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Original Article

Obstructive sleep apnea and incident type 2 diabetes

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ABSTRACT

Objectives: To determine whether severity of obstructive sleep apnea is associated with incident diabetes in middle-aged and older adults.
Methods: A prospective analysis of 1453 non-diabetic participants of both the Atherosclerosis Risk in Communities Study and the Sleep Heart Health Study (mean age 63 years, 46% male) had in-home polysomnography (1996–1998) and was followed up for incident diabetes. Using the apnea–hypopnea index derived from home polysomnography, study participants were categorized as follows: <5.0 (normal), 5.0–14.9 (mild), 15.0–29.9 (moderate), and ≥30.0 events/h (severe). Incident diabetes was ascertained during annual follow-up telephone calls through 2013.
Results: During a median follow-up of 13 years, there were 285 incident diabetes cases among the 1453 participants. Participants with severe obstructive sleep apnea were at greater risk of incident diabetes compared to persons classified as normal after adjustment for confounders including body mass index and waist circumference (1.71 [1.08, 2.71]). The association between severe obstructive sleep apnea and incident diabetes was similar when analyses were restricted to obese individuals.
Conclusions: Severe obstructive sleep apnea was associated with greater risk of incident diabetes, independent of adiposity in a community-based sample. Healthcare professionals should be cognizant of the high prevalence of OSA in the general population and the potential link to incident diabetes.

1. Introduction

Given the morbidity and mortality associated with type 2 diabetes mellitus [1], the identification of potentially modifiable risk factors for diabetes remains a clinical and public health priority. Obstructive sleep apnea (OSA) is a common condition with approximately 13% of adult men and 6% of adult women having moderate to severe undiagnosed OSA [2]. Evidence collected over the last two decades from clinical and community-based studies suggests that OSA is associated with insulin resistance, glucose intolerance, and type 2 diabetes independent of the confounding effects of obesity [3,4]. Moreover, data from murine models [5] and experimental human studies [6] have also shown that exposure to intermittent hypoxia and sleep fragmentation can lead to alterations in insulin sensitivity and glucose disposal. Thus, observational [7–11] and experimental data [12,13] are convergent and implicate OSA as an independent risk factor for development of diabetes. Unfortunately, interventional data examining the effects of OSA treatment on metabolic outcomes such as insulin sensitivity, glucose tolerance, and glycosylated hemoglobin have been equivocal [12,13], and thus have raised significant doubt regarding the role of OSA in the pathogenesis of type 2 diabetes. Thus, recommendations regarding case-identification for OSA in those at risk for metabolic dysfunction need to be tempered by the lack of a strong empirical base. Part of the challenge in interpreting the available interventional data on the effects of OSA treatment on metabolic parameters is due to the wide range of methodological limitations in the available studies [7]. Relatively limited sample sizes, poor adherence with treatment, and duration of treatment are some of the many pitfalls in the treatment-related data available to date. There is also a dearth of longitudinal data on whether untreated OSA in those free of diabetes increases the predisposition for developing diabetes [14,15]. Longitudinal evidence to support temporality of the association between OSA and diabetes, and whether the

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association is independent of obesity, is lacking. Availability of such evidence would motivate case-identification and early intervention for OSA to mitigate some of the risk for developing diabetes. The longitudinal studies that have examined the impact of OSA on incident diabetes have either been based on clinical samples [10,11] or have not included full montage polysomnography [9,11]. Therefore, using data from a subset of Atherosclerosis Risk in Communities Study (ARIC) participants who took part in the Sleep Heart Health Study (SHHS), the current study sought to determine whether OSA is associated with incident diabetes, independent of known confounding factors such as obesity.

2. Methods

2.1. Study population

In 1987–1989, using population-based probability sampling, the ARIC study enrolled 15,792 adults (aged 45–64 years) from four US communities [16]. A total of four follow-up visits have taken place (1990–1992, 1993–1995, 1996–1998, and 2011–2013) since the initial visit. During the fourth ARIC visit (1996–1998), which constitutes baseline for the present study, a subset of 1920 ARIC participants from the study sites of Washington County, MD and suburban Minneapolis, MN were recruited into the SHHS [17] and underwent an in-home overnight polysomnogram. For the current analysis, 467 participants were excluded for the following reasons: (1) prevalent diabetes at baseline defined as a fasting glucose ≥126 mg/dL or non-fasting glucose of ≥200 mg/dL, self-reported history of physician-diagnosed diabetes, or medication use for diabetes over the last two weeks ($N = 261$); (2) non-white race ($N = 11$); (3) lack of follow-up information ($N = 28$); and (4) incomplete data on OSA severity ($N = 167$). The final analytic sample included 1453 participants (Fig. 1). Institutional review boards at each participating institution approved the study and all participants provided written informed consent.

