SLEEP, 2023, 47, 1–9
https://doi.org/10.1093/sleep/zsad233
Advance access publication 6 September 2023
Original Article

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Sleep apnea, hypoxia, and late-onset epilepsy: the Atherosclerosis Risk in Communities study

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Abstract

Study Objective: Sleep apnea is associated with unexplained epilepsy in older adults in small studies. We sought to determine the relationship between sleep apnea and additional sleep characteristics and late-onset epilepsy (LOE), adjusting for comorbidities, using data from the large, prospective Atherosclerosis Risk in Communities (ARIC) Study cohort.

Methods: We used Medicare claims to identify cases of LOE in ARIC participants. We used polysomnography data from 1309 ARIC participants who also participated in the Sleep Heart Health Study in 1995–1998, and demographic and comorbidity data from ARIC. Later risk of LOE was evaluated using survival analysis with a competing risk of death. We also used survival analysis in 2672 ARIC participants to identify the association between self-reported obstructive sleep apnea (2011–2013), and the risk of subsequent LOE.

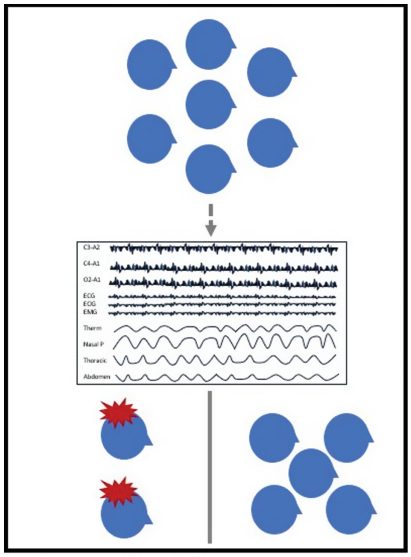
Results: Late-midlife oxygen desaturation to less than 80% during sleep was associated with subsequent development of LOE, adjusted subhazard ratio 3.28 (1.18–9.08), but the apnea–hypopnea index was not related. Participant report of diagnosis of sleep apnea in 2011–2013 was also associated with subsequent LOE, adjusted subhazard ratio 2.59 (1.24–5.39).

Conclusions: Sleep apnea and oxygen saturation nadir during sleep are associated with LOE, independently of hypertension and other comorbidities. These potentially modifiable risk factors could have large clinical implications for LOE.

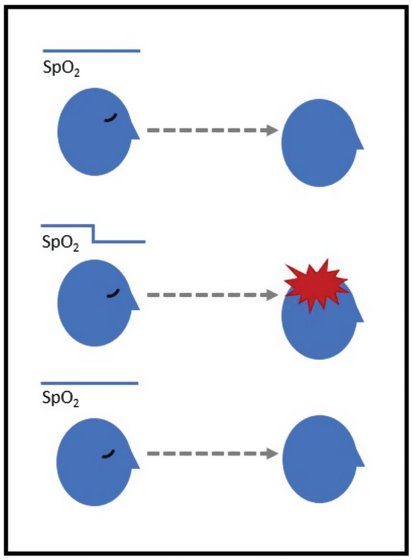
Key words: epilepsy; late-onset epilepsy; sleep apnea; hypoxia

Submitted for publication: March 7, 2023; **Revised:** July 7, 2023

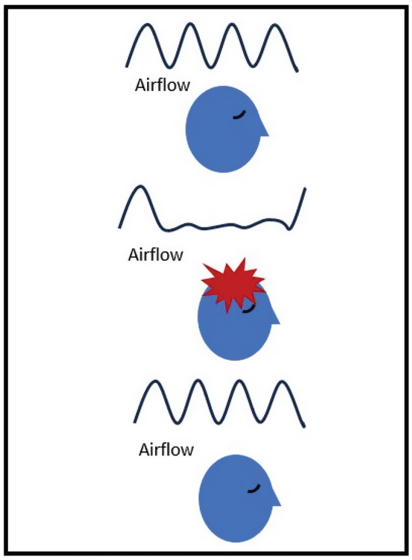
Graphical Abstract



Participants selected from ARIC study with polysomnography data, then further separated by presence or absence of late life development of epilepsy.



Nocturnal hypoxemia in early midlife is associated with subsequent increased risk of late-onset epilepsy.



Late midlife sleep apnea is associated with late-onset epilepsy.

