Sleep apnoea, cognition and aspirin's effects in healthy older people: an ASPREE substudy

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Shareable abstract (@ERSpublications)
This study found that undiagnosed obstructive sleep apnoea, in otherwise healthy older community-dwelling people, is associated with a small decline in global cognitive function over 3 years. This decline was not attenuated by daily low-dose aspirin. https://bit.ly/3SFdlim

Cite this article as: Ward SA, Woods RL, Naughton MT, *et al*. Sleep apnoea, cognition and aspirin's effects in healthy older people: an ASPREE substudy. *ERJ Open Res* 2025; 11: 00581-2024 [DOI: 10.1183/23120541.00581-2024].

Received: 6 June 2024
Accepted: 3 Aug 2024

Abstract

Importance Obstructive sleep apnoea (OSA) may increase the risk of dementia; however, studies have reported variable findings. We investigated if undiagnosed OSA in healthy older adults is associated with cognitive decline, and whether low-dose aspirin could attenuate this.

Methods This was conducted as a substudy of the ASPirin in Reducing Events in the Elderly study. Participants were aged 70 years and above, free of dementia, cardiovascular disease and known OSA. A limited channel home sleep study calculated the oxygen desaturation index. Participants were randomised to daily aspirin 100 mg or placebo**.** Outcomes were the association of OSA, and the interaction of aspirin with OSA, with change in the Modified Mini-Mental State examination (3MS), a test of global cognition, over 3 years. Secondary outcomes were changes in domain-specific cognitive tests. Analyses were adjusted for relevant demographic, lifestyle and cardiometabolic factors.

Results Mild OSA, detected in 630 (49.0%) participants, and moderate/severe OSA, detected in 405 (31.5%) participants, were associated with lower 3MS scores over 3 years (mild OSA: β −0.58, 95% CI −1.15 to −0.00, p=0.049; moderate/severe OSA: β −0.69, 95% CI −1.32 to −0.05, p=0.035), compared to the 250 (19.5%) participants without OSA. No associations of OSA with decline in domain-specific cognitive tests were observed. Interaction terms were not significant for the effects of aspirin with OSA on change in any cognitive test score.

Conclusions OSA was associated with a small decline in global cognition over 3 years in this healthy older cohort. This decline was not attenuated by aspirin.

Introduction

Obstructive sleep apnoea (OSA) is highly prevalent, yet often asymptomatic and underdiagnosed, in older age [1]. It may contribute to the risk of cognitive decline and subsequent dementia [2], but this relationship has not been definitively resolved [3]. This association appears strongest in studies conducted in

clinic-based populations [4, 5], which may be confounded by including participants with more symptomatic OSA and/or by comorbidities such as cardiovascular diseases. Fewer community-based studies have prospectively evaluated this relationship, and with varying findings [6–13]. Clarifying the extent to which highly prevalent, yet mostly asymptomatic, OSA in older people independently contributes to risk of cognitive decline is critically important to clarify, given the high prevalence of both OSA [1] and dementia [14] in older age.

Equally important is identifying interventions that could mitigate any adverse effects of OSA on cognitive outcomes. Continuous positive airway pressure (CPAP) therapy, the standard treatment for OSA, has not been demonstrated to improve cognitive function in randomised controlled trials in older people [15]. Furthermore, adherence to CPAP may be poorer in both older patients and in people with asymptomatic OSA [1, 16]. There is therefore a need to evaluate other interventions that could prevent any adverse cognitive sequelae of OSA in older people.

Low-dose aspirin presents such an intervention for investigation in this context. OSA has been found to associate with sympathetic activation [17], endothelial dysfunction [18], platelet activation [19], hypertension [20] and stroke [21], which may lead to cerebral small vessel disease (CSVD) [22]. CSVD is a major contributor to all dementia cases, and it may also promote the pathogenesis of Alzheimer's disease [23]. The antithrombotic and anti-inflammatory effects of aspirin [24] could potentially attenuate some of these adverse cerebrovascular impacts of OSA, whilst at the same time presenting a treatment that is widely available and is relatively well tolerated.

The Study of Neurocognitive Outcomes, Radiological and retinal Effects of Aspirin in Sleep Apnoea (SNORE-ASA) sought to further the understanding of OSA as an independent risk factor for cognitive decline, by examining the association of OSA with change in cognitive function over 3 years in a cohort of healthy community-dwelling, cognitively normal older adults with no prior diagnosis of OSA. SNORE-ASA furthermore investigated the effects of low-dose aspirin in attenuating any such cognitive decline attributable to OSA.

Material and methods

Study subjects

SNORE-ASA was conducted as a substudy of the ASPirin in Reducing Events in the Elderly (ASPREE) multicentre clinical trial. ASPREE evaluated the effects of daily low-dose aspirin in extending dementia-free and disability-free survival in 19 114 healthy older adults. The ASPREE protocol [25] and primary outcomes have been published previously [26]. The study protocol for SNORE-ASA has also been published [27].

In brief, in Australia ASPREE recruited community-dwelling adults, aged 70 years and above, by partnering with general practitioners (GPs). Exclusion criteria included any known life-limiting illness, a history of occlusive cardio- or cerebrovascular disease, congestive cardiac failure, atrial fibrillation, a current indication for antithrombotic therapy, anaemia, independence-limiting physical disability, severe renal or hepatic disease, dementia or a score of <78/100 on the Modified Mini-Mental State examination (3MS).

SNORE-ASA substudy participation was offered at the time of recruitment into ASPREE, in certain Australian states and territories only, from March 2012 through December 2014 to interested participants who did not have a prior diagnosis of OSA, and/or current use of CPAP therapy for any indication.

ASPREE had primary ethical approval from the Monash University Human Research Ethics Committee (MUHREC) (2006/745MC) in Australia. SNORE-ASA had primary ethical approval from the Alfred Hospital Ethics Committee (452/11). All participants provided written informed consent.

