical disease progression in Aβ- (Figure 3-2C) [241]. Previous research shows that *APOE* ε4 reduces clearance of cerebral Aβ but does not affect rates of Aβ production [242]; therefore, the findings of this study indicate that the impaired clearance of Aβ due to *APOE* ε4 is most clinically significant in individuals who have high levels of Aβ.

As progression to MCI/dementia was observed in a small number of individuals with normal Aβ levels (8.1%), risk factors within the Aβ+ and Aβ- groups were investigated. Previous studies indicate that health conditions such as hypertension, diabetes, or stroke/TIA can contribute to cognitive decline and clinical disease progression in older adults [237,238,243]. Although higher prevalence of hypertension and lower BMI was observed in the Aβ+ group, these differences were very small. Thus, both groups had similar

cardiovascular risk profiles and these factors did not influence risk of progression within either Aβ group. For both Aβ groups, higher age at baseline was associated with increased risk of progression to MCI/dementia (Table 3-3). Although Aβ deposition, and therefore risk of disease progression, is known to increase with age [244], other neuropathological processes such as brain atrophy are also associated with age [150]. Higher relative Aβ deposition increased progression risk in the Aβ+ group by 150%; however, PET SUVR/BeCKeT for Aβ- progressors was not near the threshold for Aβ+ (median 1.16, range 1.02-1.39) making it unlikely that progression in the Aβ- group was due to any unrecognized increase in Aβ. While it remains unknown whether abnormal levels of Aβ deposition play a causative role in the development of dementia due to AD, the recent NIA-AA Research Framework proposed that AD be defined by the presence of cortical Aβ and tau aggregates and neurodegeneration rather than by clinical symptoms due to the poor specificity of cognitive symptoms to detect AD neuropathological processes [32]. Taken together, these data suggest that Aβ-associated clinical progression is consistent with AD neuropathological changes, whereas progression in the absence of elevated Aβ deposition is the result of disease processes other than AD that accumulate with age [245]. This indicates that the prognostic value of Aβ+ is specific to dementia due to AD.

Despite the longer time interval and greater statistical control over demographic, health and clinical characteristics, the 17.7% incidence of progression due to Aβ+ was consistent with that observed previously over 6 years (19%) in the AIBL sample [231]. However, the current 8-year estimate of Aβ-associated progression remained lower than those reported in the ADNI (32.2%) and Knight ADRC (26.4%) cohorts over similar time periods [58,204], and was equal to that reported by the MCSA (17.7%) over an average of 3.7 years [55]. The relatively lower incidence of progression in AIBL may reflect differences

in the samples studied and the respective inclusion/exclusion criteria. For example, the ADNI and Knight ADRC cohorts were, on average, 2-4 years older than AIBL and the MCSA cohort was 6 years older than the AIBL cohort. The population-based MCSA cohort reports higher prevalence of risk factors other than Aβ+ for MCI/dementia: at baseline, 79.4% of the MCSA participants had hypertension, 18.7% had diabetes, and 14.3% had history of stroke [239], compared to 38.8%, 7.3% and 1.8%, respectively, in the AIBL CN cohort. Despite the increased presence of these factors and older age in the MCSA, the estimates of Aβ-associated progression were similar and may also reflect comparable methods for measuring Aβ deposition and defining Aβ+ using PET; however, the follow-up time for the MCSA was shorter than that for AIBL and may be expected to increase with similar follow-up. It is also possible that the higher incidence of disease progression in the other samples reflects some unreliability in their estimates due to small sample size or differences in method of Aβ+ classification. Both ADNI and Knight ADRC used different cut-off values and either PET neuroimaging or CSF amyloid sampling to classify Aβ status across participants, while both AIBL and the MCSA used only PET to measure Aβ levels in all participants; therefore, differences between the Aβ+ samples identified in these studies may also reflect different prospective estimates of incident MCI/dementia. Measuring Aβ levels with a common method for all participants rather than using different biomarkers to do so will increase the reliability of classification. Finally, the methods utilized to define clinical status vary across the different studies. The Knight ADRC relies on CDR score to classify participants and, while AIBL and the MCSA both use a consensus panel to determine clinical status, these panels define cognitive impairment differently ($\leq$ -1.5 SD on two tests vs $\leq$ -1 SD on one domain score). ADNI also utilizes clinical consensus classifications; however, the public availability of this data has meant different researchers have also utilized CDR ratings

and actuarial neuropsychological approaches to define clinical status, which itself has resulted in different estimates of Aβ-associated progression [58,246,247]. These varying approaches to clinical classification and sample selection may explain the differences in estimates of Aβ+ progression between studies. Findings of consistency or inconsistency in outcomes between different samples is crucial because this provides information about the effects of potential sampling bias associated with the different studies on models of disease progression and the disease processes reported from these individual cohorts. Lower incidence of progression in the current study may reflect the larger sample sizes at longer follow-up times, the more stringent criteria for cognitive impairment, the use of consensus classification, and the more exclusive sample when compared to the other large studies of preclinical AD. Nonetheless, these data indicate that Aβ+ is an important factor for clinical disease progression in AD.

A recent consensus group reported the importance of established and putative risk factors for dementia among older adults, and stated that the predictive value of Aβ+ for progression to MCI/dementia was equivocal over 3 years [13]. While they agreed that age and *APOE* ε4 carriage were important risk factors of clinical progression to symptomatic disease, these factors are non-modifiable. The group, therefore, considered other potentially modifiable risk factors and concluded that hearing loss, hypertension and obesity in midlife, and smoking, depression, physical inactivity, social isolation and diabetes in late-life held greater prognostic utility than did Aβ [13]. The present study examined risk factors for progression accounting for age and *APOE* ε4 carriage and showed that Aβ+ was a strong predictor of clinical disease progression in CN adults over 8 years, while health factors such as hypertension, diabetes and obesity were not. The current findings converge with that from other prospective studies of Aβ+ risk for MCI/dementia, suggesting that the consensus

position be reconsidered with data from longer prospective studies, given that the preclinical stages of AD can extend for up to 20 years [22].

Some aspects of this study limit the generalizability of its findings to a wider population. First, the AIBL study utilized a convenience sample and recruited healthy and well-educated older adults. Participants who did not progress were more likely to have attended all study visits, suggesting the presence of a healthy survivor effect. This may have contributed to the lack of relationship between health factors and disease progression in this study; hence, conclusions drawn here about the influence of these aspects of health on late-life risk for MCI/dementia should be challenged in similar studies using population-based sampling methods, such as the MCSA, using midlife health risk factors where possible. Although the number of participants retained in AIBL at 8 years was larger than the sample sizes of the other studies at their longest intervals and AIBL had the longest average follow-up time, even longer follow-ups are necessary to elucidate the disease course and risk factors for MCI/dementia. For this reason, it is not known whether those who did not progress over the study period will go on to progress in the future. Furthermore, as Aβ-associated progression was the focus on this study, neurodegeneration measures were not examined. Despite these caveats, the current results indicate that Aβ+ has strong prognostic value for the development of clinical symptoms of dementia due to AD even when health factors and competing risks for progression are taken into account. *APOE* ε4 carriage provides further predictive value in the presence of elevated Aβ; therefore, Aβ+ *APOE* ε4 carriers are ideal candidates for early intervention trials of disease-modifying therapies.

Chapter 4: Superior memory reduces 8-year risk of mild cognitive impairment and dementia but not amyloid β-associated cognitive decline in older adults

This study has been published in *Archives of Clinical Neuropsychology* and is reproduced here. The published manuscript is included in Appendix A. Preliminary results were also presented during a poster session at the Alzheimer's Association International Conference in July 2018, where this abstract was selected as a student poster competition finalist.

4 Superior memory reduces 8-year risk of mild cognitive impairment and dementia but not amyloid β-associated cognitive decline in older adults

4.1 Abstract

Objective: To prospectively examine eight-year risk of clinical disease progression to mild cognitive impairment (MCI)/dementia in older adults ≥60 with superior episodic memory (SuperAgers) compared to those cognitively normal for their age (CNFA). Additionally, to determine the extent to which SuperAgers were resilient to the negative effects of elevated amyloid-beta (Aβ+) on cognition.
Method: Participants were classified as SuperAgers based on episodic memory performance consistent with younger adults aged 30-44 and no impairment on non-memory tests (n=179), and were case-matched with CNFA on age, sex, education, and follow-up time (n=179). Subdistribution hazard models examined risk of clinical progression to MCI/dementia. Linear mixed models assessed the effect of Aβ on cognition over time.
Results: Prevalence of Aβ+ and *APOE* ε4 was equivalent between SuperAgers and CNFA. SuperAgers had 69-73% reduced risk of clinical progression to MCI/dementia compared to CNFA (HR: 0.27-0.31, 95% CI: 0.11-0.73, p<0.001). Aβ+ was associated with cognitive decline in verbal memory and executive function, regardless of SuperAger/CNFA classification. In the absence of Aβ+, equivalent age-associated changes in cognition were observed between SuperAgers and CNFA.
Conclusions: SuperAgers displayed resilience against clinical progression to MCI/dementia compared to CNFA despite equivalent risk for Alzheimer's disease (AD); however, SuperAgers had no greater protection from Aβ+ than CNFA. The deleterious effects of Aβ on cognition persist regardless of baseline cognitive ability. Thus, superior cognitive performance does not reflect resistance against the neuropathological processes associated with AD, and the observed resilience for SuperAgers may instead reflect neuropsychological criteria for cognitive impairment.

4.2 Introduction

Neuropsychological models indicate that cognitive decline is an expected consequence of increasing age beyond 60 years [112,114,122]. For example, a recent meta-analysis of international aging studies observed that cognitive aging extends across all aspects of cognition, with the magnitude ranging from -0.26 to -0.12 SD units per decade from 60 years [119]. Most studies infer cognitive aging by observing that group mean test performance declines with the increasing age of the cohorts studied. However, variability associated with these means also increases with age, indicating that individual differences in cognitive aging become greater with increasing age [111,120–122]. Some of the increased individual differences in cognitive aging have been explained by the uncontrolled effects of preclinical neurodegenerative disease, such as Alzheimer's disease (AD), in aging samples [139,230,248]. For example, amyloid-beta (Aβ) biomarker studies show that approximately 16-44% of older adults classified as cognitively normal (CN) have abnormally elevated Aβ in the brain (Aβ+) that is indicative of preclinical AD [22]. Despite being clinically asymptomatic, older adults with preclinical AD show subtle, but clear, cognitive decline, particularly in episodic memory and executive function [60,61]. Consequently, inclusion of these individuals in samples of CN older adults can introduce negative biases in group mean performance that increase with age and lead to increased estimates of inter-individual variability [123,142,230,248].

Another explanation for increasing individual differences in cognitive aging is the presence of older adults who are resilient to cognitive decline despite their increasing age. Theoretical constructs proposed to describe these individuals include successful cognitive agers [177–179], resilient-agers [181], cognitively elite [182], supernormals [183], optimal

memory performers [184], and SuperAgers [185]. While each construct describes similar phenomena with different operational definitions, the construct of SuperAgers currently provides the clearest psychological definition with the greatest neurobiological validity to date [187]. The SuperAger concept originates from the perspective of Mesulam that individual differences in cognitive aging reflect a stochastic combination of non-modifiable factors such as time and genetics, and modifiable factors such as the cumulative neurobiological effects of a lifetime history of injuries and exposures (e.g. systemic illnesses, stress, head trauma, etc.) [110]. In this context, age, or the passage of time, increases the probability of encountering these events but does not guarantee them. Thus, a SuperAger is an older adult who has had reduced exposure, or is resilient, to these effects and their cognitive abilities have consequently been maintained from mid-life through to late-life. SuperAging studies therefore define SuperAgers as older adults with episodic memory performance at, or above, the mean of normative samples 20-30 years younger and with normal-for-age performance (i.e., scores not below -1 SD compared to normative means) on other cognitive domains [185,189].

The SuperAger construct provides a useful foundation for studying resilience to age-associated cognitive decline because of its clear and well-validated psychometric classification criteria. For example, neurobiological investigations show that SuperAgers ≥80 years of age have greater preservation of cortical thickness compared to middle-aged adults, and reduced rates of cortical atrophy compared to cognitively normal for age (CNFA) adults [185,190,191]. SuperAgers also show lower frequency of Aβ plaques and AD-type neurofibrillary tangles than CNFA on *post-mortem* examination, suggesting these individuals also possess increased resilience to neurodegenerative disease [190]. Together, these observations suggest that SuperAger classification is associated with some protection

against the biological changes associated with both aging and neurodegenerative disease such as AD [187]. This is consistent with findings from two prospective studies that these individuals are protected against cognitive decline measured from baseline over 18 months [188] and up to an average of five years [180]. A recent prospective study also extended prior findings by showing that individuals classified as successful agers were also resilient to decline in episodic memory associated with Aβ+ [180]. This study retrospectively classified older adults ≥70 enrolled in the Berkeley Aging Cohort Study (BACS) as successful agers if their performance on a list learning test was within the normative range of performance for 18-32 year-old adults on the same test, and normal-for-age performance on the Trail Making Test B (i.e. SuperAgers, as per [189]). In their sample of 150 adults with an average age of 75 years, 26 (17.3%) were classified as successful agers. Group mean levels of Aβ and the proportion of adults with Aβ+ were equivalent between the successful agers and the typical older adults (i.e. CNFA) at baseline assessment, consistent with another study of "optimal agers" [184]. Although higher Aβ levels were associated with memory decline in the typical older adult group over an average of five years, individuals classified as successful agers showed no Aβ-associated decline in episodic memory [180]. Thus, while the superior memory performance characteristic of SuperAging was not associated with reduced accumulation of Aβ, it did provide resilience to the downstream effects of Aβ on episodic memory in these individuals.

The possibility that superior memory performance in older adults reflects resilience to the deleterious effects of Aβ must be considered cautiously with respect to the limitations of the aforementioned study [180]. First, the sample of successful agers was relatively small (i.e. n=26) and the sub-sample of Aβ+ successful agers even smaller (n=10). Studies measuring the effect of Aβ on cognitive decline in older adults show that such

decline is only observed with abnormally high levels of Aβ (i.e. Aβ+) [145]; thus, it is likely that the absence of any Aβ-associated memory decline in the successful ager group was due to a small sample and therefore inadequate statistical power for detecting group differences and interactions in longitudinal analyses [249]. A related issue is that the length of time for which follow-up data is available varies substantially between participants in the BACS study sample. Reduced numbers of data points at the longer follow-up intervals also reduces the statistical power of analyses comparing slopes of cognitive change between groups and may additionally inflate the influence of any sample biases [250]. Third, although it is important to examine cognitive change over time in individuals classified as successful agers or SuperAgers, the clinical implications of these changes are difficult to determine when considered in isolation. One more meaningful criterion by which to assess the clinical consequences of SuperAger classification is the extent to which this protects individuals against clinical disease progression to mild cognitive impairment (MCI) or dementia.

The overarching aim of this study was to investigate the extent to which individuals classified as SuperAgers displayed resilience against cognitive decline associated with age and with AD neuropathological changes. The first aim was to compare the eight-year risk of clinical disease progression to MCI/dementia in a large group of older adults with superior episodic memory at baseline (SuperAgers) compared to CNFA. The second aim was to determine the extent to which SuperAgers were resilient to the negative effects of Aβ+ on cognition. The first hypothesis was that individuals classified as SuperAgers would be at reduced risk of progression to a clinical classification of MCI/dementia over eight years when compared to well-matched CNFA adults. The second hypothesis was that SuperAgers would show greater resilience to the cognitive decline associated with preclinical AD (i.e.

Aβ+) compared to their matched CNFA counterparts. We also explored the extent to which age influenced relationships between SuperAger classification, Aβ status and prognosis.

4.3 Method

4.3.1 Participants

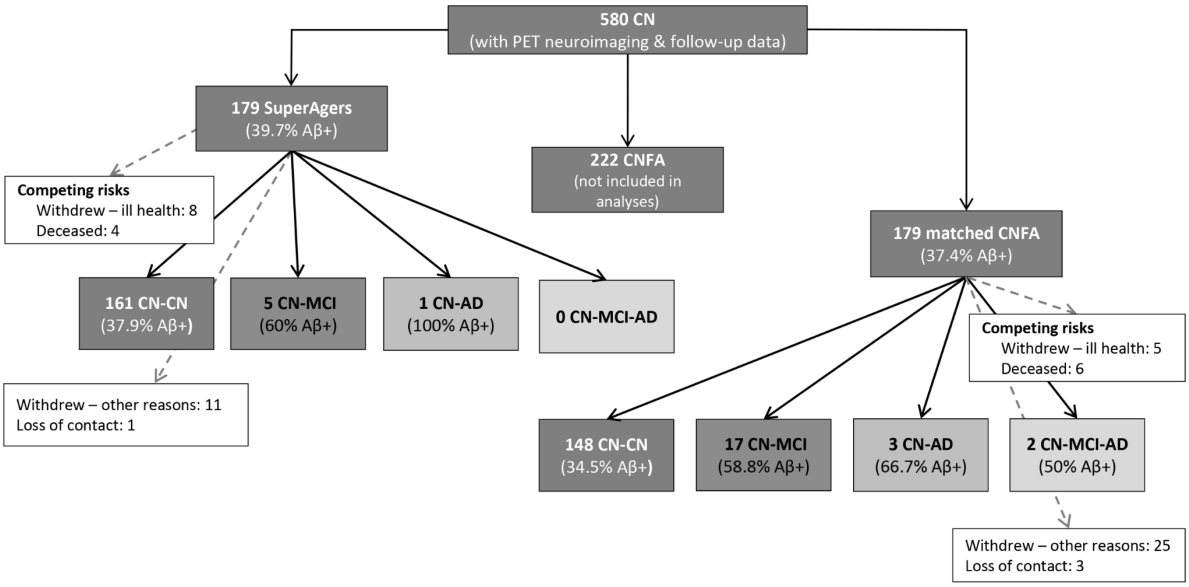
Participants were from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. The full study protocol has been previously reported [192]. Briefly, volunteers were ineligible for study entry if they met any of the following exclusion criteria: non-AD dementia, history of schizophrenia or bipolar disorder, current depression (Geriatric Depression Scale score >5), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, obstructive sleep apnea, past head injury with >1 hour of post-traumatic amnesia, or current regular alcohol intake of >4 standard drinks per day for men or >2 per day for women [193]. Health status was determined from a medical assessment that included measurement of vital signs (height, weight, blood pressure, and abdominal circumference), blood tests, and self-reported medical history. Current health was reviewed for all participants at each study visit for the present study, and all included participants were identified to have no, or medically well-controlled systemic illnesses at baseline. Ethics approval for the AIBL study was granted by St Vincent's Health, Austin Health, Hollywood Private Hospital, and Edith Cowan University, and written informed consent was collected from all participants prior to undertaking any assessment procedures.

The AIBL study currently includes 620 CN adults who satisfied the baseline inclusion criteria, were aged over 60 with MMSE>24, underwent Aβ PET neuroimaging, and who have attended at least two study visits. These participants were recruited in two waves: an

inception cohort (n=439) followed every 18 months for up to eight years, and an enrichment cohort (n=181) followed for up to 4.5 years. Data were available for assessments spanning from November 2006 through to April 2016. The sample was further restricted to those who reported no history of stroke, transient ischemic attack (TIA), or serious head injury at baseline (n=599). Participants whose clinical classification or Aβ status fluctuated during the study period were excluded (n=19). This left 580 CN older adults with complete data available for analysis, 179 of whom were classified as SuperAgers.

Baseline SuperAger classification required performance above the sex-adjusted normative average for 30-44 year olds on the California Verbal Learning Test – Second Edition (CVLT-II) Long Delay Free Recall trial (≥13 for women, ≥12 for men) [196], and above -1 SD using published normative data for all non-memory tests identified to be optimal for the study of cognitive aging, including the Digit Symbol Substitution Test, the Victoria Stroop Test (words trial), Digit Span, letter fluency (FAS), and category fluency (total animals and male names, and fruit and furniture) (as per [204]). These psychometric criteria are consistent with those originally used by the Northwestern SuperAging Study [185] and other studies [180,189], despite the greater number of non-memory tests used for classification in the current study. SuperAgers were then case-matched with the remaining CN participants (i.e. CNFA) based on age, sex, education, and follow-up time to ensure that the study results were not driven by demographic differences. Therefore, 358 participants were included in this study (179 SuperAgers, 179 CNFA, Figure 4-1).

Figure 4-1: Sample classification and clinical disease progression in the AIBL sample over 8 years



Abbreviations used: AD = Alzheimer's disease; CN = cognitively normal; CNFA = cognitively normal for age; MCI = mild cognitive impairment.

4.3.2 Measures

A comprehensive neuropsychological battery was administered to all participants at each visit, the details of which are described elsewhere [192]. Four composite domain scores were derived via exploratory factor analysis, as previously reported, and were calculated for each participant visit by averaging z-scores of the respective tests for each domain [145]. Z-scores were calculated relative to the full CN AIBL sample at baseline. The verbal memory composite included California Verbal Learning Test – Second Edition (CVLT-II) Long Delay Free Recall, CVLT-II Immediate Recall Trials 1-5, and Logical Memory II. The executive function composite included category fluency (total animals and male names, and fruit and furniture), letter fluency (FAS), the Victoria Stroop Test (words trial), and the Digit Symbol Substitution Test. Working memory included two Cogstate tasks (One Back, One Card Learning). Finally, processing speed included the Cogstate Identification and Detection tasks. Education was coded as ≤12 years or >12 years. Mood symptomology was assessed using the Hospital Anxiety and Depression Scale (HADS) [207]. The Memory Complaint

Questionnaire (MAC-Q) [209] raw score was used to assess subjective memory complaint. *APOE* genotype was determined from whole blood extracted DNA as per previously described methodology [210].

4.3.3 Cognitive status assessment

An expert clinical panel made consensus classifications using standard clinical criteria for MCI [205] and AD [27], and was blinded to any information concerning Aβ and *APOE* ε4 status. The panel reviewed all available neuropsychological and psychiatric information for participants who performed below -1.5 SD on published age- and education-adjusted normative data on at least two neuropsychological tests. Participants who performed within normal limits for their age on cognitive testing were classified as CN, and those who were classified with MCI/dementia during the follow-up period were coded as progressors.

4.3.4 Amyloid-β PET neuroimaging

PET neuroimaging was conducted using one of the following Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB, n=140), ^{18}F-NAV4694 (NAV, n=44), ^{18}F-Florbetapir (FBP, n=87), or ^{18}F-Flutemetamol (FLUTE, n=87). PET methods and procedures have been reported previously [211,212]. Briefly, PET acquisitions were performed up to 90 minutes following tracer injection. Standardized uptake value (SUV) data were summed and normalized to a reference region (the cerebellar cortex for PiB and NAV, the whole cerebellum for FBP, and the pons for FLUTE) to generate a SUV ratio (SUVR). The accepted cut-off values for significant Aβ deposition vary by radiotracer, so a linear regression transformation was applied to the FBP and FLUTE SUVR to create a "PiB-like" SUVR unit called Before the Centiloid Kernel Transformation (BeCKeT) [212]. All particiants with SUVR/BeCKeT $\geq$ 1.40 at

their most recent PET scan were classified as Aβ+, and those below the threshold were classified as Aβ-.

4.3.5 Statistical methods

R version 3.4.3 [251] and SPSS 23 were used for all statistical analyses, with statistical significance set at $p<0.05$. SuperAgers were case-matched with CNFA using the FUZZY extension command in SPSS. Exact matches were required for education and sex. Tolerances for age and follow-up time were ±2 years and ±1 visit, respectively. Eligible matches were selected at random.

4.3.5.1 *Baseline group differences in clinical characteristics*

Normality of continuous variables were assessed by visual inspection of Q-Q plots. Between-group comparisons by SuperAger status were conducted using a one-way analysis of variance (ANOVA) for normally distributed variables. A Kruskal-Wallis one-way ANOVA was used for non-normally distributed variables. Differences in dichotomous variables were assessed using Fisher's exact tests. No adjustments were made for multiple comparisons due to their conservative nature; rather, Cohen's *d* was used to guide interpretation of statistically significant results, such that significant comparisons with very small effect sizes ($d<0.20$) were suspected Type I errors.

4.3.5.2 *Survival analysis*

Fine-Gray subdistribution hazard modelling was used instead of cause-specific Cox modelling due to its ability to account for the presence of competing risks, which were defined as death or withdrawal from the study due to illness unrelated to dementia. Progression to MCI/dementia were coded as events, and time to event was entered in months from the baseline visit. Non-progressors were right-censored at the time of their most recent study visit. Schoenfeld residuals tests were non-significant for predictors and the global value was non-significant for the entire model, indicating that the proportional

hazards assumption was met. All DFBETA values were within the size-adjusted cut-score; therefore, no outliers were detected.

Survival models evaluated the first hypothesis in five stages to determine whether SuperAger classification can predict non-progression to MCI/dementia. Model 1 included only SuperAger status. Model 2 added estimated IQ. Standard demographic predictors that have been indicated as risk factors for MCI/dementia were added to Model 3: baseline age and sex. Presence of the *APOE* ε4 allele was added in Model 4. Finally, Model 5 included Aβ status (+/-). Cumulative hazard functions were plotted, and hazard ratios were calculated with 95% confidence intervals.

4.3.5.3 *Influence of Aβ on cognitive change*

Multiple linear mixed model (LMM) analyses with maximum likelihood estimation were conducted with each of the four cognitive domain composite scores as continuous dependent measures. Nonlinear models did not improve model fit nor the amount of variance explained, and visual examination indicated that the data most closely fit a linear pattern. Fixed factors were SuperAger status, Aβ status, time from baseline assessment in years, and their interactions. Participant was entered as a random factor with random slopes for time. Covariates were baseline age, progression status, estimated IQ, and *APOE* ε4 status. To explore the extent to which the effects of SuperAger classification on cognitive change were influenced by age, additional LMMs were run to test interactions between SuperAger status, Aβ status and age.

4.4 Results

4.4.1 Sample characteristics

Over the eight-year period, 28 participants progressed to clinically-classified MCI/dementia (22 CNFA, 6 SuperAgers), 10 died, 13 withdrew due to ill health, 36 formally withdrew from

the study for reasons unrelated to health, and 4 could not be contacted for follow-up (Figure 4-1). Median follow-up time for the full sample was 90 months (interquartile range: 20) and 62.8% of all participants were followed throughout the entire study period. Participants were 68.5 years of age on average (range: 60-83), and most were educated beyond 12 years (65.4%). See Table 4-1 for demographic and clinical characteristics.

4.4.2 Baseline group differences

As expected, no group differences (SuperAgers vs CNFA) were observed in baseline age, sex, education, or follow-up time (Table 4-1). The groups also did not differ on any clinical factors. SuperAgers had higher estimated IQ (two points) compared to matched CNFA. The proportion of *APOE* ε4 carriers and participants with Aβ+ was similar between both groups. These findings were also observed between groups in the full sample before case-matching. Consistent with the classification criteria, SuperAgers had significantly higher mean verbal memory and executive function performance at baseline; however, the differences in working memory and processing speed were not significant. No differences were observed between SuperAgers and CNFA on subjective memory assessment.

Table 4-1: Baseline group differences

Measure	Total sample	CNFA	SuperAgers	*p*	*d*
n	358	179	179		
Aβ+, %	38.50	37.40	39.70	0.75	
APOE ε4 carrier, %	27.90	27.40	28.50	0.91	
Age at baseline, years	68.48, 68.00 (9)	68.53, 68.00 (8)	68.43, 68.00 (9)	0.89	
Female, %	53.60	53.60	53.60	1	
Estimated IQ	112.24, 114.00 (8)	111.28, 114.00 (8)	113.25, 114.00 (5)	**0.002**	0.31
Education >12 years, %	65.40	65.40	65.40	1	
HADS A	4.40, 4.00 (5)	4.45, 4.00 (5)	4.34, 4.00 (5)	0.43	
HADS D	2.66, 2.00 (3)	2.50, 2.00 (3)	2.82, 2.00 (3)	0.39	
MAC-Q	25.25, 25.00 (6)	24.89, 25.00 (6.75)	25.61, 25.00 (6)	0.86	
Progressors, %	7.80	12.30	3.40	**0.003**	0.77
Withdrawn due to ill health/deceased, %	6.40	6.10	6.70	1	
Subsequent stroke/TIA, %	5.00	5.00	5.00	1	
Hypertension, %	50.60	54.20	46.90	0.21	
Diabetes, %	8.90	11.70	6.10	0.09	
People followed up at all assessment time points (6 over 90 months), %	62.80	63.70	62.00	0.83	
Length of follow up (months)	75.75, 90.00 (20)	77.38, 90.00 (19)	74.04, 90.00 (35)	0.33	
Verbal memory composite score	0.26, 0.30 (1.08)	-0.08, -0.12 (1.06)	0.63, 0.63 (0.79)	**<0.0005**	1.13
Executive function composite score	0.12, 0.19 (0.91)	-0.10, -0.12 (1.02)	0.36, 0.35 (0.71)	**<0.0005**	0.74
Working memory composite score	0.00, 0.006 (0.85)	-0.03, -0.04 (0.81)	0.03, 0.04 (0.84)	0.16	
Processing speed composite score	0.21, 0.27 (1.03)	0.14, 0.25 (1.09)	0.27, 0.28 (0.96)	0.16	

All descriptive statistics for continuous variables reported as mean, median (interquartile range); categorical variables reported as percentages. *P*-values shown for comparisons between Aβ +/- groups.

Abbreviations used: Aβ+ = elevated cerebral amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele carriage; CNFA = cognitively normal for age; HADS A = Hospital Anxiety and Depression Scale – Anxiety; HADS D = Hospital Anxiety and Depression Scale – Depression; MAC-Q = Memory Complaint Questionnaire; TIA = transient ischemic attack.

4.4.3 Prognostic utility of SuperAging criteria

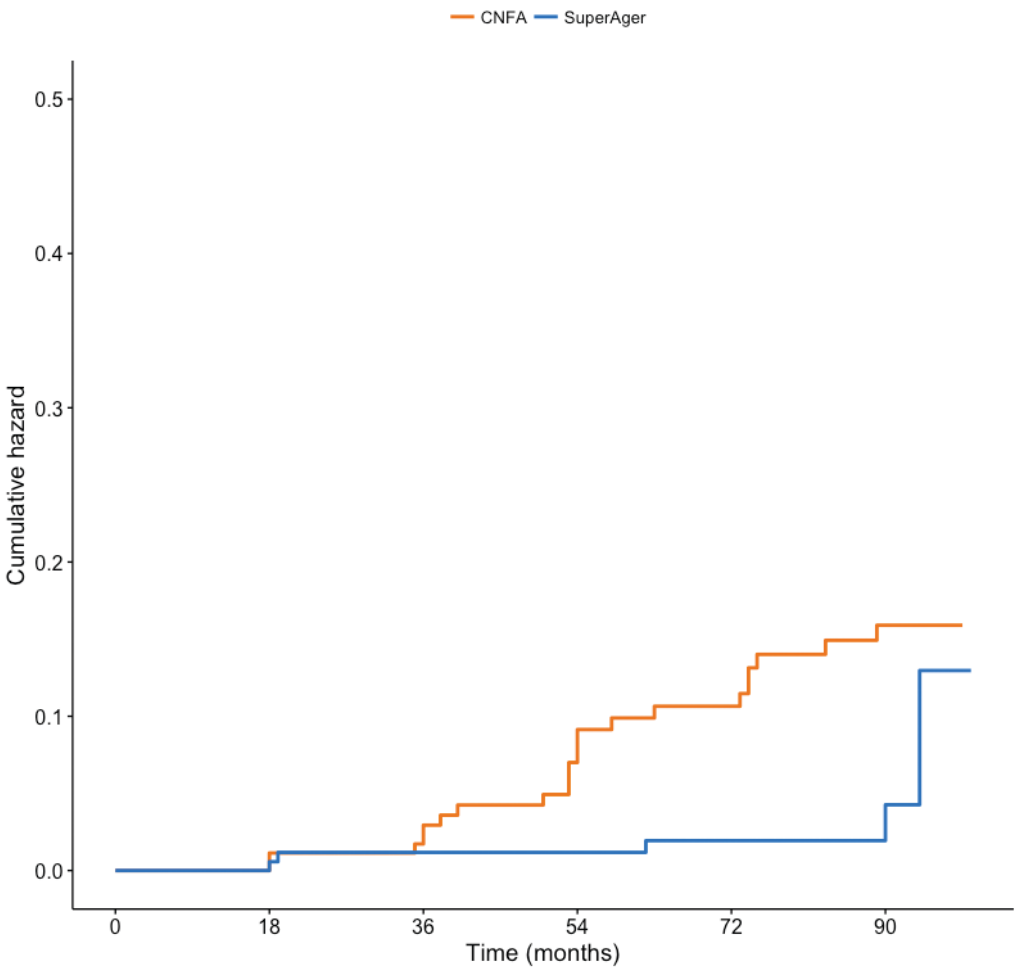
Fisher's exact test showed that SuperAgers were less likely to progress to MCI/dementia than CNFA (OR: 0.248, 95% CI: 0.098-0.626; p=0.003). Survival analyses results are shown in Table 4-2. SuperAger status decreased risk of progression to MCI/dementia in all models by 69-73% compared to CNFA (Figure 4-2). In Model 2, estimated IQ did not influence risk of progression. Females had 68% less risk than males in Model 3, and estimated IQ reduced risk by 8% for each point increase with the addition of sex in the model. In Model 4, *APOE* ε4 carriage increased risk by 227%. Aβ status conferred no additional risk in Model 5, but reduced the risk conferred by *APOE* ε4 status to 188%. The effect of age was significant and remained consistent across Models 3-5, which showed 8-9% increased risk of progression to MCI/dementia per additional year of age at baseline, although this risk was not influenced by SuperAger classification or Aβ status.

Table 4-2: Survival analyses

MODEL 1	*p*-value	HR	95% confidence interval	
SuperAger status	**0.004**	**0.27**	**0.11**	**0.65**
MODEL 2	*p*-value	HR	95% confidence interval	
SuperAger status	**0.008**	**0.31**	**0.13**	**0.73**
Estimated IQ	0.082	0.96	0.91	1.01
MODEL 3	*p*-value	HR	95% confidence interval	
SuperAger status	**0.008**	**0.31**	**0.13**	**0.74**
Estimated IQ	**0.007**	**0.92**	**0.86**	**0.98**
Baseline age	**0.013**	**1.08**	**1.02**	**1.15**
Sex	**0.011**	**0.32**	**0.13**	**0.76**
MODEL 4	*p*-value	HR	95% confidence interval	
SuperAger status	**0.007**	**0.30**	**0.13**	**0.72**
Estimated IQ	**0.015**	**0.93**	**0.87**	**0.99**
Baseline age	**0.005**	**1.09**	**1.03**	**1.16**
Sex	**0.017**	**0.33**	**0.13**	**0.82**
APOE ε4 carrier	**0.003**	**3.27**	**1.52**	**7.05**
MODEL 5	*p*-value	HR	95% confidence interval	
SuperAger status	**0.008**	**0.31**	**0.13**	**0.74**
Estimated IQ	**0.013**	**0.92**	**0.87**	**0.98**
Baseline age	**0.013**	**1.08**	**1.02**	**1.15**
Sex	**0.015**	**0.31**	**0.12**	**0.80**
APOE ε4 carrier	**0.005**	**2.88**	**1.39**	**5.97**
Aβ+	0.180	1.69	0.78	3.63

Abbreviations used: Aβ+ = elevated cerebral amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele carriage; HR = hazard ratio.

Figure 4-2: Cumulative hazard functions between SuperAgers and CNFA



Abbreviation used: CNFA = cognitively normal for age.

4.4.4 Effect of Aβ status on longitudinal cognitive performance in SuperAgers

The LMM parameters are shown in Table 4-3, and the annualized group mean slopes for performance over time in each cognitive domain for the Aβ+ and Aβ- CNFA and SuperAger groups are summarized in Table 4-4. Table 4-4 shows that mean slopes for verbal memory performance over time in the Aβ- CNFA and SuperAger groups were both positive, showing improvement over time. In comparison, group mean slopes in the Aβ+ CNFA and SuperAger groups were both negative, showing decline over time. These relationships are shown graphically in Figure 4-3. A similar pattern of outcomes was evident for performance over time on the executive function composite, with Aβ+ CNFA and SuperAger groups showing

more negative slopes compared to Aβ-. However, for working memory, the slopes of performance over time remained close to zero for the SuperAger and CNFA groups irrespective of Aβ status, and all groups showed a decline over time for processing speed (Table 4-4). The LMMs identified no significant interaction between SuperAger status and time, or SuperAger status and Aβ for any composite (Table 4-3). For verbal memory, SuperAger status, time, age, progression status, and estimated IQ were significant main effects, and there was a significant Aβ status by time interaction. For executive function, SuperAger status, Aβ status, time, *APOE* ε4 status, age, progression status, and estimated IQ were all significant main effects, and the interaction between Aβ status and time was also significant. No significant main effects or interactions were observed for working memory. For processing speed, significant main effects were observed for time, age and estimated IQ with no significant interactions. These overall findings were unchanged when estimated IQ was removed from the LMMs. Age did not significantly interact with SuperAger status or Aβ status on any cognitive domain.

Table 4-3: Linear mixed model parameters

	Verbal memory			**Executive function**			**Working memory**			**Processing speed**		
	Estimate	Std. Error	*p*	Estimate	Std. Error	*p*	Estimate	Std. Error	*p*	Estimate	Std. Error	*p*
Intercept	-0.94	0.64	0.14	-0.73	0.62	0.24	-0.32	0.54	0.56	0.32	0.71	0.66
SuperAger classification	0.57	0.08	**<0.0005**	0.36	0.07	**<0.0005**	0.13	0.07	0.07	0.02	0.10	0.86
Aβ status (+/-)	0.02	0.10	0.83	0.18	0.09	**0.04**	0.11	0.08	0.19	-0.06	0.12	0.60
Time (years)	0.04	0.01	**0.002**	-0.01	0.01	0.31	0.00	0.01	0.86	-0.09	0.01	**<0.0005**
***APOE* ε4 carrier status (+/-)**	0.05	0.07	0.45	-0.21	0.07	**0.002**	0.02	0.06	0.74	-0.13	0.08	0.10
Baseline age	-0.03	0.01	**<0.0005**	-0.04	0.01	**<0.0005**	0.00	0.00	0.29	-0.02	0.01	**<0.0005**
Progression	-0.74	0.11	**<0.0005**	-0.34	0.11	**0.003**	-0.05	0.10	0.64	-0.18	0.13	0.17
Estimated IQ	0.02	0.005	**<0.0005**	0.03	0.00	**<0.0005**	0.00	0.00	0.85	0.01	0.01	**0.01**
SuperAger * Aβ status	-0.10	0.13	0.43	-0.07	0.12	0.55	-0.19	0.11	0.10	0.22	0.16	0.18
SuperAger * Time	-0.03	0.02	0.12	-0.02	0.01	0.09	-0.01	0.01	0.59	0.02	0.02	0.19
Aβ status * Time	-0.06	0.02	**0.001**	-0.03	0.01	**0.04**	-0.03	0.02	0.13	-0.01	0.02	0.71
SuperAger * Aβ status * Time	0.03	0.03	0.30	0.01	0.02	0.69	0.04	0.02	0.10	-0.02	0.03	0.57

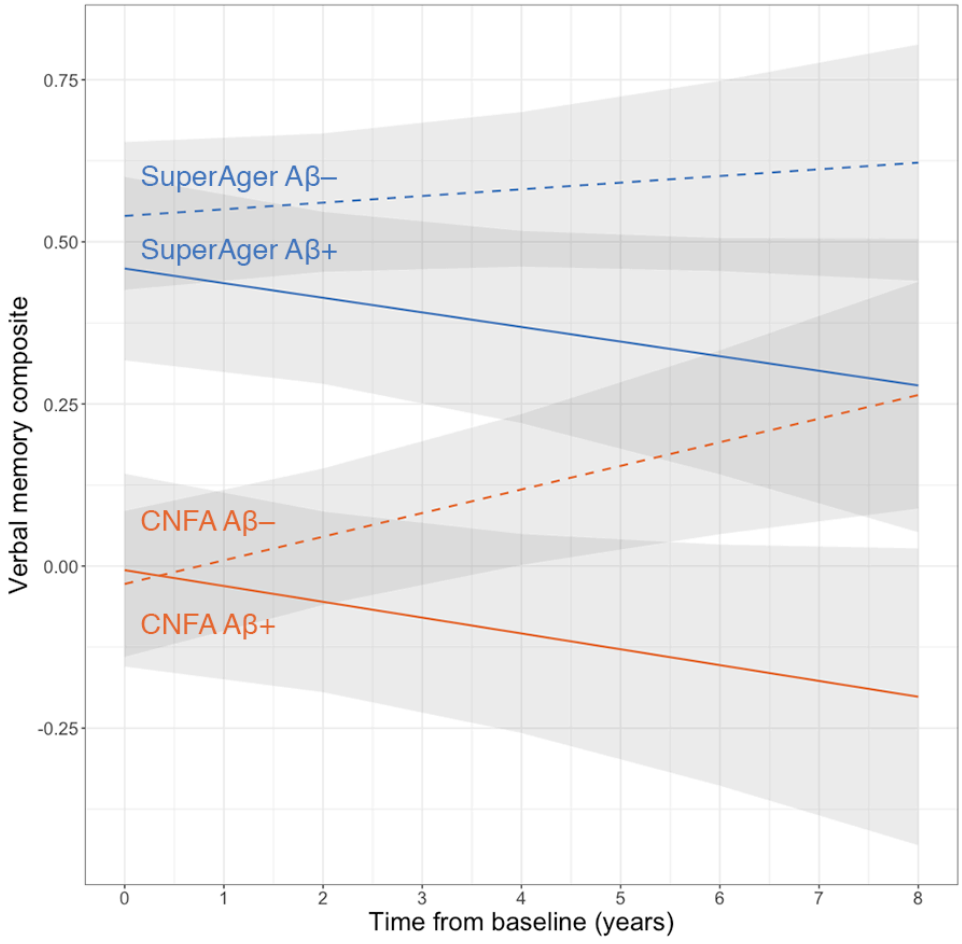
Abbreviations used: Aβ = amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele carriage

Table 4-4: Annualized group mean slopes for cognitive performance by SuperAger and Aβ status

	CNFA		SuperAgers	
	Aβ-	**Aβ+**	**Aβ-**	**Aβ+**
Verbal memory	0.04 (0.12)	-0.02 (0.12)	0.01 (0.12)	-0.02 (0.13)
Executive function	-0.01 (0.08)	-0.03 (0.08)	-0.03 (0.08)	-0.05 (0.09)
Working memory	-0.002 (0.10)	-0.03 (0.11)	-0.01 (0.11)	0.005 (0.11)
Processing speed	-0.09 (0.13)	-0.10 (0.14)	-0.07 (0.13)	-0.09 (0.13)

Presented as mean slopes (SD). Abbreviations used: Aβ- = cerebral amyloid-beta within normal range (PET SUVR<1.40); Aβ+ = elevated cerebral amyloid-beta; CNFA = cognitively normal for age; SD = standard deviation.

