Diabetes Ther
DOI 10.1007/s13300-015-0141-z

REVIEW

Sleep Optimization and Diabetes Control: A Review of the Literature

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Received: September 1, 2015

ABSTRACT

Pre-diabetes and diabetes occur secondary to a constellation of pathophysiological abnormalities that culminate in insulin resistance, which results in reduced cellular glucose uptake and increased glucose production. Although pre-diabetes and diabetes have a strong genetic basis, they are largely environmentally driven through lifestyle factors. Traditional lifestyle factors such as diet and physical activity do not fully explain the dramatic rise in the incidence and prevalence of diabetes mellitus. Sleep has emerged as an additional lifestyle behavior, important for metabolic health and energy homeostasis. In this article, we review the current evidence surrounding the sleep-diabetes association.

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Keywords: Circadian misalignment; Chronotype; Obesity; Sleep quality; Sleep duration; Type 2 diabetes mellitus

INTRODUCTION

The onset, progression and management of type 2 diabetes mellitus remain a major challenge. Given the many accompanying complications and comorbidities of diabetes, a comprehensive understanding of all factors underpinning its development and progression is absolutely essential. A profusion of literature surrounds the role of sleep and type 2 diabetes. Sleep is a significant and modifiable lifestyle behavior. Understanding the relationship between sleep and diabetes mellitus is crucial and will enable the development of strategies to improve the life of those with diabetes.

Sleep is regulated by two interconnected processes, named Process S (homeostatic drive) and Process C (circadian drive) [1]. Process S is appetitive in that a sleep debt occurs throughout the day and this increases the pressure to sleep. This sleep debt is repaid once sleep occurs. If the sleep debt is not sufficiently repaid, it accumulates, resulting in

Published online: 04 November 2015

poor daytime function and potentially metabolic abnormalities. Process S is associated with central adenosine accumulation. Caffeine is an adenosine receptor blocker. Therefore, caffeine intake around bedtime will reduce the homeostatic drive and reduce sleep duration. If Process S were the only regulator, then because of accumulated sleep debt, one would fall asleep in the early evening. This is prevented by Process C, which determines the timing of sleep. Circadian regulation occurs via the hypothalamic suprachiasmatic nucleus and is synchronized by light via the retino-hypothalamic tract. Thus, light exposure near bedtime delays sleep, and if this is combined with early morning awakening for work, then sleep duration is reduced. Many hormones are released in a circadian manner, a typical example being cortisol, which is high in the morning and low in the evening. If Process S and Process C are desynchronized, as occurs in jet lag or night shift work, then metabolic consequences can ensue, secondary to hormonal alterations. Once sleep occurs, several hormones are released specifically linked to sleep stages. For example, growth hormone and prolactin are released during the deep stages of sleep. Thus, sleep loss can also impact the release of hormones that regulate metabolic function. Sleep is assessed using several approaches, each with its own advantages and disadvantages (Table 1).

The aim of this review is to highlight and discuss the relevant literature surrounding the relationship between sleep parameters and diabetes outcomes. Specifically, we provide a comprehensive review of the literature for multiple components of sleep (quantity, quality and timing, circadian misalignment and daytime sleep) and diabetes outcomes, which we present according to study design (case-control, cross-sectional, prospective and experimental). We further discuss potential mechanisms, limitations of the current literature as well as future directions.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Study Selection Criteria

Our review focused on the literature surrounding multiple sleep features and the relationship with measures/indicators of type 2 diabetes mellitus. Specifically, we reviewed the literature for human, adult ($\geq$18 years) populations and excluded animal studies or studies not published in the English language. We selected studies using a comprehensive search of the electronic databases, PubMed and MEDLINE. The search terms entered into these electronic databases in May 2015 included: type 2 diabetes mellitus, insulin resistance, insulin sensitivity, glycemic control, glucose control and sleep duration, sleep quality, circadian misalignment, circadian preference, chronotype and napping. The search highlighted a total of 83 studies of which there were 6 case-control, 41 cross-sectional, 15 prospective cohort and 21 experimental studies.

Sleep Quantity, Insulin Resistance and Diabetes

Sleep curtailment is now widespread, usually to accommodate busy lifestyles within contemporary society, mirroring the increases in global diabetes mellitus [2]. The use of modern technology is also increasingly

Table 1 The advantages and limitations of the various methods used to measure sleep

Sleep measure	Measure	Advantages	Limitations
Polysomnography (PSG)	Objective	Accurate for determining multiple sleep parameters	Expensive
	Gold standard	Can be used to diagnose sleep disorders	Experienced/trained technicians are needed to score the data
	Physiological	Can be combined with other physiological measures (hormone sampling under controlled conditions)	May not be able to capture usual sleep because of equipment and/or environment (first night effect)
		Determines sleep architecture (sleep stages and percentages of each stage)	Invasive/uncomfortable
	Sleep architecture (stages 1, 2, 3 and REM sleep)	Measures brain activity as well as other physiological outcomes (muscle relaxation, eye movements respiratory effort and more)	Unsuitable for long-term sleep assessment; unless portable requires laboratory attendance
			Inter-/intraobserver variation
Actigraphy (wrist)	Objective estimate	Objective measure of sleep-wake timings	Cannot determine sleep architecture (sleep stages)
		Can be used in the individual's natural environment in free-living conditions	Provides an estimate of sleep-wake timings
	Worn on wrist	Some devices have been validated for sleep duration against PSG	Some devices are not waterproof and will not capture information upon removal
	Based on movement	Ability to collect data over prolonged periods of time (up to 3 consecutive months)	Absence of physiological measures to determine sleep
		Cost-effective alternative to PSG	Requires concurrent sleep diary and minimum wear time
		Noninvasive	May over estimate sleep during periods of inactivity
			Multiple software and cut points for analysis
Actiheart	Objective estimate	Objective	Not validated against PSG for sleep
		Additional physiological measures are obtained (heart rate) for sleep determination	Loss of signal if skin contact is poor or the ECG pads become loose/removed