Study design

The main objectives were to, over 3 years: 1) determine the association of undiagnosed OSA with change in cognitive function; and to 2) determine whether aspirin interacted with OSA on change in cognitive function over this same period. The study was conducted as a substudy of a randomised clinical trial. The intervention was enteric-coated aspirin 100 mg taken orally each day. The control was an identical-appearing, enteric-coated placebo tablet. Randomisation to aspirin or placebo (50:50 allocation) occurred through ASPREE, stratified by recruitment site and age (<80 and 80 years and over). Participants, study staff and participants' medical practitioners were blinded to treatment allocation.

Sleep measures

Participants completed an unattended, limited channel, home sleep study (ApneaLink Plus; Resmed, North Ryde, Australia) [28] at study entry. The oxygen desaturation index (ODI) 3% was used as the primary measure to define the presence and to grade the severity of OSA: <5 (no OSA), ⩾5 and <15 (mild OSA) and ⩾15 (moderate/severe OSA). Secondary sleep measures were the apnoea–hypopnoea index (AHI), with cut-offs as follows: <5 (no OSA), ⩾5 and <15 (mild OSA) and ⩾15 (moderate/severe OSA); the mean oxygen saturation, dichotomised as >92% *versus* ⩽92% (the lowest quartile); and the percentage of time with oxygen saturation ⩽90% (T<90), dichotomised as <14.6 and ⩾14.6 (the highest quartile). Participants also completed the Epworth Sleepiness Scale [29] at baseline with daytime sleepiness defined as a score of ⩾10. Each participant's GP received a report of the sleep study. Information on whether any OSA treatment, including CPAP, was subsequently commenced thereafter was obtained by self-report from participants at their year 3 study visit.

Outcomes

The primary outcome was global cognitive decline as measured by change in the 3MS score [30]. Secondary outcomes were decline in domain-specific cognitive tests: the Hopkins Verbal Learning Test Delayed Recall (HVLT-R) [31]; the Controlled Oral Word Association Test – F (COWAT) [32]; the Symbol Digit Modalities Test (SDMT) [33]; the Color Trails Test 1 and 2 [34]; and the Stroop Test (Victoria University version) [35] (see table 1). These were obtained at baseline and were pre-specified to be measured at 3 years post SNORE-ASA study enrolment (March 2015 through to December 2017). The ASPREE trial was terminated early on 12 June 2017 due to futility [26]. Cognitive data continued to be collected on SNORE-ASA participants who were due to complete cognitive tests in the subsequent 6 months; however, by then the intervention (study drug) had ended.

Covariates

These were obtained at baseline at in-person study visits and included age; sex; education levels, dichotomised as ⩾12 years and <12 years; body mass index (BMI); alcohol use, dichotomised as currently using or not; smoking history dichotomised as current/former use *versus* never; hypertension as defined by an mean reading of >140 mmHg systolic and/or >90 mmHg diastolic blood pressure and/or on antihypertensive therapy; diabetes as defined by self-report or fasting glucose of >7 $mmol \cdot L^{-1}$ or on treatment for diabetes mellitus; dyslipidaemia, as defined by a total cholesterol level of ⩾212 $mg \cdot dL^{-1}$ or >5.5 $mmol \cdot L^{-1}$ or LDL >160 $mg \cdot dL^{-1}$ or >4.1 $mmol \cdot L^{-1}$ or self-reported statin use.

TABLE 1 Outline of cognitive tests performed in the SNORE-ASA study

Cognitive test	Domains assessed	Scoring
Modified Mini-Mental State examination (3MS)	Global cognitive function	Maximum score 100 Higher scores=better function
Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R)	Verbal anterograde episodic memory	Maximum score 12 Higher scores=better function
Controlled Oral Word Association Test (COWAT) F	Fluency (executive function and language)	Higher scores=better function
Symbol Digit Modalities Test (SDMT)	Psychomotor speed	Maximum score 110 Higher scores=better function
Color Trails 2	Sustained attention, sequencing, alternation and processing speed	Time in seconds Shorter time=better function
Color Trails Interference	Divided attention	Calculated as: (Color Trails 2 time minus Color Trails 1 time) divided by Color Trails 2 time Lower score=better function
Stroop Test: • Colour Dot – Colour of dots named • Word – Coloured word read • Colour Word – Colour of word named	Cognitive inhibition (executive function), processing speed	Time in seconds Shorter time=better function
Stroop Interference Index	Cognitive inhibition	Calculated as: Colour Word divided by Colour Dot Lower score=better function

SNORE-ASA: Study of Neurocognitive Outcomes, Radiological and retinal Effects of Aspirin in Sleep Apnoea.

Statistical analysis

A target sample size of 1500 participants was calculated to provide 80% power (2-sided α= 0.05) to detect an aspirin/OSA interaction based on mean 3-year 3MS changes of −3.8 and −2.0 points/100 for placebo and aspirin groups with moderate/severe OSA, respectively, and −0.5 and 0 points/100 for placebo and aspirin groups without OSA, respectively. This assumed a SD of 4.34 in each treatment group around 3-year changes in the 3MS and allowed for 5% loss to follow-up and ∼95% of participants having technically adequate sleep studies.

SNORE-ASA outcomes were analysed on an intention-to-treat basis. Multivariable linear regression models were used to determine the associations of OSA severity, based on the ODI, with 3MS scores at year 3. Multivariable logistic regression models tested the associations of OSA severity with a decline of ⩾1 SD drop from an individual's baseline 3MS score. These were both adjusted for baseline cognitive test scores and for pre-specified demographic (age, sex, education levels), lifestyle (alcohol use, smoking history, BMI) and cardiometabolic risk factors (hypertension, diabetes and dyslipidaemia), and then further adjusted for daytime sleepiness and treatment of OSA in an exploratory analysis. These analyses were repeated using the AHI, mean oxygen saturation and T <90 as secondary measures of OSA. Multivariable linear regression models were also used to investigate associations of OSA severity, based on the ODI, with change in domain-specific cognitive test scores over 3 years, with adjustment for covariates as above.

