CHAPTER 25

IMPACT OF SLEEP AND CIRCADIAN DISTURBANCES ON GLUCOSE METABOLISM AND TYPE 2 DIABETES

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SUMMARY

The term "sleep disturbance" is widely used to refer to a variety of conditions, including sleep insufficiency, sleep fragmentation, sleep disorders, such as sleep apnea, and misaligned sleep, as occurs in shift workers. Insufficient sleep and sleep fragmentation are linked to abnormal glucose metabolism, insulin sensitivity reduction of 20%–30%, and increased diabetes risk. Well-controlled laboratory studies have provided insights regarding the underlying mechanisms. Multiple large prospective studies have found that that these sleep disturbances increase the risk of incident diabetes by as much as 30%–50%. Obstructive sleep apnea (OSA), which combines sleep fragmentation and hypoxemia, has been identified as a risk factor for insulin resistance and diabetes. OSA is highly prevalent in patients with type 2 diabetes, affecting roughly two out of three patients, and its severity correlates with glycemic control. Whether glycemic control can be improved by treating OSA remains controversial. Sleep disturbances during pregnancy are linked to gestational diabetes and hyperglycemia, and there is evidence for potential adverse effects on maternal and fetal health. Evidence from animal models has identified disruption of the circadian system as a putative risk factor for adverse metabolic outcomes. Shift work, a condition of chronic circadian disruption, is linked to weight gain and incident obesity and diabetes.

As sleep disturbances are increasingly common in modern society and may play a role in the epidemic of type 2 diabetes, strategies to prevent diabetes or reduce its severity should consider optimizing sleep health in at-risk populations. Intervention studies demonstrating that treating sleep disturbances may help prevent diabetes or improve glycemic control are lacking but have become an area of intense research.

INTRODUCTION

Humans spend approximately one-third of their lifetime sleeping. Sleep is viewed as a state of energy conservation and replenishment of energy stores. Normal human sleep is composed of rapid-eye-movement (REM) sleep and stages N1, N2, and N3 of non-REM (NREM) sleep. N3 is the deepest stage of NREM sleep and is also known as slow wave sleep (SWS). Oscillations between REM and NREM stages occur roughly every 90 minutes and repeat four to six times throughout the night.

This important physiologic process is controlled in part by an internal circadian clock and in part by a homeostatic mechanism where the pressure for sleep increases in proportion to the duration of prior wakefulness. Human behavior may override these physiologic control mechanisms, resulting in alterations of sleep duration, quality, or timing. Increasing prevalence of sleep disorders, such as obstructive sleep apnea (OSA), parallels the increase in obesity rates. According to the definition proposed by the National Heart, Lung, and Blood Institute, "sleep deficiency" occurs when an individual has insufficient sleep, poor sleep, a diagnosed sleep disorder, or abnormal timing of sleep (1). Multiple reviews (2,3,4) have elected to use the term "sleep disturbances" to designate insufficient or excessive sleep duration, poor self-reported sleep quality, or a diagnosed sleep disorder, such as OSA. Experimental and epidemiologic data have linked insufficient sleep duration, abnormal sleep timing, and poor sleep quality to insulin resistance, increased risk of obesity, and diabetes. In patients with type 2 diabetes, sleep disturbances may adversely affect glycemic control.

OSA is well recognized as a risk factor for insulin resistance, independent of the degree of obesity, and is highly prevalent in patients with type 2 diabetes. OSA is a complex disorder involving intermittent hypoxia, sleep fragmentation, low amounts of SWS, and reduced total sleep

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time. Well-documented studies in animal models indicate that intermittent hypoxia is one of the mechanisms linking OSA to abnormal glucose metabolism. Whether treatment of OSA with continuous positive airway pressure (CPAP) may improve glucose metabolism remains controversial.

Pregnant women are a special population that may be particularly vulnerable to adverse effects of abnormal sleep. Sleep disturbances in pregnancy are associated with adverse maternal and fetal outcomes, including gestational diabetes, preeclampsia, and premature delivery.

Because of these potential complications, the body of literature on this topic has grown rapidly.

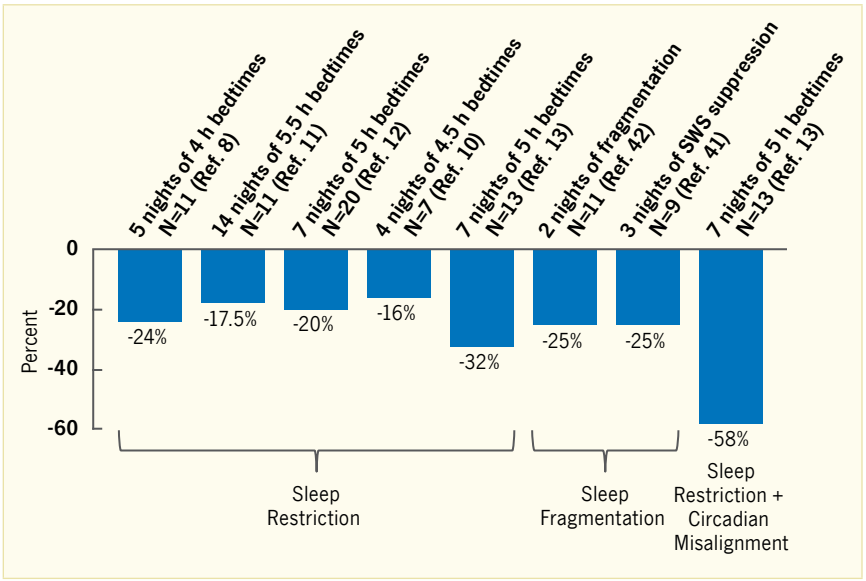
Besides sleep duration, sleep quality, and OSA, emerging evidence from well-controlled clinical research studies has revealed that conditions where the behavioral sleep/wake cycle is not in synchrony with the biological circadian timing system, so-called "circadian misalignment," may result in impaired glucose tolerance (IGT). In cross-sectional analyses, circadian misalignment is associated with increased diabetes risk in nondiabetic individuals and with poor glycemic control in patients with established type 2 diabetes.

This chapter summarizes the evidence linking different types of sleep disturbances to abnormal glucose metabolism, including insufficient sleep, sleep fragmentation, OSA, and circadian misalignment. Potential underlying mechanisms are discussed, as well as findings from prospective and cross-sectional epidemiologic studies and from intervention studies.

INSUFFICIENT SLEEP

While it is important to note that the amount of sleep that optimizes physical and mental health is an individual characteristic that tends to decrease with age, it is generally considered that 7–8 hours of sleep nightly is adequate for most adults (5). Partly due to changes in work and social demands, sleep duration in the United States has been declining (6). In data from 110,441 adults participating in the National Health Interview Surveys 2004–2007, the prevalences of self-reported short sleep duration were 7.8% for sleeping ≤5 hours and 20.5% for sleeping 6 hours per day (7). In 2009, >30% of U.S. men and women age 30–65 years reported sleeping <6 hours per night on workdays (6).

FIGURE 25.1. Reduction in Insulin Sensitivity as Assessed by Intravenous Glucose Tolerance Test From Laboratory Studies Involving Sleep Restriction, Sleep Fragmentation, and Intermittent Hypoxia



h, hour; SWS, slow wave sleep.

SOURCE: References are listed within the figure.

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Insufficient sleep has been linked to reduced insulin sensitivity and increased risk of type 2 diabetes, both in laboratory studies in healthy humans and in epidemiologic studies. A causative role of partial sleep restriction in promoting alterations in glucose metabolism was first established in 1999 (8). Intravenous glucose tolerance testing (IVGTT) following sleep restriction to 4 hours per night for five nights resulted in a 24% decrease in insulin sensitivity (Figure 25.1), as well as a 30% decrease in the acute insulin response to intravenous glucose (8,9). Moreover, an increase in the HOMA (homeostatic model assessment, an index of insulin resistance) response to breakfast was observed on the following day and occurred despite similar insulin secretory responses. These findings indicated that a state of sleep debt caused a decrease in insulin sensitivity that was not compensated by increased insulin release, leading to a more than 40% decrease in glucose tolerance compared to the fully rested condition.

Several subsequent, well-controlled experimental studies in healthy human subjects involving sleep restriction to 4–5.5 hours per night for 5–14 nights and assessments of glucose metabolism by IVGTT or euglycemic-hyperinsulinemic clamp have confirmed a reduction of insulin sensitivity ranging from 16% to 32% in response to sleep restriction without simultaneous increases in insulin levels, resulting in reduced glucose tolerance and an increased risk of diabetes (Figure 25.1) (10,11,12,13). A few studies that included assessments after sleep recovery found that the metabolic disturbances induced by sleep restriction were at least partially reversible (improved glucose tolerance as assessed by IVGTT (8) and a reduction in the insulin-to-glucose ratio (14)).

Further, 2 weeks of sleep extension in habitual short sleepers resulted in changes in indices of fasting insulin sensitivity that were correlated with the amount of sleep extension, with those obtaining more sleep having the largest increases in insulin sensitivity (15). Lastly, a small study indicated that three nights of in-laboratory "catch-up" sleep in men with chronic, repetitive, lifestyle-driven sleep restriction led to improved insulin sensitivity as assessed by a 2-hour frequently sampled glucose tolerance test (16).

Multiple cross-sectional epidemiologic studies have indicated that self-reported short sleep duration (usually <6 hours per night) is associated with increased odds of prediabetes and diabetes. Relevant population-based studies examining associations between these conditions of abnormal glucose tolerance and self-reported short sleep duration in the United States and Canada are listed in Tables 25.1 and 25.2. Importantly, 12 of 16 large prospective studies with a follow-up duration of 2–32 years have observed that short sleep duration is associated with an increased risk of incident diabetes (Table 25.3) (17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32). All five studies conducted in the United States, including the Nurses' Health Study (17), National Health and Nutrition Examination Survey (NHANES) I (20), NIH-AARP Diet and Health Study (24), Massachusetts Male Aging Study (25), and Millennium Cohort by the Department of Defense (28), have found the associations. A meta-analysis including 11 of these 16 studies (total 447,124 participants) concluded that short sleep (≤5–6 hours per night) predicts the development of type 2 diabetes with a relative risk (RR) of 1.33 (95% confidence interval [CI] 1.20–1.48) (21). In addition, multiple studies, the majority of which were conducted in the United States, have found that long sleep duration (>8–9 hours per night) also predicts incident diabetes (Table 25.3) (17,20,22,24,25,30), with a meta-analysis indicating a pooled relative risk of 1.48 (33). This suggests a U-shaped relationship between sleep duration and risk of incident diabetes. The main limitation of these studies is that sleep duration was self-reported.

Only a few studies have examined the impact of insufficient sleep on glycemic control in patients with established type 2 diabetes. A questionnaire survey study of 161 African Americans with type 2 diabetes found that 3 hours of perceived sleep debt per day (i.e., a self-report of insufficient sleep duration) predicted a glycosylated hemoglobin (A1c) level of 1.1% above the median (34). The magnitude of this difference is comparable to the effect size of several U.S. Food and Drug Administration-approved diabetes medications. A U-shaped relationship may exist between sleep duration and glycemic control, with excessive sleep duration predicting poorer glycemic control. A large cross-sectional study of 4,870 Japanese participants revealed higher A1c levels in patients with self-reported sleep duration <5.5 hours per night and ≥8.5 hours per night

TABLE 25.1. Studies Exploring the Relationship Between Self-Reported Sleep Duration and Dysglycemia

STUDY, YEARS (REF.)	POPULATION	SAMPLE SIZE	STUDY DESIGN	OUTCOME	RESULTS
NHANES, 2005–2006, 2007–2008 (44)	Age ≥30 years	2,285	Cross-sectional	Clinically identified prediabetes, defined as FPG 100–125 mg/dL, plus physician diagnosis of prediabetes	Sleeping ≤5 h/night was associated with clinically identified prediabetes, OR 2.06 (95% CI 1.00–4.22), compared to sleeping 7 h/night. Sleeping ≥9 h/night was not associated with prediabetes.
Sleep Heart Health Study, 1995–1998 (374)	Mean age 70.2 years	1,486	Cross-sectional	IGT, defined as 2-hour glucose value 140–199 mg/dL, post 75 g glucose load	Sleeping ≤5 h/night was not associated with IGT. Sleeping 6 h/night was associated with IGT, OR 1.58 (95% CI 1.15–2.18). Sleeping ≥9 h/night was associated with IGT, OR 1.88 (95% CI 1.21–2.91).
Western New York Health Study, 1996–2004 (375)	Age 35–79 years	1,455 (91 cases; 272 controls)	Nested case-control within a 6-year longitudinal cohort	IFG at a follow-up examination, defined as FPG 100–125 mg/dL	Sleeping <6 h/night was associated with development of IFG, OR 3.0 (95% CI 1.05–8.59). Sleeping >8 h/night was not associated with IFG.
Quebec Family Study, 1989–2001 (30)	French Canadians from Quebec area, age 21–64 years	276	Longitudinal 6-year follow-up	Type 2 diabetes, defined as FPG ≥126 mg/dL or 2-hour glucose ≥200 mg/dL, post 75 g glucose challenge IGT, defined as 2-hour glucose value 140–199 mg/dL, post 75 g glucose load	Sleeping ≤6 h/night was associated with type 2 diabetes/IGT, OR 2.78 (95% CI 1.61–4.12). Sleeping ≥9 h/night was associated with type 2 diabetes/IGT, OR 2.54 (95% CI 1.42–3.53).

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions.* CI, confidence interval; FPG, fasting plasma glucose; h, hour; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

SOURCE: References are listed within the table.

TABLE 25.2. Cross-Sectional Studies Exploring Associations Between Self-Reported Sleep Duration and Diabetes

STUDY, YEARS (REF.)	POPULATION	SAMPLE SIZE	OUTCOME	RESULTS
National Sleep in America Survey, 2003 (46)	Age 55–84 years	1,506	Self-reported diabetes	Sleeping <6 h/night was not associated with diabetes.
National Health Interview Survey-Sample Adult Files (NHIS-SAF), 2004–2007 (7)	Age ≥18 years; mean age 46 years	110,441	Self-reported diabetes	Compared to sleeping 7 h, sleeping ≤5 h and 6 h were associated with diabetes, OR 1.19 (95% CI 1.07–1.33) and OR 1.09 (95% CI 1.01–1.19), respectively. Sleeping 8 h and ≥9 h were associated with diabetes, OR 1.12 (95% CI 1.03–1.20) and OR 1.25 (95% CI 1.13–1.38), respectively.
NHANES, 2007–2008 (376)	Mean age 49.3 years	5,649	Self-reported diabetes	Sleeping <5 h/night was associated with self-reported diabetes, OR 1.76 (95% CI 1.13–2.74). Sleeping ≥9 h/night was not associated with self-reported diabetes.
National Health Interview Survey, 2004–2011 (377)	Mean age 50.6 years	130,943 (13% non-Hispanic black)	Self-reported diabetes	In non-Hispanic whites, sleeping <7 h/night and >7 h/night were associated with diabetes, PR 1.49 (95% CI 1.40–1.58) and PR 1.32 (95% CI 1.25–1.40), respectively. In non-Hispanic blacks, corresponding PRs were 1.21 (95% CI 1.09–1.34) and 1.11 (95% CI 1.00–1.23), respectively. Racial/ethnic differences in short sleep-diabetes association were nonsignificant after adjusting for socioeconomic status.
Behavioral Risk Factor Surveillance System, 2010 (378)	14 U.S. states, age ≥45 years	54,269	Self-reported diabetes	Sleeping ≤6 h/day was associated with diabetes, OR 1.25 (95% CI 1.12–1.40). Sleeping ≥10 h/day was associated with diabetes, OR 1.79 (95% CI 1.46–2.20).
National Health Interview Survey, 2010 (379)	Age 18–85 years	29,818 (15% non-Hispanic black)	Self-reported diabetes	In non-Hispanic whites, sleeping ≤5 h or ≥9 h was associated with diabetes, OR 1.87 (95% CI 1.57–2.24) and OR 2.33 (95% CI 1.98–2.73), respectively. In non-Hispanic blacks, the corresponding ORs were 1.66 (95% CI 1.19–2.30) and 1.68 (95% CI 1.21–2.33), respectively. Greater diabetes risk was seen in non-Hispanic black short and long sleepers compared to non-Hispanic whites.

CI, confidence interval; h, hour; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PR, prevalence ratio.

SOURCE: References are listed within the table.

TABLE 25.3. Prospective Studies Exploring the Relationship Between Self-Reported Sleep Duration and Incident Diabetes

STUDY/LOCATION, YEARS (REF.)	POPULATION	SAMPLE SIZE	FOLLOW-UP (YEARS)	OUTCOME AND ASSESSMENT	RESULTS
Nurses' Health Study, 1986–1996 (17)	Age 30–55 years	70,026	10	Questionnaire: symptoms of diabetes, plus FPG ≥140 mg/dL or random glucose ≥200 mg/dL, two elevated glucose levels on two occasions (fasting or random), or use of hypoglycemic medication	Sleeping ≤5 h/day was associated with increased diabetes risk, RR 1.57 (95% CI 1.28–1.92), but became nonsignificant after adjusting for BMI. Sleeping ≤5 h/day was associated with increased risk of symptomatic diabetes, even after adjusting for BMI, RR 1.34 (95% CI 1.04–1.72). Sleeping ≥9 h/day was associated with diabetes risk, RR 1.29 (95% CI 1.05–1.59).
Insulin Resistance Atherosclerosis Study, 1992–1999 (18)	Multiethnic: non-Hispanic white, African American, and Hispanic; age 40–69 years	900	5	Report of using diabetes medications OGTT in those not taking diabetes medication—diabetes defined as 2-hour glucose value ≥200 mg/dL	Sleeping ≤7 h/night was associated with diabetes risk, OR 2.36 (95% CI 1.21–3.79) in non-Hispanic whites and Hispanics, but not in African Americans. Sleeping ≥9 h/night was not associated with diabetes risk.
Sweden, 1969–2001 (19)	Mean age 46.8 years	1,462	32	Report of physician diagnosis of diabetes or use of medication, FPG ≥140 mg/dL on two separate occasions, or diagnosis documented in death certificate	No association between sleep duration (number of hours or quintiles of long versus short sleep) and diabetes risk.
NHANES I, 1982–1984, 1986–1987, and 1992 (20)	Mean age 56.1 years	8,992	8–10	Report of diabetes diagnosis by physician, hospital diagnosis, or cause of death	Sleeping ≤5 h/day was associated with increased diabetes risk, OR 1.47 (95% CI 1.03–2.09). Sleeping ≥9 h/day was associated with diabetes risk, OR 1.52 (95% CI 1.06–2.18).