Table 1 continued

Sleep measure	Measure	Advantages	Limitations
	Physiological	Can be used in free-living conditions and natural environments	Does not have the ability to determine sleep architecture (sleep staging)
		Can collect data over prolonged periods of time	Accurate accompanying sleep diary is usually required
		Noninvasive	May overestimate sleep during periods of inactivity
			Can be uncomfortable and/or result in skin irritation where ECG electrodes are placed
			Expensive
Self-reported questionnaires	Subjective	Can be administered to large populations	Subject to a number of biases (recall, social desirability)
		Quick/easy to administer	Variable response rates
		Cost-effective	Subjective
		Some are validated in different age groups to investigate different age-appropriate sleep problems (pain in the elderly, bedroom sharing in children)	Inaccurate for detecting sleep disorders
		Less labor intensive compared to PSG	May be subject to missing data
		Some are validated for sleep duration against objective measures of sleep	May result in time in bed being reported rather than total sleep time
		Can help to ascertain information about multiple sleep parameters and other related factors	Information collected may not be accurate and some only ask one question
Parental questionnaire	Subjective	Inexpensive	Subjective
		Administration is quick	Subject to a number of biases (recall, social desirability)
		Immediate output	May have missing data
		Permits data collection in large samples relating to pediatric sleep information	Likely to be inaccurate for older children and adolescents (parents may be unaware of night awakenings and/or other sleep features)
		Less labor intensive compared to PSG	Variable response rates

Table 1 continued

Sleep measure	Measure	Advantages	Limitations
			May result in time in bed being reported rather than total sleep time, thus overestimating sleep causing inaccuracies
Sleep/time diary	Subjective	Obtains prospective sleep-wake data	Completion is tedious
		Provides additional information about other sleep features (time in bed, sleep duration, night awakenings, napping, sleep quality)	Response rates may be low or diaries may be only partially completed (missing data)
		Inexpensive	Subjective
		Permits data collection in large samples	Labor intensive for the participant
		Less labor intensive compared to PSG	Requires participants to be motivated to complete
		Swift administration	Subject to inaccuracies/biases (recall, social desirability)

REM rapid eye movement, *PSG* polysomnography

intruding into sleep time. The Sleep Heart Health Study is an early study that observed, in a large sample of US men and women, that short self-reported sleep duration (≤5 h per night) was associated with a 251% increased odds ratio (OR) of T2DM [3]. Furthermore, compared to those with sleep duration of 7–8 h, those with sleep duration of ≥9 h had a 79% increased odds of T2DM and an 88% increased odds of pre-diabetes. This early study adjusted for age, gender, ethnicity, the apnea hypopnea index (AHI), study recruitment site, and waist circumference as potential confounders, although data on primary drivers of diabetes (physical activity, dietary habits, family history) were not included in the analyses [3]. Further evidence has resulted from a small number of case-control studies that are highlighted in Table 2.

Cross-Sectional Studies

The cross-sectional evidence linking sleep duration to T2DM has continued to accumulate (Table 3). The majority of studies have indicated an increased possibility of various diabetes outcomes with differing definitions of short sleep duration [4–17]. Understanding pre-diabetes provides a key insight into the development of T2DM. Chaput and colleagues performed an oral glucose tolerance test in 740 participants, aged 21–64 years without a known diabetes diagnosis. Sleep duration (h) was self-reported from only one question, inserted into a self-administered physical activity questionnaire. After adjustment for major confounders such as physical activity and energy intake (self-reported) along with age, marital and employment status, education,

Table 2 Case-control studies to investigate the association between sleep features and diabetes outcomes

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Trento (2008) [50]	32 men, 15 women with T2DM; 23 controls; Italy	Case-control	Wrist actigraphy for 3 nights	Previously diagnosed T2DM vs. controls without T2DM	Age, gender, and education	Increased sleep fragmentation index in those with T2DM vs. controls
Tsujimura (2009) [51]	11 men, 8 women; aged 46–85 years with T2DM (cases); 7 men, 12 women; aged 45–85 years healthy controls; Japan	Case-control	Wrist actigraphy for 7 days/nights and corresponding sleep diary	Fasted blood sample to assess glucose level; T2DM defined according to WHO	None	Significantly longer mean wake episodes, reduced sleep efficiency in cases vs. controls
Pallayova (2010) [58]	8 women, 36 men (22 without T2DM, 22 with T2DM); mean age 58 ± 6 years; Slovakia	Retrospective case-control	1 night PSG	Physician diagnosed T2DM/use of oral hypoglycemic/insulin		Those with T2DM had less SWS (2%) vs. controls (8%) and more REM (24% vs. 14%)
Rafalson (2010) [99]	1455 with no diabetes at baseline; cases = 91, controls = 272;	Prospective case-control	Self-reported questionnaire (<6 h, 6–8 h, >8 h)	Fasting bloods to determine fasting plasma glucose level; IFG defined as 100–125 mg/dl	Sex, race, age, year of baseline interview, abdominal height, weight change, baseline weight, family history of diabetes, smoking, hypertension, depression, HOMA-IR	No significant association after adjustment for <6 h vs. 6–8 h
Nakanishi-Minami (2012) [100]	56 men, 50 women; aged 36–84 years; Japan	Case-control study ($n = 32$ controls, $n = 74$ cases of T2DM)	Questionnaire	Fasting blood glucose, HbA1c; T2DM diagnosed using WHO criteria	None	T2DM associated with later bed/wake times on free days and increased daytime sleepiness

Table 2 continued

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Liu (2013) [101]	56 without T2DM (23 men, 33 women) overweight or obese; US	Case-control study (IR = 35 vs. IS = 21)	Self-reported	Fasting blood glucose; OGTT	BMI	Mean sleep duration was lower in IR (6.5 h) vs. IS (7.2 h)

T2DM type 2 diabetes mellitus, *PSG* polysomnography, *OGTT* oral glucose tolerance test, *BMI* body mass index, *WHO* World Health Organization, *HOMA-IR* homeostasis model assessment-insulin resistance, *SWS* slow wave sleep, *IFG* impaired fasting glucose, *IR* insulin resistant, *IS* insulin sensitive

household income, alcohol and coffee consumption, hypertension and heart disease, the OR for insulin resistance, determined using the homeostasis model assessment (HOMA-IR), for men and women reporting short sleep duration (5–6 h per night) was 2.27 and 1.82, respectively (both $p < 0.05$). Long sleep duration (9–10 h per night) was also significantly associated with pre-diabetes in both men and women, but with smaller ORs of 1.51 and 1.67, respectively [4]. While this study included many potential confounders and benefited from a relatively large sample, a major concern is the limited subjective sleep information.

