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Signature:

Sanober Ismaily Date

The association of sleep duration and sleep quality with type 2 diabetes mellitus: The CARRS study

By

Sanober Ismaily
Master of Public Health

Hubert Department of Global Health

_____

Shivani A. Patel
Committee Chair

_____

Mohammed K. Ali
Committee Member

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By

Sanober Ismaily

Bachelor of Arts
Vanderbilt University
2014

Thesis Committee Chair: Shivani A. Patel, MPH, PhD

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Abstract

The association of sleep duration and sleep quality with type 2 diabetes mellitus: The CARRS study

By Sanober Ismaily

Background: A literature supporting short sleep duration and poor sleep quality as risk factors for type 2 diabetes mellitus. Little research has been done, however, in the urban South Asian population, who tends to experience type 2 diabetes at a lower BMI and younger age than other ethnic groups.

Objective: We sought to examine the association of night sleep duration and sleep quality (daytime napping, sleep apneas, habitual snoring, and daytime sleepiness, and overall sleep quality) with type 2 diabetes mellitus among adults in three large South Asian cities. Further, we assessed whether associations between sleep measures and type 2 diabetes mellitus varied by age, sex, or weight status.

Methods: We conducted a cross-sectional analysis of participants enrolled in the 2011 baseline survey of the Center for cArdiometabolic Risk Reduction in South Asia, a representative sample of non-pregnant adults in urban blocks of Chennai and Delhi, India and Karachi, Pakistan. The analytic sample consisted of n=11,351 with complete data on covariates of interest. We estimated odds ratios describing the association between measures of sleep duration and quality and diabetes using logistic regression models accounting for the survey design. Adjusted models included city, age, sex, religion, educational level, occupation, number of assets owned, time spent sedentary per day, and weight status measured as body mass index (BMI).

Results: We observed no association between duration of nightly sleep and prevalent diabetes in adjusted models. In contrast, four of five measures of sleep quality—daytime napping (aOR: 1.20, 95% CI: 1.02, 1.40), sleep apneas (aOR: 1.32, 95% CI: 1.06, 1.63), habitual snoring (aOR: 1.37, 95% CI: 1.14, 1.65), and overall sleep quality (aOR: 2.13, 95% CI: 1.24, 3.66) demonstrated moderate associations with prevalent diabetes in the overall sample. Point estimates of odds ratios were largely consistent in strata of sex, age group, and weight status.

Conclusion: While sleep duration was not associated with prevalent diabetes, we found that poor sleep quality was associated with prevalent diabetes. Specifically, daytime napping, observed apneas, habitual snoring, and overall poor sleep quality were significantly associated with higher prevalent type 2 diabetes. Of the indicators of poor sleep quality, overall poor sleep quality showed the strongest relationship with type 2 diabetes. Further investigation may probe the directionality of these associations to better understand the potential to mitigate diabetes risk by improving sleep quality among urban South Asians.

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Chapter I. Introduction

A. Introduction and Rationale

The absolute number of people with and prevalence of diabetes mellitus, more commonly known as diabetes, has increased significantly within the past decade in all regions of the world. Currently 415 million adults have diabetes; this number will have risen to 642 million by 2040. The incidence rate continues to grow steeply and like other cardio-metabolic diseases, the factors that contribute to the onset of diabetes are diverse but interconnected ("IDF Diabetes Atlas," 2015). Higher than normal blood glucose is the defining feature of diabetes. There are two major types of diabetes mellitus, type-1 diabetes and type-2 diabetes. In type-1 diabetes, the body is unable to produce insulin and so is unable to control glucose or sugar levels in the blood through the insulin-glucose pathway. Type-1 diabetes is characterized as “juvenile diabetes” since it mostly diagnosed in children and young adults; only about 5% of the people with diabetes have type-1 diabetes. Type-2 diabetes, on the other hand, is largely considered a condition in which the body does not use insulin properly, known as having insulin resistance, and this leads to higher than normal glucose levels in the body. Type-2 diabetes has been referred to as “adult onset diabetes,” though this terminology is not used often today when insulin resistance is observed even in young age. Higher than normal glucose levels can be pathological, and in particular, may harm functioning of the eyes, kidneys, nerves, or heart. Type-2 diabetes will be the major focus of this discussion, as this variant appears to be closely related to behavioral/lifestyle factors; in addition, most of the absolute number of diabetes cases and most of the number of incident diabetes cases are of the type-2 variety ("Diabetes Basics," 2016).

Leading known risk factors for type-2 diabetes are age, BMI, diet, physical activity, race, family history, and other cardio-metabolic co-morbidities ("IDF Diabetes Atlas," 2015). However, these exposures have complicated relationships with one another and are different for each individual. Having multiple risk factors leads to a compounded risk of developing diabetes.

South Asians are people originating from countries in the South Asian subcontinent such as India, Pakistan, Nepal, and Bangladesh. For South Asians, the risk starts earlier in life and several authors argue that this is due to a mix of higher genetic susceptibility (Gujral et al., 2015) and exposure to environmental risk factors ("IDF Diabetes Atlas," 2015) compared to other subpopulations (Dashti et al., 2015). Diabetes onset occurs at a younger age and at a lower BMI for South Asians when compared to other populations (Ramachandran, Snehalatha, Shetty, & Nanditha, 2012). Because of the prevalence of type-2 diabetes in the South Asian population without the presence of the more significant traditional exposures outlined above, it may be necessary to look beyond the traditional factors into other exposures that could be contributing to the onset of type-2 diabetes in the South Asian population.

Mounting evidence suggests that sleep duration and sleep quality may be associated with diabetes and cardio-metabolic risks (Grandner, Chakravorty, Perlis, Oliver, & Gurubhagavatula, 2014; Roopa, Deepa, Indulekha, & Mohan, 2010; Wu et al., 2015). Sleep duration appears to have a U-shaped association with diabetes in which shorter and longer sleep duration relative to the median of 7-8 hours of sleep is significantly associated with higher Hb1Ac levels and impaired fasting plasma glucose levels, quantitative measures for diagnosing type-2 diabetes (Fang et al., 2013; Gottlieb et

al., 2005; Ohkuma et al., 2013). Poor nighttime sleep quality has been operationalized using a variety of self-reported measures. Daytime napping, a proxy measure for poor quality night time sleep, has also been shown to be significantly associated with type-2 diabetes, and the association has been further examined for disorders and overall sleep quality, such as sleep apneas, snoring, as well as daytime sleepiness (Fang et al., 2013; Roopa et al., 2010; Schwartz et al., 2015; Shadyab et al., 2015). Sleep apnea is a common disorder in which one stops breathing one or more times throughout the night. Though the disorder is common, it is hard to diagnose since there are no clinical tests to definitively diagnose the condition. One is more likely to suffer from poor nighttime sleep quality if one experiences snoring as well, since both of these conditions are likely to move an individual out of the deep sleep portion of the sleep cycle into the light sleep stage ("Diabetes Basics," 2016). Sleep apneas tend to be more common among overweight and obese individuals (Foster et al., 2009; Punjabi, 2008; Udwadia, Doshi, Lonkar, & Singh, 2004). That said, those who experience sleep apnea, habitual snoring, or daytime sleepiness have a higher prevalence of type 2 diabetes, even after adjusting for age, sex, and central obesity; this has also been observed in the Asian population (Bakker et al., 2015; Foster et al., 2009; Roopa et al., 2010; Schwartz et al., 2015).

Though the biological mechanisms by which sleep duration and quality and type 2 diabetes relate is still to be elucidated, circadian rhythms have been implicated in the literature (Reutrakul & Van Cauter, 2014). Eckel et al. (2015) present an argument for the mechanism to be through insulin sensitivity. Short sleep duration and quality may impact circadian rhythms causing morning circadian misalignment, which can impact insulin sensitivity, leading to prediabetes and type 2 diabetes. Getting as little as approximately 5

hours of sleep per night can reduce insulin sensitivity by 20% (Eckel et al., 2015). Furthermore, gene-environment interactions of circadian related genes for diabetes and fasting glucose could play a role in the relationship between sleep and type 2 diabetes (Dashti et al., 2015). It remains to be seen however if this mechanism operates in the same way in a South Asian population.

B. Problem Statement

South Asians are at disproportionately high risk for diabetes relative to other ethnic groups, and this risk is not explained by traditional risk factors. Few examinations of the association between sleep duration and sleep quality with cardio-metabolic health have been conducted among South Asians, who disproportionately experience cardio-metabolic disease at younger ages and at a relatively leaner body mass relative to other populations (Ramachandran et al., 2012). The few studies that exist have been limited by relatively small sample sizes or use data prior to the surge in obesity (Patel, Shaikh, & Singh, 2012; Roopa et al., 2010). A more robust cross-sectional study examining relationships between sleep and diabetes is valuable for several reasons. First, Asian countries contribute approximately 60% of the world's absolute number of diabetes cases (Ramachandran et al., 2012). Second, the South Asian population offers a relatively unique opportunity for examining the association between diabetes and sleep independent of obesity and aging because there are a substantial number of non-obese and young individuals with diabetes. Third, these early analyses may help us understand the influence of sleep duration and quality, relative to other traditional risk factors like age, weight, and lifestyle (alcohol and tobacco use, physical inactivity) in this large and heterogeneous population. Fourth, we contribute to the literature by examining these

relationships in a large, representative sample with objective assessment of diabetes, including fasting plasma glucose and HbA1c levels collected in the field.

C. Purpose Statement

The objective of this study is to examine the relationship of sleep duration and sleep quality with type-2 diabetes mellitus within the CARRS Surveillance Study. The objective can be further broken down into three aims:

1. To assess whether sleep duration is associated with prevalent diabetes in the 3 cities combined and separately (Chennai, Delhi, and Karachi).
2. To assess whether sleep quality is associated with prevalent diabetes in the 3 cities combined and separately (Chennai, Delhi, and Karachi).
3. To quantify whether discrimination between people with and without type 2 diabetes is improved by including measures of sleep duration and sleep quality in models.

D. Research Questions

Question 1: Is sleeping less than 7 hours or more than 8 hours associated with the prevalence of type-2 diabetes?

Null Hypothesis: There is no association between sleep duration and type-2 diabetes mellitus.

Alternative Hypothesis: There is an association between sleep duration and type-2 diabetes mellitus.

Question 2: Are daytime napping, sleep apneas, snoring, or daytime sleepiness associated with the prevalence of type-2 diabetes?

Null Hypothesis: There is no association between daytime napping, sleep apneas, snoring, or daytime sleepiness and type-2 diabetes mellitus.

Alternative Hypothesis: There is an association between daytime napping, sleep apneas, snoring, or daytime sleepiness and type-2 diabetes mellitus.

Question 3: How much of the variance in the proportion of type 2 diabetes within the CARRS Study is explained by sleep duration and sleep quality?

Null Hypothesis: None of the variance in the proportion of type 2 diabetes cases within the CARRS Study is explained by sleep duration and sleep quality.

Alternative Hypothesis: Some of the variance in the proportion of type 2 diabetes cases within the CARRS Study is explained by sleep duration and sleep quality.

E. Significance Statement

Examining the association of sleep duration and sleep quality with type-2 diabetes within the CARRS Study will allow for the elucidation of novel factors that contribute to diabetes within the South Asian population. The absolute number and prevalence of diabetes in the South Asian population is increasing at an alarming rate and the traditional factors that contribute to the onset of diabetes are less relevant within the South Asian population. While age, BMI, and waist circumference have been implicated in the onset of diabetes, South Asians with diabetes tend to be leaner and younger. Thus, a preliminary cross-sectional analysis of the association between sleep duration and quality with prevalent diabetes conducted using the Center for cArdiometabolic Risk Reduction in South Asia (CARRS) Study may help clarify whether alternative, non-traditional risk factors contribute to diabetes prevalence in this group. This research may also contribute

to the diabetes literature more broadly and inform future recommendations for prevention of type 2 diabetes.