Figure 4-3: Verbal memory performance over time by SuperAger and Aβ status



Abbreviations used: Aβ- = cerebral amyloid-beta within normal range (PET SUVR<1.40); Aβ+ = elevated cerebral amyloid-beta; CNFA = cognitively normal for age.

4.5 Discussion

The first hypothesis, that SuperAger classification would be associated with reduced risk of progression to a clinical diagnosis of MCI or dementia, was supported. In the total AIBL CN cohort, 30.9% met the SuperAger criteria (i.e. n=179 with 71 Aβ+) and a CNFA group of the same size was matched to the SuperAger group on age, sex, education, and follow up time. The relatively high proportion of individuals classified as SuperAgers in the AIBL CN cohort most likely reflects the rigorous inclusion/exclusion criteria for AIBL as well as selection and survivor biases. Although SuperAger and CNFA groups were not matched *a priori* on general health or known AD risk factors, all clinical measures as well as the prevalence of AD risk factors, Aβ+ and *APOE* ε4 carriage, were equivalent between groups (Table 4-1). This equivalence was also observed prior to case-matching, consistent with reports from previous studies [180,184], and *APOE* ε4 carriage remained similar between SuperAger and CNFA groups when the imaging inclusion criterion was lifted despite the AIBL imaging sub-sample being enriched for *APOE* ε4 carriers. Similarity between the groups in physical health characteristics most likely reflects the well-documented homogeneity of the AIBL sample due to its rigorous exclusion criteria [192]. In this context, the similar prevalence of AD risk factors indicates that SuperAger classification, reflective of superior baseline cognitive performance, did not reflect resistance against neuropathological processes central to the development of AD [226,252]. Despite the equivalent risk for AD, only 3.4% of the SuperAger group progressed to a clinical classification of MCI/dementia over the eight-year follow-up interval compared to 12.3% of the CNFA group. When examined in survival models, this difference reflected a 69-73% reduction in risk of progression to MCI/dementia for SuperAgers compared to CNFA. Furthermore, the reduced risk of clinical progression in

SuperAgers was not modified by *APOE* ε4 carriage, Aβ+ or age (Table 4-2). The continued resilience of SuperAgers to clinical progression despite similar levels of AD risk suggested that, while SuperAgers are not resistant to the accumulation of Aβ, they do have some resilience to the effects of elevated Aβ on cognitive change. Although clinical disease outcomes associated with SuperAging have not been explored previously, it has been reported that individuals classified as SuperAgers display less Aβ-associated memory decline compared to CNFA despite equivalent levels of Aβ burden [180].

The second hypothesis, that SuperAgers would show greater resilience to the cognitive decline associated with preclinical AD (i.e. Aβ+), was not supported. While, by definition, SuperAgers had superior verbal memory compared to CNFA adults at baseline, cognitive change over the following eight years was equivalent between the Aβ+ SuperAgers and Aβ+ CNFA adults in both nature and magnitude (Figure 4-3), consistent with that reported in other prospective studies of cognitive change associated with Aβ+ [60,61]. In the absence of preclinical AD (i.e. Aβ-), both the SuperAger and CNFA groups showed little-to-no decline in verbal memory or executive function and equivalent rates of decline in processing speed and working memory (Table 4-4). Thus, individuals classified as SuperAgers showed no unique protection from age- or Aβ-associated cognitive decline in this study. These findings are inconsistent with two recent studies of SuperAging, which suggest that SuperAger classification reflects increased resilience against the effects of AD-associated pathological change [180,253]. A *post-mortem* study found maintenance of superior episodic memory in 7/10 of the studied SuperAgers despite moderate or frequent neuritic plaques and neurofibrillary tangles in more than half of them [253]. Furthermore, a study of the BACS cohort reported that successful agers displayed no episodic memory decline compared to CNFA over an average of five years. Although levels of Aβ burden were

equivalent between groups, the successful agers were resilient to Aβ-associated memory decline whereas the CNFA older adults were not [180]. The discrepancy in findings may reflect methodical differences between these studies. First, the present study had a much larger sample of SuperAgers (n=179 with 71 Aβ+) than the BACS sample of successful agers (n=25 with longitudinal follow-up, of whom 10 were Aβ+). Second, the length of follow-up in the BACS sample varies between participants and it is unknown how many successful agers were assessed at the longest follow-up interval. In contrast, 62.8% of the present study sample provided complete data over the full eight-year period of available AIBL data (i.e. 111 SuperAgers), providing the current design with greater statistical power. Therefore, the BACS finding that individuals classified as SuperAgers displayed no memory decline associated with Aβ+ was likely due to the small sample sizes studied resulting in lack of statistical power to detect these effects. Finally, differences between studies with regard to specific neuropsychological and age criteria for SuperAger classification can limit comparisons from one study to another. The BACS sample included individuals over 70 years old and classified successful agers using the CVLT-II normative mean for 18-32 year olds that was not adjusted for sex [180]. In the present study, the criteria for SuperAger classification included adults over age 60 whose memory performance was defined using the sex-adjusted CVLT-II normative mean for 30-44 year olds. Although the gap between participants' age and the reference age varies between studies, these differences should be negligible if SuperAgers do indeed maintain their "youthful" cognitive ability into late-life; however, older age was associated with lower cognitive performance for verbal memory, executive function and psychomotor speed across all participants with no differential effects between SuperAgers and CNFA. Despite these methodological differences, the current finding that a substantial sample of CN older individuals classified as SuperAgers using

careful psychometric and rigorous inclusion/exclusion criteria have no greater protection from the negative effects of Aβ+ than do well-matched CNFA indicates that the deleterious effects of Aβ on cognition persist regardless of baseline cognitive ability.

Results of the current study are consistent with the proposition that the increasing individual differences in cognition, which become greater with age, are likely to reflect the presence of at least two distinct subgroups of older adults. First, individuals with occult neurodegenerative disease such as preclinical AD cannot be considered to be aging normally; therefore, their inadvertent inclusion in aging study samples will negatively bias estimated effects of cognitive aging [145]. A second subgroup of older adults who exhibit baseline cognition superior to other CN adults of the same age can also be present in aging samples. Previous SuperAging studies have used different minimum age criteria for SuperAger classification (i.e. 60-80) [180,185,189], but only one has examined how age influences the cognitive and neurobiological outcomes of psychometrically-defined SuperAgers [180]. They report a negative relationship between age and Aβ deposition in SuperAgers; however, this relationship became non-significant following removal of outlier data [180]. Although the present study found that increasing age was associated with greater risk of clinical disease progression to MCI/dementia and lower cognitive performance, the effect of age on cognition was consistent across all individuals regardless of SuperAger classification or Aβ status. This suggests that cognitive decline in preclinical AD is due to neuropathological changes beyond the effect of age, itself, and that individuals classified as SuperAgers are no more resilient to changes in cognition associated with age or with preclinical AD than are CNFA.

In contrast, studies of cognitive reserve report that the relationship between Aβ and cognitive decline is modified by greater years of education and higher estimated IQ [254–

256]. It has additionally been reported that greater participation in cognitively stimulating activities is associated with lower Aβ deposition [256]. It is possible that the SuperAger and cognitive reserve constructs overlap; however, they are not the same. Individuals with high cognitive reserve are typically identified using proxy measures such as education, estimated IQ and cognitive activity, and may display greater cognitive performance with equivalent levels of AD neuropathological markers compared to individuals with low cognitive reserve [257]. Classification criteria for SuperAgers are psychometrically-based; therefore, while the superior cognitive performance observed in SuperAging samples may be reflective of higher cognitive reserve, this study specifically matched SuperAgers and CNFA on education suggesting equivalent levels of cognitive reserve between groups. Additionally, previous studies report no difference in estimated IQ between SuperAgers and their CNFA controls [189,191]. While SuperAgers in the current study did show slightly better estimated IQ than the CNFA group, the magnitude of this benefit was trivial when considered clinically (i.e. two points). Because individuals classified as SuperAgers exhibited better cognitive ability than CNFA at all time points despite similar levels of Aβ deposition, cross-sectional examinations may support the notion that SuperAgers represent a population with high cognitive reserve; however, this does not bear out in the longitudinal examination conducted in this study given that Aβ+ older adults, regardless of classification, showed clear Aβ-associated cognitive decline compared to Aβ- participants. According to these findings, SuperAgers are not resilient to Aβ-associated cognitive decline as suggested by the construct of cognitive reserve [257], although one small study examining Aβ-associated cognitive change in successful agers did find evidence of such resilience [180]. Finally, studies of cognitive reserve indicate that individuals with high cognitive reserve experience more rapid cognitive decline than those with low cognitive reserve, which was not observed in this study as rates

of cognitive change were equivalent between SuperAgers and CNFA. Together, these observations suggest the possibility that the SuperAger and cognitive reserve constructs are different, a point that was also noted by the group who pioneered the SuperAger construct [187].

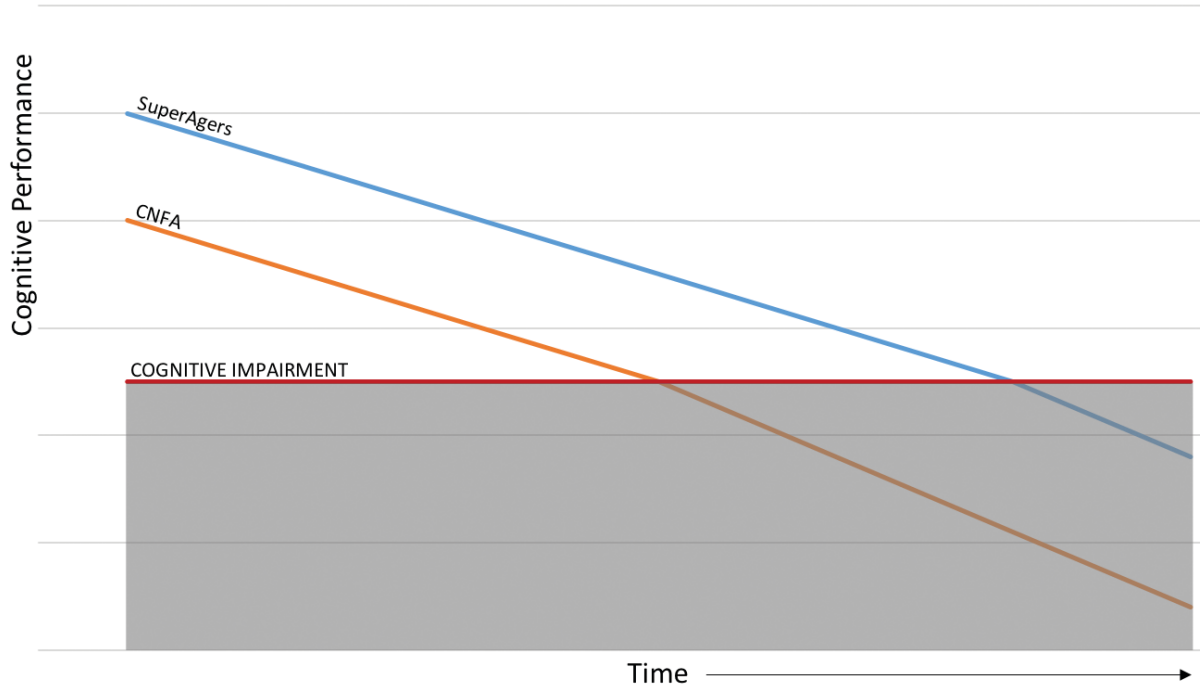
The SuperAger construct is based on the observation that some adults progress from middle-age to old-age without showing any decline in their cognitive abilities [190]. Because it is rare to possess neuropsychological data across the entire adult lifespan for individuals, studies of SuperAging approximate "youthful" cognition [187] in their samples by comparing neuropsychological performance of their older adults to normative data derived from individuals 20-30 years younger [185]. While the results of the current study confirm the validity of the SuperAgers construct, they raise the question of what is actually reflected by the superior cognition observed in SuperAgers. This study matched the SuperAger and CNFA groups on age, sex, education and follow-up time, and found similar physical health and AD risk profiles between groups (Table 4-1). However, as individual differences in cognitive aging reflect complex interactions between time, genetics and a stochastic combination of events [110], it is not feasible to experimentally or statistically control all possible differences. For example, higher occupational complexity has been associated with greater white matter integrity and cognitive function in later life [258], and increased physical activity has been linked to better cognition and attenuated age-associated brain atrophy [259]. The inconsistency between risk factors for MCI/dementia, defined psychometrically (i.e. SuperAger classification, which reflects superior baseline cognitive performance) and biologically (i.e. Aβ and *APOE* ε4) in the current study, indicates that other neuroimaging biomarkers are necessary to understand how SuperAging can influence cognitive aging. For example, future studies in large cohorts, like AIBL, should seek to examine volumetric and

functional differences between SuperAgers and CNFA in brain regions associated with verbal memory and executive function by Aβ status. Previous studies have reported cross-sectional differences in regional volumes and cortical thickness, albeit without consideration to Aβ status [185,189]. Although one study did examine longitudinal morphological changes in successful agers with respect to Aβ burden, reporting no differences between successful agers and typical older adults and no Aβ-associated differences, the sample size was limited (n=19 successful agers) [180]. If these differences are observed in a larger sample and persist even in preclinical AD, such a finding would indicate that SuperAgers' resilience to progression is a consequence of greater neuronal integrity [185]. Furthermore, although imaging and pathological studies consistently show that SuperAgers have superior brain and neuronal structure to CNFA adults, an observation that would be consistent with SuperAgers having lower levels of tau even in the presence of Aβ+ [226,260], no study of SuperAging has yet measured levels of cortical tau.

Given that SuperAgers progressed to MCI/dementia at a lower rate than did CNFA despite being equally affected by cognitive aging and Aβ+, consideration must be given to the clinical classification process. Classification of clinical disease progression in AIBL is guided by considering the level of performance on neuropsychological tests at each visit with reference to published normative data for those tests. Consequently, because of their superior test performance, SuperAgers who are Aβ+ and have exhibited the cognitive decline pathognomonic of preclinical AD continue to have their test performance classified as unimpaired relative to the normative data. This can be interpreted in two ways. First, superior cognitive performance in SuperAgers allows them to tolerate AD neuropathological changes for longer than CNFA. Alternatively, reliance on static published normative data to guide clinical classification is unsatisfactory. More accurate identification of MCI/dementia

in SuperAgers may occur if classification decisions took into consideration cognitive change over time; however, this is limited by the lack of available normative data for longitudinal change [118,164]. It is, therefore, possible that SuperAger classification may not prevent, but rather delays, clinical classification of MCI/dementia due to the greater amount of time needed for high baseline test performance to decline past the threshold for defined cognitive impairment, as illustrated in Figure 4-4.

Figure 4-4: Theoretical trajectory to cognitive impairment for CNFA and SuperAgers



The same rate of change in cognition was observed between SuperAgers and case-matched cognitively normal for age (CNFA) participants on all cognitive domains. Because cognitive impairment is determined by neuropsychological test performance in reference to normative data and SuperAgers exhibit superior cognitive performance at baseline, SuperAgers may take longer to reach the threshold for cognitive impairment.

The generalizability of the present findings must be considered in the context of the following caveats. AIBL is a convenience sample of relatively healthy, well-educated and ethnically homogeneous individuals with strict inclusion criteria; therefore, the characteristics of SuperAgers and CNFA in this study may differ from the general population.

Nearly one-third of the CN AIBL sample were classified as SuperAgers, which may be greater than that expected in the general population; however, the prevalence of SuperAgers has not been reported in previous SuperAging studies. Furthermore, participants of the AIBL study have completed the neuropsychological battery up to six times over eight years and display considerable practice effects, particularly in the memory tests. While it has been observed in AIBL and in other prospective studies that CN Aβ+ individuals do not necessarily display decline in cognition over time, but rather a loss of practice effects [71,261–263], this study did observe that CN Aβ+ individuals declined on verbal memory over time. Despite these caveats, the present study has a number of strengths. First, no other study of SuperAgers has case-matched CNFA based on age, sex, education and follow-up time. Second, this is the first study to examine longitudinal cognitive performance in SuperAgers with consideration to Aβ status in this large a sample over a relatively long time interval. Finally, there is great potential to further study the SuperAger construct in AIBL, particularly with reference to the effects of Aβ on brain volumetric measures over time to determine whether SuperAger classification offers any protection against neurodegeneration or tau accumulation downstream of elevated Aβ deposition.

The process of aging is complex, in which considerable inter-individual variability is inherent, and this is partially reflected by different individual levels of Aβ deposition and neurodegenerative disease markers. Therefore, the present findings indicate that the study of normal cognitive aging necessitates examination of individuals without evidence of clinically significant pathologic change or neurodegenerative disease, regardless of baseline cognitive performance, as these individuals have clearly displayed resistance to the accumulation of these neuropathological markers in aging.

Chapter 5: Rates of age- and amyloid β-associated cortical atrophy in older adults with superior memory performance

This study has been published in *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* and is reproduced here. The published manuscript is included in Appendix A.

The results from this chapter were presented at the National Conference of Emerging Researchers in Ageing and the Organization for Human Brain Mapping – Australian Chapter Symposium in late 2018.

A response to commentaries received from others was also published, please see Appendix A.

5 Rates of age- and amyloid β-associated cortical atrophy in older adults with superior memory performance

5.1 Abstract

Introduction: Superior cognitive performance in older adults may reflect underlying resistance to age-associated neurodegeneration. While elevated Aβ deposition (Aβ+) has been associated with increased cortical atrophy, it remains unknown whether "SuperAgers" may be protected from Aβ-associated neurodegeneration.

Method: Neuropsychologically-defined SuperAgers (n=172) and cognitively normal for age (CNFA; n=172) older adults from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study were case-matched. Rates of cortical atrophy over 8 years were examined by SuperAger classification and Aβ status.

Results: 40.7% of SuperAgers and 40.1% of CNFA were Aβ+. Rates of age- and Aβ-associated atrophy did not differ between the groups on any measure. Aβ- individuals displayed the slowest rates of atrophy.

Conclusions: Maintenance of superior memory in late-life does not reflect resistance to age- or Aβ-associated atrophy. However, those individuals who reached old age without elevated Aβ deposition (i.e. Aβ-) displayed reduced rates of cortical atrophy.

5.2 Introduction

Although cognitive decline is considered characteristic of aging [112,114], the existence of older adults with superior cognitive ability for their age suggests that cognitive decline is not inevitable [206]. Studies describe such individuals as successful agers [177–180], optimal memory performers [184], supernormals [183,264,265] or SuperAgers [185,189]. Despite similar goals, each study employs different classification criteria. For example, SuperAger classification originally included individuals over age 80 with episodic memory performance equivalent to, or above, the normative mean for adults aged 50-65 and age-appropriate performance in other cognitive domains [185,187,190,191]. SuperAgers are thus considered to have maintained "youthful" memory performance into old age [187]. Other studies have used similar neuropsychological criteria but lowered the minimum age criterion to 70 (i.e. "successful agers") [180] and 60 years (i.e. "SuperAgers") [189,206]. While the chronological age at which SuperAging can be classified is still being determined, elucidation of the neurobiological basis of aging without cognitive decline could yield important insights into prevention of age-associated neurodegenerative diseases such as Alzheimer's disease (AD).

Cross-sectional comparisons of brain morphology between SuperAgers and elderly controls report that SuperAgers do not show typical age-associated atrophy on magnetic resonance imaging (MRI) measures of cortical thickness and volume [185]. SuperAgers also show greater left hippocampal volume and greater cortical thickness in anterior cingulate cortex, and default mode and salience network regions [189,190]. Greater regional cortical thickness and hippocampal volume, and lower burden of white matter lesions was observed in successful agers compared to typical older adults [180]. Given that normal aging is associated with gradual loss of brain volume [160], larger brain volumes and reduced

markers of cerebral small vessel disease are inferred to reflect preservation of cortical integrity despite aging, raising the possibility that maintenance of superior memory performance in old age reflects some resistance or protection against age-associated neurodegeneration [187].

SuperAging may also reflect some protection from AD [190]. Abnormally high levels of amyloid-beta (Aβ+) and carriage of the *APOE* ε4 allele are AD risk factors [266]; however, prevalence of Aβ+ and *APOE* ε4 carriage are consistently similar between individuals with superior memory performance and typical older adults [180,184,190,206,265]. These individuals maintain superior cognitive ability despite Aβ+ [180,184,206] or substantial markers of AD neuropathology upon *post-mortem* examination [253], suggesting that any resilience to AD pathogenesis experienced by SuperAgers either ameliorates or acts independently from the risk conferred by Aβ+ and *APOE* ε4. For example, neurobiological factors associated with SuperAging may protect against Aβ-associated neurodegeneration. Although the adverse effects of Aβ+ on brain volume over time have been well-described [23,65,68,267–269], it remains unknown whether SuperAgers may be protected from them.

Large prospective studies are necessary to disentangle the effects of baseline brain structural characteristics, age, and neuropathological markers in SuperAgers; however, results of studies to date are mixed. One group reported slower whole-brain cortical atrophy for 24 SuperAgers compared to cognitively average elderly adults over 18 months, although this study did not take into account Aβ levels [191]. While significant baseline differences were found between 19 successful agers and 70 typical older adults in another study, rates of whole-brain cortical thinning and hippocampal atrophy over an average of 5 years were equivalent between groups [180]; however, this study also reported no association between Aβ deposition and loss of brain volume within the total sample, which

is inconsistent with previous research [23,65,68,267–269] and may be a consequence of the small sample studied. Despite consistent cross-sectional reports that individuals with superior memory performance display relatively preserved brain morphology compared to older adults who are cognitively normal for their age (CNFA) despite varying minimum age criteria, divergent findings in prospective studies highlight the need for larger samples and longer follow-up times to examine age- and Aβ-associated brain morphological changes in SuperAging.

The Australian Imaging, Biomarkers and Lifestyle (AIBL) study is a large prospective cohort in which multiple studies have described Aβ-associated loss of brain volume [23,68,231]. This study is well-positioned to examine whether SuperAgers are resistant to age- and Aβ-associated neurodegeneration compared to CNFA older adults. The first hypothesis was that greater rate of volume loss in white matter (WM), grey matter (GM) and hippocampus would be associated with Aβ+ in CNFA older adults. The second hypothesis was that individuals classified as SuperAgers would display reduced rates of age- and Aβ-associated cortical atrophy compared to CNFA. Finally, to examine the influence of SuperAger classification on cerebrovascular disease markers, this study also explored differences between SuperAgers and CNFA in white matter hyperintensity (WMH) volume and accumulation over time, and whether this was mediated by Aβ.

5.3 Method

5.3.1 Participants

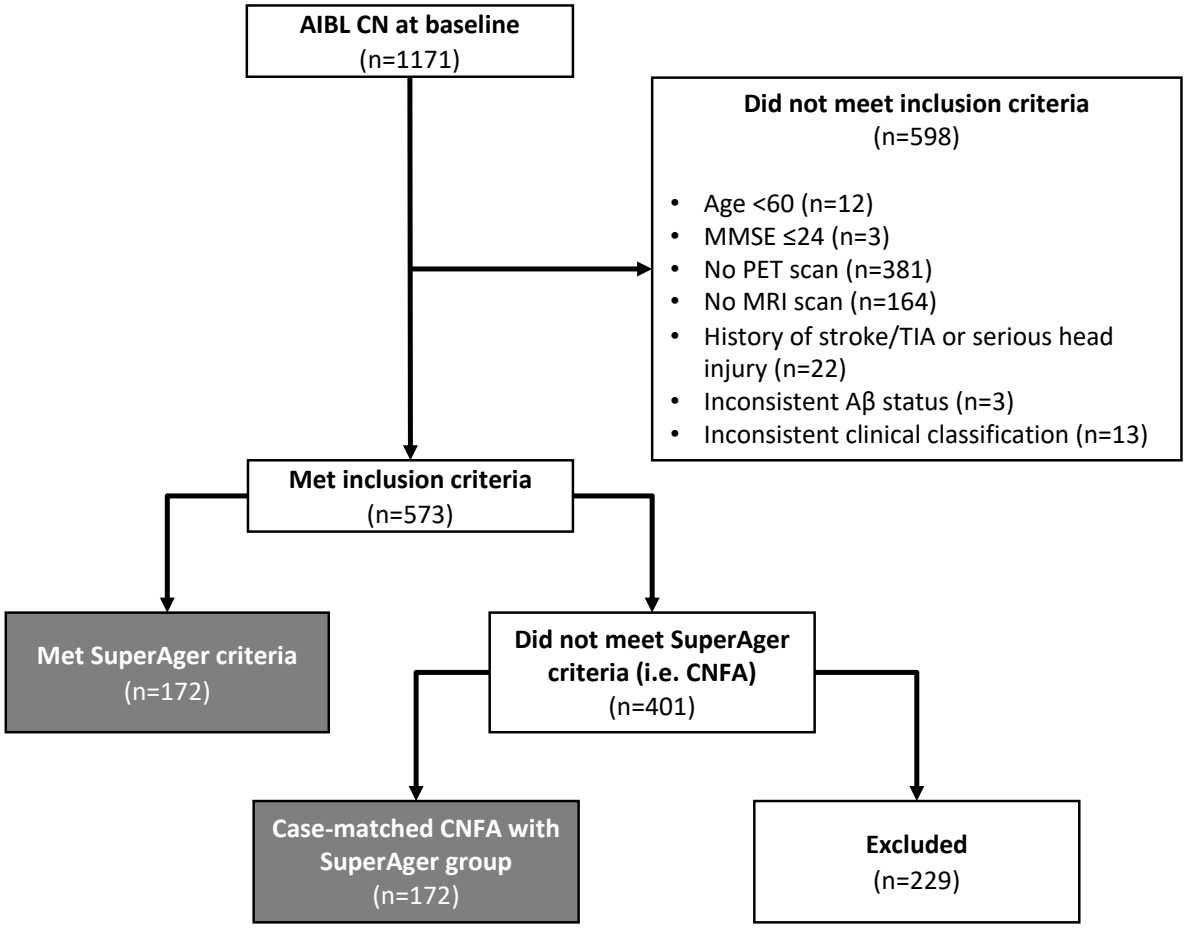
The Australian Imaging, Biomarkers and Lifestyle (AIBL) study protocol has been reported previously [192]. Volunteers were ineligible for enrolment if they met any of the following exclusion criteria: non-AD dementia, history of schizophrenia or bipolar disorder, current

depression (Geriatric Depression Scale score >5), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, obstructive sleep apnea, past head injury with >1 hour of post-traumatic amnesia, or current regular alcohol intake beyond recommended limits [193]. All included participants were identified to have no, or medically well-controlled systemic illnesses at baseline. Ethics approval for the AIBL study was granted by St Vincent's Health, Austin Health and Edith Cowan University, and all participants provided written informed consent at each visit.

5.3.1.1 *Sample selection*

The AIBL study currently includes 611 CN adults who satisfied the baseline inclusion criteria above, were aged over 60 with MMSE>24, and underwent both Aβ PET and MRI neuroimaging. These participants were recruited in two waves: an inception cohort (n=400) followed every 18 months for up to 8 years, and an enrichment cohort (n=211) followed for up to 4.5 years. The sample was further restricted to those who reported no history of stroke, transient ischemic attack (TIA), or serious head injury at baseline (n=589). Participants who were classified with mild cognitive impairment (MCI) or dementia by a clinical panel during the follow-up period were coded as progressors; those whose clinical classification or Aβ status were inconsistent across the study period were excluded to ensure reliability of classification (n=16). Following these exclusions, 172 of the eligible participants were classified as SuperAgers (see criteria below). SuperAgers were then case-matched with the remaining CN participants (i.e. CNFA) based on age, sex, education, follow-up time, and number of serial MRI scans. The final analyses included 344 participants (172 SuperAgers, 172 CNFA; Figure 5-1).

Figure 5-1: Sample selection



5.3.1.2 *SuperAger classification*

Individuals were classified as SuperAgers at baseline using neuropsychological criteria adapted from the Northwestern SuperAging Study criteria as described previously [206]. A greater number of non-memory tests were included in the classification criteria for this study compared to that used in the Northwestern SuperAging Study [185] to increase classification specificity. Classification required performance above the normative average for adults aged 30-44 on the California Verbal Learning Test – Second Edition (CVLT-II) Long Delay Free Recall trial [196] (≥13 for women, ≥12 for men), and performance above -1 SD for their age on all non-memory tests identified to be suitable for the study of cognitive aging: Digit Symbol Substitution Test, Victoria Stroop Test (words trial), Digit Span, letter

fluency (FAS), and category fluency (total animals and male names, and fruit and furniture) [204]. CN participants who were not classified as SuperAgers were classified as CNFA.

5.3.1.3 *Assessment*

A comprehensive neuropsychological battery was administered at each study visit. Medical assessments included anthropometric measures, blood tests, and self-reported medical history (e.g. hypertension) [192]. Education was coded as ≤12 years or >12 years. *APOE* genotype was determined from whole blood extracted DNA as per previously described methodology, and participants were classified as *APOE* ε4 carriers or non-carriers [210].

5.3.2 Neuroimaging

5.3.2.1 *MRI neuroimaging*

Participants underwent a 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence using the following acquisition parameters: in-plane resolution 1×1 mm, slice thickness 1.2 mm, repetition time (TR)/echo time (TE)/inversion time (TI)=2300/2.98/900, flip angle 9°, and field of view (FOV) 240×256. MPRAGE images for all participants were segmented into WM, GM and cerebrospinal fluid using an implementation of the expectation maximization algorithm [214]. Hippocampal extraction was done using a multi-atlas approach based on the Harmonized Hippocampus Protocol [219]. Some participants also underwent a 3D fluid attenuation inversion recovery (FLAIR) sequence (133 SuperAgers, 131 CNFA); therefore, exploratory analyses of WMH were conducted within this sample. Three different sets of FLAIR acquisition parameters were used: 1) in-plane resolution 0.98×0.98 mm, slice thickness 0.9 mm, TR/TE/TI=6000/420/2100, flip angle 120°, FOV 240×256, and 176 slices; 2) in-plane resolution 0.5×0.5 mm, slice thickness 1.0 mm, TR/TE/TI=5000/355/1800, flip angle 120°, FOV 512×512, and 160 slices; 3) in-plane resolution 1.0×1.0 mm, slice thickness 1.0 mm, TR/TE/TI=5000/391/1800, flip angle 120°, FOV 256×256, and 192 slices. WMH were automatically segmented using the HyperIntensity

Segmentation Tool based on an ensemble of pre-trained neural network classifiers [220,221] and quantified from the segmented lesion masks in the common Montreal Neurological Institute space. All measures were corrected for scanner and total intracranial volume.

5.3.2.2 *Amyloid-β PET neuroimaging*

PET neuroimaging was conducted using one of four Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB, n=137), ^{18}F-NAV4694 (NAV, n=38), ^{18}F-Florbetapir (FBP, n=88), or ^{18}F-Flutemetamol (FLUTE, n=81). Detailed PET methods and procedures are described elsewhere [211,212]. Briefly, PET acquisitions were performed up to 90 minutes following tracer injection. Standardized uptake value (SUV) data were summed and normalized to a reference region to generate a SUV ratio (SUVR). Image analysis was done using the MR-less method, CapAIBL [270]. A linear regression transformation was applied to the NAV, FBP and FLUTE SUVRs to create a "PiB-like" SUVR unit called Before the Centiloid Kernel Transformation (BeCKeT) so that SUVRs across the different radiotracers were expressed on the same scale [212]. All particiants with SUVR/BeCKeT$\geq$1.40 at their most recent PET scan were classified as Aβ+ and those below the threshold were classified as Aβ-.

5.3.3 Statistical analyses

R version 3.4.3 [251] and SPSS 23 were used for all statistical analyses, with statistical significance set at $p<0.05$. No adjustments were made for multiple comparisons due to their conservative nature; the early and important stage of this research highlights the importance of encouraging future studies in this area. Therefore, estimates of effect size were computed for all comparisons to guide interpretation of the results (i.e. $d<0.20$ may be due to Type I error). SuperAgers were case-matched with CNFA using the FUZZY extension command in SPSS. Exact matches were required for education and sex. Tolerances for age,

follow-up time and number of serial MRI scans were ±2 years, ±1 visit and ±1 scan, respectively. Eligible matches were selected randomly.

5.3.3.1 *Baseline group differences*

Between-group comparisons by SuperAger classification and Aβ status were conducted using one-way analyses of variance (ANOVAs) and Kruskal-Wallis one-way ANOVAs for continuous variables and Fisher's exact tests for categorical variables. Linear regressions examined baseline differences between groups for each neuroimaging measure with age as a covariate, both before and after case-matching SuperAgers with CNFA.

5.3.3.2 *Assessment of Aβ status and SuperAger classification on longitudinal neuroimaging measures*

Separate linear mixed models (LMMs) were run with each of the neuroimaging measures as dependent measures. Fixed factors were SuperAger classification, Aβ status, time (years from baseline scan), and their interactions. Random intercepts and slopes were calculated for each participant. Covariates were baseline age and progression status; *APOE* ε4 status and number of serial MRI scans did not significantly contribute to the models and were therefore removed.

To test the first hypothesis, the interaction of Aβ status x time was examined only in the CNFA group. To test the second hypothesis, interactions between SuperAger classification, Aβ status and time were examined for the full study sample. Having controlled for baseline age in the analyses, interactions with time were interpreted to reflect changes associated with aging. For each comparison, the magnitude of effect was expressed using Cohen's *d*.

Associations of Aβ+ and SuperAger classification with WMH volume were explored using a gamma generalized linear mixed model (GLMM) fitted with a log link function. The

same fixed and random factors from the LMMs were included in the GLMM. Covariates were baseline age, *APOE* ε4 status and self-reported hypertension.

5.4 Results

Across the 344 SuperAgers and CNFA included in this study, average age was 71 years (range 60-93). The majority had >12 years education (65.1%) and 55.8% were female. Participants were followed for a median of 89 months (interquartile range: 37) with an average of 2 MRI scans each (maximum 6). As expected due to the case-matching parameters, no differences in demographics or follow-up time were observed between the SuperAger and CNFA groups, and prevalence of both Aβ+ and *APOE* ε4 carriage were nearly equivalent (Table 5-1). Compared to the Aβ- group, the Aβ+ group had higher prevalence of *APOE* ε4 carriage (OR: 4.08, 95% CI: 2.47-6.73; $p<0.0005$) and were 2 years older on average [$F(1,343)=10.84$, $p=0.001$; $d=0.36$)]. As previously reported for this sample, SuperAgers were less likely to progress to MCI/dementia compared to CNFA (24 CNFA and 5 SuperAgers; OR: 0.19, 95% CI: 0.07-0.50; $p<0.0005$) [206].

Table 5-1: Baseline group characteristics

	Total sample	CNFA Aβ-	CNFA Aβ+	SuperAger Aβ-	SuperAger Aβ+	Sig. factors
n	344	103	69	102	70	
Aβ PET SUVR	1.51, 1.32 (0.49)	1.21, 1.22 (0.14)	1.97, 1.81 (0.84)	1.21, 1.20 (0.14)	1.92, 1.87 (0.74)	A***
***APOE* ε4 carrier (%)**	27.30	14.60	43.50	17.60	44.30	
Age at baseline	71.75, 71.00 (9)	71.30, 71.00 (7)	73.67, 73.00 (12)	70.57, 70.00 (9)	72.26, 72.00 (7)	A***
Female (%)	55.80	61.20	47.80	57.80	52.90	
Education >12 years (%)	65.10	62.10	69.60	64.70	65.70	
Hypertension (%)	50.30	15.41	12.21	13.08	9.59	
Progressors (%)	8.40	10.70	18.80	2.00	4.30	S***
Number of MRIs	2.47, 2.00 (2.25)	2.49, 2.00 (3)	2.67, 2.00 (2.50)	2.34, 2.00 (3)	2.46, 2.00 (2)	
Length of follow up (months)	71.98, 89.00 (37)	77.97, 90.00 (19)	71.30, 89.00 (37)	70.85, 89.00 (40)	65.46, 89.00 (55)	
Baseline white matter volume (cm^3)	394.24, 394.52 (33.44)	394.40, 394.44 (32.33)	396.48, 397.26 (39.10)	390.49, 392.62 (26.55)	397.28, 398.22 (34.95)	
Baseline grey matter volume (cm^3)	461.10, 461.86 (23.28)	459.83, 461.04 (25.55)	457.97, 457.76 (25.99)	463.45, 465.32 (25.81)	462.61, 462.98 (19.88)	S* ^
Baseline hippocampal volume (cm^3)	2.96, 2.96 (0.34)	2.96, 2.95 (0.35)	2.93, 2.91 (0.40)	2.96, 2.94 (0.34)	2.99, 3.00 (0.31)	
Baseline white matter hyperintensity volume (cm^3)	14.15, 11.43 (5.41)	13.48, 12.01 (11.86)	17.28, 12.74 (11.68)	13.40, 10.99 (4.21)	13.01, 11.80 (4.79)	

Abbreviations used: Aβ = amyloid-beta, *APOE* ε4 = apolipoprotein E epsilon 4 allele, CNFA = cognitively normal for age; A indicates significant effect of Aβ status; S indicates significant effect of SuperAger classification.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$; continuous variables are expressed: mean, median (IQR); categorical variables are expressed as percentages.
^ this difference becomes non-significant when adjusted for age.

5.4.1 Baseline brain morphological differences

Prior to case-matching, significantly greater WM, GM and hippocampal volumes were observed in SuperAgers compared to CNFA. These differences were no longer significant after adding age as a covariate. After case-matching, a significant group difference was found only for GM volume; however, the effect size was small (*d*=0.22) and this became non-significant after adjusting for age. No Aβ group differences were observed on any MRI measure.