Statement of Significance

This manuscript demonstrates an association between sleep apnea, sleep-related hypoxia, and late-onset epilepsy (LOE). LOE represents a large emerging subgroup of patients that remains only partially understood. Interestingly, our study failed to detect an association between the apnea–hypopnea index, a traditional measure of sleep apnea severity, and LOE but did detect an association with nocturnal hypoxia and LOE in a dose-dependent manner. These results may have implications for the causal relationship between sleep disorders and LOE and may indicate an association driven by hypoxia rather than other effects of sleep apnea. This paper adds additional evidence and context to risk factors for development of LOE and suggests new avenues for research and intervention for LOE.

Introduction

Compared to other age groups, older adults have the highest incidence of new cases of epilepsy, termed late-onset epilepsy (LOE). The incidence of epilepsy follows a U-shaped curve, being high in childhood, lower in midlife, and rising again after age 60. By age 70, adults in developed countries have an annual incidence of 50–125 cases per 100 000 persons [1]. Up to half of these cases have no clear precipitating cause (such as stroke or neurodegenerative disease) [2, 3].

Vascular risk factors including hypertension are associated with LOE, as is the apolipoprotein E4 genotype (APOE4; the most common genetic risk factor for Alzheimer's disease) [4]. However, many cases of LOE are unexplained. Some case–control studies have suggested a link between obstructive sleep apnea (OSA), a highly prevalent sleep disorder, and later epilepsy [5, 6].

OSA represents the most common subtype of sleep-disordered breathing [7]. Like LOE, the risk of OSA increases with age, and prevalence of OSA of any severity increases with age in both men and women (plateauing after age 65 in some studies) [7–9]. Furthermore, OSA is also associated with other known LOE risk factors such as hypertension, stroke, and neurodegenerative diseases [5, 10–12].

One prior study in adults 20–65 years of age, showed an increased risk of epilepsy in those with sleep-disordered breathing in earlier life [13]. Smaller studies, primarily cross-sectional, in middle-aged, and younger patients have established a strong association between epilepsy and OSA. Patients with epilepsy have a higher impact of OSA compared to the general population [6]. The severity of epilepsy also correlates with increased overall incidence of concomitant OSA diagnosis; those with drug-resistant epilepsy experience the highest costs of OSA [5]. Furthermore, patients with epilepsy and concomitant OSA demonstrate poorer seizure control than do their peers without OSA; conversely, treatment of OSA has been shown to improve seizure control among patients with both conditions [14]. Therefore, understanding the relationship between OSA and LOE may not only yield insights into the development of LOE, but may also identify a potential target for prevention or treatment.

Given the existing evidence, OSA has emerged as an intriguing area of study in patients with LOE, and as a possible cause of or risk factor for LOE. We therefore sought to determine the association between sleep characteristics and LOE, particularly between apnea and hypoxia during sleep, and subsequent development of LOE. We hypothesized that persons with sleep apnea or hypoxia are at increased risk of LOE, after controlling for other risk factors associated with both LOE and OSA.

Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) study started in 1987–1989 with 15 792 mostly Black and White individuals aged 45–64 years from 4 US communities: Forsyth County, NC; Jackson,

MS; suburbs of Minneapolis, MN; and Washington County, MD. The ARIC study consists of seven in-person visits through 2019, with eight visits conducted solely by telephone in 2020 due to coronavirus disease 2019 and ongoing visit nine (Figure 1). Participants and their informants have also had annual (and since 2012, semiannual) telephone calls, and hospital and death certificate records are surveilled. Medicare fee-for-service (FFS) claims from 1991 to 2018 have been merged with participant data.

We excluded participants with noncontiguous FFS coverage periods, those without at least 2 years of FFS coverage (to allow for a minimum of 2 years prior to the first seizure-related code, to define incident epilepsy), races other than Black or White, Black participants from MN or MD (as is standard in ARIC due to small numbers), and those who did not give permission for DNA to be analyzed.

Sleep data

A subset of ARIC participants from the MN and MD field centers also participated in the Sleep Heart Health Study (SHHS) in 1995–1998. Participants underwent at-home polysomnography (PSG) with a portable monitor (Compumedics P-series, Abbotsford, Victoria, Australia) with electrocardiogram, pulse oximetry, limited electroencephalogram, electrooculogram, chin electromyogram, inductance plethysmography, airflow, and body position channels [15]. PSG data was scored by sleep experts at a central reading center in Cleveland, Ohio according to a standardized protocol [15].