Chapter II. Literature Review

A. Sleep duration and type 2 diabetes in the non-Asian population

Prospective data supporting the role of above or below average sleep duration and poor sleep quality in the development of diabetes come from studies in high income countries. Shan et al. (2015) conducted a meta-analysis of prospective studies to determine the dose-response relationship between sleep duration and risk of type 2 diabetes. The authors determined that a dose-response relationship was observed between sleep duration and risk of type 2 diabetes, with the lowest risk observed among those who had sleep duration of 7-8 hours per day. Shorter than 7 hours of sleep duration and longer than 7 hours of sleep duration both had a significant increased risk of type 2 diabetes (Shan et al., 2015).

The relationship between sleep duration and type 2 diabetes has been examined extensively in Caucasian cohorts based in the US or other developed countries. The association of sleep duration and type 2 diabetes was examined through use of the Quebec Family Study cohort, in a predominantly Caucasian cohort. Chaput et al. (2009) sampled 276 people aged 21-64 years of age and found that short (≤6 hours) and long (≥9 hours) sleep durations compared to the reference group of 7-8 hours of sleep are associated with a higher risk of developing type 2 diabetes. This association remained significant after adjustment for body mass index (BMI), waist circumference, or percent body fat, indicating that the association is independent of obesity status (Chaput, Despres, Bouchard, Astrup, & Tremblay, 2009).

Rafalson et al. (2010) also examined the association between short sleep duration and the development of impaired fasting glucose in an US-based cohort: the Western

New York Health Study. The odds ratio of impaired fasting glucose among short (< 6 hours) sleepers was 3.0 compared to mid-range (6-8 hours) sleepers. There was no association between long sleep duration and impaired fasting glucose and the adjustment for insulin resistance changed the relationship between sleep duration and impaired fasting glucose for those with short sleep duration driving down the odds ratio and rendering it insignificant, leading to the conclusion that insulin resistance is a mediator in the association between sleep duration and impaired fasting glucose. Impaired fasting glucose is often defined as pre-diabetes, and so while this cannot be assessed as a study examining the direct association between sleep duration and type 2 diabetes, it is useful in understanding the mechanisms by which the exposure-outcome relationship is created. The mediation of insulin resistance is also interesting to note, as this is a departure from the meta-analysis results found by Upala and Sanguankeo (2015). The differences in results may be due to the fact that insulin resistance may be an important mechanism linking sleep duration and prediabetes but not sleep duration and type 2 diabetes. Another reason may be due to the power of each study, as the meta-analysis included a larger sample by which to examine these associations of interest (Rafalson et al., 2010).

Shadyab et al. (2015) were interested in whether the association of sleep duration and daytime napping with prevalent type 2 diabetes differed by ethnicity. In a multi-ethnic US cohort, the authors examined ethnic-specific associations among white, black, and Filipina post-menopausal women. Sleep duration was significantly associated with type 2 diabetes in Filipina women, with an increased odds of diabetes at both low and high sleep durations, even after adjustment for age, BMI, triglyceride to high-density

lipoprotein (HDL) ratio, hypertension, and daytime napping duration. Daytime napping was associated with type 2 diabetes only among white women (Shadyab et al., 2015).

A study conducted by Brondel et al. (2010) found that acute partial sleep deprivation for one night was significantly associated with consuming more food (higher food intake). While this was observed over one night of short sleep duration, sustained short sleep duration at night could contribute to obesity through higher food intake over a longer period of time. Since obesity and type 2 diabetes have also been linked, obesity may be a connecting factor between sleep duration and type 2 diabetes. However, several studies have exhibited that sleep duration and type 2 diabetes are significantly associated even after adjusting for the effects caused by obesity in the exposure-outcome relationship (Brondel, Romer, Nougues, Touyarou, & Davenne, 2010).

B. Sleep quality and type 2 diabetes in the non-Asian population

The association of snoring and type 2 diabetes incidence was examined in a cohort of female US nurses aged 40-65 years of age (Nurses' Health Study cohort) without diagnosed diabetes, cardiovascular disease, or cancer. The authors found that both occasional snoring and regular snoring compared to not snoring was significantly associated with risk of diabetes even after adjustment for age and BMI (Al-Delaimy, Manson, Willett, Stampfer, & Hu, 2002).

Bakker et al. (2015) examined the association between sleep apnea and abnormal fasting glucose in the US. However, this study contributed more to the understanding of these associations between sleep quality and type 2 diabetes since the study was conducted on the Multi-Ethnic Study of Atherosclerosis cohort, which allowed researchers to understand how these associations might differ between ethnic groups.

Relative to subjects without apnea, severe obstructive sleep apnea was significantly associated with abnormal fasting glucose in African Americas and Caucasians, but not among participants of Chinese or Hispanic descent. These significant associations were present after adjusting for site of collection, age, sec, waist circumference, and sleep duration. The researchers also found that there was not significant interaction present between ethnicity and obstructive sleep apnea severity. The authors also conducted a secondary analysis to examine the association between sleep duration and abnormal fasting glucose, but this association was not significant after adjusting for the effect of obstructive sleep apnea on the relationship between sleep duration and abnormal fasting glucose (Bakker et al., 2015).

The authors believe that the lack of a significant association between obstructive sleep apnea and abnormal fasting glucose in the Chinese and the Hispanic populations may be due to competing risk factors as well as the biological and lifestyle factors. In the Chinese population, there may be a weaker association between obstructive sleep apnea and abnormal fasting glucose due to the fact that there is less hypoxemia caused by less obesity present in this population. In the Hispanic population, a weaker association may be seen due to the fact that there are other competing risks that outweigh the relationship between obstructive sleep apnea and abnormal fasting glucose. Previous studies have shown that Hispanic populations have a higher degree of inflammatory biomarkers compared to other ethnic groups, and so obstructive sleep apnea may not be as strong of a risk factor as other risk factors for abnormal fasting glucose and type 2 diabetes. Difference in genes associated with the insulin repose and glucose homeostasis among different ethnic groups may also contribute to the difference in the association between

obstructive sleep apnea and abnormal fasting glucose among the different ethnic groups (Bakker et al., 2015).

Priou et al. (2015) also found differences in the associations between obstructive sleep apnea severity and glucose control in patients with untreated versus treated diabetes. In newly diagnosed and untreated type 2 diabetic patients, HbA1c levels were significantly associated with obstructive sleep apnea, after adjustment for age gender, BMI, alcohol habits, metabolic dyslipidaemia, hypertension, statin use, and study site. In patients with treated diabetes, the same significant association between HbA1c levels and obstructive sleep apnea was not seen. Thus the authors concluded, that obstructive sleep apnea may affect glucose control in newly diagnosed and untreated type 2 diabetes but has limited impact in patients whose diabetes has been diagnosed previously and is currently being treated (Priou et al., 2015).

C. Sleep duration and sleep quality and type 2 diabetes in the Asian population

Several association studies have been conducted examining the link between sleep duration and sleep quality and type 2 diabetes in the larger Asian population. Hsieh et al. (2011) examined the association of short sleep duration with diabetes in a cohort of Japanese men. Compared to those who sleep between 5-7 hours those who slept less than 5 hours displayed a significant association of sleep duration with type 2 diabetes even after adjustment for age and poor sleep quality (Hsieh, Muto, Murase, Tsuji, & Arase, 2011). Heianaza et al. (2014) also presented similar results as Hsieh et al. (2011) but tried to further clarify the relationship between sleep duration and type 2 diabetes. The authors were interested in examining the role of sleep duration as a risk factor for type 2 diabetes among different age groups. The study enrolled Japanese disease-free subjects and

followed them for 8 years to determine the risk of developing type 2 diabetes. The authors found that those who had a sleep duration of less than 6.5 hours had an increased risk of diabetes compared to those who had between 7-7.5 hours of sleep. After stratifying the results by age, the relationship continued to be significant among those less than 45 years of age but not among those aged 60 years or older. The effect of short sleep duration on the risk of diabetes became weaker with increasing age, indicating that age may be a more significant risk factor for type 2 diabetes compared to short sleep duration, especially among the elderly population. However, sleep duration may play a more significant role among the younger population in developing type 2 diabetes (Heianza et al., 2014).

Many also believe that BMI and body fat also play a role in the association of sleep duration with type 2 diabetes and may explain the link between the exposure and the outcome (Hsieh et al., 2011; Ohkuma et al., 2013). However Liu et al. (2011) found that short sleep duration was independently associated with a higher level of insulin resistance in women, even after adjustment for adiposity and other confounders (Liu et al., 2011).

Zheng et al. (2015) sought to further define the relationship between night sleep duration and type 2 diabetes by different glycemic status in a Chinese population. The authors were interested in determining if the association differed among those with diabetes, impaired fasting glucose, or those individuals determined to have normal glucose regulation. Long night sleep duration (>9 hours) was associated with higher HbA1c, fasting plasma-glucose levels and 2-h post-load plasma glucose levels compared with sleep duration of 6-9 hours in those with both impaired glucose regulation and type

2 diabetes. The association remained significant after adjusting for BMI, depressive symptoms, and snoring. No significant association was observed between short night sleep duration and HbA1c levels (Zheng et al., 2015).

China presents an excellent cohort for studying the effects of sleep quality on type 2 diabetes risk. Daytime napping, a proxy measure for nighttime quality of sleep, is a common practice in China and so allows for an easily accessible study population in which to measure the association of daytime napping with type 2 diabetes. Fang et al. (2013) described the relationship between the exposure and outcome in an elderly Chinese adult population: those who took longer naps had a higher prevalence of impaired fasting glucose (IFG) levels and type 2 diabetes. >60 min of nap duration was significantly associated with increased risk of IFG while >90 nap duration was significantly associated with an increased risk of diabetes mellitus, thus solidifying the relationship between IFG and DM and daytime napping as dose-dependent (Fang et al., 2013).

Sleep quality, measured as sleep disturbance was also examined in a Japanese male cohort as a prospective study conducted over 8 years. Hazard ratios were used to describe the relationship between sleep disturbance (having trouble falling asleep and waking up in the middle of the night) and type 2 diabetes incidence. Those who self-reported higher frequencies of trouble falling asleep showed an approximately 3 times higher risk of onset of type 2 diabetes while those self-reported a higher frequency of trouble sleeping through the night had an approximately 2 times higher risk of onset of type 2 diabetes (Kawakami, Takatsuka, & Shimizu, 2004).

Kita et al. (2012) investigated whether short sleep duration and poor sleep quality are associated with type 2 diabetes in those with no previous family history of diabetes. Participants were gathered from a prospective occupational-based study among Japanese government employees. The odds ratio of developing diabetes was 5.37 in those with a sleep duration ≤ 5 hours compared to those with a sleep duration of greater than 7 hours in subject without family history of diabetes. Other sleep quality risk factors were also significantly and highly associated with type 2 diabetes, including awakening during the night, self-perceived insufficient sleep duration, and unsatisfactory overall quality of sleep. These relationships became weaker and not significant in those with prior family history of diabetes, indicating that prior family history of diabetes may be a more significant predictor of type 2 diabetes than sleep duration and sleep quality (Kita et al., 2012).

Some studies have also examined the combined effects of sleep duration and quality. Lou et al. (2015) examined the effects of sleep duration and sleep quality on prevalence of type 2 diabetes in a five year follow up study in Chinese adults. Participants with short sleep duration, poor sleep quality, or long sleep duration all had a higher risk of development of type 2 diabetes. Interaction between poor sleep quality and short sleep duration also existed and had an additive effect. Type 2 diabetes occurred more frequently in subjects who had poor sleep quality but also had short average sleep duration. The authors further suggested that insulin resistance and the contribution of the sleep duration to insulin resistance may play a role in the development of type 2 diabetes (Lou et al., 2015).

Upala et al. (2015) conducted a meta-analysis to assess the relationship between sleep duration and insulin resistance in individuals without type 2 diabetes. The authors found that subjects with short or long sleep duration compared to those with a normal sleep duration showed no difference in levels of insulin resistance among the population without type 2 diabetes, indicating that other mechanisms not involving insulin resistance might be involved in facilitating the association of sleep duration with increased risk of diabetes mellitus. This study was not only exclusive to the Asian population, however (Upala, Sanguankeo, Congrete, & Romphothong, 2015).