5.4.2 Influence of Aβ on brain morphological changes in CNFA older adults

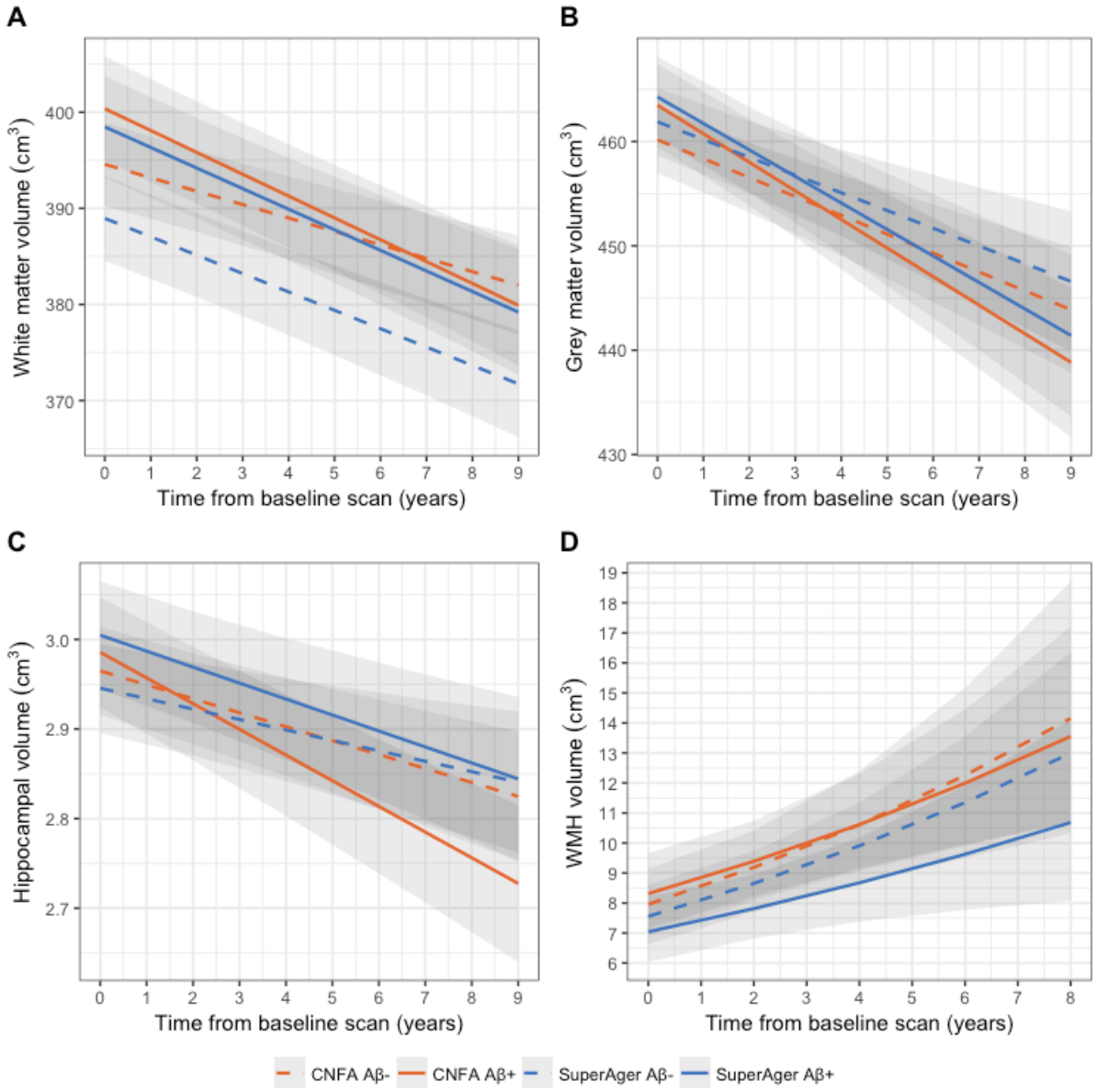
Annualized rate of volume loss within CNFA was 1.37 cm^3 (0.35%) for WM, 1.80 cm^3 (0.39%) for GM, and 0.015 cm^3 (0.52%) for hippocampus. Significant Aβ status x time interactions were observed for all MRI measures. Mean slopes for both Aβ+ and Aβ- CNFA showed that Aβ+ was associated with faster loss of WM, GM, and hippocampal volume over time (Table 5-2). This translates to greater volume loss of 0.88 cm^3 in WM, 0.93 cm^3 in GM and 0.07 cm^3 in hippocampus per year for Aβ+ compared to Aβ- CNFA. Progressors had lower GM and hippocampal volume across all time points. Both older age at baseline and longer time in study were associated with smaller WM, GM and hippocampal volumes.

Table 5-2: Annualized group mean slopes and Cohen's d for Aβ-associated neurodegeneration in CNFA

	Aβ-	Aβ+	Cohen's *d*	Lower 95% CI	Upper 95% CI
White matter volume	-1.40 (2.16)	-2.27 (2.05)	0.42	0.11	0.72
Grey matter volume	-1.81 (3.00)	-2.74 (2.85)	0.32	0.01	0.62
Hippocampal volume	0.04 (0.57)	-0.03 (0.03)	0.17	-0.14	0.47

Presented as mean slopes (SD). Abbreviations used: Aβ- = cerebral amyloid-beta within normal range (PET SUVR<1.40); Aβ+ = elevated cerebral amyloid-beta; CI = confidence interval; CNFA = cognitively normal for age; SD = standard deviation.

Figure 5-2: Morphological changes over time by SuperAger and Aβ status



Abbreviations used: Aβ- = cerebral amyloid-beta within normal range (PET SUVR<1.40); Aβ+ = elevated cerebral amyloid-beta; CNFA = cognitively normal for their age; WMH = white matter hyperintensity

Slopes for Aβ+ (solid lines) were significantly steeper than slopes for Aβ- (dashed lines) for white matter, grey matter and hippocampal volumes (panels A-C). No difference in slopes between CNFA (orange lines) and SuperAgers (blue lines) was observed for any measure.

5.4.3 Influence of SuperAger classification and Aβ on brain morphological changes

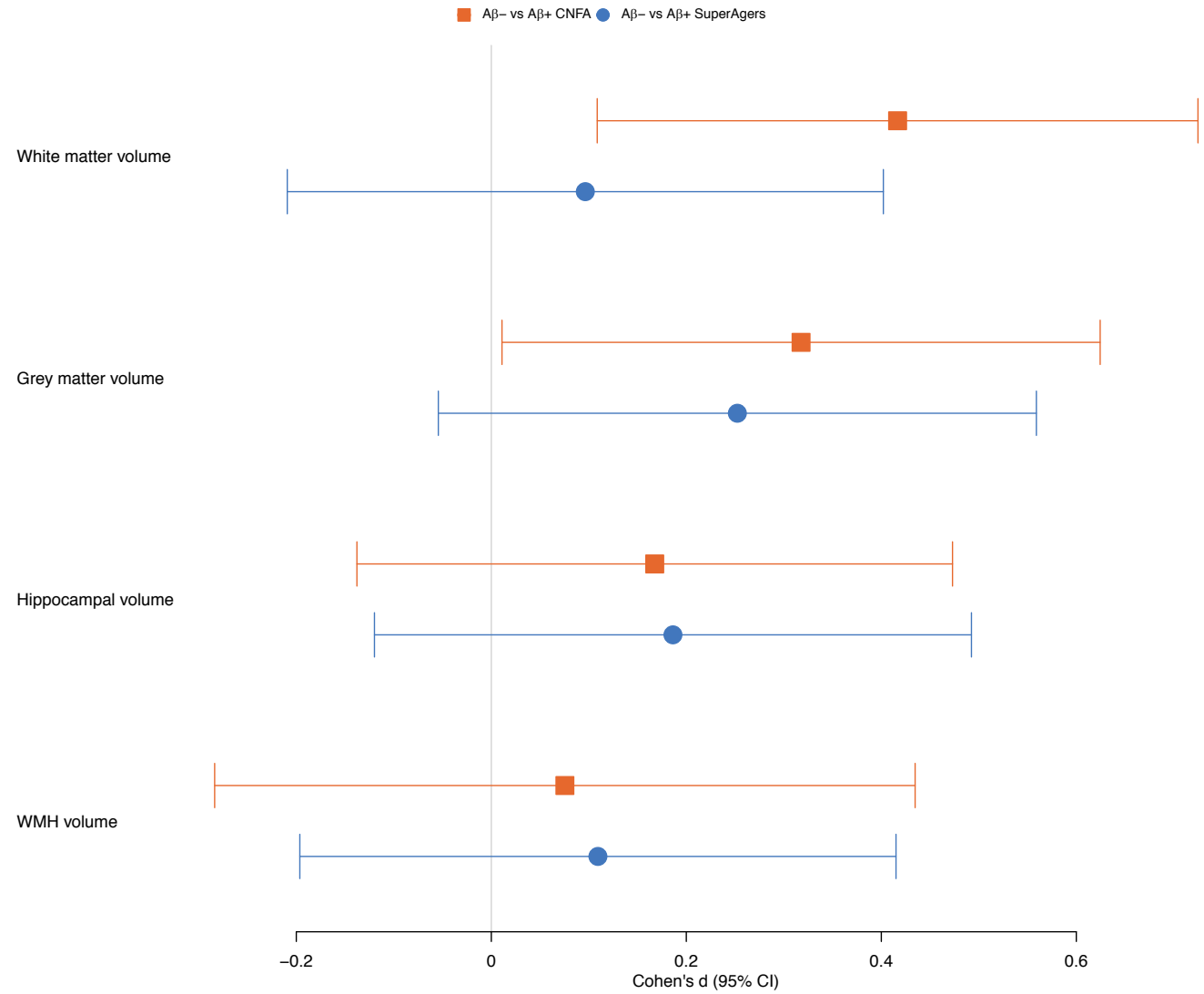
The LMM results for WM, GM and hippocampal volume for the full study sample are summarized in Table 5-3. Mean slopes for each of the morphological measures are shown graphically in Figure 5-2. The Aβ status x time interaction remained significant for all MRI

measures after accounting for SuperAger classification. However, the SuperAger status x Aβ status x time interaction was not statistically significant for any MRI measure. Slopes were not significantly different between SuperAgers and CNFA within the Aβ- and Aβ+ groups, nor were they different between Aβ groups within the SuperAger and CNFA groups. Figure 5-3 shows that Aβ+ was associated with greater volume loss over time in both SuperAger and CNFA groups for each MRI measure but there was substantial overlap in the 95% confidence intervals for each effect size. The two-way interaction of SuperAger classification x time was not significant for any morphological measure with data collapsed across Aβ groups. Although there was a significant main effect of baseline age on all measures, no interactions with age were observed. Analyses restricted to participants over age 80 were not conducted due to small cell sizes.

5.4.4 Exploratory analyses of SuperAger classification and Aβ on WMH

No baseline differences were observed between SuperAger or Aβ groups. WMH accumulation increased at an average rate of 7% per year for all participants. Older age at baseline and longer time in study were associated with increased WMH volume (Table 5-3). No main effect of Aβ status nor SuperAger classification were observed, and no interactions with time were observed.

Figure 5-3: Comparison of effect sizes for rates of Aß-associated atrophy



Abbreviations used: Aβ- = cerebral amyloid-beta within normal range (PET SUVR<1.40); Aβ+ = elevated cerebral amyloid-beta; CNFA = cognitively normal for age; WMH = white matter hyperintensity.

Substantial overlap in the 95% CIs for each effect size reflects no difference in the slopes of Aβ-associated volume loss between the SuperAger and CNFA group.

Table 5-3: Mixed model parameters

	White matter volume+			Grey matter volume+			Hippocampal volume+			WMH volume^		
	Estimate	Std. Error	*p*	Estimate	Std. Error	*p*	Estimate	Std. Error	*p*	Estimate	Std. Error	*p*
Intercept	500.96	15.34	<0.001	570.81	11.40	<0.001	4.03	0.18	<0.001	0.59	0.53	0.27
SuperAger classification	-5.62	3.14	0.07	1.72	2.29	0.45	-0.02	0.04	0.59	0.19	0.13	0.13
Aβ status (-/+)	5.79	3.52	0.10	3.32	2.57	0.20	0.02	0.04	0.60	0.28	0.14	0.05
Time	-1.40	0.21	**<0.001**	-1.81	0.30	**<0.001**	-0.02	0.00	**<0.001**	0.07	0.02	**<0.001**
Baseline age	-1.49	0.21	**<0.001**	-1.54	0.16	**<0.001**	-0.01	0.00	**<0.001**	0.02	0.01	**0.002**
Progression	-6.04	4.34	0.16	-11.18	3.25	**<0.001**	-0.13	0.05	**0.01**	0.20	0.15	0.17
***APOE* ε4 carrier status (-/+)**	-	-	-	-	-	-	-	-	-	0.11	0.10	0.25
Hypertension (-/+)	-	-	-	-	-	-	-	-	-	0.07	0.08	0.37
SuperAger * Aβ status	3.73	4.91	0.45	-0.94	3.58	0.79	0.04	0.06	0.49	-0.32	0.20	0.10
SuperAger * Time	-0.52	0.32	0.11	0.11	0.45	0.81	0.00	0.00	0.38	-0.03	0.03	0.29
Aβ status * Time	-0.88	0.33	**0.01**	-0.93	0.45	**0.04**	-0.01	0.00	**0.004**	-0.02	0.03	0.45
SuperAger * Aβ status * Time	0.65	0.49	0.19	0.09	0.69	0.90	0.01	0.01	0.31	0.02	0.04	0.70

Abbreviations used: Aβ = amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele.
+ Analyzed using a linear mixed model, total n=344.
^ Analyzed using a gamma generalized linear mixed model fitted with a log link function, total n=264.

5.5 Discussion

The first hypothesis, that Aβ+ was associated with greater loss of volume in WM, GM and hippocampal structures in older adults classified as CNFA, was supported. These data are consistent with previous findings from the AIBL cohort and others that Aβ+ is associated with GM loss and hippocampal atrophy in CN individuals [23,65,68,267–269]. The second hypothesis, that individuals classified as SuperAgers would display reduced rates of age- and Aβ-associated cortical atrophy compared to CNFA, was not supported: no differences between SuperAgers and CNFA were observed for rates of Aβ-associated atrophy (Figure 5-2, Figure 5-3). Furthermore, no differences were observed for age-associated brain volume loss between SuperAger and CNFA despite controlling for Aβ. Exploratory analyses of WMH also showed no differences between SuperAgers and CNFA in baseline WMH volume nor rate of accumulation, and neither were influenced by Aβ status. Taken together, the results indicate that SuperAger classification based entirely on neuropsychological criteria does not reflect any unique protection from age- or Aβ-associated neurodegeneration or cerebral small vessel disease.

The SuperAging construct was developed to describe a phenotype of preserved cognitive function in older age that may reflect unique neurobiological characteristics such as protection from neurodegeneration and consequent cognitive decline in aging. This notion was supported by early cross-sectional studies conducted in small samples of SuperAgers [185,188–190,271]. Consistent with past reports, the present study observed significantly greater WM, GM and hippocampal volumes in SuperAgers at baseline prior to case-matching with CNFA, but these differences were not maintained after adjusting for age. SuperAging studies have not adjusted for age for cross-sectional analyses, although

only one morphological study of successful agers did so for longitudinal analyses [180]; therefore, it is possible that the reported findings may be confounded by demographic characteristics rather than reflecting true group differences. Furthermore, prospective findings have been mixed, potentially because of limited power to conduct longitudinal analyses due to small sample sizes [180,191]. The finding that individuals classified as SuperAgers were not any more protected against age- or Aβ-associated atrophy than CNFA regardless of baseline age does not support the conclusion that maintenance of cognitive abilities from mid-life to late-life reflects preservation of brain structure in aging [180,185,187,189–191]. These early studies provide important and provocative foundations for models of SuperAging; however, the use of small samples and lack of adjustment for age may limit the generalizability of their conclusions due to low statistical power, potential for sampling bias and Type I error.

In contrast to a previous report of successful agers [180], the present study observed similar levels of WMH between SuperAgers and CNFA both cross-sectionally and longitudinally that was not modified by Aβ status. This may reflect a larger sample with strict exclusion of high vascular risk factors. Additionally, the previous study measured WM hypointensities using T1-weighted images, which can result in lower volume estimates compared to the 3D FLAIR sequences used here to measure WMH [272]. The lack of association between Aβ status and WMH observed in the present study is, however, consistent with reports that Aβ and WMH accumulation reflect independent processes whose deleterious effects on cognition are additive [238,273,274].

Limitations to the generalizability of these results are related to the experimental nature of the AIBL cohort; due to rigorous inclusion criteria, AIBL participants are healthier and more educated than the general population [275]. Not enough information is available

to ascertain the prevalence of SuperAgers in the general population although experimental cohorts have reported rates of 17.3-42.5% in their respective samples [180,189]. Taking into account sample and survivor biases, it may not be unexpected that 30% of the CN AIBL cohort were classified as SuperAgers despite differences in age criteria and using more stringent neuropsychological criteria compared to other studies [180,185,189]. Unfortunately, operational definitions of successful aging lack consistency between studies [167], which is also the case in studies of youthful memory performance or "SuperAging". Comparisons between studies may thus be limited despite similar goals; however, a strength of the present study was case-matching SuperAgers with CNFA to ensure that the results adequately captured differences due to neuropsychological classification. Whole-brain and hippocampal volumetric measures were most appropriate for the aims of this study due to the increased likelihood of widespread cortical Aβ deposition in Aβ+ individuals [276]. Future studies should conduct region of interest and surface-based analyses of longitudinal morphological change due to Aβ in SuperAgers to determine whether cortical regions reported to be relatively preserved (e.g. anterior cingulate) are protected from Aβ-associated neurodegeneration [180,183,189,190]. Furthermore, although previous studies have suggested that Aβ-associated neurodegeneration occurs only in the presence of elevated tau [260] or that neurodegeneration is more strongly associated with tau than with Aβ [277], this study did not include measures of tau, which future studies should endeavor to do.

5.6 Conclusions

Despite significant differences in baseline cognitive ability, individuals in the AIBL CN cohort classified as SuperAgers displayed similar levels of AD neuropathological markers such as

Aβ+ compared to CNFA. While this may be suggestive of some resilience to the effects of Aβ, SuperAgers and CNFA displayed similar rates of cognitive and morphological change due to both age and Aβ over 8 years [206]. Therefore, defining SuperAging on the basis of neuropsychological criteria alone has limited ability to identify individuals who are uniquely protected from the effects of age or neuropathological changes. The results of this study suggest that the most advantageous characteristic for attenuated brain volume loss in older adults was to have reached old age without elevated Aβ deposition.

Chapter 6: Examining the moderating effect of amyloid-β on associations between cortical volume loss and cognitive change in cognitively normal older adults

6 Examining the moderating effect of amyloid-β on associations between cortical volume loss and cognitive change in cognitively normal older adults

6.1 Introduction

Studies of cognitive aging generally conclude that older age is associated with cognitive decline across multiple domains, such as memory and executive function [114]. For example, a recent meta-analysis of cognitive aging studies found evidence of systematic decline in cognitive function beyond age 60 on measures of global cognition (-0.12 SD/decade), memory (-0.23 SD/decade), executive function (-0.23 SD/decade), language (-0.16 SD/decade), and processing speed (-0.26 SD/decade) [119]. Further, neuroimaging studies have consistently shown that whole brain and regional cortical volumes become smaller as a function of increasing age [160,278]. Although rates of volume reduction vary across brain regions, average annual cortical volume losses of about 0.50% have been reported in healthy elderly [151,278,279]. Taken together, typical models of cognitive and brain aging suggest that some cognitive decline and cortical volume loss is normal in aging; however, recent evidence suggests it is now necessary to consider a more precise definition of "aging".

Studies examining trajectories of cognitive and cortical volume change in aging may inadvertently include participants with preclinical Alzheimer's disease (AD), which is classified by the presence of abnormally high levels of cerebral amyloid-β (Aβ+) in cognitively normal (CN) older adults [32]. Aβ+ can be detected *in vivo* either via positron emission tomography (PET) scanning or through cerebrospinal fluid sampling up to 30 years

prior to the appearance of any observable cognitive impairment or dementia [22,23,126]. Approximately 16-44% of CN adults aged 60-90 are Aβ+ [22], and display progressive decline in cognitive functions such as memory and executive function [61,62]. Given the prevalence of Aβ+ and its negative effects on cognition, rates of age-associated decline are likely to have been overestimated due to inclusion of Aβ+ participants in prospective cohort studies of cognitive aging. Our group has previously observed that rate of age-associated verbal memory decline was overestimated by 0.02 SD/year when Aβ status was not taken into consideration, and no decline in memory due to age was observed after statistically controlling for Aβ+ [145]. Similarly, studies examining Aβ-associated differences in cognitive trajectories have reported little-to-no decline in memory and executive function for older adults with levels of Aβ below the clinical threshold (Aβ-) over periods of 5-10 years [66,71,147,206]. These findings in addition to those presented in Chapter 4 of this thesis suggest that cognition may not normally decline as part of aging, and that previous estimates [119] were biased by the inadvertent inclusion of individuals with preclinical AD in study samples [145].

It is also possible that inclusion of Aβ+ older adults in studies of brain aging with otherwise CN samples has led to overestimating the influence of age on cortical volume loss. Cortical volume loss has been observed for Aβ- older adults at substantially reduced rates compared to those who are Aβ+ [63–68; Chapter 5]. For example, one study reported an annual whole brain atrophy rate of 0.35% for Aβ- older adults who remained CN for at least 3 years [63], suggesting that previously reported rates of 0.50% whole brain atrophy per year were overestimated by inclusion of both Aβ- and Aβ+ participants. While loss of cortical volume in Aβ+ individuals may be related to neuropathological changes associated with AD [68], observations that cortical volume does continue to reduce in Aβ- individuals

suggests that cortical volume loss does normally occur in the process of aging; however, no studies have yet sought to investigate how the presence of occult neurodegenerative disease can influence models of brain aging. Converging evidence to date suggests that Aβ+ is associated with both cognitive decline and cortical volume loss, and not controlling for this in aging study samples may lead to overestimated rates of age-associated change in these measures.

Age-associated cognitive decline may be attributable to concomitant cortical volume loss in aging [114,122,280–282]. Observed trajectories of cortical atrophy and cognitive decline for Aβ+ older adults are consistent with this theory; however, no age-associated memory changes are observed in CN Aβ- older adults despite the presence of cortical and hippocampal atrophy. This dissociation was also evident in the results from Chapters 4-5 and suggest that relationships between cortical volume and cognitive change in CN older adults may be moderated by Aβ. No studies have yet examined whether longitudinal relationships between cortical volume and cognitive change are different between Aβ- and Aβ+ samples, but such an investigation may provide insight into why some studies of CN older adults report associations between whole brain or hippocampal volume loss and rate of decline on global cognition, verbal memory or executive function [63,153,283–288], and others do not [289–292] (Table 6-1).

Preservation of cognitive function in the presence of cortical and hippocampal volume loss in Aβ- may be explained by at least two mechanistic and methodological considerations. Mechanistically, this dissociation may reflect some brain reserve that supports preservation of cognition despite progressive age-associated cortical atrophy [52,293]. The theory of brain reserve suggests that cognitive decline occurs only after volume loss reaches a certain threshold, and that individuals with greater brain reserve

would take longer to reach that threshold [52]. A second possible mechanism for these findings is that general cortical volume loss observed on magnetic resonance imaging (MRI) in aging does not specifically reflect neurodegenerative processes necessary to affect cognitive functioning, such as neuronal death [294,295]. These possibilities suggest that cortical volume loss in the absence of neuropathological changes associated with AD is not associated with changes in cognitive function, and that cognitive decline is not a normal part of aging.

However, it may be that cognition, like cortical volume, does decline with age. Repeated administration of neuropsychological tests may give rise to performance improvements (i.e., practice effects) that mask true age-associated cognitive decline, even at retest intervals of 12-18 months [296–298]. Previous studies have reported that poorer practice effects are associated with elevated Aβ, which suggests that the difference between Aβ- and Aβ+ memory trajectories may be inflated by the respective presence and absence of practice effects [299–302]. Therefore, observing no association between concurrent measures of cortical volume and cognitive change may instead reflect the superimposition of a practice effect on cognitive performance. Finally, it may be that describing average rates of cortical and cognitive change at the group level does not adequately reflect intra-individual relationships between these measures. If this is the case, then intra-individual associations between these measures will be observed and suggest that cognitive decline does occur in tandem with age-associated cortical volume loss.

This study aimed to examine relationships between concurrent changes in cortical volume (white matter (WM), grey matter (GM) and hippocampus) and cognition (verbal memory and executive function) in CN older adults with and without evidence of AD neuropathological changes (i.e. Aβ- and Aβ+). Verbal memory and executive function were

selected because the results of Chapter 4 indicated that trajectories of cognitive change in these two domains were different between the Aβ groups. It was first necessary to confirm that rates of cortical volume and cognitive change were different between the Aβ- and Aβ+ groups in the present sample without consideration of SuperAging status as had been done in the previous two chapters of this thesis. We hypothesized that associations between cortical volume loss and cognitive change in CN older adults would be moderated by Aβ status. The presence or absence of these associations were then explored within both Aβ groups, and the findings were interpreted with respect to the implications for models of cognitive and brain aging.

Table 6-1: Review of relevant findings in previous research examining longitudinal associations between cortical volume change and cognitive change

							Reported associations between cortical volume change and cognitive change			
Cohort	**Diagnostic groups**	**n**	**BL age**	**# of visits**	**Follow up time**	**Statistical methods**	**Δ Whole brain**	**Δ GM**	**Δ Hippocampus**	**Notes and references**
Minimum Interval Resonance Imaging in Alzheimer's Disease (MIRIAD)	Probable sporadic AD	46	55+	7	1 year	Correlations	*MMSE: p*=0.55 *VM: p*=0.28 *Visual memory: p*=0.52			[303]
Memory clinic patients	CN, MCI, AD	10 CN 27 SCD 45 MCI 65 AD	50-87	2	0.92-4.17 years (mean 1.8 years)	Correlations	**MMSE:** *r*=0.48, *p*<0.001 <u>Subgroups</u> *No association with MMSE for CN or SCD* **MMSE (MCI):** *r*=0.33, *p*<0.05 **MMSE (AD):** *r*=0.34, *p*<0.01			[289]
Singapore-Longitudinal Aging Brain Study (SLABS)	CN	111	56-83	5	8 years	Correlations	**Global cognition:** *r*=0.35, *p*<0.001 **VM:** *r*=0.24, *p*=0.02	**Global cognition:** *r*=0.35, *p*<0.001	**Global cognition:** *r*=0.21, *p*=0.04 **VM:** *r*=0.21, *p*=0.03 **EF:** *r*=0.22, *p*=0.03	[283]
The Betula Study	CN	155	55-80	2 MRI 6 nψ	4 years MRI 15 years nψ	Correlations			**Episodic memory:** *r*=0.35, *p*<0.05	[285]
Study specific cohort	Probable AD	29	Mean 58.1	2+	0.42-6 years	Correlations		**MMSE:** r=0.80, p<0.001		[304]
Mayo Alzheimer's Disease Patient Registry (ADPR) and Alzheimer's Disease	CN, MCI, AD	55 CN 41 MCI 64 AD	52-94		Up to 5 years (up to 2.5 for AD)	Correlations	<u>CN</u> **MMSE:** ρ=0.37, *p*=0.01 **VM:** ρ=0.37, *p*=0.01		<u>CN</u> *MMSE:* ρ=0.14, *p*=0.35 *VM:* ρ=0.29, *p*=0.05	[153]

Research Center (ADRC)							*EM:* ρ=0.22, *p*=0.16 MCI **MMSE:** ρ=0.38, *p*=0.02 *EM:* ρ=0.29, *p*=0.07 AD **MMSE:** ρ=0.47, *p*<0.05		*EM:* ρ=0.10, *p*=0.51 MCI *MMSE:* ρ=0.22, *p*=0.19 *EM* ρ=-0.03, *p*=0.88 AD **MMSE:** ρ=0.35, *p*=0.01	
Study specific cohort	CN women	25	50+, mean 60.6	2	2 years	Correlations			*All 14 cognitive measures:* mean *r*=0.02 (range -0.29 to 0.28), all *p*>0.05	[290]
Alzheimer's Disease Neuroimaging Initiative (ADNI)	CN, MCI	90 CN 103 MCI	55-90	2	2 years	Correlations			**Left medial temporal lobe and verbal memory (MCI):** *r*=0.30, *p*<0.001	*No significant correlations for CN between any cortical and cognitive measures* [291]
Recruited from 3 academic dementia centres	CN	50	Mean 73.9	2	1.1-6.8 years (mean 3.75)	Hierarchical multiple regression		*Memory:* β=0.23, *p*=0.10 **EF:** β=0.37, *p*=0.003	**Memory:** β=0.28, *p*=0.048 *EF:* β=0.14, *p*=0.24	[284]
ADNI	CN	132	60-90	2	1 year	Hierarchical multiple regression			**Memory (learning):** β=0.25, *p*<0.01 **Memory (recall):** β=0.28, *p*<0.005	[63]
Three-City Study	No dementia	306	66.5-81.9 (mean 72.7)	2 MRI 5 nψ	4 years MRI 12 years nψ	Multiple linear regressions			**Memory:** *q*<0.05 FDR corrected	Analysis done with combined bilateral amygdala-hippocampus complex and parahippocampal region, not just hippocampus alone [286]

Women's Healthy Ageing Project (WHAP)	CN	23	Mean 59.4	2	10 years	Linear regression	**VEM:** β=-0.59, *p*=0.008 *EF:* β=-0.16, *p*=0.87		**VEM:** β=-0.61, *p*=0.02 *EF:* β=-0.35, *p*=0.56	% atrophy coded as positive (hence negative associations) [287]
Austrian Stroke Prevention Study	N/A	292	Mean 60	3	Up to 6 years	Generalized estimating equation	**Memory:** β=8.61, *p*=0.0001 **Attention/speed:** β=4.51, *p*=0.0001			[288]
Australian Imaging Biomarkers and Lifestyle (AIBL) Study	CN, MCI	178 CN 49 MCI	60+	3	3 years	Joint latent growth curve models			**Learning/working memory:** β=-0.03, *p*=0.03	Negative association [305]
Lothian Birth Cohort 1936	No dementia	461-465	Mean 69.5	2	3 years	Latent difference score model	*Memory: r*=-0.09, *p*=0.021 **Speed:** *r*=0.15, *p*=0.04	*Memory: r*=0.04, *p*=0.56 **Speed:** *r*=0.18, *p*=0.01		Association between Δ whole brain and Δ speed was n.s. after excluding MMSE <24 [306]
Study specific cohort	CN	90	19-79 (mean 52.8)	2	2 years	Latent change score models			*Unrelated to cognitive change* (no parameters reported)	[292]
Multi-center study	Normal, impaired, demented	103	56-87	2 to 6+	1-9 years (mean 4.8)	Multivariate growth models		*Memory:* B=-1.62, *p*=0.14 **EF:** B=1.71, *p*=0.04	**Memory:** B=5.72, *p*=0.002 **EF:** B=4.01, *p*=0.004	Results were the same when people with dementia excluded from analyses [307]
UC Davis Aging Diversity Cohort	CN, MCI, dementia	295	60+, mean 74.5	2+	Not reported. Up to 9 years?	Parallel process longitudinal analyses		**Global cognitive change:** B=0.06, *p*=0.001		[308,309]

Abbreviations used: Δ = change in; AD = Alzheimer's disease; BL = baseline; CN = cognitively normal; EF = executive function; EM = episodic memory; GM = grey matter; nψ = neuropsychology; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; VM = verbal memory; VEM = verbal episodic memory.

Notes: Bolded indicates significant associations, italics indicates non-significant associations. Only associations for whole brain, total grey matter and hippocampal volume change with either memory, executive function or global cognition were reported here. Some studies may have done more extensive analyses with more brain areas or cognitive domains.

6.2 Methods

6.2.1 Participants

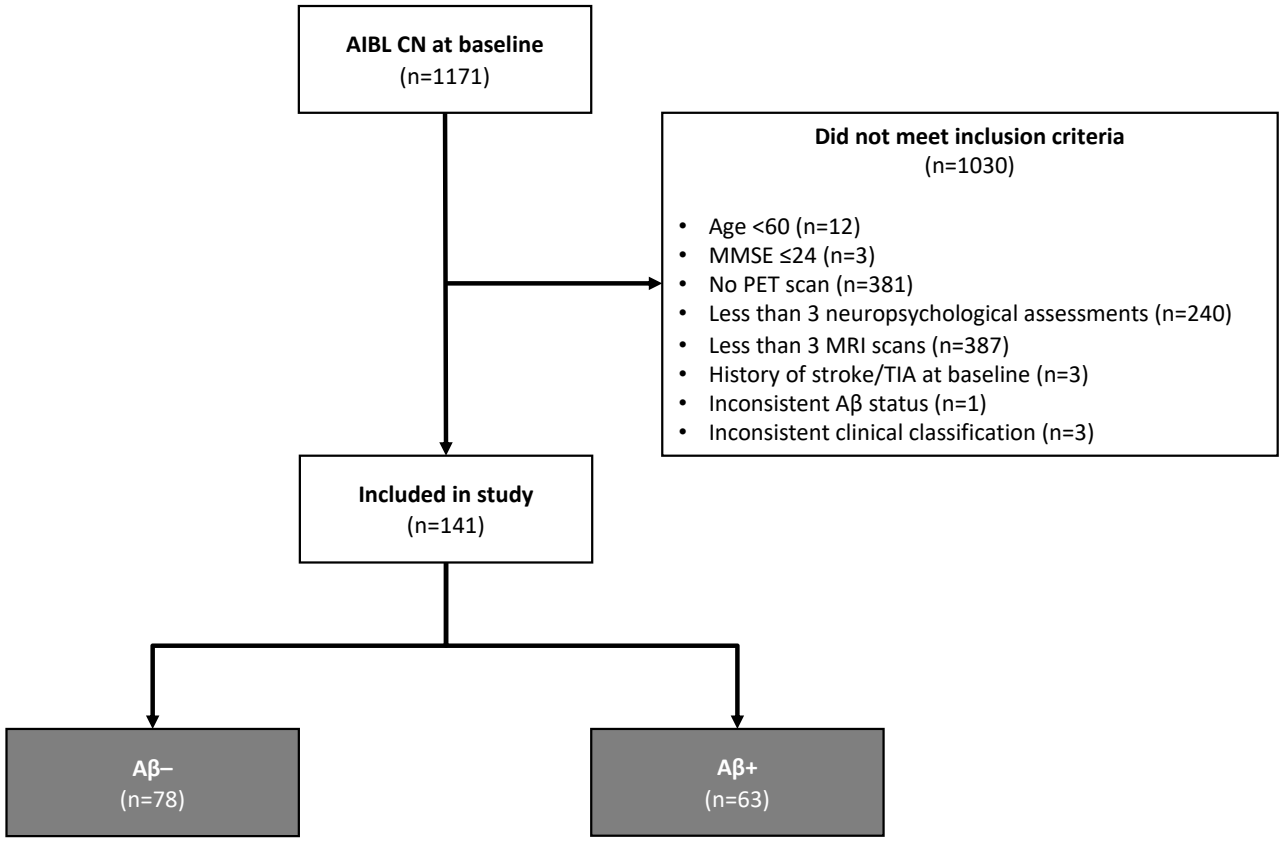
Participants were from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. The full study protocol is reported elsewhere [192]. Briefly, volunteers were ineligible for enrolment if they met any of the following exclusion criteria: non-AD dementia, history of schizophrenia or bipolar disorder, current depression (Geriatric Depression Scale score >5), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, obstructive sleep apnea, past head injury with >1 hour of post-traumatic amnesia, or current regular alcohol intake beyond recommended limits [193]. All included participants were identified to have no, or medically well-controlled systemic illnesses at baseline (described in [145]). Ethics approval for the AIBL study was granted by St Vincent's Health, Austin Health and Edith Cowan University, and all participants provided written informed consent at each visit.

6.2.2 Sample selection

The AIBL study currently includes 148 CN adults who satisfied the baseline inclusion criteria above and also met the following additional criteria: aged over 60 at baseline, baseline MMSE>24, had undergone an Aβ positron emission tomography (PET) scan, and completed at least three neuropsychological assessments and three structural magnetic resonance imaging (MRI) scans. These participants were recruited in two waves: an inception cohort (n=141), which was assessed every 18 months for up to 8 years, and an enrichment cohort (n=7), which was assessed every 18 months for up to 4.5 years. The sample was further restricted to those who reported no history of stroke, transient ischemic attack, or serious head injury at baseline (n=145). Participants who were classified with mild cognitive

impairment (MCI) or dementia by a clinical panel during the follow-up period were classified as progressors. Individuals whose clinical classification or Aβ status were inconsistent across the study period were excluded to ensure reliability of clinical and Aβ status classification (n=4). The final sample included a total of 141 participants (78 Aβ- and 63 Aβ+). See Figure 6-1.

Figure 6-1: Sample selection figure



6.2.3 Clinical and neuropsychological assessment

All participants underwent a comprehensive neuropsychological battery and medical assessments that included measurement of vital signs (height, weight, blood pressure, and

abdominal circumference), blood tests, and self-reported medical history (e.g. hypertension) at each study visit [192]. Apolipoprotein E (*APOE*) genotype was determined from whole blood extracted DNA as per previously described methodology and participants were classified as *APOE* ε4 carriers or non-carriers [210]. Full-scale IQ was estimated from baseline performance on the Wechsler Test of Adult Reading (WTAR) [198].

Composite cognitive scores were calculated for each participant visit by averaging z-scores for each cognitive domain relative to the full CN AIBL sample at baseline [145,206]. The verbal memory composite included the Long Delay Free Recall, and Immediate Recall Trials 1-5 from the California Verbal Learning Test second edition (CVLT-II), and Logical Memory II (only Story A from the Wechsler Memory Scale). The executive function composite included category fluency (total animals and male names, and fruit and furniture), letter fluency (FAS), the Victoria Stroop Test (words trial), and the Digit Symbol Substitution Test. These were the same measures used in Chapter 4.

6.2.4 Neuroimaging

6.2.4.1 *MRI neuroimaging*

All participants underwent a 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence using the following acquisition parameters: in-plane resolution 1×1 mm, slice thickness 1.2 mm, repetition time (TR)/echo time (TE)/inversion time (TI) = 2300/2.98/900, flip angle 9°, field of view (FOV) 240×256. MPRAGE images for all participants were segmented into WM, GM and cerebrospinal fluid using an implementation of the expectation maximization algorithm [214]. A multi-atlas approach based on the Harmonized Hippocampus Protocol was used to extract the hippocampus [219]. All measures were corrected for scanner and total intracranial volume using ordinary least squares regression. These were the same measures used in Chapter 5.

6.2.4.2 *Amyloid-β PET neuroimaging*

PET neuroimaging was conducted using one of four Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB, n=137), ^{18}F-NAV4694 (NAV, n=38), ^{18}F-Florbetapir (FBP, n=88), or ^{18}F-Flutemetamol (FLUTE, n=81). Detailed PET methods and procedures are described elsewhere [211,212]. Briefly, PET acquisitions were performed up to 90 minutes following tracer injection. Standardized uptake value (SUV) data were summed and normalized to a reference region to generate a SUV ratio (SUVR). Image analysis was done using the MR-less method, CapAIBL [270]. A linear regression transformation was applied to the NAV, FBP and FLUTE SUVRs to create a "PiB-like" SUVR unit called Before the Centiloid Kernel Transformation (BeCKeT) so that SUVRs across the different radiotracers were expressed on the same scale [212]. All participants with SUVR/BeCKeT≥1.40 at their most recent PET scan were classified as Aβ+ and those below the threshold were classified as Aβ-. This ensured that the Aβ+ group included any participants who were initially Aβ- but were later classified as Aβ+. These classifications are consistent with those used in all previous chapters.

6.2.5 Statistical analyses

R version 3.4.3 [251] and MPlus were used for all statistical analyses, with statistical significance set at $p<0.05$. No adjustments were made for multiple comparisons to minimize the risk of Type II error. To address multiplicity, estimates of effect size (Cohen's *d* and β coefficients) were computed for all comparisons and guided interpretation of the results in addition to statistical significance.

6.2.5.1 *Baseline group differences*

Between-group comparisons by Aβ status were conducted using one-way analyses of variance (ANOVAs) or Kruskal-Wallis tests for continuous variables, and Fisher's exact tests for categorical variables.

6.2.5.2 *Confirmatory analyses of differential cortical volume and cognitive changes between Aβ groups*

To confirm that trajectories were different between the Aβ- and Aβ+ groups used in the current sample, linear mixed models (LMMs) were conducted in turn for both of the composite cognitive scores (verbal memory and executive function) and all three of the MRI measures (WM, GM and hippocampal volume). For each LMM, time (years from baseline neuropsychological assessment or MRI scan) and Aβ status (-/+) were entered as fixed factors, as well as the interaction between time and Aβ status. Participant was entered as a random factor with random intercepts and slopes. Covariates were baseline age and progression status. *APOE* ε4 carrier status did not contribute significantly to the models and was therefore removed. To describe rates of change for the full sample without consideration to Aβ status, the above LMMs were conducted without Aβ status or its interaction with time in the model.

Because baseline age was added to these models, any effects of time reflected changes in the relevant outcome measure associated with increasing age. Significant differences in trajectories for the cortical volume and cognitive measures were determined by the presence of a Aβ status x time interaction for each model.

6.2.5.3 *Rates of intra-individual change (i.e. slopes)*

After confirming the presence of different trajectories for cortical volume and cognitive change between Aβ groups, the relationships between concurrent changes in cortical volume and cognition were then investigated. To achieve this, individual slopes for each measure (WM, GM, hippocampus, verbal memory and executive function) were derived from LMMs conducted separately for the Aβ- and Aβ+ groups. In each LMM, time was included as a fixed factor with random intercepts and slopes. No other covariates or fixed factors were included in order to calculate unadjusted slopes. Linear models showed the

best fit compared to non-linear models, and no difference in amount of variance explained was observed between linear and quadratic models; therefore, it was appropriate to model the changes over time as a linear function.

6.2.5.4 *Relationships between changes in cortical volume and cognition*

The main hypothesis for this study was examined by submitting the slopes for each measure to a series of simultaneous multiple regression analyses. Structural equation modelling software (Mplus) was used to examine the relationships between changes in cortical volumes and cognition while simultaneously modelling the inter-relationships among baseline measurements and change variables. In each regression analysis, the cognitive slope was regressed onto the corresponding baseline cognitive measure and the three baseline cortical volume measures (WM, GM, hippocampal volume). Following this, the slope of cognitive change was regressed with the three cortical volume slopes to identify the presence of any associations between cortical volume and cognitive changes. The three cortical volume measures were included simultaneously in each regression analysis to ensure that significant associations between any cortical volume measure and cognitive composite reflected specific associations independent of general changes in cortical volume. The analyses were first run in the full sample without consideration to Aβ status to examine these relationships in a CN sample. The analyses were then run again with Aβ status as a dichotomous moderator variable. Any relationships that showed a significant moderation effect of Aβ status were then analyzed separately within the Aβ- and Aβ+ groups. Between-group comparisons of the observed associations were conducted to examine Aβ-associated differences. Finally, in order to compare the strength of the associations with those reported by other studies, bivariate correlations assessed inter-relationships between

slopes of cortical volume change and cognitive change without adjustment for any other variables.