Table 25.3 continues on the next page.

TABLE 25.3. (continued)

STUDY/LOCATION, YEARS (REF.)	POPULATION	SAMPLE SIZE	FOLLOW-UP (YEARS)	OUTCOME AND ASSESSMENT	RESULTS
The 45 and UP Study, 2007–2010 (21)	Australian prospective cohort, mean age 62.3 years	241,949	2–3	Hospital admissions data and mortality data	Sleeping <6 h/day was associated with increased diabetes risk, HR 1.29 (95% CI 1.08–1.53). Sleeping ≥9 h/day was not associated with diabetes risk.
Finnish Diabetes Prevention Study, 1993–2000 (22)	Mean age 55.2 years	522	7	OGTT with FPG ≥140 mg/dL or 2-hour glucose value ≥200 mg/dL	Sleeping ≤6.5 h/day was not associated with diabetes risk. Sleeping 9–9.5 h and ≥10 h were associated with diabetes risk in the control group, HR 2.29 (95% CI 1.38–3.80) and HR 2.74 (95% CI 1.67–4.50), respectively. These sleep durations were not associated with diabetes risk in the lifestyle intervention group.
European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study, Germany, 2004–2007 (23)	Age 35–65 years	23,620	7.8	Report of diabetes diagnosis verified by chart review	No associations were found between sleep duration and diabetes risk.
National Institutes of Health-AARP Diet and Health Study, 1996–2006 (24)	Age 50–71 years	174,542	3–10	Report of diabetes diagnosis by physicians	Sleeping <5 h and 5–6 h were associated with diabetes risk, OR 1.46 (95% CI 1.31–1.63) and OR 1.11 (95% CI 1.06–1.16), respectively. Sleeping ≥9 h was associated with diabetes risk, OR 1.11 (95% CI 0.99–1.24).
Massachusetts Male Aging Study, 1987–2004 (25)	Age 40–70 years	1,139	15–16	Report of diabetes diagnosis by physician	Sleeping ≤5 h was associated with diabetes risk, RR 1.95 (95% CI 0.95–4.01). This became nonsignificant after adjusting for testosterone level. Sleeping >8 h was associated with diabetes risk, RR 3.12 (95% CI 1.53–6.37), and remained significant after adjusting for testosterone.
High-risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP), 1999–2004 (26)	Mean age 38.2 years	6,509	4.2	Report of diabetes diagnosis or using medication, FPG ≥140 mg/dL, or random glucose ≥200 mg/dL	No associations were found between sleep duration and diabetes risk.
Sweden, 1983–1995 (27)	Age 45–65 years	2,663	12	Questionnaire ascertained by using two questions	Sleeping ≤5 h was associated with diabetes risk in men only, RR 2.8 (95% CI 1.1–7.3). No associations were found between sleep duration and diabetes risk in women.
Millennium Cohort by the Department of Defense, 2001–2007 (28)	Mean age 36.7 years	47,093	6	Report of diabetes diagnosis	Sleeping <5 h and 5 h were associated with increased diabetes risk, OR 2.04 (95% CI 1.49–2.81) and OR 1.46 (95% CI 1.15–1.84), respectively. Sleeping ≥8 h was not associated with diabetes risk.
Japan, 2003–2008 (29)	Government employees in Sapporo, Japan, age 35–55 years	3,570	3–5	Having been prescribed diabetes medication or FPG ≥126 mg/dL	Sleeping ≤5 h was associated with diabetes risk, OR 5.37 (95% CI 1.38–20.91), in those without family history of diabetes. No association was found in those with family history of diabetes.
Quebec Family Study, 1989–2001 (30)	Mean age 38.6 years	276	6	Type 2 diabetes, defined as FPG ≥126 mg/dL, 2-hour glucose value ≥200 mg/dL after OGTT, or use of insulin or oral hypoglycemic agents IGT, defined as 2-hour glucose value ≥140 mg/dL in those not meeting diabetes criteria	Sleeping ≤6 h was associated with type 2 diabetes/IGT risk, RR 2.78 (95% CI 1.61–4.12). Sleeping ≥9 h was associated with type 2 diabetes/IGT, RR 2.54 (95% CI 1.42–3.53).

Table 25.3 continues on the next page.

TABLE 25.3. (continued)

STUDY/LOCATION, YEARS (REF.)	POPULATION	SAMPLE SIZE	FOLLOW-UP (YEARS)	OUTCOME AND ASSESSMENT	RESULTS
Spain, 1997–2010 (31)	Population-based study, age 18–65 years	1,145	11	Fasting and 2-hour glucose values from OGTT	Sleeping ≤7 h compared to ≥8 h was associated with diabetes at 6-year follow-up, OR 1.96 (95% CI 1.10–3.50). The effect was not independent of obesity. No association was found at 11-year follow-up. Sleeping ≥10 h versus 7–9 h was not associated with diabetes.
Study by the Niigata Association of Occupational Health in Niigata, Japan, 1999–2012 (32)	Occupational health participants, Japan, age 18–83 years	38,987	8	FPG ≥126 mg/dL, self-reported diabetes diagnosis, or A1c level ≥6.5%	Sleeping <5.5 h and 5.5–<6.5 h were associated with diabetes, OR 1.53 (95% CI 1.19–1.97) and OR 1.25 (95% CI 1.10–2.42), respectively. The effect was found mainly in those age ≤45 years, but not age ≥60 years.

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; h, hour; HR, hazard ratio; IGT, impaired glucose tolerance; NHANES, National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; OR, odds ratio; RR, relative risk.

SOURCE: References are listed within the table.

compared to those with 6.5–7.4 hours per night (35). A study using data from the Korean National Health and Nutrition Examination Survey found a U-shaped relationship between sleep duration and fasting glucose and A1c values (36), while another study of 18,121 participants in China found that only long sleep (>9 hours) was significantly associated with poorer glycemic control (37). These findings from large studies based on self-reported sleep duration were not confirmed in the limited number of studies where sleep was measured using an objective method, such as actigraphy. Indeed, in these studies (total 91 participants), sleep duration was not found to be correlated with glycemic control in patients with type 2 diabetes (38,39). This contradiction between self-reported and objectively measured sleep duration on glycemic control could be due to a very small number of participants in the latter studies, and more research is needed to confirm the findings. Taken together, the epidemiologic evidence suggests a role of self-reported sleep duration on glycemic control in type 2 diabetes.

Despite well-documented evidence for a causal relationship between sleep insufficiency and glucose metabolism, not a single interventional study to date has explored the role of sleep extension in diabetes prevention or treatment.

SLEEP FRAGMENTATION, SHALLOW SLEEP, AND INSOMNIA

Sleep fragmentation is a hallmark of poor sleep quality that can be objectively assessed by low sleep efficiency (a ratio of time spent asleep versus time in bed) or by a long cumulated "wake time after sleep onset [WASO]" by polysomnography (PSG), the "gold standard" diagnostic test used to study sleep patterns and circadian rhythms in the medical setting. (PSG is described in more detail in the section *Obstructive Sleep Apnea: Disease Definition and Diagnosis*.) Actigraphy recordings, from a device that is worn on the wrist for a week or more and is less cumbersome, also provide good estimations of sleep efficiency.

Even in the absence of sleep fragmentation, shallow sleep, as reflected polygraphically from PSG by a low amount of deep NREM sleep (also known as SWS), has also been shown to be associated with adverse metabolic consequences. A laboratory study of healthy volunteers demonstrated that SWS suppression without changes in total sleep duration results in abnormal glucose metabolism. Suppression of SWS using acoustic stimuli for three nights resulted in a 25% decrease in insulin sensitivity as assessed by minimal model analysis of a frequently sampled IVGTT (40) without a compensatory increase in insulin secretion as assessed by the acute insulin response to intravenous glucose (Figure 25.1) (41). The acoustic stimuli were calibrated as to not induce full arousals and thus not affect sleep efficiency. In a similar study, sleep fragmentation by acoustic stimuli and mechanical vibrations for two full nights was associated with a 25% decrease in insulin sensitivity (Figure 25.1) (42). The experimental manipulation resulted in a marked decrease of SWS and also of other sleep stages.

Insomnia is one of the manifestations of subjective poor sleep quality. According to *Diagnostic and Statistical Manual of Mental Disorders-V* criteria, insomnia symptoms include one or more of the following: a report of difficulty initiating sleep, difficulty maintaining sleep, early-morning awakening with inability to return to sleep, or a report of unrefreshing sleep (43). Multiple cross-sectional studies in the United States have found a significant association between poor sleep quality or insomnia symptoms and prediabetes or diabetes (Table 25.4) (44,45,46,47,48). To date, 11 of 12 prospective studies have linked poor sleep quality to incident diabetes (Table 25.5) (19,26,27,28,29,49,50,51,52,53,54,55). One of the largest studies, conducted in U.S. military personnel, confirmed the association between trouble sleeping and diabetes risk (odds ratio [OR] 1.21, 95% CI

TABLE 25.4. Cross-Sectional Studies Exploring Associations Between Sleep Quality and Prediabetes or Diabetes

STUDY/LOCATION, YEARS (REF.)	POPULATION	SAMPLE SIZE	OUTCOME	RESULTS
NHANES, 2005–2006, 2007–2008 (44)	Age ≥30 years	2,285	Clinically identified prediabetes, defined as FPG 100–125 mg/dL, plus physician diagnosis of prediabetes	Trouble maintaining sleep ≥5 times/month was associated with clinically identified prediabetes, OR 3.50 (95% CI 1.30–9.45). Waking up too early ≥5 times/month was associated with clinically identified prediabetes, OR 2.69 (95% CI 1.21–5.98).
NHANES, 2009–2010 (45)	Age >40 years	3,668	Diabetes, defined as FPG >125 mg/dL, A1c >6.4%, or 2-hour glucose >199 mg/dL, post 75 g glucose challenge	Sleep disturbance (i.e., reported to health professional that they had trouble sleeping) was associated with diabetes, OR 1.36 (95% CI 1.06–1.73).
National Sleep in America Survey, 2003 (46)	Age 55–84 years	1,506	Self-reported diabetes	Insomnia symptoms were not associated with diabetes.
Detroit, Michigan, NR (47)	Community-based sample, age 18–65 years	3,282 (621 had PSG)	Self-reported diabetes	Insomnia symptoms were associated with diabetes, OR 1.40 (95% CI 1.05–2.00). Sleep efficiency obtained from PSG was not different in those with or without diabetes.
Penn State Cohort, NR (48)	Age ≥20 years	1,741	Diabetes, defined as FPG ≥126 mg/dL or use of medication	Chronic insomnia for ≥1 year was associated with diabetes, OR 1.84 (95% CI 1.05–3.20). The risk was highest in those with PSG-measured sleep duration ≤5 h, OR 2.95 (95% CI 1.24–7.05). Poor sleep (difficulty falling asleep or staying asleep, early final awakening, or unrefreshing sleep) without insomnia complaint was not associated with diabetes.

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; CI, confidence interval; FPG, fasting plasma glucose; NHANES, National Health and Nutrition Examination Survey; NR, not reported; OR, odds ratio; PSG, polysomnogram.

SOURCE: References are listed within the table.

TABLE 25.5. Prospective Studies Exploring the Relationship Between Sleep Quality or Insomnia Symptoms and Incident Prediabetes or Diabetes

STUDY/LOCATION, YEARS (REF.)	POPULATION	SAMPLE SIZE	FOLLOW-UP (YEARS)	SLEEP ASSESSMENT	OUTCOME AND ASSESSMENT	RESULTS
Stockholm Diabetes Prevention Program, Sweden, 1992–2006 (49)	Mean age 47 years	5,227	8–10	Reported sometimes or frequent insomnia	Prediabetes, defined as FPG 110–125 mg/dL or 2-hour glucose value 140–199 mg/dL after 75 g OGTT or both Diabetes, defined as FPG ≥126 mg/dL or 2-hour glucose value ≥200 mg/dL	Men with high insomnia symptoms had increased risk of prediabetes/diabetes compared to low insomnia symptoms, OR 2.0 (95% CI 1.2–3.4). No association was found in women.
Japan, 1984–1992 (50)	Male employees of electrical plant	2,649	8	Reported difficulty initiating or maintaining sleep	FPG ≥144 mg/dL or 2-hour glucose value ≥200 mg/dL after 75 g OGTT	High frequency of difficulty initiating sleep (often or almost every day) was associated with diabetes, HR 2.98 (95% CI 1.36–6.53). Difficulty maintaining sleep was associated with diabetes, HR 2.23 (95% CI 1.08–4.61).
Germany, 1984–1998 (51)	Population-based cohort in Southern Germany, age 25–74 years	8,269	7.5	Reported difficulty initiating or maintaining sleep	Self-reported diabetes diagnosis and verified by chart review	Difficulty maintaining sleep was associated with diabetes, HR 1.60 (95% CI 1.05–2.45) in men and HR 1.98 (95% CI 1.20–3.20) in women. Difficulty initiating sleep was not associated with diabetes.

Table 25.5 continues on the next page.

TABLE 25.5. (continued)

STUDY/LOCATION, YEARS (REF.)	POPULATION	SAMPLE SIZE	FOLLOW-UP (YEARS)	SLEEP ASSESSMENT	OUTCOME AND ASSESSMENT	RESULTS
Malmo Preventive Project, Sweden, 1974–1996 (52)	Age 35–51 years	6,599	14.8	Reported difficulty initiating sleep and regular use of hypnotic drugs	Self-reported diabetes diagnosis or use of medication. A subgroup of 1,551 subjects received a fasting blood test (diabetes diagnosed when fasting whole blood glucose was ≥6.1 mmol/L).	Difficulty falling asleep or regular use of hypnotics was associated with diabetes, OR 1.52 (95% CI 1.05–2.20).
Norwegian HUNT study, 1984–2008 (53)	Mean age 43.5 years	53,394	11–22	Symptoms of insomnia per DSM-IV criteria	Type 2 diabetes: report of diabetes diagnosis with verification by another interview on history and treatment Autoimmune diabetes: GAD Ab and C-peptide level	Insomnia symptoms were associated with type 2 diabetes in men, HR 1.25 (95% CI 1.08–1.44), but not in women. Insomnia symptoms were associated with autoimmune diabetes in men, HR 1.83 (95% CI 1.05–3.20), but not in women.
GAZEL Cohort study, 1990–2009 (54)	Employees of the French national electric and gas company, mean age 45 years	16,989	19	Questionnaire using Nottingham Health Profile*	Self-report of diabetes diagnosis	Sleep disturbances were associated with diabetes, both in men, HR 1.59 (95% CI 1.15–2.20), and women, HR 2.18 (95% CI 1.37–3.45).
High-risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP), 1999–2004 (26)	Mean age 38.2 years	6,509	4.2	Reported difficulty initiating or maintaining sleep	Report of diabetes diagnosis or using diabetes medication or FBG ≥126 mg/dL or random plasma glucose ≥200 mg/dL	Difficulty initiating sleep was associated with diabetes, HR 1.42 (95% CI 1.05–1.91) for a medium frequency and HR 1.61 (95% CI 1.00–2.58) for a high frequency. Difficulty maintaining sleep was not associated with diabetes.
Sweden, 1983–1995 (27)	Population-based study, age 45–65 years	2,663	12	Self-reported sleep duration, difficulty initiating or maintaining sleep	Self-reported diabetes diagnosis by questionnaire, ascertained by using two questions	Difficulty maintaining sleep was associated with diabetes in men, RR 4.8 (95% CI 1.9–12.5), but not in women. Difficulty initiating sleep was not associated with diabetes.
Millennium Cohort by the Department of Defense, 2001–2007 (28)	Mean age 36.7 years	47,093	6	Reported trouble falling asleep or staying asleep	Self-reported diabetes diagnosis	Trouble sleeping was associated with diabetes, OR 1.21 (95% CI 1.03–1.42).
Japan, 2003–2008 (29)	Government employees, age 35–55 years	3,570	3–5	Poor sleep quality†	Having been prescribed diabetes medication and/or FPG ≥126 mg/dL	Awakening during the night and unsatisfactory overall quality of sleep were associated with diabetes, OR 5.03 (95% CI 1.43–17.64) and OR 6.7 (95% CI 2.09–21.87), respectively, in those without family history of diabetes. No associations were found in those with family history of diabetes.
Hong Kong, 2003–2010 (55)	Population-based study of Hong Kong Chinese, mean age 46.3 years	Non-restorative sleep: 2,291	5	Non-restorative sleep (morning unfreshness after getting up ≥3 times/week over the past 12 months)	Self-reported diabetes diagnosis	Non-restorative sleep was associated with diabetes, OR 2.63 (95% CI 1.23–5.63).

Table 25.5 continues on the next page.

TABLE 25.5. (continued)

STUDY/LOCATION, YEARS (REF.)	POPULATION	SAMPLE SIZE	FOLLOW-UP (YEARS)	SLEEP ASSESSMENT	OUTCOME AND ASSESSMENT	RESULTS
Sweden, 1968–2001 (19)	Cohort study of women, mean age 46.8 years	1,462	32	Sleep problems, defined as having reported sleep problems and/or having consulted a doctor for sleep problems and/or hospital admission for this reason, use of sleep medication	Self-reported of diabetes diagnosed by physician or use of diabetes therapy or FPG ≥126 mg/dL on two occasions or more	Sleep complaints or use of sleep medications were not associated with diabetes.