D. Sleep duration and sleep quality and type 2 diabetes in South Asia

Below we review the handful of studies that have described the relationship of sleep duration and sleep quality among people with type 2 diabetes in South Asia.

Of cross-sectional studies, Rajendran et al. (2012) examined the prevalence and correlates of sleep disorders in Southeast Asian Indians with type 2 diabetes. Of particular interest was that duration of diabetes and the global Pittsburg Sleep Quality Index (PSQI) score were found to be significantly correlated; the authors interpreted this by suggesting that longer duration of diabetes negatively impacts sleep quality. Other factors like BMI, age, gender, and choice of medications were found to not be statistically correlated with global PSQI score. The authors also reported that 69% patients with type 2 diabetes had poor quality of sleep (Rajendran, Parthsarathy, Tamilselvan, Seshadri, & Shuaib, 2012).

Most other studies on sleep and diabetes have taken place India, with sparse data collected from other South Asian countries. In particular, one cross-sectional study examined the association of sleep duration with blood glucose levels in Gujarati Indian

adolescents, finding that less than 7 hours of sleep duration at night was not significantly associated with blood glucose level of Gujarati Indian teens aged 13-20 years of age (Patel et al., 2012). While this study was not specifically examining the relationship between sleep duration and type 2 diabetes mellitus, it provides data on the relationship of interest for this thesis. To our knowledge, there are no prospective studies on sleep duration and sleep quality and risk of developing type 2 diabetes in the South Asian population.

Studies of sleep quality and type 2 diabetes have also been rare in South Asia, especially those examining the association of sleep quality with type 2 diabetes. Roopa et al. (2010) examined the association of sleep abnormalities with glucose intolerance and type 2 diabetes in Asian Indians. The study was a cross-sectional with participants drawn from the Chennai Urban Rural Epidemiology Study based in southern India. The study evaluated four types of sleep abnormalities: snoring, daytime sleepiness, lack of refreshing sleep, and number of hours of sleep (sleep duration). The authors determined that both snoring and daytime sleepiness were more prevalent among participants with impaired glucose metabolism compared to those with normal glucose metabolism. Both snoring and daytime sleepiness were also significantly associated with higher type 2 diabetes risk scores (Roopa et al., 2010).

The researchers also performed a stratified analysis of the four sleep abnormalities by glucose metabolism status (impaired glucose tolerance versus impaired fasting glucose versus diabetes). All sleep abnormalities of interest were present in a higher percentage among those who reported impaired glucose metabolism compared to normal glucose metabolism but only snoring, daytime sleepiness, and number of hours of

sleep per night showed a statistically significant association. Thus, data suggest that snoring and daytime sleepiness are more frequent among those with impaired glucose tolerance and type 2 diabetes. This study is of particular interest due to the fact that sleep abnormalities were present in different categorizations of type 2 diabetes. In addition, the study found that the prevalence of snoring and daytime sleepiness was high among those with a BMI less than 30 kg/m^2, indicating that obesity status may not influence the presence of sleep abnormalities in this population. The authors also determined that the sleep abnormalities of interest were also present at a higher frequency in the Asian Indian population compared to other Asian populations, including the Chinese and the Malays . This finding is of particular significance as the association between sleep abnormalities and type 2 diabetes could differ even among subgroups within the Asian population, indicating the need for more studies examining not only inter-ethnic differences but also the intra-ethnic differences among levels of a particular ethnicity (Roopa et al., 2010).

Chapter III. Manuscript

The association of sleep duration and sleep quality with type 2 diabetes mellitus: The CARRS study

Sanober Ismaily[1], Shivani A. Patel[1], Mohammed K. Ali[1], Roopa Shivashankar[2,3], M. Deepa[4], V Mohan[4], K.M. Venkat Narayan[1], M. Masood Kadir[5], Zafar Fatmi[5], Dorairaj Prabhakaran[2,3], and Nikhil Tandon,[6] on behalf of the CARRS investigators

[1]Rollins School of Public Health, Emory University, USA
[2]Public Health Foundation of India, New Delhi, India
[3]Centre for Chronic Disease Control, New Delhi, India
[4]Madras Diabetes Research Foundation, Chennai, India
[5]Aga Khan University, Karachi, Pakistan
[6]All India Institute of Medical Sciences, New Delhi, India

Contribution of the Student

The work herein is the product of a secondary data analysis performed by the student. The student did not have a role in producing the survey or the collection of data. However, the student did perform all work after data collection independently, including the analysis of the data, the construction of regression models, summation of results in tables, and writing of the manuscript. Throughout the process, advisement was provided by the student's thesis committee chair.

Abstract

Title: The association of sleep duration and sleep quality and type 2 diabetes mellitus: The CARRS study

Authors: Sanober Ismaily, Shivani A. Patel, Mohammed K. Ali, K.M. Venkat Narayan, Roopa Shivashankar, D Prabhakaran, Nikhil Tandon, Deepa Mohan, V Mohan, Zafar Fatmi, and Masood Kadir

Background: A literature supporting short sleep duration and poor sleep quality as risk factors for type 2 diabetes mellitus. Little research has been done, however, in the urban South Asian population, who tends to experience type 2 diabetes at a lower BMI and younger age than other ethnic groups.

Objective: We sought to examine the association of night sleep duration and sleep quality (daytime napping, sleep apneas, habitual snoring, and daytime sleepiness, and overall sleep quality) with type 2 diabetes mellitus among adults in three large South Asian cities. Further, we assessed whether associations between sleep measures and type 2 diabetes mellitus varied by age, sex, or weight status.

Methods: We conducted a cross-sectional analysis of participants enrolled in the 2011 baseline survey of the Center for cArdiometabolic Risk Reduction in South Asia, a representative sample of non-pregnant adults in urban blocks of Chennai and Delhi, India and Karachi, Pakistan. The analytic sample consisted of n=11,351 with complete data on covariates of interest. We estimated odds ratios describing the association between measures of sleep duration and quality and diabetes using logistic regression models accounting for the survey design. Adjusted models included city, age, sex, religion, educational level, occupation, number of assets owned, time spent sedentary per day, and weight status measured as body mass index (BMI).

Results: We observed no association between duration of nightly sleep and prevalent diabetes in adjusted models. In contrast, four of five measures of sleep quality—daytime napping (aOR: 1.20, 95% CI: 1.02, 1.40), sleep apneas (aOR: 1.32, 95% CI: 1.06, 1.63), habitual snoring (aOR: 1.37, 95% CI: 1.14, 1.65), and overall sleep quality (aOR: 2.13, 95% CI: 1.24, 3.66) demonstrated moderate associations with prevalent diabetes in the overall sample. Point estimates of odds ratios were largely consistent in strata of sex, age group, and weight status.

Conclusion: While sleep duration was not associated with prevalent diabetes, we found that poor sleep quality was associated with prevalent diabetes. Specifically, daytime napping, observed apneas, habitual snoring, and overall poor sleep quality were significantly associated with higher prevalent type 2 diabetes. Of the indicators of poor sleep quality, overall poor sleep quality showed the strongest relationship with type 2 diabetes. Further investigation may probe the directionality of these associations to better understand the potential to mitigate diabetes risk by improving sleep quality among urban South Asians.

Introduction

The absolute number of people with and prevalence of type 2 diabetes has increased significantly within the past decade in all regions of the world (Ramachandran et al., 2012). Mounting evidence suggests that sleep duration and disorders may be associated with diabetes and cardio-metabolic risks (Grandner et al., 2014; Roopa et al., 2010; Wu et al., 2015). In particular, shorter and longer sleep duration (lower or greater than the median of 7-8 hours of sleep) has shown to be significantly associated with higher Hb1Ac levels and impaired fasting plasma glucose levels (Fang et al., 2013; Gottlieb et al., 2005; Ohkuma et al., 2013). Sleep quality, measured by—sleep quality include daytime napping, sleep disorders and sleep apneas, snoring, as well as daytime sleepiness—may also play a role in diabetes development (Fang et al., 2013; Roopa et al., 2010; Schwartz et al., 2015; Shadyab et al., 2015). Although sleep apneas and diabetes tend to be more common among overweight and obese individuals (Foster et al., 2009; Punjabi, 2008; Udwadia et al., 2004), those who experience sleep apnea, habitual snoring, or daytime sleepiness have a higher prevalence of type 2 diabetes, even after adjusting central obesity (Bakker et al., 2015; Foster et al., 2009; Roopa et al., 2010; Schwartz et al., 2015).

South Asians are a special population for cardio-metabolic disease who disproportionately experience cardio-metabolic diseases at younger ages and at a relatively leaner body mass in comparison to other populations (Ramachandran et al., 2012). In particular, type 2 diabetes is on the rise in this population and lifestyle factors are believed to be the driving force of this trend; sleep patterns could be a lifestyle risk factor that contributes to this rise of type 2 diabetes since in the Asian Indian population.

Previous studies examining sleep duration and sleep quality and cardio-metabolic health among South Asians yielded inconsistent results (Patel et al., 2012; Roopa et al., 2010). While one study in Western India found that sleep duration was not significantly associated fasting blood glucose in adolescents (Roopa et al., 2010), another study in Chennai found that sleep abnormalities, including snoring and daytime sleepiness, were both associated with a higher diabetes risk score (Patel et al., 2012).We sought to add to this area of research by examining the relationship between sleep and diabetes in urban-dwelling adults in north India and Pakistan. Additionally, the South Asian population offers a unique opportunity for investigating the independent relationship between inadequate sleep and diabetes in non-obese and relatively young individuals. Given that Asian countries account for 60% of the world's absolute number of diabetes cases (Ramachandran et al., 2012), identifying key diabetes correlates in this region is important to improve the global burden.

We examined the cross-sectional association between sleep duration and quality and prevalent diabetes in three large cities of South Asia – Chennai, Delhi, and Karachi – among participants enrolled in the baseline assessment the Center for cArdiometabolic Risk Reduction in South Asia (CARRS) Study. We also examined the additional contribution of sleep duration and quality, above and beyond other traditional risk factors like age, weight, and lifestyle behaviors (diet and physical activity) on diabetes status in this large and geographically diverse population in order to ascertain where sleep patterns fit into the relationship of risk factors and their predictability of type 2 diabetes.

Methods

Study population

Our study population was a subset of the Center for CArdiometabolic Risk Reduction in South Asia (CARRS) Study cohort at baseline. The methods and design of the study are described in detail elsewhere (Nair et al., 2012). The CARRS study cohort was designed as a cross-sectional multi-center surveillance study to be carried out over four years. The objective of the main study was to generate data on the prevalence and incidence of cardio-metabolic disease and its risk factors by enrolling and longitudinally following a representative sample of adults residing in urban blocks of Chennai and Delhi, India and Karachi, Pakistan. The cohort was assembled using multi-stage cluster random sampling to recruit 16,288 non-pregnant adults age 20 years and older from three cities across South Asia. Municipal sub-divisions already present in each city, made up or wards and Census Enumeration Blocks (CEB) were used sequentially as sampling frame to randomly select household. Wards were used as the primary sampling units (PSUs) for Chennai and Delhi, CEBs or clusters were the PSUs for Karachi. Manual listing and mapping of all households in each ward and CEB respectively gave each household an equal chance of being selected for the study and allowed for random selection of households. One man and one woman were randomly selected from each selected household for participation. Interviews in the local language and anthropometric and blood pressure assessments were conducted at the home of participants. Fasting blood samples were collected in the home (Karachi) or in local neighborhood camps (Chennai and Delhi). Response rates overall were 94.7% for the completion of the questionnaire

and 84.3% for collection of bio-specimens. Written consent was obtained from participants prior to enrollment in the study (Ali et al., 2016).

Cross-sectional survey data collected in the 2011 baseline interview and assessment was used in this analysis. Of baseline CARRS participants, 94 were excluded due to missing data on sleep duration or quality, 10 were excluded to missing data on diabetes status, and another 4,862 were excluded due to missing data on other potential confounders of the sleep and diabetes association. The analytic sample thus consisted of 11,351 individuals with complete data for variables used in the analysis; all analyses were based on this subset unless otherwise specified.