To overcome the issue of subjective sleep reports, Vgontzas and colleagues employed polysomnography (PSG; the gold-standard sleep measure) to investigate the relationship between sleep and T2DM. A fasted blood glucose sample was obtained the morning after 1 night's PSG had been conducted to screen participants for sleep-disordered breathing (SDB), known to be closely associated with T2DM. Severe short sleep duration (≤5 h) was significantly associated with a 2.95 times odds of T2DM [18]. While the authors adjusted for a range of potential confounders including age, race, sex, BMI, sampling weight, smoking, alcohol, depression and SDB, the two major lifestyle drivers (diet and physical activity) and family history of diabetes were unaccounted for. Investigating sleep in those susceptible to diabetes has provided key information regarding the sleep-diabetes relationship. Darukhanavala et al. studied 47 at-risk participants with a family history of diabetes but who were otherwise healthy and monitored them with wrist actigraphy for 14 consecutive days/nights. Insulin sensitivity was determined using HOMA-IR, and a significant linear relationship

Table 3 Cross-sectional studies investigating the association between sleep features and diabetes outcomes

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Gottlieb (2005) [3]	722 men; 764 women; age 53–93 years; US	Self-reported sleep duration (h) from questionnaire	Fasting blood sample OGTT; T2DM and IGT (ADA and WHO)	Age, gender, ethnicity, AHI, study site, waist circumference	T2DM ≤5 h HR = 2.51*; T2DM ≥9 h HR = 1.79*; IGT ≤5 h HR = 1.33; IGT ≥9 h HR = 1.88*
Fiorentini (2007) [43]	220 (men and women); no age range provided; Italy	Self-reported sleep quality (PSQI)	Diagnosed T2DM (ADA)	None	Prevalence of T2DM was 19.4% in 'poor sleepers' versus 8.8% in 'good sleepers' ($p < 0.0001$)
Knutson (2006) [41]	161 (42 men; 119 women); African American; mean age 57 years; US	Sleep quality and sleep duration from self-reported PSQI; additional question on preferred sleep duration to calculate perceived sleep debt	Diagnosed T2DM patients; measure of glycemic control determined using HbA1c		3 h sleep debt p/night associated with 1.1% significant increase in HbA1c
Chaput (2007) [4]	323 men, 417 women; 21–64 years; Canada	Self-reported sleep duration (one question)	IGT and T2DM (ADA/WHO) from fasting bloods and OGTT	Age, marital status, employment status, education, income, physical activity, alcohol, caffeine, energy intake, hypertension, heart disease, WC/BMI/BF%	Men: 5–6 h sleep OR 2.27*, 9–10 h OR 1.51*; women: 5–6 h OR 1.82*, 9–10 h OR 1.67*; both genders 5–6 h OR 2.09*, 9–10 h OR 1.58*

Table 3 continued

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Tuomilehto (2008) [5]	1336 men, 1434 women aged 45–74 years; Finland	Questionnaire	OGTT	Age, BMI, medication(s), possible OSA, smoking, physical activity	Women with diagnosed T2DM: <6 h OR 2.55*, >8 h OR 1.76*; diagnosed T2DM or screened T2DM >8 h OR 1.71* no association for men
Suarez (2008) [54]	115 men, 95 women; aged 18–65 years; US	PSQI	Fasted blood sample to assess insulin and glucose; HOMA-IR calculated		SOL associated with HOMA-IR $F = 4.79$, $p = 0.004$: frequent problems with sleep initiation associated with greater IR mean = 1.96 vs. 1.10 (no problems); women taking >30 m to initiate sleep had significantly increased HOMA-IR, vs. those <30 m
Cunha (2008) [44]	50 diabetes patients; Brazil	PSQI	Previous physician diagnosed T2DM	None	HbA1c >7%, 33.3% had poor sleep quality

Table 3 continued

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Vgontzas (2009) [18]	1714 (48% men); mean age 49 ± 14 years; US	One night PSG and questionnaire with 3 groups: >6 h (normal), 5–6 h (moderately short), ≤5 h (severely short)	T2DM diagnosis and treatment or fasting blood glucose >126 mg/dl on the morning after sleep study	Age, race, sex, BMI, sampling weight, smoking, alcohol, depression, sleep-disordered breathing	T2DM associated with insomnia (<5 h) OR 2.95*
Kim (2009) [6]	1652 men, aged 20–60 years with central adiposity; Korea	Self-reported from questionnaire	T2DM: previous physician diagnosis/use of diabetes medication/fasting blood glucose ≥7.0 mmol/l	Age, smoking, alcohol, physical activity, education, income, residential area, hypertension, obesity, abdominal obesity, high triglycerides, low HDL-C, high cholesterol	OR 2.40* for T2DM if ≤5 h without abdominal obesity
Chao (2011) [7]	3470 adults; Taiwan	Self-reported questionnaire (<6 h, 6–8.49 h, ≥8.5 h)	Pre-diabetes and T2DM diagnosed from either fasted blood sample or OGTT	Age, sex, smoking, alcohol, caffeine, physical activity, family history of diabetes, obesity	Short sleep and T2DM OR 1.55*; long sleep and T2DM OR 2.83; no association with pre-diabetes
Knutson (2011) [39]	115 without T2DM, 40 with T2DM; 18–30 years; US	Wrist actigraphy for 6 days/nights and questionnaires (PSQI, Berlin)	Fasting bloods to measure insulin/glucose and calculate HOMA-IR	Age, race, sex, BMI, education, income	Sleep fragmentation and positively associated with insulin and HOMA-IR
Luyster (2011) [45]	300 with T2DM; mean age 64 years; US	PSQI	Physician diagnosis of T2DM for at least 1y and taking oral medication		55% of the sample had poor sleep quality