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; CI, confidence interval; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders-IV*; FBG, fasting blood glucose; FPG, fasting plasma glucose; GAD Ab, glutamic acid decarboxylase antibody; HR, hazard ratio; OGTT, oral glucose tolerance test; OR, odds ratio; RR, relative risk.

* Three or more of the following: I take a tablet to help me sleep; I lie awake most of the night; I sleep badly at night; It takes me a long time to fall asleep; or I wake up in the early hours of the morning.

† Two or more of the following: problems with sleep induction, awakening during the night, final awakening earlier than desired, insufficient sleep, or overall poor sleep quality.

SOURCE: References are listed within the table.

1.03–1.42) (28). Meta-analyses, pooling five of these studies, revealed that self-reported difficulty in maintaining sleep predicted the development of diabetes with a relative risk of 1.84 (total 24,192 participants), while self-reported difficulty in initiating sleep was associated with an increased relative risk of 1.57 (total 18,213 participants) (33). By comparison, estimates of the relative risk of developing diabetes associated with a family history of type 2 diabetes have ranged from 1.7 to 2.3 (56,57,58,59,60), with only one study in South African blacks estimating the relative risk at a substantially higher value of 4.1 (61). Thus, the relative risk of incident diabetes in individuals reporting insufficient sleep or difficulty initiating or maintaining sleep is of the same order of magnitude as the relative risk imparted by having a family history of type 2 diabetes, usually considered as one of the strongest predictors of diabetes risk. Interestingly, one study also found an association of poor sleep quality and an increased risk of autoimmune diabetes (53).

Only a few cross-sectional studies have examined the relationship between sleep quality and glycemic control in patients with type 2 diabetes. The largest study in the United States included 161 African American patients and found that in those with at least one diabetic complication (i.e., retinopathy, neuropathy, nephropathy, cardiovascular, or cerebrovascular diseases), there was a graded relationship between glycemic control as assessed by A1c and the score on the Pittsburgh Sleep Quality Index (PSQI) (34). Specifically, a 5-point increase in PSQI score predicted an elevation of A1c level of 1.9% above the median. Another cross-sectional study of 46 Taiwanese patients found an association between poor glycemic control (defined as A1c ≥7% [≥53 mmol/mol]) and poor sleep quality (PSQI ≥8), as well as poor sleep efficiency (62). Similarly, poor sleep quality as assessed by questionnaire in 551 Chinese type 2 diabetes patients found an association between lower sleep quality and higher insulin resistance as measured by HOMA-IR (63).

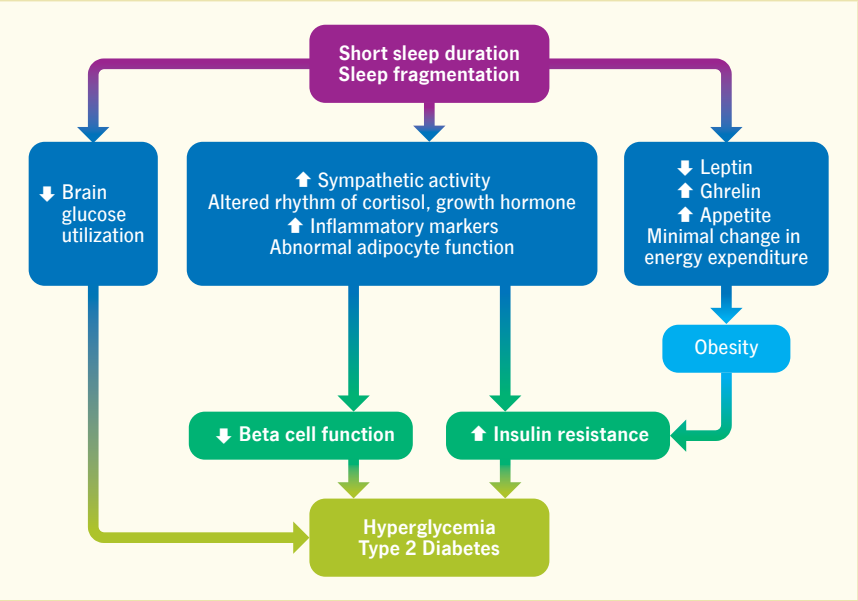
A few studies have utilized objective measurement of sleep quality. Knutson *et al.* reported a cross-sectional association between an objective estimation of sleep quality and markers of glucose metabolism in participants of the Coronary Artery Risk Development in Young Adults (CARDIA) study (38). The sleep parameters were derived from actigraphy recordings, which have been shown to be well correlated with those obtained by PSG (64). While there were no correlations between sleep and metabolic variables in nondiabetic participants, sleep fragmentation and insomnia were associated with significantly higher fasting glucose, insulin, and HOMA levels in diabetic participants (38). Another study conducted in Italy, involving 47 patients with type 2 diabetes, reported that A1c correlates inversely with sleep efficiency as measured by actigraphy (39). Interestingly, in the NHANES 2005–2006, a study of 958 adults with prediabetes (fasting glucose 100–125 mg/dL [5.55–6.94 mmol/L], 2-hour oral glucose tolerance values of 140–199 mg/dL [7.77–11.04 mmol/L], or A1c 5.7%–6.4% [39–46 mmol/mol]) did not find a relationship between insomnia symptoms and A1c levels (65). However, those with insomnia symptoms were less active as measured by steps walked during the 2-day recordings. The findings suggest that insomnia in adults with prediabetes may be a barrier to adopting an active lifestyle.

Despite the link between poor sleep quality and diabetes risk or poor glycemic control in patients with type 2 diabetes, there has not been a single study so far exploring whether improving sleep quality may be a viable strategy to prevent diabetes or reduce its severity.

PATHWAYS INVOLVED IN THE ADVERSE METABOLIC IMPACT OF INSUFFICIENT SLEEP AND POOR SLEEP QUALITY

Laboratory studies in healthy humans have provided evidence for the implication of multiple pathways in the link between reduced sleep duration and/or quality, insulin resistance, and hyperglycemia (Figure 25.2) (2).

FIGURE 25.2. Pathways Linking Sleep Insufficiency and Fragmentation to Abnormal Glucose Metabolism and Type 2 Diabetes



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Decreased Brain Glucose Utilization During Waking Hours

The brain utilizes glucose in an insulin-independent manner and is responsible for at least 50% of total glucose utilization in the fasting state. The rate of cerebral glucose metabolism as measured by positron emission tomography and ^{18}Fluorine-2-deoxyglucose following a 24-hour period of total sleep deprivation has been found to be significantly decreased, especially in several cortical and subcortical areas (66). This is in agreement with the findings of a sleep debt study that revealed a 30% reduction in glucose effectiveness, an index of insulin-independent glucose disposal (8).

Increased Sympathetic Nervous System Activity

Sleep deprivation and sleep fragmentation lead to a shift in sympathovagal balance toward an increase in sympathetic nervous system activity as reflected by lower heart rate variability (8,41,42). Increased sympathetic nervous system activity has inhibitory effects on insulin secretion and promotes insulin resistance and the development of the metabolic syndrome (67,68). In addition, some studies have documented increased serum and urine norepinephrine and epinephrine concentrations following sleep deprivation (11,12,69). These hormones promote gluconeogenesis.

Alterations in the Hypothalamic-Pituitary-Adrenal Axis and Growth Hormone

Several studies observed an increase in salivary and serum cortisol levels following sleep deprivation, particularly in the evening and early part of the night, at the time when the levels are normally very low following the normal circadian pattern (8,12,70,71). In one study, there was no change in corticotropin (ACTH) level, suggesting an enhanced adrenal reactivity (70). Evening elevations of cortisol may promote morning insulin resistance (72). An increase in morning serum cortisol levels was also reported after sleep fragmentation (73). In a sleep debt study, growth hormone secretion was found to increase prior to sleep onset and to limit the amplitude of post-sleep onset growth hormone release (9). Prolonged nighttime exposure to growth hormone may promote hyperglycemia.

Increase in Systemic Inflammatory Response

Inflammatory responses to sleep deprivation have been reviewed in detail (74). Multiple studies have demonstrated increases in leukocyte and monocyte counts (75,76,77), as well as elevations in the levels of proinflammatory cytokines, including interleukin (IL)-1 beta, IL-6, IL-17, tumor necrosis factor (TNF)-alpha, and high sensitivity C-reactive protein (hsCRP) (13,78,79,80,81). Increased proinflammatory cytokines have been linked to insulin resistance (82). Some studies, however, did not observe an association between alterations in the circulating levels of some of these cytokines and sleep disturbances, possibly partly due to variability of baseline levels within the population, as well as timing of specimen collection relative to the circadian cycle (74).

Alterations in Appetite-Regulating Hormones and Increased Obesity Risk

Appetite-regulating hormones, including leptin, which is one of the satiety hormones, and ghrelin, which is a hunger hormone, have been studied in the context of sleep restriction experiments. The first study that assessed these changes involved two nights of 4 hours in bed versus two nights of 10 hours in bed in healthy, normal-weight young men (83). During sleep restriction, leptin decreased by 18% and ghrelin increased by 28%. These changes were associated with a 23% increase in hunger ratings and a 33% increase in appetite for carbohydrate-rich foods. More than 10 subsequent studies have explored these hormonal changes in response to sleep restriction with some variations in participants' characteristics (i.e., adiposity and sex distribution), severity of sleep restriction, blood sampling methodology, and dietary protocols (*ad libitum* food access or controlled caloric consumption) (84,85). Not surprisingly, since leptin levels are highly sensitive to energy balance and modulated by sex and adiposity,

the findings have been inconsistent, with decreased (83,86,87,88), unchanged (89,90), or increased (14,91,92,93) concentrations. However, most of the studies that utilized multiple blood samplings in normal-weight men under conditions of controlled food intake consistently revealed a reduction in leptin amplitude or mean levels, suggesting that the discrepancies may, at least in part, be due to modulation of leptin secretion by obesity, sex, and food intake. Whether the results obtained in short-term laboratory studies may be extrapolated to real-life conditions is debatable. In a field study of 80 obese adults, no associations were found between leptin levels and sleep duration or quality (94). In contrast, the Wisconsin Sleep Cohort Study (1,024 participants) found an association between reduced leptin levels, along with elevated ghrelin levels and increased body mass index (BMI), in those reporting sleeping 5 hours compared to 8 hours (95).

Multiple studies documented increased ghrelin levels along with increased hunger in response to partial sleep restriction (83,91,93), as well as increased caloric intake, mostly from snacks. Several studies have observed that the excessive caloric consumption was mostly from carbohydrate-rich foods, although increased intake of fat or of all macronutrients has also been reported (96,97,98,99,100). However, similar to the findings regarding leptin levels, not all studies observed increased ghrelin levels (11,97,101). Two studies utilizing functional magnetic resonance imaging revealed increased neuronal activity in certain brain areas involved in the reward system in response to presentation of food stimuli after total and partial sleep restriction (102,103). These imaging findings are consistent with a report showing an increase in the levels of circulating endocannabinoid 2-arachidonoylglycerol (2-AG) after three days of sleep restriction compared to normal sleep (89).

Since sleep restriction provides more wake time, it has been suggested that the caloric need of extended wakefulness may counterbalance the increase in hunger and food intake. Several studies have addressed changes in energy expenditure following sleep restriction. Surprisingly, three independent studies failed to detect an increase in energy expenditure assessed by the doubly labeled water method in individuals who underwent experimental partial sleep restriction (96,97,98). However, when the subjects were confined to a calorimetry room in order to monitor minute-to-minute energy expenditure during normal sleep and total sleep deprivation (104), the caloric cost per hour of wakefulness under sedentary conditions compared to sleep averaged only 17 Kcal, suggesting that the stimulation of hunger and food intake far exceeds the caloric need of extended wakefulness. A study involving 5 days of partial sleep restriction, similar to a work week, under controlled laboratory conditions indeed observed that the approximate 5% increase in daily energy expenditure was overcompensated by energy intake, particularly at night, resulting in significant weight gain (99). Additionally, there is evidence that the sleepiness and fatigue associated with insufficient sleep may result in a reduction in voluntary physical activity (105,106).

Collectively, these changes in appetite regulation in favor of increased hunger and food intake without commensurate increase in energy expenditure place individuals at risk for obesity. These results are supported by multiple prospective studies that found a significant association between short sleep and greater weight gain in both adults and children (107,108,109,110).

Abnormal Adipocyte Function

Adipocytes play a pivotal role in the regulation of energy balance and appear to play an important role in the changes in energy balance in response to sleep restriction (111). Leptin is released primarily from subcutaneous fat depot in direct proportion to insulin-stimulated glucose uptake and total subcutaneous fat mass (112). Increased sympathetic nervous activity leads to stimulation of lipolysis and increased free fatty acids which could lead to insulin resistance (113). A randomized crossover trial of 4 days of sleep restriction (4.5 hours per night) versus 4 days of normal sleep (8.5 hours per night) in healthy, young, lean men studied under controlled conditions of caloric intake and physical activity showed an increase in nocturnal free fatty acid levels that was correlated with the reduction in insulin sensitivity (114). In addition, elevated levels of glucocorticoids facilitate visceral fat accumulation, increased lipolysis, and insulin resistance. Molecular mechanisms involved in insulin signaling in adipocytes collected from individuals who were sleep restricted were examined by Broussard *et al.* (10) in a subset of the participants in the randomized crossover study of 4 days with 4.5 hours in bed versus 8.5 hours in bed. Subcutaneous fat biopsy under restricted sleep conditions revealed a 30% reduction in the ability of insulin to increase levels of phosphorylated Akt (also known as protein kinase B), a crucial early step in the insulin signaling pathway, compared to during normal sleep conditions. This impaired cellular insulin sensitivity paralleled the decrease in total body insulin sensitivity as assessed by IVGTT.

In summary, a large body of evidence supports a causal relationship between sleep insufficiency and sleep fragmentation and alterations in multiple physiologic pathways, resulting in abnormal glucose metabolism, increased diabetes risk, and possibly contributing to poor glycemic control in individuals who have prediabetes or diabetes. Further research studies should explore whether optimizing sleep duration and quality will, in the long term, result in decreased diabetes risk or improved glycemic control in patients with established type 2 diabetes.

PATHWAYS INVOLVED IN THE ADVERSE METABOLIC IMPACT OF LONG SLEEP DURATION

In contrast to short sleep duration, the mechanisms linking long sleep duration and abnormal glucose metabolism are poorly understood. One of the limitations is that most, if not all, studies documenting an adverse metabolic impact of long sleep (typically >8–9 hours per night) have been based on self-reported sleep duration. Additionally, it has been speculated that long sleepers are actually poor sleepers who extend their time in bed to try to compensate for poor sleep quality (115). Another possibility is that long sleepers suffer from fatigue resulting from an undiagnosed preclinical condition. In a study of type 2 diabetes patients, long sleepers (≥8.5 hours per night) were more likely to have depressive symptoms and to be more physically inactive compared to those who reported sleeping 6.5–7.4 hours per night (35). Increased sedentarity, a correlate of long sleep, could also have adverse cardiometabolic effects. A prerequisite to the identification of putative mechanisms that could mediate adverse effects of long sleep is the demonstration that these effects are still present when sleep duration is assessed objectively, rather than by self-report.

OBSTRUCTIVE SLEEP APNEA

DISEASE DEFINITION AND DIAGNOSIS

OSA is a common sleep disorder that is characterized by recurrent episodes of complete or partial collapse of the upper airway during sleep. The cessation or reduction in airflow is often associated with decreased oxygen saturation and/or arousal from sleep. Patients with OSA present with a constellation of nocturnal symptoms that include loud disruptive snoring, bed partner-reported breathing pauses (apneas), choking and gasping episodes during sleep, and frequent awakenings. Common daytime consequences include excessive daytime sleepiness, fatigue, irritability, and deficits in attention and memory. Epidemiologic data from several community- and population-based studies from North America, Europe, and Asia indicate that sleep apnea affects approximately 3%–7% of adult men and 2%–5% of adult women (Table 25.6) (116). However, the prevalence is likely to have increased due to the increasing obesity rates. For example, between 1988–1994 and 2007–2010, the prevalence in the Wisconsin Sleep Cohort increased by as much as 55% (117). In 2007–2010, the estimates of OSA prevalence in obese adults ranged between 33% and 77% in men and between 11% and 46% in women (117). Despite the increasing body of literature recognizing the adverse health consequences and public health impact of sleep apnea, a considerable number of affected individuals remain undiagnosed (118,119).

The diagnosis of OSA is based on an overnight sleep study or a polysomnogram (PSG). It involves simultaneous recordings of several electrophysiological signals, including the right and left electrooculograms, the submental electromyogram, and the electroencephalogram (EEG). Collectively, these physiological signals are used to distinguish wakefulness from sleep and assess the distribution of various sleep stages. In addition, breathing patterns are assessed with measurements of respiratory effort, airflow, and oxygen saturation. Airflow is recorded with an oronasal thermistor (a probe sensitive to temperature changes that occur with breathing) and/or a nasal cannula configured to monitor pressure changes in the nasal airway. The PSG also includes other measurements, such as continuous electrocardiography, which is used to detect occurrence of cardiac arrhythmias during sleep. The analysis of the PSG for OSA requires identification of abnormal or disordered breathing patterns during sleep. Two basic types of disordered breathing events are assessed: apneas and hypopneas (Table 25.7). An apnea is defined as the complete cessation of airflow for at least 10 seconds. A hypopnea is defined as a reduction in airflow that is associated with an EEG arousal or a decrease in oxygen saturation (120).