In order to determine which sleep disorders, if any, may contribute to LOE, we selected specific sleep parameters, which were representative of sleep disorders known to worsen seizures and or epilepsy in some way; specifically, we chose respiratory categories—sleep apnea (AHI and oxygen saturation nadir), sleep length/quantity (wake after sleep onset and sleep duration) and a mix of respiratory and sleep continuity (respiratory disturbance index) [16–19].

From the SHHS PSG data, we examined the overall apnea–hypopnea index to investigate the presence and severity of sleep apnea (AHI; number of apneas or hypopneas per hour of sleep, categorized as normal [<5], mild [≥5 but < 15], moderate [≥15 but < 30], and severe [≥30]), and hypoxemia with oxygen saturation < 80% (categorized into a binary variable of ever having oxygen saturation < 80%, versus oxygen saturation never falling < 80%). In secondary analyses, we examined the obstructive apnea–hypopnea index (obstructive apneas and hypopneas per hour of sleep, categorized as above), arousal index (arousals/awakenings per hour of sleep, by quartile), respiratory disturbance index (respiratory disturbances per hour, by quartile), wake time after sleep onset (WASO; minutes of wake time after initial sleep onset, by quartile), and sleep duration (modeled as a categorical value by tertiles).

The available measured thresholds for oxygen desaturation were 75%, 80%, 85%, and 90%. We chose 80% as a threshold to represent severe hypoxemia. While severity of hypoxemia is not usually defined using pulse oximetry, generally < 90% is considered hypoxemia, and the Medicare threshold for home oxygen coverage is < 88%. Severe hypoxemia on pulse oximetry does not have a consistent definition, but some prior studies use 80% as a threshold definition representing high severity in OSA [20, 21]. Since pulse oximetry is not as reliable as arterial blood gas for hypoxemia < 90%, we chose to use this lower threshold to ensure it was representative of more severe hypoxemia. We also performed a sensitivity analysis examining association of LOE with hypoxemia at each of the available thresholds.

At the fifth in-person ARIC visit (2011–2013, participant age range: 66–90 years), attending participants were queried whether they had ever been informed by a physician that they had a diagnosis of OSA.

SHHS data quality and artifact

Each channel of the SHHS PSG data were scored by expert polysomnographers for data quality including presence of artifact, and the study was assigned an overall quality grade. Epochs with artifacts were not scored, and data from studies with overall poor or unsatisfactory data were not fully scored and were not used in this study [15].

Outcome ascertainment

We used the definition of 2 or more epilepsy or seizure-related CMS codes (in the first five diagnostic positions; Supplementary Table 1) to