Table 3 continued

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Darukhanavala (2011) [19]	47 healthy individuals with parental history of T2DM (26 women, 21 men); mean age 26 years; US	14 days/night wrist actigraphy	OGTT, HOMA-IR	Age, BMI, sex, familial diabetes risk, ethnicity, physical activity	Sleep duration associated with insulin sensitivity $\beta = 2.5^*$ and HOMA-IR $\beta = -0.27$
Tsai (2012) [46]	46 with T2DM; aged 43–83 years; Taiwan	PSQI	HbA1c from blood draw	Age, gender, BMI	OR 6.83* for sleep efficiency and HbA1c; Poor quality sleep associated with worse glycemic control OR 6.94*
Liu (2011) [8]	854 men, 640 women; aged 20–70 years; twin cohort; China	Sleep duration self-reported from PSQI	Fasting plasma glucose and HOMA-IR	Age, physical activity, education, snoring, sleep disturbances, BMI/%TF	Short sleep duration (≤7 h) associated with higher HOMA-IR in women only
St-Onge (2012) [55]	305 (122 men, 183 women); mean age 61 years with T2DM, overweight or obesity; US	Portable PSG in home environment	HbA1c, and glucose from fasting blood sample	Study site, age, gender, ethnicity, WC, smoking, alcohol, diabetes duration, medication	Sleep efficiency associated with fasting plasma glucose $\beta = -0.53$, $p = 0.041$
Rajendran (2012) [47]	120 with T2DM; India	PSQI	Fasting, postprandial blood glucose and HbA1c measured	Age, sex, medications, BMI, HbA1c	Diabetes duration was negatively associated with global PSQI B = −0.20, $p = 0.02$

Table 3 continued

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Harada (2012) [56]	275 men; mean age 44 years; Japan	Wrist actigraphy and corresponding sleep diary for 7 days/nights to determine sleep duration and sleep quality	Fasting plasma glucose	Age, WC, RDI, ESS, sleep duration/ fragmentation	IFG present in 20%; sleep duration nor sleep quality (fragmentation) was associated with FPG
Kachi (2012) [9]	20,744 men; aged 30–64 years; Japan	Self-reported (continuous) then categorized $\leq$5 h, 6 h, 7 h and 8 $\geq$ h	Fasting blood glucose and HbA1c to determine undiagnosed T2DM (JDS)	Age, obesity, smoking, alcohol and physical activity	Untreated T2DM (3.4%); $\leq$5 h sleep associated with T2DM OR 1.52*; 8 $\geq$ h associated with T2DM OR 1.39*
Hung (2013) [49]	1805 (healthy, pre-diabetes, T2DM); Taiwan	PSQI	Fasting glucose or OGTT to determine normal glucose tolerance ($n = 1217$), IFG = 118, IGT = 287, IFG and IGT = 80, T2DM = 103	Age, gender, glycemic status, sleep duration, alcohol, smoking, physical activity, BMI, systolic blood pressure, HDL, triglyceride	Poor sleep quality associated with FPG $\beta = 1.28$*, post-prandial glucose $\beta = 1.07$* and T2DM $\beta = 2.27$*
Lou (2012) [10]	16,893 men and women; aged 18–75 years; China	Self-reported sleep quality and duration	Two fasting blood samples; T2DM defined according to WHO criteria	Age, sex, education, occupation, BMI, family history of diabetes, smoking, alcohol, hypertension, sleep duration/ quality	Poor sleep quality associated with T2DM OR 1.76*; short sleep $\leq$6 h associated with T2DM OR 1.25*

Table 3 continued

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Ohkuma (2013) [11]	4870 with T2DM; aged ≥20 years; Japan	Self-reported sleep duration	HbA1c	Age, sex, energy intake, depressive symptoms, duration of diabetes, smoking, alcohol, physical activity, insulin use	Short and long sleep duration associated with higher HbA1c
Merikanto (2013) [12]	4589; aged 25–74 years; Finland	Self-reported chronotype and sleep duration (questionnaires)	Fasted blood sample to determine glucose and insulin; OGTT to determine insulin sensitivity	Sex, age, education, civil status, sleep duration, assessment time	Evening chronotypes had 2.6 increased risk of T2DM vs. morning types; short sleep (≤6 h) associated with 1.6 increased risk of T2DM; no association with insulin resistance
Chasens (2013) [57]	107 with T2DM; aged 31–82 years; US	PSQI and ESS	Self-reported T2DM diagnosis; questionnaire to assess diabetes care profile	Sex, age, education, marital status, ESS	Poor sleep quality associated with worse diabetes care profile; daily disturbance was significantly associated with increased diabetes control problems

Table 3 continued

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Najafian (2013) [13]	6123 men, 6391 women; aged >19 years; Iran	Self-reported	Fasting blood glucose and OGTT	Age, sex, WC, BMI	Men sleeping ≤5 h had 35% increased risk of T2DM/IGT and women had 54% increased risk and <60 years had 34% increased risk
Reutrakul (2013) [63]	194 (135 women) with T2DM; mean age 58 years; US	PSQI	HbA1c from medical records	Age, sex, race, BMI, insulin use, depressed mood, diabetes complications, perceived sleep debt	Later mid-sleep time positively associated with HbA1c level
Kim (2013) [14]	2134 T2DM (1065 men, 1,069 women); aged >20 years; Korea	Self-reported	Fasting blood glucose; HbA1c; HOMA-IR	Study year, age, sex, socioeconomic status, education, marital status, residential area, income, alcohol, smoking, physical activity, hypertension, BMI, WC, treatment, T2DM duration, calorie intake	No association between HbA1c and sleep duration after full adjustment; highest levels of HOMA-IR with <6 h and ≥9 h sleep duration
Andersson (2013) [40]	2816 aged 30–75 years; Sweden	Self-reported lack of sleep	OGTT to determine normal glucose ($n = 2314$) and IGT ($n = 213$)	Age, BMI, smoking, education, physical activity	IGT and lack of sleep OR 2.3* for men only