TABLE 25.6. Studies on the Prevalence of Obstructive Sleep Apnea

LOCATION, YEARS (REF.)	SAMPLE SIZE	ETHNICITY	SLEEP ASSESSMENT	PREVALENCE (%)	
				Men	Women
U.S., 1988 (380)	602	White	Polysomnography	4.0	2.0
U.S., NR (381)	741	White	Polysomnography	3.3	NA
U.S., NR (382)	1,000	White	Polysomnography	NA	1.2
Australia, NR (383)	485	White	Respiratory polygraphy	3.1	NA
India, 1999–2000 (384)	250	Indian	Polysomnography	7.5	4.5
China, 1997–1999 (385)	258	Chinese	Polysomnography	4.1	NA
China, 1998–2000 (386)	NR	Chinese	Polysomnography	NA	2.1
Korea, 2001 (387)	457	Korean	Polysomnography	4.5	2.3

NA, not applicable; NR, not reported.

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TABLE 25.7. Types of Disordered Breathing Events During Sleep

TERM	DEFINITION
Disordered breathing event	
Apnea	Cessation of airflow ≥10 seconds
Hypopnea	Reduction in airflow associated with oxygen desaturation and/or arousal
Type of disordered breathing event	
Obstructive	An event with absence of airflow but with continued respiratory effort
Central	An event with absence of airflow and no respiratory effort
Mixed	An event that typically starts with a period that meets the criteria for a central event but ends with respiratory effort without airflow
Indices on disordered breathing severity	
Apnea-Hypopnea Index	Number of apneas and hypopneas per hour of total sleep time
Apnea Index	Number of apneas per hour of total sleep time
Hypopnea Index	Number of hypopneas per hour of total sleep time
Central Apnea Index	Number of central apneas per hour of total sleep time

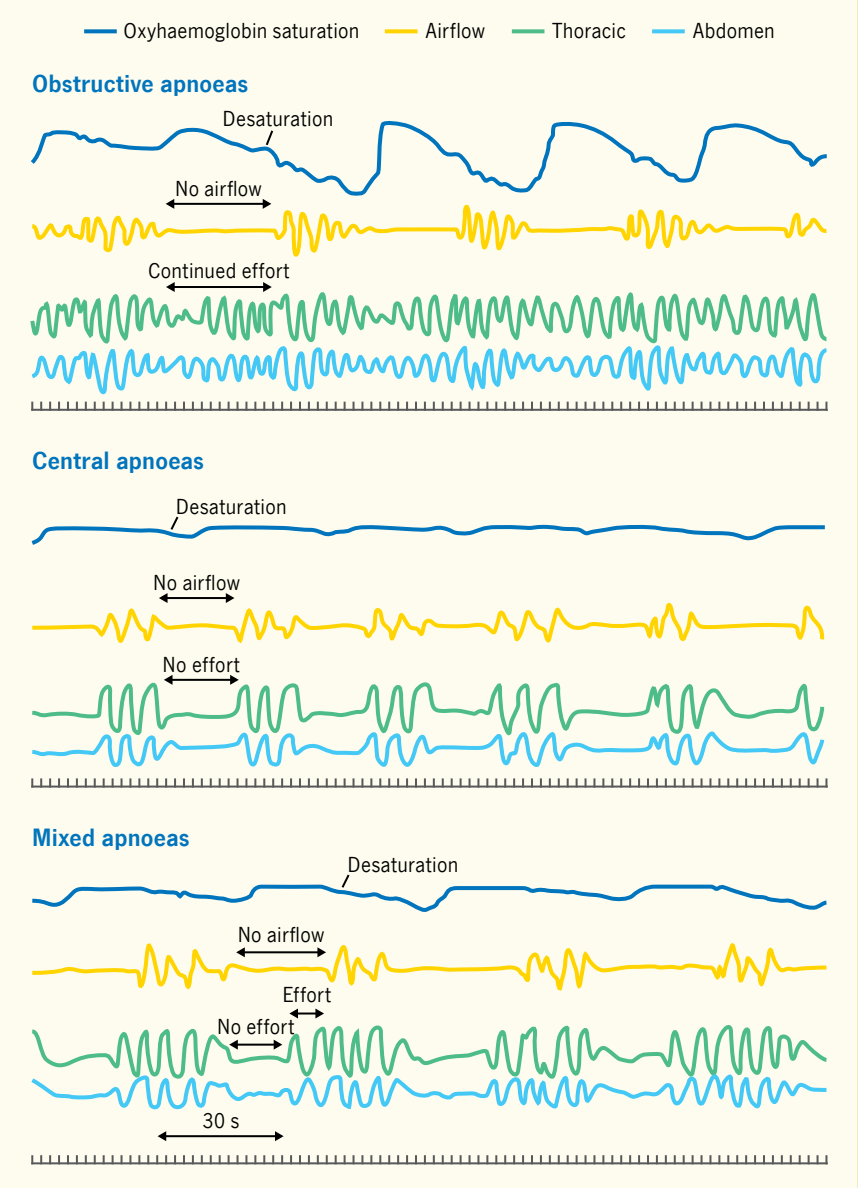
SOURCE: Original table constructed by N. M. Punjabi.

Disordered breathing events are further classified into obstructive, central, or mixed events. The classification of an abnormal breathing event is dependent on whether, in the absence of oronasal airflow, there is evidence of respiratory effort. An obstructive event is defined as the absence of airflow in the presence of continued effort. In contrast, a central event is defined as the absence of airflow without associated effort. Finally, a mixed event manifests characteristics of an obstructive and a central event. Mixed events typically start with a period that meets the criteria for a central event but end with increasing effort but without associated airflow. Figure 25.3 illustrates tracings of the three types of abnormal breathing patterns (obstructive, central, and mixed apneas) during sleep (121). PSG yields a quantification of episodes of apnea and hypopnea per hour of sleep, an apnea-hypopnea index (AHI). A diagnosis of OSA is made when the AHI is ≥5.

OBSTRUCTIVE SLEEP APNEA AND METABOLIC DYSFUNCTION

In addition to reductions in sleep duration and quality, intermittent hypoxia is the hallmark of OSA. Only one experimental study in humans has examined the impact of intermittent hypoxemia on glucose metabolism. In this study, 13 healthy volunteers were subjected to 5 hours of intermittent hypoxia while awake, resulting in an average of 24.3 desaturation events per hour (122), equivalent to hypoxia in OSA of moderate severity (AHI ≥15–30). Insulin sensitivity and glucose

FIGURE 25.3. Types of Disordered Breathing Events



Three-minute recordings characteristic of obstructive, central, and mixed apneas during sleep. Traces shown represent oxyhemoglobin saturation, airflow, and thoracic and abdominal movement.

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effectiveness, as assessed by IVGTT, were reduced by 17% and 31%, respectively, without simultaneous increase in insulin secretion. These results suggest that hypoxic stress may have an intrinsic adverse impact on glucose metabolism and diabetes risk.

Over the last two decades, a number of observational studies have demonstrated that OSA is associated with insulin resistance, glucose intolerance, type 2 diabetes, and the metabolic syndrome, independent of such factors as age, sex, race, BMI, and measures of visceral adiposity (Tables 25.8 and 25.9). Epidemiologic data from community- and population-based cohorts, including the Sleep Heart Health Study (123) and the Wisconsin Sleep Cohort Study (124), have shown that the severity of OSA, as assessed by the AHI, is directly associated with fasting hyperglycemia, glucose intolerance, and the prevalence of physician-diagnosed type 2 diabetes. Irrespective of the method used for assessing insulin sensitivity, a majority of published reports indicate that the severity of OSA (i.e., AHI) is inversely related to the degree of insulin sensitivity. Moreover, metrics of nocturnal hypoxemia (e.g., oxyhemoglobin desaturation and average oxygen saturation during sleep) strongly correlate with the degree of whole body insulin resistance (Table 25.8).

TABLE 25.8. Studies on the Association Between Obstructive Sleep Apnea and Measures of Insulin Resistance

YEARS (REF.)	STUDY SAMPLE	SAMPLE SIZE	SLEEP ASSESSMENT	INDEPENDENT VARIABLE	DEPENDENT VARIABLE	CONFOUNDERS ASSESSED	ASSOCIATION
NR (388)	OSA	18	Oximetry	ODI	Insulin resistance index from OGTT	BMI, age	+
1991–1993 (389)	OSA	261	PSG	AHI	I_0	BMI	+
NR (390)	OSA and controls	66	PSG	AHI	I_0	BMI, waist/hip ratio, age	–
1991 (391)	Primary care	1,190	Self-report	OSA symptoms	I_0	BMI, visceral fat, age	+
NR (392)	Healthy participants	50	MESAM*	ODI	Insulin suppression test	BMI, age, sex, activity	–
NR (246)	OSA	10	PSG	AHI	Hyperinsulinemic clamp	BMI	–
NR (393)	OSA and controls	60	PSG	AHI	I_0 and I_0/G_0 ratio	BMI, waist, hip, age, sex	+
NR (394)	OSA and controls	37	PSG	AHI	I_0	BMI, visceral fat	+
1996–1998 (395)	Hypertensive men	116	Edentec*	ODI	I_0	BMI, waist/hip ratio, age	+
1999–2000 (396)	OSA	270	PSG	AHI	HOMA IR	BMI, waist, age	+
NR (397)	OSA	20	PSG	AHI	Hyperinsulinemic clamp	BMI, sex, age	+
NR (398)	Community sample	151	PSG	AHI	HOMA IR	BMI, waist, percent body fat	+
1998–2000 (399)	OSA and snorers	595	PSG	AHI	G_0/I_0 ratio	BMI, age	+
NR (400)	OSA and controls	57	PSG	AHI	Insulin sensitivity index from OGTT	BMI, waist/hip ratio, age	+
NR (401)	OSA and controls	65	PSG	AHI	HOMA IR	BMI, age	–
1994–1999 (123)	Community sample	2,565	PSG	AHI	HOMA IR	BMI, waist, age, sex	+
NR (402)	OSA	213	PSG	AHI	HOMA IR	BMI, visceral fat, age	+
NR (244)	OSA and controls	42	PSG	AHI	HOMA IR	BMI, waist, age	+
2003–2005 (245)	OSA and controls	120	PSG	AHI	HOMA IR	BMI, waist	–
NR (403)	OSA	67	PSG	AHI	HOMA IR	BMI, waist	–
2002–2004 (404)	Population sample	400	PSG	AHI	Insulin sensitivity index	Waist/hip ratio, age, activity	+
NR (405)	OSA	98	PSG	AHI	HOMA IR	BMI, sex, age	+
NR (406)	OSA and controls	118	PSG	AHI	Insulin sensitivity from IVGTT	BMI, waist, percent fat, age	+
NR (407)	OSA and controls	98	PSG	AHI	HOMA IR	BMI, age	+
NR (408)	OSA	23	PSG	AHI	HOMA IR	BMI	+

AHI, apnea-hypopnea index; BMI, body mass index; G_0, fasting glucose; HOMA IR, homeostasis model assessment of insulin resistance; I_0, fasting insulin; IVGTT, intravenous glucose tolerance test; NR, not reported; ODI, oxygen desaturation index; OGTT, oral glucose tolerance test; OSA, obstructive sleep apnea; PSG, polysomnogram. In the Association column, a plus sign (+) denotes a statistically significant association and a minus sign (-) denotes no significant association.
* Edentec and MESAM are portable sleep monitoring units.

SOURCE: References are listed within the table.

To date, nine prospective cohort studies, with approximately 65,000 participants, have been conducted to explore whether the presence of OSA, using objective sleep assessments, at baseline predicted incident diabetes during a follow-up, after adjusting for BMI or other measures of adiposity and other confounders (Table 25.10) (28,124,125,126,127,128,129,130,131). The studies varied in the methods and criteria used to diagnose OSA (pulse oximetry vs. full or limited PSG, and cutoff for AHI/oxygen desaturation index), verification of diabetes diagnosis, and duration of follow-up period (2.7–16 years). A meta-analysis including five of these studies (total 5,953 participants) revealed that moderate to severe OSA was associated with a significantly greater risk of developing diabetes, with a relative risk

TABLE 25.9. Studies on the Association Between Obstructive Sleep Apnea, Glucose Tolerance, Type 2 Diabetes, and the Metabolic Syndrome

YEARS (REF.)	STUDY SAMPLE	SAMPLE SIZE	SLEEP ASSESSMENT	INDEPENDENT VARIABLE	DEPENDENT VARIABLE	CONFOUNDERS ASSESSED	ASSOCIATION
NR (398)	Community sample	151	PSG	AHI	OGTT	BMI, waist, percent fat	+
1998–2000 (399)	OSA and snorers	594	PSG	AHI	OGTT	BMI, age	+
NR (400)	OSA and controls	57	PSG	AHI	OGTT	BMI, waist/hip ratio	+
1994–1999 (123)	Community sample	1,930	PSG	AHI	OGTT	BMI, waist, age, sex	+
2002–2004 (404)	Population sample	400	PSG	AHI	OGTT	Waist/hip ratio, age, activity	+
1994–1999 (409)	Community sample	2,588	PSG	AHI	OGTT	BMI, waist, age, sex	+
2004–2005 (410)	Population sample	2,896	Self-report	OSA symptoms	OGTT	BMI, age, sex	+
1994 (395)	Hypertensive men	116	Portable monitor	ODI	Diabetes prevalence	BMI, waist/hip ratio, age	+
1986–1996 (411)	Nurses' Health Study	69,852	Self-report	OSA symptoms	Self-reported diabetes	BMI, age, menopause	+
1991–1994 (412)	Population sample	295	Self-report	Snoring	Metabolic syndrome	Age, smoking, activity, exercise	+
NR (413)	OSA and controls	104	PSG	AHI	Metabolic syndrome	BMI, age, smoking, alcohol	+
NR (414)	OSA	87	PSG	AHI	Metabolic syndrome	None	+
NR (415)	OSA	819	PSG	AHI	Metabolic syndrome	BMI, age	+
NR (416)	OSA and controls	79	Portable monitor	AHI	Metabolic syndrome	BMI, age, smoking	+
1997–1999 (417)	Community sample	255	PSG	AHI	Metabolic syndrome	BMI, age, sex	+
2004–2005 (418)	Population sample	1,946	Self-report	OSA symptoms	Metabolic syndrome	Age, sex, smoking	+
NR (419)	OSA	98	PSG	AHI	Metabolic syndrome	BMI	+
2002–2006 (420)	OSA and controls	94	PSG	AHI	Metabolic syndrome	BMI, visceral fat, sex	+
2004 (421)	Sleep clinic sample	225	PSG	AHI	Metabolic syndrome	BMI, age	+
1983–1987 (422)	OSA	40	PSG	Diabetes status	OSA prevalence	Age, BMI	+
1996–1998 (423)	Population sample	593	Self-report	Diabetes status	OSA prevalence	BMI, neck, sex	+
NR (424)	Diabetic patients	938	Self-report	Diabetes status	OSA prevalence	BMI, neck, age	+
2001 (425)	Population sample	993	Self-report	Glucose tolerance	OSA prevalence	BMI, waist, sex, activity	+
NR (137)	Diabetic patients	279	Portable monitor	Diabetes status	OSA prevalence	BMI, age	+
2005 (426)	Patients with the metabolic syndrome	24	PSG	Metabolic syndrome	OSA prevalence	None	+
2003–2007 (427)	Patients with the metabolic syndrome	195	Portable monitor	Metabolic syndrome	OSA prevalence	Age, sex, hypertension	+

AHI, apnea-hypopnea index; BMI, body mass index; NR, not reported; ODI, oxygen desaturation index; OGTT, oral glucose tolerance test; OSA, obstructive sleep apnea; PSG, polysomnogram. In the Association column, a plus sign (+) denotes a statistically significant association and a minus sign (-) denotes no significant association.

SOURCE: References are listed within the table.

of 1.63 (95% CI 1.09–2.45), compared to those without OSA (132). In those with mild OSA (AHI <15), the relative risk was 1.22 (95% CI 0.91–1.63), but this was not statistically significant. These data strongly support the concept that the presence of moderate to severe OSA is a risk factor for diabetes development independent of other confounding factors.

In patients with an established diagnosis of type 2 diabetes, who were generally obese, OSA was shown to be highly prevalent, from a lowest estimate of 58% to a highest estimate of 86%, based on seven independent studies involving a total of 1,272 participants (Figure 25.4) (133,134,135,136,137,138,139). The weighted average was 67%.