Study measures and definitions

Exposures: sleep duration and quality. All sleep measures were based on interview data. Questions were largely based on the Sleep Heart Health Study (SHHS) instrument (Quan et al., 1997). The main exposure variable of interest was weekday nighttime duration of sleep specified as a three level categorical variable. The categorical specification was chosen because of previous literature suggesting that sleep measures have a U-shaped association with cardio-metabolic outcomes (Fang et al., 2013). Sleep duration was categorized as less than 7 hours of sleep, between 7-9 hours of sleep, and greater than 9 hours of sleep. Four additional measures of sleep quality were also analyzed for their association with type 2 diabetes. Daytime napping, a proxy measure for quality of nighttime duration of sleep, was defined as those who self-reported at least one instance or more of napping during the day and those who self-reported not napping during the day. Instances of sleep apnea and habitual snoring, also proxies for quality of sleep, were classified according to participant self-reporting or a family member

reporting observing the behavior on behalf of the participant. Participants were categorized as having sleep apnea if the individual or a family member identified one instance of where the participant stopped breathing during the night at least one night in a typical week. Habitual snoring was classified as those who self-reported snoring or a family member reported that the participant snored at least 3 nights a week or more. Daytime sleepiness was also analyzed an indicator of sleep quality according to a questionnaire based on the Epworth Sleepiness Scale (ESS). Participants were asked "what is the chance that you would doze off or fall asleep (not just "feel tired") in each of the following situations: sitting and reading, watching TV, sitting inactive in a public place, riding as a passenger in a car for an hour without a break, lying down to rest in the afternoon when circumstances permit, sitting and talk to someone, sitting quietly after a lunch, or in a car while stopped for a few minutes in traffic." Participants were then given a summed daytime sleepiness score between 0-24. Those with a daytime sleepiness score of less than 10 were categorized as having an adequate amount of daytime sleepiness while those with a score of 10 or greater were categorized as having excessive daytime sleepiness. Finally, an overall sleep quality variable was also created from the summation of the presence of daytime napping, sleep apnea, habitual snoring, and daytime sleepiness. Individuals were assigned a sleep quality score, which ranged from 0-4. Those with a sleep quality score of less than 3 were characterized as having adequate sleep quality while those with a score of 3-4 were characterized as having poor sleep quality.

Outcome: type 2 diabetes mellitus. Type 2 diabetes mellitus was the outcome of interest. The outcome was defined using clinical outcomes for diabetes and was obtained from the sample blood collection using standardized techniques. Fasting plasma glucose

(FPG) was estimated using hexokinase/kinetic methods while glycated hemoglobin (HbA1c) was estimated using high-performance liquid chromatography (NGSP standardized) (Ali et al., 2016). Individuals were identified as having type 2 diabetes if they met any of the following four criteria: having a FPG level of 126 mg/dl or higher, HbA1c levels of 6.5% or higher, self-reported use of medication for diabetes, or self-reporting receiving a diabetes diagnosis.

Other covariates of interest. We also examined several demographic and socioeconomic factor expected to be associated with both sleep and diabetes. These included age, sex, religion, education, occupation, and asset score were categorized according to interview responses. Age was categorized into three groups, 20-44 years, 45-64 years, and 65 years and older, while sex was dichotomized as male and female. Religion was categorized into three categories: Hindu, Muslim, and other. Education was grouped by level: no education, primary schooling, high schooling, or college degree or higher. Occupation was categorized into 4 groups: not working (housewife, student, retired, unemployed), manual labor, skilled labor, or white-collar worker. As a measure of household socioeconomic status, we created an asset score by summing the number of the following assets owned by the household: television, refrigerator, washing machine, microwave, mixer grinder, DVD player, computer, car, motorcycle, or bicycle. The summed score was then categorized into tertiles based on the number of interview responses. Tobacco use and alcohol consumption were also characterized as separate dichotomous variables, ever use of tobacco and never use of tobacco and ever use of alcohol and never use of alcohol. Body mass index (kg/m^2) was computed from participants' measured weight and height and was grouped using the international

standard categories of BMI: BMI < 23 kg/m^2; BMI 23-24.9 kg/m^2; BMI 25-29.9 kg/m^2, and BMI ≥ 30 kg/m^2. Sedentary behavior was defined as a binary variable in which low sedentary behavior was reported as less than 6 hours of time spent sedentary (the mean level of sedentary behavior in the sample) while high sedentary behavior was reported as 6 hours or more of time spent sedentary during a typical day.

Statistical analysis

We used SAS software (version 9.4; SAS Institute Inc., NC, USA) to conduct data analysis. Appropriate strata and sampling weights were used in the analysis to account for the cluster-randomized survey design and to maintain the representativeness of the results to the target population. Calculations for the sampling weights are described in detail elsewhere (Gujral et al., 2015). First, we described the socio-demographic, behavioral, and physiological profiles of CARRS participants in Chennai, Delhi, and Karachi and overall. We then estimated logistic regression models to determine the association (odds ratios, OR) and Wald 95% confidence intervals (CI) between each sleep exposure and the type 2 diabetes outcome. We report both unadjusted models as well as the adjusted models controlling for the confounders of interest, including city, sex, age, religion, education, occupation, asset score, tobacco use, alcohol consumption, BMI, and sedentary behavior.

The decision to include a potential confounder was based on *a priori* review of the literature and empirically observed statistically significant relationships between both sleep measures and diabetes in the analytic sample. City, age, and occupation was found to be significantly associated with all exposures and outcome. Sex, tobacco use, alcohol consumption, and sedentary behavior were not found to significantly be associated with

the outcome. Sex was found to be associated with all of the sleep exposures, except for daytime sleepiness and overall quality of sleep. Religion was found to be significantly associated with all of the sleep exposures, except for snoring and overall quality of sleep. Education level was found to be significantly associated with all of the sleep exposures, except for sleep apnea and the overall quality of sleep. Asset score was found to be significantly associated with all of the sleep exposures, except for weekday nighttime duration of sleep, sleep apnea, daytime sleepiness, and overall quality of sleep. BMI was found to be significantly related to all of the sleep exposures, except for weekday nighttime duration of sleep, daytime sleepiness, and overall sleep quality. Sedentary behavior was significantly associated with all of the sleep exposures, except for overall sleep quality. Tobacco use was found to not be significantly related to most of the sleep exposures, except for weekday nighttime duration of sleep and habitual snoring. Alcohol consumption was found to not be significantly related to most of the sleep exposures, except for daytime napping, habitual snoring, and overall sleep quality. Since all of the confounders of interest were related to some of the sleep exposures and not all of the confounders were related to the outcome, we settled for the *a priori* definition of inclusion of the confounders into the adjusted models created for analysis.

We also conducted stratified analyses for the sleep exposures and outcome relationships. Unadjusted and adjusted models were stratified by city, age, sex, and BMI to see if the relationship between sleep duration and sleep quality differed among levels of the stratification variables of interest.

A sensitivity analysis was performed for the main exposure variable of weekday nighttime duration of sleep. Weekday nighttime duration of sleep was also assessed as a

continuous variable to see if the relationship between weekday nighttime sleep duration and type 2 diabetes differed due to the categorization of the main exposure.

We also computed c-statistics to determine the contribution of sleep duration and sleep quality exposures to explaining prevalent type 2 diabetes in the sample. *C*-statistics, or areas under the logistic curve, can be interpreted as how well the model discriminates between individuals with and without the outcome; higher c-statistics indicate better discrimination. A base model of all other predictors of diabetes was established and included age, sex, city, religion, education, occupation, asset score, tobacco use, alcohol consumption, sedentary behavior, and BMI. Sleep exposures were then added to the model individually and together to ascertain whether there was a difference in the *c*-statistic from the base model. The c-statistics were obtained using logistic regression (ignoring the survey design).

Results

The unweighted frequency and percentages of socio-demographic, behavioral, and physiological characteristics of CARRS participants included in the analytic sample are reported in Table 1; weighted frequencies and percentages for the analytic sample are shown in Supplementary Table 1. Mirroring the demographics of the full CARRS cohort, there were more women (54.8%) than men in the sample. The majority of participants were between 20-44 years (58.9%), and only 7.0% of the sample was 65 years or older. 59.3% of the respondents were Hindu while 30.2% of the respondents were Muslim. 61.5% of the population had received high schooling while 55.4% of the population was not working (i.e. a housewife, student, retired, or unemployed). Key background characteristics that differed in large proportion by city of residence included religion,

such that participants from Indian cities were largely Hindu and participants from Pakistan were largely Muslim, and educational attainment and assets, which were both higher among participants from Delhi.

Of the health risk factors, engaging in sedentary behavior for over 6 hours per day was most prevalent. Respondents in Chennai more often reported spending ≥ 6 hours in sedentary in sedentary activities (64.8%) than respondents in Delhi (27.7%) and Karachi (39%). 23.9% of the population reported using tobacco while 14.7% reported consuming alcohol. Nearly one-third of the sample had a BMI < 23 kg/m^2, 15.0% had a BMI between 23-24.9 kg/m^2, 33.6% had a BMI between 25-29.9 kg/m^2 (overweight), and 18.0% of the population had a BMI ≥ 30 kg/m^2 (obese).

Mean hours of sleep per night during a typical weekday was reported to be 7.23 hours (standard error (SE): 0.039). Most respondents (69.6%) reported a weekday nighttime duration of sleep between the ideal 7-9 hours. Roughly one-third (35.8%) of the sample reported one or more daytime naps during a typical week. 4.1% of the sample observed any stoppage in breathing, or observed sleep apnea for one or more nights. 14.4% reported habitual snoring, while 1.8% reported above average amount of daytime sleepiness, or ESS score ≥ 10. Less than 1% (0.8%) of respondents reported having an poor quality of sleep, a composite index created from daytime napping, observed sleep apneas, habitual snoring, and daytime sleepiness. These patterns of sleep exposures were also similar across the three cities of Chennai, Delhi, and Chennai for all reported measures.

Table 2 displays the distribution of socio-demographic, behavioral, and physiological characteristics of CARRS participants by type 2 diabetes status. The

distribution of men and women is similar by diabetes status. Those without diabetes were mostly in the youngest age group of 20-44 years (72.4%) while those with diabetes were mostly in the middle age group of 45-64 years of age (52.7%). The proportions of Hindus (59.1% and 64.0%), having completed high school (62.7% and 60.7%), and those not working at the time of the interview (52.9% and 57.4%) did not differ between those with and without diabetes, respectively. Ownership of between 6-10 assets was higher in those with diabetes compared to those without (47.1% versus 31.8%). Asset ownership and BMI status were two risk factors that differed by diabetes status. Tobacco use (75.8% and 77.2%) and current alcohol consumption (84.5% and 84.7%) also did not differ in those with or without diabetes, respectively. Finally, the sleep exposures patterns largely did not differ by diabetes status.