6.3 Results

Participants from the AIBL CN sample included in this study sample were an average 69.5 years of age at their baseline assessment (SD 6.4, range 60-86). More than half the sample were female (54.1%). The majority of participants had received more than 12 years of education (59.5%) with no sex differences in educational attainment. Median follow-up time for the full sample was 7.4 years, and median time between the baseline neuropsychological assessment and the baseline MRI scan was 6 months. The Aβ+ group contained a greater proportion of *APOE* ε4 carriers compared to Aβ-. No group differences were observed on any other demographic, clinical, neuropsychological or neuroimaging measure (Table 6-2).

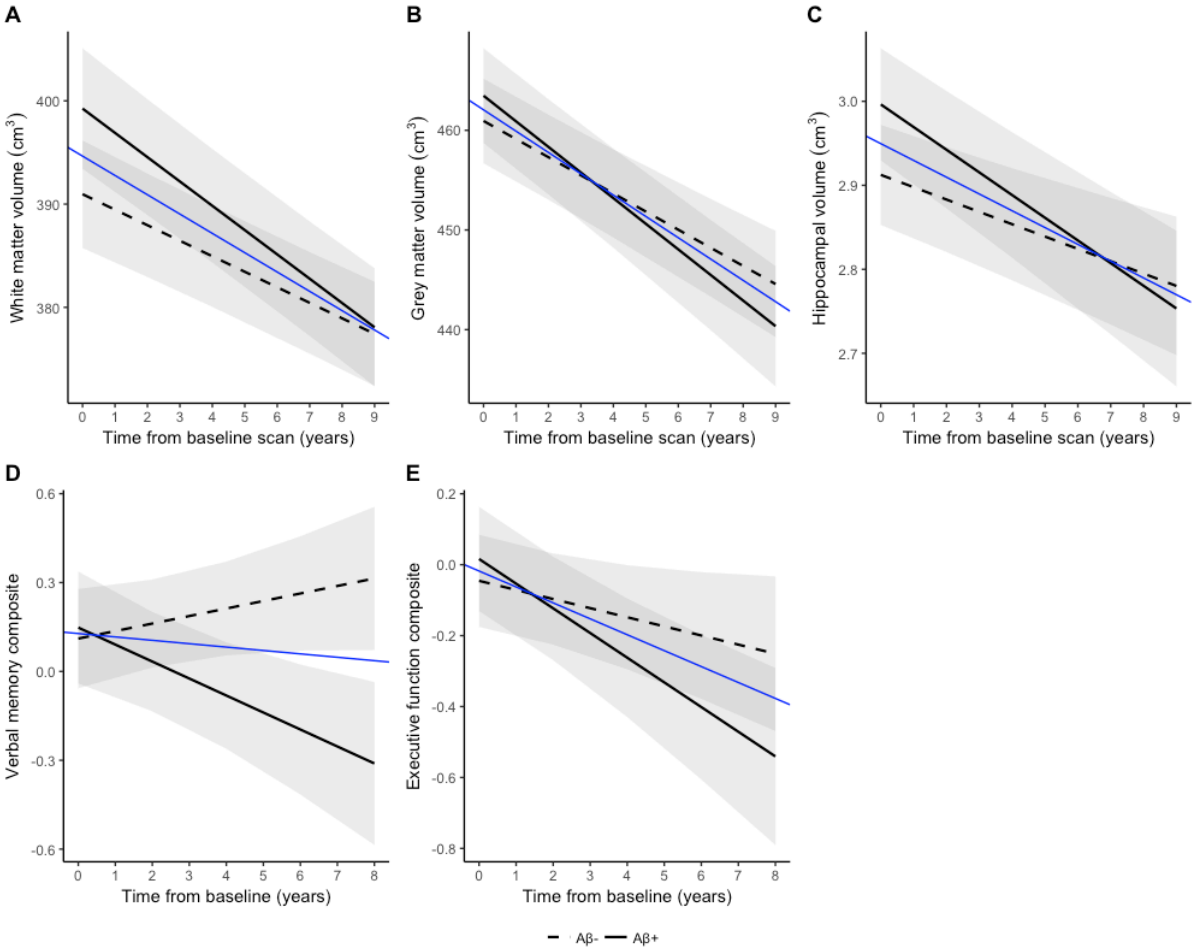
6.3.1 Rates of cortical volume change and cognitive change in CN older adults

Group mean slopes and effect sizes on all measures for the full sample and between Aβ groups are reported in Table 6-2 and Figure 6-2A-E. Significantly different rates of change over time for WM, GM and hippocampal volumes were observed between the Aβ- and Aβ+ groups, where rates of volume loss were significantly lower for the Aβ- group (Table 6-3, Figure 6-2A-C). The main effect of time was significant for all three measures for both Aβ- and Aβ+ groups. Older age at baseline was associated with lower volumes on all measures. Participants who later progressed to MCI or dementia had significantly smaller GM volumes.

Significant differences were also observed between Aβ- and Aβ+ groups for change in verbal memory and executive function, where the Aβ- group displayed significantly less decline compared to Aβ+ (Table 6-4, Figure 6-2D-E). The Aβ- group showed no significant

change on any measure of cognitive function over time, while significant decline was observed for both verbal memory and executive function in the Aβ+ group (Table 6-2).

Figure 6-2: Trajectories of cognitive and cortical volume change between Aβ groups



Dashed lines represent the Aβ- group. Solid lines represent the Aβ+ group. The blue line represents the trajectory of the full sample without consideration to Aβ status.

A-C: Trajectories of cortical volume change over 8 years between Aβ groups. Group differences are significant at $p<0.05$ for all measures.

D-F: Trajectories of cognitive change over 8 years between Aβ groups. Group differences are significant at $p<0.05$ for verbal memory and executive function.

Table 6-2: Baseline characteristics of the full sample and by Aß status

Measure	Full sample	Aβ-	Aβ+	*p*	*d*
n	141	78	63		
Age	69.94 (6.65)	69.50 (6.76)	70.48 (6.53)	0.39	0.15
Female (%)	46.8	52.6	39.7	0.17	0.29
Education (% >12 years)	57.4	60.3	54	0.50	0.14
***APOE* ε4 carriers (%)**	36.2	23.1	52.4	**<0.0005**	**0.72**
Aβ PET SUVR	1.37 [1.19-1.86]	1.20 [1.14-1.27]	2.05 [1.43-2.40]	**<0.0005**	**3.37**
Number of neuropsychological assessments	6 [5-6]	6 [5-6]	6 [5-6]	0.68	0.16
Number of MRI scans	4 [3-5.50]	5 [3.75-5]	4 [3-6]	0.39	0.09
Time between baseline neuropsychological assessment and baseline MRI scan (months)	6.11 [2.10-10.14]	5.22 [1.51-9.67]	6.9 [3.22-11.93]	0.14	0.19
Length of follow up (years)	7.42 [6.17-7.50]	7.42 [6.17-7.50]	7.50 [6.17-7.58]	0.41	0.10
Progressed to MCI/dementia (%)	15.6	10.3	22.2	0.06	0.51
Baseline measures					
White matter volume (cm^3)	395.02 (23.68)	392.32 (21.55)	398.35 (25.88)	0.13	0.26
Grey matter volume (cm^3)	461.14 (21.64)	462.27 (20.69)	459.74 (22.85)	0.49	0.12
Hippocampal volume (cm^3)	2.95 (0.28)	2.92 (0.27)	2.98 (0.28)	0.21	0.22
Verbal memory (z-score)	0.11 (0.83)	0.20 (0.84)	0.01 (0.82)	0.18	0.23
Executive function (z-score)	-0.08 (0.65)	-0.04 (0.54)	-0.11 (0.77)	0.52	0.11
Calculated slopes (adjusted)					
White matter volume (cm^3/year)	-1.87 (1.62)	-1.50 (1.56)	-2.35 (1.61)	**0.002**	**0.54**
Grey matter volume (cm^3/year)	-2.14 (1.83)	-1.82 (1.75)	-2.57 (1.82)	**0.01**	**0.42**
Hippocampal volume (cm^3/year)	-0.02 (0.02)	-0.01 (0.02)	-0.03 (0.02)	**0.003**	**0.52**
Verbal memory (SD/year)	-0.01 (0.16)	0.03 (0.15)	-0.06 (0.15)	**0.002**	**0.54**
Executive function (SD/year)	-0.04 (0.12)	-0.03 (0.12)	-0.07 (0.12)	**0.02**	**0.37**

Abbreviations used: Aβ = amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; PET SUVR = positron emission tomography standardized uptake value ratio; SD = standard deviation.

For normally distributed variables, data are presented as mean (SD). For non-normally distributed variables, data are presented as median [Quartile 1 – Quartile 3].

Table 6-3: Linear mixed model parameters for changes in cortical volumes by Aß group

	White matter volume			**Grey matter volume**			**Hippocampal volume**		
	Estimate	Std. Error	*p*	Estimate	Std. Error	*p*	Estimate	Std. Error	*p*
Intercept	447.22	20.40	**<0.0005**	573.17	17.68	**<0.0005**	3.54	0.24	**<0.0005**
Aβ status (-/+)	8.29	4.01	**0.04**	2.53	3.27	0.44	0.08	0.05	0.07
Time	-1.50	0.18	**<0.0005**	-1.82	0.20	**<0.0005**	-0.01	0.00	**<0.0005**
Baseline age	-0.78	0.29	**0.008**	-1.55	0.25	**<0.0005**	-0.01	0.00	**0.01**
Progression status (N/Y)	-7.47	5.18	0.15	-14.24	4.48	**0.002**	-0.07	0.06	0.29
Aβ status * Time	-0.85	0.27	**0.002**	-0.75	0.30	**0.01**	-0.01	0.00	**0.003**

Table 6-4: Linear mixed model parameters for changes in cognition by Aß group

	Verbal memory			**Executive function**		
	Estimate	Std. Error	*p*	Estimate	Std. Error	*p*
Intercept	2.14	0.60	**<0.0005**	2.46	0.52	**<0.0005**
Aβ status (-/+)	0.04	0.13	0.77	0.06	0.10	0.54
Time	0.03	0.02	0.14	-0.03	0.01	0.05
Baseline age	-0.03	0.01	**0.002**	-0.03	0.01	**<0.0005**
Progression status (N/Y)	-1.18	0.16	**<0.0005**	-0.70	0.14	**<0.0005**
Aβ status * Time	-0.08	0.03	**0.002**	-0.04	0.02	**0.03**

6.3.2 Relationships between concurrent cortical volume and cognitive changes

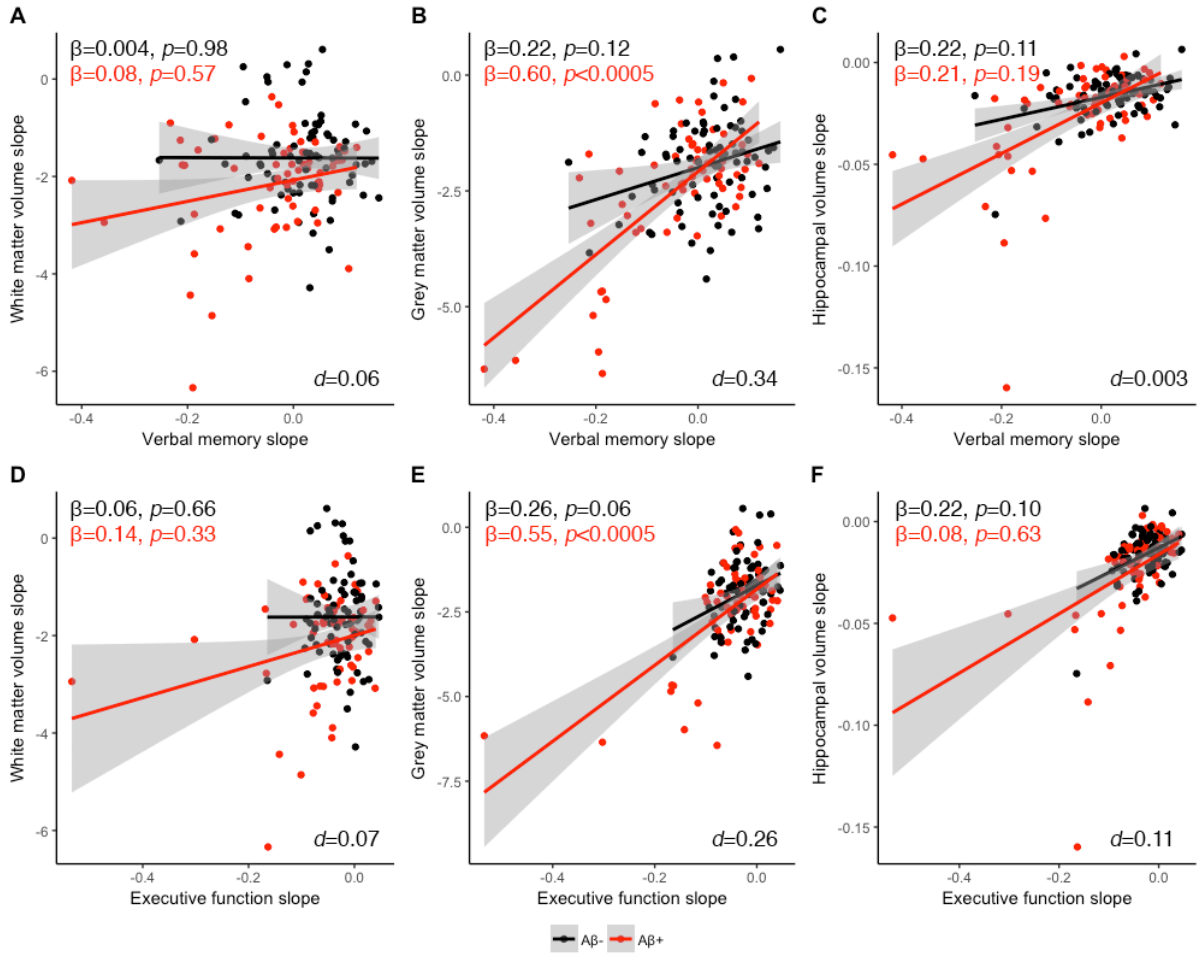
The magnitude and direction of the relationships between changes in cortical volume and cognition were tested in a series of regression analyses summarized in Table 6-5. Examining these relationships in the full CN sample without consideration to Aβ status showed significant associations between both GM and hippocampal volume loss with verbal memory decline, and also between GM volume loss and executive function decline. Lower GM volume at baseline was associated with greater decline in both verbal memory and executive function.

Moderator analyses indicated that the relationships between GM volume loss and decline in both verbal memory and executive function were significantly different between Aβ groups (β=0.60, p<0.0005 and β=0.65, p<0.0005, respectively). No Aβ group differences were observed in the relationships between changes in WM or hippocampal volume with any cognitive measure. Controlling for baseline age did not change the results. A post-hoc analysis assessed whether the results were influenced by the length of time between neuropsychological testing and neuroimaging at each time point, and found that the results did not change when analyses were restricted to only participants whose neuropsychological assessments and MRI scans were less than 6 months apart (the median time between assessments).

Separate analyses were conducted in the Aβ- and Aβ+ groups to examine the way in which Aβ status moderated the relationships between GM volume loss and change in verbal memory and executive function. In the Aβ- group, no associations were observed between rates of GM volume loss and either of the composite cognitive scores (a scatterplot of the raw data is shown in Figure 6-3). For the Aβ+ group, faster GM volume loss was associated

with greater decline in verbal memory and executive function (Table 6-6, Figure 6-3). Adding age to the models did not change the results for either group. Calculation of Cohen's *d* effect sizes indicated that associations were stronger for Aβ+ compared to Aβ- for the relationships between GM volume loss and decline in both verbal memory (*d*=0.34) and executive function (*d*=0.26) (Table 6-6, Figure 6-3).

Figure 6-3: Relationships between cognitive change and cortical atrophy for both Aß groups



Cortical volume slopes are on the vertical axes and cognitive composite slopes are on the horizontal axes. Cohen's *d* displayed for the comparison of associations between Aβ groups.

A-C: Associations between slopes of white matter volume, grey matter volume and hippocampal volume with verbal memory slope between Aβ groups. The difference between Aβ groups in panel B is significant at $p<0.05$.

D-F: Associations between slopes of white matter volume, grey matter volume and hippocampal volume with executive function slope between Aβ groups.

Table 6-5: Associations between changes in cortical volumes and cognition in the full CN sample

	Verbal memory slope				**Executive function slope**			
	β	S.E.	*p*	*r*	β	S.E.	*p*	*r*
Baseline cognition	0.03	0.07	0.69		0.07	0.07	0.30	
Baseline WM volume	0.06	0.08	0.44		0.12	0.08	0.13	
Baseline GM volume	0.23	0.08	**0.01**		0.25	0.08	**<0.0005**	
Baseline hippocampal volume	-0.02	0.08	0.82		0.07	0.08	0.39	
WM volume slope	0.10	0.10	0.28	0.20	0.16	0.09	0.09	0.21
GM volume slope	0.44	0.09	**<0.0005**	0.57	0.48	0.08	**<0.0005**	0.57
Hippocampal volume slope	0.27	0.10	**0.01**	0.54	0.18	0.11	0.08	0.51

Baseline cognition refers to verbal memory or executive function, respectively. Pearson's r reflects the correlation coefficient without adjustment for covariates.
Abbreviations used: WM = white matter; GM = grey matter; S.E. = standard error.

Table 6-6: Associations between changes in cortical volumes and cognition between Aβ groups

	Verbal memory slope									**Executive function slope**								
	Aβ-				Aβ+					Aβ-				Aβ+				
	β	S.E.	*p*	*r*	β	S.E.	*p*	*r*	*d*	β	S.E.	*p*	*r*	β	S.E.	*p*	*r*	*d*
Baseline cognition	0.08	0.10	0.46		0.007	0.10	0.95		0.08	0.03	0.10	0.75		0.08	0.10	0.42		0.06
Baseline WM volume	0.05	0.12	0.69		0.07	0.12	0.54		0.03	0.21	0.11	0.05		0.11	0.12	0.32		0.10
Baseline GM volume	0.34	0.12	**0.005**		0.09	0.13	0.46		0.24	0.34	0.12	**0.003**		0.19	0.13	0.16		0.15
Baseline hippocampal volume	0.00	0.12	0.98		0.04	0.12	0.72		0.05	-0.01	0.11	0.91		0.17	0.12	0.14		0.19
WM volume slope	0.004	0.14	0.98	-0.002	0.08	0.14	0.57	0.24	0.06	0.06	0.14	0.66	0.001	0.14	0.15	0.33	0.26	0.07
GM volume slope	0.22	0.14	0.12	0.28	0.60	0.11	**<0.0005**	0.71	**0.34**	0.26	0.14	0.06	0.31	0.55	0.12	**<0.0005**	0.66	0.26
Hippocampal volume slope	0.22	0.13	0.10	0.39	0.21	0.16	0.19	0.56	0.003	0.22	0.13	0.10	0.43	0.08	0.18	0.63	0.51	0.11

Pearson's r reflects the correlation coefficient without adjustment for covariates. Significant differences between Aβ groups shown by bolded Cohen's *d* values. Baseline cognition refers to verbal memory or executive function, respectively.
Abbreviations used: WM = white matter; GM = grey matter; S.E. = standard error.

6.4 Discussion

The study results supported the hypothesis that associations between cortical volume loss and cognitive change in CN older adults would be moderated by Aβ status (i.e. Aβ- or Aβ+). When examined in the full sample without consideration to Aβ status, moderate associations were observed between both GM and hippocampal volume loss with verbal memory decline, and also between GM volume loss and executive function decline. However, the relationship between GM volume loss and decline in cognitive function was moderated by whether participants were classified Aβ- or Aβ+. For the Aβ- group, GM volume loss was not associated with change in either verbal memory or executive function, but strong associations were observed for the Aβ+ group. These findings are consistent with the group-level trajectories of cognitive and brain aging for both Aβ- and Aβ+ observed in Chapters 4-5 and other published studies [61,62,206,63–68,71,147]. However, no other study has yet examined the moderating effect of Aβ status on relationships between cortical volume loss and cognitive change despite accumulating evidence that models of aging need to be reconceptualized with respect to preclinical neuropathological processes. Taken together, the results suggest that cortical volume loss associated with AD neuropathological changes may give rise to declines in cognitive function; however, age-associated cortical volume loss in the absence of Aβ+ may not affect cognitive ability in aging. It is, therefore, possible that cognitive decline is not a normal part of aging.

The finding that cognitive function is preserved in this sample of CN Aβ- older adults despite loss of cortical volume in aging appears to be inconsistent with theories that neural substrates underlie cognitive function [114,122,280–282]. However, it may be that the observed preservation of cognitive function is an artefact of practice effects masking the

true rate of age-associated cognitive change [310]. Verbal memory improvements for the Aβ- group over the study period suggest the presence of a practice effect while the Aβ+ group showed declining performance (Figure 6-2D, Table 6-2). This is consistent with reports from previous studies that Aβ status can be characterized by the presence or absence of practice effects [299–302]. While practice effects have been effectively used as a diagnostic and screening tool for cognitive impairment and AD risk [311,312], they are an important and ever-present confounder in prospective studies of cognitive aging [313]. Not controlling for these practice effects can therefore limit the ability of researchers to accurately measure the magnitude of cognitive change associated with aging. However, these effects can also be conceptualized as a measure of learning such that reduced practice effects observed for Aβ+ older adults represents dysfunction in learning from repetition [302]. Although the rates of cognitive change for Aβ- older adults indicate improvement in verbal memory and stability in executive function, these may be overestimated due to the superimposition of a practice effect on cognitive performance and the true rate of cognitive change may be lower than reported here. Regardless, the presence of a practice effect for Aβ- older adults indicates that learning ability remains intact in aging although cortical volume loss continues to occur.

One possible explanation for the mechanism underlying this dissociation is that Aβ- older adults have higher levels of brain reserve compared to Aβ+; however, the results showed no difference in GM or hippocampal volumes between the Aβ- and Aβ+ groups over the study period. If Aβ- older adults had higher brain reserve, larger volumes would be observed compared to Aβ+. Another possibility is that general cortical volume loss observed in aging does not specifically reflect neurodegenerative processes necessary to affect cognitive functioning. Because the association between GM volume loss and verbal memory

decline was significantly stronger for the Aβ+ group compared to the Aβ- group, it is necessary to understand what is reflected by loss of GM volume observed on structural MRI. GM consists of neuronal cell bodies, neuropil, glial cells, synapses and capillaries. It was previously thought that loss of GM volume reflected loss of neurons; however, studies have consistently shown that number of neurons remains consistent from middle-age through to very old age even though overall volume declines with age in both MRI and stereological examinations [294,314–317]. These studies indicated that normal aging is not associated with any substantial neuronal loss. Age-associated GM volume loss is therefore more likely due to reductions in neuronal size and other changes in neuropil organization [294,295], while cortical atrophy observed in preclinical AD may reflect loss of neurons. The aggregation of Aβ has been associated with neuronal death although the exact mechanisms of its indirect or direct effects remain unclear [318–322], and clinical-pathological studies have reported extensive neuron loss that contribute directly to cognitive impairment in AD [314,323,324]. If neuron loss indeed contributes to cognitive decline, researchers were unable to reconcile the observations that neuronal count does not change in normal aging but that cognition did appear to decline with age. However, stereological studies of neuronal counts screened samples for *post-mortem* evidence of AD neuropathology such as Aβ plaques, but studies of cognitive aging have not done any similar screening and included participants classified as CN regardless of Aβ status. Thus, cognitive trajectories determined from samples excluding Aβ+ may more accurately reflect the populations examined by the neuronal cell count studies. The present study follows from a body of work indicating that models of cognitive and brain aging must be developed using samples screened for the presence of AD neuropathological markers; therefore, the notion that neuronal death contributes to cognitive decline and subsequent impairment remains plausible.

Taken together, these findings suggest that studies of aging require greater precision in defining aging: while "aging" in most studies refers to average age-associated changes observed in the general population and may include the presence of preclinical AD or other neurodegenerative diseases, this is a very general and non-specific definition. Therefore, this thesis conceptualizes "aging" as the cognitive and neurobiological changes that occur with the passage of time independent of neuropathological processes such as Aβ+. The results from this study extended previous findings [145] and confirmed that studies of aging can overestimate rates of age-associated cortical volume loss and cognitive decline due to inadvertent inclusion of participants with preclinical AD in otherwise CN samples. Therefore, in order to isolate the effects of aging from the effects of AD neuropathological changes, studies aiming to elucidate the neurocognitive changes that occur in normal aging should include only those CN participants who are Aβ-. It is recommended that future studies aiming to examine relationships between age-associated cortical volume loss and any associated cognitive changes do so with consideration to two important confounders: the potential inclusion of individuals with preclinical AD in otherwise CN samples, and the potential for practice effects due to repeated neuropsychological testing.

6.4.1 Limitations

The generalizability of these present findings to the wider population may be limited because the CN AIBL cohort is a well-educated, ethnically-homogeneous convenience sample with rigorous inclusion criteria. The presence of a practice effect, particularly for the Aβ- group, is an important confounding issue for all studies of cognitive aging. For this reason, reported rates of age-associated cognitive change may not accurately reflect changes associated with the passage of time due to the difficulty disentangling the effects of time and practice. Future prospective studies must control for practice effects either

methodologically (e.g. using different test versions) or statistically [313]. It is also difficult to compare the magnitude of results across all studies examining relationships between cortical volume change and cognitive change beyond the presence or absence of statistically significant effects due to the wide range of methodological differences between studies. A recent review acknowledged that a meta-analysis was not possible because studies vary with regard to the study participants, cognitive measures, brain regions and statistical methods used [325] (Table 6-1). To facilitate comparison with other studies, the present results were also reported as correlation coefficients and future studies are encouraged to do the same. Finally, while the theory that preservation of neurons in aging reflects maintenance of cognition in Aβ- older adults is provocative, this study was not able to directly assess the contribution of changing neuronal count or density to cognitive change in aging, as technology to measure these *in vivo* remains limited. However, it would be valuable for future studies to include longitudinal measures of cell volume fraction (using quantitative sodium MRI [295]) or neuronal density (using ^{18}F-flumazenil PET [326]) in order to elucidate the functional impact of age-associated changes in brain morphology.

6.5 Conclusions

This study found no robust relationships between GM volume loss and cognitive change for CN Aβ- older adults. However, rates of GM volume loss were associated with rates of decline in verbal memory and executive function for CN Aβ+ older adults. Overall, the results suggest that cortical volume loss is not associated with any concurrent cognitive decline in the process of normal aging when examined in the absence of AD neuropathological markers such as Aβ+. This body of work challenges previously well-established findings that aging is associated with cognitive decline by showing no age-

associated decline in cognition when studies include only CN older adults who are Aβ-. Rates of age-associated cortical volume loss reported by previous studies have also been overestimated by inadvertent inclusion of Aβ+ participants. Although Aβ- older adults displayed some volume loss, previous studies have shown that reductions in GM volume observed on structural MRI is not reflective of neuronal loss in aging. One neural substrate of cognitive decline may be loss of neurons, and preservation of neurons in aging is a plausible explanation for why cognition does not decline in Aβ- older adults despite observations of cortical volume loss in the same group. Thus, while some age-associated cortical volume loss does occur with normal aging, this does not necessarily give rise to loss of cognitive ability in older age.

Chapter 7: Examining the moderating effect of *APOE* ε4 carriage on associations between cortical volume loss and cognitive change in a robust sample of aging older adults

7 Examining the moderating effect of *APOE* ε4 carriage on associations between cortical volume loss and cognitive change in a robust sample of aging older adults

7.1 Introduction

Models of aging need to be reconceptualized with respect to preclinical neuropathological processes. Converging evidence suggests that studying normative rates of brain morphological and cognitive changes in late-life aging requires careful consideration of the sample population. Otherwise cognitively normal (CN) older adults with evidence of neurodegenerative processes associated with Alzheimer's disease (AD) such as elevated amyloid-β (Aβ+) have shown faster rates of cortical atrophy and cognitive decline than CN older adults with subthreshold levels of Aβ (Aβ-) [61,62,147,206,63–68,71,145]. As a result, studies of aging that include both Aβ- and Aβ+ participants may be unable to accurately estimate rates of change associated with aging. All studies included in this thesis have supported this view by consistently reporting different risk profiles and trajectories of cortical atrophy and cognitive change when a sample of CN older adults is divided into groups based on Aβ status (i.e. Aβ- or Aβ+). Therefore, in order to isolate the effects of aging from the effects of AD neuropathological changes, studies aiming to elucidate the neurocognitive changes that occur in normal aging should include only those CN participants who are Aβ-. This idea is consistent with that proposed by Sliwinski et al., who showed that normative estimates of memory performance were negatively biased by the inclusion of older adults with undetected preclinical dementia at the time of testing. By retrospectively excluding those individuals, estimates of normative cognitive performance

generated from these "robust" samples were higher with lower variability, and detected deviations from normal-for-age cognitive performance with greater sensitivity compared to "conventional" samples that include all participants classified as CN at study entry [26,123,129–132]. Therefore, an ideal robust sample for studies of aging would include only individuals with no evidence of preclinical neuropathological processes, detected through both prospective clinical assessment of cognitive status and measurement of biomarkers such as Aβ.

Further investigation is required to determine whether a study sample including only Aβ- older adults who remain CN throughout the entire study period (i.e. a robust sample) will be reflective of normal changes associated with the process of aging or if other sources of variance remain present. The results of the previous study (Chapter 6) suggested that aging is not necessarily associated with declining cognitive ability; however, some variance in slopes of verbal memory change was observed. Although the median rate was 0.04 SD/year (interquartile range 0.0002 SD/year to 0.07 SD/year), indicating that most Aβ- older adults displayed intact learning over time (i.e. practice effects), declining performance was observed for approximately 25% of the Aβ- sample (range -0.15 SD/year to 0.16 SD/year). This variance may simply reflect normal inter-individual differences in cognitive ability, or may reflect the presence of incipient neurodegenerative disease processes.

Genetic factors may explain some of the observed variance. Carriage of the apolipoprotein (*APOE*) ε4 allele has been associated with increased risk of Alzheimer's disease (AD), potentially due to *APOE* ε4 impairing clearance and processing of Aβ [86,91]. Therefore, *APOE* ε4 carriage is also associated with greater Aβ burden, increased risk of Aβ+ relative to *APOE* ε4 non-carriers of similar age, and faster rates of Aβ accumulation in Aβ- older adults [95,327–329]. Previous studies have consistently shown an additive effect of

Aβ+ and *APOE* ε4 carriage such that Aβ+ older adults who also carry the *APOE* ε4 allele display faster rates of cortical atrophy and cognitive decline compared to Aβ+ *APOE* ε4 non-carriers [96] and increased risk for future development of MCI or dementia [266; Chapter 3]. Other studies have reported differential trajectories of brain and cognitive aging as a function of *APOE* ε4 carrier status but did not control for Aβ [119,290,330–332]. A meta-analysis of the *APOE* ε4 effect on cognition and neuroimaging in young adults, adolescents and children, in whom the probability of Aβ+ is very low [22], reported no evidence for any detrimental effect of *APOE* ε4 carriage [333]. However, it has been reported that different cognitive trajectories for *APOE* ε4 begin to emerge between ages 50-60 [330], coinciding with ages during which Aβ may be accumulating [23]. Overall, few studies have examined effects of *APOE* ε4 carriage specifically in Aβ- older adults to investigate whether *APOE* ε4 may influence cognitive aging trajectories independent of its association with Aβ, and none have examined the influence of *APOE* ε4 on cortical volume changes in aging without AD neuropathological changes. Findings from these studies suggest that there is no effect of *APOE* ε4 carriage on longitudinal memory performance in the absence of Aβ+ [96,334,335]; however, it is difficult to disentangle the independent contributions of *APOE* ε4 and Aβ in human studies of aging because of the association between *APOE* ε4 carriage and Aβ accumulation in Aβ- older adults [95], making these individuals more likely to be classified as Aβ+ in the future [336].

Some incipient Aβ-associated neurodegenerative changes may be occurring in *APOE* ε4 carriers even prior to classification as Aβ+, but studies of *APOE* ε4 effects on trajectories of cortical volume and cognitive change in aging may not be sensitive enough to detect these early changes. One way to assess whether such changes may be occurring is to examine whether *APOE* ε4 carriage moderates relationships between concurrent changes in

cortical volume and cognition. Chapter 6 found that Aβ status moderated the relationship between GM volume loss and cognitive decline, raising the possibility that GM volume loss in Aβ+ is associated with neuronal death and consequent cognitive decline. Therefore, assessing the relationship between cortical volume and cognitive change may enable identification of Aβ-associated neurodegenerative processes occurring in Aβ- *APOE* ε4 carriers. If these relationships are not moderated by *APOE* ε4, this would suggest that *APOE* ε4 carriage itself is not detrimental in the absence of Aβ+ and thus may not affect normal aging trajectories. However, if a moderating effect of *APOE* ε4 carriage is observed, it suggests one of two things: that *APOE* ε4 carriage exerts some deleterious effect on cortical atrophy and/or cognitive decline independent of Aβ, or that the effect may reflect increased rates of Aβ accumulation for Aβ- *APOE* ε4 carriers likely to become Aβ+ in the future.

This study aimed to examine the effects of *APOE* ε4 carriage on trajectories of cortical volume and cognitive changes in a robust sample of CN Aβ- older adults. Following from the results of Chapter 6, we explored the association between *APOE* ε4 carriage and trajectories of grey matter (GM) volume loss and decline in verbal memory or executive function. Further exploratory analyses then examined whether relationships between concurrent changes in cortical GM volume and cognition in aging were moderated by *APOE* ε4 carrier status.

7.2 Methods

7.2.1 Participants

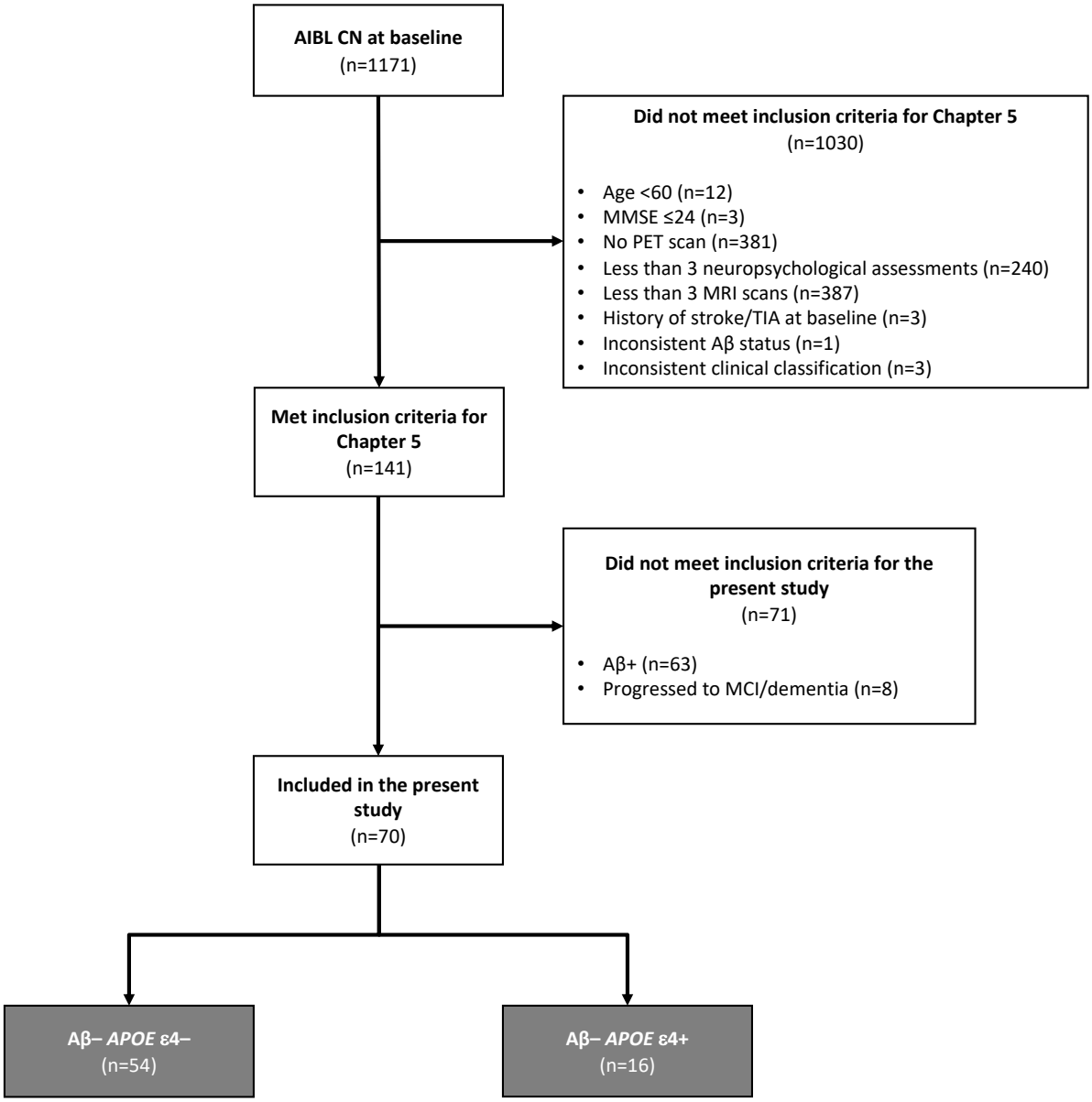
Participants were from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. The full study protocol is reported elsewhere [192]. Briefly, volunteers were ineligible for enrolment if they met any of the following exclusion criteria: non-AD dementia, history of

schizophrenia or bipolar disorder, current depression (Geriatric Depression Scale score >5), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, obstructive sleep apnea, past head injury with >1 hour of post-traumatic amnesia, or current regular alcohol intake beyond recommended limits [193]. All included participants were identified to have no, or medically well-controlled systemic illnesses at baseline (described in [337]). Ethics approval for the AIBL study was granted by St Vincent's Health, Austin Health and Edith Cowan University, and all participants provided written informed consent at each visit.

7.2.2 Sample selection

A robust sample was drawn from the sample of older adults included in the Chapter 5 analyses. The sample was further restricted to participants who were classified Aβ- at their most recent positron emission tomography (PET) scan. Participants who were classified with mild cognitive impairment (MCI) or dementia during the study period (i.e. progressors) were also excluded from the present analyses in order to examine trajectories associated with aging in the absence of clinical disease progression and evidence of AD neuropathological changes. Thus, all participants included in the present study remained classified both Aβ- and CN at each assessment. The final sample included a total of 70 participants. See Figure 7-1.

Figure 7-1: Sample selection



7.2.3 Clinical and neuropsychological assessment

A full neuropsychological battery was administered at each 18-month assessment, and fasting blood samples were collected [192]. *APOE* genotype was determined from whole blood extracted DNA [210]. Participants who carried at least one *APOE* ε4 allele were coded as *APOE* ε4+ and participants with no *APOE* ε4 allele were coded *APOE* ε4-.

Verbal memory was defined using a composite score derived using average standardized performance relative to baseline scores on the California Verbal Learning Test Second Edition (CVLT-II) Long Delay Free Recall, CVLT-II Immediate Recall Trials 1-5, and the Wechsler Memory Scale Logical Memory II Story A subtest [337]. The executive function composite included category fluency (total animals and male names, and fruit and furniture), letter fluency (FAS), the Victoria Stroop test (words trial), and the Digit Symbol Substitution Test. Both of these measures were also used in Chapters 4 and 6.

7.2.4 Neuroimaging

7.2.4.1 *MRI neuroimaging*

All participants underwent 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequences using the following acquisition parameters: in-plane resolution 1×1 mm, slice thickness 1.2 mm, repetition time (TR)/echo time (TE)/inversion time (TI) = 2300/2.98/900, flip angle 9°, field of view (FOV) 240×256. MPRAGE images were segmented into white matter (WM), gray matter (GM) and cerebrospinal fluid using an implementation of the expectation maximization algorithm [214]. A multi-atlas approach based on the Harmonized Hippocampus Protocol was used to extract the hippocampus [219]. The present analyses included total GM volume, with WM and hippocampal volume as covariates. These measures were corrected for scanner and total intracranial volume, and were also used in Chapters 5 and 6.

7.2.4.2 *Amyloid-β PET neuroimaging*

Positron emission tomography (PET) neuroimaging was conducted using one of three Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB, n=36), ^{18}F-NAV4694 (NAV, n=29), or ^{18}F-Flutemetamol (FLUTE, n=5). Detailed PET methods and procedures are described elsewhere and in earlier chapters of this thesis [211,212]. Briefly, PET acquisitions were performed to 90 minutes following tracer injection. Standardized uptake value (SUV) data were summed

and normalized to a reference region to generate a SUV ratio (SUVR). CapAIBL was used for image analysis [270]. A linear regression transformation was applied to the NAV and FLUTE SUVRs to create a SUVR unit called Before the Centiloid Kernel Transformation (BeCKeT) so that SUVRs across the different radiotracers were expressed on the same scale relative to PiB [212]. All participants with SUVR/BeCKeT≥1.40 at their most recent PET scan were classified as Aβ+ and those below the threshold were classified as Aβ-. This ensured that all participants included in the present study had remained Aβ- during the study period. These classifications are consistent with those used in all previous chapters.

7.2.5 Statistical analyses

R version 3.4.3 [251] and MPlus were used for all statistical analyses, with statistical significance set at $p<0.05$. No adjustments were made for multiple comparisons but to address multiplicity, estimates of effect size (Cohen's *d* and standardized β coefficients) were computed for all comparisons and guided interpretation of the results in addition to statistical significance.