This proportion is alarming given that, in 2011, 20.9 million Americans were estimated to have diabetes, which could possibly translate to as many as 14 million individuals suffering from both diabetes and OSA. Unfortunately, this highly prevalent comorbidity of type 2 diabetes often remains unrecognized. A retrospective analysis of 27 primary

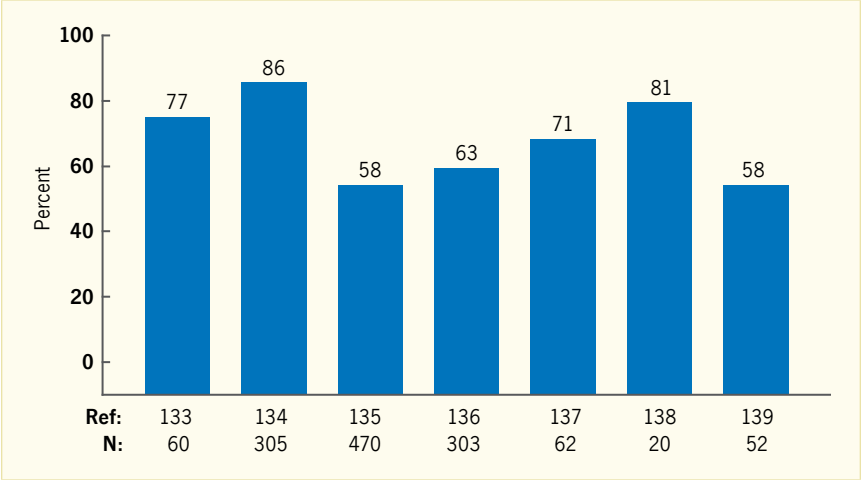
TABLE 25.10. Prospective Studies on the Relationship Between Obstructive Sleep Apnea and Incident Diabetes

STUDY/LOCATION, YEARS (REF.)	POPULATION	SAMPLE SIZE	FOLLOW-UP (YEARS)	OSA ASSESSMENT	DIABETES ASSESSMENT	RESULTS
Connecticut, 2000–2005 (125)	Patients referred to the Veterans Affairs Sleep Center, mean age 61.5 years	1,233	2.7	AHI ≥8 by PSG	Fasting glucose >126 mg/dL, ascertained by chart review	OSA was associated with diabetes, HR 1.43 (95% CI 1.10–1.86).
Sweden, 1991–2007 (126)	Patients referred to sleep laboratory, mean age 48.2 years	318	16	4% ODI ≥30 events/night using an oximetry, a nasal and oral airflow, and respiration and body movement monitoring	Self-reported diabetes diagnosis, verified by chart review	OSA was associated with diabetes in women, OR 11.78 (95% CI 1.14–121.7), but not in men.
Sweden, 1996–2008 (127)	Population-based, men who responded to postal questionnaires, mean age 57.5 years	141	11.3	AHI ≥5 by PSG	Self-reported diabetes diagnosis, verified by FPG ≥126 mg/dL	OSA was associated with diabetes, OR 4.4 (95% CI 1.1–18.1).
Australia, 1990–1995 (128)	Population-based study, mean age 53.1 years	399	4	RDI ≥5 from a 4-channel home monitoring device (heart rate, oxygen saturation, snoring, and body position)	Self-reported diabetes diagnosis, use of medication, or FPG ≥126 mg/dL	Moderate to severe OSA (RDI ≥15) was associated with diabetes, OR 13.45 (95% CI 1.59–114.11).
Japan, 2001–2007 (129)	Population-based study in five communities, mean age 57.6 years	4,606	3	3% ODI ≥5 events/hour from a pulse oximetry	FPG ≥126 mg/dL, random glucose ≥200 mg/dL, or use of diabetes medications/insulin	Moderate OSA (ODI ≥15) was associated with diabetes, HR 1.69 (95% CI 1.04–2.76).
Wisconsin Sleep Cohort, 1988–1993 (124)	Mean age 49.0 years	1,387	4	AHI ≥5 by PSG	Self-reported diabetes diagnosis or FPG ≥126 mg/dL	No association between OSA and diabetes development
Millennium Cohort by the Department of Defense, 2001–2007 (28)	Mean age 36.7 years	47,093	6	Reported a physician diagnosis of OSA	Self-reported diabetes diagnosis	OSA was associated with diabetes, OR 1.78 (95% CI 1.39–2.28).
Australia, 2000–2012 (130)	Population-based study, mean age 59.7 years	736	4.7	Eight-channel, unattended, in-home PSG performed at the last visit	Self-reported diabetes diagnosis or use of medication or FPG ≥126 mg/dL or A1c ≥6.5%	Current severe OSA (AHI ≥30) was associated with diabetes, OR 2.6 (95% CI 1.1–6.1). Current ODI ≥16 was associated with diabetes, OR 1.85 (95% CI 1.06–3.21).
Canada, 1994–2011 (131)	Patients referred to sleep lab	8,678	5.6	AHI ≥5 by PSG	At least one hospitalization record or at least two physician services claims bearing a diagnosis of diabetes within a 2-year period	AHI >30 was associated with diabetes, HR 1.31 (95% CI 1.07–1.61).

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; AHI, apnea-hypopnea index; CI, confidence interval; FPG, fasting plasma glucose; HR, hazard ratio; ODI, oxygen desaturation index; OR, odds ratio; OSA, obstructive sleep apnea; PSG, polysomnogram; RDI, respiratory disturbance index.

SOURCE: References are listed within the table.

FIGURE 25.4. Prevalence of Obstructive Sleep Apnea Among Persons With Type 2 Diabetes



Obstructive sleep apnea was assessed by polysomnogram in all studies.

SOURCE: References are listed within the figure.

care practices involving 16,066 diabetes patients found that only 18% were diagnosed with OSA, suggesting that a majority of diabetic patients may not be diagnosed, and therefore, their OSA is left untreated (140).

Similar to nondiabetic populations, the severity of untreated OSA is associated with poorer glycemic control in diabetic populations. Aronsohn *et al.* utilized PSG to assess OSA severity in 60 diabetic patients (133). There was a graded relationship between the severity of untreated OSA as measured by AHI and higher A1c levels after adjusting for age, sex, race, BMI, years of diabetes, numbers of diabetes medications, exercise, and total sleep time, with an effect size as large as that associated with the impact of diabetes drugs. Another cross-sectional study in 52 diabetic patients also found that increased severity of OSA was associated with increased A1c levels, after adjusting for age, sex, BMI, diabetes duration, and insulin dose (139). Adjusted mean A1c was 8.6% (70 mmol/mol) in those without OSA, 9.4% (79 mmol/mol) in mild OSA, 10.6% (92 mmol/mol) in moderate OSA, and 9.9% (85 mmol/mol) in severe OSA. However, not all of the studies supported a link between OSA severity and glycemic control. The Sleep AHEAD study, involving obese type 2 diabetes patients, analyzed the relationship between sleep and metabolic parameters in 305 subjects (141). The only significant association was an inverse correlation between fasting glucose levels and sleep efficiency, but not AHI or other sleep variables. A limitation of this study is that PSG was performed in the homes of the participants and, thus, was often of lower quality and shorter duration than in the laboratory.

Altogether, evidence supports an adverse impact of OSA on glycemic control in patients with type 2 diabetes. As differences in A1c levels among patients with different degrees of severity of OSA are comparable to the effect size of the most powerful combinations of available diabetes medications, multiple studies have attempted to determine whether OSA treatment with CPAP in patients with diabetes improves glycemic control, as discussed later in this chapter.

OBSTRUCTIVE SLEEP APNEA AND DIABETES COMPLICATIONS

The development of microvascular complications of diabetes is associated with poor long-term glycemic control and increased health care costs. Because OSA is associated with activation of the sympathetic nervous system and of inflammatory processes, as well as oxidative stress, it is likely that OSA contributes to the development and/or progression of these complications irrespective of strategies to optimize diabetes control. Although the details are beyond the scope of this chapter, there is evidence that type 2 diabetes patients with OSA may suffer more complications, including peripheral neuropathy, retinopathy, and nephropathy (142,143,144), than those without OSA, with the degree of oxygen desaturation being an independent predictor in some studies (142,143). This field is a subject of ongoing research to establish whether OSA is an independent predictor of diabetes complications and whether OSA treatment delays the development or decreases the severity of microvascular complications.

REM-RELATED OBSTRUCTIVE SLEEP APNEA

The reduction in pharyngeal muscle activity that normally occurs during REM sleep is associated with more prolonged obstructive events and more severe oxygen desaturation in OSA patients (145). In some patients, the respiratory events occur predominantly during REM sleep. This phenomenon has been termed "REM-related OSA" and is prevalent in 10%–36% of OSA patients (146). Compared to NREM sleep, apneas and hypopneas during REM sleep are associated with higher sympathetic nervous system activation and greater degrees of hypoxemia (147). REM-related OSA may lead to greater cardiometabolic derangements and more adverse health consequences (146). This hypothesis was addressed for the first time in a cross-sectional study involving laboratory PSG in 115 participants with type 2 diabetes. Higher REM AHI and REM microarousal index were significantly correlated with higher A1c levels, supporting the significance of REM-related OSA for glucose metabolism (148). In contrast, associations between NREM AHI or NREM microarousal index and A1c were nonsignificant. An important implication of this study is that metabolic benefits of CPAP treatment of OSA may not be achieved with CPAP use of only 3–5 hours per night.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT ON GLUCOSE METABOLISM AND DIABETES CONTROL

Given the large body of relatively consistent data relating OSA to abnormalities in glucose metabolism, it is somewhat surprising to find that studies on the effects of treatment with CPAP therapy on glucose metabolism in OSA have produced equivocal results (149,150,151). While some investigators have demonstrated a favorable effect of CPAP therapy on glucose metabolism (152), others have found no effect. Among the nine randomized controlled trials (RCTs) comparing active CPAP to sham-CPAP with treatment duration between 1 week and 3 months and device use of 2.8–6.2 hours per night, six found that active CPAP did not improve fasting glucose levels or insulin sensitivity (153,154,155,156,157), one observed an improvement of insulin sensitivity at 24 weeks (nonrandomized part of the study) but not at 12 weeks during randomization (158), and two reported an improvement in insulin sensitivity, mainly in obese patients or those with severe OSA (159,160). In a study focusing only on patients with relatively well-controlled diabetes (A1c 6.5%–8.5% [48–69 mmol/mol]), CPAP treatment did not result in significant changes in A1c levels (161).

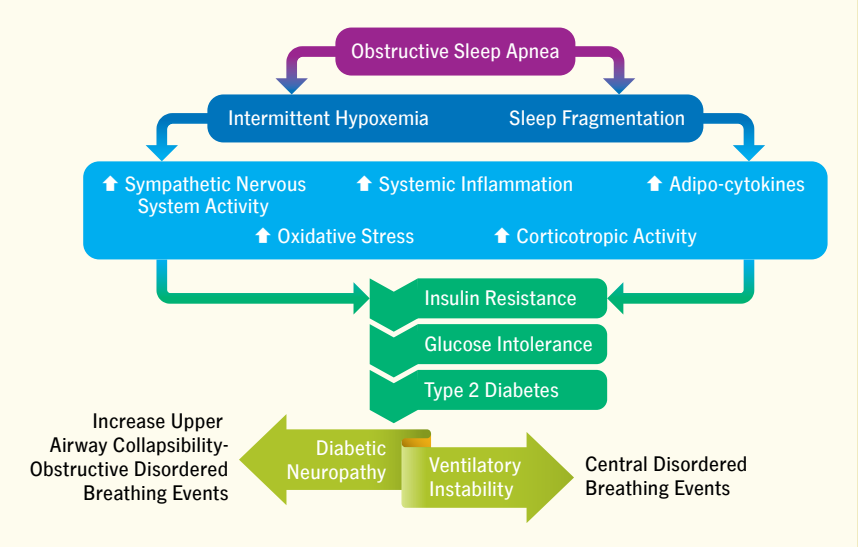
Five meta-analyses have tried to summarize the impact of CPAP treatment on markers of glucose metabolism (162,163,164,165,166). The inclusion criteria of these meta-analyses varied between including only studies with inactive control or sham CPAP, including both observational studies and RCTs, or including only the studies that utilized A1c as a part of the outcome measures. Therefore, these five meta-analyses included different studies with some overlap. Hecht *et al.* reported no effect of CPAP treatment on insulin, HOMA, or A1c levels from six studies utilizing inactive control or sham CPAP (total 296 participants) (164). Iftikhar *et al.* reported no effects on A1c from nine studies (both observational and RCTs) involving 151 participants (162). This conclusion is in agreement with the study by Chen *et al.* that found no improvement in A1c levels, although the index of insulin resistance improved significantly (165). In nondiabetic subjects, there seems to be an improvement of insulin resistance after CPAP therapy. Yang *et al.* found an improvement in HOMA-IR with a mean difference of -0.55 (95% CI -0.91 to -0.20) in nondiabetic subjects with moderate to severe OSA (from nine studies, both observational and RCTs, totaling 248 subjects) but no differences in fasting glucose levels in 39 diabetic participants from two studies (163). Similar results were found in the analysis by Iftikhar *et al.* (166).

The inconsistency of results in the published literature is most likely due to a number of methodologic limitations, such as small sample sizes, inadequate consideration for the confounding effects of obesity, lack of data on CPAP compliance, or suboptimal CPAP compliance. As mentioned earlier, there is evidence that the adverse impact of untreated OSA on glycemic control in diabetes may be primarily caused by obstructive events occurring during REM, rather than NREM, sleep (148). CPAP use of 3–5 hours per night only treats a small portion of REM-related events and could be the reason why several RCTs of CPAP in diabetic patients have failed to observe a beneficial effect on glycemic control. Alternatively, it is plausible that the metabolic effects of OSA are irreversible, particularly if recurrent exposure to intermittent hypoxemia and sleep fragmentation causes irreparable changes in insulin sensitivity, insulin secretion, or both. In light of the limited data, it is indeed premature to infer whether CPAP therapy in OSA does or does not improve glucose metabolism. Ongoing research efforts in the form of randomized clinical trials will hopefully help determine whether CPAP therapy has favorable effects on glucose metabolism among patients with OSA. Of note, a RCT examining the impact of 8 hours of nightly CPAP in the laboratory on glucose tolerance in individuals with prediabetes reported positive findings (167).

MECHANISTIC LINKS BETWEEN OBSTRUCTIVE SLEEP APNEA AND METABOLIC DYSFUNCTION

If the link between OSA and abnormalities in glucose metabolism is eventually proven to be causal, what are the potential mechanisms that underlie the association? Most likely, alterations in glucose homeostasis induced by OSA are mediated by a complex set of interactive mechanisms that are triggered by the cyclical hypoxemia and recurrent arousals from sleep (Figure 25.5) (168). In the sections that follow, physiological systems

FIGURE 25.5. Putative Mechanisms Linking Sleep Apnea to Type 2 Diabetes



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that may play an important role in mediating the effects of OSA on glucose metabolism are highlighted. Particular focus is given to the sympathetic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, formation of reactive oxygen species (ROS), and low-grade systemic inflammation. It is important to recognize that for each physiological system influenced by OSA, intermittent hypoxemia and sleep fragmentation may perturb the system independently or synergistically.

Role for the Sympathetic Nervous System

Compared to normal subjects, patients with OSA exhibit higher levels of sympathetic nervous system activity not just during sleep, but also during wakefulness (169). The decrease in oxyhemoglobin saturation and the concurrent increase in carbon dioxide with each disordered breathing event elicit a chemoreflex-mediated surge in sympathetic activity (170,171). Observational and experimental studies have demonstrated that even brief arousals from sleep can lead to a surge in sympathetic activity (172,173). Thus, intermittent hypoxemia and recurrent arousals from sleep can shift autonomic balance in patients with OSA. Although the exact mechanisms through which sympathetic activation affects insulin sensitivity are not well defined, there is little doubt that it has a central role in the regulation of glucose and fat metabolism (174). Catecholamines reduce insulin sensitivity and insulin-mediated glucose uptake (175). Administration of epinephrine in normal subjects can decrease insulin-mediated glycogenesis, increase glycolysis, and dampen the ability of glucose to stimulate its own disposal (176,177). Higher levels of sympathetic activity have lipolytic effects through signaling pathways that activate hormone-sensitive lipase, which can mobilize nonesterified fatty acids (178). An abrupt increase in circulating free fatty acids can worsen insulin sensitivity, while a decrease can improve insulin sensitivity, hyperinsulinemia, and glucose tolerance (179,180). In addition to the above effects, activation of the sympathetic nervous system can lead to systemic vasoconstriction, which can also affect glucose metabolism. A decrease in vascular lumen size in skeletal muscle from vasoconstriction shunts glucose and insulin to less metabolically active areas of skeletal muscle (181) and, thus, decreases overall glucose uptake (182). Sympathetic activation can also alter skeletal muscle morphology to a more insulin resistant type (183), inhibit insulin signaling, and decrease insulin-mediated glucose uptake by adipocytes (184). Thus, there is sufficient basis to speculate that an increase in sympathetic nervous system activity due to recurrent intermittent hypoxemia and sleep fragmentation plays a central role in altering glucose metabolism in sleep apnea.

Role of the Hypothalamic-Pituitary-Adrenal Axis

Recurrent intermittent hypoxemia and arousals in OSA could alter glucose metabolism by modulating the function of the HPA axis. Specifically, a stress-related increase in HPA activity and cortisol secretion could lead to insulin resistance and hyperglycemia. Observational data from studies of high altitude or of hypobaric conditions indicate that hypoxia modifies the diurnal pattern of the HPA axis and increases circulating cortisol (185,186,187,188,189,190,191). Moreover, brief arousals or sustained awakenings from sleep can activate the HPA axis and can further augment corticotropic function (192,193). However, experimentally induced micro-arousals designed to selectively suppress SWS for three consecutive nights in healthy young adults had no significant impact on the 24-hour profile of cortisol levels, despite an overall sleep fragmentation in the range of that associated with moderate to severe OSA (41). A notable limitation in many of the available studies on HPA axis activity in OSA is that corticotropic function was assessed with a single measurement of serum cortisol. While convenient, isolated cortisol measurements cannot reveal diurnal changes or the temporal variability in cortisol secretion.

Characterizing HPA dysfunction in OSA has scientific and clinical relevance, as it would help clarify its putative role in mediating insulin resistance and glucose intolerance. It is well established that cortisol and other glucocorticoids interfere with glucose metabolism at several different levels (194,195). Cortisol increases hepatic gluconeogenesis and causes protein degradation. It also activates lipoprotein lipase, which mobilizes nonesterified fatty acids and can greatly diminish insulin sensitivity. Moreover, cortisol inhibits beta cell secretion of insulin and sequentially modifies multiple aspects of the insulin-mediated glucose transport system. In a small study of CPAP treatment of OSA in obese women with the polycystic ovary syndrome, there was a trend for reduced evening cortisol concentrations following CPAP (196). Given the myriad of adverse metabolic effects of HPA dysfunction, further research is needed to determine whether OSA affects HPA activity and, thus, alters glucose metabolism function.

Reactive Oxygen Species as a Causal Intermediate

Repetitive cycles of hypoxemia followed by re-oxygenation in OSA could increase ROS production similar to what has been observed with ischemia-reperfusion injury (197,198). Data indeed suggest that OSA is associated with higher concentrations of ROS that may, in turn, negatively influence glucose metabolism. Using study samples of modest size along with assessments before and after initiation of CPAP therapy, a number of studies have shown abnormalities in lipid peroxidation, higher isoprostane levels, and elevated markers of DNA oxidation in patients with OSA compared to normal subjects and a decline in these markers after treatment with CPAP (199,200,201,202,203). Moreover, antioxidant defenses may also be diminished in OSA (204,205). Finally, a number of *in vitro* studies have shown that apneic patients have increased adhesion molecule expression and production of ROS in leukocytes (206), an augmented release of neutrophil superoxide (207), and increased oxidized low-density lipoprotein (LDL) autoantibodies (208).