Table 3 shows the results of unadjusted and adjusted logistic regression analysis modeling the association of sleep exposures with prevalent type 2 diabetes. In a model with a continuous duration of nighttime sleep variable, the unadjusted odds of prevalent type 2 diabetes were lower with each additional hour of sleep (OR:0.93, 95% CI: (0.89, 0.98)); after adjustment, this relationship was no longer statistically significant (aOR: 0.98, 95% CI: (0.93, 1.04)). For the main exposure variable of weekday average nightly duration of sleep, the unadjusted odds of prevalent type 2 diabetes was 1.12 times higher among those who on average sleep less than 7 hours compared with those reporting 7-9 hours of nightly sleep (odds ratio [OR]: 1.12, 95% CI: (1.00, 1.25)). After adjustment for potential confounding factors of sex, age, religion, education level, occupation, number of assets owned, amount of sedentary behavior per day, and BMI, the relationship between sleeping less than 7 hours compared with the referent and diabetes was

attenuated toward the null value and no longer statistically significant at the 95% significance level (OR: 0.98, 95% CI: (0.88, 1.10)). Conversely, the unadjusted odds ratio of type 2 diabetes associated with sleeping more than 9 hours was OR=0.85 (95% CI: 0.62, 1.17). This association, too, was attenuated and not statistically significant after adjustment (adjusted odds ratio [aOR]: 0.94, 95% CI: (0.64, 1.38). Models assessing the cross-sectional associations of multiple sleep quality measures with diabetes are also shown in Table 3. In the overall sample, the unadjusted odds ratio of prevalent type 2 diabetes associated with taking at least one nap in a week was OR=1.32 (95% CI: (1.14,1.52)). This relationship did not remain statistically significant in the total adjusted model (aOR: 1.14, 95% CI: (0.97, 1.33)). The same pattern was present in Chennai and Delhi but the relationship between type 2 diabetes and daytime napping was statistically significant in Karachi even after adjustment (aOR: 1.37, 95% CI: (1.11, 1.70)) in Karachi.

The odds of prevalent type 2 diabetes was 1.47 times higher in those reporting sleep apneas compared to with no apneas in the overall sample in unadjusted (OR: 1.47, 95% CI: (1.20, 1.82) and adjusted (aOR: 1.31, 95% CI: (1.05, 1.63)) models. In the models stratified by city, point estimates were in the positive direction in all cities, but the association was statistically significant only in Chennai (OR: 2.00, 95% CI: (1.30, 3.07); aOR: 1.57, 95% CI: (1.04, 2.39)).

Habitual snoring was strongly associated with prevalent type 2 diabetes in the overall sample (OR: 2.31, 95% CI: (1.95, 2.73); aOR: 1.46, 95% CI: (1.23, 1.74)). In the models stratified by city, we observed similar magnitudes of this association at all sites.

However, the adjusted association between habitual snoring and type 2 diabetes was only statistically significant in Delhi and Karachi.

The unadjusted odds of prevalent type 2 diabetes was 1.46 times higher in those with an ESS score <10 compared to those with an ESS score ≥ 10 (OR: 1.46, 95% CI: (1.13, 1.89)). The odds ratio for the overall sample lost significance at the 95% confidence level after adjustment for potential confounders (aOR: 1.22, 95% CI: (0.90, 1.67)). While Delhi and Karachi did not report significant adjusted ORs for the association between daytime sleepiness and type 2 diabetes, Chennai reported significant unadjusted (OR: 3.47, 95% CI: (1.27, 9.49)) and adjusted (aOR: 2.80, 95% CI: (1.09, 7.19)) ORs for the association between daytime sleepiness and prevalent type 2 diabetes.

The unadjusted odds of type 2 diabetes as 3.32 times higher in those with poor sleep quality compared to those with adequate sleep quality (OR: 3.32, 95% CI: (1.94, 5.68)), indicating a strong statistically significant association. The relationship remained highly significant after adjustment (aOR: 2.19, 95% CI: (1.25, 3.83)). In Chennai, the unadjusted odds of type 2 diabetes was 4.61 times higher in those with poor sleep quality compared to the referent (OR: 4.61, 95% CI: (2.08, 10.24)). The adjusted OR reported for Chennai remained highly significant after adjustment for confounders (aOR: 3.48, 95% CI: (1.69, 7.16)), indicating a higher level of poor sleep quality in Chennai compared to the other two cities.

In models stratified by city (Table 4), point estimates in Chennai and Karachi resembled those observed in the overall sample. In Delhi, however, those reporting less than 7 hours of sleep compared with 7-9 hours of sleep had *lower* odds of prevalent type 2 diabetes in the adjusted model (aOR: 0.82, 95% CI: (0.73, 0.91)) and similarly, there

was a positive association between higher sleep measured continuously and prevalent diabetes (aOR: 1.11, 95% CI (1.03, 1.20)). Again, this was the opposite of the total population trend, such that in Delhi, as participants get one more hour of sleep their odds of prevalent type 2 diabetes increased by 1.11 units.

Table 5 shows the shows the results of unadjusted and adjusted logistic regression analysis modeling the association of sleep exposures with prevalent type 2 diabetes stratified by sex. In the overall sample and the sample stratified by sex, we found no statistically significant associations between sleep duration and prevalent diabetes. The OR and aOR point estimates, however, describing the association between sleep duration and prevalent diabetes were very similar in the models shown in Tables 3 and 4.
Table 5 also shows that several statistically significant associations between sleep quality measures and prevalent diabetes were observed in only men or only women. For example, taking at least one nap in a week was associated with higher adjusted odds of diabetes in men (aOR: 1.22, 95% CI: (1.01, 1.48)) but not women. Conversely, observed sleep apneas (aOR: 1.54, 95% CI: (1.13, 2.10)), habitual snoring (aOR: 1.55, 95% CI: (1.24, 1.93)), and poor overall sleep quality (aOR: 2.59, 95% CI: (1.13, 5.92)) were each statistically significantly associated with higher adjusted odds of diabetes. The daytime sleepiness scale (ESS) was not associated with diabetes in either sex.

Table 6 shows the results of unadjusted and adjusted logistic regression analysis modeling the association of sleep exposures with prevalent type 2 diabetes stratified by age group (20-44y, 45-64y, and 65y and older). Sleep duration variables were not associated with diabetes in any of the Table 6 models. Taking at least one nap in a week (aOR: 1.22, 95% CI: (1.06,1.44)) and observed sleep apneas (aOR: 1.68, 95% CI: (1.22,

2.31) was associated with higher adjusted odds of diabetes compared with the respective reference groups in the 45-64y age group but no others. On the other hand, the daytime sleepiness measure was statistically significantly associated with higher adjusted odds of diabetes in the youngest age group (OR: 1.74, 95% CI: (1.03, 2.94)). Finally, habitual snoring (aOR 20-44 y: 1.83, 95% CI: (1.41, 2.37)); aOR 45-64: 1.22, 95% CI: (1.01, 1.48)) and overall sleep quality (aOR 20-44 y: 2.29, 95% CI: (1.02, 5.14); aOR 45-64 y: 2.15, 95% CI: (1.15, 4.01)) were associated with statistically significant higher adjusted odds of diabetes in both the youngest and middle age groups, respectively.

Table 7 shows the results of unadjusted and adjusted logistic regression analysis modeling the association of sleep exposures with prevalent type 2 diabetes stratified by weight status (BMI < 23 kg/m^2,, 23-24.9 kg/m^2, 25-29.9 kg/m^2, and $\geq$ 30 kg/m^2). Sleep duration measures were not associated with diabetes in any of the BMI strata. Three of five sleep quality measures were related to diabetes in some BMI strata. Specifically, observed apneas was associated with higher adjusted odds of diabetes in the obese (aOR: 1.74, 95% CI: (1.03, 2.97)), habitual snoring was associated with higher adjusted odds of diabetes in those with BMI <23 (aOR: 2.01, 95% CI: (1.50, 2.69)), and the overall sleep quality measure was associate with higher odds of diabetes in the overweight (aOR: 2.54, 95% CI: (1.35, 4.78)) and the obese (aOR: 2.46, 95% CI: (1.02, 5.91)).

Table 8 shows c-statistics from a base model with only sociodemographic and risk factors, and subsequent models that included individual sleep measures. The *c*-statistic is used to describe how well the model discriminates individuals with and without prevalent diabetes; higher c-statistics indicate better discrimination. The c-statistic for the base model was 0.768, indicating that there is a 0.768 probability that a randomly selected

person with prevalent diabetes would have a higher model-based predicted probability of diabetes than a randomly selected person without diabetes. The c-statistic in subsequent models adding individual sleep duration and sleep quality variables ranged from 0.768-0.769, suggesting that sleep measures did not add to the discrimination offered by the base model.

Discussion

Main findings

We found that while sleep duration was not associated with prevalent diabetes, measures of sleep quality were associated with prevalent diabetes in the total sample and in various subgroups. Specifically, daytime napping, observes apneas, habitual snoring, and overall sleep quality were statistically significantly associated with type 2 diabetes in several models, and point estimates were largely positive and consistently moderate across the examined subgroups. Our findings are consistent with the hypothesis that measures of sleep quality may be contributing to diabetes in urban South Asians, but we find no consistent evidence that sleep duration impacts diabetes in this population.

Chennai reported greater associations of observed sleep apneas, daytime sleepiness, and overall sleep quality with type 2 diabetes. This result is similar to that observed for the association of daytime sleepiness and type 2 diabetes seen in the CURES study conducted in Chennai (Roopa et al., 2010). However, a non-significant association between habitual snoring and type 2 diabetes unlike the results observed in the CURES study. However, Delhi and Karachi reported a higher and significant association of habitual snoring with type 2 diabetes compared to Chennai. Karachi also reported a greater significant association of daytime napping with type 2 diabetes. Cultural norms

may be a reason for this observation, as daytime napping may be more culturally acceptable in Karachi over the other two sites in India. Daytime napping showed a more significant association with type 2 diabetes among males, while observed apneas, habitual snoring and overall sleep quality were more likely to be significantly associated at a higher level with type 2 diabetes among females. Stratification by age categories led to the distinction that among 20-44 year olds, daytime sleepiness was significantly associated with type 2 diabetes while daytime napping and observed apneas were significantly associated with type 2 diabetes only among the 45-64 year old population after adjustment for potential covariates. Habitual snoring was significantly associated with type 2 diabetes among those with BMI <23 while observed apneas was significantly associated with type 2 diabetes in the obese population. Overall sleep quality was significantly associated with type 2 diabetes in the overweight and obese populations indicating that these two populations are more likely to contribute to the significant relationship of overall sleep quality with type 2 diabetes in the total population. Reasons for the differences in sleep quality exposures seen across BMI status may be biological in nature. Poor sleep quality is also associated with higher food intake and greater feelings of hunger, which can also lead to inflammation and impaired glucose tolerance, and insulin resistance. Thus, poor sleep quality may be more prevalent in overweight and obese populations, impacting the relationship of sleep quality with type 2 diabetes (Lou et al., 2015).

Limitations and strengths

Using cross-sectional data to report odd ratios and associations of sleep duration and sleep quality with type 2 diabetes does not distinguish the temporal ordering between

sleep disturbances and diabetes, and bidirectional associations are a possibility. Furthermore, we cannot quantify the risk of developing incident type 2 diabetes associated with any of the sleep measures because of the cross-sectional design. Categorizing exposure variables and covariates also leads to reduced sample sizes and power among those variables, which may obscure otherwise present associations between those exposures and type 2 diabetes (as may have occurred in the categorization of age as data was sparse for those at or above 65 years of age). However, there is a benefit to categorizing variables in a non-linear association. Many sleep quality measures were self-reported which may indicate strong information bias and misclassification of exposures. There is opportunity for error in the measurement, which could have produced statistically significant results in some groups where an association was not truly present. There are cultural differences in the way sleep is understood and many of the metrics used to measure sleep duration and sleep quality were from Western models. Also some sleep quality variables are harder to explain; snoring is more universally known and that is why a more positive and significant association was found for habitual snoring over apneas and daytime sleepiness, which are harder to explain to the lay population. Recall bias may also have been present in the categorization of the daytime sleepiness variable (as the variable is created from an index where eight questions about feeling sleepy while conducting routine activities) may have contributed to the non-significant association of daytime sleepiness with type 2 diabetes. The outcome of type 2 diabetes also contained a self-reported type 2 diabetes component, which may have led to slight misclassification of the outcome. In addition, glucose tolerance tests are better instruments through which to categorize diabetes status; these tests were not used in this study. However, the

strength of the study lies in the large sample size and varied sample from three large urban cities across South Asia, leading to a diverse population in which to examine type 2 diabetes trends. The outcome of type 2 diabetes also contained objectively measured clinical indicators of type 2 diabetes, and most of the population was characterized as having type 2 diabetes by these medical criteria. In addition, the survey reported high response and lab specimen collection rates, further indicating the diversity and richness of the sample captured and its generalizability to the urban South Asian population.