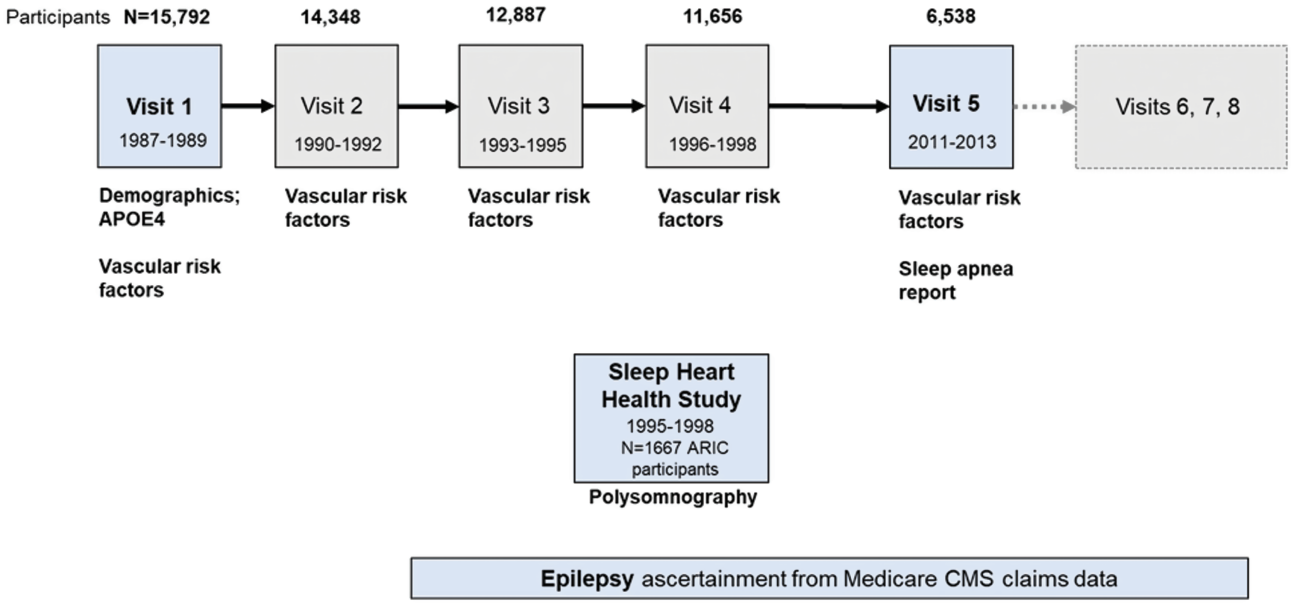


Figure 1. Timeline of the Atherosclerosis Risk in Communities (ARIC) study and study data collection.

define epilepsy. Claims-based definitions using two or more seizure-related codes have high sensitivity and specificity (>90%) in medical record-validated studies [22]. To identify incident epilepsy, we required at least 2 years of FFS coverage without a seizure-related code prior to the first seizure-related code [23]. Because most participants reached Medicare eligibility at age 65, this meant that the earliest age at which a participant could qualify for LOE was 67.

Covariates

Date of birth, sex, race, educational attainment, and the apolipoprotein E genotype (Taqman) were collected at visit 1. As is standard in ARIC, we constructed a combined field center/race variable due to racial distribution across sites, as all participants in Jackson are Black, and the majority of participants in MD and MN are White.

Blood pressure, blood glucose, medications, weight, and height are recorded at each ARIC visit, and smoking and alcohol use are reported at each visit. Hypertension was defined as the use of an antihypertensive agent, mean systolic blood pressure ≥ 140 mmHg, or mean diastolic blood pressure ≥ 95 mmHg. Diabetes was defined as the use of diabetic medication or insulin, self-report of physician diagnosis of diabetes, fasting blood

Table 1. Characteristics of ARIC/Sleep Heart Health Study Participants at Age 67

Sleep Heart Health Study participants	Without epilepsy at any time N (%)	With LOE at any time N (%)	P-value
N	1283	26	
Visit 1 age mean (SD)	54.3 (5.3)	54.8 (4.6)	0.62
Female	671 (52.3)	12 (46.2)	0.53
Center			0.18
MD	615 (47.9)	9 (34.6)	
MN	668 (52.1)	17 (65.4)	
Education level			0.20
<HS	138 (10.8)	0 (0.0)	
HS graduate	609 (47.5)	13 (50.0)	
College graduate	536 (41.8)	13 (50.0)	
APOE4 genotype			0.014
0 e4 alleles	902 (70.3)	13 (50.0)	
≥1 e4 allele	381 (29.7)	13 (50.0)	
Hypertension	471 (36.7)	6 (23.1)	0.15
Diabetes	128 (10.0)	2 (7.7)	0.70
BMI mean (SD)	28.5 (4.9)	28.3 (3.5)	0.84
Smoking status			0.26
Current	889 (69.3)	21 (80.8)	
Former	607 (47.3)	16 (61.5)	
Never	74 (5.8)	2 (7.7)	
Alcohol use			0.17
Current	889 (69.3)	21 (80.8)	
Former	245 (19.1)	5 (19.2)	
Never	149 (11.6)	0 (0.0)	
Lung function			0.600
Normal	971 (75.6)	22 (84.63)	
Restrictive	43 (3.4)	0 (0)	
Obstructive	239 (18.6)	4 (15.4)	
Mixed	30 (2.3)	0 (0)	
Stroke	116 (9.0)	4 (15.4)	0.27
Diagnosis of dementia	260 (21.0)	14 (53.8)	<0.001
Head injury	466 (36.3)	15 (57.7)	0.025

N (%) unless otherwise specified. Hypertension, diabetes, body mass index (BMI), smoking, alcohol use, and lung function were taken from visit closest to age 67. Stroke, dementia, and brain injury are at any point during study follow-up (occurring prior to first seizure, if the participant had LOE). SD, standard deviation; BMI, body mass index; MD, Maryland; MN, Minnesota. HS, high school.
Continuous variables are compared using a *t*-test; categorical variables are compared using a chi-square test.

glucose ≥ 126 mg/dL, or nonfasting blood glucose ≥ 200 mg/dL. Smoking was classified as current smoker, former smoker (having quit prior to the visit of interest), and never smoker.