Excessive concentrations of ROS can be harmful particularly to the pancreatic beta cell given that this cell population is relatively low in antioxidant enzyme mechanisms, such as catalase, glutathione peroxidase, and superoxide dismutase (209). ROS formation is also accompanied by an inhibition of insulin-stimulated substrate uptake in insulin-sensitive tissues, such as muscle and adipose tissue (210,211,212). Moreover, several studies also suggest that pharmacological doses of the antioxidants vitamin E, vitamin C, and lipoic acid in healthy volunteers and diabetic patients may improve insulin sensitivity and metabolic control (213,214,215,216). While mechanisms underlying the effects of an altered redox state on insulin sensitivity require further elucidation, several converging lines of evidence, including clinical and experimental data, indicate that oxidative stress is a causative factor. Thus, OSA-associated increase in free radical generation could represent a causal component for the development of insulin resistance.

Importance of Systemic Inflammation and Adipocytokines

Low-grade systemic inflammation may be yet another mechanism relating OSA to disorders of glucose metabolism. Compared to normal subjects, patients with OSA have higher levels of circulating adhesion molecules (217,218,219,220,221,222) and inflammatory cytokines, including IL-6 and TNF-alpha, which decrease with CPAP therapy (223,224,225,226). Studies examining specific leukocyte populations also reveal that OSA patients exhibit monocyte and lymphocyte activation, which improve with CPAP therapy (227,228,229). In normal subjects, hypoxia increases circulating leukocyte concentration and alters the functional characteristics of lymphocytes (230,231,232). Sympathetic hyperactivity in sleep apnea may also influence the innate immune response given that adrenergic stimulation enhances macrophage and lymphocyte activity and alters their proliferation, circulation, and cytokine production (233,234). A concern in invoking systemic inflammation as an intermediate between OSA and metabolic dysfunction is the confounding effects of obesity. Adipose tissue can increase systemic inflammation, as visceral adiposity has an enhanced capacity to produce numerous cytokines, including IL-6 and TNF-alpha. However, it appears that even after considering the effects of BMI and measures of visceral obesity, sleep apnea severity is independently correlated with the degree of inflammatory burden (235). Thus, low-grade systemic inflammation could potentially mediate the adverse metabolic effects of OSA.

In addition to the systemic inflammation, adipocyte-derived factors, such as leptin, adiponectin, and resistin, may play a role in the genesis of sleep apnea-related abnormalities in glucose metabolism. Leptin regulates hunger and weight gain by increasing anorexigenic and decreasing orexigenic neuropeptides in the hypothalamus (236). Peripherally, leptin appears to be involved in governing glucose homeostasis (237,238). A growing body of literature shows that patients with sleep apnea have higher leptin levels (239,240,241,242,243,244,245), which decrease with CPAP therapy independent of any changes in body weight (246,247,248,249). Moreover, exposure to hypoxic conditions increases leptin levels in normal subjects (250). Thus, higher leptin levels in OSA could certainly alter glucose metabolism. Adiponectin has endogenous insulin-sensitizing properties. Adiponectin is lower in patients with sleep apnea than in normal subjects, and circulating levels appear to correlate with the nadir in oxygen saturation (251,252,253,254,255,256,257). Resistin is another adipocytokine that inhibits insulin action and may have a role in the pathogenesis of type 2 diabetes (258,259). At present, there are limited data on whether resistin levels differ between patients with OSA and control subjects (251,260,261). Clearly, additional work is needed to determine whether adiponectin and resistin are affected by intermittent hypoxemia and recurrent arousals and whether these adipocytokines could be involved in causing metabolic dysfunction in OSA.

IMPACT OF TYPE 2 DIABETES ON BREATHING DISORDERS DURING SLEEP

While much of the discussion has been focused on the consideration that OSA contributes to metabolic dysfunction, there is also the possibility of reverse causation. That is, once hyperglycemia and type 2 diabetes develop, can these then contribute to the incidence or worsening of OSA? Cross-sectional studies demonstrating a high prevalence of OSA in type 2 diabetes do not provide evidence for a direction of causality.

Data on the occurrence and temporal progression of OSA in diabetic individuals are lacking, as are studies exploring the possibility that type 2 diabetes could worsen OSA severity (262,263,264,265,266). Experimental data from animal models show that insulin resistance is associated with reduced ventilatory response that can be enhanced with insulin treatment (267). Whether such abnormalities in ventilatory control have downstream consequences and increase human predisposition to apneas and hypopneas during sleep is not known. Ongoing research efforts based on longitudinal studies will hopefully clarify whether progression of OSA differs between diabetic and nondiabetic subjects and is affected by glycemic control or the type of pharmacological treatment of diabetes.

Type 2 diabetes may also promote the expression of central sleep apnea. Using data from the community-based Sleep Heart Health Study, Resnick *et al.* (135) showed that participants with type 2 diabetes had a higher prevalence of Cheyne-Stokes or periodic breathing and central respiratory events during sleep than those without type 2 diabetes. In this cross-sectional analysis, the higher prevalence of periodic breathing in diabetic versus nondiabetic individuals (OR 1.74) persisted even after accounting for multiple covariates, including age, sex, BMI, and prevalent cardiovascular disease. It is possible that diabetes-associated autonomic dysfunction may lead to instability of the respiratory

control system via enhanced central chemoreceptor-mediated gain, as well as cardiac impairments with prolonged circulatory time. Evidence supporting the notion that diabetic individuals with autonomic neuropathy may have a heightened response to hypercapnia has been previously described (268). Coupled with numerous clinical case series (269,270,271), the available research suggests that central sleep-disordered breathing is prevalent in type 2 diabetes, particularly if there is concurrent evidence of autonomic dysfunction.

SLEEP DISTURBANCES DURING PREGNANCY: RELATIONSHIP WITH GLUCOSE METABOLISM AND GESTATIONAL DIABETES

Sleep alterations are common during pregnancy due to hormonal and physical changes. Progesterone has sedative effects and can stimulate respiratory drive, while estrogen increases hyperemia, mucosal edema, and upper airway resistance, resulting in nasal stuffiness and snoring (272). Upward displacement of the diaphragm may cause a reduction in functional residual volume of the lungs and, therefore, oxygen reserve. Nausea, vomiting, frequent urination, and backache can decrease sleep efficiency and increase nocturnal awakenings.

During the first trimester, sleepiness is common, and women report an increase in sleep duration of approximately 0.7 hours (273). However, sleep efficiency and percentage of SWS decrease significantly (274). Sleep duration decreases in the late second trimester (274), although there is an observed increase in percentage of SWS (275). During the third trimester, a majority of women report sleep disturbances. There is a decrease in percentage of SWS and REM sleep (272) with an increase in time spent in light NREM sleep (stage N1) (276). Wake time after sleep onset increases, but total sleep time approximates the prepregnancy state (274). At this stage of pregnancy, a majority of women report taking daytime naps (277). Snoring is quite common, as two large studies, including in total more than 2,700 pregnant women, revealed that about one-third of participants reported snoring, with 25% reporting pregnancy-onset snoring (278,279). Symptoms of OSA increased during pregnancy in a prospective study, especially in women whose BMI exceeded 25 kg/m^2 (280).

Gestational diabetes mellitus affects 2%–25% of pregnant women and is associated with adverse maternal-fetal outcomes, as discussed in Chapter 4 *Gestational Diabetes*. An increased risk for gestational diabetes or hyperglycemia is associated with sleep disturbances, including OSA and snoring, short sleep duration, and increased daytime sleepiness. A review of the literature found 15 studies that investigated sleep and glucose intolerance in pregnancy: eight using questionnaires, six using objective sleep measurements, and one using both methods (Table 25.11) (278, 279,281,282,283,284,285,286,287, 288,289,290,291,292,293). Seven studies assessed sleep duration (five by self-report, one by combined self-report and PSG, and one by actigraphy) (281,282,284,286,289,290,293). Of these seven studies, four found a significant association between short sleep duration and increased risk for gestational diabetes/hyperglycemia (281,282,284,290). Twelve studies assessed symptoms of OSA or a diagnosis of OSA (278,279,281,282,283,284,287, 288,289,291,292,293). Of the eight studies using questionnaires, five found significant associations between OSA symptoms and gestational diabetes or maternal hyperglycemia (279,281,282,284,289). Among the six studies using objective measurements (five used PSG and one used portable home monitoring) (287,288,289,291,292,293), four found a significant association between OSA and increased gestational diabetes/hyperglycemia risks (287,288,291,292). A meta-analysis included nine of these studies (total 9,795 participants) and found a significant association between OSA and gestational diabetes, with an odds ratio of 2.18 (95% CI 1.59–2.99) (294). When considering only studies including BMI as a covariate, the adjusted odds ratio was 3.06 (95% CI 1.89–4.96). One study found an association between severe daytime sleepiness and gestational diabetes, although the number of women with severe daytime sleepiness was small (285). In addition, increased daytime napping was found to be associated with maternal hyperglycemia in one study (289). The mechanisms by which sleep disturbances increase the risk for gestational diabetes are likely to overlap those linking sleep disturbances and metabolic alterations in nonpregnant populations but have not been studied specifically in pregnancy.

Short sleep, snoring, and OSA in pregnancy have been linked to other adverse maternal and fetal outcomes, including an increased risk of preeclampsia, gestational hypertension (GHTN), preterm birth, and unplanned caesarean delivery (278,279,288,295,296,297). A meta-analysis revealed an association between sleep-disordered breathing and GHTN, with an odds ratio of 2.34 (95% CI 1.60–3.03), as well as with low birth weight, with an odds ratio of 1.39 (95% CI 1.14–1.65) (298). Oxidative stress, release of proinflammatory cytokines, increased sympathetic activation, peripheral vasoconstriction, and endothelial dysfunction resulting from sleep disturbances are all likely to contribute to these complications (299).

Treatment with CPAP has been shown to be safe during pregnancy and to improve blood pressure control and pregnancy outcomes in women with hypertension and chronic snoring (300). The question of whether treating OSA during pregnancy improves glucose metabolism is crucial as maternal glycemia affects fetal health, but it has not yet been addressed.

TABLE 25.11. Studies Investigating the Association Between Sleep in Pregnancy and Gestational Diabetes or Hyperglycemia

YEARS (REF.)	SAMPLE SIZE	TIME OF ASSESSMENT	ASSESSMENT	OUTCOMES OF INTEREST*	RESULTS
Studies utilizing questionnaires					
2003–2006 (281)	1,290	Early pregnancy	Sleep duration Snoring	Gestational diabetes	Sleeping ≤4 h was associated with increased risk of gestational diabetes compared to sleeping 9 h (RR 5.56 [95% CI 1.31–23.69], with RR 3.23 [95% CI 0.34–30.41] for lean and RR 9.83 [95% CI 1.12–86.32] for overweight women), adjusting for age and race/ethnicity. Women who snored "most or all of the time" had increased risk of gestational diabetes compared to those who did not snore (RR 1.86 [95% CI 0.88–3.94], with RR 6.9 [95% CI 2.87–16.2] for overweight women who snored).
NR (279)	1,000	Immediate postpartum period	Multivariable Apnea Prediction Index	Gestational diabetes	SDB symptoms were associated with gestational diabetes, OR 2.1 (95% CI 1.3–3.4), adjusting for age, BMI at delivery, multiple pregnancies, and current smoking.
2007–2008 (282)	189	Early pregnancy (6–20 weeks) and third trimester	Sleep duration Snoring	Gestational diabetes 1-h glucose values from 50 g OGTT	Women sleeping <7 h had higher glucose values and higher incidence of gestational diabetes, OR 11.7 (95% CI 1.2–114.5) than those who slept ≥7 h adjusting for age, race/ethnicity, BMI, and frequent snoring. Women who snored ≥3 times/week had higher glucose values and higher incidence of gestational diabetes, OR 6.9 (95% CI 1.4–33.9), adjusting for age, race/ethnicity, BMI, and sleeping <7 h.
NR (283)	465	During pregnancy or admission for labor	Berlin Questionnaire	Gestational diabetes	More women with positive Berlin Questionnaire had gestational diabetes, but not after adjusting for BMI and maternal medical disorders.
2008–2010 (284)	169	Second trimester (26 weeks)	Pittsburgh Sleep Quality Index, Berlin Questionnaire, Epworth Sleepiness Scale	Gestational diabetes 1-h glucose values from 50 g OGTT	Each hour of reduced sleep time was associated with 4% increase in glucose levels. Increased OSA risk was associated with gestational diabetes, OR 3.0 (95% CI 1.2–7.4). Sleeping <7 h was associated with gestational diabetes, OR 2.4 (95% CI 1.0–5.9). Combination of increased SDB risk and sleeping <7 h was associated with gestational diabetes, OR 3.4 (95% CI 1.3–8.7). Frequent snoring (>3–4 days/week) was associated with gestational diabetes, OR 3.4 (95% CI 1.3–8.8).
2007–2010 (278)	1,719	Third trimester	Snoring	Gestational diabetes	No association between chronic snoring (3–4 times/week) or pregnancy-onset snoring with gestational diabetes.
2006–2008 (285)	1,000	Immediate postpartum period	Epworth Sleepiness Scale	Gestational diabetes	No association with gestational diabetes in those with score >10. Significant association with gestational diabetes was found in those with score >16 after adjusting for age, BMI at delivery, and current smoking. The authors cautioned that the number of women with score >16 was small.
NR (286)	1,211	Second to third trimester	Self-reported sleep duration	Maternal hyperglycemia defined as 1-h glucose value ≥140 mg/dL after 50 g OGTT	No differences in glucose values were found between short sleepers (≤6 h/night), normal sleepers (7–9 h/night), or long sleepers (≥10 h/night).
Studies utilizing objective measures of sleep					
2000–2009 (287)	143	PSG: 46% before and 54% after delivery	PSG; mild (AHI 5–14.9) and moderate to severe OSA (AHI ≥15)	Gestational diabetes (as a part of adverse pregnancy outcomes)	Thirty-four women with mild and 26 with moderate to severe OSA. Six women had gestational diabetes. None of the women without OSA had gestational diabetes, while 5.9% of those with mild OSA and 11.5% of those with moderate to severe OSA had gestational diabetes (p=0.004).

Table 25.11 continues on the next page.

TABLE 25.11. (continued)

YEARS (REF.)	SAMPLE SIZE	TIME OF ASSESSMENT	ASSESSMENT	OUTCOMES OF INTEREST*	RESULTS
2005 (288)	791 with OSA and 3,955 age-matched women presumed without OSA	Women with OSA had PSG within 1 year prior to index deliveries. Matched controls did not have PSG.	PSG; diagnosis of OSA	Gestational diabetes	One hundred and sixty-seven women were diagnosed with gestational diabetes. OSA was significantly associated with gestational diabetes, OR 1.63 (95% CI 1.07–2.48) after adjusting for education, marital status, gestational hypertension, anemia, coronary heart disease, hyperlipidemia, obesity, geographic region, paternal age, infant's sex, and parity.
NR (289)	104	First trimester, 83 had repeated PSG in third trimester	PSG Pittsburgh Sleep Quality Index, Multivariable Apnea Prediction Index	Maternal hyperglycemia defined as 1-h glucose value ≥135 mg/dL after 50 g OGTT	Eleven women had hyperglycemia. Self-reported loud snoring, snorting/gasping, and apneas were associated with maternal hyperglycemia, OR 3.37 (95% CI 1.44–8.32) after adjusting for age, race, neck circumference, and shift work. Self-reported nap duration was associated with hyperglycemia, OR 1.64 (95% CI 1.00–2.68) after adjusting for age, race, and neck circumference. First trimester AHI, self-reported sleep duration, sleep duration and efficiency by PSG were not associated with hyperglycemia.
2009–2010 (290)	76	21 weeks of gestation	Actigraphy for 6 days; sleep duration	1-h glucose after 50 g OGTT	Each hour of reduced sleep time was associated with 8.2 mg/dL increase in glucose levels. Shorter night time sleep was associated with hyperglycemia (glucose ≥130 mg/dL) after adjusting for age and BMI, OR 0.2.
NR (291)	75 (high-risk group for preeclampsia)	17 weeks of gestation	Portable monitor (WPAT200); diagnosis of OSA	Gestational diabetes	OSA was significantly associated with gestational diabetes, OR 3.7 (95% CI 1.1–13.3) after adjusting for maternal age, BMI, and history of chronic hypertension.
2009–2012 (292)	45 (15 GDM, 15 pregnant NGT, and 15 nonpregnant NGT; matched for age and ethnicity)	Late second to early third trimester in pregnant women	PSG; diagnosis of OSA (AHI ≥5)	Risk of OSA in women with gestational diabetes	Eleven women with gestational diabetes (73%) had OSA. Gestational diabetes was significantly associated with OSA, OR 6.6 (95% CI 1.15–37.96), after adjusting for prepregnancy BMI. In NGT women, pregnancy was associated with higher AHI, microarousal index, and wake time after sleep onset.
Study utilizing questionnaire and objective measure of sleep					
2010–2012 (293)	52 (26 GDM and 26 NGT, BMI <35 kg/m^2); matched by gestational age at PSG, age, and BMI	24–32 weeks of gestation	PSG; diagnosis of OSA (AHI ≥5), self-reported sleep duration	Risk of OSA in women with gestational diabetes	No significant differences in OSA diagnosis between controls and participants with gestational diabetes, 20% versus 31%, respectively, prepregnancy BMI-adjusted OR 1.90 (95% CI 0.52–6.88). No significant differences in AHI (control vs. gestational diabetes; mean 4.2 vs. 3.8), oxygen desaturation index, snoring, and flow limitation, self-reported sleep duration between the two groups.