Manuscript Tables

Table 1. Sociodemographic, behavioral, and physiological characteristics of CARRS participants in Chennai, Delhi, and Karachi, 2011

	TOTAL		Chennai		Delhi		Karachi		
	n=	11,351	n=	4,809	n=	3,540	n=	3,002	
	n	%	n	%	n	%	n	%	p-value for difference across sites[b]
Outcome									
Type 2 diabetes (FBG ≥ 126 mg/dl, Hba1c ≥ 6.5%, or medication for diabetes), %									<.0001
No	8,591	75.7	3,708	77.1	2,397	67.7	2,486	82.8	
Yes	2,760	24.3	1,101	22.9	1,143	32.3	516	17.2	
Sociodemographic risk factors									
Sex, %									<.0001
Male	5,136	45.2	2,029	42.2	1,744	49.3	1,363	45.4	
Female	6,215	54.8	2,780	57.8	1,796	50.7	1,639	54.6	
Age, %									<.0001
20-44 y	6,689	58.9	3,038	63.2	1,799	50.8	1,852	61.7	
45-64 y	3,870	34.1	1,523	31.7	1,407	39.7	940	31.3	
≥65 y	792	7.0	248	5.2	334	9.4	210	7.0	
Religion, %									<.0001
Hindu	6,736	59.3	4,077	84.8	2,631	74.3	28	0.9	
Muslim	3,428	30.2	244	5.1	593	16.8	2,591	86.3	
Other	1,187	10.5	488	10.1	316	8.9	383	12.8	
Education, %									<.0001
None	1,944	17.1	481	10.0	619	17.5	844	28.1	
Primary schooling	574	5.1	356	7.4	148	4.2	70	2.3	
High schooling	6,977	61.5	3,434	71.4	1,891	53.4	1,652	55.0	
College degree or higher	1,856	16.4	538	11.2	882	24.9	436	14.5	
Occupation, %									<.0001
Not Working (housewife, student, retired, unemployed)	6,289	55.4	2,605	54.2	1,857	52.5	1,827	60.9	
Manual labor	2,318	20.4	1,181	24.6	625	17.7	512	17.1	
Skilled labor	2,398	21.1	968	20.1	868	24.5	562	18.7	
White-collar worker	346	3.0	55	1.1	190	5.4	101	3.4	
Asset Score, %									<.0001
0-3	3,851	33.9	1,742	36.2	1,144	32.3	965	32.1	
4-5	3,598	31.7	1,727	35.9	775	21.9	1,096	36.5	
6-10	3,902	34.4	1,340	27.9	1,621	45.8	941	31.3	
Behavioral risk factors									
Self-reported tobacco use, %									0.0042
Never user	8,640	76.1	3,821	79.5	2,633	74.4	2,186	72.8	
Ever user	2,711	23.9	988	20.5	907	25.6	816	27.2	
Alcohol consumption, %									<.0001[c]
Never drinker	9,677	85.3	3,848	80.0	2,920	82.5	2,909	96.9	
Ever drinker	1,674	14.7	961	20.0	620	17.5	93	3.1	
Sedentary behavior, %									<.0001
< 6 hours of sitting	6,086	53.6	1,693	35.2	2,561	72.3	1,832	61.0	
≥ 6 hours of sitting	5,265	46.4	3,116	64.8	979	27.7	1,170	39.0	
Physiological risk factors									
Body mass index, %									0.0070
< 23 kg/m^2	3,792	33.4	1,502	31.2	1,203	34.0	1,087	36.2	
23-24.9 kg/m^2	1,701	15.0	776	16.1	508	14.4	417	13.9	
25-29.9 kg/m^2	3,817	33.6	1,737	36.1	1,162	32.8	918	30.6	
≥ 30 kg/m^2	2,041	18.0	794	16.5	667	18.8	580	19.3	
Sleep duration and quality									
Mean hours of sleep per night (SE)	7.23	0.039	7.59	0.038	6.93	0.035	7.03	0.038	
Hours of sleep per night, %									<.0001
< 7 hours	3,109	27.4	729	15.2	1,208	34.1	1,172	39.0	
7-9 hours	7,905	69.6	3,942	82.0	2,280	64.4	1,683	56.1	
≥ 9 hours	337	3.0	138	2.9	52	1.5	147	4.9	
Number of naps per week, %									<.0001[c]
0 times per week	7,283	64.2	2,500	52.0	2,608	73.7	2,175	72.5	
≥ 1 time per week	4,068	35.8	2,309	48.0	932	26.3	827	27.5	
Observed apneas, %									<.0001
< 1 night a week	10,885	95.9	4,666	97.0	3,402	96.1	2,817	93.8	
≥ 1 night a week	466	4.1	143	3.0	138	3.9	185	6.2	
Habitual snoring, %									<.0001
< 3 nights a week	9,717	85.6	4,395	91.4	2,693	76.1	2,629	87.6	
≥ 3 nights a week	1,634	14.4	414	8.6	847	23.9	373	12.4	
Daytime sleepiness, %									<.0001
ESS[a] Score < 10	11,142	98.2	4,784	99.5	3,426	96.8	2,932	97.7	
ESS Score ≥ 10	209	1.8	25	0.5	114	3.2	70	2.3	
Overall sleep quality, %									0.0291
Adequate sleep quality	11,260	99.2	4,783	99.5	3,499	98.8	2,978	99.2	
Poor sleep quality	91	0.8	26	0.5	41	1.2	91	0.8	

[a]Epworth Sleepiness Scale

[b]Rao-Scott chi-square values reported

[c]Chi-square values reported

Table 2. Sociodemographic, behavioral, and physiological characteristics of CARRS participants with diabetes in Chennai, Delhi, and Karachi, 2011

	Total		Chennai		Delhi		Karachi	
	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes
	n= 8,591	n= 2,760	n= 3,708	n= 1,101	n= 2,397	n= 1,143	n= 2,486	n= 3,002
	%	%	%	%	%	%	%	%
Sociodemographic risk factors								
Sex, %								
Male	45.1	45.9	42.8	42.1	48.4	49.7	45.0	45.0
Female	54.9	54.1	57.2	57.9	51.6	50.3	55.0	55.0
Age, %								
20-44 y	72.4	36.2	76.6	39.8	70.1	34.9	67.7	31.0
45-64 y	24.1	52.7	21.0	49.4	26.9	54.4	26.3	55.9
≥65 y	3.5	11.1	2.5	10.7	3.0	10.7	6.0	13.1
Religion, %								
Hindu	59.1	64.0	83.4	83.2	71.6	72.3	0.9	1.6
Muslim	30.0	22.2	4.6	3.9	20.4	13.3	86.6	84.1
Other	10.9	13.8	12.0	12.9	8.0	14.4	12.6	14.4
Education, %								
None	16.5	14.2	8.5	11.0	18.8	9.7	27.6	32.3
Primary schooling	4.4	5.8	6.3	9.1	3.4	4.1	2.4	2.6
High schooling	62.7	60.7	72.6	72.9	54.6	52.9	55.1	52.1
College degree or higher	16.4	19.3	12.7	6.9	23.1	33.4	14.8	13.0
Occupation, %								
Not Working (housewife, student, retired, unemployed)	52.9	57.4	50.8	59.8	49.9	51.3	60.4	66.6
Manual labor	23.7	15.2	28.4	20.0	21.9	12.1	17.6	12.0
Skilled labor	20.8	23.3	19.8	19.8	24.1	28.4	18.6	18.6
White-collar worker	2.6	4.1	1.0	0.4	4.1	8.2	3.5	2.8
Asset Score, %								
0-3	36.4	24.3	36.6	30.2	38.7	17.8	33.2	27.0
4-5	31.8	28.5	35.2	34.6	23.0	19.8	36.7	35.9
6-10	31.8	47.1	28.1	35.2	38.3	62.4	30.1	37.1
Behavioral risk factors								
Self-reported tobacco use, %								
Never user	75.8	77.2	78.9	78.6	73.1	79.1	73.4	69.9
Ever user	24.2	22.8	21.1	21.4	26.9	21.0	26.6	30.1
Alcohol consumption, %								
Never drinker	84.5	84.7	79.4	80.5	81.9	83.0	96.7	97.8
Ever drinker	15.5	15.3	20.6	19.5	18.1	17.0	3.3	2.2
Sedentary behavior, %								
< 6 hours of sitting	51.9	50.0	29.1	25.4	76.8	69.1	61.2	58.7
≥ 6 hours of sitting	48.1	50.0	70.9	74.6	23.2	30.9	38.8	41.3
Physiological risk factors								
Body mass index, %								
< 23 kg/m^2	37.7	18.2	33.8	19.0	41.7	17.5	39.6	17.9
23-24.9 kg/m^2	15.7	13.2	16.8	12.6	15.4	13.2	14.2	14.9
25-29.9 kg/m^2	32.0	40.8	35.3	44.0	29.9	38.5	28.8	39.0
≥ 30 kg/m^2	14.6	27.8	14.0	24.4	13.0	30.8	17.4	28.2
Sleep duration and quality								
Mean hours of sleep per night (SE)	7.29 (0.064)	7.18 (0.051)	7.69 (0.058)	7.56 (0.061)	6.90 (0.045)	6.96 (0.047)	7.06 (0.035)	6.84 (0.077)
Hours of sleep per night, %								
< 7 hours	25.9	28.2	12.8	17.1	34.6	32.0	38.3	44.2
7-9 hours	71.1	69.3	84.2	80.1	64.2	66.3	56.5	52.3
≥ 9 hours	3.0	2.5	3.0	2.8	1.2	1.8	5.2	3.5
Number of naps per week, %								
0 times per week	65.6	59.1	54.8	41.8	74.8	73.0	73.1	64.3
≥ 1 time per week	34.4	40.9	45.2	58.2	25.2	27.0	26.9	35.7
Observed apneas, %								
< 1 night a week	96.2	94.5	97.5	95.1	95.8	94.8	94.4	92.3
≥ 1 night a week	3.8	5.5	2.5	4.9	4.2	5.2	5.6	7.7
Habitual snoring, %								
< 3 nights a week	88.9	77.6	93.8	86.8	81.6	68.3	89.2	79.1
≥ 3 nights a week	11.1	22.4	6.2	13.2	18.4	31.7	10.8	20.9
Daytime sleepiness, %								
ESS[a] Score < 10	98.4	97.7	99.8	99.2	97.0	96.8	97.7	96.5
ESS Score ≥ 10	1.6	2.3	0.2	0.8	3.0	3.2	2.3	3.5
Overall sleep quality, %								
Adequate sleep quality	99.5	98.3	99.7	98.8	99.3	97.8	99.3	98.5
Poor sleep quality	0.5	1.7	0.3	1.2	0.7	2.2	0.7	1.5

[a]Epworth Sleepiness Scale

Table 3. Odds ratios (95 % CI) of type 2 diabetes in the total sample

	TOTAL			
	Unadjusted		Adjusted[b]	
	OR	95% CI	OR	95% CI
Sleep Duration				
Hours of sleep per night	0.93	(0.89, 0.98)	0.98	(0.93, 1.04)
Hours of sleep per night				
< 7 hours	1.12	(1.00, 1.25)	0.95	(0.85, 1.07)
7-9 hours		*Ref.*		
≥ 9 hours	0.85	(0.62, 1.17)	0.98	(0.68, 1.43)
Sleep Quality				
Number of naps per week				
0 times per week		*Ref.*		
≥ 1 time per week	**1.32**	**(1.14, 1.52)**	**1.20**	**(1.02, 1.40)**
Observed apneas				
< 1 night a week		*Ref.*		
≥ 1 night a week	**1.47**	**(1.20, 1.82)**	**1.32**	**(1.06, 1.63)**
Habitual snoring				
< 3 nights a week		*Ref.*		
≥ 3 nights a week	**2.31**	**(1.95, 2.73)**	**1.37**	**(1.14, 1.65)**
Daytime sleepiness				
ESS[a] Score < 10		*Ref.*		
ESS Score ≥ 10	**1.46**	**(1.13, 1.89)**	1.15	(0.85, 1.56)
Overall sleep quality				
Adequate sleep quality		*Ref.*		
Poor sleep quality	**3.32**	**(1.94, 5.68)**	**2.13**	**(1.24, 3.66)**