The effects of aspirin on cognitive test scores in the setting of OSA were tested in linear regression models using an interaction term for aspirin against the categories of OSA severity for treatment effect heterogeneity, and by stratifying analyses based on OSA severity. Only participants whose year 3 cognitive data had been collected prior to the termination date for aspirin intervention were included in the main analysis to assess for the aspirin interaction with OSA severity. A sensitivity analysis that included all participants with year 3 follow-up assessments was also conducted.

The statistical significance was set at p=0.05 for all analyses. All analyses were performed on Stata/MP-17.

Results

1399 of 16 703 Australian ASPREE participants were recruited at study sites offering SNORE-ASA participation and completed a home sleep study with ⩾4 h of recording, with 721 randomised to aspirin and 678 randomised to placebo (see figure 1). The mean age of participants was 74.0 years, 46% were female, 49.5% had mild OSA, 31.2% had moderate/severe OSA and 9.0% had daytime sleepiness (see table 2 for baseline characteristics by study drug randomisation). Baseline characteristics of participants who were unable to complete year 3 cognitive tests had slightly lower scores on most cognitive tests at baseline (n=111) (see supplementary table A). Baseline characteristics of participants across categories of OSA severity based on the ODI and AHI are displayed in supplementary tables B and C. Table 3 reports the number of participants who commenced treatment for OSA by study drug randomisation. 42 participants (3.2%) commenced any OSA treatment, and 22 (1.7%) reported ongoing CPAP use at year 3. Supplementary table D reports OSA treatments across categories of OSA severity.

OSA and global cognition

Figure 2 displays mean±SD 3MS scores across severity of OSA, as defined by the ODI (figure 2a) and the AHI (figure 2b) at baseline and after 3 years, in the 1288 participants who completed the tests at both time points (1284 participants with an AHI). Overall, cognitive scores rose between the two time points, suggesting a practice effect, as participants also completed these tests 1 year after baseline. Table 4 reports the results of both linear and logistic regressions of OSA measures with the year 3 3MS score. Both mild (n=630) and moderate/severe OSA (n=405), as defined by the ODI, were associated with lower 3MS scores over 3 years (mild OSA: β −0.58, 95% CI −1.15 to −0.00, p=0.049; moderate/severe OSA: β −0.69, 95% CI −1.32 to −0.05, p=0.035), compared to participants without OSA (n=250) in analyses that adjusted for the pre-specified demographic, lifestyle and cardiometabolic risk factors (total n=1285). These associations were slightly attenuated when further adjusted for daytime sleepiness and OSA treatment (mild OSA: β −0.52, 95% CI −1.11 to −0.06, p=0.081; moderate/severe OSA: β −0.67, 95% CI −1.33 to −0.02, p=0.044). Moderate/severe OSA was associated with an increased odds ratio of a deterioration in 3MS score of at least 1 SD from baseline scores (OR 1.99, 95% CI 1.03 to 3.85, p=0.039). There were no significant associations observed of alternate measures of OSA with change in 3MS scores; however, in an analysis that did not adjust for baseline 3MS scores, moderate/severe OSA, as defined by the AHI, was associated with lower year 3 3MS scores (β coefficient −0.87 (−1.56 to −0.17), p=0.014).