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions.* AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; h, hour; NGT, normal glucose tolerance; NR, not reported; OGTT, oral glucose tolerance test; OR, odds ratio; OSA, obstructive sleep apnea; PSG, polysomnogram; RR, relative risk; SDB, sleep-disordered breathing.

* Many studies had other outcomes of interest, but only outcomes related to glucose metabolism are summarized in this table.

SOURCE: References are listed within the table.

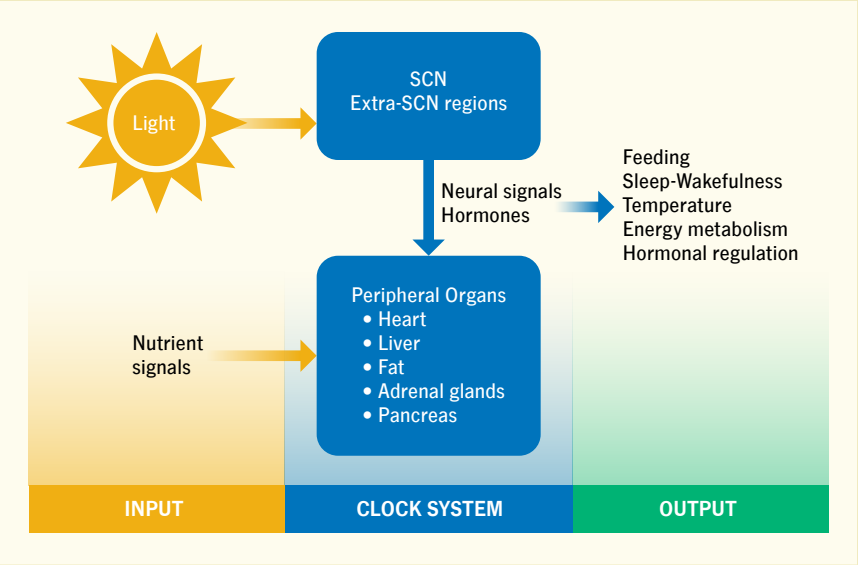
THE CIRCADIAN SYSTEM AND GLUCOSE METABOLISM

The circadian system, controlled by the master circadian clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus, plays a major role in regulating daily rhythms of sleep/wake cycle, feeding behavior, central and peripheral tissue metabolism, and hormonal secretions (301). The clock in the SCN is synchronized to the 24-hour day primarily by light signal via the retinohypothalamic tract. It then relays the information via hormonal and neuronal pathways to the rest of the brain and to peripheral organs, such as the heart, liver, adipose tissue, muscle, adrenals, and pancreas, which all possess "peripheral clocks," leading to coordinated rhythms and behaviors (Figure 25.6) (2,302). The central clock mechanism consists of a transcription-translation negative feedback loop involving several core clock genes including *Clock* (circadian locomotor output cycles kaput), *Bmal1* (brain and muscle Arnt-like protein-1), *Per 1-3* (Period 1-3), and *Cry1-2 (*Cryptochrome 1-2), as well as feedback signals from nutrient intake (303).

There is evidence that circadian disruption has detrimental effects on energy metabolism. It was first shown that *Clock* mutant mice shift their feeding and activity behavior to their normally inactive phase and develop obesity and the metabolic syndrome (hyperlipidemia, hepatic steatosis, hyperglycemia, and hypoinsulinemia) (304). Habitual sleep duration in this mutant animal is about 1 hour shorter than in the wild type animal, thus resulting in a condition of lifelong insufficient sleep (304). In another study, wild type mice exposed to dim light during their usual biological night were shown to shift their food intake into the inactive phase. This was associated with reduced glucose tolerance and a greater gain in body mass, suggesting that eating at an adverse circadian time may contribute to metabolic dysfunction (305).

In humans, living in modern industrialized societies with 24-hour access to light coupled with work/social obligations often leads to behaviors that are inappropriately timed relative to endogenous circadian rhythms. This mismatch in timing is termed "circadian misalignment." Night shift work is an example of severe circadian misalignment, as workers are awake, active, and eating during their biological night and trying to sleep and fast during their biological day. In 2004, 14.8% of all workers in the United States had work schedules differing from a daytime schedule (306). This proportion was much higher for workers in service occupations, such as security (50.6%), and for health care professionals (38.3%). Shift work is associated with abnormal glucose metabolism, including IGT and diabetes. In a retrospective study of 6,413 participants in Japan followed for 9.9 years, two groups of rotating shift workers with slightly different schedules both had a significantly increased risk of developing IGT (defined as A1c ≥5.9% [≥41 mmol/mol]) with hazard ratios of 1.78 (95% CI 1.49–2.14) and 2.62 (95% CI 2.17–3.14) (307). In addition, longer duration of shift work, in a dose response fashion, was associated with a gradual increase in A1c levels over time in those without diabetes at baseline (308). Most cross-sectional studies, all outside the United States, have also found an association between shift work and prevalence of diabetes (Table 25.12).

FIGURE 25.6. Illustration of the Circadian System Regulation



SCN, suprachiasmatic nuclei.

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To date, 11 of 12 prospective and retrospective cohort studies demonstrated that shift work was associated with an increased risk of developing diabetes (Table 25.13) (29,30,309,310,311,312,313,314,315,316,317,318). The largest study, the Nurses' Health Study I and II, followed 177,184 participants for 18–20 years and found that those who worked rotating night shifts had increased hazard ratios for diabetes of 1.03–1.24, after adjusting for traditional diabetes risk factors, as well as BMI, with higher risk in those who had a longer duration of shift work compared to those reporting no shift work (314). The risk was estimated to be a 5% increase for every 5 years of shift work. Night shift work was found to be associated with incident diabetes in participants of the Black Women's Health Study (2005–2013), with increasing risk according to the number of years night shift work was performed (HR 1.17, 95% CI 1.04–1.31, for 1–2 years; HR 1.23, 95% CI 1.06–1.41, for 3–9 years; and HR 1.42, 95% CI 1.19–1.70, for ≥10 years) (318).

There may be several reasons why shift workers are at higher risk for developing diabetes. Besides circadian misalignment, insufficient sleep and poor sleep quality, themselves associated with increased diabetes risk, are very common

TABLE 25.12. Cross-Sectional Studies Exploring Associations Between Shift Work and Diabetes

LOCATION, YEARS (REF.)	POPULATION	SAMPLE SIZE	SHIFT WORKER	OUTCOME	RESULTS
Japan, NR (428)	Male factory workers	2,167	Day workers versus three-shift workers	Diabetes, defined as glucose level after 50 g glucose challenge, >185 mg/dL at 1 hour and >150 mg/dL at 2 hours (Japanese Diabetic Society)	Prevalence of diabetes in three-shift workers was 2.1% versus 0.9% in day workers.
Japan, 1995–1998 (429)	Employees participating in yearly check-ups, age 30–59 years	3,650	Day shift versus any shift work	Hyperglycemia, defined as FPG ≥126 mg/dL	Shift work was associated with hyperglycemia in the age group 30–39 years, OR 6.75 (95% CI 1.31–56.1). No association was found in the age groups 40–49 or 50–59 years.
Sweden, 1992–1998 (430)	Employees in paper and pulp manufacturing plants, age ≥20 years	1,590	Day shift versus three-shift work	Hyperglycemia, defined as FPG ≥126 mg/dL	Three-shift work was not associated with hyperglycemia.
Japan, 2009 (431)	Male employees participating in annual health check-ups	475	Day shift versus seasonal shift work versus continuous shift work	Diabetes, defined as FPG ≥126 mg/dL and A1c ≥6.5%	No association was found between shift work and diabetes in those age <45 years. Among those age ≥45 years, the association between continuous shift work and diabetes was more pronounced, OR 2.24 (95% CI 0.71–7.06) versus OR 0.61 (95% CI 0.07–5.02) in seasonal workers.

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; CI, confidence interval; FPG, fasting plasma glucose; NR, not reported; OR, odds ratio.

SOURCE: References are listed within the table.

TABLE 25.13. Cohort Studies of the Relationship Between Shift Work and Incident Diabetes or Impaired Glucose Tolerance

STUDY, YEAR (REF.)	POPULATION	SAMPLE SIZE	FOLLOW-UP (YEARS)	SHIFT WORK ASSESSMENT	DIABETES ASSESSMENT	RESULTS
Stockholm Diabetes Prevention Program, 1992–2006 (309)	Sweden, mean age 47.1 years	5,432	8–10	Shift work from questionnaire	OGTT, FPG ≥126 mg/dL or 2-hour glucose value ≥200 mg/dL	Shift work was not associated with diabetes after adjusting for multiple factors, OR 1.9 (95% CI 0.8–4.4) in women and OR 0.8 (95% CI 0.4–1.7) in men.
China, 2008–2010 (310)	Retired workers from Dongfeng Motor Corporation, mean age 63.6 years	26,463	Retrospective	Shift work from questionnaire	FPG ≥126 mg/dL or report of diabetes diagnosis or use of medication	Longer shift work (10–19 years and ≥20 years) was associated with diabetes, OR 1.10 (95% CI 1.00–1.22) and OR 1.16 (95% CI 1.06–1.27), respectively.
Pennsylvania, NR (311)	Retired shift workers, mean age 75.4 years	1,111	Retrospective	Work overlap 12:00–6:00 a.m., from questionnaire	Self-reported diabetes diagnosis	Longer exposures to shift work (8–14 years and >20 years) were associated with diabetes, OR 1.4 and OR 1.99, respectively.
Japan, 1993–2001 (312)	Male workers in a sash and zipper company, mean age 34.3 years	2,860	8	Dayshift, rotating two or three shift, from questionnaire	A1c ≥6.1% or report of diabetes diagnosis by physician	Two-shift work was associated with diabetes, RR 2.01 (95% CI 1.00–4.34). No association was found for three-shift workers.
Germany, 1995–2006 (313)	Workers from a chemical corporation, mean age 38.1 years	31,346	11	Rotating shift, from work registry	Diabetes diagnosis according to chart review	Shift work was associated with diabetes, HR 1.33 (95% CI 1.14–1.55).
Nurses' Health Study I, 1988–2008 (314)	Age 42–67 years	69,269	18–20	Rotating night shift, from questionnaire	Self-reported diabetes diagnosis	Each 5 years of shift work was associated with diabetes, HR 1.05 (95% CI 1.02–1.07).
Nurses' Health Study II, 1989–2007 (314)	Age 25–42 years	107,915	18–20	Rotating night shift, from questionnaire	Self-reported diabetes diagnosis	Each 5 years of shift work was associated with diabetes, HR 1.05 (95% CI 1.01–1.08).
Japan, 1991–2001 (315)	Workers from a Japanese steel company, mean age 36.1 years	5,629	10	Alternating shift from work registry	Self-reported diabetes diagnosis by physicians or A1c ≥6.0%	Alternate shift work was associated with diabetes, OR 1.35 (95% CI 1.05–1.75).

Table 25.13 continues on the next page.

TABLE 25.13. (continued)

STUDY, YEAR (REF.)	POPULATION	SAMPLE SIZE	FOLLOW-UP (YEARS)	SHIFT WORK ASSESSMENT	DIABETES ASSESSMENT	RESULTS
Japan, 2002–2010 (316)	Workers from a Japanese steel company, mean age 42.3 years	8,423	8	Daytime work or shift work from questionnaire	Self-reported diabetes diagnosis by physicians, A1c ≥6.1%, or use of medication	Shift work was associated with diabetes, HR 1.24 (95% CI 1.02–1.49).
Japan, 2003–2008 (29)	Government employees, age 35–55 years	3,570	3–5	Shift work from questionnaire	Having been prescribed diabetes medication and/or FPG ≥126 mg/dL	Shift work was not associated with diabetes, unadjusted RR 0.97 (95% CI 0.65–1.47).
Quebec Family Study, 1989–2001 (30)	Mean age 38.6 years	276	6	Questionnaire on sleep duration and shift work	Diabetes, defined as FPG ≥126 mg/dL or 2-hour glucose value ≥200 mg/dL after OGTT, or use of insulin or oral hypoglycemic agents IGT, defined as 2-hour glucose value ≥140 mg/dL in those not meeting diabetes criteria	History of shift work was associated with diabetes/IGT, β 0.02, p=0.04.
Denmark, 2005–2012 (317)	Danish health care workers	7,305	7	Shift work from questionnaire	Being listed in the National Diabetes Registry*	Shift work was borderline associated with diabetes, likelihood ratio 1.27 (95% CI 0.95–1.70).
Black Women's Health Study, U.S., 2005–2013 (318)	Age 21–69 years	28,041	8	Night shift from questionnaire (00:00 hours to 08:00 hours)	Self-reported diabetes diagnosis, with a subgroup confirmed by contacting physicians	Night shift was associated with diabetes, HRs were 1.17 (95% CI 1.04–1.31) for 1–2 years of night-shift work, 1.23 (95% CI 1.06–1.41) for 3–9 years, and 1.42 (95% CI 1.19–1.70) for ≥10 years. HR for those who ever worked night shift was 1.12 (95% CI 1.01–1.23).

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; CI, confidence interval; FPG, fasting plasma glucose; HR, hazard ratio; IGT, impaired glucose tolerance; NR, not reported; OGTT, oral glucose tolerance test; OR, odds ratio; RR, relative risk.

* Criteria for being listed in the National Diabetes Registry: 1. receive a diagnosis of diabetes; 2. receive diabetes-related chiropody care; 3. have blood glucose measured five times in a calendar year; 4. have at least two annual blood glucose measurements over a period of 5 consecutive years; 5. purchase prescribed oral antidiabetic medication; 6. purchase prescribed insulin.

SOURCE: References are listed within the table.

among shift workers. Compared to day workers, shift workers have higher rates of obesity and more unfavorable lifestyle factors, including physical inactivity, alcohol consumption, and habitual smoking (313,315,319). In addition, there is evidence for excessive total energy intake (319), although it is not consistent (320,321). Adjusting for adiposity and lifestyle factors attenuated the relationship between shift work and diabetes in some studies, but significant residual effects remained (312,313,314,315). One meta-analysis of cohort studies revealed that shift work was associated with incident diabetes with an odds ratio of 1.12 (95% CI 1.06–1.19) (322), while another found a pooled adjusted relative risk for rotating shift work of 1.15 (95% CI 1.06–1.25) (323). Although the magnitude of the increased risk associated with shift work was relatively modest when other risk factors were controlled, the findings suggest that shift work may compound the risk imparted by traditional risk factors.

Human experiments in controlled laboratory settings have provided insights into metabolic alterations under experimentally induced circadian misalignment. Ten healthy adults underwent a 10-day laboratory protocol that involved sleeping and eating on a 28-hour "day." Circadian misalignment, when the participants ate and slept 12 hours out of phase from their habitual times, was associated with a 6% increase in glucose levels despite a 22% increase in insulin concentration. Further, leptin levels decreased. Three subjects had postprandial glucose responses in a prediabetic range (324). Another carefully conducted experiment combined sleep restriction with circadian disruption and involved 24 participants studied for more than 5 weeks in a controlled laboratory setting (325). After 3 weeks of sleep restriction to 5.6 hours per day sleep and recurring 28-hour "days," fasting and postprandial glucose levels were increased by 8% and 14%, respectively. These changes were apparently caused by decreased beta cell function, as plasma insulin decreased by 12% during fasting and 27% after meals. The metabolic derangements returned to baseline levels after 9 days of sleep recovery. There is also evidence that adverse effects of circadian misalignment on glucose metabolism can occur independently of sleep loss. Experimental circadian misalignment with sleep restriction (5 hours) in healthy volunteers led to a reduction in insulin sensitivity and an increase in inflammatory markers, compared to sleep-restricted participants who maintained regular nocturnal bedtimes, despite nearly identical sleep duration between the two groups (13). In addition, a 6-day simulated shift work

experiment in 14 healthy adults found reduced total daily energy expenditure during nightshift schedules, as well as in response to dinner consumed late at night (326). Lastly, an experimental study designed to distinguish the effects of the behavioral cycles (sleep/wake, fasting/feeding, and activity schedules), the endogenous circadian system, and circadian disruption on glucose and lipid metabolisms was conducted in 14 volunteers (327). The protocol involved two 8-day crossover studies when the behavioral cycles were aligned or misaligned (12-hour shift) with endogenous circadian rhythms. Glucose tolerance was assessed at 8 a.m. and 8 p.m. in response to an identical mixed meal. Postprandial glucose levels were 17% higher in the biological evening than in the morning, and the early phase postprandial insulin response was 27% lower in the biological evening, indicative of insufficient beta cell response. This endogenous circadian effect was much larger than that of the behavioral cycle effect. In addition, circadian misalignment (12-hour behavioral cycle inversion) increased postprandial glucose levels by 6% despite a 14% higher late phase postprandial insulin response, suggesting reduced insulin sensitivity during misalignment. This study reveals potential mechanisms by which shift workers who are awake and eating during their biological night may increase the risk of weight gain, obesity, and diabetes (326).

In patients with established diabetes, shift work may be associated with poor glycemic control, but the data are scarce. In a small study of 32 patients with diabetes, there were no differences in glycemic control between those working day and shift schedules (328). However, after being moved to a rotating shift pattern, insulin-treated patients had significant deterioration in their glycemic control after 6 months. In another study of 120 day and 120 shift workers in Thailand, fasting glucose levels were significantly lower in day compared to shift workers (329). A larger study was conducted in 296 type 1 diabetes patients in the United Kingdom, 23% of whom performed shift work (330). A1c levels were significantly higher in shift compared to day workers with a mean 9.02% (75 mmol/mol) versus 8.35% (68 mmol/mol) ($p<0.01$). As the world now requires a 24-hour workforce, while the number of diabetes patients and the cost of care are increasing, attention should be paid to the metabolic health of shift workers. Pharmacotherapy improves alertness and sleep quality in those with shift work disorders, including melatonin (to improve daytime sleep) and modafinil or armodafinil (wake-promoting agents) (331). It is unknown whether these agents also help improve glucose metabolism in shift workers, but a placebo-controlled study of the metabolic impact of 1 week of sleep restriction found no beneficial effect of modafinil (12). Interestingly, a study in 43 workers on different shift schedules found that those with fast clockwise direction of shift work had lower fasting glucose levels and HOMA index than those with slow counterclockwise rotation and day workers (332). The study is limited by the small sample size, and the results need to be confirmed in a larger study.