For analysis of SHHS data, we used covariate data from the visit immediately prior to the participant's 67th birthday; this was the earliest age at which participants could qualify for a diagnosis of LOE. For analysis of self-reported diagnosis of sleep apnea, we used covariate data from visit 5 (the time at which sleep apnea was reported). Lung function was measured at the first, second, and fifth visits, including forced expiratory volume in 1 second (FEV1), and FEV1 to forced vital capacity (FVC) ratios. Participants were categorized as having normal, restricted, obstructive, or mixed lung function based on FEV1/FVC to expected FEV1/FVC ratios (obstructive: FEV1/FVC < 0.70 and FVC ≥ 80% of expected; restrictive: FEV1/FVC ≥ 0.70 and FVC < 80% of predicted; mixed: FEV1/FVC < 0.70 and FVC < 80% of expected; normal: FEV1/FVC ≥ 0.70 and FVC ≥ 80% of expected).

Stroke was ascertained from participant self-report (at visit 1) and, after visit 1 from hospital surveillance data, adjudicated by clinical cerebrovascular experts. Heart failure was ascertained and adjudicated from hospital diagnostic discharge charts [24]. Dementia was ascertained from in-person or telephone-based testing, telephone calls with informants, and hospital and death certificate surveillance, via computer algorithm and expert panel adjudication [25].

Head injury was ascertained from participant self-report, CMS Medicare claims codes, and ARIC hospitalization surveillance for head injury [26] (Supplementary Table 2).

Stroke, dementia, and head injury were included as time-varying variables for the survival analysis, with 0 prior to the date of the first stroke, head injury, or dementia ascertainment and 1 thereafter.

Data analysis

To determine the relationship between sleep characteristics estimated with polysomnography and development of LOE, we used survival analysis with a competing risk of death [27] (and adjusted for age, sex, field center, education level, body mass index, hypertension, diabetes, smoking status, alcohol use, APOE4 genotype, head injury, stroke, dementia, and pulmonary function). We used the 67th birthday as the origin (as this was the earliest time at which participants could qualify for a diagnosis of LOE, using the 2-year seizure-free coverage period as above to identify incident epilepsy).

To determine the relationship between self-reported diagnosis of sleep apnea and LOE, we also used survival analysis with a competing risk of death (and adjusted for age, sex, field center/race, education level, body mass index, hypertension, diabetes, smoking status, alcohol use, APOE4 genotype, head injury, stroke, dementia, and pulmonary function). Since sleep apnea was reported at visit 5, we used the date of visit 5 as the origin (and excluded 1 participant who was younger than 67 at the time of visit 5 who would otherwise have been included).

As sleep apnea has been described as a risk factor for hypertension, stroke, and dementia, we considered these covariates as potential mediators by comparing results with and without these potential mediators added to the model. We also tested for mediation and indirect effects using the structural equation modeling package in Stata 14.2 (College Station, TX). Finally, we performed a sensitivity analysis censoring participants at the time of stroke or diagnosis of dementia (if applicable), to estimate the relationship between sleep characteristics and LOE in the absence of these conditions (which can also be linked to sleep apnea).

We checked for interactions on the association with LOE between sleep characteristics and sex, and between self-reported sleep apnea and race and sex. The ARIC participants who also completed SHHS were White, so interactions with race were not measurable.

Analysis was conducted using Stata 18.0 (College Station, TX). A two-sided P-value of 0.05 was considered significant.

IRB approval, patient consents

All participants provided written informed consent at each visit. Each field center obtained institutional IRB approval. ARIC data are available to qualified researchers who submit an approved manuscript proposal and data usage agreement.

Results

Sleep Heart Health Study polysomnography analysis

1667 ARIC participants took part in the SHHS in 1995–1998. Of those, 1309 had sufficient Medicare FFS data and non-missing covariate information and were included. Twenty-six participants developed LOE after SHHS study participation, through 2018 (median follow-up 20 years after SHHS). Characteristics are in Table 1.