[a]Epworth Sleepiness Scale

Table 4. Odds ratios (95 % CI) of type 2 diabetes stratified by CARRS sites

	Chennai				Delhi				Karachi			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sleep Duration												
Hours of sleep per night	0.90	(0.82, 0.98)	0.94	(0.86, 1.03)	1.05	(0.97, 1.13)	**1.11**	**(1.03, 1.20)**	0.91	(0.86, 0.96)	0.97	(0.90, 1.04)
Hours of sleep per night												
< 7 hours	1.40	(0.58, 1.62)	1.11	(0.88, 1.40)	1.45	(0.82, 2.55)	**0.82**	**(0.73, 0.91)**	1.24	(1.09, 1.42)	1.08	(0.94, 1.24)
7-9 hours		*Ref.*				*Ref.*				*Ref.*		
≥ 9 hours	0.97	(0.58, 1.62)	0.82	(0.46, 1.46)	0.90	(0.79, 1.02)	1.81	(0.91, 3.59)	0.73	(0.40, 1.34)	0.87	(0.41, 1.83)
Sleep Quality												
Number of naps per week												
0 times per week		*Ref.*				*Ref.*				*Ref.*		
≥ 1 time per week	**1.69**	**(1.38, 2.08)**	1.32	(0.99, 1.77)	1.10	(0.92, 1.31)	0.94	(0.77, 1.15)	**1.51**	**(1.27, 1.81)**	**1.37**	**(1.11, 1.70)**
Observed apneas												
< 1 night a week		*Ref.*				*Ref.*				*Ref.*		
≥ 1 night a week	**2.00**	**(1.30, 3.07)**	**1.57**	**(1.04, 2.39)**	1.25	(0.87, 1.81)	1.26	(0.90, 1.75)	**1.40**	**(1.08, 1.82)**	1.07	(0.79, 1.43)
Habitual snoring												
< 3 nights a week		*Ref.*				*Ref.*				*Ref.*		
≥ 3 nights a week	**2.28**	**(1.64, 3.16)**	1.45	(1.00, 2.10)	**2.05**	**(1.53, 2.75)**	**1.35**	**(1.04, 1.75)**	**2.18**	**(1.77, 2.68)**	**1.36**	**(1.05, 1.77)**
Daytime sleepiness												
ESS[a] Score < 10		*Ref.*				*Ref.*				*Ref.*		
ESS Score ≥ 10	**3.47**	**(1.27, 9.49)**	**2.80**	**(1.09, 7.19)**	1.07	(0.75, 1.53)	1.01	(0.66, 1.53)	**1.57**	**(1.14, 2.17)**	1.19	(0.79, 1.79)
Overall sleep quality												
Adequate sleep quality		*Ref.*				*Ref.*				*Ref.*		
Poor sleep quality	**4.61**	**(2.08, 10.24)**	**3.48**	**(1.69, 7.16)**	**3.16**	**(1.47, 6.79)**	1.97	(0.98, 3.96)	2.12	(0.77, 5.87)	1.34	(0.34, 5.28)

[a]Epworth Sleepiness Scale

[b]Model adjusted for city, sex, age, religion, education, occupation, asset score, tobacco use, alcohol consumption, sedentary behavior, and BMI

Table 5. Odds ratios (95 % CI) of type 2 diabetes stratified by sex

	Male				Female			
	Unadjusted		Adjusted[b]		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sleep Duration								
Hours of sleep per night	0.91	(0.86, 0.96)	1.01	(0.95, 1.07)	0.95	(0.89, 1.02)	1.00	(0.92, 1.09)
Hours of sleep per night								
< 7 hours	1.13	(0.97, 1.33)	0.89	(0.76, 1.05)	1.10	(0.91, 1.33)	1.01	(0.83, 1.21)
7-9 hours		*Ref.*				*Ref.*		
≥ 9 hours	0.73	(0.47, 1.16)	0.85	(0.52, 1.41)	0.97	(0.66, 1.43)	1.09	(0.70, 1.71)
Sleep Quality								
Number of naps per week								
0 times per week		*Ref.*				*Ref.*		
≥ 1 time per week	**1.40**	**(1.18, 1.66)**	**1.22**	**(1.01, 1.48)**	**1.26**	**(1.06, 1.50)**	1.20	(0.99, 1.46)
Observed apneas								
< 1 night a week		*Ref.*				*Ref.*		
≥ 1 night a week	1.23	(0.84, 1.80)	1.01	(0.68, 1.49)	**1.64**	**(1.26, 2.15)**	**1.54**	**(1.13, 2.10)**
Habitual snoring								
< 3 nights a week		*Ref.*				*Ref.*		
≥ 3 nights a week	**2.11**	**(1.73, 2.58)**	1.23	(0.98, 1.53)	**2.58**	**(2.07, 3.21)**	**1.55**	**(1.24, 1.93)**
Daytime sleepiness								
ESS[a] Score < 10		*Ref.*				*Ref.*		
ESS Score ≥ 10	**1.61**	**(1.14, 2.28)**	1.13	(0.69, 1.85)	1.33	(0.84, 2.09)	1.19	(0.71, 1.99)
Overall sleep quality								
Adequate sleep quality		*Ref.*				*Ref.*		
Poor sleep quality	**3.20**	**(1.64, 6.24)**	1.91	(0.93, 3.94)	**3.46**	**(1.35, 8.83)**	**2.59**	**(1.13, 5.92)**

[a]Epworth Sleepiness Scale

[b]Model adjusted for city, sex, age, religion, education, occupation, asset score, tobacco use, alcohol consumption, sedentary behavior, and BMI

Table 6. Odds ratios (95 % CI) of type 2 diabetes stratified by age categories

	20-44 y				45-64 y				≥65 y			
	Unadjusted		Adjusted[b]		Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sleep Duration												
Hours of sleep per night	0.91	(0.84, 0.98)	0.93	(0.85, 1.01)	1.03	(0.97, 1.09)	1.05	(0.98, 1.12)	1.11	(0.99, 1.25)	1.12	(0.99, 1.27)
Hours of sleep per night												
< 7 hours	1.12	(0.91, 1.17)	1.13	(0.91, 1.41)	0.85	(0.74, 0.98)	0.88	(0.76, 1.01)	0.68	(0.48, 0.95)	0.79	(0.56, 1.11)
7-9 hours		*Ref.*				*Ref.*				*Ref.*		
≥ 9 hours	0.64	(0.35, 1.17)	0.81	(0.44, 1.50)	0.84	(0.47, 1.47)	1.07	(0.58, 1.98)	1.05	(0.49, 2.26)	1.62	(0.66, 4.01)
Sleep Quality												
Number of naps per week												
0 times per week		*Ref.*				*Ref.*				*Ref.*		
≥ 1 time per week	1.20	(0.93, 1.55)	1.16	(0.88, 1.52)	**1.24**	**(1.07, 1.44)**	**1.22**	**(1.06, 1.41)**	1.18	(0.79, 1.75)	1.30	(0.88, 1.92)
Observed apneas												
< 1 night a week		*Ref.*				*Ref.*				*Ref.*		
≥ 1 night a week	1.27	(0.88, 1.84)	1.06	(0.73, 1.55)	**1.54**	**(1.11, 2.13)**	**1.68**	**(1.22, 2.31)**	0.85	(0.37, 1.91)	0.81	(0.34, 1.92)
Habitual snoring												
< 3 nights a week		*Ref.*				*Ref.*				*Ref.*		
≥ 3 nights a week	**2.49**	**(1.88, 3.29)**	**1.83**	**(1.41, 2.37)**	**1.45**	**(1.21, 1.72)**	**1.22**	**(1.01, 1.48)**	**1.88**	**(1.09, 3.26)**	1.60	(0.89, 2.87)
Daytime sleepiness												
ESS[a] Score < 10		*Ref.*				*Ref.*				*Ref.*		
ESS Score ≥ 10	**1.88**	**(1.16, 3.07)**	**1.74**	**(1.03, 2.94)**	0.95	(0.57, 1.57)	0.86	(0.52, 1.40)	0.77	(0.30, 2.03)	1.15	(0.31, 4.28)
Overall sleep quality												
Adequate sleep quality		*Ref.*				*Ref.*				*Ref.*		
Poor sleep quality	**3.18**	**(1.47, 6.89)**	**2.29**	**(1.02, 5.14)**	**2.52**	**(1.23, 5.19)**	**2.15**	**(1.15, 4.01)**	1.94	(0.46, 8.15)	2.88	(0.58, 14.22)

[a]Epworth Sleepiness Scale

[b]Model adjusted for city, sex, age, religion, education, occupation, asset score, tobacco use, alcohol consumption, sedentary behavior, and BMI

Table 7. Odds ratios (95 % CI) of type 2 diabetes stratified by body mass index (BMI) categories

	< 23 kg/m^2				23-24.9 kg/m^2				25-29.9 kg/m^2				≥ 30 kg/m^2			
	Unadjusted		Adjusted[b]		Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sleep Duration																
Hours of sleep per night	0.93	(0.86, 1.00)	1.01	(0.93, 1.09)	0.91	(0.81, 1.03)	1.04	(0.91, 1.19)	0.94	(0.86, 1.03)	1.00	(0.91, 1.09)	0.95	(0.87, 1.04)	0.99	(0.92, 1.07)
Hours of sleep per night																
< 7 hours	1.26	(1.05, 1.52)	1.03	(0.83, 1.27)	1.00	(0.69, 1.44)	0.70	(0.48, 1.00)	1.11	(0.92, 1.35)	0.98	(0.81, 1.19)	1.09	(0.88, 1.36)	1.05	(0.86, 1.29)
7-9 hours		*Ref.*				*Ref.*				*Ref.*				*Ref.*		
≥ 9 hours	0.96	(0.50, 1.84)	1.01	(0.55, 1.88)	0.94	(0.48, 1.84)	1.03	(0.49, 2.17)	1.12	(0.73, 1.73)	1.11	(0.71, 1.73)	0.72	(0.37, 1.40)	0.79	(0.38, 1.61)
Sleep Quality																
Number of naps per week																
0 times per week		*Ref.*				*Ref.*				*Ref.*				*Ref.*		
≥ 1 time per week	1.20	(0.94, 1.53)	1.00	(0.80, 1.24)	**1.40**	**(1.03, 1.90)**	1.37	(0.93, 2.02)	**1.28**	**(1.08, 1.51)**	1.25	(0.98, 1.58)	1.20	(0.97, 1.48)	1.22	(0.99, 1.50)
Observed apneas																
< 1 night a week		*Ref.*				*Ref.*				*Ref.*				*Ref.*		
≥ 1 night a week	1.40	(0.88, 2.23)	1.33	(0.81, 2.18)	1.08	(0.48, 2.43)	1.00	(0.46, 2.19)	1.12	(0.76, 1.65)	1.17	(0.85, 1.61)	1.63	(0.99, 2.70)	**1.74**	**(1.03, 2.97)**
Habitual snoring																
< 3 nights a week		*Ref.*				*Ref.*				*Ref.*				*Ref.*		
≥ 3 nights a week	**2.88**	**(2.16, 3.86)**	**2.01**	**(1.50, 2.69)**	**1.70**	**(1.15, 2.51)**	1.01	(0.70, 1.47)	**1.86**	**(1.39, 2.49)**	1.32	(0.95, 1.84)	**1.70**	**(1.23, 2.34)**	1.36	(0.94, 1.96)
Daytime sleepiness																
ESS[a] Score < 10		*Ref.*				*Ref.*				*Ref.*				*Ref.*		
ESS Score ≥ 10	1.29	(0.51, 3.26)	1.19	(0.34, 4.22)	1.98	(0.86, 4.56)	1.69	(0.56, 5.09)	1.38	(0.83, 2.30)	1.12	(0.68, 1.85)	1.45	(0.72, 2.90)	1.05	(0.56, 1.98)
Overall sleep quality																
Adequate sleep quality		*Ref.*				*Ref.*				*Ref.*				*Ref.*		
Poor sleep quality	2.74	(0.78, 9.63)	2.40	(0.45, 12.66)	2.36	(0.77, 7.25)	1.22	(0.43, 3.46)	**2.76**	**(1.37, 5.56)**	**2.54**	**(1.35, 4.78)**	**3.11**	**(1.20, 8.04)**	**2.46**	**(1.02, 5.91)**

