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The Study of Neurocognitive Outcomes, Radiological and Retinal Effects of Aspirin in Sleep Apnoea- rationale and methodology of the SNORE-ASA study

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Author's contributions

SW was responsible for project inception, design, funding, supervision of project manager, and first draft of manuscript. ES, RLW, BW, JM were involved in project inception, funding and leadership, and ES in training field staff in the cognitive testing. GH, MN and FO'D were involved in project inception, funding and design especially related to measures of sleep apnoea and reporting of sleep studies. TW, RK, LH and LR were involved in design of the retinal imaging sub-study. AJ was involved in design of MRI analyses and sub-study, and attracting funding. WA and NS were involved in leadership of the project at other sites. RW provided sample size and statistical analysis plans. CR has had input into study design and operation. RT and SF provide important input into study operations and recruitment. All authors have read and contributed to the manuscript.

Competing interests

The ASPREE study medication is provided free of cost by Bayer Healthcare. Resmed leased some of the Apnealink Plus devices used in the study, and provided the nasal cannula for the devices free of cost. Garun Hamilton and Matthew Naughton have both received equipment free of charge for use in research from Resmed, and Garun Hamilton from Phillips Respironics and Air Liquide Healthcare for the same purpose. Fergal O'Donoghue has received a speaker's fee of 1000 Euros from Agir a Dom for speaking at a symposium in Lyon, France March 2015.

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Abstract

Purpose: Sleep disordered breathing (SDB) is highly prevalent in older adults. Increasing evidence links SDB to the risk of dementia, mediated via a number of pathways, some of which may be attenuated by low-dose aspirin. This study will evaluate, in a healthy older cohort, the prospective relationship between SDB and cognitive function, changes in retinal and cerebral microvasculature, and determine whether low-dose aspirin ameliorates the effects of SDB on these outcomes over 3 years.

Design: SNORE-ASA is a sub-study of the ASPIrin in Reducing Events in the Elderly (ASPREE) randomised, multicentre, placebo-controlled trial evaluating the effect of daily 100 mg aspirin on disability-free and dementia-free survival in the healthy older adult aged 70 and over. At baseline, 1400 ASPREE participants successfully underwent a home sleep study with a home sleep study screening device for SDB; and 296 underwent both 1.5 Tesla brain magnetic resonance imaging (MRI) and retinal vascular imaging (RVI). Cognitive testing, brain MRI and RVI is being repeated after 3 years.

Primary outcome measures: Change in the modified mini-mental state examination score. Secondary outcome measures are changes in other cognitive tests, and changes in abnormal parameters on RVI and volume of white matter hyper-intensities on brain MRI.

Conclusion: Identifying preventive therapies for delaying the onset of dementia is of paramount importance. The results of this study will help clarify the impact of the SDB on risk of cognitive decline and cerebral small vessel disease, and whether low-dose aspirin can ameliorate cognitive decline in the setting of SDB.

SNORE-ASA trial registration: *ACTRN12612000891820*: The Principal ASPREE study is registered with the International Standardized Randomized Controlled Trials Register, ASPIrin in Reducing Events in the Elderly, Number: ISRCTN83772183 and clinicaltrials.gov Number .

Keywords

Sleep disordered breathing; Dementia; Cognitive decline; Low-dose aspirin; Brain magnetic resonance imaging; Retinal vascular imaging

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1. Introduction

Sleep disordered breathing (SDB) is highly prevalent in older adults [1]. Most SDB is asymptomatic and undetected, and its clinical significance is uncertain [2–4]. Emerging evidence, however, suggests SDB may be a risk factor for cognitive decline and dementia [5–8]. SDB may increase the risk of cognitive decline via the potential intermediary effects of systemic hypertension, inflammation, endothelial dysfunction, and platelet hyper-reactivity on cerebral small vessel disease (SVD) [9–12]. Some of these pathways and effects may be responsive to aspirin therapy. This paper discusses the rationale and methodology of the Study of Neuro-cognitive Outcomes, Radiological and Retinal Effects of Aspirin in Sleep Apnoea (SNORE-ASA), a sub-study of the larger ASPirin in Reducing Events in the Elderly (ASPREE) trial [13].

2. Rationale for the SNORE-ASA study

2.1. Growing burden of dementia

Dementia is a leading cause of disability and death globally in the setting of ageing populations [14]. Despite significant investment into clinical trials, to date no disease-modifying agent is available. This underpins the imperative to identify and implement preventive strategies for both cognitive decline and dementia. Several risk factors for dementia, apart from age and family history, have been well-established including hypertension, diabetes, physical inactivity and smoking and collectively such risk factors have been estimated to contribute to nearly 50% of all prevalent Alzheimer's dementia cases [15]. Trials investigating the modification of singular or multiple risk factors on cognitive outcomes are of current interest [16]. In this context, sleep disorders have recently emerged as another possible, and modifiable, risk factor for cognitive decline and dementia in older adults, with perhaps the most robust evidence existing for SDB [5].

2.2. Sleep disordered breathing (SDB)

2.2.1. Sleep disordered breathing in older adults—SDB refers to changes in respiration that occur during sleep. Obstructive Sleep Apnea (OSA) is by far the most common sub-type, and occurs when temporary obstructions in the upper airway occur during sleep, leading to an intermittent reduction (hypopnea) or complete cessation (apnea) in respiration. Physiological sequelae include large intra-thoracic pressure swings and intermittent hypoxemia, associated with sympathetic activation, endothelial dysfunction and hypertension [17]. Clinical outcomes of atrial fibrillation, stroke, cardiovascular and renal disease as well as mortality have been found to be associated with OSA in middle-aged populations [18]. OSA also causes multiple, imperceptible arousals from sleep, with resultant daytime sleepiness and reduced quality of life. Furthermore, in middle-aged adults

untreated OSA has been associated with cognitive dysfunction, in particular in the domains of attention, psychomotor speed and executive function [19].