7.2.5.1 *Baseline group differences*

Between-group comparisons by *APOE* ε4 status were conducted using one-way analyses of variance (ANOVAs) or Kruskal-Wallis tests for continuous variables, and Fisher's exact tests for categorical variables.

7.2.5.2 *Effect of APOE ε4 carriage on cortical atrophy and cognitive decline in Aβ- older adults*

Linear mixed models (LMMs) were conducted to examine change over time in GM volume and cognition (verbal memory and executive function) as a function of *APOE* ε4 carriage, and covarying for baseline age. *APOE* ε4 status (-/+), time (years from baseline neuropsychological assessment or MRI scan) and their interaction were entered as fixed factors. Participant was entered as a random factor with random intercepts and slopes.

Baseline Aβ level did not significantly contribute to the models and was therefore removed. Significant differences in trajectories were determined by the presence of an *APOE* ε4 status x time interaction for each model. Confidence intervals were also reported to aid interpretation of the findings given the small sample sizes.

7.2.5.3 *Effect of APOE ε4 status on relationships between changes in cortical volume and cognition in Aβ- older adults*

These analyses follow from the analyses conducted in Chapter 5, where relationships between concurrent changes in cortical volume and cognition were examined in Aβ- older adults. The present study extended the analyses to further examine whether relationships between GM volume and cognitive change in Aβ- older adults are moderated by *APOE* ε4 status.

The slopes that were calculated for each measure in the last chapter were again submitted to a series of simultaneous multiple regression analyses in Mplus to examine the relationships between changes in GM volume and cognition while simultaneously modelling the inter-relationships among baseline measurements and change variables. In each regression analysis, the cognitive slope was regressed onto the corresponding baseline cognitive measure (verbal memory or executive function) and baseline GM volume. Following this, the slope of cognitive change was regressed with the GM volume slope to identify any associations between GM volume change and cognitive changes. Baseline and change measures for WM and hippocampal volume were added as covariates. The first regression analysis included *APOE* ε4 status as a dichotomous moderator variable. Exploratory regressions were then conducted within both the *APOE* ε4 groups to investigate the potential for between-group differences that the moderator analysis may have been underpowered to detect due to the relatively small *APOE* ε4+ sample. Analyses were all bootstrapped at 5000.

7.3 Results

Participants were 69.5 years of age on average (SD 6.8, range 60-86). Nearly 53% of the sample were female and 61% had received more than 12 years of education. *APOE* genotypes were: *APOE* ε3/ε2 (n=10), *APOE* ε3/ε3 (n=44), *APOE* ε4/ε2 (n=2), *APOE* ε4/ε3 (n=14). Thus, the sample included 54 *APOE* ε4 non-carriers (i.e. *APOE* ε4-) and 16 *APOE* ε4 carriers (i.e. *APOE* ε4+). The *APOE* ε4+ group was younger than the *APOE* ε4- group by 4 years [$F(1,68)=5.38$, $p=0.02$]. No group differences were observed on any other demographic, clinical, neuropsychological or neuroimaging measure (Table 7-1).

7.3.1 No effect of *APOE* ε4 carriage on rates of cortical atrophy or cognitive decline in Aβ- older adults

Group mean slopes and effect sizes for each of the neuroimaging and neuropsychological measures are displayed in Table 7-1. Significant reduction in GM volume (1.69 cm^3/year) was observed over time in the full sample. Verbal memory performance significantly increased at a rate of 0.05 SD/year for all participants, while a significant decrease in executive function was observed (-0.01 SD/year). Older age at baseline was associated with lower verbal memory and executive function performance, and with smaller GM volume. No differences in rate of change were observed between the *APOE* ε4- and *APOE* ε4+ groups for any measure (Table 7-2, Figure 7-2). However, while non-significant, the effect size of the difference in verbal memory slopes between *APOE* ε4 groups was $d=0.30$ (Table 7-1).

Table 7-1: Baseline characteristics and mean slopes for the full sample and by APOE ε4 status

Measure	Full	*APOE* ε4-	*APOE* ε4+	*p*	*d*
n	70	54	16		
Age	69.31 (6.84)	70.31 (6.87)	65.94 (5.70)	**0.02**	0.67
Female (%)	52.9%	51.9%	56.3%	0.78	0.10
Education (% >12 years)	61.4%	61.1%	62.5%	1.00	0.03
Aβ PET SUVR	1.22 (0.09)	1.21 (0.09)	1.22 (0.11)	0.78	0.08
Number of assessments	6 [5-6]	6 [5-6]	6 [6-6]	0.23	0.01
Number of MRI scans	4.57 (1.10)	4.56 (1.11)	4.63 (1.09)	0.83	0.06
Time between baseline neuropsychological assessment and baseline MRI scan (months)	5.22 [1.31-9.74]	4.52 [0.95-8.39]	7.67 [2.87-13.36]	0.11	0.31
Length of follow up (years)	7.42 [6.52-7.50]	7.42 [6.17-7.50]	7.42 [7.35-7.50]	0.92	0.02
Baseline measures					
Verbal memory (z-score)	0.27 (0.81)	0.24 (0.82)	0.39 (0.81)	0.52	0.19
Executive function (z-score)	0.02 (0.51)	0.03 (0.53)	-0.005 (0.49)	0.81	0.07
Grey matter volume (cm^3)	463.07 (20.46)	461.68 (20.55)	467.77 (20.07)	0.30	0.30
Adjusted slopes					
Verbal memory (SD/year)	0.05 (0.10)	0.05 (0.10)	0.02 (0.10)	0.29	0.30
Executive function (SD/year)	-0.01 (0.05)	-0.02 (0.05)	-0.005 (0.05)	0.44	0.21
Grey matter volume (cm^3/year)	-1.69 (1.38)	-1.60 (1.40)	-1.95 (1.35)	0.37	0.25

Abbreviations used: Aβ = amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; PET SUVR = positron emission tomography standardized uptake value ratio; SD = standard deviation.

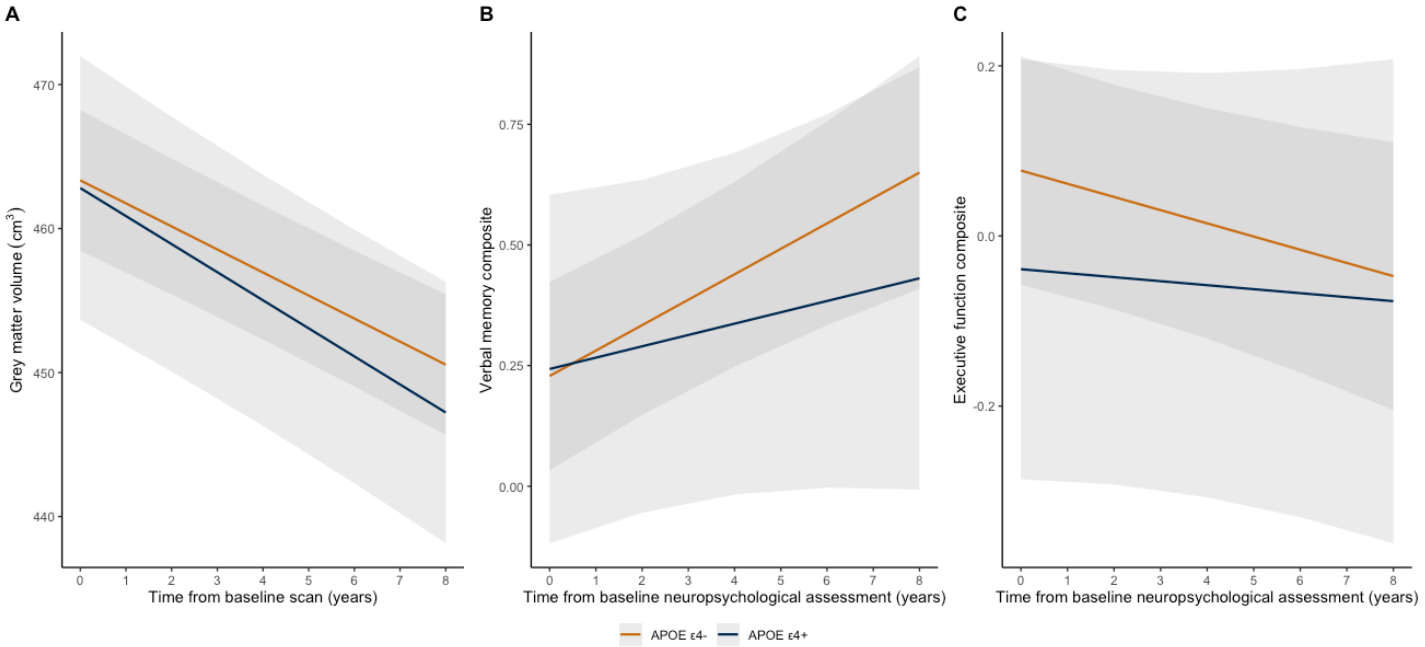
For normally distributed variables, data are presented as mean (SD). For non-normally distributed variables, data are presented as median [Quartile 1 – Quartile 3].

Table 7-2: Linear mixed model parameters for changes in GM volume, verbal memory and executive function by APOE ε4 status

	Grey matter volume					Verbal memory					Executive function				
	Estimate	S.E.	95% CI		*p*	Estimate	S.E.	95% CI		*p*	Estimate	S.E.	95% CI		*p*
Intercept	575.95	22.94	531.41	620.57	**<0.0005**	2.50	0.89	0.77	4.23	**0.006**	2.43	0.63	1.19	3.67	**<0.0005**
***APOE* ε4 status (-/+)**	-0.53	5.34	-10.92	9.86	0.92	0.01	0.21	-0.40	0.43	0.95	-0.12	0.15	-0.40	0.17	0.43
Time	-1.60	0.19	-1.98	-1.23	**<0.0005**	0.05	0.01	0.03	0.08	**<0.0005**	-0.02	0.01	-0.03	0.00	**0.03**
Baseline age	-1.61	0.32	-2.23	-0.98	**<0.0005**	-0.03	0.01	-0.06	-0.01	**0.01**	-0.03	0.01	-0.05	-0.02	**<0.0005**
***APOE* ε4 status * Time**	-0.35	0.39	-1.11	0.41	0.37	-0.03	0.03	-0.08	0.02	0.29	0.01	0.01	-0.02	0.04	0.44

Abbreviations used: *APOE* ε4 = apolipoprotein E epsilon 4 allele; CI = confidence interval; S.E. = standard error.

Figure 7-2: Trajectories of cortical volume and cognitive change between APOE ε4 groups



Trajectories of (A) GM volume, (B) verbal memory, and (C) executive function change over 8 years between *APOE* ε4 groups. Group differences are not significant (p>0.05) for all measures.

7.3.2 Relationships between concurrent cortical volume and cognitive changes for *APOE* ε4 non-carriers and carriers

Moderator analyses indicated no significant moderating effect of *APOE* ε4 status on the relationships between change GM volume and verbal memory or executive function. Controlling for baseline Aβ levels or age did not change any of the results. Separate analyses were then conducted in both the *APOE* ε4- and *APOE* ε4+ groups. The magnitude and direction of the relationships between changes in GM volume and cognition are shown in Table 7-3 and Table 7-4. Confidence intervals were reported to aid interpretation of the findings due to the small sample size in each group. In the *APOE* ε4- group, no associations were observed between rates of GM volume loss and either of the composite cognitive scores. However, faster GM volume loss was associated with greater decline in verbal memory performance for the *APOE* ε4+ group (Table 7-3). Calculation of Cohen's *d* effect sizes indicated that the association between GM volume loss and verbal memory decline was moderately stronger in the *APOE* ε4+ group (*d*=0.47). Given the small sample of *APOE* ε4+ carriers, a false positive risk analysis was conducted to calculate the likelihood that the observed finding was the result of Type I error [338]. If the prior probability of finding a true difference is 50%, the false positive risk was found to be 21.3%. In other words, the observed association between GM volume loss and verbal memory decline in the *APOE* ε4+ group was 2.7 times more likely to be a true positive than a false positive.

Table 7-3: Associations between changes in grey matter volume and verbal memory between APOE ε4 groups

	***APOE* ε4-**					***APOE* ε4+**					
	β	S.E.	95% CI		*p*	β	S.E.	95% CI		*p*	*d*
Baseline verbal memory	0.001	0.15	-0.28	0.28	0.99	0.04	0.30	-0.54	0.62	0.90	0.03
Baseline grey matter volume	0.28	0.17	-0.05	0.61	0.09	0.68	0.29	0.12	1.24	**0.02**	0.33
Grey matter volume slope	0.11	0.20	-0.28	0.49	0.59	0.80	0.36	0.10	1.50	**0.03**	0.47
Covariates											
Baseline white matter volume	0.12	0.20	-0.26	0.50	0.55	0.21	0.17	-0.13	0.55	0.22	0.07
Baseline hippocampal volume	0.02	0.13	-0.25	0.28	0.90	-0.25	0.30	-0.85	0.34	0.41	0.26
White matter volume slope	-0.03	0.19	-0.41	0.34	0.87	0.13	0.34	-0.54	0.80	0.71	0.11
Hippocampal volume slope	0.12	0.19	-0.24	0.49	0.51	-0.02	0.36	-0.72	0.67	0.95	0.11

Cohen's *d* presented as the effect size of the difference between *APOE* ε4 groups. Abbreviations used: *APOE* ε4 = apolipoprotein E epsilon 4 allele; CI = confidence interval; S.E. = standard error.

Table 7-4: Associations between changes in grey matter volume and executive function between APOE ε4 groups

	***APOE* ε4-**					***APOE* ε4+**					
	β	S.E.	95% CI		*p*	β	S.E.	95% CI		*p*	*d*
Baseline executive function	0.04	0.15	-0.26	0.33	0.81	-0.007	0.31	-0.60	0.59	0.98	0.04
Baseline grey matter volume	0.41	0.15	0.11	0.71	0.007	0.35	0.32	-0.28	0.98	0.28	0.05
Grey matter volume slope	0.27	0.16	-0.05	0.59	0.10	-0.06	0.46	-0.97	0.86	0.91	0.24
Covariates											
Baseline white matter volume	0.16	0.13	-0.09	0.41	0.21	0.27	0.32	-0.35	0.90	0.39	0.11
Baseline hippocampal volume	-0.01	0.14	-0.28	0.27	0.96	-0.14	0.33	-0.80	0.52	0.68	0.12
White matter volume slope	-0.09	0.17	-0.42	0.24	0.60	-0.14	0.39	-0.91	0.63	0.73	0.04
Hippocampal volume slope	-0.05	0.15	-0.34	0.23	0.71	-0.47	0.38	-1.21	0.26	0.21	0.35

Cohen's *d* presented as the effect size of the difference between *APOE* ε4 groups. Abbreviations used: *APOE* ε4 = apolipoprotein E epsilon 4 allele; CI = confidence interval; S.E. = standard error.

7.4 Discussion

This study aimed to explore the effects of *APOE* ε4 carriage on trajectories of GM volume and cognitive changes in a robust sample of CN Aβ- older adults. Initial results from the exploratory analyses suggested that *APOE* ε4 carriage in CN Aβ- older adults was not associated with GM volume loss nor decline in verbal memory or executive function: *APOE* ε4 non-carriers and carriers displayed similar trajectories for GM volume and cognitive change over the 8-year study period. These findings appear to be consistent with a recent study also conducted with the AIBL cohort reporting that *APOE* ε4 carriage was associated with poorer verbal memory trajectories in Aβ+ older adults, but no difference was observed in verbal memory performance between *APOE* ε4 non-carriers and carriers in the Aβ- group [96]. However, it must be noted that the small sample of Aβ- *APOE* ε4 carriers may limit the statistical power of these models to detect true group differences. While the present study also observed no statistically significant difference in verbal memory change between Aβ- *APOE* ε4 non-carriers and carriers, the observed effect was of moderate magnitude (*d*=0.30). Inspection of the fitted model plots and confidence intervals (Figure 7-2B, Table 7-2) suggests that *APOE* ε4 non-carriers may display faster trajectories of verbal memory improvement compared to carriers, and that a significant effect could potentially be observed with a larger sample and less variance. Therefore, *APOE* ε4 carriage, even in the absence of measurable AD neuropathological changes, may be associated with reduced practice effects similar to that previously reported for CN Aβ+ older adults [299–302]. If this is the case, then screening for *APOE* ε4 carriage may be necessary when identifying robust samples for studies of aging because cognitive aging trajectories may be affected by *APOE* genotype.

APOE ε4 carriage in CN Aβ- older adults may, therefore, reflect the presence of incipient Aβ-associated neurodegenerative processes. Further exploratory analyses initially showed no moderating effect of *APOE* ε4 carriage on the relationships between concurrent GM volume and cognitive changes. However, when the analyses were conducted within the *APOE* ε4- and *APOE* ε4+ groups separately, a strong positive association between rate of GM volume loss and verbal memory decline for *APOE* ε4 carriers was observed. While the initial moderator analyses may have been underpowered to detect any effect of *APOE* ε4 status due to the small sample of *APOE* ε4 carriers, separate group-level analyses suggest the possibility that *APOE* ε4 status does moderate the relationship between rate of GM volume loss and verbal memory decline in Aβ- older adults. The effect size of the difference between the two *APOE* ε4 groups was moderate (d=0.47) with minimal overlap of confidence intervals but was not statistically significant, likely due to small sample sizes. No previous studies assessing relationships between cortical volume and cognitive changes have done so with consideration to both Aβ and *APOE* ε4 status; therefore, future studies should attempt to replicate these findings in larger prospective cohorts. Given that Aβ- *APOE* ε4 carriers are also more likely to accumulate Aβ at faster rates [95] and to later be classified Aβ+ [336], the results of this study constitute preliminary evidence that early effects of Aβ-associated neurodegenerative processes may be observable even before individuals reach the threshold for Aβ+. Robust studies of aging must, therefore, account for these incipient neurodegenerative processes in order to examine the process of aging independent of these changes.

The mechanisms through which *APOE* ε4 carriage increases risk for Aβ+ and AD remains to be understood. It is not, however, a deterministic gene, and *APOE* ε4 carriers do not necessarily develop Aβ+ or AD in their lifetimes despite having greater genetic

susceptibility to doing so. The three *APOE* alleles (ε2, ε3, ε4) code for different isoforms of the apoE protein, which transports cholesterol and other lipids in the brain. The apoE4 isoform coded by *APOE* ε4 has been associated with impaired clearance and processing of Aβ compared to the more common isoform, apoE3 [86,91]. However, in addition to its effects on Aβ, apoE4 may also impair intercellular trafficking and mitochondrial function, and contribute to phosphorylation of tau proteins and formation of neurofibrillary tangles [339,340]. Therefore, while it is possible that the observed association between GM volume loss and verbal memory decline only for *APOE* ε4 carriers is reflective of early Aβ-associated neurodegenerative processes, further studies are necessary to elucidate whether this association is due to Aβ-dependent processes that are more likely with *APOE* ε4 carriage, or due to the effects of *APOE* ε4 carriage itself. One way to examine this would be with longitudinal PET scans or cerebrospinal fluid (CSF) analyses to measure and control for actual rates of Aβ accumulation. Two recent prospective studies of CN Aβ- older adults reported that faster rate of Aβ accumulation was associated with greater memory decline over 4 years, but no effect of *APOE* ε4 carriage on memory change was observed while controlling for rate of Aβ accumulation [334,335]. If differences in verbal memory trajectories do exist between *APOE* ε4 groups that the present study was underpowered to detect, the cited findings suggest that the *APOE* ε4-associated difference could be driven by Aβ accumulation in *APOE* ε4 carriers. However, if examining the association between concurrent cortical volume loss and cognitive decline is a more sensitive measure of early neurodegenerative changes, then future studies should test these relationships while controlling for Aβ accumulation to disentangle the effects of *APOE* ε4 and Aβ accumulation in Aβ- older adults. Doing so would determine whether *APOE* ε4 carriage in the absence of Aβ+ is sufficient to alter estimated trajectories of brain and cognitive aging in the absence of

preclinical neurodegenerative processes, and therefore conclude whether robust samples for aging studies should endeavour to screen out individuals who carry at least one *APOE* ε4 allele.

7.4.1 Limitations

The CN AIBL cohort is a well-educated, ethnically-homogeneous convenience sample with rigorous inclusion criteria: participants were specifically screened to have low cardiovascular risk and no uncontrolled systemic disease. This may, therefore, limit generalizability of the present findings to the wider population. Additionally, a small number *APOE* ε4 carriers were included in the present sample, which may limit the statistical power to detect true effects. Adjusting the inclusion criteria to require at least 2 serial neuropsychological assessments and MRI scans instead of 3 increased the sample of *APOE* ε4 carriers from n=16 to n=25. Because the gain in sample size was relatively small in comparison to the reduction in average number of data points per participant, the number of assessments required for inclusion in the sample was not changed to prioritize reliability in longitudinal estimates. Although a false positive risk of 21.3% may seem quite high for the finding that GM volume loss was associated with verbal memory decline in Aβ- *APOE* ε4 carriers, the amount of risk remains less than that of well-powered studies reporting significant results at the level of p=0.049, where the chance of there being no true effect is 29% [341]. In order to assist the reader in making appropriate interpretations of the results given the small sample size, confidence intervals are provided for the exploratory analyses. Despite the sample size limitation, the results provide preliminary evidence that *APOE* ε4 carriage may negatively bias estimated rates of brain and cognitive aging even in robust samples, and encourage future studies of aging to further examine this possibility. Rather than testing hypotheses, exploratory analyses were conducted in the present study with the aim of hypothesis

generation and to provide a springboard for future studies to investigate these questions with larger samples. There have been limited investigations specifically into the role of *APOE* ε4 carriage in Aβ- older adults. Because *APOE* ε4 carriers are more likely than non-carriers to later become Aβ+ and develop AD, studying individuals who remain Aβ- and CN despite their genetic risk can elucidate the effects of carrying this allele and whether its effects are dependent or independent of other factors that may influence Aβ accumulation. Finally, the present study could not examine gene-dose effects of *APOE* ε4 on trajectories of cortical atrophy or cognitive change because no *APOE* ε4 homozygotes were included in the Aβ- sample. Replication analyses with large prospective population-based samples such as the Mayo Clinic Study of Aging [55] would be ideal to isolate the effects of *APOE* ε4 in aging while controlling for gene-dose effects and for Aβ accumulation.

7.4.2 Conclusions

It is proposed that studies of aging should include only individuals with no evidence of preclinical neuropathological processes, detected either through prospective clinical assessment of cognitive status or through measurement of AD-associated biomarkers such as Aβ. This "robust" sample would therefore be more adequately suited to examine changes associated with the normal process of aging than samples than contain individuals with incipient neurodegenerative disease. The main question this study endeavoured to answer is whether *APOE* ε4 carriers, who are at increased risk for AD, can be considered to be aging normally even in the absence of AD neuropathological markers such as Aβ+ or clinical disease progression. Initial results suggested that aging studies need not be concerned about inclusion of *APOE* ε4 carriers in robust samples because no effect of *APOE* ε4 carriage was observed on rates of cortical atrophy or cognitive change over the 8-year study period. However, further exploratory analyses found that faster GM volume loss was associated

with greater verbal memory decline in *APOE* ε4 carriers. This suggests that inclusion of *APOE* ε4 carriers may bias results of studies aiming to examine the process of aging in the absence of preclinical neurodegenerative processes. Whether the observed effect is due to the effect of *APOE* ε4 carriage itself or whether it is reflective of an indirect effect of Aβ due to increased Aβ accumulation for Aβ- *APOE* ε4 carriers is yet to be determined. Overall, the results of this study provide preliminary evidence suggesting that studies of aging endeavouring to employ robust sampling methods should be cautious about including *APOE* ε4 carriers, or should at least ensure that carrier status is statistically controlled in their models.

Chapter 8: General Discussion

8 General Discussion

Models of cognitive and brain aging suggest that some cognitive decline and cortical volume loss is normal in aging beyond age 60 [281]. However, these models have failed to account for the presence of incipient neurodegenerative disease processes such as preclinical Alzheimer's disease (AD), which is detected by abnormally high levels of amyloid-β (Aβ). Prospective longitudinal studies of cognitive aging in older adults who are cognitively normal (CN) at baseline have reported general declines in cognitive functioning over time across multiple domains (e.g. memory, executive function, processing speed), supporting the commonly held belief that cognitive decline is a normal part of the aging process [112,116–119]. However, the evidence to support this is conflicting [81,111,115]: individuals aged over 90 or 100 can remain CN [80–84], and there have been reports of little-to-no decline in memory and executive function for CN older adults up to age 95 with subthreshold levels of Aβ (i.e. Aβ-) over 5-10 years [66,71,147]. Therefore, cognitive decline may not be universal nor inevitable. While existing estimates of brain aging for CN older adults also suggest that some cortical volume loss is likely with aging [151–157], estimated rates of atrophy are attenuated when examined in Aβ- samples [63–68].

Overall, these findings suggest that existing models of cognitive and brain aging are inaccurate because the process of aging must be examined independent of any incipient neuropathological processes. Aging persons need not expect their cognitive abilities to decline as they get older; negative beliefs about aging may lead to stigma and discrimination against older people, and cause undue worry and stress [342–344]. These beliefs may also adversely affect cognition [345–347], increase risk of future dementia [348–352], quality of life [353] and longevity [354]. Finally, although prevalence of Aβ+ increases with age, the

majority of older adults – even at advanced ages – maintain Aβ levels within normal range (Aβ-; 56-84% of CN aged 60-90) [22]. Taken together, these findings suggest that it is not only possible, but reasonably probable, to reach old age without cognitive decline or Aβ+.

The overarching aim of this thesis was to characterize the cognitive and brain morphological changes associated with normal aging, defined as the cognitive and neurobiological changes that occur with the passage of time independent of neuropathological processes such as Aβ+.

8.1 Summary of findings

8.1.1 Detrimental effects of Aβ+

The studies in this thesis consistently found that presence of Aβ+ in otherwise CN older adults was associated with poorer outcomes compared to those who were Aβ-. The first study [Chapter 3] reported greater risk of future clinical progression to mild cognitive impairment (MCI) or dementia for older adults with Aβ+, which was amplified by also being a carrier of the *APOE* ε4 allele or having relatively higher levels of Aβ burden. While some Aβ- participants also progressed to MCI or dementia, risk of clinical progression was not affected by *APOE* ε4 carriage or continuous Aβ levels. This finding suggested that clinical progression associated with Aβ+ is consistent with clinical-pathological models of AD, whereas progression in the absence of elevated Aβ deposition may be the result of neuropathological processes other than AD that accumulate with age. The subsequent studies [Chapters 4-6] further characterized the deleterious effects of Aβ+ on trajectories of cognitive and brain morphological changes, reporting faster rates of memory and executive function decline [Chapters 4, 6] and cortical atrophy [Chapters 5, 6] for Aβ+ compared to Aβ- older adults. These results suggest that, given the consistently poorer outcomes

associated with Aβ+ [65,66,206,337,355–357], trajectories of cognitive and brain morphological changes in Aβ+ are not reflective of normal aging processes.

Finding no age-associated memory changes for CN Aβ- older adults despite the presence of cortical and hippocampal atrophy in Chapters 4-5 led to the investigation conducted in Chapter 6 to further examine this unexpected dissociation, which suggested that relationships between cortical volume and cognitive change in CN older adults may be moderated by Aβ. In this study, cortical volume loss was not associated with any concurrent cognitive decline in CN Aβ- older adults; however, a relationship between grey matter volume loss and cognitive decline was observed when examined in the Aβ+ group. Thus, while some age-associated cortical volume loss does occur with normal aging, this does not necessarily give rise to cognitive decline. This suggests that so-called "age-associated cognitive decline" may be driven by incipient neurodegenerative processes rather than by the process of aging, itself.

8.1.2 Limited utility of neuropsychologically-defined SuperAging

Contrary to our hypotheses, classification of older adults as SuperAgers on the basis of neuropsychological performance was not reflective of a unique phenotype of aging above and beyond normal. No differences were observed in prevalence of Aβ+ or *APOE* ε4 carriage, nor in trajectories of cognitive or brain morphological changes between SuperAgers and case-matched individuals who were cognitively normal for their age (CNFA) in both Chapters 4 and 5. Individuals classified as SuperAgers were also not any more resilient to the deleterious effects of Aβ+ on cognition and cortical volume than were CNFA.

Overall, the studies included in this thesis found that neuropsychologically-defined SuperAging had limited utility in identifying individuals who would display preserved cognitive function and attenuated cortical atrophy over time. However, both studies

showed that Aβ- was associated with little-to-no cognitive decline and attenuated rates of cortical atrophy over time regardless of SuperAger classification. Given that the SuperAging construct was developed to describe a phenotype of preserved cognitive function in older age that may reflect unique neurobiological characteristics such as reduced cortical volume loss in aging, the observed trajectories for Aβ- older adults were better suited to this construct than were those of neuropsychologically-defined SuperAgers. Therefore, these results challenge those of previous SuperAging studies and suggest that classification criteria for SuperAging should be reconsidered to incorporate Aβ- status.

8.1.3 Estimates of cognitive and brain aging are negatively biased by Aβ+

The results from Chapter 6 extended previous findings [145] and confirmed that studies of aging can overestimate rates of age-associated cortical volume loss and cognitive decline due to inadvertent inclusion of Aβ+ older adults in otherwise CN samples. This work challenges previously well-established reports of cognitive decline with aging by showing no age-associated cognitive decline and attenuated rates of cortical volume loss for CN Aβ- older adults, as described in Section 1.1 above and in Chapters 4-6. Chapter 7 examined this further with a small, but robust, sample of older adults who remained both CN and Aβ- for at least 8 years. This study provided preliminary evidence that *APOE* ε4 carriage in CN Aβ- older adults may reflect the presence of pre-preclinical Aβ-associated neurodegenerative processes; however, further research with larger samples are necessary to support this finding. Taken together, the results suggest that studies aiming to examine the process of aging should do so with robust samples containing individuals that remain CN and Aβ-, and who also do not carry the *APOE* ε4 allele.

8.2 Implications for aging studies

The results of this thesis indicate that, in order to study the process of aging, the effects of incipient neurodegenerative disease must be separated from the cognitive and neurobiological changes that occur due to the passage of time. However, studies of cognitive and brain aging to date have not specifically excluded individuals with evidence of preclinical dementia or preclinical AD. Therefore, estimated rates of changes associated with aging have been conflated with preclinical disease processes [337]. The inadvertent inclusion of older adults who later progress from CN to MCI or dementia, or who have elevated levels of cerebral Aβ (Aβ+) leads to inflated estimates of cognitive decline or cortical volume loss that cannot be entirely attributed to the process of aging due to the presence of incipient neurodegenerative disease processes. The results from this thesis, other studies of Aβ-associated changes, and neuropathological studies suggest that little-to-no cognitive decline and attenuated rates of cortical atrophy are observed in aging when no neuropathological markers are present [63,139,337,358,359]. Therefore, current models of cognitive and brain aging provide inaccurate estimates of change associated with aging. Taken together, these results highlight the need for greater clarification in how "aging" is defined.

While this thesis defined aging as the passage of time and its effect on cognitive and neurobiological systems independent of any incipient or overt disease processes that may also act over time, other studies of cognitive or brain aging have not used such a precise definition. Such studies have not explicitly defined aging, but generally use the term in reference to longitudinal cognitive and brain morphological changes observed in the general population with increasing age. Although this approach can describe changes that are

commonly observed with aging, it does not separate the effects of age-associated diseases from the effect of aging, itself. Thus, little is understood about what changes are attributable to the process of aging independent of any other co-occurring processes.

If cognitive decline is not inevitable in aging, then understanding the cognitive changes that are associated with aging provides a relative baseline against which to examine changes observed in the presence of neuropathological processes to enable earlier detection of diverging trajectories. Additionally, by understanding the ways in which cognitive and brain morphological changes occur in aging, future translational research can make recommendations to increase the probability of successful aging by implementing modifiable lifestyle changes where possible to minimize the divergence from normal aging trajectories due to non-age-associated processes.

8.3 Implications for studies of successful cognitive aging

Identifying neuroprotective factors that support the maintenance of superior cognitive performance into old age could provide valuable insights into the process of successful aging that can then be applied to developing global health promotion initiatives. The construct of SuperAging was developed to describe a phenotype of preserved cognitive function in older age that may reflect unique neurobiological characteristics such as reduced cortical volume loss in aging [185,187,189]. Ideally, the SuperAging construct should be viewed as separate from any associated SuperAging criteria, which vary widely between studies. Future studies should formally test different classification criteria including neuropsychological, age and biomarker information to determine which criteria most adequately reflects the construct of SuperAging. The proposed pattern of little-to-no cognitive decline and minimal loss of cortical volume was not observed for individuals

classified as SuperAgers based on neuropsychological performance in Chapters 4-5. It was, however, observed in older adults who were Aβ-. Aside from SuperAgers displaying better memory and cognitive performance at baseline, there were no other substantial differences between SuperAgers and CNFA in the AIBL cohort. Maintenance of superior memory performance in older age could reflect a number of different things unrelated to the process of aging, such as early life conditions and childhood cognitive ability [360] or increased test-taking aptitude. Thus, the present findings suggest that the construct of SuperAging does represent a real phenomenon that is more readily identified using biomarker information than using neuropsychological criteria. However, what constitutes normal aging must first be understood in order to contextualize the concept of "successful" or "super" aging.

The results of this thesis suggest that normal cognitive and brain aging is characterized by preserved cognitive function and reduced cortical volume loss; therefore, instead of reflecting characteristics above and beyond that of normal aging, the constructs of SuperAging (or successful cognitive aging) and normal aging appear to have converged into one construct. Taken together, what was previously understood as "successful" aging may actually reflect the process of aging in the absence of neuropathological processes, i.e. what this thesis defines as normal aging. Old and old-old individuals who have maintained normal levels of Aβ can be argued to have displayed some degree of resistance to accumulation of Aβ, or to have been resilient to the cumulative exposures and biological wear-and-tear in aging that influence Aβ deposition. Whether a phenotype of aging exists that is "super" relative to normal remains unknown; however, the concept of "successful" or "super" aging in the context of this thesis would now suggest a pattern of resistance to the effects of time on cognitive and neurobiological systems. Future studies would need to

examine this possibility relative to changes associated with normal aging to identify any truly “super” patterns.

The concept of successful aging is an evocative one; for the average person, the notion evokes an intuitive and subjective picture of successful aging even without being given an operational definition. In other words, most people already know what “successful aging” means to them. However, the words “successful” or “super” also imply a value judgement that may consequently devalue the concept of normal aging or any other description of aging that may be viewed as lesser-than (e.g. “not successful”), despite the possibility that the constructs of SuperAging and normal aging actually represent the same phenomenon. Such a response would be counter to the intentions of proposing the concept of successful aging in the first place. Therefore, while the proposed construct of SuperAging may represent a real phenomenon, the results presented in this thesis suggest that this phenomenon is more reflective of normal aging processes independent of incipient neurodegenerative disease processes. In conclusion, it may be more beneficial for this to be described as normal aging rather than successful or SuperAging in order to promote the value of normal aging with the general population.

8.4 Limitations

Specific limitations of each study included in this thesis have been discussed within each chapter. An overall limitation is that all analyses were focused on the abnormality of Aβ, determined by Aβ burden being greater than a predefined threshold. While Aβ+ was a significant risk factor for clinical disease progression, it is a poor predictor of progression over an 8-year period as indicated by 17.7% of the Aβ+ group having progressed to MCI or dementia during the study period. This suggests that progression may be driven by the co-

occurrence of other neuropathological changes with Aβ+. Aβ was the only neuropathological marker consistently available for a large proportion of the AIBL CN sample; therefore, measures of tau or markers of other non-AD neurodegenerative processes that can be measured *in vivo* such as hippocampal sclerosis, neurofilament light, or infarcts, for example, were not included in the present studies. However, differential trajectories of cognitive and brain morphological changes were still observable on the basis of Aβ abnormality alone, despite lacking information about the presence of any other co-occurring neuropathological markers in this sample. This thesis, therefore, provides a foundation for future studies to examine the process of aging independent of neuropathological processes beyond just Aβ+. While defining robust samples as older adults who remain CN and Aβ- may more accurately describe the aging process than previous cognitive and brain aging studies to date, refining these samples using more markers of neuropathological changes that can be measured *in vivo* will further increase the specificity of these robust samples to examine the process of aging in the absence of any incipient disease processes.

8.5 Future directions

Prospective cohort studies and clinical-pathological studies agree that the presence of Aβ+ is associated with poorer cognitive and brain morphological outcomes [63,139,337,358,359], and that more advantageous outcomes are observed for individuals who remain Aβ- across their lifespan. However, whether any modifiable lifestyle factors can prevent the accumulation of Aβ or increase its clearance remains unknown. Some possible factors from recent research include increased lifetime coffee consumption [361], better quality sleep [362], and stress reduction [363,364], but no findings have yet been strong

enough to substantiate definitive recommendations to increase likelihood of remaining Aβ- in aging. More research is required to examine modifiable factors that can reduce Aβ burden in older age. Future prospective research may also conduct analyses within the group of people who remain Aβ- to the most recent time point to determine if any factors indicative of resistance to Aβ+ can be identified. By determining ways to reduce the probability of becoming Aβ+ in older age, the risk of developing MCI or AD dementia will also be reduced, which can enable older adults to live well for longer.

Aging was examined in this thesis with reference to chronological age; however, it has been shown that an individual's chronological age and biological age are not necessarily the same, and that biological age would reflect the presence of any incipient neurodegenerative or systemic disease [365–367]. This suggests that examinations of cognitive and brain morphological changes associated with biological age in the absence of neuropathological processes may reveal more specific insights into the nature of normal aging processes.

8.6 Conclusions

This thesis challenges widely-accepted models of cognitive and brain aging by showing that aging, defined as the passage of time and its effect on biological systems independent of any incipient or overt disease processes that may also act over time, is characterized by preserved cognitive function and minimal cortical volume loss. Therefore, cognitive decline is not inevitable in aging. It may be argued that the presence of Aβ+, AD, dementia and any other age-associated neurodegenerative conditions in older age are not reflective of normal aging; instead, these may reflect disease processes and accumulation of biological wear-and-tear interacting with the passage of time that, therefore, cannot be considered

"normal" in the process of aging. The results of this thesis show that it is possible, and even probable, for individuals to reach old age without Aβ+ or cognitive decline; however, it is of great importance that future research endeavour to develop models to make these beneficial outcomes even more probable.

Overall, simply highlighting the existence of older adults who are able to reach old age without significant cognitive decline, cortical atrophy or markers of age-associated neuropathological disease is extremely important in igniting a sense of hope in young and old adults that so-called successful aging, which may really be normal aging, is a real possibility. The evidence presented by this thesis can potentially replace the common belief that aging is necessarily associated with declining memory and cognitive ability with the understanding that cognition does not have to decline as we get older. It is hoped that sharing this message with the aging population will increase the sense of agency that older people have to remain positively engaged with life.

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Appendix A: Published Work Arising from Thesis

Journal of Alzheimer's Disease 65 (2018) 1313–1325
DOI 10.3233/JAD-180507
IOS Press

Relationship Between Amyloid-β Positivity and Progression to Mild Cognitive Impairment or Dementia over 8 Years in Cognitively Normal Older Adults

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ISSN 1387-2877/18/$35.00

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Accepted 26 July 2018

Background: Preclinical Alzheimer's disease (AD) is defined by cerebral amyloid-β positivity (Aβ+) in cognitively normal (CN) older adults.
Objective: To estimate the risk of progression to the symptomatic stages of AD due to PET Aβ+ and the extent that progression was influenced by other demographic, genetic, and clinical characteristics in a large prospective study.
Methods: Fine-Gray subdistribution modeling was used to examine the risk of progression from CN to MCI/dementia due to Aβ+, *APOE ε*4 carriage, and their interaction in the Australian Imaging, Biomarkers and Lifestyle (AIBL) flagship study of aging CN cohort ($n = 599$) over 8 years.
Results: 17.7% Aβ+ and 8.1% Aβ– progressed over 8 years (OR: 2.43). Risk of progression for Aβ+ was 65–104% greater than Aβ–. Aβ+ *APOE ε*4 carriers were at 348% greater risk than all other participants. Significant risk factors of progression in Aβ+ were age (HR: 1.05), PET SUVR (HR: 2.49) and APOE *ε*4 carriage (HR: 2.63); only age was a significant risk factor in Aβ– (HR: 1.09). Aβ– progressors were not near the threshold for Aβ+. These relationships were not moderated by hypertension, diabetes, obesity, or stroke/TIA.
Conclusion: Aβ+ is an important prognostic marker for progression from CN to MCI/dementia in older adults and *APOE ε*4 carriage provides further predictive value in the presence of Aβ+. These data suggest that Aβ-associated clinical progression is consistent with clinical-pathological models of AD, whereas progression in the absence of elevated Aβ deposition may be the result of neuropathological processes other than AD that accumulate with age.