Table 3 continued

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Reutrakul (2014) [62]					Late chronotype associated with higher HbA1c levels
Inkster (2013) [102]	898 with T2DM (51% men); mean age 68 years; UK	Self-reported daytime sleepiness from ESS	Existing T2DM diagnosis; history of severe hypoglycemia obtained by questionnaire	Age, sex, T2DM duration, HbA1c%, BMI, T2DM medications, insulin use	ESS was a significant independent predictor of severe hypoglycemia $\beta = 0.537^{*}$
Ohkuma (2014) [103]	4402 with T2DM (2494 men and 1908 women); aged ≥20 years; Japan	Self-reported sleep duration, including daytime nap(s)	Fasted bloods to determine HbA1c, glucose; HOMA-IR calculated in 3816	Age, sex, DM duration, energy intake, smoking, alcohol, physical activity, depression, DM medication, insulin use, BMI/WC	After adjustment for BMI/WC, no significant association was found between HOMA-IR and sleep duration
Cho (2014) [48]	614 with T2DM (381 men, 233 women); mean age 60 years; Korea	PSQI, ESS, Sleep Disorders Questionnaire Sleep Apnea; poor sleep quality used as outcome	OGTT	Age, sex, sleep apnea score, depression, T2DM duration	No significant association between glucose regulation and any sleep variable; T2DM duration associated with significantly higher PSQI
Iwasaki (2013) [65]	101 men with T2DM; 40–65 years; Japan	MEQ, PSQI	HbA1c from blood sample	Age, BMI, systolic blood pressure, HDL-C, LDL-C, T2DM duration, triglycerides	HbA1c negatively associated with chronotype; HbA1c and PSQI were lower in morning types

Table 3 continued

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Pyykkonen (2014) [104]	722 without T2DM (400 women, 322 men); Finland	Basic Nordic Sleep Questionnaire: sleep duration, complaints of sleep apnea and insomnia	OGTT	Age, sex, sleep apnea complaints, insomnia, family history of T2DM, smoking, alcohol, physical activity, occupation, BMI, depressive symptoms	Long (≥9 h) sleep duration associated with increased insulin resistance
Zheng (2015) [105]	18,121(6412 men and 11,709 women); aged ≥40 years; Japan	Self-reported sleep duration	Fasting plasma glucose; OGTT and classified: normal glucose ($n = 9578$), impaired glucose regulation ($n = 4318$), T2DM ($n = 4225$)	Age, sex, BMI, snoring, depressive symptoms	Long sleep duration (>9 h) associated with higher HbA1c, fasting glucose and post-prandial glucose
Osonoi (2014) [64]	725 with T2DM (63% men); mean age 58 years; Japan	Self-reported chronotype from MEQ ($n = 117$ morning types; $n = 424$ neither type; $n = 184$ evening type)	Fasting blood sample to determine HbA1c and glucose	Age, gender, BMI, PSQI, depressive symptoms, energy intake, smoking, alcohol, physical activity	Evening chronotypes had significantly higher mean fasting glucose and HbA1c

Table 3 continued

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Baoying (2014) [106]	7568 (3060 men, 4508 women) without T2DM; mean age 51 years; China	Self-reported sleep duration	OGTT to determine HOMA-IR	Age, gender, fasting blood glucose, hypertension, FHD, dyslipidemia, smoking, alcohol, snoring frequency, physical activity, education, BMI, waist-hip ratio	Longer daytime nap duration (>1 h) positively associated with HbA1c level >6% OR 1.26* and insulin resistance OR 1.69*; long sleep duration (>8 h) had protective effect on HbA1c% and insulin resistance OR 0.57* and OR 0.84*
Wong (2015) [15]	224 without T2DM (52% women); mean age 45 years; US	Self-reported sleep duration	IVGTT to determine insulin sensitivity		Short sleep duration was associated with reduced insulin sensitivity in Caucasians and men
Tang (2014) [16]	551 with T2DM; China	PSQI to determine sleep quality and quantity	HbA1c; HOMA-IR	Gender, age, BMI, T2DM duration	Short sleep associated with poorer glycemic control; poor sleep quality associated with increased insulin resistance
Byberg (2012) [69]	771; mean age 47 years; Denmark	Self-reported sleep duration (including naps) and sleep quality	OGTT; HOMA-IR		2% increase in insulin sensitivity with improving sleep quality

Table 3 continued

First author (year)	Sample/country	Sleep measure	Diabetes measure	Covariates	Findings
Zuo (2012) [17]	1124 without T2DM (45% men); mean age ~48–49 years; China	Self-reported sleep duration	HOMA-IR		OR 3.26* for those with short sleep (<7 h) and low physical activity for insulin resistance; no association for sleep duration alone

OGTT oral glucose tolerance test, *T2DM* type 2 diabetes mellitus, *IGT* impaired glucose tolerance, *ADA* American Diabetes Association, *WHO* World Health Organization, *AHI* apnea hypopnea index, *OR* odds ratio, *OSA* obstructive sleep apnea, *BMI* body mass index, *WC* waist circumference, *BF%* body fat percent, *HOMA-IR* homeostasis model assessment-insulin resistance, *PSQI* Pittsburgh Sleep Quality Index, *PSG* polysomnography, *HDL-C* high density lipoprotein-cholesterol, *LDL-C* low high density lipoprotein-cholesterol, *IFG* impaired fasting glucose, *FPG* fasting plasma glucose, *RDI* respiratory disposition index, *ESS* Epworth Sleepiness Scale, *MEQ* morningness-eveningness questionnaire, *IVGTT* intravenous glucose tolerance test

* $p < 0.05$

was observed between actigraphy-estimated sleep duration and insulin sensitivity ($\beta = 2.5$, $p = 0.006$), after adjustment of major confounders such as physical activity and diabetes family history [19].

Currently, there are no cross-sectional studies that have objectively investigated the sleep-diabetes link while adjusting for the three key drivers of diabetes (energy intake, energy expenditure and diabetes family history). The issue with obtaining data from populations with existing diabetes comorbidities, such as SDB, is that sleep insufficiency may be a result of the condition itself, which may have already driven physiological alterations. Thus, case-control (Table 3) and prospective studies provide key evidence for unraveling this and clarifying temporal associations.