[a]Epworth Sleepiness Scale

Table 8. Contributions to type 2 diabetes prediction in the CARRS study

	Unadjusted		Adjusted[c]		*c*-Statistic
	OR	**(95% CI)**	**OR**	**(95% CI)**	
Base model[a]	N/A		N/A		0.768
Base model +					
Hours of sleep per night					0.768
< 7 hours	1.12	(1.00, 1.25)	0.95	(0.85, 1.07)	
≥ 9 hours	0.85	(0.62, 1.17)	0.98	(0.68, 1.43)	
Number of naps per week	1.32	(1.14, 1.52)	**1.20**	**(1.02, 1.40)**	0.769
Observed apneas	1.47	(1.20, 1.82)	**1.32**	**(1.06, 1.63)**	0.769
Habitual snoring	2.31	(1.95, 2.73)	**1.37**	**(1.14, 1.65)**	0.769
Daytime sleepiness[b]	1.46	(1.13, 1.89)	1.15	(0.85, 1.56)	0.768
Overall sleep quality	3.32	(1.94, 5.68)	**2.13**	**(1.24, 3.66)**	0.768
All sleep variables	N/A		N/A		0.770

[a]Base model defined as: city, sex, age, religion, education, occupation, asset score, tobacco use, alcohol consumption, sedentary behavior, and BMI

[b]Measured by the Epworth Sleepiness Scale

[c]Model adjusted for city, sex, age, religion, education, occupation, asset score, tobacco use, alcohol consumption, sedentary behavior, and BMI

Supplementary Table 1. Weighted sociodemographic, behavioral, and physiological characteristics of CARRS participants in Chennai, Delhi, and Karachi, 2011

	TOTAL		Chennai		Delhi		Karachi	
	n=	12,820	n=	5,525	n=	4,300	n=	2,995
	n	%	n	%	n	%	n	%
Outcome								
Type 2 diabetes (FBG ≥ 126 mg/dl, Hba1c ≥ 6.5%, or medication for diabetes), %								
No	9,926	77.4	4,379	79.3	3,066	71.3	2,481	82.8
Yes	2,894	22.6	1,145	20.7	1,234	28.7	514	17.2
Sociodemographic risk factors								
Sex, %								
Male	5,801	45.2	2,357	42.7	2,097	48.8	1,347	45.0
Female	7,019	54.8	3,168	57.3	2,203	51.2	1,648	55.0
Age, %								
20-44 y	8,229	64.2	3,809	68.9	2,581	60.0	1,839	61.4
45-64 y	3,920	30.6	1,484	26.9	1,496	34.8	940	31.4
≥65 y	671	5.2	231	4.2	223	5.2	216	7.2
Religion, %								
Hindu	7,721	60.2	4,605	83.4	3,086	71.8	29	1.0
Muslim	3,620	28.2	248	4.5	791	18.4	2,580	86.1
Other	1,479	11.5	671	12.1	422	9.8	386	12.9
Education, %								
None	2,045	16.0	496	9.0	696	16.2	852	28.5
Primary schooling	609	4.8	380	6.9	156	3.6	74	2.5
High schooling	7,977	62.2	4,014	72.7	2,328	54.1	1,635	54.6
College degree or higher	2,189	17.1	635	11.5	1,120	26.0	434	14.5
Occupation, %								
Not Working (housewife, student, retired, unemployed)	6,913	53.9	2,909	52.7	2,163	50.3	1,841	61.5
Manual labor	2,790	21.8	1,473	26.7	819	19.0	498	16.6
Skilled labor	2,739	21.4	1,092	19.8	1,090	25.3	556	18.6
White-collar worker	378	2.9	55	0.9	190	5.3	101	3.3
Asset Score, %								
0-3	4,318	33.7	1,950	35.3	1,406	32.7	961	32.1
4-5	3,984	31.1	1,940	35.1	949	22.1	1,095	36.6
6-10	4,518	35.2	1,635	29.6	1,945	45.2	939	31.3
Behavioral risk factors								
Tobacco use, %								
Never user	9,755	76.1	4,357	44.7	3,217	33.0	2,181	22.4
Ever user	3,065	23.9	1,168	38.1	1,083	35.3	815	26.6
Alcohol consumption, %								
Never drinker	10,838	84.5	4,402	79.7	3,534	82.2	2,902	96.9
Ever drinker	1,982	15.5	1,123	20.3	766	17.8	93	3.1
Sedentary behavior, %								
< 6 hours of sitting	6,593	51.4	1,565	23.7	3,208	48.7	1,820	27.6
≥ 6 hours of sitting	6,227	48.6	3,960	63.6	1,092	17.5	1,175	18.9
Physiological risk factors								
Body mass index, %								
Underweight, < 23 kg/m^2	4,268	33.3	1,699	30.8	1,494	34.7	1,074	35.9
Normal, 23-24.9 kg/m^2	1,946	15.2	881	16.0	635	14.8	429	14.3
Overweight, 25-29.9 kg/m^2	4,358	34.0	2,051	37.1	1,392	32.4	915	30.5
Obese, ≥ 30 kg/m^2	2,249	17.5	893	16.2	778	18.1	577	19.3
Sleep duration and quality								
Mean hours of sleep per night (SE)	7.26	0.060	7.66	0.055	6.92	0.039	7.02	0.036
Hours of sleep per night, %								
< 7 hours	3,391	26.5	758	13.7	1,455	33.8	1,179	39.3
7-9 hours	9,061	70.7	4,604	83.3	2,787	64.8	1,670	55.8
≥ 9 hours	367	2.9	163	2.9	58	1.3	146	4.9
Number of naps per week, %								
0 times per week	8,217	64.1	2,880	52.1	3,192	74.2	2,145	71.6
≥ 1 time per week	4,603	35.9	2,645	47.9	1,108	25.8	850	28.4
Observed apneas, %								
< 1 night a week	12,283	95.8	5,360	97.0	4,108	95.5	2,815	94.0
≥ 1 night a week	537	4.2	165	3.0	192	4.5	180	6.0
Habitual snoring, %								
< 3 nights a week	11,065	86.3	5,101	92.3	3,344	77.8	2,620	87.5
≥ 3 nights a week	1,755	13.7	424	7.7	955	22.2	375	12.5
Daytime sleepiness, %								
ESS[a] Score < 10	12,593	98.2	5,504	99.6	4,167	96.9	2,921	97.5
ESS Score ≥ 10	227	1.8	20	0.4	133	3.1	74	2.5
Overall sleep quality, %								
Adequate sleep quality	12,720	99.2	5,500	99.6	4,250	98.8	2,970	99.2
Poor sleep quality	100	0.8	24	0.4	50	1.2	25	0.8

[a]Epworth Sleepiness Scale

[b]Rao-Scott chi-square values reported

[c]Chi-square values reported

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Chapter IV. Public Health Recommendations

A. Conclusion

While sleep duration was not associated with prevalent diabetes, measures of sleep quality were associated with prevalent diabetes in the total sample and in various subgroups. Specifically, daytime napping, observes apneas, habitual snoring, and overall sleep quality were significantly associated with type 2 diabetes in several models, and point estimates were largely positive and consistently moderate across the examined subgroups. Our findings are consistent with the hypothesis that measures of sleep quality may be contributing to diabetes in urban South Asians, but we find no evidence that sleep duration impacts diabetes in this population. However, we found very small potential value of using sleep quality to discriminate individuals who have type 2 diabetes from those who do not have diabetes above and beyond traditional risk factors of city, sex, age, religion, education, occupation, asset score, tobacco use, alcohol consumption, sedentary behavior, and BMI.

Significant and largely consistent findings of sleep quality in subgroups defined by city, age, and sex suggest the robustness of findings across the population. However, there were some noteworthy findings that could be explored further in prospective examination. Chennai reported greater associations of observed sleep apneas, daytime sleepiness, and overall sleep quality with type 2 diabetes. However, Delhi and Karachi reported a higher and significant association of habitual snoring with type 2 diabetes compared to Chennai. Karachi also reported a greater significant association of daytime napping with type 2 diabetes. Daytime napping showed a more significant association with type 2 diabetes among males, while observed apneas, habitual snoring and overall sleep quality were more likely to be significantly associated at a higher level with type 2

diabetes among females. Stratification by age categories led to the distinction that among 20-44 year olds, daytime sleepiness was significantly associated with type 2 diabetes while daytime napping and observed apneas were significantly associated with type 2 diabetes only among the 45-64 year old population after adjustment for potential covariates. Habitual snoring was significantly associated with type 2 diabetes among those with BMI < 23 while observed apneas was significantly associated with type 2 diabetes in the obese population. Overall sleep quality was significantly associated with type 2 diabetes in the overweight and obese populations indicating that these two populations are more likely to contribute to the significant relationship of overall sleep quality with type 2 diabetes in the total population.

Future research in the area may benefit from focusing on improving the measurement of sleep quality, prospective data to understand the directionality of the associations observed, and biological mechanisms linking sleep quality to diabetes.

B. Implications for the Future

Since sleep duration was determined to have no association with type 2 diabetes in our South Asian sample, recommendations based on an adequate amount of sleep to prevent type 2 diabetes are not warranted at this time. Instead, our preliminary findings suggest that future public health efforts around diabetes may benefit from considering sleep quality.

Individual sleep quality exposures such as habitual snoring and sleep apneas as less likely to be fixed without surgery or medication, and thus are not likely to be scalable strategies for diabetes prevention. The effects of fixing these sleep habits through surgery or medication on type 2 diabetes risk remains to be determined, but a more probable

cause for the link between the exposures and type 2 diabetes outcome, may lie in the interaction between biological and lifestyle factors. Thus, one recommendation would be further biological and environmental interaction studies that try to elucidate the causal pathway by which sleep quality exposures and type 2 diabetes are related.

Further research on the ways in which individuals may attain better quality sleep could be another possibility for public health oriented research. Measures of daytime sleepiness and daytime napping are considered measures of poor sleep quality because they reflect that sufficient sleep was not attained during the night. Understanding how environments (e.g., noise, light) or lifestyles (e.g., consuming alcohol at night, eating dinner late at night) be adjusted to promote better night time sleep is a potential area for public health impact on this issue.

A second recommendation would be to use these sleep quality exposures as screening factors for type 2 diabetes, especially in those subgroups that showed a stronger and more significant association of sleep quality exposures with type 2 diabetes. In particular, females showed a stronger association of daytime napping, sleep apneas, and habitual snoring with type 2 diabetes. Habitual snoring, in particular showed a strong positive relationship in females, such that the odds of type 2 diabetes in those who snored more than or equal to 3 nights a week was approximately three times the odds compared to the reference group. Habitual snoring may prove to be a strong screening factor for type2 diabetes in the future, though a thorough examination of the clinical feasibility in using this variable as well as specificity and sensitivity analyses must be conducted before putting it in user. The younger population also exhibited significant associations with the sleep quality exposures, indicating a higher, independent association among 20-

64 year olds. However, those above 65 years of age did not display significant associations of the sleep quality exposures with prevalent diabetes, indicating that age may be stronger risk factor than sleep quality for type 2 diabetes in the elderly population. Therefore, utilizing daytime napping, sleep apneas, and habitual snoring as screening variables would only be relevant in a younger population. Thus, habitual snoring and observed sleep apneas may be used to identify individuals at potentially high-risk for diabetes, and might be fruitfully incorporated into screening questionnaires to determine whether further testing is required for diabetes status. This may be particularly important to younger age groups, among whom diabetes status may not be routinely screened.

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