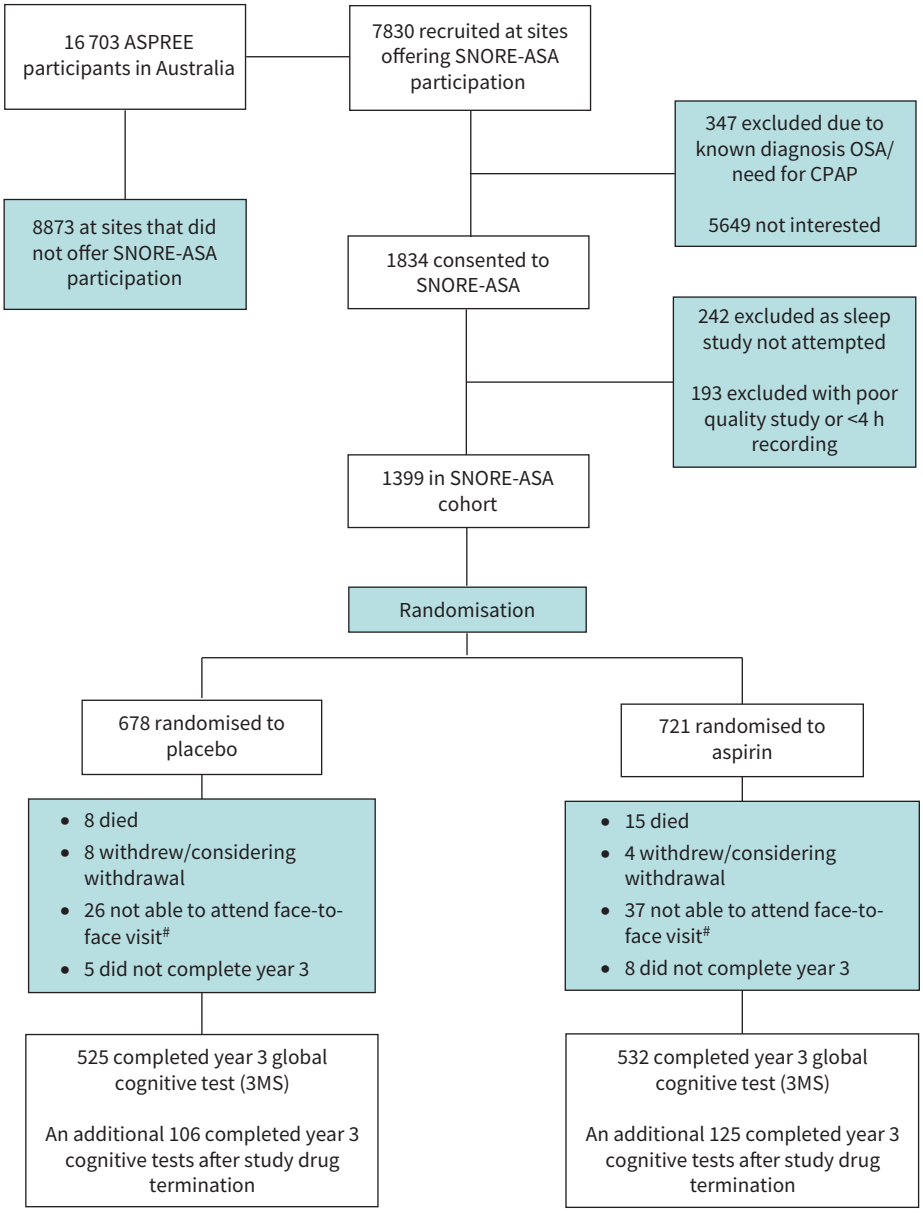


FIGURE 1 Consort flow diagram for the SNORE-ASA study. OSA: obstructive sleep apnoea; CPAP: continuous positive airway pressure therapy; SNORE-ASA: Study of Neurocognitive Outcomes, Radiological and retinal Effects of Aspirin in Sleep Apnoea; ASPREE: ASPirin in Reducing Events in the Elderly; 3MS: Modified Mini-Mental State examination. #: participants who had either moved away or had chosen to have "phone call only" follow-up (precluding conduct of face-to-face visits), or had chosen to have follow-up *via* review of medical records only.

OSA and domain-specific cognition

Supplementary figures A, B and C display the mean±SD scores of each domain-specific cognitive test across severity of OSA as defined by the ODI at baseline and year 3. Table 5 displays the results of linear regressions of OSA categories, based on the ODI, with changes in domain-specific cognitive test scores over 3 years, and Supplementary table E displays the results of logistic regressions of OSA severity, as based on the ODI, with a fall of ⩾1 SD from individual's baseline cognitive test scores. Mild, but not moderate/severe, OSA was associated with improved cognitive test scores on the Color Trails interference index, compared to no OSA. No other statistically significant associations were found.

TABLE 2 Baseline characteristics, sleep study measures and cognitive test scores of the SNORE-ASA cohort

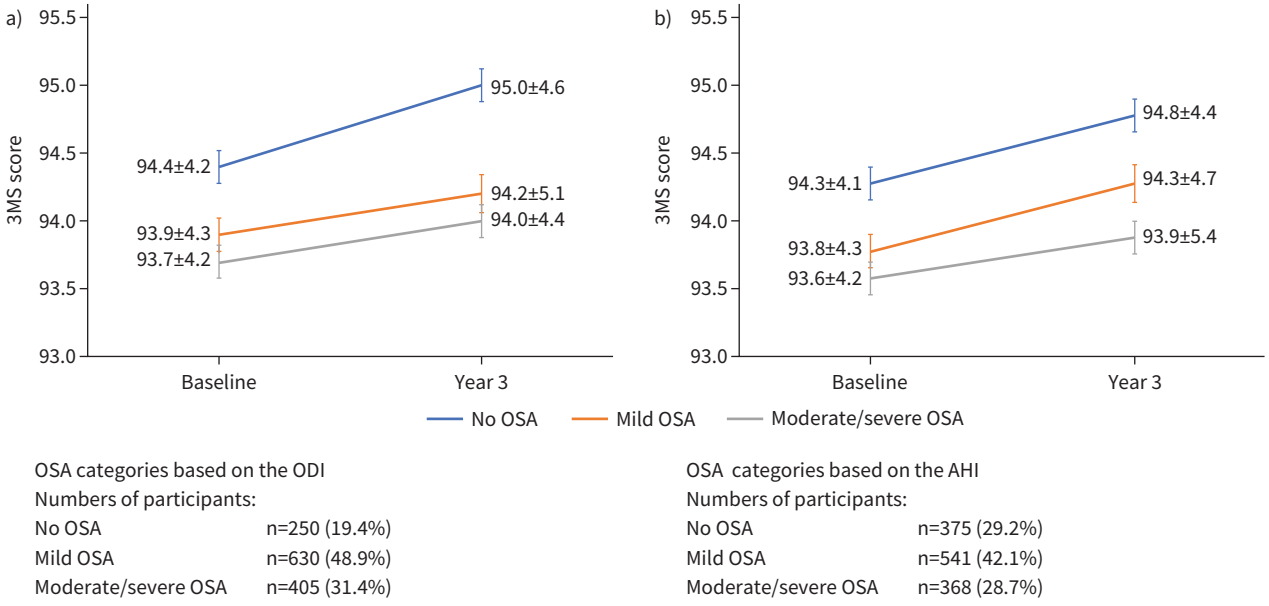
	Placebo	Aspirin	Overall
Subjects n	678	721	1399
Demographics and lifestyle variables			
Age years, mean±SD	73.8±3.7	74.1±3.6	74.0±3.7
Female, n (%)	312 (46.0)	334 (46.3)	646 (46.2)
Education ⩾12 years, n (%)	393 (58.0)	419 (58.1)	812 (58.0)
Body mass index $kg \cdot m^{-2}$, mean±SD	28.3±4.2	28.2±4.3	28.2±4.3
Smoking (current/former), n (%)	303 (44.7)	350 (48.5)	653 (46.7)
Alcohol use (current), n (%)	558 (82.3)	602 (83.5)	1160 (82.9)
Hypertension, n (%)	506 (74.6)	527 (73.1)	1033 (73.8)
Dyslipidaemia, n (%)	445 (65.6)	461 (63.9)	906 (64.8)
Diabetes, n (%)	71 (10.5)	65 (9.0)	71 (10.5)
Sleep measures			
Oxygen desaturation index, mean±SD	12.5±10.3	12.5±9.9	12.5±10.1
Oxygen saturation %, mean±SD	93.1±1.9	93.1±1.8	93.1±1.9
T<90%, mean±SD	12.6±19.3	12.7±18.9	12.7±19.1
OSA categories based on ODI			
No OSA (ODI <5), n (%)	125 (18.4)	145 (20.1)	270 (19.3)
Mild OSA (ODI 5 to <15), n (%)	348 (51.3)	344 (47.7)	692 (49.5)
Moderate/severe OSA (ODI ⩾15), n (%)	205 (30.2)	232 (32.2)	437 (31.2)
AHI, mean±SD	12.2±12.0	11.3±10.5	11.7±11.3
OSA categories based on AHI			
No OSA (AHI <5), n (%)	192 (28.4)	219 (30.4)	411 (29.5)
Mild OSA (AHI 5 to <15), n (%)	285 (42.2)	300 (41.7)	585 (41.9)
Moderate/severe OSA (AHI ⩾15), n (%)	198 (29.3)	201 (27.9)	399 (28.6)
Epworth Sleepiness Scale score, mean±SD	4.8±3.3	4.9±3.3	4.9±3.3
Excessive daytime sleepiness, n (%)	57 (8.9)	63 (9.1)	120 (9.0)
Cognitive test scores, mean±SD			
3MS	93.8±4.3	93.8±4.2	93.8±4.2
HVLT-R	7.8±2.8	7.9±2.8	7.9±2.8
COWAT	12.1±4.5	12.6±4.6	12.3±4.6
SDMT	39.4±9.3	38.5±9.5	38.9±9.4
Color Trails 2 (time in seconds)	103.4±32.5	103.7±31.2	103.6±31.8
Color Trails Interference	1.07±0.60	1.05±0.57	1.06±0.58
Stroop: Dot (time in seconds)	14.9±4.5	15.1±6.4	15.0±5.5
Stroop: Word Time (time in seconds)	19.3±5.4	19.6±7.5	19.5±6.6
Stroop: Colour Word (time in seconds)	35.2±13.7	35.8±13.2	35.5±13.5
Stroop: Colour Interference Score	2.46±1.44	2.47±0.86	2.47±0.35