Prospective Studies

A summary of prospective studies that have examined the sleep-diabetes relationship can be found in Table 4. The Niigata Wellness Study, which prospectively studied 38,987 Japanese participants without diabetes over an 8-year period, found that younger individuals (<60 years old) who reported sleeping <5.5 h per night had a 53% significant increased risk of developing diabetes compared to those that slept for 7–7.5 h per night, after adjustment [20]. Gangwisch and colleagues reported a similar significant risk for incident diabetes with short sleep. Participants, aged 32–86 years ($n = 8992$), recruited into the National Health and Nutrition Examination Survey were examined over a 10-year period. Short sleep duration was defined as ≤5 h and was associated with 1.47 increased odds of incident diabetes [21]. Other prospective data suggest similar effect sizes but vary according to adjustment of confounders and short sleep duration definition [22, 23]. The prospective evidence is, however, less consistent with some reporting a diminished relationship after adjustment for

BMI [24]. Furthermore, at least one study has reported an increased risk for incident diabetes in long sleepers by more than three-fold [25]. The longitudinal data are less convincing than the cross-sectional evidence with several prospective studies indicating no association between sleep duration and incident diabetes [26–28]. Further prospective data are necessary to determine cause-effect associations, and while the majority of studies benefit from large samples, including both genders and incorporating different ethnic backgrounds, the lack of objective sleep data is a significant limitation [20–30]. Also, the majority of prospective studies assessing sleep duration and diabetes outcomes have focused on incident diabetes, with few investigating sleep with pre-diabetes [29, 30]. Both studies, however, documented similar effect sizes that were statistically significant for short sleep duration (albeit with different definitions and varied adjustments). Uncertainty from prospective data has been somewhat offset by evidence from experimental studies. Experimental sleep manipulation in a controlled laboratory environment has shown a consistent relationship between sleep duration and diabetes outcomes.

Experimental Studies

Increasing numbers of experimental sleep studies (summarized in Table 5) have explored the association between sleep and diabetes using objective measures to confront the problems associated with subjective sleep. One of the earliest experimental sleep studies to examine the effects of sleep upon glucose metabolism recruited healthy, young, male volunteers ($n = 11$) for 16 consecutive nights of laboratory attendance [31]. Participants spent 3 nights of 8 h time in bed (TIB) for baseline assessment, followed by 6 nights of sleep restriction with 4 h TIB and finally 7 nights of sleep recovery with 12 h TIB. PSG was used to monitor sleep outcomes on the last nights of each of the three conditions and blood sampling performed at the end of the sleep restriction and sleep recovery conditions to assess multiple hormones and carbohydrate metabolism. An intravenous glucose tolerance test (IVGTT) and breakfast meal response were performed to investigate insulin sensitivity and glucose effectiveness. Findings from the study indicated a 40% reduced glucose clearance after the IVGTT following sleep restriction compared to sleep recovery. The insulin response to glucose was reduced by 30% after sleep restriction, an early indicator of diabetes. Furthermore, glucose effectiveness, which is independent of insulin, was significantly reduced by 30% after sleep loss versus sleep recovery [31].

To overcome several issues including the potential confounding effect of the presence of diabetes-related comorbidities as well as laboratory attendance and extreme sleep restriction, Zielinski et al. studied 40 healthy individuals (aged 50–70 years) utilizing continuous wrist actigraphy monitoring for 10 weeks [32]. Two weeks of baseline sleep was acquired for determination of habitual sleep habits/duration, and volunteers were subsequently randomized into one of two conditions: (1) 90-min TIB reduction, compared to the pre-determined baseline median TIB, with fixed bedtimes for 8 consecutive weeks ($n = 22$), or (2) control condition with fixed bedtimes, matching the baseline TIB ($n = 18$). An oral glucose tolerance test was conducted to determine glucose and glucose tolerance; insulin sensitivity was assessed using the quantitative insulin-sensitivity check index. The results were not consistent with the findings from

Table 4 A summary of prospective studies that have examined the relationship between sleep features and diabetes outcomes

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Gangwisch (2007) [21]	8992; aged 32–86 years; US	Prospective cohort with 10-year follow-up data	Self-reported sleep duration (h) from questionnaire	IDM cases from physician/ hospital diagnosis/T2DM death	Physical activity, depression, alcohol, ethnicity, education, marital status, age, overweight/obesity, hypertension	IDM ≤5 h 1.47*; IDM ≥9 h 1.52*
Ayas (2003) [24]	70,026 (women) aged 30–55 years at baseline; US	Prospective cohort with 1-year follow-up IDM data	Self-reported sleep duration (h) from questionnaire	Self-reported by questionnaire (diagnosis/ symptoms)	Age, smoking, hypertension, alcohol, physical activity, menopause, depression, family history of T2DM, hypercholesterolemia	IDM ≤5 h OR 1.29*; IDM ≥9 h OR 1.32*; adjustment for BMI resulted in nonsignificant association for short sleepers
Nilsson (2004) [59]	6599 men; mean age 45 years; Sweden	Prospective cohort with mean follow-up of 15 years	Self-reported sleep difficulties from questionnaire (hypnotics/ difficulty falling to sleep	Self-reported from questionnaire with objective verification in subsample ($n = 1551$)	Age, BMI, baseline glucose, length of follow-up, lifestyle, family history of diabetes, social	One of the two sleep features 1.52*; both sleep features 1.78
Meisinger (2005) [53]	4140 men; 4129 women; aged 25–74 years; Germany	Prospective cohort study with 7.5-year follow-up	Self-reported: (1) difficulty initiating sleep and (2) difficulty maintaining sleep	Self-reported from questionnaire and validated with hospital records	Age, survey, education, parental history, smoking, alcohol, hypertension, physical activity, dyslipidemia, history of angina, BMI	DIS in women OR 1.42, in men OR 1.10; DMS in women OR 1.98*, in men OR 1.60*