Keywords: Alzheimer's disease, *APOE ε*4, biomarkers, dementia, mild cognitive impairment

INTRODUCTION

Clinical-pathological models propose that Alzheimer's disease (AD) begins with accumulation of amyloid-β (Aβ) followed by aggregation of tau, which result in cortical atrophy, cognitive decline and, ultimately, dementia [1, 2]. Biomarker studies using positron emission tomography (PET) neuroimaging or cerebrospinal fluid (CSF) sampling show that Aβ accumulation begins up to 20 years prior to the onset of dementia [3]. According to these models, cognitively normal (CN) older adults with elevated levels of Aβ (Aβ+) are in the preclinical stages of AD [2, 4]. Even though CN Aβ+ individuals are clinically asymptomatic, preclinical AD is characterized by subtle progressive cognitive decline, primarily in episodic memory [5], which may reflect insidious loss of cortical brain volume due to Aβ+ [6–8]. Prospective studies in both experimental and epidemiological cohorts have indicated that CN Aβ+ adults have higher risk of progression to clinical classification of mild cognitive impairment (MCI) or dementia compared to those without elevated Aβ (i.e., Aβ–) [9, 10]. Clinical trials of Aβ-lowering drugs have endeavored to recruit CN Aβ+ older adults based on their increased risk for incident MCI/dementia in an attempt to slow cognitive decline and prevent onset of symptomatic AD (e.g. Clinical Trials NCT02569398 and NCT02008357) [11]. Furthermore, recently proposed guidance from the US Food and Drug Administration (FDA) acknowledges the centrality of biomarkers such as Aβ+ for recruitment of participants for early AD clinical trials, where Stage 0 includes individuals who are asymptomatic but have evidence of AD pathophysiologic changes [12]. Understanding the risk of progression to MCI/dementia associated with Aβ+ over the long time periods characteristic of preclinical AD is therefore necessary to inform models of disease etiology and guide recruitment and outcome expectations in clinical trials or clinical studies of preclinical AD and AD.

Incidence of progression to MCI/dementia in large samples of Aβ+ CN adults ranges from 17.7% over an average of 3.7 years in the Mayo Clinic Study of Aging (MCSA, mean age 76) [10], 26.4% over 5 years in the Knight Alzheimer's Disease Research Center study (Knight ADRC, mean age

72) [13], 19% over 6 years in the Australian Imaging, Biomarkers and Lifestyle study (AIBL, mean age 73) [14], to 32.2% over an average of 4 years in the Alzheimer's Disease Neuroimaging Initiative (ADNI, mean age 74) [15]. In all studies, the incidence of progression was at least two times greater in Aβ+ compared to Aβ–. Together, these studies show that Aβ+ increases risk for clinical disease progression in CN adults, although the error associated with some risk estimates is increased by the small sample sizes at the longer follow-up intervals [16]. For example, in ADNI, data beyond 4 years were available for 16% of the initial Aβ+ sample [15]. Similarly, estimates of progression at 5 years were based on 25% of the baseline MCSA sample [10], and 35% of the Knight ADRC data were available beyond 5 years [17]. These small samples limit the use of complex analyses to examine the influence of other characteristics proposed to hasten progression to symptomatic disease (e.g., age, interactions between apolipoprotein E (*APOE*) ε4 carriage and Aβ status) [18]. *APOE* ε4 carriage is associated with increased risk of both Aβ+ and dementia in CN older adults [19, 20], and neuropsychological studies show that Aβ+ *APOE* ε4 carriers experience greater cognitive decline than Aβ+ *APOE* ε4 non-carriers [18, 21, 22]; therefore, the prognostic value of Aβ and *APOE* ε4 may be increased by examining their effects combined. Finally, although there is evidence that vascular and metabolic conditions increase risk of cognitive impairment and dementia in CN adults [23, 24], few studies have sought to account for their influence on estimates of Aβ-associated clinical progression. Although the prevalence of vascular disease in the population-based MCSA is higher than that found in controlled experimental samples [25], it was reported that adjustment for vascular diseases did not change their progression risk estimates [10]. Whether this remains the case in a large experimental cohort is yet to be seen.

The first aim of this study was to examine the incidence of Aβ-associated progression to MCI/dementia among CN older adults. The second aim was to identify demographic and clinical characteristics that moderate the relationship between Aβ status and progression. The first hypothesis was that Aβ+ would be associated with greater risk of clinical disease progression over 8 years. The second hypothesis was that Aβ-associated progression to MCI/dementia would be increased further by *APOE* ε4 carriage. *Post-hoc* analyses explored how demographic and clinical risk factors influenced clinical disease progression in Aβ+ and Aβ– CN adults.

METHODS

Participants

Participants were enrolled in the AIBL flagship study of aging, details of which have been described elsewhere [26]. Briefly, volunteers were excluded from entry if they had any of the following: non-AD dementia, history of schizophrenia or bipolar disorder, current depression (Geriatric Depression Scale score >5), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, obstructive sleep apnea, past head injury with >1 hour of post-traumatic amnesia, or current regular alcohol intake above recommended limits [27]. Health status at each study visit was determined from clinical assessment comprising measurement of vital signs (height, weight, waist circumference, and blood pressure using an electric sphygmomanometer) and self-reported medical history. Blood pathology for all participants was assessed at baseline. All included participants were identified to have no, or medically well-controlled systemic illnesses at baseline. Ethics approval for the AIBL study was granted by St Vincent's Health, Austin Health, and Edith Cowan University, and written informed consent was collected from all participants prior to clinical and neuropsychological assessment at every 18-month interval.

Currently, the AIBL study includes 787 CN adults aged above 60 years who have undergone Aβ PET neuroimaging. Participants were recruited in two waves: an inception cohort ($n = 444$) followed for up to 8 years, and an enrichment cohort ($n = 343$) followed for up to 4.5 years. Of the initial cohort, 70.5% have remained active in the study for all visits up to 8 years. This study sample was restricted to those who attended at least two visits over the 8-year period ($n = 621$). Data for 19 participants with inconsistent clinical classification ($n = 16$) or Aβ status ($n = 3$) during the study period were excluded from all analyses. Twenty participants had incomplete covariate data, which were imputed based on information contained in their clinical visit notes where possible. One participant who met exclusion criteria but was inadvertently included in the AIBL study was also excluded. Thus, the total sample for this study consisted of 599 older adults (Fig. 1).

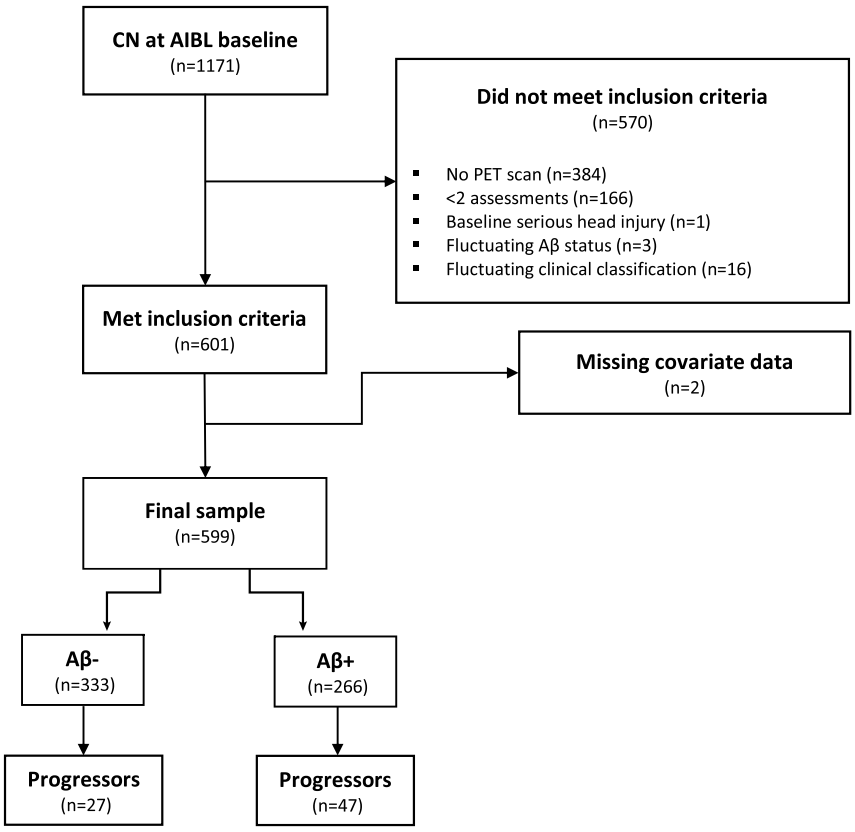

Fig. 1. Sample selection criteria. Selection criteria and final sample sizes for the present study.

Clinical classification of cognitive status

An expert clinical panel reviewed all available neuropsychological and psychiatric information for participants at each visit based on neuropsychologist referral. They were blinded to information about Aβ and *APOE* ε4 status, and consensus classifications were made using standard clinical criteria for MCI [28] and AD [29]. Participants classified with MCI/dementia during the follow-up period were coded as "progressors"; participants who did not meet those criteria were classified CN.

Measures

Self-reported history of stroke/TIA at any time before or during the study period and current hypertension or diabetes was recorded. *APOE* ε4 carriage was determined from whole blood extracted DNA [30], and fasting glucose and lipid concentrations were measured. Body mass index (BMI) was calculated using height and weight (kg/m^2). Education was coded as $\leq$12 years or >12 years. Baseline mood was assessed using the Hospital Anxiety and Depression Scale (HADS) [31], and the Memory Complaint Questionnaire (MAC-Q) [32] was used to assess subjective memory complaint.

Amyloid PET neuroimaging

PET neuroimaging was conducted using one of the following Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB, $n = 216$), ^{18}F-NAV4694 (NAV, $n = 56$), ^{18}F-Florbetapir (FBP, $n = 158$), or ^{18}F-Flutemetamol (FLUTE, $n = 169$). PET methods and

procedures have been reported previously [33, 34]. Briefly, PET acquisitions were performed up to 90 min following tracer injection. Standardized uptake value (SUV) data were summed and normalized to a reference region (the cerebellar cortex for PiB and NAV, the whole cerebellum for FBP, and the pons for FLUTE) to generate a SUV ratio (SUVR). Threshold values for elevated Aβ deposition vary by radiotracer, so a linear regression transformation was applied to the FBP and FLUTE SUVR to create a "PiB-like" SUVR unit called Before the Centiloid Kernel Transformation (BeCKeT) [34]. All participants with SUVR/BeCKeT$\geq$1.40 at their most recent PET scan were classified Aβ+ and those below the threshold were classified Aβ–; however, participants whose SUVR/BeCKeT fluctuated around the threshold on multiple PET scans could not be accurately classified and were therefore excluded from all analyses.

Statistical analyses

Baseline group differences

All continuous variables were assessed for normality by visual inspection of Q-Q plots. Between-group comparisons for Aβ status were conducted using a one-way analysis of variance (ANOVA) for normally distributed variables. Kruskal-Wallis one-way ANOVAs were used for non-normally distributed variables. Fisher's exact tests were used for dichotomous variables. Effect sizes (Cohen's *d*) were calculated for all comparisons reaching statistical significance.

Survival analysis

Fine-Gray subdistribution hazards models were fit to examine risk of clinical disease progression in the presence of competing risks. Progression to MCI/dementia were coded as events, and time to event or censoring was entered in months from the baseline visit. Death or withdrawal from the study due to illness were coded as competing risks because the deceased have no risk of clinical progression and those who withdraw due to illness may have higher risk [35]. Schoenfeld residuals tests indicated that the proportional hazards assumption was met. No outliers were detected.

Survival models evaluated the main hypotheses in 5 stages. Model 1 included characteristics that differed between Aβ groups at baseline (age, hypertension, and BMI). Model 2 added Aβ status, and Model 3 added *APOE* ε4 status. To examine the effects of health factors proposed to influence disease progression, diabetes and stroke/TIA were added in Model 4. Finally, Model 5 included an Aβ status by *APOE* ε4 interaction to compare the hazard of progression between participants who had both Aβ+ and *APOE* ε4 against all other participants. Sex and education were not included in these models because no baseline differences were observed between Aβ groups on these factors. Hazard ratios with 95% confidence intervals were calculated, and the cumulative hazard functions were plotted. All statistical analyses were performed using R version 3.4.3 and SPSS 23, with statistical significance at $p < 0.05$. Results were interpreted on the basis of the hazard ratios and confidence intervals; therefore, no adjustments were made for multiple comparisons.

Post-hoc analyses

Model 4 was repeated within the Aβ+ and Aβ– groups separately to examine differences in risk of clinical disease progression associated with Aβ status. These analyses used continuous PET SUVR/BeCKeT to assess the relative effect of Aβ deposition on progression within the pre-defined ranges for the Aβ– and Aβ+ groups.

RESULTS

Sample characteristics and attrition

Details of the study sample are shown in Fig. 1. Of the 599 included participants, 74 progressed to MCI or dementia over the 8-year period (CN->MCI->dementia = 7, CN->MCI = 58, CN->dementia = 9; median time to progression: 36.5 months, ranging from 16–94 months). During the study period, 15 participants died, 20 withdrew due to ill health (3 of whom did so after progressing), 50 withdrew formally from the study and 4 were not contactable for follow-up. The median follow-up time was 88 months (interquartile range 54).

Average age of participants was 70 (range 60–90), and 55.8% had >12 years of education. Demographic and clinical characteristics, and prevalence of vascular and metabolic risk factors are shown in Table 1.

Baseline group differences

Table 1 summarizes the differences between Aβ groups at baseline. Aβ+ participants were 3 years older on average and more likely to be *APOE* ε4 carriers (odds ratio (OR): 3.45, 95% confidence

Table 1
Baseline sample characteristics

Measure	Full sample	Aβ–	Aβ+	*p*	*d*
n	599	333	266		
Aβ+, %	44.4	0	100		
APOE ε4 carrier, %	28.4	17.4	42.1	**<0.0005**	0.68
Age at baseline (y)	70.21, 70 (10)	68.99, 68 (9)	71.77, 72 (10)	**<0.0005**	0.47
Female, %	55.6	57.4	53.4	0.36	
Education >12 y, %	55.8	56.2	55.3	0.87	
HADS A	4.36, 4 (4)	4.44, 4 (5)	4.25, 4 (4)	0.37	
HADS D	2.69, 2 (3)	2.74, 2 (3)	2.63, 2 (3)	0.39	
MAC-Q	25.61, 25 (5)	25.50, 26 (5)	25.74, 25 (6)	0.82	
Stroke/TIA, %	8.7	8.7	8.6	1.00	
Hypertension, %	50.8	46.5	56.0	**0.02**	0.21
Systolic BP	138.00, 137 (22)	136.67, 135 (22)	139.67, 140 (20)	**0.03**	0.19
Diastolic BP	79.22, 80 (13)	79.03, 80 (13)	79.46, 80 (16)	0.82	
Diabetes, %	9.8	8.4	11.7	0.22	
Fasting glucose	5.12, 5 (0.70)	5.08, 5 (0.70)	5.17, 5 (0.70)	0.45	
Total cholesterol	5.51, 5.50 (1.40)	5.53, 5.50 (1.45)	5.49, 5.50 (1.40)	0.60	
Triglycerides	1.29, 1.10 (0.70)	1.33, 1.10 (0.80)	1.23, 1.10 (0.70)	0.09	
HDL	1.64, 1.58 (0.59)	1.63, 1.56 (0.61)	1.65, 1.62 (0.57)	0.44	
LDL	3.28, 3.30 (1.40)	3.28, 3.30 (1.35)	3.27, 3.30 (1.40)	0.71	
Waist circumference	93.00, 92 (17.50)	93.53, 92 (17)	92.32, 92 (18)	0.28	
BMI	26.55, 25.86 (5.59)	26.87, 26.30 (5.50)	26.14, 25.60 (5.35)	**0.02**	0.19
Current smoker, %	10.2	9.8	10.7	0.88	
Attended all 6 study visits, %	49.4	52.9	45.1	0.07	
Length of follow-up (months)	66.90, 88.50 (53)	68.62, 89 (53)	64.73, 75 (54)	0.10	

All descriptive statistics for continuous variables reported as mean, median (IQR); categorical variables reported as percentages. *p*-values shown for comparisons between Aβ groups; Cohen's *d* shown for comparisons with $p < 0.05$. Aβ+, elevated cerebral amyloid-β; *APOE* ε4, apolipoprotein epsilon 4 allele carriage; HADS A, Hospital Anxiety and Depression Scale – Anxiety; HADS D, Hospital Anxiety and Depression Scale – Depression; MAC-Q, Memory Complaint Questionnaire; TIA, transient ischemic attack; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

interval (CI): 2.37–5.01) than were Aβ– participants. Hypertension was more frequent in the Aβ+ group (OR: 1.46, 95% CI: 1.06–2.02), who also had higher systolic blood pressure (3mmHg) and lower BMI (0.7 kg/m^2) than the Aβ– group. *APOE* ε4 carriage in Aβ+ was associated with higher PET SUVR/BeCKeT [$F(1,264) = 19.79$, $p < 0.0005$; $d = 0.56$], but not in the Aβ– group [$F(1,331) = 0.45$, $p = 0.50$; $d = 0.10$].

Risk of progression to MCI or dementia

Aβ+ participants were significantly more likely to progress to MCI/dementia than Aβ– (17.7% vs 8.1%, OR: 2.43, 95% CI: 1.47–4.03). In all 5 survival models, every additional year of age at baseline conferred greater risk (7%) of progressing over the 8-year period for all participants (Table 2). In Model 2, Aβ+ status increased the risk of progression by 104% (Fig. 2a). In Model 3, *APOE* ε4 carriers had 114% greater risk than non-carriers (Fig. 2b). The risk conferred by Aβ+ was mediated by the addition of *APOE* ε4 into the model. Model 4 showed that the health factors had no influence on risk of progression, nor did they mediate risk due to Aβ+; no interactions were observed in *post-hoc* analyses. In Model 5, the Aβ and *APOE* ε4 interaction was significant: Aβ+ *APOE* ε4 carriers had 348% greater risk of progressing to MCI/dementia compared to all other participants. Further analysis showed that progression risk in Aβ+ *APOE* ε4 non-carriers (hazard ratio (HR): 1.08, 95% CI: 0.56–2.07) and Aβ– *APOE* ε4 carriers (HR: 0.72, 95% CI: 0.21–2.45) was not significantly greater than in Aβ– *APOE* ε4 non-carriers (Fig. 2c); therefore, it was appropriate to combine these three groups in the interaction analysis.

Clinical disease progression within Aβ+ and Aβ– groups

Examination of risk factors within the Aβ+ group showed that higher age, higher PET SUVR/BeCKeT, and *APOE* ε4 carriage increased risk of progression (Table 3). Risk increased by 5% for each additional year of age at baseline, and by 149% for every whole PET SUVR/BeCKeT unit increase. Lastly, risk of progression was 163% greater with *APOE* ε4 carriage. Within the Aβ– group, the only risk factor for

Table 2
Fine-Gray subdistribution models for the full study sample

MODEL 1	*p*	HR	95% CI	
Age	**<0.0005**	1.07	1.04	1.10
Hypertension	0.70	0.91	0.56	1.47
BMI	0.30	1.03	0.97	1.09
MODEL 2	*p*	HR	95% CI	
Age	**<0.0005**	1.06	1.03	1.09
Hypertension	0.61	0.88	0.55	1.42
BMI	0.20	1.04	0.98	1.09
Aβ status	**0.004**	2.04	1.25	3.33
MODEL 3	*p*	HR	95% CI	
Age	**<0.0005**	1.07	1.04	1.10
Hypertension	0.78	0.94	0.58	1.50
BMI	0.19	1.04	0.98	1.09
Aβ status	**0.04**	1.65	1.02	2.65
APOE ε4	**0.001**	2.14	1.36	3.36
MODEL 4	*p*	HR	95% CI	
Age	**<0.0005**	1.07	1.03	1.10
Hypertension	0.77	0.93	0.58	1.49
BMI	0.17	1.04	0.98	1.10
Aβ status	**0.04**	1.65	1.03	2.66
APOE ε4	**0.001**	2.10	1.34	3.28
Diabetes	0.62	0.82	0.37	1.80
Stroke/TIA	0.30	1.36	0.76	2.44
MODEL 5	*p*	HR	95% CI	
Age	**<0.0005**	1.07	1.04	1.10
Hypertension	0.88	0.97	0.60	1.55
BMI	0.23	1.03	0.98	1.09
Aβ status	0.88	1.05	0.55	2.02
APOE ε4	0.57	0.71	0.21	2.36
Diabetes	0.80	0.90	0.41	2.00
Stroke/TIA	0.50	1.23	0.68	2.24
Aβ+ and *APOE* ε4+	**0.03**	4.48	1.14	17.60

HR, hazard ratio; CI, confidence interval; Aβ, amyloid-β; *APOE* ε4, apolipoprotein epsilon 4 allele carriage; BMI, body mass index; TIA, transient ischemic attack.

progression to MCI/dementia was higher age (9%). Overlap in 95% confidence intervals were observed for all predictor variables between Aβ+ and Aβ– groups, although these overlaps were smallest for *APOE* ε4 carriage and PET SUVR/BeCKeT. The degree of overlap suggests that *APOE* ε4 carriage and greater Aβ deposition increased risk of progression for the Aβ+ group but not for the Aβ– group, and that this difference was significant [36].

DISCUSSION

Rates of Aβ+ progression from CN to MCI/dementia in the AIBL sample and the associated risk factors for both Aβ– and Aβ+ progression over 8 years are reported for the first time. The results supported the first hypothesis that Aβ+ would be associated with greater risk of progression to MCI/dementia. Eight-year risk of progression to MCI/dementia in CN Aβ+ adults from the AIBL study was increased by 65–104% compared to Aβ– (Table 2). This indicates that Aβ+ is an important prognostic marker for progression to MCI/dementia in CN older adults. The second hypothesis, that Aβ-associated risk for progression to MCI/dementia would be increased further by *APOE* ε4 carriage, was also supported. The large sample studied here allowed the risk of progression conferred by concurrent Aβ+ and *APOE* ε4 carriage to be estimated, taking into account health factors posited to influence progression to MCI/dementia as well as competing risks such as death or withdrawal due to illness. Risk of progression to MCI/dementia was 348% greater in Aβ+ *APOE* ε4 carriers compared to all other participants (Table 2). Similar findings were observed in the MCSA, although their risk estimate was reported relative to Aβ– *APOE* ε4 non-carriers (190%) [37]. In this study, no difference in risk was observed between Aβ– *APOE* ε4 non-carriers, Aβ– *APOE* ε4 carriers and Aβ+ *APOE* ε4 non-carriers, suggesting an additive effect between Aβ+ and *APOE* ε4 carriage that is greater than the sum of their individual contributions. This is consistent with results of neuropsychological studies showing that CN Aβ+ *APOE* ε4 carriers experience greater cognitive decline over time with earlier onset [18, 21, 22, 38]. In agreement with a recent report that episodic memory performance remains stable in Aβ– regardless of *APOE* ε4 status, *APOE* ε4 carriage did not increase the risk of clinical disease progression in Aβ– (Fig. 2c) [38]. Previous research shows that *APOE* ε4 reduces clearance of cerebral Aβ but does not affect rates of Aβ production [39]; therefore, the findings of this study indicate that the impaired clearance of Aβ due to *APOE* ε4 is most clinically significant in individuals who have high levels of Aβ.

As progression to MCI/dementia was observed in a small number of individuals with normal Aβ levels (8.1%), risk factors within the Aβ+ and Aβ– groups were investigated. Previous studies indicate that health conditions such as hypertension, diabetes, or stroke/TIA can contribute to cognitive decline and clinical disease progression in older adults [23, 24, 40]. Although higher prevalence of hypertension and lower BMI was observed in the Aβ+ group, these differences were very small. Thus, both groups had similar cardiovascular risk profiles and these factors did not influence risk of progression within either Aβ group. For both Aβ groups, higher age at baseline

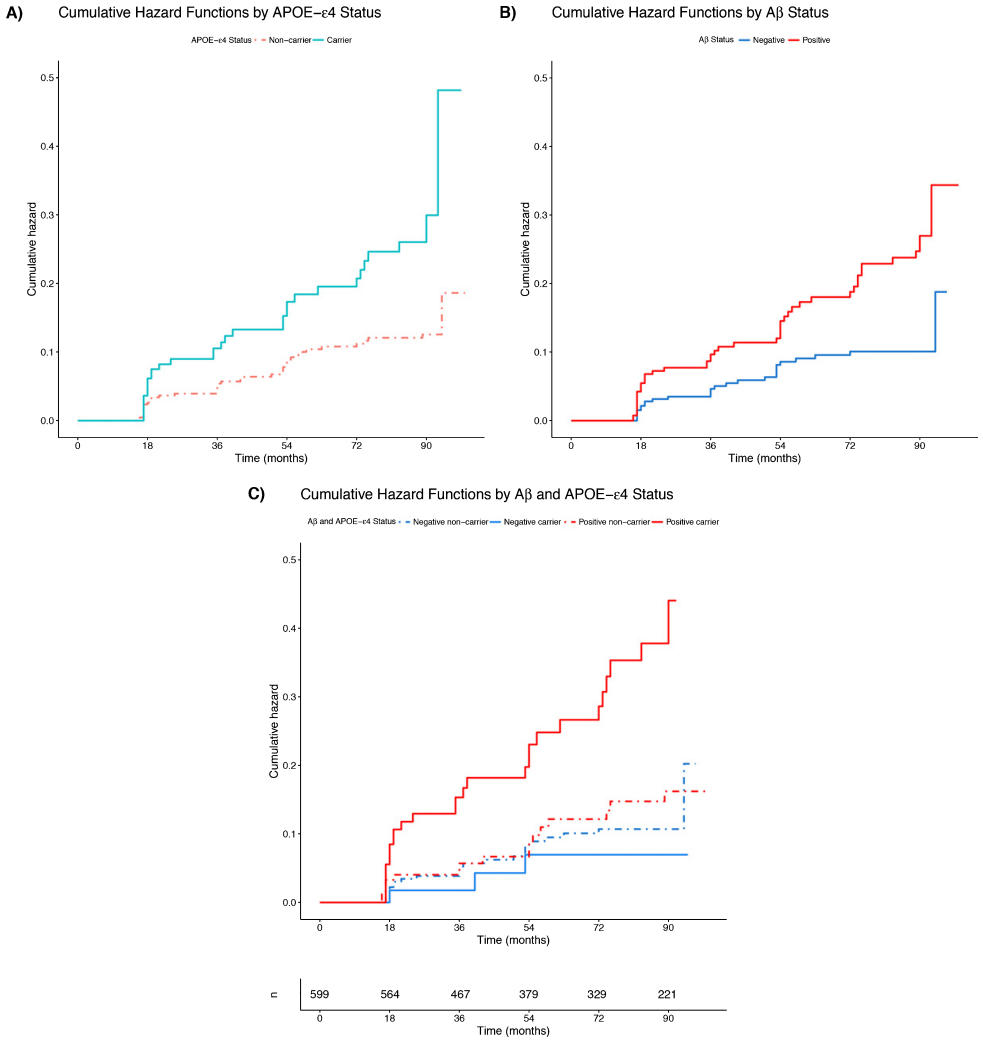

Fig. 2. Cumulative hazard functions for APOE ε4 status, Aβ status, and combined APOE ε4 and Aβ status. Cumulative hazard functions shown for A) APOE ε4 status, B) Aβ status, and C) combined APOE ε4 and Aβ status, indicating that APOE ε4 carriage and Aβ+ are independently and cumulatively associated with increased risk of progression to MCI/dementia. Total sample size at each time point is displayed at the bottom.

was associated with increased risk of progression to MCI/dementia (Table 3). Although Aβ deposition, and therefore risk of disease progression, is known to increase with age [41], other neuropathological processes such as brain atrophy are also associated with age [42]. Higher relative Aβ deposition increased progression risk in the Aβ+ group by 150%; however, PET SUVR/BeCKeT for Aβ− progressors was not near the threshold for Aβ+ (median 1.16, range 1.02–1.39) making it unlikely that progression in the Aβ− group was due to any unrecognized increase in Aβ. While it remains unknown whether abnormal levels of Aβ deposition play a causative role in the development of dementia due to AD, the recent

Table 3
Fine-Gray subdistribution models within the Aβ– and Aβ+ groups

	Aβ–				Aβ+			
	p	HR	95% CI		*p*	HR	95% CI	
Age	**0.01**	1.09	1.02	1.16	**0.01**	1.05	1.01	1.08
Hypertension	0.57	0.78	0.33	1.84	0.63	1.15	0.65	2.06
BMI	0.35	1.05	0.95	1.16	0.56	1.02	0.95	1.09
Aβ (PET SUVR)	0.10	0.02	0.00	2.00	**<0.0005**	2.49	1.60	3.88
APOE ε4	0.61	0.73	0.22	2.46	**0.004**	2.63	1.37	5.03
Diabetes	0.63	0.72	0.19	2.74	0.98	1.01	0.37	2.78
Stroke/TIA	0.96	0.97	0.30	3.17	0.57	1.22	0.62	2.39

HR, hazard ratio; CI, confidence interval; Aβ, amyloid-β; PET SUVR, positron emission tomography standardized uptake value ratio; *APOE* ε4, apolipoprotein epsilon 4 allele carriage; BMI, body mass index; TIA, transient ischemic attack.

NIA-AA Research Framework proposed that AD be defined by the presence of cortical Aβ and tau aggregates and neurodegeneration rather than by clinical symptoms due to the poor specificity of cognitive symptoms to detect AD neuropathological processes [4]. Taken together, these data suggest that Aβ-associated clinical progression is consistent with AD neuropathological changes, whereas progression in the absence of elevated Aβ deposition is the result of disease processes other than AD that accumulate with age [43]. This indicates that the prognostic value of Aβ+ is specific to dementia due to AD.

Despite the longer time interval and greater statistical control over demographic, health and clinical characteristics, the 17.7% incidence of progression due to Aβ+ was consistent with that observed previously over 6 years (19%) in the AIBL sample [14]. However, the current 8-year estimate of Aβ-associated progression remained lower than those reported in the ADNI (32.2%) and Knight ADRC (26.4%) cohorts over similar time periods [15, 44], and was equal to that reported by the MCSA (17.7%) over an average of 3.7 years [10]. The relatively lower incidence of progression in AIBL may reflect differences in the samples studied and the respective inclusion/exclusion criteria. For example, the ADNI and Knight ADRC cohorts were, on average, 2–4 years older than AIBL and the MSCA cohort was 6 years older than the AIBL cohort. The population-based MCSA cohort reports higher prevalence of risk factors other than Aβ+ for MCI/dementia: at baseline, 79.4% of the MCSA participants had hypertension, 18.7% had diabetes, and 14.3% had history of stroke [25], compared to 38.8%, 7.3% and 1.8%, respectively, in the AIBL CN cohort. Despite the increased presence of these factors and older age in the MCSA, the estimates of Aβ-associated progression were similar and may also reflect comparable methods for measuring Aβ deposition and defining Aβ+ using PET; however, the follow-up time for the MCSA was shorter than that for AIBL and may be expected to increase with similar follow-up. It is also possible that the higher incidence of disease progression in the other samples reflects some unreliability in their estimates due to small sample size or differences in method of Aβ+ classification. Both ADNI and Knight ADRC used different cut-off values and either PET neuroimaging or CSF amyloid sampling to classify Aβ status across participants, while both AIBL and the MCSA used only PET to measure Aβ levels in all participants; therefore, differences between the Aβ+ samples identified in these studies may also reflect different prospective estimates of incident MCI/dementia. Measuring Aβ levels with a common method for all participants rather than using different biomarkers to do so will increase the reliability of classification. Finally, the methods utilized to define clinical status vary across the different studies. The Knight ADRC relies on CDR score to classify participants and, while AIBL and the MCSA both use a consensus panel to determine clinical status, these panels define cognitive impairment differently ($\leq$–1.5 SD on two tests versus $\leq$–1 SD on one domain score). ADNI also utilizes clinical consensus classifications; however, the public availability of this data has meant different researchers have also utilized CDR ratings and actuarial neuropsychological approaches to define clinical status, which itself has resulted in different estimates of Aβ-associated progression [15, 45, 46]. These varying approaches to clinical classification and sample selection may explain the differences in estimates of Aβ+ progression between studies. Findings of consistency or inconsistency in outcomes between different samples is crucial because this provides information about the effects of potential sampling bias associated with the

different studies on models of disease progression and the disease processes reported from these individual cohorts. Lower incidence of progression in the current study may reflect the larger sample sizes at longer follow-up times, the more stringent criteria for cognitive impairment, the use of consensus classification, and the more exclusive sample when compared to the other large studies of preclinical AD. Nonetheless, these data indicate that Aβ+ is an important factor for clinical disease progression in AD.

A recent consensus group reported the importance of established and putative risk factors for dementia among older adults, and stated that the predictive value of Aβ+ for progression to MCI/dementia was equivocal over 3 years [47]. While they agreed that age and *APOE ε*4 carriage were important risk factors of clinical progression to symptomatic disease, these factors are non-modifiable. The group, therefore, considered other potentially modifiable risk factors and concluded that hearing loss, hypertension and obesity in midlife, and smoking, depression, physical inactivity, social isolation, and diabetes in late-life held greater prognostic utility than did Aβ [47]. The present study examined risk factors for progression accounting for age and *APOE ε*4 carriage and showed that Aβ+ was a strong predictor of clinical disease progression in CN adults over 8 years, while health factors such as hypertension, diabetes and obesity were not. The current findings converge with that from other prospective studies of Aβ+ risk for MCI/dementia, suggesting that the consensus position be reconsidered with data from longer prospective studies, given that the preclinical stages of AD can extend for up to 20 years [3].

Some aspects of this study limit the generalizability of its findings to a wider population. First, the AIBL study utilized a convenience sample and recruited healthy and well-educated older adults. Participants who did not progress were more likely to have attended all study visits, suggesting the presence of a healthy survivor effect. This may have contributed to the lack of relationship between health factors and disease progression in this study; hence, conclusions drawn here about the influence of these aspects of health on late-life risk for MCI/dementia should be challenged in similar studies using population-based sampling methods, such as the MCSA, using midlife health risk factors where possible. Although the number of participants retained in AIBL at 8 years was larger than the sample sizes of the other studies at their longest intervals and AIBL had the longest average follow-up time, even longer follow-ups are necessary to elucidate the disease course and risk factors for MCI/dementia. For this reason, it is not known whether those who did not progress over the study period will go on to progress in the future. Furthermore, as Aβ-associated progression was the focus on this study, neurodegeneration measures were not examined. Despite these caveats, the current results indicate that Aβ+ has strong prognostic value for the development of clinical symptoms of dementia due to AD even when health factors and competing risks for progression are taken into account. *APOE ε*4 carriage provides further predictive value in the presence of elevated Aβ; therefore, Aβ+ *APOE ε*4 carriers are ideal candidates for early intervention trials of disease-modifying therapies.

ACKNOWLEDGMENTS

CD is a recipient of the Melbourne Research Scholarship. Funding for the AIBL study was provided in part by the study partners [Australian Commonwealth Scientific Industrial and research Organization (CSIRO), Edith Cowan University (ECU), Mental Health Research Institute (MHRI), Alzheimer's Australia (AA), National Ageing Research Institute (NARI), Austin Health, CogState Ltd., Hollywood Private Hospital, Sir Charles Gardner Hospital]. The study also received support from the National Health and Medical Research Council (NHMRC) and the Dementia Collaborative Research Centres program (DCRC2), as well as ongoing funding from the Science and Industry Endowment Fund (SIEF). The authors acknowledge the financial support of the CRC for Mental Health. The Cooperative Research Centre (CRC) program is an Australian Government Initiative.

The AIBL study would like to thank all of the participants who took part in the study, their families, and the clinicians who referred participants.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-0507r1).

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Superior Memory Reduces 8-year Risk of Mild Cognitive Impairment and Dementia But Not Amyloid β-Associated Cognitive Decline in Older Adults

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Editorial Decision 5 September 2018; Accepted 11 September 2018

Abstract

Objective: To prospectively examine 8-year risk of clinical disease progression to mild cognitive impairment (MCI)/dementia in older adults ≥60 with superior episodic memory (SuperAgers) compared to those cognitively normal for their age (CNFA). Additionally, to determine the extent to which SuperAgers were resilient to the negative effects of elevated amyloid-beta (Aβ+) on cognition.

Method: Participants were classified as SuperAgers based on episodic memory performance consistent with younger adults aged 30–44 and no impairment on non-memory tests (n = 179), and were matched with CNFA on age, sex, education, and follow-up time (n = 179). Subdistribution hazard models examined risk of clinical progression to MCI/dementia. Linear mixed models assessed the effect of Aβ on cognition over time.

Results: Prevalence of Aβ+ and *APOE* ε4 was equivalent between SuperAgers and CNFA. SuperAgers had 69%–73% reduced risk of clinical progression to MCI/dementia compared to CNFA (HR: 0.27–0.31, 95% CI: 0.11–0.73, $p < .001$). Aβ+ was associated with cognitive decline in verbal memory and executive function, regardless of SuperAger/CNFA classification. In the absence of Aβ+, equivalent age-related changes in cognition were observed between SuperAgers and CNFA.

doi:10.1093/arclin/acy078

Conclusions: SuperAgers displayed resilience against clinical progression to MCI/dementia compared to CNFA despite equivalent risk for Alzheimer's disease (AD); however, SuperAgers had no greater protection from Aβ+ than CNFA. The deleterious effects of Aβ on cognition persist regardless of baseline cognitive ability. Thus, superior cognitive performance does not reflect resistance against the neuropathological processes associated with AD, and the observed resilience for SuperAgers may instead reflect neuropsychological criteria for cognitive impairment.

Keywords: Alzheimer's disease; Dementia; Mild cognitive impairment; Elderly/geriatrics/aging

Introduction

Neuropsychological models indicate that cognitive decline is an expected consequence of increasing age beyond 60 years (Harada, Natelson Love, & Triebel, 2013; Salthouse, 2009). For example, a recent meta-analysis of international aging studies observed that cognitive aging extends across all aspects of cognition, with the magnitude ranging from −0.26 to −0.12 *SD* units per decade from 60 years (Lipnicki et al., 2017). Most studies infer cognitive aging by observing that group mean test performance declines with the increasing age of the cohorts studied. However, variability associated with these means also increases with age, indicating that individual differences in cognitive aging become greater with increasing age (Christensen, 2001; Deary et al., 2009; Mungas et al., 2010; Wilson et al., 2002). Some of the increased individual differences in cognitive aging have been explained by the uncontrolled effects of preclinical neurodegenerative disease, such as Alzheimer's disease (AD), in aging samples (Harrington et al., 2017; Hassenstab et al., 2016; Jansen et al., 2018). For example, amyloid-beta (Aβ) biomarker studies show that approximately 16%–44% of older adults classified as cognitively normal (CN) have abnormally elevated Aβ in the brain (Aβ+) that is indicative of preclinical AD (Jansen et al., 2015). Despite being clinically asymptomatic, older adults with preclinical AD show subtle, but clear, cognitive decline, particularly in episodic memory and executive function (Baker et al., 2017; Hedden, Oh, Younger, & Patel, 2013). Consequently, inclusion of these individuals in samples of CN older adults can introduce negative biases in group mean performance that increase with age and lead to increased estimates of inter-individual variability (Harrington et al., 2017; Hassenstab et al., 2016; Hohman et al., 2017; Sliwinski, Lipton, Buschke, & Stewart, 1996).

Another explanation for increasing individual differences in cognitive aging is the presence of older adults who are resilient to cognitive decline despite their increasing age. Theoretical constructs proposed to describe these individuals include successful cognitive agers (Lin et al., 2017b; Negash et al., 2011; Pudas et al., 2013), resilient-agers (Bott et al., 2017), cognitively elite (Dixon & de Frias, 2014), supernormals (Lin et al., 2017a), optimal memory performers (Dekhtyar et al., 2017), and SuperAgers (Harrison, Weintraub, Mesulam, & Rogalski, 2012). While each construct describes similar phenomena with different operational definitions, the construct of SuperAgers currently provides the clearest psychological definition with the greatest neurobiological validity to date (Rogalski et al., 2013). The SuperAger concept originates from the perspective of Mesulam (2000) that individual differences in cognitive aging reflect a stochastic combination of non-modifiable factors such as time and genetics, and modifiable factors such as the cumulative neurobiological effects of a lifetime history of injuries and exposures (e.g., systemic illnesses, stress, head trauma, etc.). In this context, age, or the passage of time, increases the probability of encountering these events but does not guarantee them. Thus, a SuperAger is an older adult who has had reduced exposure, or is resilient, to these effects and their cognitive abilities have consequently been maintained from mid-life through to late-life. SuperAging studies therefore define SuperAgers as older adults with episodic memory performance at, or above, the mean of normative samples 20–30 years younger and with normal-for-age performance (i.e., scores not below −1 *SD* compared to normative means) on other cognitive domains (e.g., Harrison et al., 2012; Sun et al., 2016).