SNORE-ASA: Study of Neurocognitive Outcomes, Radiological and retinal Effects of Aspirin in Sleep Apnoea; T<90: percentage of recording time with oxygen saturation <90%; OSA: obstructive sleep apnoea; ODI: oxygen desaturation index; AHI: apnoea–hypopnoea index; 3MS: Modified Mini-mental State examination; HVLT-R: Hopkins Verbal Learning Test-Revised Delayed Recall; COWAT: Controlled Oral Word Association Test; SDMT: Symbol Digit Modalities Test.

TABLE 3 OSA treatments commenced between baseline and year 3

	Placebo	Aspirin	All
Subjects n	639	663	1302
Status of OSA treatment, n (%)			
Any OSA treatment commenced	21 (3.3)	21 (3.2)	42 (3.2)
CPAP therapy commenced	14 (2.2)	14 (2.1)	28 (2.2)
CPAP therapy ongoing at year 3	11 (1.7)	11 (1.7)	22 (1.7)

OSA: obstructive sleep apnoea; CPAP: continuous positive airway pressure.



OSA categories based on the ODI

Numbers of participants:	
No OSA	n=250 (19.4%)
Mild OSA	n=630 (48.9%)
Moderate/severe OSA	n=405 (31.4%)

OSA categories based on the AHI

Numbers of participants:	
No OSA	n=375 (29.2%)
Mild OSA	n=541 (42.1%)
Moderate/severe OSA	n=368 (28.7%)

FIGURE 2 Mean±SD Modified Mini-Mental State (3MS) examination scores as defined by a) ODI and b) AHI at baseline and at 3 years by category of OSA. Bars indicate standard error. OSA: obstructive sleep apnoea; ODI: oxygen desaturation index; AHI: apnoea–hypopnoea index.

Effects of aspirin

The results of interaction tests of aspirin with severity of OSA on the 3MS and the domain-specific cognitive tests are displayed in table 6 for the 1057 participants in whom year 3 cognitive tests were acquired before or at termination of randomised study drug, and in supplementary table F, which included the 111 participants whose study drug had been ceased up to 6 months before the cognitive tests were performed. There was no effect of aspirin, as compared to placebo, for any severity of OSA, on cognitive test score change over 3 years, and interaction tests confirmed an absence of evidence for different aspirin effects across OSA severity categories for any individual cognitive test. There was an exception for an interaction between aspirin and moderate/severe OSA for change in HVLT-R scores over 3 years (p=0.048) in the sensitivity analysis (supplementary table F). This arose because in moderate/severe OSA, the aspirin group had a lesser increase in HVLT-R over 3 years compared to placebo (β coefficient −0.5, CI −0.9 to 0.0, p=0.032) in contrast to more similar changes in the two groups with no OSA over 3 years.

Discussion

In this cohort of healthy older adults, undiagnosed OSA was associated with slightly lower scores on a test of global cognitive function over a 3-year period, but was not associated with decline in domain-specific cognitive tests. Conversely, mild OSA was associated with slightly less impaired performance on a test of divided attention, sequencing and alternation. There were no associations, however, observed with moderate/severe OSA, nor with OSA and any other cognitive tests evaluating this cognitive domain (such as the Stroop Test), so this finding is of uncertain significance and may have been due to chance. Daily low-dose aspirin did not attenuate decline in any cognitive domain that was associated with OSA.