In older age, OSA becomes more prevalent, with community-based studies reporting a prevalence of OSA, of at least moderate severity, in 7–53% of adults aged over 70 [1–3,5,20]. The increased prevalence in older adults may reflect age-related changes in upper airway muscle tone, as well as weight, medication use and co-morbid conditions [21]. The majority of OSA in older adults is undetected, frequently asymptomatic [3], and its clinical significance is not firmly established. A growing body of evidence, however, suggests SDB may be a risk factor for dementia in older adults [5–8].

2.2.2. Mechanisms by which SDB may contribute to risk of dementia in older adults—SDB has been postulated to contribute to the risk of cognitive decline and neuro-degeneration via a number of mechanisms (see Fig. 1). The relationship may in some part be explained by intermediaries, such as hypertension, atrial fibrillation and stroke, which are themselves complications of untreated SDB, as well as contributors to cognitive decline and dementia.

SDB itself, however, may potentiate neuro-degeneration independently of these effects, via the direct and/or indirect effects of hypoxia, inflammation and sleep fragmentation. Neuronal structures, in particular the hippocampus and prefrontal cortex [22,23], are vulnerable to the effects of hypoxia as well as oxidative stress [24]. Hypoxia may play an important role in altering the metabolism of amyloid-beta, the pathological hallmark and trigger of Alzheimer's related tauopathy, as suggested by both animal [25] and human studies [26].

Intermittent hypoxia also appears to drive localised inflammatory changes (increase in neural cytokines and microglial activation) in the hippocampus in animal models [27], as well as peripheral activation of inflammatory pathways [28], with inflammation implicated in the propagation of Alzheimer's pathology [29].

SDB has also been associated with vascular endothelial dysfunction, increased platelet reactivity [30], and evidence of structural and functional change in intra-cerebral vessels in vivo [31], whilst SDB indices, particularly of hypoxia, have been prospectively associated with prevalence of micro-infarcts and gliosis in an autopsy study [32]. Several neuroimaging studies conducted in both middle and older aged groups have also found an association between OSA and measures of cerebral small vessel disease, such as white matter hyper-intensity volume and silent brain infarction [12,30,33,34].

Another mechanism by which SDB may impact cognition adversely is by the deleterious impacts of sleep deprivation and fragmentation, substantiated by seminal animal studies demonstrating the role of sleep in clearing amyloid beta [35] and neurotoxins from the cerebrospinal fluid [36], as well as studies of self-reported sleep quality and duration showing association with amyloid burden on PET imaging [37,38], and measured sleep duration correlating with Alzheimer's pathology at autopsy [39]. Multiple observational

studies have also found prospective relationships between poor sleep quality (both self-reported and measured with actigraphy) and incident cognitive decline and dementia.

As further evidence of the link between SDB and neuro-degeneration, OSA has also been associated with localised changes on MRI in gray matter volume [40,41], brain metabolites [42] and abnormalities of white matter tracts as revealed by Diffusion Tensor Imaging (DTI) [43] including use of Fractional Anisotropy (FA) [43,44].

2.2.3. Evidence of a relationship between SDB and dementia—Several epidemiological studies of older populations lend increasing weight to SDB as a risk factor for cognitive decline and dementia. The most compelling longitudinal study was conducted in elderly women aged 82 at baseline and followed for nearly 5 years, in whom the presence of SDB of at least moderate severity was associated with an adjusted odds ratio (OR) of developing MCI or dementia of 1.85 (confidence interval [CI] 1.11–3.08) over the follow-up period [5]. A similar odds ratio has been found for the risk of developing dementia within 5 years of an OSA diagnosis in a larger Taiwanese population database [6]. Individuals with untreated SDB reported a diagnosis of MCI, and AD, approximately 10 and 5 years respectively before individuals without SDB in an analysis of the large Alzheimer's Disease Neuroimaging Initiative [7]. Several studies have found the relationships between SDB indices and cognitive outcomes were strongest for measures of hypoxia, compared with those for measures of sleep fragmentation [5,8,45]. In contrast, two large population based studies with cognitive measures conducted 8 [46] and 15 [47] years after a sleep study found no, or only mild, associations between baseline SDB measures and cognitive function, although survival bias may have impacted these results. A recent meta-analysis of six prospective studies evaluating the relationship between SDB and cognitive decline reported a risk ratio of 1.26 (CI 1.05–1.50) for the outcome of cognitive impairment [48]. A summary of relevant studies evaluating these relationships are presented in Tables A and B in the Appendix.

2.3. Preventing cognitive decline in the setting of SDB

2.3.1. Effect of CPAP on cognitive outcomes in SDB—Continuous Positive Airway Pressure (CPAP) is the first line treatment for symptomatic OSA, providing benefits in improving daytime sleepiness and quality of life [49], and modest effects on blood pressure control [50] and glycaemic profile [51]. Observational studies have suggested CPAP may improve cognitive function in older adults with OSA [52] and in those with MCI or dementia [53,54].

The role of CPAP for improvement of OSA-associated cognitive dysfunction has been evaluated in middle-aged adults with improvements in some domains observed [55], although a large, randomised and sham-controlled trial of CPAP therapy in > 1000 middle-aged adults with clinically diagnosed OSA reported no significant difference in cognitive outcomes between the CPAP and sham arms after 6 months of follow-up [56]. The role of CPAP in preventing cognitive decline or dementia in older adults merits investigation. A large RCT of CPAP for older patients with an average age of 71 and with outcomes reported after 3 and 12 months of therapy, examined change in cognition as a secondary outcome. No

difference was reported between the two arms (although the study was not powered to assess this outcome adequately) [57].