Any time spent with oxygen saturation < 80% was associated with a 3-fold higher risk of LOE, subhazard ratio (SHR) 3.26 (95% confidence interval (CI): 1.25 to 8.53; Table 2) after adjusting for age, sex, field center, education level, diabetes, head injury, smoking, alcohol use, body mass index, the APOE4 genotype, and pulmonary function. Adding potential mediators, hypertension, stroke, and dementia, to the model did not weaken the association. In the fully adjusted model, the SHR was 3.28 (95% CI: 1.18 to 9.08), indicating a consistent 3-fold higher risk of LOE in participants with earlier-life hypoxia during sleep compared to participants without hypoxia during sleep (Table 2). We also tested mediation by checking for indirect effects of hypertension, stroke, and dementia through structural equation modeling, and did not find significant mediation effects (all $p > 0.05$).

The apnea–hypopnea index was not associated with LOE (SHR 0.997, 95% CI: 0.46 to 2.12 for any abnormal AHI; SHR by AHI category in Supplementary Table 3). In secondary analyses, the other

Table 2. Association of Oxygen Saturation < 80% During PSG and Later LOE, With Competing Risk of Death

	Oxygen saturation during PSG		
	<80%	>80%	
N Total	158	1151	
N with LOE	7	19	
Subhazard ratio (95% CI)			P-value
Model 1	2.16 (0.94 to 4.97)	Reference	0.071
Model 2	3.26 (1.25 to 8.53)	Reference	0.016
Model 3	3.28 (1.18 to 9.08)	Reference	0.022

Model 1 adjusted for demographics (age, sex, field center, and education level).
Model 2 adjusted for demographics, diabetes, smoking status, alcohol use, head injury, apolipoprotein e4 alleles, and pulmonary function.
Model 3 adjusts for Model 2 covariates, as well as hypertension, and stroke and/or dementia when present (as time-varying variables).

Table 3. Characteristics of ARIC Participants in Analysis of Self-Reported Sleep Apnea Diagnosis

ARIC participants	Without LOE N (%)	With LOE developing after visit 5 N (%)	*P*-value
N	2633	39	
Visit 1 age mean (SD)	75.6 (5.0)	75.7 (4.4)	0.83
Female	1533 (58.2)	22 (56.4)	0.82
Center-Race			0.32
NC—White	401 (15.2)	2 (5.1)	
NC—Black	20 (0.8)	1 (2.6)	
MS—Black	463 (17.6)	8 (20.5)	
MD—White	939 (35.7)	14 (35.9)	
MN—White	810 (30.8)	14 (35.9)	
Education level			0.94
<HS	31 (11.9)	5 (12.8)	
HS graduate	1100 (41.8)	17 (43.6)	
College Graduate	1219 (46.3)	17 (46.6)	
APOE4 genotype			0.013
0 e4 alleles	1900 (72.2)	22 (56.4)	
≥1 allele	733 (27.8)	17 (43.6)	
Hypertension	1931 (73.3)	31 (79.5)	0.39
Diabetes	784 (29.8)	20 (51.3)	0.004
BMI mean (SD)	29.6 (5.5)	29.0 (5.2)	0.59
Smoking status			0.31
Current	127 (4.8)	2 (5.1)	
Former	1300 (49.4)	25 (64.1)	
Never	1088 (41.3)	11 (28.2)	
Declined/Unknown	118 (4.5)	1 (2.6)	
Alcohol use			0.083
Current	1358 (51.6)	18 (46.2)	
Former	754 (28.6)	17 (43.6)	
Never	521 (19.8)	4 (10.3)	
Lung function			0.085
Normal	2116 (80.4)	31 (79.5)	
Restrictive	86 (3.3)	1 (2.6)	
Obstructive	395 (15.0)	7 (17.9)	
Mixed	36 (1.4)	0 (0.0)	
Stroke (prior to LOE if applicable)	142 (5.4)	7 (17.9)	<0.001
Dementia diagnosis (prior to LOE if applicable)	413 (15.7)	11 (28.2)	0.034
Head injury (prior to LOE if applicable)	678 (25.8)	13 (33.3)	0.28
Self-reported sleep apnea diagnosis	303 (11.5)	10 (25.6)	0.006

N (%) unless otherwise specified. Hypertension, diabetes, body mass index (BMI), smoking, alcohol use, lung function taken from ARIC visit 5. Stroke, dementia, and head injury are at any point during study follow-up (occurring prior to first seizure, if the participant had LOE).
SD, standard deviation; BMI, body mass index; MD, Maryland; MN, Minnesota. HS, high school.
Continuous variables are compared using a *t*-test; categorical variables are compared using a chi-square test.

sleep characteristics analyzed including obstructive apnea–hypopnea index, arousal index, respiratory disturbance index, WASO, and sleep duration were not associated with LOE ($p > 0.10$ on each unadjusted model).