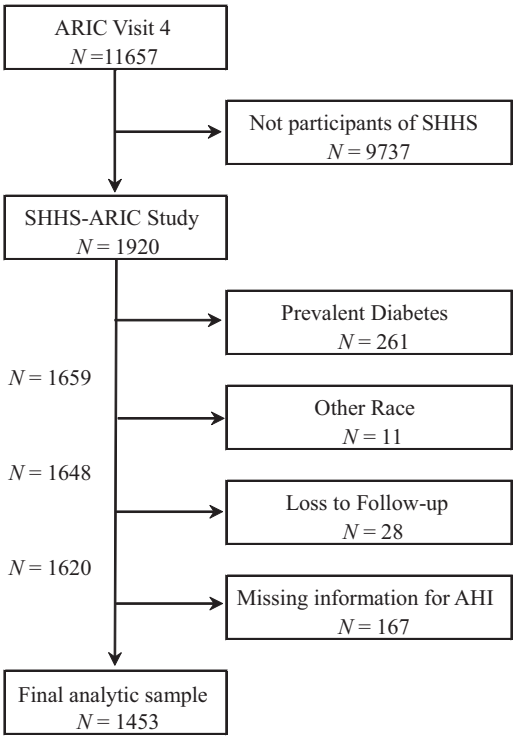

Fig. 1. Study sample flow chart. AHI, apnea–hypopnea index; ARIC Study, Atherosclerosis Risk in Communities Study; SHHS, Sleep Heart Health Study.

2.2. Sleep assessments

An overnight unattended in-home polysomnogram was conducted using a portable monitor (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia), using (previously described) methods [18]. As in previous analyses of SHHS data, an apnea was defined if there was an absence or near absence of airflow (at least <25% of baseline) for at least 10 s [18]. Hypopnea was defined as a 30% decrease in the amplitude of the airflow for at least 10 s. The apnea–hypopnea index (AHI) was derived as the number of obstructive apneas (regardless of the oxygen desaturation level) plus hypopneas (with at least a 4% decrease in oxygen saturation) per hour of sleep, which corresponds to current definitions used by Medicare for reimbursement. Central sleep-disordered breathing events were excluded from the AHI definition. Participants were categorized based on the AHI as follows: <5.0 events/h (normal), 5.0–14.9 events/h (mild), 15.0–29.9 events/h (moderate), and ≥30.0 events/h (severe).

Nocturnal hypoxemia was characterized by the average oxyhemoglobin saturation during non-rapid eye movement (non-REM) and REM sleep, and by the oxygen desaturation index which was defined as the average number of 4% or greater oxygen desaturation events per hour of sleep (4% ODI). Arousals were identified as abrupt shifts ≥3 sec in electroencephalogram frequency [19]. The arousal index was defined as the average number of arousals per hour of sleep. As detailed in the results, only about 5% of the ARIC sample was classified as having severe OSA, defined by AHI ≥ 30 events/h. In order to make the distributions of nocturnal hypoxemia and the arousal index comparable to the definition of severe OSA, for analytic purposes we categorized these variables into quintiles, and then further divided the most adverse category at the 5th percentile. Thus, for average oxyhemoglobin saturation, the main comparison is the lower 5th percentile of the distribution to those in the highest quintile (percentiles 80–100). For 4% ODI and the arousal index the main comparison is of those in the ≥95th percentile to those in the lowest quintile (percentiles 0–20).

Habitual sleep duration per week was assessed with the following questions: "How much sleep do you usually get at night (or in your main sleep period): on weekdays or workdays?" and "on weekends or non-work days?" Average usual sleep time (h) per week was determined as a weighted average: [(habitual total sleep time during the workdays) × 5 + (habitual total sleep time during the weekends) × 2]/7.

2.3. Incident diabetes and assessment of covariates

Diabetes was diagnosed using information collected from ARIC annual follow-up phone calls that took place from the baseline visit (1996–1998) through 2013. Participants who reported physician-diagnosed diabetes or diabetes medication use were categorized as having incident diabetes. Covariates and potential mediators were assessed at the baseline examination (1996–1998). Information on socioeconomic status, marital status, smoking status, and alcohol use was self-reported. Measures of socioeconomic status included educational attainment (less than high school, high school graduate, beyond high school), income (<$25,000, $25,000–$49,999, ≥$50,000), and occupation (managerial and professional job or not). Physiologic variables were measured by trained technicians. BMI was assessed as weight (kg) divided by height (m) squared. Waist circumference was measured at the umbilicus. High-sensitivity C-reactive protein (hsCRP) was measured using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics, Indianapolis, IN 46250, USA).