Our finding of an association of OSA with a small decline in global cognition is in line with the few other prospective community-based studies that have used objective measures to detect OSA. In 2636 men with a median age of 76 years, increased severity of OSA as defined by the ODI, as well as T<90, was associated with a steeper decline in the 3MS over 3 years [9], the same global cognition measure as used in the SNORE-ASA study. Also like the SNORE-ASA study, that study reported no significant associations with cognitive decline when OSA was alternatively defined by the AHI [9]. In 358 adults with a mean age of 71 years, measures of OSA-related hypoxaemia, such as mean oxygen saturation and T<90, predicted a steeper decline over 5 years in global cognition as measured by the mini-mental state examination (MMSE) (β −0.12 on a 30-point scale), whilst the ODI and AHI predicted decline only in older participants, men and in APOE4 carriers [11]. In 5946 adults comprising the Sleep and Dementia Consortium, with mean ages ranging from 58 to 89 years, OSA was found to significantly associate with slightly reduced global cognition over 5 years; however, the effect sizes were particularly small (pooled β −0.06 for both mild and moderate/severe OSA) [10].

https://doi.org/10.1183/23120541.00581-2024

TABLE 4 Association of OSA measures with Modified Mini-Mental State (3MS) examination scores at 3 years: results of multivariable linear and logistic regressions

OSA measures	Year 3 3MS score Unadjusted	Change in 3MS Scores over 3 years Unadjusted	Model 1	Model 2
Subjects n	1288	1288	1285	1212
β coefficients (95% CI), p-values: results of linear regressions				
ODI categories				
None (N=250)[#]	Ref	Ref	Ref	Ref
Mild (N=630)[#]	**−0.84 (−1.54–−0.13), 0.021**	−0.49 (−1.06–0.08), 0.094	**−0.58 (−1.15–−0.00), 0.049**	−0.52 (−1.11–0.06), 0.081
Moderate/severe (N=405)[#]	**−1.01 (−1.77–−0.25), 0.009**	−0.58 (−1.20–0.04), 0.066	**−0.69 (−1.32–−0.05), 0.035**	**−0.67 (−1.33–−0.02), 0.044**
Oxygen saturation, mean	−0.16 (−0.73–0.41), 0.585	0.12 (−0.34–0.58), 0.614	0.13 (−0.35–0.60), 0.594	0.23 (−0.26–0.71), 0.359
T<90	−0.18 (−0.79– −0.43), 0.558	−0.06 (−0.55–0.43), 0.801	−0.11 (−0.61–0.39), 0.655	0.01 (−0.50–0.52), 0.961
AHI categories	n=1284	n=1284	n=1281	n=1208
None (N=374)	Ref	Ref	Ref	Ref
Mild (N=540)	−0.47 (−1.11–0.16), 0.145	−0.15 (−0.66–0.37), 0.579	−0.14 (−0.65–0.37), 0.591	−0.07 (−0.59–0.46), 0.800
Moderate/severe (N=367)	**−0.87 (−1.56–−0.17), 0.014**	−0.40 (−0.96–0.17), 0.166	−0.44 (−1.00–0.13), 0.132	−0.37 (−0.95–0.22), 0.223
Odds ratios (95% CI), p-values: results of logistic regressions for drop ⩾1 SD from baseline scores				
ODI categories				
None (N=250)[#]		Ref	Ref	Ref
Mild (N=630)[#]		1.41 (0.78–2.55), 0.260	1.56 (0.84–2.88), 0.156	1.56 (0.82–2.96), 0.178
Moderate/severe (N=405)[#]		1.66 (0.90–3.08), 0.108	**1.99 (1.03–3.85), 0.039**	**2.03 (1.01–4.06), 0.046**
Oxygen saturation, mean		1.16 (0.76–1.77), 0.488	1.21 (0.77–1.88), 0.407	1.11 (0.68–1.80), 0.681
T<90		1.17 (0.75–1.82), 0.485	1.27 (0.80–2.02), 0.315	1.05 (0.62–1.75), 0.866
AHI categories		n=1284	n=1281	n=1208
None (N=374)[#]		Ref	Ref	Ref
Mild (N=540)[#]		1.19 (0.74–1.92), 0.481	1.17 (0.71–1.91), 0.525	1.08 (0.65–1.81), 0.763
Moderate/severe (N=367)[#]		0.98 (0.57–1.69), 0.949	1.02 (0.58–1.78), 0.943	0.90 (0.49–1.64), 0.722

Model 1: adjusted for baseline 3MS score, age, sex, education level, smoking history, alcohol use, baseline body mass index, hypertension, diabetes, dyslipidaemia, aspirin randomisation. Model 2: as above plus adjusted for treatment for OSA and excessive daytime sleepiness. Significant results are shown in bold font. Note different numbers for participants with AHI as specified. OSA: obstructive sleep apnoea; ODI: oxygen desaturation index; T<90: percentage of time with oxygen saturation <90%; AHI: apnoea–hypopnoea index. [#]: number of participants in each category of OSA severity with complete data for inclusion in Model 1.

TABLE 5 Associations of categories of OSA as based on the ODI with change in domain-specific cognitive test scores: results of multivariable linear regressions