The SuperAger construct provides a useful foundation for studying resilience to age-associated cognitive decline because of its clear and well-validated psychometric classification criteria. For example, neurobiological investigations show that SuperAgers ≥80 years of age have greater preservation of cortical thickness compared to middle-aged adults, and reduced rates of cortical atrophy compared to cognitively normal for age (CNFA) adults (Cook et al., 2017; Gefen et al., 2015; Harrison et al., 2012). SuperAgers also show lower frequency of Aβ plaques and AD-type neurofibrillary tangles than CNFA on post-mortem examination, suggesting these individuals also possess increased resilience to neurodegenerative disease (Gefen et al., 2015). Together, these observations suggest that SuperAger classification is associated with some protection against the biological changes associated with both aging and neurodegenerative disease such as AD (Rogalski et al., 2013). This is consistent with findings from two prospective studies that these individuals are protected against cognitive decline measured from baseline over 18 months (Gefen et al., 2014) and up to an average of 5 years (Harrison, Maass, Baker, & Jagust, 2018). A recent prospective study also extended prior findings by showing that individuals classified as successful agers were also resilient to decline in episodic memory associated with Aβ+ (Harrison et al., 2018). This study retrospectively

classified older adults ≥70 enrolled in the Berkeley Aging Cohort Study (BACS) as successful agers if their performance on a list learning test was within the normative range of performance of 18–32 year-old adults on the same test, and normal-for-age performance on the Trail Making Test B (i.e., SuperAgers, as per Sun et al., 2016). In their sample of 150 adults with an average age of 75 years, 26 (17.3%) were classified as successful agers. Group mean levels of Aβ and the proportion of adults with Aβ+ were equivalent between the successful agers and the typical older adults (i.e., CNFA) at baseline assessment, consistent with another study of "optimal agers" (Dekhtyar et al., 2017). Although higher Aβ levels were associated with memory decline in the typical older adult group over an average of five years, individuals classified as successful agers showed no Aβ-associated decline in episodic memory (Harrison et al., 2018). Thus, while the superior memory performance characteristic of SuperAging was not associated with reduced accumulation of Aβ, it did provide resilience to the downstream effects of Aβ on episodic memory in these individuals.

The possibility that superior memory performance in older adults reflects resilience to the deleterious effects of Aβ must be considered cautiously with respect to the limitations of the aforementioned study (Harrison et al., 2018). First, the sample of successful agers was relatively small (i.e., $n = 26$) and the sub-sample of Aβ+ successful agers even smaller ($n = 10$). Studies measuring the effect of Aβ on cognitive decline in older adults show that such decline is observed only with abnormally high levels of Aβ (i.e., AB+) (Harrington et al., 2018). Thus, it is likely that the absence of any Aβ-associated memory decline in the successful ager group was due to a small sample and, therefore, inadequate statistical power for detecting group differences and interactions in longitudinal analyses (Button et al., 2013). A related issue is that the length of time for which follow-up data is available varies substantially between participants in BACS study sample. Reduced numbers of data points at the longer follow-up intervals also reduces the statistical power of analyses comparing slopes of cognitive change between groups and may additionally inflate the influence of any sample biases (Hansen & Collins, 1994). Third, although it is important to examine cognitive change over time in individuals classified as successful agers or SuperAgers, the clinical implications of these changes are difficult to determine when considered in isolation. One more meaningful criterion by which to assess the clinical consequences of SuperAger classification is the extent to which this protects individuals against clinical disease progression to mild cognitive impairment (MCI) or dementia.

The overarching aim of this study was to investigate the extent to which individuals classified as SuperAgers displayed resilience against cognitive decline associated with age and with AD. The first aim was to compare the 8-year risk of clinical disease progression to mild cognitive impairment (MCI)/dementia in a large group of older adults with superior episodic memory at baseline (SuperAgers) compared to CNFA. The second aim was to determine the extent to which SuperAgers were resilient to the negative effects of Aβ+ on cognition. The first hypothesis was that individuals classified as SuperAgers would be at reduced risk of progression to a clinical classification of MCI/dementia over 8 years when compared to well-matched CNFA adults. The second hypothesis was that SuperAgers would show greater resilience to the cognitive decline associated with preclinical AD (i.e., Aβ+) compared to their matched CNFA counterparts. We also explored the extent to which age influenced relationships between SuperAger classification, Aβ status, and prognosis.

Method

Participants

Participants were from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. The full study protocol has been previously reported (Ellis et al., 2009). Briefly, volunteers were ineligible for study entry if they met any of the following exclusion criteria: non-AD dementia, history of schizophrenia or bipolar disorder, current depression (Geriatric Depression Scale score >5), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, obstructive sleep apnea, past head injury with >1 hr of post-traumatic amnesia, or current regular alcohol intake of >4 standard drinks per day for men or >2 per day for women (National Health and Medical Research Council, 2001). Health status was determined from a medical assessment that included measurement of vital signs (height, weight, blood pressure, and abdominal circumference), blood tests, and self-reported medical history. Current health was reviewed for all participants at each study visit for the present study, and all included participants were identified to have no, or medically well-controlled systemic illnesses at baseline. Ethics approval for the AIBL study was granted by St Vincent's Health, Austin Health, Hollywood Private Hospital, and Edith Cowan University, and written informed consent was collected from all participants prior to undertaking any assessment procedures.

The AIBL study currently includes 620 CN adults who satisfied the baseline inclusion criteria, were aged over 60 with MMSE>24, underwent Aβ PET neuroimaging, and who have attended at least two study visits. These participants were recruited in two waves: an inception cohort ($n = 439$) followed every 18 months for up to 8 years, and an enrichment cohort ($n = 181$)

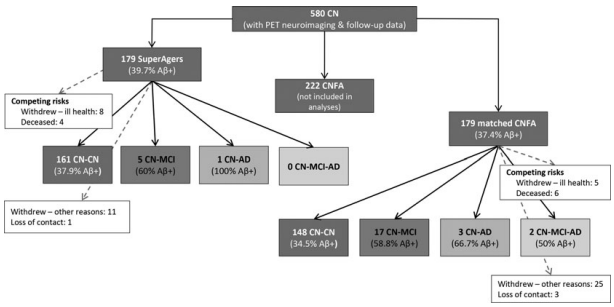

Fig. 1. Sample classification and clinical disease progression in the AIBL sample over 8 years.

followed for up to 4.5 years. Data were available for assessments spanning from November 2006 through to April 2016. The sample was further restricted to those who reported no history of stroke, transient ischemic attack (TIA), or serious head injury at baseline ($n = 599$). Participants whose clinical classification or Aβ status fluctuated during the study period were excluded ($n = 19$). This left 580 CN older adults with complete data available for analysis, 179 of whom were classified as SuperAgers.

Baseline SuperAger classification required performance above the sex-adjusted normative average for 30–44 year olds on the California Verbal Learning Test – Second Edition (CVLT-II) Long Delay Free Recall trial (≥13 for women, ≥12 for men) (Delis, Kramer, Kaplan, & Ober, 2000), and above −1 *SD* using published normative data for all non-memory tests identified to be optimal for the study of cognitive aging, including the Digit Symbol Substitution Test, the Victoria Stroop Test (words trial), Digit Span, Letter Fluency (FAS), and Category Fluency (total animals and male names, and fruit and furniture) (e.g., Harrington et al., 2016). These psychometric criteria are consistent with those originally used by the Northwestern SuperAging Study (Harrison et al., 2012) and other studies (Harrison et al., 2018; Sun et al., 2016), despite the greater number of non-memory tests used for classification in the current study. SuperAgers were then case-matched with the remaining CN participants (i.e., CNFA) based on age, sex, education, and follow-up time to ensure that the study results were not driven by demographic differences. Therefore, 358 participants were included in this study (179 SuperAgers, 179 CNFA, Fig. 1).

Measures

A comprehensive neuropsychological battery was administered to all participants at each visit, the details of which are described elsewhere (Ellis et al., 2009). Four composite domain scores were derived via exploratory factor analysis, as previously reported, and were calculated for each participant visit by averaging z-scores of the respective tests for each domain (Harrington et al., 2018). Z-scores were calculated relative to the full CN AIBL sample. The verbal memory composite included CVLT-II Long Delay Free Recall, CVLT-II Immediate Recall Trials 1–5, and Logical Memory II. The executive function composite included Category Fluency (total animals and male names, and fruit and furniture), Letter Fluency (FAS), Victoria Stroop Test (words trial), and Digit Symbol Substitution Test. Working memory included two Cogstate tasks (One Back, One Card Learning). Finally, processing speed included the Cogstate Identification and Detection tasks. Education was coded as ≤12 years or >12 years. Mood symptomology was assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The Memory Complaint Questionnaire (MAC-Q) (Crook, Feher, & Larrabee, 1992) raw score was used to assess subjective memory complaint. *APOE* genotype was determined from whole blood extracted DNA as per previously described methodology (Porter et al., 2018).

Cognitive Status Assessment

An expert clinical panel made consensus classifications using standard clinical criteria for MCI (Winblad et al., 2004) and AD (McKhann et al., 1984), and was blinded to any information concerning Aβ and *APOE* ε4 status. The panel reviewed all available neuropsychological and psychiatric information for participants who performed below −1.5 *SD* on published age- and education-adjusted normative data on at least two neuropsychological tests. Participants who performed within normal limits for their age on cognitive testing were classified as CN, and those who were classified with MCI/dementia during the follow-up period were coded as progressors.

Amyloid-beta PET Neuroimaging

PET neuroimaging was conducted using one of the following Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB, $n = 140$), ^{18}F-NAV4694 (NAV, $n = 44$), ^{18}F-Florbetapir (FBP, $n = 87$), or ^{18}F-Flutemetamol (FLUTE, $n = 87$). PET methods and procedures have been reported previously (Rowe et al., 2010; Villemagne et al., 2014). Briefly, PET acquisitions were performed up to 90 min following tracer injection. Standardized uptake value (SUV) data were summed and normalized to a reference region (the cerebellar cortex for PiB and NAV, the whole cerebellum for FBP, and the pons for FLUTE) to generate a SUV ratio (SUVR). The accepted cut-off values for significant Aβ deposition vary by radiotracer, so a linear regression transformation was applied to the FBP and FLUTE SUVR to create a "PiB-like" SUVR unit called Before the Centiloid Kernel Transformation (BeCKeT; Villemagne et al., 2014). All particiants with SUVR/BeCKeT ≥ 1.40 at their most recent PET scan were classified as Aβ+, and those below the threshold were classified as Aβ−.

Statistical Methods

R version 3.4.3 (R Core Team, 2017) and SPSS 23 were used for all statistical analyses, with statistical significance set at $p < .05$. SuperAgers were case-matched with CNFA using the FUZZY extension command in SPSS. Exact matches were required for education and sex. Tolerances for age and follow-up time were ±2 years and ±1 visit, respectively. Eligible matches were selected at random.

Baseline group differences in clinical characteristics. Normality of continuous variables was assessed by visual inspection of Q–Q plots. Between-group comparisons by SuperAger status were conducted using a one-way analysis of variance (ANOVA) for normally distributed variables. A Kruskal–Wallis one-way ANOVA was used for non-normally distributed variables. Differences in dichotomous variables were assessed using Fisher's exact tests. No adjustments were made for multiple comparisons due to their conservative nature; rather, Cohen's d was used to guide interpretation of statistically significant results, such that significant comparisons with very small effect sizes ($d < 0.20$) were suspected Type I errors.

Survival analysis. Fine-Gray subdistribution hazard modeling was used instead of cause-specific Cox modeling due to its ability to account for the presence of competing risks, which were defined as death or withdrawal from the study due to illness unrelated to dementia. Progression to MCI/dementia was coded as events, and time to event was entered in months from the baseline visit. Non-progressors were right-censored at the time of their most recent study visit. Schoenfeld residuals tests were non-significant for predictors and the global value was non-significant for the entire model, indicating that the proportional hazards assumption was met. All DFBETA values were within the size-adjusted cut-score; therefore, no outliers were detected.

Survival models evaluated the first hypothesis in five stages to determine whether SuperAger classification can predict non-progression to MCI/dementia. Model 1 included only SuperAger status. Model 2 added estimated premorbid IQ. Standard demographic predictors that have been indicated as risk factors for MCI/dementia were added to Model 3: baseline age and sex. Presence of the *APOE* ε4 allele was added in Model 4. Finally, Model 5 included Aβ status (+/−). Cumulative hazard functions were plotted, and hazard ratios were calculated with 95% confidence intervals.

Influence of Aβ on cognitive change. Multiple linear mixed model (LMM) analyses with maximum likelihood estimation were conducted with each of the four cognitive domain composite scores as continuous dependent measures. Nonlinear models did not improve model fit nor the amount of variance explained, and visual examination indicated that the data most closely fit a linear pattern. Fixed factors were SuperAger status, Aβ status, time from baseline assessment in years, and their interactions. Participant was entered as a random factor with random slopes for time. Covariates were baseline age, progression status, premorbid IQ, and *APOE* ε4 status. To explore the extent to which the effects of SuperAger classification on cognitive change were influenced by age, additional LMMs were run to test interactions between SuperAger status, Aβ status, and age.

Results

Sample Characteristics

Over the 8-year period, 28 participants progressed to clinically-classified MCI/dementia (22 CNFA, 6 SuperAgers), 10 died, 13 withdrew due to ill health, 36 formally withdrew from the study for reasons unrelated to health, and 4 could not be

Table 1. Baseline group differences

Measure	Total sample	CNFA	SuperAgers	*p*-value	*d*
n	358	179	179		
Aβ+, %	38.50	37.40	39.70	.75	
APOE ε4 carrier, %	27.90	27.40	28.50	.91	
Age at baseline, years	68.48, 68.00 (9)	68.53, 68.00 (8)	68.43, 68.00 (9)	.89	
Female, %	53.60	53.60	53.60	1	
Premorbid IQ	112.24, 114.00 (8)	111.28, 114.00 (8)	113.25, 114.00 (5)	**.002**	0.31
Education >12 years, %	65.40	65.40	65.40	1	
HADS A	4.40, 4.00 (5)	4.45, 4.00 (5)	4.34, 4.00 (5)	.43	
HADS D	2.66, 2.00 (3)	2.50, 2.00 (3)	2.82, 2.00 (3)	.39	
MAC-Q	25.25, 25.00 (6)	24.89, 25.00 (6.75)	25.61, 25.00 (6)	.86	
Progressors, %	7.80	12.30	3.40	**.003**	0.77
Withdrawn due to ill health/deceased, %	6.40	6.10	6.70	1	
Subsequent stroke/TIA, %	5.00	5.00	5.00	1	
Hypertension, %	50.60	54.20	46.90	.21	
Diabetes, %	8.90	11.70	6.10	.09	
People followed up at all assessment time points (6 over 90 months), %	62.80	63.70	62.00	.83	
Length of follow up (months)	75.75, 90.00 (20)	77.38, 90.00 (19)	74.04, 90.00 (35)	.33	
Verbal memory composite score	0.26, 0.30 (1.08)	−0.08, −0.12 (1.06)	0.63, 0.63 (0.79)	**<.0005**	1.13
Executive function composite score	0.12, 0.19 (0.91)	−0.10, −0.12 (1.02)	0.36, 0.35 (0.71)	**<.0005**	0.74
Working memory composite score	0.00, 0.006 (0.85)	−0.03, −0.04 (0.81)	0.03, 0.04 (0.84)	.16	
Processing speed composite score	0.21, 0.27 (1.03)	0.14, 0.25 (1.09)	0.27, 0.28 (0.96)	.16	

All descriptive statistics for continuous variables reported as mean, median (interquartile range); categorical variables reported as percentages. *p*-values shown for comparisons between SuperAger and CNFA groups; Cohen's *d* shown for comparisons with $p < .05$

Note: Aβ+ = elevated cerebral amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele carriage; CNFA = cognitively normal for age; HADS A = Hospital Anxiety and Depression Scale – Anxiety; HADS D = Hospital Anxiety and Depression Scale – Depression; MAC-Q = Memory Complaint Questionnaire; TIA = Transient ischemic attack.

contacted for follow-up (Fig. 1). Median follow up time for the full sample was 90 months (interquartile range: 20) and 62.8% of all participants were followed throughout the entire study period. Participants were 68.5 years of age on average (range: 60–83), and most were educated beyond 12 years (65.4%). See Table 1 for demographic and clinical characteristics.

Baseline Group Differences

As expected, no group differences (SuperAgers vs. CNFA) were observed in baseline age, sex, education, or follow-up time (Table 1). The groups also did not differ on any clinical factors. SuperAgers had higher estimated premorbid IQ (two points) compared to matched CNFA. The proportion of *APOE* ε4 carriers and participants with Aβ+ was similar between both groups. These findings were also observed between groups in the full sample before case-matching. Consistent with the classification criteria, SuperAgers had significantly higher mean verbal memory and executive function performance at baseline; however, the differences in working memory and processing speed were not significant. No differences were observed between SuperAgers and CNFA on subjective memory assessment.

Prognostic Utility of SuperAging Criteria

Fisher's exact test showed that SuperAgers were less likely to progress to MCI/dementia than CNFA (OR: 0.248, 95% CI: 0.098–0.626; $p = .003$). Survival analyses results are shown in Table 2. SuperAger status decreased risk of progression to MCI/dementia in all models by 69%–73% compared to CNFA (Fig. 2). In Model 2, premorbid IQ did not influence risk of progression. Females had 68% less risk than males in Model 3, and premorbid IQ reduced risk by 8% for each point increase with the addition of sex in the model. In Model 4, *APOE* ε4 carriage increased risk by 227%. Aβ status conferred no additional risk in Model 5, but reduced the risk conferred by *APOE* ε4 status to 188%. The effect of age was significant and remained consistent across Models 3–5, which showed 8%–9% increased risk of progression to MCI/dementia per additional year of age at baseline, although this risk was not influenced by SuperAger classification or Aβ status.

Table 2. Survival analyses

MODEL 1	*p*-value	HR	95% confidence interval	
SuperAger status	**.004**	**0.27**	**0.11**	**0.65**
MODEL 2	*p*-value	HR	95% confidence interval	
SuperAger status	**.008**	**0.31**	**0.13**	**0.73**
Estimated premorbid IQ	.082	0.96	0.91	1.01
MODEL 3	*p*-value	HR	95% confidence interval	
SuperAger status	**.008**	**0.31**	**0.13**	**0.74**
Estimated premorbid IQ	**.007**	**0.92**	**0.86**	**0.98**
Baseline age	**.013**	**1.08**	**1.02**	**1.15**
Sex	**.011**	**0.32**	**0.13**	**0.76**
MODEL 4	*p*-value	HR	95% confidence interval	
SuperAger status	**.007**	**0.30**	**0.13**	**0.72**
Estimated premorbid IQ	**.015**	**0.93**	**0.87**	**0.99**
Baseline age	**.005**	**1.09**	**1.03**	**1.16**
Sex	**.017**	**0.33**	**0.13**	**0.82**
APOE ε4 carrier	**.003**	**3.27**	**1.52**	**7.05**
MODEL 5	*p*-value	HR	95% confidence interval	
SuperAger status	**.008**	**0.31**	**0.13**	**0.74**
Estimated premorbid IQ	**.013**	**0.92**	**0.87**	**0.98**
Baseline age	**.013**	**1.08**	**1.02**	**1.15**
Sex	**.015**	**0.31**	**0.12**	**0.80**
APOE ε4 carrier	**.005**	**2.88**	**1.39**	**5.97**
Aβ+	.180	1.69	0.78	3.63

Note: HR = hazard ratio; Aβ+ = elevated cerebral amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele carriage.

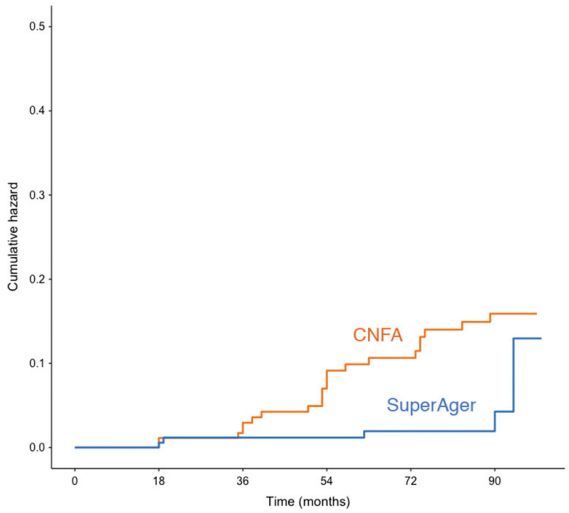

Fig. 2. Cumulative hazard functions between SuperAgers and CNFA (cognitively normal for their age).

Effect of Aβ Status on Longitudinal Cognitive Performance in SuperAgers

The LMM parameters are shown in Table 3, and the annualized group mean slopes for performance over time in each cognitive domain for the Aβ+ and Aβ− SuperAger and CNFA groups are summarized in Table 4. Table 4 shows that mean slopes for verbal memory performance over time in the Aβ− CNFA and SuperAger groups were both positive, showing improvement over time. In comparison, group mean slopes in the Aβ+ CNFA and SuperAger groups were both negative,

showing decline over time. These relationships are shown graphically in Fig. 3. This same pattern of outcomes was evident for performance over time on the executive function composite. However, for working memory, the slopes of performance over time remained close to zero for the SuperAger and CNFA groups irrespective of Aβ status, and all groups showed a decline over time for processing speed (Table 4). The LMMs identified no significant interaction between SuperAger status and time, or SuperAger status and Aβ for any composite (Table 3). For verbal memory, SuperAger status, time, age, progression status, and premorbid IQ were significant main effects, and there was a significant Aβ status by time interaction. For executive function, SuperAger status, Aβ status, time, *APOE* ε4 status, age, progression status, and premorbid IQ were all significant main effects, and the interaction between Aβ status and time was also significant. No significant main effects or interactions were observed for working memory. For processing speed, significant main effects were observed for time, age and premorbid IQ with no significant interactions. These overall findings were unchanged when premorbid IQ was removed from the LMMs. Age did not significantly interact with SuperAger status or Aβ status on any cognitive domain.

Discussion

The first hypothesis, that SuperAger classification would be associated with reduced risk of progression to a clinical diagnosis of MCI or dementia, was supported. In the total AIBL CN cohort, 30.9% met the SuperAger criteria (i.e., $n = 179$ with 71 Aβ+) and a CNFA group of the same size was matched to the SuperAger group on age, sex, education, and follow up time. The relatively high proportion of individuals classified as SuperAgers in the AIBL CN cohort most likely reflects the rigorous inclusion/exclusion criteria for AIBL as well as selection and survivor biases. Although SuperAger and CNFA groups were not matched a priori on general health or known AD risk factors, all clinical measures as well as the prevalence of the AD risk factors, Aβ+ and *APOE* ε4 carriage, were equivalent between groups (Table 1). This equivalence was also observed prior to case-matching, consistent with reports from previous studies (Dekhtyar et al., 2017; Harrison et al., 2018), and *APOE* ε4 carriage remained similar between SuperAger and CNFA groups when the imaging inclusion criterion was lifted despite the AIBL imaging sub-sample being enriched for *APOE* ε4 carriers. Similarity between the groups in physical health characteristics most likely reflects the well-documented homogeneity of the AIBL sample due to its rigorous exclusion

Table 3. Linear mixed model parameters

	Verbal memory			Executive function			Working memory			Processing speed		
	Estimate	Std. error	*p*-value	Estimate	Std. error	*p*-value	Estimate	Std. error	*p*-value	Estimate	Std. error	*p*-value
Intercept	−0.94	0.64	.14	−0.73	0.62	.24	−0.32	0.54	.56	0.32	0.71	.66
SuperAger classification	0.57	0.08	**<.0005**	0.36	0.07	**<.0005**	0.13	0.07	.07	0.02	0.10	.86
Aβ status (+/−)	0.02	0.10	.83	0.18	0.09	**.04**	0.11	0.08	.19	−0.06	0.12	.60
Time (years)	0.04	0.01	**.002**	−0.01	0.01	.31	0.00	0.01	.86	−0.09	0.01	**<.0005**
APOE ε4 carrier status (+/−)	0.05	0.07	.45	−0.21	0.07	**.002**	0.02	0.06	.74	−0.13	0.08	.10
Baseline age	−0.03	0.01	**<.0005**	−0.04	0.01	**<.0005**	0.00	0.00	.29	−0.02	0.01	**<.0005**
Progression	−0.74	0.11	**<.0005**	−0.34	0.11	**.003**	−0.05	0.10	.64	−0.18	0.13	.17
Premorbid IQ	0.02	0.005	**<.0005**	0.03	0.00	**<.0005**	0.00	0.00	.85	0.01	0.01	**.01**
SuperAger * Aβ status	−0.10	0.13	.43	−0.07	0.12	.55	−0.19	0.11	.10	0.22	0.16	.18
SuperAger * Time	−0.03	0.02	.12	−0.02	0.01	.09	−0.01	0.01	.59	0.02	0.02	.19
Aβ status * Time	−0.06	0.02	**.001**	−0.03	0.01	**.04**	−0.03	0.02	.13	−0.01	0.02	.71
SuperAger * Aβ status * Time	0.03	0.03	.30	0.01	0.02	.69	0.04	0.02	.10	−0.02	0.03	.57

Note: Aβ = amyloid-beta; *APOE* ε4 = apolipoprotein E epsilon 4 allele carriage.

Table 4. Annualized group mean slopes for cognitive performance for Aβ− and Aβ+ SuperAgers and CNFA

	CNFA		SuperAgers	
	Aβ−	Aβ+	Aβ−	Aβ+
Verbal memory	0.04 (0.12)	−0.02 (0.12)	0.01 (0.12)	−0.02 (0.13)
Executive function	−0.01 (0.08)	−0.03 (0.08)	−0.03 (0.08)	−0.05 (0.09)
Working memory	−0.002 (0.1)	−0.03 (0.11)	−0.01 (0.11)	0.005 (0.11)
Processing speed	−0.092 (0.13)	−0.1 (0.14)	−0.07 (0.13)	−0.09 (0.13)

Presented as mean slopes (SD). Abbreviations used: Aβ− = cerebral amyloid-beta within normal range (PET SUVR<1.40); Aβ+ = elevated cerebral amyloid-beta; CNFA = cognitively normal for their age; SD = standard deviation.

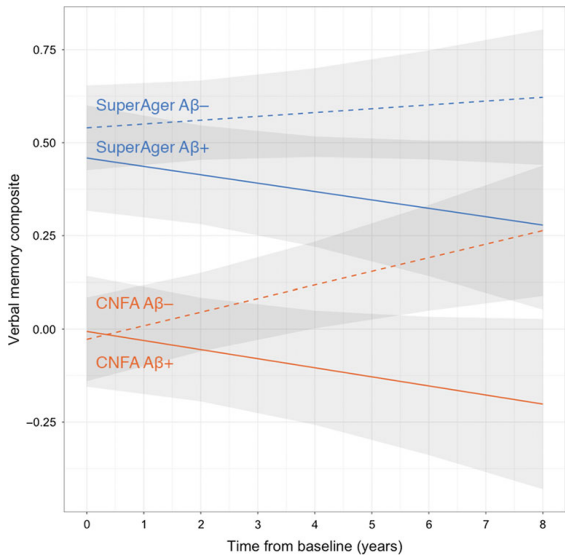

Fig. 3. Verbal memory performance over time by SuperAger and Aβ status. Abbreviations used: Aβ− = cerebral amyloid-beta within normal range (PET SUVR < 1.40); Aβ+ = elevated cerebral amyloid-beta; CNFA = cognitively normal for their age.

criteria (Ellis et al., 2009). In this context, the similar prevalence of AD risk factors indicates that SuperAger classification, reflective of superior baseline cognitive performance, did not reflect resistance against neuropathological processes central to the development of AD (Jack et al., 2013; Selkoe & Hardy, 2016). Despite the equivalent risk for AD, only 3.4% of the SuperAger group progressed to a clinical classification of MCI/dementia over the 8-year follow-up interval compared to 12.3% of the CNFA group. When examined in survival models, this difference reflected a 69%–73% reduction in risk of progression to MCI/dementia for SuperAgers compared to CNFA. Furthermore, the reduced risk of clinical progression in SuperAgers was not modified by *APOE* ε4 carriage, Aβ+ or age (Table 2). The continued resilience of SuperAgers to clinical progression despite similar levels of AD risk suggests that, while SuperAgers are not resistant to the accumulation of Aβ, they may have some resilience to the effects of elevated Aβ on cognitive change. Although clinical disease outcomes associated with SuperAging have not been explored previously, it has been reported that individuals classified as SuperAgers display less Aβ-associated memory decline compared to CNFA despite equivalent levels of Aβ burden (Harrison et al., 2018).

The second hypothesis, that SuperAgers would show greater resilience to the cognitive decline associated with preclinical AD (i.e., Aβ+), was not supported. While, by definition, SuperAgers had superior verbal memory compared to CNFA adults at baseline, cognitive change over the following 8 years was equivalent between the Aβ+ SuperAgers and Aβ+ CNFA adults in both nature and magnitude (Fig. 3), consistent with that reported in other prospective studies of cognitive change associated with Aβ+ (Baker et al., 2017; Hedden et al., 2013). In the absence of preclinical AD (i.e., Aβ−), both the SuperAger and CNFA groups showed no decline in verbal memory or executive function and equivalent rates of decline in processing speed and working memory (Fig. 2). Thus, individuals classified as SuperAgers showed no unique resilience to Aβ-associated cognitive decline in this study. These findings are inconsistent with two recent studies of SuperAging, which suggest that SuperAger classification reflects increased resilience against the effects of AD-associated pathological change (Harrison et al., 2018; Rogalski et al., 2018). A post-mortem study found maintenance of superior episodic memory in 7/10 of the studied SuperAgers despite moderate or frequent neuritic plaques and neurofibrillary tangles in more than half of them (Rogalski et al., 2018). Furthermore, a study of the BACS cohort reported that successful agers displayed no episodic memory decline compared to CNFA over an average of 5 years. Although levels of Aβ burden were equivalent between groups, the successful agers were resilient to Aβ-associated memory decline whereas the CNFA older adults were not (Harrison et al., 2018). The discrepancy in findings may reflect methodical differences between these studies. First, the present study had a much larger sample of SuperAgers ($n = 179$ with 71 Aβ+) than the BACS sample of successful agers ($n = 25$ with longitudinal follow-up, of whom 10 were Aβ+). Second, the

length of follow-up in the BACS sample varies between participants and it is unknown how many successful agers were assessed at the longest follow-up interval. In contrast, 62.8% of the present study sample provided complete data over the full 8-year period of available AIBL data (i.e., 111 SuperAgers), providing the current design with greater statistical power. Therefore, the BACS finding that individuals classified as successful agers displayed no memory decline associated with Aβ+ was likely due to the small sample sizes studied resulting in lack of statistical power to detect these effects. Finally, differences between studies with regard to specific neuropsychological and age criteria for SuperAger classification can limit comparisons from one study to another. The BACS sample included individuals over 70 years old and classified successful agers using the CVLT-II normative mean for 18–32 year olds that was not adjusted for sex (Harrison et al., 2018). In the present study, the criteria for SuperAger classification included adults over age 60 whose memory performance was defined using the sex-adjusted CVLT-II normative mean for 30–44 year olds. Although the gap between participants' age and the reference age varies between studies, these differences should be negligible if SuperAgers do indeed maintain their "youthful" cognitive ability into late-life; however, older age was associated with lower cognitive performance for verbal memory, executive function and psychomotor speed across all participants with no differential effects between SuperAgers and CNFA. Despite these methodological differences, the current finding that a substantial sample of CN older individuals classified as SuperAgers using careful psychometric and rigorous inclusion/exclusion criteria have no greater protection from the negative effects of Aβ+ than do well-matched CNFA indicates that the deleterious effects of Aβ on cognition persist regardless of baseline cognitive ability.

Results of the current study are consistent with the proposition that the increasing individual differences in cognition, which become greater with age, are likely to reflect the presence of at least two distinct subgroups of older adults. First, individuals with occult neurodegenerative disease such as preclinical AD cannot be considered to be aging normally; therefore, their inadvertent inclusion in aging study samples will negatively bias estimated effects of cognitive aging (Harrington et al. 2018). A second subgroup of older adults who exhibit baseline cognition superior to other CN adults of the same age can also be present in aging samples. Previous SuperAging studies have used different minimum age criteria for SuperAger classification (i.e., 60–80; Harrison et al., 2018, 2012; Sun et al., 2016), but only one has examined how age influences the cognitive and neurobiological outcomes of psychometrically-defined SuperAgers. They report a negative relationship between age and Aβ deposition in SuperAgers; however, this relationship became non-significant following removal of outlier data (Harrison et al., 2018). Although the present study found that increasing age was associated with greater risk of clinical disease progression to MCI/dementia and lower cognitive performance, the effect of age on cognition was consistent across all individuals regardless of SuperAger classification or Aβ status. This suggests that cognitive decline in preclinical AD is due to neuropathological changes beyond the effect of age, itself, and that individuals classified as SuperAgers are no more resilient to changes in cognition associated with age or with preclinical AD than are CNFA.

In contrast, studies of cognitive reserve report that the relationship between Aβ and cognitive decline is modified by greater years of education and higher premorbid IQ (Rentz et al., 2010; Yaffe et al., 2011). It has additionally been reported that greater participation in cognitively stimulating activities is associated with lower Aβ deposition (Landau et al., 2012). It is possible that the SuperAger and cognitive reserve constructs overlap; however, they are not the same. Individuals with high cognitive reserve are typically identified using proxy measures such as education, premorbid IQ and cognitive activity, and may display greater cognitive performance with equivalent levels of AD neuropathological markers compared to individuals with low cognitive reserve (Stern, 2012). Classification criteria for SuperAgers are psychometrically-based; therefore, while the superior cognitive performance observed in SuperAging samples may be reflective of higher cognitive reserve, this study specifically matched SuperAgers and CNFA on education. Additionally, previous studies report no difference in premorbid IQ between SuperAgers and their CNFA controls (Cook et al., 2017; Sun et al., 2016). While SuperAgers in the current study did show slightly better premorbid IQ than the CNFA group, the magnitude of this benefit was trivial when considered clinically (i.e., two points). Because individuals classified as SuperAgers exhibited better cognitive ability than CNFA at all time points despite similar levels of Aβ deposition, cross-sectional examinations may support the notion that SuperAgers represent a population with high cognitive reserve; however, this does not bear out in the longitudinal examination conducted in this study given that Aβ+ older adults, regardless of classification, showed clear Aβ-associated cognitive decline compared to Aβ− participants. According to these findings, SuperAgers are not resilient to Aβ-associated cognitive decline as suggested by the construct of cognitive reserve (e.g., Stern, 2012), although one small study examining Aβ-associated cognitive change in successful agers did find evidence of such resilience (Harrison et al., 2018). Finally, studies of cognitive reserve indicate that individuals with high cognitive reserve experience more rapid cognitive decline than those with low cognitive reserve, which was not observed in this study as rates of cognitive change were equivalent between SuperAgers and CNFA. Together, these observations suggest the possibility that the SuperAger and cognitive reserve constructs are different, a point that was also noted by the group who pioneered the SuperAger construct (Rogalski et al., 2013).

The SuperAger construct is based on the observation that some adults progress from middle-age to old-age without showing any decline in their cognitive abilities (Gefen et al., 2015). Because it is rare to possess neuropsychological data across

the entire adult lifespan for individuals, studies of SuperAging approximate "youthful" cognition (Rogalski et al., 2013) in their samples by comparing neuropsychological performance of their older adults to normative data derived from individuals 20–30 years younger (Harrison et al., 2012). While the results of the current study confirm the validity of the SuperAgers construct, they raise the question of what is actually reflected by the superior cognition observed in SuperAgers. This study matched the SuperAger and CNFA groups on age, sex, education and follow-up time, and found similar physical health and AD risk profiles between groups (Table 1). However, as individual differences in cognitive aging reflect complex interactions between time, genetics and a stochastic combination of events (Mesulam, 2000), it is not feasible to experimentally or statistically control all possible differences. For example, higher occupational complexity has been associated with greater white matter integrity and cognitive function in later life (Kaup et al., 2017), and increased physical activity has been linked to better cognition and attenuated age-associated brain atrophy (Gomez-Pinilla & Hillman, 2013). The inconsistency between risk factors for MCI/dementia, defined psychometrically (i.e., SuperAger classification, which reflects superior baseline cognitive performance) and biologically (i.e., Aβ and *APOE* ε4) in the current study, indicates that other neuroimaging biomarkers are necessary to understand how SuperAging can influence cognitive aging. For example, future studies in large cohorts, like AIBL, should seek to examine volumetric and functional differences between SuperAgers and CNFA in brain regions associated with verbal memory and executive function by Aβ status. Previous studies have reported cross-sectional differences in regional volumes and cortical thickness, albeit without consideration to Aβ status (Harrison et al., 2012; Sun et al., 2016). Although one study did examine longitudinal morphological changes in successful agers with respect to Aβ burden, reporting no differences between successful agers and typical older adults and no Aβ-associated differences, the sample size was limited ($n = 19$ successful agers) (Harrison et al., 2018). If these differences are observed in a larger sample and persist even in preclinical AD, such a finding would indicate that SuperAgers' resilience to progression is a consequence of greater neuronal integrity (Harrison et al., 2012). Furthermore, although imaging and pathological studies consistently show that SuperAgers have superior brain and neuronal structure to CNFA adults, an observation that would be consistent with SuperAgers having lower levels of tau even in the presence of Aβ+ (Desikan et al., 2011; Jack et al., 2013), no study of SuperAging has yet measured levels of cortical tau.

Given that SuperAgers progressed to MCI/dementia at a lower rate than did CNFA despite being equally affected by cognitive aging and Aβ+, consideration must be given to the clinical classification process. Classification of clinical disease progression in AIBL is guided by considering the level of performance on neuropsychological tests at each visit with reference to published normative data for those tests. Consequently, because of their superior test performance, SuperAgers who are Aβ+ and have exhibited the cognitive decline pathognomonic of preclinical AD continue to have their test performance classified as unimpaired relative to the normative data. This can be interpreted in two ways. First, superior cognitive performance in SuperAgers allows them to tolerate AD neuropathological changes for longer than CNFA. Alternatively, reliance on static published normative data to guide clinical classification is unsatisfactory. More accurate identification of MCI/dementia in SuperAgers may occur if classification decisions took into consideration cognitive change over time; however, this is limited by the lack of available normative data for longitudinal change (Fuchs et al., 2013; Stein et al., 2012). It is, therefore, possible that SuperAger classification may not prevent, but rather delays, clinical classification of MCI/dementia due to the greater

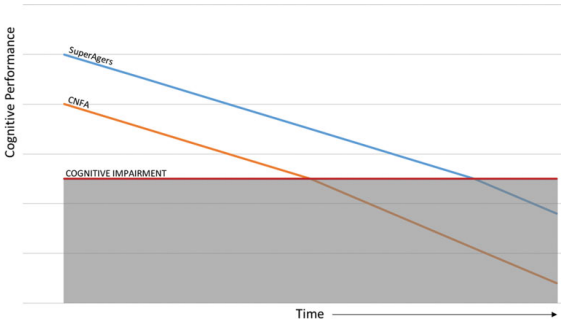

Fig. 4. Theoretical trajectory to cognitive impairment for CNFA and SuperAgers. The same rate of change in cognition was observed between SuperAgers and case-matched cognitively normal for age (CNFA) participants on all cognitive domains. Because cognitive impairment is determined by neuropsychological test performance in reference to normative data and SuperAgers exhibit superior cognitive performance at baseline, SuperAgers may take longer to reach the threshold for cognitive impairment.

amount of time needed for high baseline test performance to decline past the threshold for defined cognitive impairment, as illustrated in Fig. 4.

The generalizability of the present findings must be considered in the context of the following caveats. AIBL is a convenience sample of relatively healthy, well-educated and ethnically homogeneous individuals with strict inclusion criteria; therefore, the characteristics of SuperAgers and CNFA in this study may differ from the general population. Nearly one-third of the CN AIBL sample were classified as SuperAgers, which may be greater than that expected in the general population; however, the prevalence of SuperAgers has not been reported in previous SuperAging studies. Furthermore, participants of the AIBL study have completed the neuropsychological battery up to six times over 8 years and display considerable practice effects, particularly in the memory tests. While it has been observed in AIBL and in other prospective studies that CN Aβ+ individuals do not necessarily display decline in cognition over time, but rather a loss of practice effects (Duff, Foster, & Hoffman, 2014; Hassenstab et al., 2015; Lim et al., 2016; Mormino et al., 2014), this study did observe that CN Aβ+ individuals declined on verbal memory over time. Despite these caveats, the present study has a number of strengths. First, no other study of SuperAgers has case-matched CNFA based on age, sex, education, and follow-up time. Second, this is the first study to examine longitudinal cognitive performance in SuperAgers with consideration to Aβ status in this large a sample over a relatively long time interval. Finally, there is great potential to further study the SuperAger construct in AIBL, particularly with reference to the effects of Aβ on brain volumetric measures over time to determine whether SuperAger classification offers any protection against neurodegeneration or tau accumulation downstream of elevated Aβ deposition.

The process of aging is complex, in which considerable inter-individual variability is inherent, and this is partially reflected by different individual levels of Aβ deposition and neurodegenerative disease markers. Therefore, the present findings indicate that the study of normal cognitive aging necessitates examination of individuals without evidence of clinically significant pathologic change or neurodegenerative disease, regardless of baseline cognitive performance, as these individuals have clearly displayed resistance to the accumulation of these neuropathological markers in aging.

Funding

CD is a recipient of the Melbourne Research Scholarship. Funding for the AIBL study was provided in part by the study partners [Australian Commonwealth Scientific Industrial and research Organization (CSIRO), Edith Cowan University (ECU), Mental Health Research Institute (MHRI), Alzheimer's Australia (AA), National Ageing Research Institute (NARI), Austin Health, CogState Ltd., Hollywood Private Hospital, Sir Charles Gardner Hospital]. The study also received support from the National Health and Medical Research Council (NHMRC) and the Dementia Collaborative Research Centres program (DCRC2), as well as ongoing funding from the Science and Industry Endowment Fund (SIEF).

Conflict of Interest

None declared.