In the sensitivity analysis censoring participants at time of stroke or dementia diagnosis (when applicable), the association between hypoxia and LOE persisted, with SHR 3.21 (95% CI: 1.05 to 9.77).

We performed a sensitivity analysis examining each available threshold of hypoxemia (any time below 75%, 80%, 85%, and 90%) and found that lower oxygen nadir was associated with a higher risk of epilepsy in a dose-dependent manner; lower oxygenation

Table 4. Association of Visit 5 Self-Reported Physician Diagnosis of Sleep Apnea And Incident LOE, With Competing Risk of Death

	Sleep apnea	Without sleep apnea	
N Total	313	2359	
N with LOE	10	303	
Subhazard ratio (95% CI)			*P*-value
Model 1	2.87 (1.60 to 5.14)	Reference	<0.001
Model 2	2.58 (1.22 to 5.49)	Reference	0.014
Model 3	2.59 (1.24 to 5.39)	Reference	0.011

Model 1 adjusted for demographics (age, sex, field center/race, and education level).
Model 2 adjusted for demographics, diabetes, smoking status, alcohol use, head injury, apolipoprotein e4 alleles, and pulmonary function.
Model 3 adjusts for Model 2 covariates as well as hypertension, and stroke or dementia occurring prior to LOE.

nadirs were more strongly associated with LOE (Supplementary Table 4).

Due to the association between heart failure and sleep, we also performed a sensitivity analysis adjusting for heart failure by visit 5; this did not significantly affect the association between hypoxemia and LOE (adjusted for heart failure, SHR 3.29, 95% CI: 1.19 to 9.07; unadjusted for heart failure, 3.29, 95% CI: 1.20 to 9.05. Heart failure was not associated with epilepsy in unadjusted ($p = 0.86$) or adjusted ($p = 0.92$) analysis).

There was no evidence for interactions between PSG characteristics and sex (all $p > 0.10$).

Visit 5 sleep apnea analysis

Two thousand and seventy-two ARIC participants with sufficient Medicare FFS coverage and covariate data who attended visit 5 were included (including 786 who also participated in SHHS and were included in the analysis of SHHS data). Of these, 39 developed LOE after visit 5 during follow-up through 2018. Those who developed LOE were more likely to have had a history of dementia, stroke, diabetes, and at least one APOE4 allele compared to those without LOE (Table 3).

A self-reported diagnosis of sleep apnea at visit 5 was associated with an increased risk of subsequent LOE, adjusted SHR 2.58 (95% CI: 1.22 to 5.49; Table 4). After adding the potential mediators of hypertension, stroke, and dementia to the models, the association persisted (SHR 2.59, 95% CI: 1.24 to 5.39; Table 4). We also tested mediation by checking for indirect effects of hypertension, stroke, and dementia through structural equation modeling, and did not find significant mediation effects for stroke or dementia ($p > 0.05$); there was a slight mediation by hypertension (indirect effect HR 1.001 (1.0009–1.0025), $p = 0.035$).

There was no interaction between self-reported sleep apnea and race (p-interaction = 0.324) or sex (p-interaction = 0.657) with regard to LOE.

Discussion

Late-onset epilepsy is a complex and poorly understood disease. We found evidence of an association between hypoxia during sleep in late midlife and subsequent development of LOE; this persisted after controlling for vascular risk factors and comorbidities known to be associated with LOE, including head injury [28]. Participants with oxygen desaturation < 80% during sleep had a 3-fold higher risk of later developing LOE than those who did without < 80% desaturation. In sensitivity analysis, we also found that oxygen nadir demonstrated a dose-dependent relationship with risk of development of LOE, with lower oxygenation nadir corresponding to a stronger association with LOE. In addition, participants with self-reported sleep apnea in later life were twice as likely to develop LOE as were those without sleep apnea, although no association was found between severity of sleep apnea, as measured by AHI, and development of LOE.

Our findings are consistent with prior studies showing an association between epilepsy and sleep apnea [6, 17, 29], with the added benefit of demonstrating a longitudinal relationship and the ability to control for vascular risk factors associated with both sleep apnea and LOE. One prior longitudinal study (in which the majority of participants were aged 20–65 years of age) showed an increased risk of epilepsy following diagnosis of sleep-disordered breathing in this younger cohort, with a 1.5× higher risk of epilepsy in those with sleep-disordered breathing [13]. We now demonstrate a similar association specifically among older individuals who later develop LOE.