Table 4 continued

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Yaggi (2006) [25]	1139 men, aged 40–70 years; US	Prospective cohort with 15-year follow-up	Self-reported sleep duration	Self-reported physician diagnosis at follow-up to determine IDM	Age, hypertension, smoking, self-rated health, waist circumference, education	IDM ≤5 h OR 1.95; 6 h OR 1.95*; > 8 h OR 3.12*
Hayashino (2007) [26]	6509 (26.1% women); aged 19–69 years; Japan	Prospective cohort study with median follow-up of 4.2 years	Self-reported sleep duration and difficulty initiating sleep from questionnaire	Fasted/non-fasted blood glucose level to determine IDM	Age, gender, smoking, hypertension, high cholesterol, potential history of T2DM, physical activity, intervention, BMI	No association with sleep duration; dose-dependent relationship between IDM and DIS
Beihl (2009) [29]	390 men, 510 women; aged 40–69 years at baseline; US	Prospective study with 5-year follow-up	Researcher-led questionnaire with ≤7 h as 'short sleep' and ≥9 h as 'long sleep'	Fasted blood sample, OGTT and IVGTT to determine normal glucose, IGT or T2DM and insulin sensitivity as well as insulin response. IDM determined at 5-year follow-up	Age, sex, glucose tolerance at baseline, study site, hypertension, family history of diabetes, smoking, education, BMI, insulin sensitivity and acute insulin response	Non-Hispanic white/ Hispanic ≤7 h OR 2.36* and ≥9 h OR 2.15; African Americans no significant association
Chaput (2009) [30]	117 men, 159 women; aged 21–64 years; Canada	Prospective study with 6-year follow-up	Self-administered questionnaire with ≤6 h (short) 7–8 h (referent) and ≥9 h (long)	OGTT following overnight fast. AUC for glucose and insulin as well as HOMA-IR was calculated. T2DM and IGT determined using ADA/ WHO criteria. IDM also determined	Age, smoking, employment status, income, shift-work history, resting metabolic rate, caffeine, physical activity, WC/BMI/BF%	IDM/IGT RR = 2.42* in those ≤6 h and RR = 2.31* in those ≥9 h

Table 4 continued

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Olsson (2012) [107]	53,394 without T2DM; aged ≥20 years; Norway	Prospective cohort followed for 11–22 years	Self-reported sleep disturbance, sleep initiation, sleep maintenance	IDM ($n = 2344$; $n = 1895$ T2DM) identified by follow-up questionnaire	Age, BMI	Men had 25% increased risk of incident T2DM with sleep disturbance
Boyko (2013) [22]	47,093 (25.6% women); mean age 35 years; US	Prospective cohort study of US military with 6-year follow-up	Self-reported trouble sleeping, sleep duration	Self-reported IDM ($n = 871$)	Age, sex, race/ethnicity, education, BMI	Trouble sleeping at baseline had 45% increased risk of IDM; short sleep duration also associated with IDM
Holliday (2013) [23]	192,728 sample; aged ≥45 years free of T2DM at baseline; Australia	Prospective cohort study	Self-reported sleep duration	Self-reported IDM, verified through medical records based on overnight hospital admission ($n = 4648$)	Age, sex, education, marital status, residential remoteness, alcohol, smoking, health insurance status, income, BMI, physical activity, baseline health status	HR = 1.23* for IDM with <6 h sleep duration
Heianza (2014) [20]	38,987 without T2DM at baseline; aged 18–83 years; Japan	Prospective cohort study with 8-year follow-up	Self-reported sleep duration	Fasting blood sample to determine glucose and HbA1c; IDM after 8-year follow-up $n = 2085$	Sex, physical activity, smoking, alcohol, occupation/shift work, BMI, dyslipidemia, hypertension, IFG	Short sleep (<5.5 h) duration for IDM OR 1.53*

Table 4 continued

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Gutierrez-Repiso (2014) [28]	1145; aged 18–65 years; Spain	Prospective cohort study with 6-year ($n = 968$) and 11-year ($n = 673$) follow-up	Self-reported sleep duration	OGTT in those unaware of T2DM status to determine HOMA-IR	Age, sex, physical activity, smoking, weight gain, abnormal glucose regulation at baseline	No association between sleep duration and IDM after adjustment at 6 or 11 years
Bjorkelund (2005) [27]	1462 women born 1908–1930; Sweden	Prospective study with 32-year follow-up	Self-reported sleep duration, problems, medications	IDM determined by fasting blood/plasma glucose	Age, BMI, waist-hip ratio, subscapular skinfold, physical activity, triglycerides, blood pressure, socioeconomic group, education	No association between any sleep feature and IDM

IDM incident diabetes mellitus, *BMI* body mass index, *DIS* difficulty initiating sleep, *DMS* difficulty maintaining sleep, *OGTT* oral glucose tolerance test, *IVGTT* intravenous glucose tolerance test, *T2DM* type 2 diabetes mellitus, *OR* odds ratio, *IGT* impaired glucose tolerance, *RR* relative risk, *AUC* area under curve, *HOMA-IR* homeostasis model assessment-insulin resistance, *ADA* American Diabetes Association, *WHO* World Health Organization, *WC* waist circumference, *BF%* body fat percent, *HR* hazard ratio

* $p < 0.05$

Table 5 A summary of experimental studies that have investigated the association between sleep features and diabetes outcomes

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Schmid (2007) [108]	10 men; 20–40 years; Germany	Randomized crossover design: 1 night TSD vs. 1 night of 8 h TIB	PSG	Hypoglycemic clamp at the end of each condition	None	Levels of glucose and insulin were unaffected by sleep condition
Tasali (2008) [84]	5 men, 4 women, aged 20–31 years; US	Randomized crossover with 2 conditions: 2 nights baseline sleep vs. 3 nights SWS suppression	PSG	Glucose regulation assessed by IVGTT at the end of each condition	None	Significant decrease (~25%) in insulin sensitivity and reduced glucose tolerance (~23%) after 3 nights of SWS suppression
Stamatakis (2010) [52]	9 men, 2 women; aged 18–29 years; US	Experimental	PSG: 2 nights of induced sleep fragmentation	IVGTT to determine insulin sensitivity, glucose effectiveness and insulin secretion at baseline and end of experimental condition		Insulin sensitivity significantly decreased (25.2%) after sleep fragmentation; glucose effectiveness significantly decreased by 20.9% after sleep fragmentation