Many individuals in modern society experience a form of mild circadian misalignment, especially during the work or school week, as they follow social rhythms imposed by professional obligations, school schedules, family, and other commitments rather than their own biological rhythms (333). The degree of misalignment is dependent on the individual's "chronotype" (333). Chronotype is a construct that captures an individual's preference for being a "morning" or "evening" person. Late chronotype is typically associated with a greater degree of misalignment between social rhythms and the circadian clock (333). Chronotype can be evaluated in several ways. In 1976, Horne and Ostberg developed the Morningness-Eveningness questionnaire to categorize respondents into five types (definitely morning, moderately morning, neither morning nor evening, moderately evening, and definitely evening) (334). These chronotypes correlate with the participants' circadian timing of core body temperature. The core body temperature minimum is a classic phase marker and usually occurs during the second half of the habitual sleep period (334). Subsequently, Roenneberg *et al.* proposed the *mid-sleep time on free days (MSF)* as a metric of chronotype. MSF is derived from mid-sleep time (midpoint between sleep start and wake time) on weekend nights with further correction for calculated sleep debt, with the assumption that sleep timing on days when unconstrained by the social clock would more accurately reflect the underlying phase of the circadian system (335,336). A large cross-sectional study in Finland involving 4,589 participants found that those who were evening types had an odds ratio of 2.5 (95% CI 1.5–4.4) for type 2 diabetes compared to morning types. This association was independent of sleep duration and sleep sufficiency (337). Two separate cohorts (1,244 and 483 participants, respectively) provided similar findings, where eveningness was associated with increased risk of the metabolic syndrome (OR 1.4 and OR 2.2, respectively) (338,339) and diabetes (OR 2.0) (339). In addition, several genetic studies have shown that individuals carrying specific variants of the canonical circadian genes *Clock* and *Bmal-1* had evening preference, resistance to weight loss, the metabolic syndrome, and susceptibility to type 2 diabetes (340,341,342).

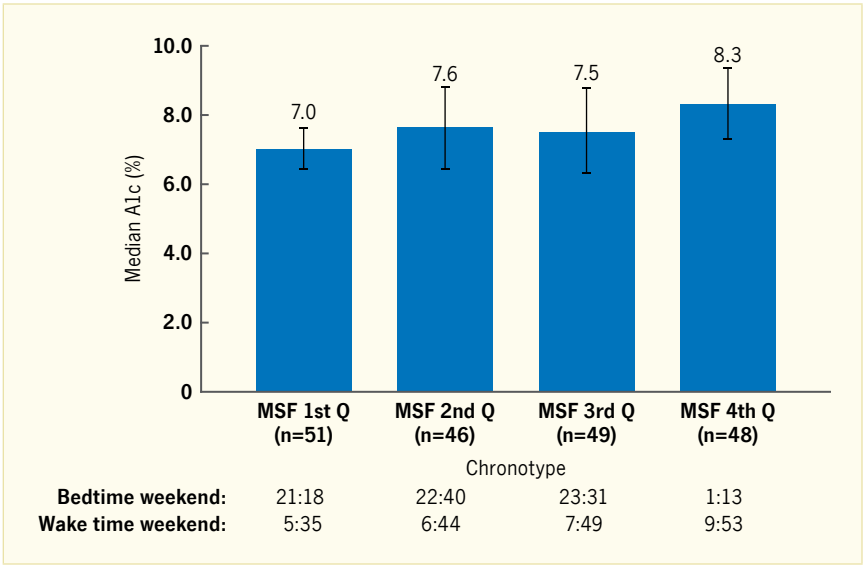
Furthermore, evening chronotype in nondiabetic individuals was found to be associated with unfavorable cardiometabolic profiles (343). A study involving 119 obese short sleepers (≤6.5 hours per night) revealed that eveningness was associated with eating later and larger food portion size, an increase in BMI, and lower high-density lipoprotein (HDL) cholesterol level. Evening types were also found to have more sleep apnea and higher stress hormones. These results are suggestive of a higher risk of cardiovascular disease in this population.

The first study to address the contribution of chronotype on glycemic control in patients with type 2 diabetes involved comprehensive questionnaires to assess sleep and eating habits in 194 non-shift worker participants who all had an established diagnosis of diabetes (344).

After adjusting for age, sex, race, BMI, insulin use, depressed mood, diabetic complications, and perceived sleep debt, chronotype, as assessed by MSF, was significantly associated with glycemic control (Figure 25.7). The difference in median A1c between participants in the 4th quartile of MSF compared to the 1st quartile was approximately 1.3%, a remarkably strong effect size. Besides having significant later bedtime/wake time and poorer glycemic control, participants with later chronotype were more depressed, had a higher BMI, and were significantly more likely to require insulin. This finding suggested that patients with type 2 diabetes who have a late chronotype may be more hypoinsulinemic, consistent with the findings in the *Clock* mutant mice. Subsequently, two studies in Japanese type 2 diabetes patients (total 826 participants) found that more evening preference as assessed by questionnaire was associated with higher A1c and lower HDL cholesterol levels, as well as poorer sleep quality (345,346).

Another neurohormone that plays an important role in circadian regulation is melatonin, secreted by the pineal gland. Its secretion is modulated by the light-dark cycle via the retinohypothalamic tract and the SCN and by the sympathetic nervous system (347). Melatonin is released during the biological night and inhibited by light exposure. Melatonin secretion follows a diurnal pattern with low levels during the day, an abrupt increase 1–2 hours before habitual bedtime, high levels throughout the night, and a progressive decrease initiated prior to habitual wake-up time (348,349). Melatonin exerts its effects through membrane receptors belonging to the class of G-protein coupled receptors (350). In mammals, there are two receptor isoforms: MT1 and MT2 (found in the brain, SCN, retina, and peripheral tissues) (351). Melatonin can entrain circadian rhythms due to the presence of MT1 and MT2 receptors in the SCN (352). In addition, both isoforms of melatonin receptors are found in the pancreatic beta cells and alpha cells (350), and melatonin has been shown to modulate insulin secretion through rather complex cascades involving several

FIGURE 25.7. Median A1c Levels Across Quartiles of Mid-Sleep Time on Free Days



Those with later chronotypes had significantly higher A1c levels and later bedtimes/wake times than those with earlier chronotypes. Error bars represent interquartile ranges. Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions.* A1c, glycosylated hemoglobin; MSF, mid-sleep time on free days; Q, quartile.

SOURCE: Reference 344

secondary messengers and possibly through alpha cell stimulation (350,353). Therefore, melatonin may act as a mediator between the central circadian regulation and peripheral metabolism, as well as an internal signal synchronizing the central circadian clock and clocks in peripheral tissues. A review has suggested that the increased duration of exposure to light that is common in modern society may inhibit melatonin release and disrupt seasonal cycles. The authors further suggest that these factors could be involved in causing metabolic disturbances (354).

Genetic studies have linked the gene encoding MT2, *MTNR1B,* to abnormal glucose metabolism and diabetes risk (355,356,357,358). In a study involving 19,605 Europeans, the *MTNR1B* intronic variant, rs10830963, was associated with a significantly increased risk of impaired fasting glucose with an odds ratio of 1.6 (355). In addition, analyses in subgroups of this population revealed an association of this genetic variant with increased type 2 diabetes risk with odds ratios of 1.19 (95% CI 1.08–1.32) (French case-control study) and 1.23 (95% CI 1.10–1.37) (Danish case-control study). This allele was associated with decreased insulin secretion after oral and intravenous glucose challenges. Another study in 1,276 healthy individuals of European ancestry revealed that this *MTNR1B* variant was associated with higher fasting glucose levels, decreased early insulin response, and decreased beta cell glucose sensitivity as evaluated by an oral glucose tolerance test (OGTT) and a euglycemic-hyperinsulinemic clamp (356). Because the effect of this allele on diabetes risk was modest, a large-scale exon resequencing was conducted in 7,632 Europeans, including 2,186 individuals with type 2 diabetes (359). This identified 40 nonsynonymous variants, including 36 very rare variants, which were associated with a much higher increased risk for type 2 diabetes (OR 3.31, 95% CI 1.78–6.18). Among the rare variants, those with partial or total loss of function (i.e., complete loss of melatonin binding and signaling capabilities), but not the neutral ones, significantly contributed to diabetes risk (OR 5.67, 95% CI 2.17–14.82).

A well-documented epidemiologic study demonstrated a link between low nocturnal melatonin secretion and development of diabetes (360). In this case-control study nested within the Nurses' Health Study Cohort, 370 women who developed type 2 diabetes during a follow-up of 10–12 years were matched with 370 controls. Women with

the lowest baseline urine secretion of 6-sulfatoxymelatonin, a major metabolite of melatonin, had an increased risk of subsequent diabetes development with an odds ratio of 2.17 (95% CI 1.18–3.98) compared to those with the highest levels, after adjusting for demographic factors, lifestyle habits, sleep duration, snoring, and biomarkers of inflammation and endothelial dysfunction. The authors postulated several mechanisms by which low melatonin may be associated with diabetes, including reduced sleep duration and sleep apnea, which are known to be associated with low melatonin levels (361,362) but could not be accurately captured by the study questionnaires.

Increasing melatonin level by exogenous supplementation in patients with diabetes was tested in a randomized, double blinded, cross-over study involving 36 type 2 diabetes patients with insomnia (363). Prolonged-release melatonin administration significantly improved sleep efficiency and reduced wake time after sleep onset as assessed by actigraphy at 3 weeks, but without changes in glucose levels. A1c improved significantly at 5 months during the open-labeled phase (-0.6% compared to baseline) without changes in C-peptide levels, but the magnitude of this improvement was not predicted by sleep improvements as assessed by actigraphy. The study was limited by the lack of assessment of the circadian system. Interestingly, an experimental study in 21 healthy women revealed that acute melatonin administration, both in the morning and evening, resulted in IGT as assessed by OGTT (364). Therefore, the role of melatonin in human glucose metabolism remains controversial.

Taken together, these human experimental studies, results from cross-sectional studies, and genetic data support the contribution of the circadian system and sleep timing in metabolic regulation. Prospective and interventional studies are required to evaluate the role of the circadian system in the development and severity of type 2 diabetes.

COMBINED EFFECTS OF MULTIPLE DISTURBANCES OF SLEEP AND/OR CIRCADIAN FUNCTION ON GLUCOSE METABOLISM

While there has been little systematic study of the combined effects of the presence of several subtypes of sleep disturbances in the same individual, this situation may be very common. For example, since population studies have associated shift work with higher BMI, it is possible that a substantial proportion of shift workers in the United States have OSA, while suffering at the same time from insufficient sleep and circadian misalignment. Another example is that of insomnia with short sleep duration. Lastly, individuals with poor sleep quality, particularly shallow sleep that may be easily fragmented, often have shorter sleep duration. Despite the fact that coexistence of multiple sleep disturbances may be a common condition, there have been few studies addressing the potential metabolic consequences.

In a cross-sectional study of insomnia evaluating glucose regulation by an OGTT, 14 nondiabetic participants with insomnia and short sleep (PSG confirmed sleep efficiency ≤80% and overnight sleeping ≤6 hours) were compared to 14 participants with insomnia and >6 hours of sleep (365). While A1c and glucose values were similar between the two groups, those with insomnia with short-sleep had lower fasting insulin and glucose-stimulated insulin secretion, but increased insulin sensitivity. The authors speculated that these alterations in glucose metabolism could represent an adaptive mechanism in response to increased fuel needs related to the physiologic hyperarousal thought to be a hallmark of insomnia. Furthermore, analyses of the Penn State Cohort, a large prospective study of 1,741 participants who had one night of laboratory PSG and were followed for 14 years, found that men with a complaint of insomnia for ≥1 year who also had a sleep duration of <6 hours on PSG had significantly higher mortality compared to men with "normal sleep duration and no insomnia" (OR 4.00, 95% CI 1.14–13.99) after adjusting for confounders (366). This analysis suggested that "insomnia with short sleep" may be a more biologically severe phenotype than insomnia with normal sleep duration, at least in men. Insomnia with short sleep in women was not associated with increased mortality. In the same cohort, the risk of type 2 diabetes was nearly threefold higher in individuals with insomnia with PSG-defined sleep duration <5 hours, irrespective of sex, while those with insomnia with longer sleep duration did not have an increased risk (48). The fact that sleep duration was assessed via a single night of PSG is a limitation of these Penn State Cohort studies. In another cross-sectional study of 15,227 U.S. Hispanics/Latinos, those with short sleep (self-reported <6 hours) and insomnia were more likely to have diabetes (OR 1.46, 95% CI 1.02–2.11) than average sleepers (>6–9 hours) with insomnia (OR 1.28, 95% CI 1.02–1.61) (367). These associations, however, were attenuated after adjusting for BMI.

A combination between OSA and short sleep duration has been explored in a few studies. In participants of the Korean Genome and Epidemiology Study, the combination of self-reported short sleep duration (<5 hours) and presence of OSA (as assessed by a portable home sleep device) was associated with a much higher risk of having visceral obesity (OR 4.40, 95% CI 1.80–10.77) than sleeping ≥7 hours and not having OSA (368). Interestingly, the adjusted odds ratio for visceral obesity was 2.05 (95% CI 1.09–3.86) in individuals sleeping <5 hours compared with those sleeping >7 hours, while the adjusted odds ratio for visceral obesity was 1.57 (95% CI 1.08–2.26) in individuals with OSA compared with those without OSA. This study thus suggests a synergy in the adverse effects of insufficient sleep and OSA, respectively, on adiposity. Another study in 136 Japanese participants with and without the metabolic syndrome,

matched by age and BMI, revealed that the severity of OSA (as measured by a portable monitor) was comparable between the two groups (369). However, participants with the metabolic syndrome had significantly shorter sleep duration (5.8 vs. 6.1 hours) assessed by actigraphy. The combination of insufficient sleep and OSA could potentially also affect glycemic control in type 2 diabetes. In a small study of 71 type 2 diabetes patients with untreated OSA, sleep duration (measured by actigraphy) was inversely associated with A1c, while AHI itself was not. Each hour of reduction in sleep duration was associated with a 4.8% increase in A1c above its reference value (95% CI 1.5–8.0) (370).

Shift workers may be at risk of having sleep disturbances aside from having circadian misalignment. In a study of 26,463 workers in China, shift work was significantly associated with poor sleep quality as assessed by questionnaires. Sleep quality improved after leaving shift work. In another study of 121 hospital employees performing shift work and 150 day-workers, shift work status was associated with poor sleep quality, as well as with the metabolic syndrome (OR 2.29, 95% CI 1.12–4.70) (371). Interestingly, poor sleep quality did not mediate the relationship between shift work and the metabolic syndrome. The combined presence of shift work and OSA has also been explored in a few studies, although none addressed metabolic aspects. Two studies of shift workers with OSA (total 52 participants) found that the AHI assessed by PSG was significantly higher if the PSG was performed after a night shift compared to after a day shift (372,373). Whether the repeated exposure to a higher severity of OSA during daytime sleep after a night of work may affect the metabolic health of shift workers is not known. Lastly, an experimental study has compared the metabolic impact of 8 days of sleep restriction (5 hours per night) with or without circadian misalignment. The reduction in insulin sensitivity (derived from intravenous glucose tolerance testing) was nearly twofold higher when the subjects were exposed to both insufficient sleep and circadian misalignment than when they were exposed to sleep restriction alone (13).

The existing evidence thus suggests that some combinations of sleep disturbances may be more detrimental to metabolic health than each component alone, but more research in this area is needed.

CONCLUSIONS

Disturbances of different aspects of sleep, including sleep duration, quality, respiratory function during sleep, and circadian timing have all been linked to abnormal glucose metabolism. Epidemiologic studies controlled for age and adiposity in the analyses. Many studies also included some measure of self-perceived stress or of socioeconomic status (e.g., using income and/or education as surrogate measures) in their analyses. The epidemiologic evidence linking sleep and adverse metabolic outcomes has come from a very large number of studies conducted in a wide variety of social and geographic environments, as well as in populations with very different demographic characteristics. Nonetheless, the findings have been remarkably consistent. Well-controlled in-laboratory experiments have provided causative evidence and suggested mechanistic pathways. As the prevalence and costs of care for the metabolic syndrome, type 2 diabetes, and gestational diabetes show no signs of decline, the efficacy and effectiveness of interventions that optimize sleep and circadian function to prevent the development or reduce the severity of these metabolic disorders need to be urgently evaluated.

LIST OF ABBREVIATIONS

A1c	glycosylated hemoglobin
AHI	apnea-hypopnea index
BMI	body mass index
CI	confidence interval
CPAP	continuous positive airway pressure
EEG	electroencephalogram
GHTN	gestational hypertension
HDL	high-density lipoprotein
HOMA/HOMA-IR	homeostatic model assessment, an index of insulin resistance
HPA	hypothalamic-pituitary-adrenal
IGT	impaired glucose tolerance
IL	interleukin
IVGTT	intravenous glucose tolerance test
MSF	mid-time sleep on free days
MT1/MT2	melatonin receptors 1 and 2
NHANES	National Health and Nutrition Examination Survey
NREM	non-REM sleep
OGTT	oral glucose tolerance test
OR	odds ratio
OSA	obstructive sleep apnea
PSG	polysomnography/polysomnogram
PSQI	Pittsburgh Sleep Quality Index
RCT	randomized controlled trial
REM	rapid-eye-movement sleep
ROS	reactive oxygen species
RR	relative risk
SCN	suprachiasmatic nuclei
SWS	slow wave sleep
TNF	tumor necrosis factor

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*.

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