AHI is the traditional measurement of severity of sleep-disordered breathing. In this study, AHI severity in earlier life was not associated with later LOE in the subset of participants who had PSG and LOE ascertainment. This may be due to the length of time between AHI ascertainment and LOE, or power limitations. Hypoxia, our other sleep variable of interest, did show an association with LOE, even when controlling for overlap conditions such as obstructive lung disease and heart failure. We checked for possible mediation of effects of comorbidities associated with OSA and LOE (hypertension, stroke, and dementia), and found that there was minimal change in the association between sleep and LOE; this suggests that there may be other associations between hypoxia and LOE beyond those caused by recognized stroke or hypertension. We note that if we use a Bonferroni correction for all comparisons in the primary and secondary analyses, the analysis of hypoxia and later LOE would not demonstrate a relationship; however, when correcting for the two initial hypotheses (that the AHI and hypoxia would be related to LOE), this relationship persists.

The finding of an association between hypoxia and LOE suggests one possible contributor to LOE. In OSA, desaturations are often relatively brief. However, the recurrent reduction in oxygen delivery to the CNS over time may cause cellular injury or stress [30], and has been proposed as a possible mechanism for the development of epilepsy [31, 32], though this is debated [33]. The hypoxia associated with desaturation and OSA during sleep may worsen microvascular disease, and is linked with cortical and subcortical atrophy, which are also associated with LOE [34]. Therefore, hypoxia during sleep may be an important potential link in the complex pathway to the development of LOE, and warrants further investigation.

Sleep disruption and disturbances of the sleep–wake cycle are also associated with amyloid impact, and with an increased risk of dementia [35]. Amyloid deposition is also proposed as a potential mechanism for LOE [36]. In secondary analyses in this study, we did not find an association between the arousal index, WASO, or sleep duration and later LOE. However, this may be limited by the relatively small number of participants who both had PSG in 1995–1998 and later developed LOE, or by the collection of PSG measurements relatively early in life compared to the development of LOE.

The strengths of this study include the large size, biracial cohort, longitudinal follow-up of participants, and PSG data collection prior to the development of LOE. There are also weaknesses, notably the reliance on ICD codes for ascertainment of LOE. ICD-9 codes 780.39 and ICD-10 R56.9 for seizures could be used for seizure-like activity that is not epilepsy, including nonepileptic physiologic or nonepileptic psychogenic events. However, studies of similar definitions find >90% sensitivity and specificity for the identification of epilepsy, compared to the gold standard of medical record review [22]. For the analysis of sleep apnea from visit 5, we rely on participant self-report of sleep apnea, and do not have data on the severity of OSA. Additionally, due to the claims-based definition of LOE, we do not have information about participants' severity of epilepsy or type of seizures.

The relationships between sleep, sleep-disordered breathing, and epilepsy are complex and multifactorial. We have demonstrated that nocturnal hypoxia and self-reported OSA may be associated with LOE, independently of other vascular risk factors. As sleep disorders are well-characterized and highly prevalent disease processes with available diagnostic testing and straightforward treatment modalities, these findings support future research on this set of potentially modifiable risk factors for the prevention of LOE.

Supplementary Material

Supplementary material is available at *SLEEP* online.

Funding

The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I, and HHSN268201700005I). Neurocognitive data are obtained by grants U01 HL096812, U01 HL096814, U01 HL096899, U01 HL096902, and U01 HL096917 from the National Heart, Lung, and Blood Institute, with funding also provided by the National Institute of Neurological Disorders and Stroke. This study was also supported by contract K23 AG063899 (Dr. Johnson), RF1 AG050745 (Dr. Spira) from the National Institute on Aging, and K24 HL159246 from the NHLBI (Dr. Lutsey). Dr. Gottesman was supported by the National Institute of Neurological Disorders and Stroke intramural research program.

Acknowledgments

The authors gratefully acknowledge the important contributions of ARIC participants and staff

Disclosures Statement

Financial Disclosures: Adam Spira received payment for serving as a consultant for Merck, received honoraria from Springer Nature Switzerland AG for guest editing special issues of Current Sleep Medicine Reports, and is a paid consultant to Sequoia Neurovitality. *Nonfinancial Disclosures:* The other authors report no relevant conflicts of interest related to the current work.

Data Availability

ARIC data are available to qualified researchers who submit an approved manuscript proposal.

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