OSA severity	β coefficient (95% CI), p-value Reference=no OSA			Participant numbers: Unadjusted Model 1 Model 2
	Unadjusted	Model 1	Model 2	
HVLT-R				
Mild	0.21 (−0.12–0.53), 0.219	0.29 (−0.03–0.62), 0.077	0.29 (−0.04–0.62), 0.087	1272
Moderate/severe	0.24 (−0.12–0.59), 0.187	0.32 (−0.04–0.68), 0.078	0.36 (−0.01–0.73), 0.058	1269
				1197
COWAT				
Mild	−0.18 (−0.76–0.39), 0.531	−0.19 (−0.78–0.39), 0.519	−0.16 (−0.76–0.44), 0.602	1285
Moderate/severe	−0.35 (−0.97–0.27), 0.267	−0.27 (−0.91–0.38), 0.417	−0.31 (−0.98–0.36), 0.362	1282
				1209
SDMT				
Mild	0.27 (−0.62–1.17), 0.549	0.33 (−0.57–1.22), 0.471	0.42 (−0.49–1.34), 0.366	1278
Moderate/severe	0.01 (−0.96–0.98), 0.984	0.04 (−0.95–1.04), 0.935	0.11 (−0.91–1.13), 0.831	1271
				1202
Color Trails 2				
Mild	−2.26 (−5.98–1.46), 0.233	−2.00 (−5.75–1.74), 0.294	−2.31 (−6.13–1.52), 0.238	1275
Moderate/severe	0.06 (−3.95–4.07), 0.976	0.76 (−3.40–4.92), 0.721	0.67 (−3.61–4.95), 0.759	1272
				1211
Color Trails Index				
Mild	−0.07 (−0.16–0.01), 0.091	**−0.10 (−0.18– −0.01), 0.027**	**−0.11 (−0.20– −0.02), 0.014**	1272
Moderate/severe	−0.04 (−0.13–0.05), 0.429	−0.07 (−0.16–0.03), 0.181	−0.07 (−0.17–0.03), 0.149	1269
				1209
Stroop Dot				
Mild	−0.18 (−0.88–0.51), 0.610	−0.18 (−0.88–0.52), 0.621	−0.20 (−0.92–0.52), 0.590	1268
Moderate/severe	−0.36 (−1.11–0.39), 0.344	−0.44 (−1.21–0.34), 0.268	−0.42 (−1.22–0.39), 0.310	1265
				1205
Stroop Colour				
Mild	0.19 (−0.55–0.93), 0.620	0.11 (−0.63–0.85), 0.776	0.09 (−0.66–0.84), 0.813	1268
Moderate/severe	−0.26 (−1.06–0.54), 0.523	−0.51 (−1.33–0.31), 0.220	−0.43 (−1.27–0.41), 0.316	1265
				1205
Stroop Colour Word				
Mild	0.53 (−1.08–2.14), 0.519	0.49 (−1.13–2.12), 0.554	0.50 (−1.17–2.16), 0.560	1268
Moderate/severe	0.56 (−1.17–2.29), 0.525	0.40 (−1.40–2.20), 0.661	0.40 (−1.46–2.25), 0.673	1265
				1205
Stroop Index				
Mild	0.07 (−0.04–0.17), 0.232	0.06 (−0.05–0.16), 0.316	0.05 (−0.06–0.17), 0.330	1268
Moderate/severe	0.10 (−0.02–0.21), 0.096	0.09 (−0.03–0.21), 0.122	0.09 (−0.04–0.21), 0.172	1265
				1205

Model 1: adjusted for baseline 3MS score, age, sex, education level, smoking history, alcohol use, baseline body mass index, hypertension, diabetes, dyslipidaemia, aspirin randomisation. Model 2: as above plus adjusted for treatment for OSA and excessive daytime sleepiness. Significant results are shown in bold font. OSA: obstructive sleep apnoea; ODI: oxygen desaturation index; HVLT-R: Hopkins Verbal Learning Test delayed recall; COWAT: Controlled Oral Word Association Test; SDMT: Symbol Digit Modality Test.

We found no associations of OSA with changes in domain-specific cognitive test scores over 3 years, although we have previously reported an association of mild, and moderate/severe, OSA with lower scores on a test of executive function and psychomotor speed respectively at baseline in cross-sectional analyses in this cohort [36]. Most prospective community-based studies have similarly not reported associations between OSA and domain-specific cognitive decline. In 966 men and women with a mean age of 61 years, OSA did not associate with decline in memory, executive function or psychomotor speed when tested 15 years later [8]. In 5247 Hispanic/Latino people, with a mean age of 63 years, a respiratory event index – a measure similar to the AHI – was not associated with declines in memory, executive function and psychomotor speed in tests conducted after 7 years [6]. In 559 men and women aged 61 years at the time of a home polysomnogram, there was no significant change in memory, nor executive function 8 years later, with only a small decrement in attention reported for people with severe OSA [7]. However, in 358 older adults, measures of nocturnal hypoxaemia predicted decline in memory and executive function over 5 years [11].

TABLE 6 Effect of aspirin *versus* placebo on change in cognitive test scores over 3 years, stratified by severity of OSA as based on the ODI, and the interaction of aspirin with categories of OSA

Cognitive test	Total, n	No OSA[#]	Mild OSA[¶]		Moderate/severe OSA[+]	
		β coefficient (95% CI)	β coefficient (95% CI)	Interaction term p-value	β coefficient (95% CI)	Interaction term p-value
3MS	1057	0.03 (−1.02–1.08)	−0.41 (−1.15–0.34)	p=0.531	−0.23 (−1.01–0.55)	p=0.772
HVLT-R	1043	0.04 (−0.55–0.63)	0.19 (−0.20–0.59)	p=0.737	−0.43 (−0.91–0.05)	p=0.225
COWAT	1055	−0.57 (−1.60–0.47)	0.39 (−0.34–1.13)	p=0.135	−0.03 (−0.82–0.76)	p=0.427
SDMT	1049	0.07 (−1.69–1.84)	−0.02 (−1.11–1.07)	p=0.911	−0.36 (−1.66–0.95)	p=0.690
Color Trails 2	1041	0.85 (−5.43–7.14)	2.19 (−2.10–6.47)	p=0.753	0.04 (−6.33–6.41)	p=0.863
Color Trails Interference	1038	0.03 (−0.15–0.20)	0.03 (−0.06–0.12)	p=0.994	−0.12 (−0.25–0.00)	p=0.128
Stroop Dot	1036	−0.63 (−1.87–0.62)	0.26 (−0.61–1.13)	p=0.412	0.89 (−0.09–1.87)	p=0.130
Stroop Word	1036	−0.34 (−1.36–0.69)	−0.14 (−1.07–0.79)	p=0.868	0.67 (−0.42–1.76)	p=0.424
Stroop Word Colour	1036	−0.64 (−3.17–1.88)	0.4 (−1.79–2.59)	p=0.655	0.94 (−1.40–3.29)	p=0.496
Stroop Interference	1036	0.04 (−0.15–0.23)	0.07 (−0.05–0.20)	p=0.956	−0.07 (−0.23–0.09)	p=0.279

Results of linear regressions, adjusting for baseline cognitive scores. Analyses are for participants whose cognitive tests were completed before study drug termination. OSA: obstructive sleep apnoea; ODI: oxygen desaturation index; 3MS: Modified Mini-Mental State Examination; HVLT-R: Hopkins Verbal Learning Test Revised; COWAT: Controlled Oral Word Association Test; SDMT: Symbol Digit Modality Test. [#]: n=215; [¶]: n=512; [+]: n=330.