A limitation of CPAP for older adults is adherence. Randomised controlled trials such as those described above report low adherence to CPAP therapy amongst participants. In older adults with co-morbidities, including cognitive impairment, and given that SDB in older adults is common and commonly asymptomatic, the adherence to CPAP might be expected to be worse. Thus, alternative interventions that may mitigate the impact of SDB on cognitive outcomes warrant investigation.

2.3.2. The potential of low dose aspirin in the setting of SDB—Low-dose aspirin is a widely available and reasonably well-tolerated medication, with a well-established role in the secondary prevention of cardiovascular and cerebrovascular disease [58]. Aspirin has both anti-inflammatory and anti-thrombotic actions, each of which has the potential to confer benefit in the setting of SDB with respect to cognitive outcomes.

The role of low-dose aspirin in the prevention of cognitive decline and dementia is under investigation through the principal ASPREE trial [13], and while results from existing, largely observational data are unfavourable [59], low-dose aspirin may confer greater benefits on cognitive outcomes in populations with higher baseline risk factors [60]. In the setting of SDB, older adults with a higher baseline risk of stroke, cerebral small vessel disease and inflammation may derive such a greater benefit from low-dose aspirin. Low-dose aspirin therapy may therefore, via its anti-thrombotic effects and/or by reducing inflammation, play a role in slowing cerebral small vessel disease. This in turn may reduce the incidence of moderate to severe cerebral small vessel disease, silent brain infarction (SBI) and stroke, all associated with increased risk of cognitive decline.

Conversely, low-dose aspirin poses small risks of major intracranial and gastrointestinal bleeding, and the effects of low-dose aspirin on cognitive outcomes in the setting of SDB may be small. However, given the high prevalence of SDB in older adults, the population effects of low-dose aspirin on cognitive outcomes could be significant, and the presence of SDB may represent a sub-group in which a greater benefit of low dose aspirin exists.

2.3.3. Evaluating the effect of aspirin on cognitive outcomes and the potential of retinal vascular imaging—Retinal vessels offer a unique, and efficient, non-invasive window to assess cerebral vascular health in vivo [61,62]. Quantitative assessment of retinal vessel calibre (diameter), branching structure, and other retinopathy changes (e.g. microaneurysms), have been applied to various ocular and systemic disease assessments, with relationships found between these retinal vessel changes and risk of clinical stroke [63], lacunar stroke [64], SBI and WMH [65,66]. Retinal arteriolar narrowing may reflect cumulative small vessel damage from the effects of ageing, and hypertension and has been linked with endothelial dysfunction while retinal venular dilatation has been linked with inflammation [67]. Both predict incident stroke. Prior studies have also demonstrated that retinal vascular imaging (RVI) changes can predict the development of a range of disorders including hypertension, diabetes, stroke and coronary heart disease

[68,69]. Retinal vascular calibre changes have also been associated with cognitive impairment in general [70] and diabetic populations [71] and with Alzheimer's disease [72].

The relationship between SDB and RVI changes has been evaluated in a few studies. In one cross-sectional analysis of younger adults, no association was found [73]. In two other studies of middle and older aged participants, associations between SDB and retinal arteriolar diameter were found, although associations differed based on gender [74,75]. However, the relationship between SDB and RVI has not been evaluated prospectively, nor the impact of low-dose aspirin on these relationships. Associations have also been found between SDB and ocular diseases such as glaucoma [76,77], diabetic retinopathy [78] and diabetic macular oedema [79], perhaps mediated by alterations in ocular blood flow due to SDB. In addition to brain MRI, therefore, RVI provides another sensitive modality with which to investigate the impact of SDB on cognition, and the effects of low-dose aspirin on brain vascular pathology.

2.4. The aims and objectives of the SNORE-ASA trial

The SNORE-ASA study aims to determine the effects of SDB on cognition and measures of cerebral small vessel ischemia in a healthy elderly population over three years of follow-up, and whether daily low-dose aspirin alters cognitive decline associated with SDB.

2.4.1. Overall hypothesis—SDB impairs cognition in the elderly, mediated in part by cerebral microvascular changes that can be attenuated by low-dose aspirin. The presence of SDB identifies an elderly population in which low dose aspirin is particularly effective in reducing cognitive decline.

2.4.2. Specific hypotheses

1. A) The presence of moderate/severe SDB at baseline is associated with poorer cognitive performance (within normal range) at baseline, and B) A steeper decline in cognition across 3 years of follow-up. C) The severity of SDB (none/mild/moderate/severe) will correlate with baseline cognitive performance and the gradient of decline.
2. A) The severity of SDB at baseline will correlate with baseline levels of RVI abnormalities (as a reflection of central nervous system (CNS) microvascular disease) and with baseline CNS vascular changes on brain MRI. B) The severity of SDB at baseline will correlate with rate of accumulation of RVI and MRI changes. C) RVI and MRI changes will correlate with cognitive performance.
3. Low-dose aspirin reduces the rate of progression of cognitive decline, and this beneficial effect will be greater in those with moderate/severe SDB.
4. Low-dose aspirin reduces the rate of development of RVI changes and extent of MRI changes, and this reduction will be proportionately greater in those with moderate/severe SDB.

3. Materials and methods

3.1. Study design

This study is a randomised, placebo controlled multicentre trial of low dose aspirin (100 mg) conducted in healthy adults aged 70 and over, residing in Australia, and followed for 3 years. SNORE-ASA is a sub-study of the ASPREE trial.