Acknowledgements

Alzheimer's Australia (Victoria and Western Australia) assisted with promotion of the AIBL study and the screening of telephone calls from volunteers. The AIBL team wishes to thank the clinicians who referred patients with AD to the study: Associate Professor Brian Chambers, Professor Edmond Chiu, Dr Roger Clarnette, Associate Professor David Darby, Dr Mary Davison, Dr John Drago, Dr Peter Drysdale, Dr Jacqueline Gilbert, Dr Kwang Lim, Professor Nicola Lautenschlager, Dr Dina LoGiudice, Dr Peter McCardle, Dr Steve McFarlane, Dr Alastair Mander, Dr John Merory, Professor Daniel O'Connor, Dr Ron Scholes, Dr Mathew Samuel, Dr Darshan Trivedi, and Associate Professor Michael Woodward. We thank all those who participated in the study for their commitment and dedication to helping advance research into the early detection and causation of AD.

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Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 11 (2019) 566-575

Alzheimer's & Dementia

Featured Article

Rates of age- and amyloid β-associated cortical atrophy in older adults with superior memory performance

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Abstract

Introduction: Superior cognitive performance in older adults may reflect underlying resistance to age-associated neurodegeneration. While elevated amyloid β (Aβ) deposition (Aβ+) has been associated with increased cortical atrophy, it remains unknown whether "SuperAgers" may be protected from Aβ-associated neurodegeneration.

Methods: Neuropsychologically defined SuperAgers (n = 172) and cognitively normal for age (n = 172) older adults from the Australian Imaging, Biomarkers and Lifestyle study were case matched. Rates of cortical atrophy over 8 years were examined by SuperAger classification and Aβ status.

Results: Of the case-matched SuperAgers and cognitively normal for age older adults, 40.7% and 40.1%, respectively, were Aβ+. Rates of age- and Aβ-associated atrophy did not differ between the groups on any measure. Aβ− individuals displayed the slowest rates of atrophy.

Discussion: Maintenance of superior memory in late life does not reflect resistance to age- or Aβ-associated atrophy. However, those individuals who reached old age without cognitive impairment nor elevated Aβ deposition (i.e. Aβ−) displayed reduced rates of cortical atrophy.

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https://doi.org/10.1016/j.dadm.2019.05.005

C. Dang et al. / Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 11 (2019) 566-575

Keywords: Aging; β-amyloid; Alzheimer's disease; Neurodegeneration; Memory

1. Introduction

Although cognitive decline is considered characteristic of aging [1,2], the existence of older adults with superior cognitive ability for their age suggests that cognitive decline is not inevitable [3]. Studies describe such individuals as successful agers [4–7], optimal memory performers [8], supernormals [9–11], or SuperAgers [12,13]. Despite similar goals, each study employs different classification criteria. For example, SuperAger classification originally included individuals older than 80 years with episodic memory performance equivalent to, or above, the normative mean for adults aged 50-65 years and age-appropriate performance in other cognitive domains [12,14–16]. SuperAgers are, thus, considered to have maintained "youthful" memory performance into old age [14]. Other studies have used similar neuropsychological criteria but lowered the minimum age criterion to 70 (i.e. "successful agers") [7] and 60 years (i.e. "SuperAgers") [3,13]. While the chronological age at which SuperAging can be classified is still being determined, elucidation of the neurobiological basis of aging without cognitive decline could yield important insights into prevention of age-associated neurodegenerative diseases such as Alzheimer's disease (AD).

Cross-sectional comparisons of brain morphology between SuperAgers and elderly controls report that SuperAgers do not show typical age-associated atrophy on magnetic resonance imaging (MRI) measures of cortical thickness and volume [12]. SuperAgers also show greater left hippocampal volume and greater cortical thickness in anterior cingulate cortex and default mode and salience network regions [13,16]. Greater regional cortical thickness and hippocampal volume and lower burden of white matter lesions were observed in successful agers compared to typical older adults [7]. Given that normal aging is associated with gradual loss of brain volume [17], larger brain volumes and reduced markers of cerebral small vessel disease are inferred to reflect preservation of cortical integrity despite aging, raising the possibility that maintenance of superior memory performance in old age reflects some resistance or protection against age-associated neurodegeneration [14].

SuperAging may also reflect some protection from AD [16]. Abnormally high levels of amyloid β (Aβ+) and carriage of the *APOE* ε4 allele are AD risk factors [18]; however, prevalence of Aβ+ and *APOE* ε4 carriage are consistently similar between individuals with superior memory performance and typical older adults [3,7,8,10,16]. These individuals maintain superior cognitive ability despite Aβ+ [3,7,8] or substantial markers of AD neuropathology upon post-mortem examination [19], suggesting that any resilience to AD pathogenesis experienced by SuperAgers either ameliorates or acts independently from the risk conferred by Aβ+ and *APOE* ε4. For example, neurobiological factors associated with SuperAging may protect against Aβ-associated neurodegeneration. Although the adverse effects of Aβ+ on brain volume over time have been well described [20–25], it remains unknown whether SuperAgers may be protected from them.

Large prospective studies are necessary to disentangle the effects of baseline brain structural characteristics, age, and neuropathological markers in SuperAgers; however, results of studies to date are mixed. One group reported slower whole-brain cortical atrophy for 24 SuperAgers compared to cognitively average elderly adults over 18 months, although this study did not take into account Aβ levels [15]. While significant baseline differences were found between 19 successful agers and 70 typical older adults in another study, rates of whole-brain cortical thinning and hippocampal atrophy over an average of 5 years were equivalent between groups [7]; however, this study also reported no association between Aβ deposition and loss of brain volume within the total sample, which is inconsistent with previous research [20–25] and may be a consequence of the small sample studied. Despite consistent cross-sectional reports that individuals with superior memory performance display relatively preserved brain morphology compared to older adults who are cognitively normal for their age (CNFA) despite varying minimum age criteria, divergent findings in prospective studies highlight the need for larger samples and longer follow-up times to examine age- and Aβ-associated brain morphological changes in SuperAging.

The Australian Imaging, Biomarkers and Lifestyle (AIBL) study is a large prospective cohort in which multiple studies have described Aβ-associated loss of brain volume [21,22,26]. This study is well-positioned to examine whether SuperAgers are resistant to age- and Aβ-associated neurodegeneration compared to CNFA older adults. The first hypothesis was that greater rate of volume loss in white matter (WM), gray matter (GM), and hippocampus would be associated with Aβ+ in CNFA older adults. The second hypothesis was that individuals classified as SuperAgers would display reduced rates of age- and Aβ-associated cortical atrophy compared to CNFA older adults. Finally, to examine the influence of SuperAger classification on cerebrovascular disease markers, this study also explored differences between SuperAgers and CNFA in white matter hyperintensity (WMH) volume and accumulation over time, and whether this was mediated by Aβ.

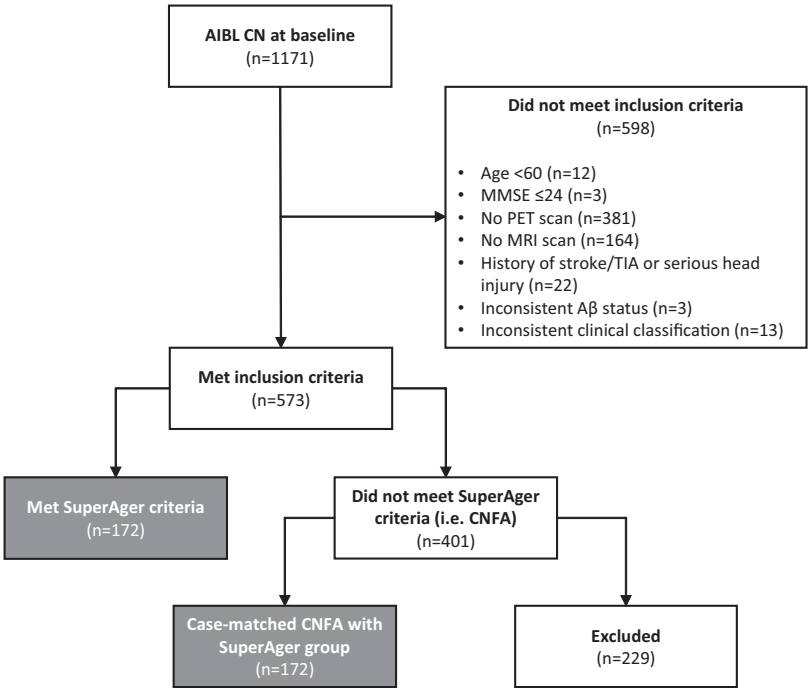

Fig. 1. Sample selection. Abbreviations: AIBL, Australian Imaging, Biomarkers and Lifestyle; CN, cognitively normal; CNFA, cognitively normal for age; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

2. Method

2.1. Participants

The AIBL study protocol has been reported previously [27]. Volunteers were ineligible for enrollment if they met any of the following exclusion criteria: non-AD dementia, history of schizophrenia or bipolar disorder, current depression (Geriatric Depression Scale score >5), Parkinson's disease, cancer (other than basal cell skin carcinoma) within the last 2 years, symptomatic stroke, uncontrolled diabetes, obstructive sleep apnea, past head injury with >1 hour of posttraumatic amnesia, or current regular alcohol intake beyond recommended limits [28]. All included participants were identified to have no or medically well-controlled systemic illnesses at baseline. Ethics approval for the AIBL study was granted by St Vincent's Health, Austin Health, and Edith Cowan University, and all participants provided written informed consent at each visit.

2.1.1. Sample selection

The AIBL study currently includes 611 CN adults who satisfied the aforementioned baseline inclusion criteria, were aged over 60 with mini-mental status examination >24, and underwent both Aβ positron emission tomography (PET) and MRI neuroimaging. These participants were recruited in two waves: an inception cohort (n = 400) followed up every 18 months for up to 8 years, and an enrichment cohort (n = 211) followed up for up to 4.5 years. The sample was further restricted to those who reported no history of stroke, transient ischemic attack, or serious head injury at baseline (n = 589). Participants who were classified with mild cognitive impairment or dementia by a clinical panel during the follow-up period were coded as progressors; those whose clinical classification or Aβ status were inconsistent across the study period were excluded to ensure reliability of classification (n = 16). Following these exclusions, 172 of the eligible participants were classified as SuperAgers (see criteria below). SuperAgers were then case matched with the remaining CN participants (i.e. CNFA) based on age, sex, education, follow-up time, and number of serial MRI scans. The final analyses included 344 participants (172 SuperAgers, 172 CNFA; Fig. 1).

2.1.2. SuperAger classification

Individuals were classified as SuperAgers at baseline using neuropsychological criteria adapted from the Northwestern SuperAging Study criteria as described previously [3]. A greater number of nonmemory tests were included

in the classification criteria for this study compared to that used in the Northwestern SuperAging Study [12] to increase classification specificity. Classification required performance above the normative average for adults aged 30-44 years on the California Verbal Learning Test–Second Edition Long Delay Free Recall trial [29] ($\geq$13 for women, $\geq$12 for men), and performance above -1 SD for their age on all nonmemory tests identified to be suitable for the study of cognitive aging: Digit Symbol Substitution Test, Victoria Stroop Test (words trial), Digit Span, Letter Fluency (FAS), and Category Fluency (total animals and male names, and fruit and furniture) [30]. CN participants who were not classified as SuperAgers were classified as CNFA.

2.1.3. Assessment

A comprehensive neuropsychological battery was administered at each study visit. Medical assessments included anthropometric measures, blood tests, and self-reported medical history (e.g. hypertension) [27]. Education was coded as $\leq$12 years or $>$12 years. *APOE* genotype was determined from whole blood extracted DNA as per previously described methodology, and participants were classified as *APOE* ε4 carriers or noncarriers [31].

2.2. Neuroimaging

2.2.1. MRI neuroimaging

Participants underwent a 3D T1-weighted magnetization-prepared rapid gradient-echo sequence using the following acquisition parameters: in-plane resolution 1 $\times$ 1 mm, slice thickness 1.2 mm, repetition time (TR)/echo time (TE)/inversion time (TI) = 2300/2.98/900, flip angle 9°, and field of view (FOV) 240 $\times$ 256. Magnetization-prepared rapid gradient-echo images for all participants were segmented into WM, GM, and cerebrospinal fluid using an implementation of the expectation maximization algorithm [32]. Hippocampal extraction was performed using a multiatlas approach based on the Harmonized Hippocampus Protocol [33]. Some participants also underwent a 3D fluid attenuation inversion recovery (FLAIR) sequence (133 SuperAgers, 131 CNFA); therefore, exploratory analyses of WMH were conducted within this sample. Three different sets of FLAIR acquisition parameters were used: (1) in-plane resolution 0.98 $\times$ 0.98 mm, slice thickness 0.9 mm, TR/TE/TI = 6000/420/2100, flip angle 120°, FOV 240 $\times$ 256, and 176 slices; (2) in-plane resolution 0.5 $\times$ 0.5 mm, slice thickness 1.0 mm, TR/TE/TI = 5000/355/1800, flip angle 120°, FOV 512 $\times$ 512, and 160 slices; (3) in-plane resolution 1.0 $\times$ 1.0 mm, slice thickness 1.0 mm, TR/TE/TI = 5000/391/1800, flip angle 120°, FOV 256 $\times$ 256, and 192 slices. WMH were automatically segmented using the HyperIntensity Segmentation Tool based on an ensemble of pretrained neural network classifiers [34,35] and quantified from the segmented lesion masks in the common Montreal Neurological Institute space. All measures were corrected for scanner and total intracranial volume.

2.2.2. Amyloid-β PET neuroimaging

PET neuroimaging was conducted using one of the four Aβ radiotracers: ^{11}C-Pittsburgh compound-B (PiB, n = 137), ^{18}F-NAV4694 (NAV, n = 38), ^{18}F-Florbetapir (FBP, n = 88), or ^{18}F-Flutemetamol (FLUTE, n = 81). Detailed PET methods and procedures are described elsewhere [36,37]. Briefly, PET acquisitions were performed up to 90 minutes following tracer injection. Standardized uptake value (SUV) data were summed and normalized to a reference region to generate a SUV ratio (SUVR). Image analysis was performed using the MR-less method, CapAIBL [38]. A linear regression transformation was applied to the NAV, FBP, and FLUTE SUVRs to create a "PiB-like" SUVR unit called Before the Centiloid Kernel Transformation so that SUVRs across the different radiotracers were expressed on the same scale [37]. All participants with SUVR/Before the Centiloid Kernel Transformation$\geq$1.40 at their most recent PET scan were classified as Aβ+ and those below the threshold were classified as Aβ−.

2.3. Statistical analyses

R version 3.4.3 [39] and SPSS 23 were used for all statistical analyses, with statistical significance set at $P < .05$. No adjustments were made for multiple comparisons due to their conservative nature; the early and important stage of this research highlights the importance of encouraging future studies in this area. Therefore, estimates of effect size were computed for all comparisons to guide interpretation of the results (i.e. $d < 0.20$ may be due to type I error). SuperAgers were case-matched with CNFA using the FUZZY extension command in SPSS. Exact matches were required for education and sex. Tolerances for age, follow-up time, and number of serial MRI scans were $\pm$2 years, $\pm$1 visit, and $\pm$1 scan, respectively. Eligible matches were selected randomly.

2.3.1. Baseline group differences

Between-group comparisons by SuperAger classification and Aβ status were conducted using one-way analyses of variance and Kruskal-Wallis one-way analyses of variance for continuous variables and Fisher's exact tests for categorical variables. Linear regressions examined baseline differences between groups for each neuroimaging measure with age as a covariate, both before and after case-matching SuperAgers with CNFA.

2.3.2. Assessment of Aβ status and SuperAger classification on longitudinal neuroimaging measures

Separate linear mixed models (LMMs) were run with each of the neuroimaging measures as dependent measures. Fixed factors were SuperAger classification, Aβ status, time (years from baseline scan), and their interactions. Random intercepts and slopes were calculated for each participant. Covariates were baseline age and progression status; *APOE* ε4 status and number of serial MRI scans did not

Table 1
Baseline group characteristics

	Total sample	CNFA Aβ−	CNFA Aβ+	SuperAger Aβ−	SuperAger Aβ+	Sig. factors
n	344	103	69	102	70	
Aβ PET SUVR	1.51, 1.32 (0.49)	1.21, 1.22 (0.14)	1.97, 1.81 (0.84)	1.21, 1.20 (0.14)	1.92, 1.87 (0.74)	A***
APOE ε4 carrier (%)	27.30	14.60	43.50	17.60	44.30	
Age at baseline	71.75, 71.00 (9)	71.30, 71.00 (7)	73.67, 73.00 (12)	70.57, 70.00 (9)	72.26, 72.00 (7)	A***
Female (%)	55.80	61.20	47.80	57.80	52.90	
Education >12 years (%)	65.10	62.10	69.60	64.70	65.70	
Hypertension (%)	50.30	15.41	12.21	13.08	9.59	
Progressors (%)	8.40	10.70	18.80	2.00	4.30	S***
Number of MRIs	2.47, 2.00 (2.25)	2.49, 2.00 (3)	2.67, 2.00 (2.50)	2.34, 2.00 (3)	2.46, 2.00 (2)	
Length of follow-up (months)	71.98, 89.00 (37)	77.97, 90.00 (19)	71.30, 89.00 (37)	70.85, 89.00 (40)	65.46, 89.00 (55)	
Baseline white matter volume (cm^3)	394.24, 394.52 (33.44)	394.40, 394.44 (32.33)	396.48, 397.26 (39.10)	390.49, 392.62 (26.55)	397.28, 398.22 (34.95)	
Baseline gray matter volume (cm^3)	461.10, 461.86 (23.28)	459.83, 461.04 (25.55)	457.97, 457.76 (25.99)	463.45, 465.32 (25.81)	462.61, 462.98 (19.88)	S* †
Baseline hippocampal volume (cm^3)	2.96, 2.96 (0.34)	2.96, 2.95 (0.35)	2.93, 2.91 (0.40)	2.96, 2.94 (0.34)	2.99, 3.00 (0.31)	
Baseline white matter hyperintensity volume (cm^3)	14.15, 11.43 (5.41)	13.48, 12.01 (11.86)	17.28, 12.74 (11.68)	13.40, 10.99 (4.21)	13.01, 11.80 (4.79)	

NOTE. *$P < .05$, ***$P < .001$; continuous variables are expressed as mean, median (IQR); categorical variables are expressed as percentages.

Abbreviations: Aβ, amyloid β, *APOE* ε4, apolipoprotein E epsilon 4 allele, CNFA, cognitively normal for their age; IQR, interquartile range; MRI, magnetic resonance imaging; PET, positron emission tomography; SUVR, standardized uptake value ratio; A, significant effect of Aβ status; S, significant effect of SuperAger classification.

†This difference becomes nonsignificant when adjusted for age.

significantly contribute to the models and were therefore removed.

To test the first hypothesis, the interaction of Aβ status × time was examined only in the CNFA group. To test the second hypothesis, interactions between SuperAger classification, Aβ status, and time were examined for the full study sample. Having controlled for baseline age in the analyses, interactions with time were interpreted to reflect changes associated with aging. For each comparison, the magnitude of effect was expressed using Cohen's *d*.

Associations of Aβ+ and SuperAger classification with WMH volume were explored using a gamma generalized LMM fitted with a log link function. The same fixed and random factors from the LMMs were included in the generalized LMM. Covariates were baseline age, *APOE* ε4 status, and self-reported hypertension.

3. Results

Across the 344 SuperAgers and CNFA included in this study, average age was 71 years (range 60-93). The majority had >12 years education (65.1%) and 55.8% were female. Participants were followed up for a median of 89 months (interquartile range: 37) with an average of 2 MRI scans each (maximum 6). As expected due to the case-matching parameters, no differences in demographics or follow-up time were observed between the SuperAger and CNFA groups, and prevalence of both Aβ+ and *APOE* ε4 carriage were nearly equivalent (Table 1). Compared to the Aβ− group, the Aβ+ group had higher prevalence of *APOE* ε4 carriage (odds ratio: 4.08, 95% confidence interval [CI]: 2.47-6.73; $P < .0005$) and were 2 years older on average [$F(1,343) = 10.84$, $P = .001$; $d = 0.36$)]. As previously reported for this sample, SuperAgers were less likely to progress to mild cognitive impairment/dementia compared to CNFA (24 CNFA and 5 SuperAgers; odds ratio: 0.19, 95% CI: 0.07-0.50; $P < .0005$) [3].

3.1. Baseline brain morphological differences

Before case-matching, significantly greater WM, GM, and hippocampal volumes were observed in SuperAgers compared to CNFA. These differences were no longer significant after adding age as a covariate. After case-matching, a significant group difference was found only for GM volume; however, the effect size was small ($d = 0.22$), and this became nonsignificant after adjusting for age. No Aβ group differences were observed on any MRI measure.

3.2. Influence of Aβ on brain morphological changes in CNFA older adults

Annualized rate of volume loss within CNFA was 1.37 cm^3 (0.35%) for WM, 1.80 cm^3 (0.39%) for GM, and 0.015 cm^3 (0.52%) for hippocampus. Significant Aβ status × time interactions were observed for all MRI measures. Mean slopes for both Aβ+ and Aβ− CNFA

Table 2
Annualized group mean slopes and Cohen's *d* for Aβ-associated neurodegeneration in CNFA

Measure	Aβ−	Aβ+	Cohen's *d*	Lower 95% CI	Upper 95% CI
White matter volume	−1.4 (2.16)	−2.27 (2.05)	0.42	0.11	0.72
Gray matter volume	−1.81 (3.00)	−2.74 (2.85)	0.32	0.01	0.62
Hippocampal volume	0.04 (0.57)	−0.03 (0.03)	0.17	−0.14	0.47

NOTE. Values are presented as mean slopes (SD).

Abbreviations: Aβ−, cerebral amyloid β within normal range (positron emission tomography standardized uptake value ratio<1.40); Aβ+, elevated cerebral amyloid β; CI, confidence interval; CNFA, cognitively normal for their age; SD, standard deviation.

showed that Aβ+ was associated with faster loss of WM, GM, and hippocampal volume over time (Table 2). This translates to greater volume loss of 0.88 cm^3 in WM, 0.93 cm^3 in GM, and 0.07 cm^3 in hippocampus per year for Aβ+ compared to Aβ− CNFA. Progressors had lower GM and hippocampal volume across all time points. Both older age at baseline and longer time in study were associated with smaller WM, GM, and hippocampal volumes.

3.3. Influence of SuperAger classification and Aβ on brain morphological changes

The LMM results for WM, GM, and hippocampal volume for the full study sample are summarized in Table 3. Mean slopes for each of the morphological measures are shown graphically in Fig. 2. The Aβ status × time interaction remained significant for all MRI measures after accounting for SuperAger classification. However, the SuperAger status × Aβ status × time interaction was not statistically significant for any MRI measure. Slopes were not significantly different between SuperAgers and CNFA within the Aβ− and Aβ+ groups nor were they different between Aβ groups within the SuperAger and CNFA groups. Fig. 3 shows that Aβ+ was associated with greater volume loss over time in both SuperAger and CNFA groups for each MRI measure but there was substantial overlap in the 95% CIs for each effect size. The two-way interaction of SuperAger classification × time was not significant for any morphological measure with data collapsed across Aβ groups. Although there was a significant main effect of baseline age on all measures, no interactions with age were observed. Analyses restricted to participants over age 80 were not conducted due to small cell sizes.

3.4. Exploratory analyses of SuperAger classification and Aβ on WMH

No baseline differences were observed between SuperAger or Aβ groups. WMH accumulation increased at an average rate of 7% per year for all participants. Older age at baseline and longer time in study were associated with increased WMH volume (Table 3). No main effect of Aβ status nor SuperAger classification were observed, and no interactions with time were observed.

4. Discussion

The first hypothesis, that Aβ+ was associated with greater loss of volume in WM, GM, and hippocampal structures in older adults classified as CNFA, was supported. These data are consistent with previous findings from the AIBL cohort and others that Aβ+ is associated with GM volume loss and hippocampal atrophy in CN individuals [20–25]. The second hypothesis that individuals classified as SuperAgers would display reduced rates of age- and Aβ-associated cortical atrophy compared to CNFA older adults was not supported: no differences between SuperAgers and CNFA older adults were observed for rates of Aβ-associated atrophy (Figs. 2 and 3). Furthermore, no differences were observed for age-associated brain volume loss between SuperAgers and CNFA older adults despite controlling for Aβ. Exploratory analyses of WMH also showed no differences between SuperAgers and CNFA older adults in baseline WMH volume nor rate of accumulation, and neither were influenced by Aβ status. Taken together, the results indicate that SuperAger classification based entirely on neuropsychological criteria does not reflect any unique protection from age- or Aβ-associated neurodegeneration or cerebral small vessel disease.

The SuperAging construct was developed to describe a phenotype of preserved cognitive function in older age that may reflect unique neurobiological characteristics such as protection from neurodegeneration and consequent cognitive decline in aging. This notion was supported by early cross-sectional studies conducted in small samples of SuperAgers [12,13,16,40,41]. Consistent with past reports, the present study observed significantly greater WM, GM, and hippocampal volumes in SuperAgers at baseline prior to case-matching with CNFA, but these differences were not maintained after adjusting for age. SuperAging studies have not adjusted for age for cross-sectional analyses, although only one morphological study of successful agers did so for longitudinal analyses [7]; therefore, it is possible that the reported findings may be confounded by demographic characteristics rather than reflecting true group differences. Furthermore, prospective findings have been mixed, potentially because of limited power to conduct longitudinal analyses due to small sample sizes [7,15]. The finding that individuals classified as SuperAgers were not any more protected against age- or Aβ-associated atrophy than CNFA, regardless of baseline age, does not support the conclusion that maintenance of cognitive abilities from midlife to late-life reflects preservation of brain structure in aging [7,12–16]. These early studies provide important and provocative foundations for models of SuperAging; however, the use of small samples and lack of adjustment for age may limit the generalizability of their conclusions

Table 3
Mixed model parameters

	White matter volume*			Gray matter volume*			Hippocampal volume*			WMH volume†		
Fixed effects	Estimate	Std. error	*P*	Estimate	Std. error	*P*	Estimate	Std. error	*P*	Estimate	Std. error	*P*
Intercept	500.96	15.34	<.001	570.81	11.40	<.001	4.03	0.18	<.001	0.59	0.53	.27
SuperAger classification	−5.62	3.14	.07	1.72	2.29	.45	−0.02	0.04	.59	0.19	0.13	.13
Aβ status (−/+)	5.79	3.52	.10	3.32	2.57	.20	0.02	0.04	.60	0.28	0.14	.05
Time	−1.40	0.21	**<.001**	−1.81	0.30	**<.001**	−0.02	0.00	**<.001**	0.07	0.02	**<.001**
Baseline age	−1.49	0.21	**<.001**	−1.54	0.16	**<.001**	−0.01	0.00	**<.001**	0.02	0.01	**.002**
Progression	−6.04	4.34	.16	−11.18	3.25	**<.001**	−0.13	0.05	**.01**	0.20	0.15	.17
APOE ε4 carrier status (−/+)	-	-	-	-	-	-	-	-	-	0.11	0.10	.25
Hypertension (−/+)	-	-	-	-	-	-	-	-	-	0.07	0.08	.37
SuperAger × Aβ status	3.73	4.91	.45	−0.94	3.58	.79	0.04	0.06	.49	−0.32	0.20	.10
SuperAger × time	−0.52	0.32	.11	0.11	0.45	.81	0.00	0.00	.38	−0.03	0.03	.29
Aβ status × time	−0.88	0.33	**.01**	−0.93	0.45	**.04**	−0.01	0.00	**.004**	−0.02	0.03	.45
SuperAger × Aβ status × time	0.65	0.49	.19	0.09	0.69	.90	0.01	0.01	.31	0.02	0.04	.70

Bolded values are significant at $P < .05$.
Abbreviations: Aβ, amyloid β; *APOE* ε4, apolipoprotein E epsilon 4 allele.
*+Analyzed using a linear mixed model, total n = 344.
†Analyzed using a gamma generalized linear mixed model fitted with a log link function, total n = 264.

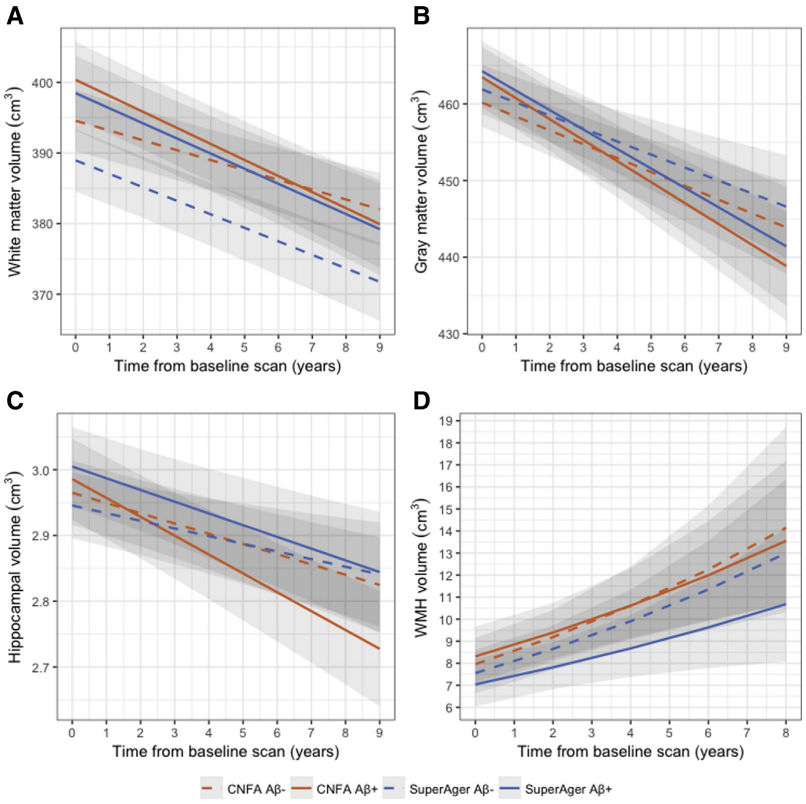

Fig. 2. Morphological changes over time by SuperAger and Aβ status; slopes for Aβ+ (solid lines) were significantly steeper than slopes for Aβ− (dashed lines) for white matter, gray matter, and hippocampal volumes (panels A-C) but no difference was observed for white matter hyperintensities (panel D). No difference in slopes between CNFA (orange lines) and SuperAgers (blue lines) was observed for any measure. Abbreviations: Aβ−, cerebral amyloid β within normal range (positron emission tomography standardized uptake value ratio<1.40); Aβ+, elevated cerebral amyloid β; CNFA, cognitively normal for their age; WMH, white matter hyperintensity.

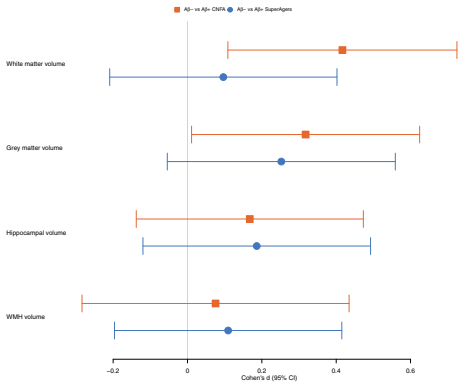

Fig. 3. Comparison of effect sizes for rates of Aβ-associated atrophy; substantial overlap in the 95% CIs for each effect size reflects no difference in the slopes of Aβ-associated volume loss between the SuperAger and CNFA groups. Abbreviations: Aβ−, cerebral amyloid β within normal range (positron emission tomography standardized uptake value ratio<1.40); Aβ+, elevated cerebral amyloid β; WMH, white matter hyperintensity.

due to low statistical power, potential for sampling bias, and type I error.

In contrast to a previous report of successful agers [7], the present study observed similar levels of WMH between SuperAgers and CNFA older adults both cross-sectionally and longitudinally that was not modified by Aβ status. This may reflect a larger sample with strict exclusion of high vascular risk factors. In addition, the previous study measured WM hypointensities using T1-weighted images, which can result in lower volume estimates compared to the 3D FLAIR sequences used here to measure WMH [42]. The lack of association between Aβ status and WMH observed in the present study is, however, consistent with reports that Aβ and WMH accumulation reflect independent processes whose deleterious effects on cognition are additive [43–45].

Limitations to the generalizability of these results are related to the experimental nature of the AIBL cohort; due to rigorous inclusion criteria, AIBL participants are healthier and more educated than the general population [46]. Not enough information is available to ascertain the prevalence of SuperAgers in the general population although experimental cohorts have reported rates of 17.3-42.5% in their respective samples [7,13]. Taking into account sample and survivor biases, it may not be unexpected that 30% of the CN AIBL cohort were classified as SuperAgers despite differences in age criteria and using more stringent neuropsychological criteria compared to other studies [7,12,13]. Unfortunately, operational definitions of successful aging lack consistency between studies [47], which is also the case in studies of youthful memory performance or "SuperAging". Comparisons between studies may thus be limited despite similar goals; however, a strength of the present study was case-matching SuperAgers with CNFA older adults to ensure that the results adequately captured differences due to neuropsychological classification. Whole-brain and hippocampal volumetric measures were most appropriate for the aims of this study due to the increased likelihood of widespread cortical Aβ deposition in Aβ+ individuals [48]. Future studies should conduct region of interest and surface-based analyses of longitudinal morphological change due to Aβ in SuperAgers to determine whether cortical regions reported to be relatively preserved (e.g. anterior cingulate) are protected from Aβ-associated neurodegeneration [7,11,13,16]. Furthermore, although previous studies have suggested that Aβ-associated neurodegeneration occurs only in the presence of elevated tau [49] or that neurodegeneration is more strongly associated with tau than with Aβ [50], this study did not include measures of tau, which future studies should endeavor to do.

5. Conclusions

Despite significant differences in baseline cognitive ability, individuals in the AIBL CN cohort classified as SuperAgers displayed similar levels of AD neuropathological markers such as Aβ+ compared to CNFA older adults. While this may be suggestive of some resilience to the effects of Aβ, SuperAgers and CNFA older adults displayed similar rates of cognitive and morphological change due to both age and Aβ over 8 years [3]. Therefore, defining SuperAging on the basis of neuropsychological criteria alone has limited ability to identify individuals who are uniquely protected from the effects of age or neuropathological changes. The results of this study suggest that the most advantageous characteristic for attenuated brain volume loss in older adults was to have reached old age without elevated Aβ deposition.

Acknowledgments

Alzheimer's Australia (Victoria and Western Australia) assisted with promotion of the AIBL study and the screening of telephone calls from volunteers. The AIBL team wishes to thank the clinicians who referred patients with AD to the study: Associate Professor Brian Chambers, Professor Edmond Chiu, Dr Roger Clarnette, Associate Professor David Darby, Dr Mary Davison, Dr John Drago, Dr Peter Drysdale, Dr Jacqueline Gilbert, Dr Kwang Lim, Professor Nicola Lautenschlager, Dr Dina LoGiudice, Dr Peter McCardle, Dr Steve McFarlane, Dr Alastair Mander, Dr John Merory, Professor Daniel O'Connor, Dr Ron Scholes, Dr Mathew Samuel, Dr Darshan Trivedi, and Associate Professor Michael Woodward. The authors would like to acknowledge the contributions of Kathryn Ellis and Jo Robertson for organizing and overseeing neuropsychological assessments in the AIBL study. They thank all those who participated in the study for their commitment and dedication to helping advance research into the early detection and causation of AD.

Funding: CD is a recipient of the Melbourne Research Scholarship. Funding for the AIBL study was provided in

part by the study partners (Australian Commonwealth Scientific and Industrial Research Organization [CSIRO], Edith Cowan University [ECU], Mental Health Research Institute [MHRI], Alzheimer's Australia [AA], National Ageing Research Institute [NARI], Austin Health, CogState Ltd., Hollywood Private Hospital, Sir Charles Gardner Hospital). The study also received support from the National Health and Medical Research Council (NHMRC) and the Dementia Collaborative Research Centres program (DCRC2), as well as ongoing funding from the Science and Industry Endowment Fund (SIEF).

Paul Maruff is an employee of Cogstate Ltd. Yen Ying Lim serves as a scientific consultant for Cogstate Ltd., Biogen, and Lundbeck. David Ames has served on scientific advisory boards for Novartis, Eli Lilly, Janssen, and Pfizer Inc. Colin L. Masters is an advisor to Prana Biotechnology Ltd and a consultant to Eli Lilly. Olivier Salvado, Jurgen Fripp, Chris Rowe, and Victor Villemagne are inventors on patent US9361686B2 that describes some aspects of the software CapAIBL. Chris Rowe has received research grants from Piramal Imaging, GE Healthcare, Cerveau, Astra Zeneca, and Biogen. Victor Villemagne is and has been a consultant or paid speaker at sponsored conference sessions for Eli Lilly, Piramal Imaging, GE Healthcare, Abbvie, Lundbeck, Shanghai Green Valley Pharmaceutical Co Ltd, and Hoffmann La Roche.

RESEARCH IN CONTEXT

1 Systematic review: Inconsistent terms are used to describe samples of older adults with "youthful" or superior memory performance; therefore, PubMed was searched for "SuperAging" and "successful agers," and author publication lists and references were perused to identify all relevant papers. PubMed was also searched for "(amyloid or beta-amyloid) and (atrophy or brain volume loss or neurodegeneration)."

2 Interpretation: Defining SuperAging on the basis of neuropsychological criteria alone has limited ability to identify individuals who are uniquely protected from brain atrophy because of age or neuropathological changes. The results of this study suggest that the most advantageous characteristic for attenuated brain volume loss in older adults was to have reached old age without elevated Aβ deposition.

3 Future directions: Longitudinal analyses with larger, population-based samples with Alzheimer's disease biomarkers and statistical age corrections are necessary to further examine protection from cognitive decline and brain atrophy associated with age or Aβ in SuperAgers.

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Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 11 (2019) 562-563

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Letter

SuperAging: Current findings yield future challenges—A response to Rogalski and Goldberg

We thank Drs Goldberg and Rogalski for their thoughtful commentaries on issues related to the construct of SuperAging that arose from their consideration of our article entitled, "Rates of age- and amyloid β-associated cortical atrophy in older adults with superior memory performance". We agree that identifying biological factors that allow some older adults to maintain memory ability comparable to adults 20–30 years younger is important because such an understanding could provide clues to strategies for the elimination of age-associated neurodegenerative diseases. In this context, Rogalski and Goldberg identify important issues for consideration in empirical studies and theoretical development of the SuperAger construct. Both commentaries and our own work acknowledge that many different terms have been used to define older individuals with cognitive function superior to that of individuals of the same age [1]. While the present study focused on the SuperAger construct, the issues raised by Rogalski and Goldberg apply to all criteria developed to classify older adults with superior cognition.

Rogalski suggests that SuperAger classification should require a minimum age of 80 years, consistent with the Northwestern SuperAging Study criteria [2]. One foundation for this recommendation is that normative data for a list-learning test used to classify SuperAgers show that decline in test performance increases with aging: decline in performance from 60 to 80 years of age is much greater than that from 40 to 60 years. Thus, the preservation of youthful memory, defined as performance equal to or better than adults 20–30 years younger, becomes more impressive as individuals become older. However, we have suggested that enforcing a minimum age criterion in the definition of SuperAging might be limiting on a number of bases. First, biological age may be a better predictor of cognitive ability and overall health than chronological age [3]. Second, defining a single criterion value from continuous scales such as age will reduce the statistical power of investigations seeking biological or clinical correlates of SuperAging, as power is maximized when relevant samples are as large as possible and the variable of interest (e.g. age) is treated as a covariate in analyses [4,5]. Finally, studies of preclinical Alzheimer's disease suggest that existing normative data for many standardized neuropsychological tests will be negatively biased, particularly at older ages, because normative samples inadvertently include participants with preclinical dementia [6]. In fact, a recent study of cognitive aging showed that typical age-associated decline observed on standardized neuropsychological tests of memory is reduced when Aβ status is controlled statistically [7]. Therefore, our challenge is now to appreciate how chronological age should be treated in defining older adults with superior cognition.

Goldberg acknowledges that superior memory performance identified in the Australian Imaging, Biomarkers and Lifestyle Study of Ageing sample was not associated with reduced effects of aging or Aβ on cortical volume loss. However, he challenges these findings and recommends consideration into how older adults identified with superior memory came to have superior memory at all; this may be achieved by examining the role of genotypes such as *APOE* ε2 carriage or BDNF val66met val/val on preserving cognition [8–10]. He also suggests that lifestyle factors such as education may have been important [11]. Finally, because SuperAgers are classified on the basis of their neuropsychological performance, it is possible that their identification is a function of normal variability where individuals achieve superior scores due to chance. Thus, if classification of superior memory performance reflects the consequences of normal variability, then subsequent changes in performance on the same measure could reflect statistical phenomena such as regression to the mean. Goldberg also cautions that we need to be careful of performance improvements or practice effects that occur with repeated application of the same tests to cognitively normal older adults [12]. These practice effects can mask subtle cognitive decline and potentially explain why no age-associated memory decline was observed in Aβ− SuperAgers nor matched cognitively normal for age controls despite both groups displaying cortical and hippocampal atrophy over the same time period [13].

These two thoughtful commentaries show that there still remains much work to do to refine and understand the SuperAger construct. Together with our own work, we are sure

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that the challenges identified by Rogalski and Goldberg will provide a fertile area for future investigations of these older adults, like whom we all hope to become.

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https://doi.org/10.1016/j.dadm.2019.05.004