Overall, the SNORE-ASA study adds to the evidence base that suggests that measures of hypoxaemia, including the ODI, more consistently predict adverse cognitive outcomes in older people with OSA than the AHI, and that OSA in older people seems to have a more consistent effect on global, more than domain-specific, cognition. Given that a diagnosis of dementia is made once overall cognitive impairment is severe enough to impact upon day-to-day function [14], this may explain why OSA has been reported to be associated with incident dementia diagnosis in two community-based studies [12, 13]. However, the magnitude of the effect of undiagnosed OSA on cognitive outcomes in healthy older people appears to be quite small.

In SNORE-ASA, aspirin was not found to confer any benefit in attenuating decline in cognition in the setting of OSA. Low-dose aspirin has anti-platelet effects driven by the inhibition of COX-1, which in turn prevents synthesis of thromboxane A2, preventing platelet aggregation and vasoconstriction [24]. Aspirin also has anti-inflammatory effects [24]. We hypothesised that low-dose aspirin could protect against some of the adverse effects of OSA on the cerebrovascular system, mediated by endothelial dysfunction [18], platelet hyperactivity and inflammation [19], and through systemic mechanisms such as hypertension and sympathetic activation [20]. In turn, we hypothesised that low-dose aspirin could attenuate the risk of CSVD, which other studies had suggested was associated with OSA [22], and which is a significant contributor to cognitive decline and dementia [23]. To our knowledge, this is the first study to investigate if aspirin could mitigate the adverse cognitive outcomes resulting from OSA. We have found that it did not mitigate decline in this very healthy older cohort with largely asymptomatic OSA, even though in this cohort OSA was associated with cognitive decline. The absence of an effect of aspirin in this regard may provide further insights into the pathogenesis of OSA-associated cognitive decline in older age, suggesting that this relationship may be driven by other mechanisms, such as through potentiating Alzheimer's disease [37]. However, in the broader ASPREE trial, aspirin was similarly not found to protect against dementia or cognitive decline, suggesting that aspirin is ineffective in preventing dementia of any subtype [38].

Limitations of this study are that the population under study was healthy, limiting generalisability to frailer and more comorbid older people. The overall rate of decline in global cognition was small, the follow-up

was only 3 years, the study drug was ceased early, and the achieved sample size of 1057 who completed cognitive tests before study drug cessation may have resulted in the study being under-powered to show a true effect of aspirin. It is conceivable that low-dose aspirin may confer greater benefits in people with symptomatic OSA, with greater associated cardiovascular morbidity, if administered for a longer time, or if used in middle-aged populations with OSA. The use of a single unattended limited channel device as opposed to a full polysomnogram may have led to misclassification of OSA. However, this device allowed for the efficient and cost-effective recruitment of participants across a wide geographical area for this community-based study. A one-off sleep study also poses limitations, as OSA can vary from one night to the next and change over time [39]. We did not collect information on pre-existing lung diseases, which may also impact the ODI. We can also not exclude the possibility that pre-symptomatic neurodegenerative changes are resulting in OSA (*i.e.* reverse causation), especially with just a 3 year follow-up.

Strengths of this study include the prospective design, the rigorous screening for cognitive impairment at baseline, the high retention of the cohort with year 3 cognitive data available on 90% of participants, and the adjustment in analyses for extensive lifestyle, demographic, metabolic and cardiovascular comorbidities. Further attributes of the study cohort, such as the exclusion of people with established occlusive cardiovascular disease, cardiac failure, stroke, atrial fibrillation and previously diagnosed OSA, further strengthen the finding that incidentally diagnosed, and highly prevalent, OSA in older age independently contributes to a slight cognitive decline.

Conclusion

In this healthy, initially cognitively normal cohort of older adults, undiagnosed OSA was found to be independently associated with a small deterioration in global cognitive function over a 3-year period. This suggests that incidentally diagnosed, and mostly asymptomatic OSA, in older age may be an independent contributor to dementia prevalence at the population level, given the high prevalence of OSA in this age group. Despite some mechanisms that may underpin the association of OSA with cognitive decline being potentially responsive to aspirin, there was no beneficial effect of aspirin on cognitive outcomes found in this study cohort.

Provenance: Submitted article, peer reviewed.

Acknowledgements: This work was performed at Monash University. The authors acknowledge the ASPREE participants who volunteered for this substudy, the general practitioners (primary care physicians) who supported recruitment and care of participants in the ASPREE study, and the study staff involved in the ASPREE study sites offering this substudy participation. The authors acknowledge Resmed Pty Ltd for provision of nasal cannulas and lease of some of the ApneaLink Plus devices.

Data sharing statement: Data can be made available for approved projects through https://ams.aspree.org/public/

This clinical trial is prospectively registered at https://www.isrctn.com/ with identifier number ISRCTN83772183.

Ethics statement: ASPREE had primary ethical approval from the Monash University Human Research Ethics Committee (2006/745MC) in Australia. SNORE-ASA had primary ethical approval from the Alfred Hospital Ethics Committee (452/11). All participants provided written informed consent.

Support statement: ASPREE was funded by the National Institute on Aging and the National Cancer Institute at the National Institutes of Health (grant numbers U01AG029824 and U19AG062682); the National Health and Medical Research Council (NHMRC) of Australia (grant numbers 334047 and 1127060); Monash University; and the Victorian Cancer Agency. SNORE-ASA was funded by the National Health and Medical Research Council of Australia (grant number 1028368). C.M. Reid is supported through an NHMRC Principal Research Fellowship (GNT1136372). Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Resmed leased some of the ApneaLink Plus devices used in the study and provided the nasal cannula for the devices free of cost. G.S. Hamilton and M.T. Naughton have both received equipment free of charge for use in research from Resmed, and G.S. Hamilton from Phillips Respironics and Air Liquide Healthcare for the same purpose. F.J. O'Donoghue has received a grant from Resmed for research purposes and also received equipment free of charge to conduct research from Resmed and Phillips Respironics. The other authors have no relevant conflicts of interest to declare.

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