3.1.1. The ASPREE principal trial—ASPREE is a multi-centre, randomised, double-blinded, placebo-controlled trial of daily, low dose aspirin being conducted in 19,114 healthy community dwelling older adults in the USA and Australia, of which 16,703 were recruited from Australia. In Australia the age eligibility was 70 years and over [13]. ASPREE is a primary prevention study and will determine whether 100 mg aspirin daily extends disability-free and dementia-free survival in the elderly.

The ASPREE study methods have been described in detail elsewhere [13]. In brief, the majority of Australian ASPREE participants have been recruited through partnerships with general practitioner (GP) co-investigators. A small proportion was recruited from direct community promotion.

Inclusion and exclusion criteria for the principal ASPREE study have been published elsewhere and are summarised in the first two columns of Table 1.

Participants meeting initial ASPREE eligibility at a screening study visit were given a four week placebo run in. A compliance check was performed at the second baseline study visit four weeks later. Randomization of study drug followed a block randomization procedure and was stratified by site and age (65–79y and > 80y) using the Stata ‘ralloc’ procedure. Participants were randomised to receive either 100 mg of enteric coated aspirin or an enteric coated placebo, which are identical in appearance, in a ratio of 1:1. A 12 month supply of study medication was dispensed and is thereafter at each annual visit. Study participants, investigators and general practitioner co-investigators remain blind to allocation.

ASPREE participants have face-to-face study visits annually. Contact is made via telephone at 3 monthly intervals in between. The 6 month phone call ascertains additional information relevant to study endpoints. The ASPREE study began in 2010, completed recruitment in December 2014 (16,703 in Australia and 2411 in the USA) and will conclude in 2017.

The primary endpoint is a composite of death or dementia (adjudicated according to the DSM-IV criteria) or persistent loss of the same Katz ADL. Pre-specified secondary endpoints include death, cardiovascular and cerebrovascular disease, cancer, cognitive impairment, depression, physical disability and clinically significant bleeding. Independent committees, who are provided with de-identified clinical information about the event, adjudicate all clinical endpoints.

3.1.2. The SNORE-ASA study—Participants for the SNORE-ASA sub-study are a sub-group of ASPREE Australian participants. The inclusion criteria for the SNORE-ASA sub-study are identical to those for ASPREE. Additional exclusion criteria specific for SNORE-ASA were a known diagnosis of OSA, or current use of a CPAP device, as

SNORE-ASA is focusing on the natural history and impact of low-dose aspirin on previously undetected and untreated SDB (see column 3 on Table 1). Participants in SNORE-ASA were recruited from March 2012 until December 2014.

We aimed to invite a sub-group of 365 SNORE-ASA participants with access to Alfred Hospital imaging facilities in Melbourne to undergo brain MRI and RVI (see column 4 of Table 1 for additional exclusion criteria).

3.1.3. Consent and ethics approval—ASPREE participants provided separate consent for the SNORE-ASA study at their second baseline ASPREE visit. SNORE-ASA has specific ethics approval from the Alfred Health Human Research Ethics Committee (primary body), and the following committees as secondary approval sites: Monash University Human Research Ethics Committee, ACT Health Human Research Ethics Committee and the Human Research Ethics Committee University of Adelaide.

3.1.4. Measures and timeline—Participants in SNORE-ASA have relevant assessments performed at study entry and at year 3. Assessments at baseline included cognitive function testing, completion of questionnaires assessing daytime sleepiness and a home sleep study (see Table 2 for timeline of ASPREE principal trial and SNORE-ASA specific measures). Cognitive function testing is repeated at year 3.

Before study medication was commenced, a sub-set of participants underwent a brain MRI and RVI. Both measures have, or will be, repeated at year three.

Measures specific to the SNORE-ASA study are detailed below:

3.1.5. Sleep disordered breathing (SDB) and daytime sleepiness—SDB was assessed at study entry using an Apnealink Plus device (Resmed Inc., Sydney, Australia) that participants wore overnight in their own home. Instructions on how to use the device were provided by study staff at the second ASPREE baseline visit. Participants were encouraged to complete the sleep study at their earliest convenience and return the device in a reply-paid envelope.

The Apnealink Plus device is a single chamber unit that measures nasal airflow and snoring via nasal prongs, and has been validated for use at home compared with the gold standard of ‘in hospital’ polysomnography [80]. The device does not measure sleep. Respiratory effort is measured by a pneumatic strain gauge and oxygen saturation is measured using a pulse oximeter. It provides measures of the Apnea-Hypopnea Index (AHI) and oxygenation desaturation index (ODI) and can distinguish between obstructive and central sleep apnoea. The AHI reported by the ApneaLink Plus is based on nasal flow and total recording time. The AHI (which is usually based upon full polysomnography) refers to a measure of the number of apneas and hypopneas occurring each hour during sleep. An AHI < 5 is considered normal. An AHI of 5–15 is considered to represent mild SDB, 15–30 represents moderate SDB and > 30 severe SDB. The ODI is a measure of the frequency of a drop in oxygen saturation of 3% from the baseline level. Similar to the scale for the AHI, an ODI of < 5 is normal, 5–15 represents mild, 15–30 moderate, and > 30 severe SDB. Both measures

have high diagnostic utility for moderate or severe OSA, however technical failure is lower with oximetry making the ODI a more robust measure [81,82].

On return of the device, the digitised output was uploaded to a central database, and one of three sleep physician investigators reviewed the raw and composite data from each sleep study. For inclusion into the study for analysis, a minimum of 4 h of recording of oximetry was required and the trace had to be free of significant artifact.

A report on the sleep study, including a grading of SDB as normal, mild, moderate or severe, was provided in a letter and sent to each participant's GP. This letter was provided even if the recording was < 4 h. Participants completed two questionnaires at home to measure daytime sleepiness- the Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ). Both are very widely used in the sleep field, and well-validated [83,84]. The ESS measures sleepiness over the preceding month and the FOSQ is a broader sleep-related quality of life instrument. These were returned along with the home sleep study, and the results of these questionnaires further informed the reports on the sleep studies to GPs. Participants also returned a short questionnaire designed for this study on the overall quality of sleep (good, average, poor), approximate time of sleep and duration of sleep the night the device was worn.

3.1.6. Treatment of SDB—Participants have been free to pursue treatment of any SDB identified, if deemed appropriate by their treating GP or physician. Reports back to participants' GPs outlined the uncertain significance of SDB in older adults, particularly for those without excessive daytime sleepiness. Information on any CPAP therapy or other sleep apnoea treatment initiated after the sleep study is collected at Year 3 by study staff at the annual study face to face visit. It is anticipated only a minority of participants identified with moderate/severe SDB will choose to go on to commence CPAP.

3.1.7. Cognitive function—Cognition was assessed at the baseline study visits on study entry, and is again at year 3, by research staff trained and certified to deliver the tests in a standardized manner. The cognitive function tests assess four key domains- see Table 3 for domains and tests utilised.

3.1.8. Brain imaging—A sub-set of 297 participants underwent a brain MRI at study entry (before study medication was dispensed) and have done or will do so again at 3 years. This sub-set was a convenience sample of participants living in proximity to the imaging facility at the Alfred Hospital in Melbourne. The MRI is acquired on a 1.5 Tesla Siemens Scanner. Several MRI sequences are used to assess various aspects of the subject's brain commencing with a sagittal T1 localiser scan. FLAIR images are used to assess deep white matter hyperintensities. Axial T1 and T2 images are then acquired to assess brain structure and volumes, followed by a coronal Gradient Echo image to ascertain the presence of cerebral microbleeds and finally by an ASL (Arterial Spin Labelling) and associated EPI T2 scan that allows a determination of blood flow in the cerebral structures.

3.1.9. MRI imaging protocol—Tri-pilot + FLAIR; T1 + T2 (Myelography T2 at $256 \times 256 \times 256$). Measurements: WMH – Total volume of WMH, as well as deep white matter

and periventricular WMH volumes separately are calculated; SBIs- the presence or absence of sub-cortical infarction as well as total volume will be measured. Also, the presence and count of cerebral microbleeds as well as whole brain and ventricular volumes are assessed.

3.1.10. MRI analyses—All analyses of MRI are performed at the Centre for Advanced Imaging, The University of Queensland using automated processing pipelines. Pre-processing for all volumetric images follows best practice that has been developed for such studies with large numbers of participants [85]. This includes: (1) N3 B0 MRI nonlinear intensity distortion correction, between scan intensity normalisation, registration to a population specific model that is then later matched to the ICBM model of cortical anatomy; (2) Model-based segmentations of whole brain, ventricular, lobar and hippocampal volumes; (3) WM/GM segmentation – a multi-spectral segmentation utilising all the acquired data types provide a good measure of the CSF and WM/GM volumes, and consequently, accurate atrophy measures as well as lobar WM/GM differences; (4) Nonlinearly register the EPI T2 from the functional scans to the gradient echo (GE) volumetric T2. The GE T2 is then be matched to the volumetric T1 and then to the ICBM model using an iterative nonlinear registration algorithm.

3.1.11. Retinal vascular imaging

Retinal photography – 311 participants underwent standardized non-mydratric retinal photography at baseline. This included 296 of the 297 participants who underwent MRI, and a further 15 participants whose MRI was not completed due to claustrophobia, contra-indication or other technical difficulty. After 5 min of dark adaptation, color retinal photographs were taken without pharmacological pupil dilation using Canon NMR 45 digital fundus cameras.

Two retinal photographs centred on the optic disc (ETDRS standard field 1) and macula (standard field 2), respectively, were taken from both eyes of each consented participant. The retinal photography took between 10 and 15 min.

Retinal vasculature assessment - The photographs are sent to the Centre for Eye Research Australia (CERA) in Melbourne for analysis by assessors blinded to treatment allocation. Photographs centred on the optic disc of each eye are examined using standard computer-assisted retinal analysis software that was developed for the Atherosclerosis Risk In Communities study [86]. The grading approach measures retinal vessel diameters and combines the measurements into central retinal artery and vein equivalents with formulas adjusting for branching, following the Parr and Hubbard formulae later modified by Knudtson [87] et al. This software has now been modified and improved and used in a number of studies, including the AusDiab and the Blue Mountains Eye studies in Australia [69,88].

In brief, using a semi-automated system the graders measure the calibres of arterioles and venules crossing a zone defined as the region from 1/2 to 1 disc diameter from the optic disc. The grader carefully corrects any misclassification of vessel type, selects appropriate vessel regions for calibre measurement according to a standardized protocol, and ensures the largest six arterioles and venules have been included by the software, adding them in if

necessary. The calibre of the six largest arteriole and venules are summarised into the central retinal artery equivalent (CRAE) and central retinal venule equivalent (CRVE) respectively as per the formula proposed by Knudtson et al. [87].

The qualitative presence of focal retinal arteriolar narrowing, arteriovenous nicking, arteriolar wall opacity and the presence of retinopathy lesions are assessed subjectively. Each lesion is classified as definite, questionable, or absent across the two retinal photographic fields. The grading is performed by trained retinal image graders at CERA with supervision and adjudication provided by ophthalmologists. Inter- and intra-grader reliability is assessed in a sub-sample of images.

3.1.12. Study outcomes—The **primary outcome** will be cognitive decline as measured by progressively lower scores on the 3MS at 3 years.

Secondary outcomes will be retinal vascular changes over 3 years and volume of WMH and SBI on MRI at 3 years, as well as incident cognitive impairment (exclusive of dementia), as defined by a fall in summed averaged z-scores of > 1 SD on any cognitive domain within 3 years.

3.2. Statistical analysis

3.2.1. Sample size and study power—The initial sample size calculation, in 2012, was based on an expected prevalence of moderate/severe OSA of 40% of people at this age [1] and a conservative estimate of the effect of SDB on cognitive outcomes, based on a paucity of longitudinal data available on the relationship between SDB and cognitive outcomes, and an estimated standard deviation (SD) in cross-sectional 3MS scores of 5. Allowing for 5% loss to follow-up, recruiting 3300 people for the SNORE-ASA trial was estimated to provide 80% power (2-sided α 0.05) to detect an aspirin/SDB interaction with a mean within-person 3 year 3MS change of -2.5 and -1.0 points/100 for placebo and aspirin groups with SDB respectively, and -0.5 and 0 for placebo and aspirin groups without SDB respectively, assuming an SD of 5 in each group for within-person 3 year changes in the 3MS.

In 2014, with recruitment well advanced, it was clear that the attained recruitment would be substantially less. However, in the setting of accumulating evidence of a more substantial effect of SDB on incident cognitive decline [5,6,8], and the observed SD of the 3MS score in the larger ASPREE study cohort being found to be 4.34 points/100 in the > 3000 ASPREE participants who had been followed to 3 years by mid-2014, the sample size target was revised. Allowing for 5% loss to follow-up and approximately 95% having reasonable sleep studies then recruiting 1500 people for the SNORE-ASA trial provides 80% power (2-sided $\alpha = 0.05$) to detect an aspirin/SDB interaction anticipating mean 3 year 3MS changes of -3.8 and -2.0 points/100 for placebo and aspirin groups with SDB, respectively, and -0.5 and 0 points/100 for placebo and aspirin groups without SDB respectively, assuming a Standard Deviation of 4.34 in each treatment group on 3 year changes in the 3MS. Our final recruited number of participants completing a sleep study was 1578, of whom 1400 had sleep studies of at least 4 h of recording and free of significant artifact, and forms the final cohort.

For the MRI/RVI sub-study 365 participants would provide 80% power to detect a 3 year 3MS change with SDB that is 0.32 SD lower, a small to moderate effect size, than without SDB (2-tailed $\alpha = 0.05$), allowing for a 10% prevalence of ungradable RVI. The achieved samples of 297 MRI and 311 RVI give approximately 72% power to detect this 3 year 3MS change. Further, these sample sizes give 80% power to detect a correlation coefficient of 0.15 based on a two-sided *p* value cutoff of 0.05 for statistical significance, i.e. small effect sizes can be detected in the other analyses relating CNS vascular changes and cognitive change implied in hypothesis 2 (See Table 4, below).

3.2.2. Statistical analysis—Descriptive statistics of baseline characteristics will be tabulated. Relevant univariable analyses will be used as a starting point for subsequent confirmatory analyses relating to each hypothesis.

Baseline values of 3MS score, RVI abnormalities, WMH, and SBI will be analyzed with linear regression models that include one of the explanatory variables: presence or absence of sleep apnea or severity of SDB (none/mild/moderate/severe) to address the cross-sectional aspects of hypotheses 1 and 2. Changes over 3 years in the same outcomes (3MS, MRI and RVI) will be analyzed using analysis of covariance (ANCOVA), i.e. assessing how change in the outcome relates to SDB or (for RVI and MRI) baseline cognition or rate of cognitive decline to address the longitudinal aspects of hypotheses 1 and 2. The same analyses with explanatory variables expanded to include the interaction of SDB and aspirin/placebo assignment will address hypotheses 3 and 4.

Continuous variables will be log transformed where their distribution is observed to be positive skewed. Further analyses will adjust in the regression models for age, gender, hypertension, cholesterol level, BMI, and diabetes. These additional analyses would have a dual purpose: to provide insight into possible mechanisms of disease incidence and progression, and to improve precision in estimated associations of interest for the study hypotheses. Incident cognitive impairment (exclusive of dementia) as defined by a fall in summed averaged z-scores of > 1 SD on any cognitive domain (see above) will also be an outcome of interest and will be analyzed using logistic regression models.

4. Discussion

SDB is highly prevalent in healthy older populations, yet in the majority it is largely undetected. The clinical significance of asymptomatic SDB in the elderly is yet to be fully established, and the findings of several studies linking SDB to incident cognitive decline and dementia warrant replication in a well-designed prospective study of a representative cohort of older adults. Further information on the mechanisms via which SDB may potentiate neuro-degeneration is also needed.

The SNORE-ASA study will add valuable data on the prospective relationship between SDB and incident cognitive decline in an older cohort, and on associations of SDB with neuroimaging and retinal biomarkers of vascular disease. Moreover, studies on the treatment of SDB to date have focused on devices, such as CPAP, for treatment, and while effective in managing symptomatic SDB (i.e. in improving daytime sleepiness), CPAP may not be

effective in reducing all complications associated with SDB, including cardiovascular [89] and cognitive outcomes [57]. Moreover, CPAP may be less acceptable to an older population, particularly if the SDB itself is asymptomatic.

Conversely, low-dose aspirin is relatively well tolerated and likely to facilitate better compliance. Low-dose aspirin, through antiplatelet and anti-inflammatory effects may modify vascular changes associated with SDB and have a role in protecting against cognitive decline and dementia, although possible adverse effects of aspirin to exaggerate bleeding must counter this. The role of aspirin in primary prevention to extend physical disability-free and dementia-free survival is being evaluated in the principal ASPREE study. Aspirin may confer greater absolute risk reduction in older adults with a higher baseline risk of dementia and cognitive impairment, such as may be present in those with SDB. The results of this sub-study will help determine whether the presence of SDB defines a sub-group who will derive a greater benefit on cognitive outcomes from aspirin therapy. Furthermore, even if the effect of aspirin on cognitive decline in the elderly with SDB is small, given the high prevalence of SDB in the elderly, the potential for a population effect is important.

The principal ASPREE study infrastructure, recruitment model, depth of data variables obtained, and processes for retention of a healthy elderly population have facilitated the development of numerous sub-studies that can explore a number of common ageing-related conditions and their interaction with low-dose aspirin. This is a particularly efficient model which adds significant value to the ASPREE trial, and which will help to identify those healthy older adults for whom differential risk:benefit profiles of low-dose aspirin for primary prevention exist. The SNORE-ASA sub-study design poses some limitations, including a study cohort that are relatively healthy at baseline and free of established cardiovascular disease, as well as free of those with prior diagnoses of OSA. Moreover, while the Apnealink Plus sleep study device facilitated participation of a large group of older adults across a wide geographic area, it cannot provide data on sleep duration, sleep fragmentation and sleep stages.

However, despite this, the results of the SNORE-ASA, expected in late 2018, are likely to be of interest. First, the study will help to establish, in a cohort of healthy elderly, whether SDB is a risk factor for incident cognitive decline over time. Second, by utilising brain MRI and RVI at two time points in a sub-set, it will investigate the impact of SDB on cerebral small vessel disease and its relationship with cognitive impairment. Third, it will investigate whether an affordable, relatively well-tolerated and convenient medication – aspirin - can ameliorate deleterious effects of SDB in the elderly. Finally, the collection of sleep study data from the SNORE-ASA trial, combined with data from the principal ASPREE study (including cardiovascular endpoints) and other sub-studies (including those dedicated to neuroimaging, depression, falls and fractures, vision and hearing loss) provides for future hypothesis-generating research through post-hoc analysis, including a differential effect of aspirin on cardiovascular outcomes in the setting of SDB.

5. Conclusion

SDB is common in older adults, often undetected and asymptomatic. A growing evidence base links SDB to an increased risk of cognitive decline and dementia. This may be mediated in part through the effects of intermittent hypoxemia on cerebral vasculature. CPAP has not yet been soundly established as effective in the prevention of cognitive decline and dementia in the setting of SDB in older adults and suffers from poor compliance. Aspirin, by contrast, may attenuate some of the mechanisms via which SDB impacts cognitive outcomes, and is reasonably well tolerated. The SNORE-ASA study will provide further valuable data on the clinical significance of SDB in older adults, and evaluate whether aspirin plays a role in moderating cognitive outcomes attributable to SDB in this age group.

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Appendix A.: Community-based, longitudinal studies evaluating relationship between SDB in older adults and cognitive outcomes

Study and year	Population	Measure of SDB	SDB prevalence	Cognitive measures	Follow-up duration	Results
Quan et al. [90]	147 men and women, mean age 57, no history of CPAP for OSA	Unattended home PSG	N/A - case control	WAIS-III Picture Completion, Digit Span, Letter-number sequencing, Digit Symbol Coding, Symbol Search sub-sets, Stroop Color and Word Test, Trail-making test, Grooved Pegboard	Mean 24 months (9–40 months) after PSG	No differences in any cognitive test between OSA and no OSA group. Reduced motor speed associated with O2 sat < 85%
Yaffe et al. [5]	298 women, mean age 82	Unattended home PSG	32.5% with AHI > 15	3MS, California Verbal Learning Test, Digit span, category and verbal fluency tests, Trails B. DSM-IV for dementia or MCI diagnosis	Mean 4.7 years	ODI > 15 associated with 1.71 (CI 1.04–2.83) adjusted OR for development of dementia or MCI
Blackwell et al. [8]	2636 men, mean age 76	Unattended home PSG	43% with AHI > 15	Trails B, 3MS	Mean 3.4 years	– 0.36 annual decline in 100 point 3MS score for each 5 unit increase in ODI

Study and year	Population	Measure of SDB	SDB prevalence	Cognitive measures	Follow-up duration	Results
Martin et al. [46]	559 men and women aged 67	Unattended nocturnal respiratory recording	72% with AHI > 15	Trails A and B, Stroop Color word, Coding sub-set of WAIS, semantic and categorical fluency, Benton Visual Retention Test form C, Free and Cued Selective Reminding Test, MMSE	Mean 7.8 years	SDB measures at baseline associated with mild reduction in attention tests after adjustment
Lutsey et al. [47]	966 men and women mean age 61	Unattended home PSG	17.6% with AHI 15	Digit Symbol Substitution Test, Delayed Word Recall Test, Word Fluency Test, Trails A and B, Digit Span Backwards, Logical Memory Test, part A; Logical Memory Test, part B; Incidental Learning, digit-symbol pairs; Clock Time Perception.	Median 14.9 years	No association of SDB measures with cognitive function

Abbreviations – AHI = Apnea Hypopnea Index, ODI = Oxygen Desaturation Index WAIS = Wechsler Adult Intelligence Scale, 3MS = Modified Mini-mental State Examination; PSG = polysomnography; MMSE = Mini-mental State Examination.

Appendix B.: Large cross-sectional studies evaluating relationship between SDB and cognitive outcomes in older adults

Study and year	Population	Measures and prevalence of SDB	Measures of cognition	Results
Boland et al. [91]	1700 with mean age 62.5	Unattended home PSG; 25% had RDI > 10%	Delayed Word Recall Test, Digit Symbol Subtest (from WAIS-R) and first letter Word Fluency	No association between cognitive function scores and RDI; Weak relationship suggested for severe RDI and psychomotor speed
Spira et al. [92]	448 women mean age 83	Unattended home PSG; 13% had AHI > 30, mean AHI 15	MMSE, Trails B	All SDB measures associated with impairment on MMSE, (but not on Trails B), especially for APOe4
Sforza et al. [1]	827 men and women aged 68	Unattended home PSG; 53% with AHI > 15	MMSE, Free and cued selective reminding test, Benton visual memory test, digit span test, memory span and Tracking Baddeley dual task, Trail Making test A and B, Stroop Test, alphabetic and category fluency test, WAIS similarities test	No association between AHI > 15 and any cognitive measure; AHI > 30 associated with lower score immediate recall and Stroop
Haba-Rubio et al. [45]	580 community dwelling men and women, 291 with cognitive	Unattended home PSG.	MMSE, Grober and Buschke Double Memory Test, DO80 naming test, Stroop, letter fluency, CERAD figures and	ODI 4% and 6% associated with presence of cognitive impairment in multivariate analysis

Study and year	Population	Measures and prevalence of SDB	Measures of cognition	Results
	impairment. Mean age 72		Clinical Dementia rating scale.	

Definitions – RDI = Respiratory Desaturation Index; other abbreviations as defined in Table 1.

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Fig. 1. Possible mechanism via which SDB may potentiate neuro-degeneration. WMH- White Matter Hyper-intensities, CMB – Cerebral Microbleeds, BBB – Blood Brain Barrier.

Table 1

Exclusion and Inclusion criteria for the ASPREE, SNORE-ASA and SNORE-ASA imaging subset.

ASPREE (Australia only)		SNORE-ASA		SNORE-ASA imaging	
Inclusion criteria		Exclusion criteria	Additional exclusion criteria	Additional exclusion criteria	
Able to give informed consent		Established CVD ^a	Known diagnosis of OSA	Cardiac pacemaker	
		Atrial Fibrillation			
Able to attend a study visit		Dementia	Current use of CPAP	Cochlear implant	
		Score < 78 on 3MS ^b		Retained metal fragment in the eye	
Aged 70 and above		Disability			
		Anaemia		Non-compatible cerebral-aneurysm clip.	
		High risk of recurrent bleeding			
		Condition likely to cause death within 5 years			
		Current use of aspirin or another antithrombotic agent			
		Uncontrolled Hypertension			
		Current use of aspirin/other antiplatelet agent for secondary prevention			

^aCVD- Cardiovascular disease.

^bModified mini-mental state examination.

Table 2

Study timeline.

Measurement	Recruitment & screening	Assessment & eligibility	Annual review	Annual review	Annual review
Year	– 4 weeks	0 year	1 year	2 years	3 years
ASPRE study					
Inclusion/exclusion criteria & consent	X				
Demographics and lifestyle factors ^a	X		X	X	X
Blood pressure and heart rate	X		X	X	X
Weight, waist circumference and height ^b		X	X	X	X
Cardiovascular biomarkers ^b	X				
Cognitive function	X ^c	X ^d	X ^{c,d}		X ^{c,d}
Clinical event recording	X	X	X	X	X
Compliance check		X ⁱ	X	X	X
Study medication dispensed (annually)	X ⁱ	X	X	X	X
SNORE-ASA					
Inclusion/exclusion criteria & consent		X			
Home sleep study		X			
Sleep questionnaires ^e		X			
Brain MRI and RVI ^f		X			X
Additional cognitive tests ^g		X			X

^aMedical history & medications, smoking and alcohol history, level of education, first language.^bincludes haemoglobin, creatinine, urine spot albumin, LDL, cholesterol and fasting glucose.^c3MS.^dHVLT-R, COWAT-F, SDMT and CES-D-10.^eESS and FOSQ.^fFor a sub-set of 296 participants.

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z_{Stroop} Stroop test and Color Trails Test.
 q_{Height} Height at baseline only.
 i_{Placebo} Placebo.

Table 3

Cognitive domains assessed and tests used.

Cognitive domain	Tests
General cognition	Modified Mini-mental State Examination (3MS)- a score of > 77 required for study eligibility
Attention/processing speed	Symbol Digit Modalities Test, Color Trails A ^a
Memory	Hopkins Verbal Learning Test- Revised: 3-trial immediate recall; delayed recall; recognition discrimination index
Executive functioning	Controlled Oral Word Association Test (COWAT)-F, Color Trails interference index ^a ; Stroop Colour-word time ^a ; Stroop Colour-word errors ^a

Cognitive testing is performed as part of principal ASPREE study.

^aIndicates tests additional for SNORE-ASA participants.

Table 4

Hypotheses and power calculations.

Hypothesis	Power calculation
Low-dose aspirin reduces the rate of progression of cognitive decline, and this beneficial effect will be greater in those with moderate/severe SDB over 3 years	1500 people provides 80% power (2-sided $\alpha = 0.05$) to detect an aspirin/SDB interaction anticipating mean 3 year within-person 3MS changes of -3.8 and -2.0 points/100 for placebo and aspirin groups with SDB, respectively, and -0.5 and 0 points/100 for placebo and aspirin groups without SDB respectively, assuming a standard deviation of 4.34 in each treatment group for 3 year within-person changes in 3MS scores.
Severity of SDB at baseline correlates with rate of accumulation of RVI and MRI changes over 3 years.	365 participants would provide 80% power to detect a mean 3 year within-person 3MS change with SDB that is 0.32 SD lower, a small to moderate effect size, than without SDB (2-tailed $\alpha = 0.05$), allowing for a 10% prevalence of ungradable RVI.