Table 5 continued

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Tuomilehto (2009) [109]	522 overweight participants with IGT at baseline; mean baseline age 55 ± 7 years; Finland	Randomized controlled trial: 265 randomized to intensive diet-exercise, 257 to control; 4 years intervention with 3 years post-intervention	Self-reported using activity diary based on 24 h prior to annual examination	Annual OGTT; IDM defined using WHO criteria	Age, sex, BMI, study center, smoking, alcohol, hypertension medication, baseline physical activity, 1 year change in body weight	Control group: Incidence p/100 person-yrs ≤6.5 h HR = 1.68; 9–9.5 h HR = 2.29*; ≥10 h HR = 2.74* Intervention: ≤6.5 h HR = 1.44; 9–9.5 h HR = 1.10; ≥10 h HR = 0.73
Nedeltcheva (2009) [110]	5 women, 6 men; mean age 39 ± 5 years	Randomized crossover with 2 conditions: 14 days/nights 8.5 h and 5.5 h TIB	PSG	OGTT and IVGTT to determine glucose tolerance, glucose effectiveness, insulin secretion and insulin sensitivity at the end of each condition	None	Glucose after 2 h OGTT 10% higher after 5.5 h vs. 8.5 h; insulin sensitivity reduced 17.5% in 5.5 h condition
Van Leeuwen (2010) [111]	23 healthy men; aged 19–29 years; Finland	Experimental study; 10 nights laboratory attendance (2 nights baseline, 5 nights of 4 h TIB, 3 nights of 8 h TIB. Control group spent 8 h TIB for 10 nights	PSG for 10 consecutive nights	Fasted blood samples during each experimental sleep condition for assessment of glucose and insulin		Insulin increased after sleep restriction to 160% and dropped back to 115% during 8 h recovery; insulin-to-glucose ratio increased significantly after sleep restriction

Table 5 continued

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Donga (2010) [38]	5 men, 4 women; mean age 45 years; Netherlands	Experimental study: 1 night baseline TIB, 1 night 4 h TIB	PSG	Insulin sensitivity measured using the hyperinsulinemic euglycemic clamp technique		Insulin sensitivity decreased 19–25% after sleep restriction
Garfinkel (2011) [112]	11 men, 25 women, aged 46–77 years with T2DM; US	Randomized double-blinded, crossover trial (3 weeks of 2 mg melatonin vs. placebo with subsequent open labeled melatonin)	Wrist actigraphy in 22 (7 men, 15 women) with insomnia complaint	Physician diagnosed T2DM (16 using oral medication; 20 insulin-dependent)		No effect on glucose or HbA1c during cross over trial; HbA1c reduced with open-label melatonin from 9.13% (baseline) to 8.47% after 5 m
Spiegel (1999) [31]	11 healthy men; aged 18–27 years; US	Experimental study	PSG	IVGTT across 24 h	None	Glucose tolerance decreased by 40% after sleep restriction
Zielinski (2008) [32]	33 healthy men and women; aged 50–70 years; US	Experimental randomized crossover study	Wrist actigraphy monitoring throughout study period	Pre and post OGTT		No significant association between sleep and glucose tolerance
Reynolds (2012) [35]	14 healthy men; aged 22–36 years; Australia	Experimental study: 5 nights 4 h TIB, 1 recovery night 10 h TIB	Wrist actigraphy and PSG	Blood sampling to determine glucose and insulin; HOMA-IR calculated; CGM	None	Glucose, insulin and HOMA-IR were significantly higher after sleep restriction vs. baseline

Table 5 continued

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Broussard (2012) [34]	7 healthy (1 woman, 6 men); aged 18–30 years; US	Randomized crossover study: 4 nights of 4.5 h TIB or 8.5 h TIB	PSG	IVGTT to determined insulin sensitivity		Insulin sensitivity significantly reduced by 16% after sleep restriction
Bell (2013) [113]	6 men, 5 women; mean age 26 years; at risk for T2DM; US	Randomized crossover study with 2 conditions: 8 nights of either 8.5 h TIB or 5.5 h TIB	Wrist actigraphy	Fasting plasma glucose obtained on the last morning of each condition	None	Sleep restriction associated with lower glucose level
Leproult (2014) [36]	26 healthy (7 women, 19 men); aged 21–39 years; US	Non-randomized experimental	PSG	IVGTT and frequent blood sampling	None	Insulin sensitivity decreased after sleep restriction; effect doubled in men with circadian misalignment
Buxton (2012) [61]		Experimental study with circadian misalignment				
Rao (2015) [33]	14 (8 men, 6 women) without T2DM; mean age 27 years; US	Randomized crossover study: 5 nights of 4 h TIB and 8 h TIB	Wrist actigraphy and PSG	Insulin sensitivity measured using OGTT and hyperinsulinemic-euglycemic clamp	None	Insulin sensitivity decreased by 25–29% following sleep restriction; hepatic insulin sensitivity was unaltered

Table 5 continued

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Broussard (2015) [37]	19 healthy men; aged 18–30 years; US	Randomized crossover study: 8.5 h TIB vs. 4.5 h TIB	Sleep diaries and continuous sleep-wake monitoring using wrist actigraphy	IVGTT to determine insulin, glucose and insulin sensitivity	None	Insulin sensitivity decreased after sleep restriction
Robertson (2013) [114]	19 healthy men; aged 20–30 years; UK	Experimental study: sleep restriction vs. control for 3 weeks	Wrist actigraphy and sleep diary	Hyperinsulinemic-euglycemic clamp to assess insulin sensitivity	None	Insulin sensitivity significantly decreased after 1 week of sleep restriction
Gonzalez-Ortiz (2000) [115]	28 healthy (14 men, 14 women); aged 19–23 years; Mexico	Randomized controlled trial: 24-h total sleep deprivation or habitual sleep	Unknown	Insulin suppression test	None	After sleep deprivation 18% increase in steady-state glucose concentration
VanHelder (1993) [116]	10 healthy men; mean age 22 years; Canada	Randomized crossover study	Unknown	OGTT	None	Insulin response to OGTT was elevated after 60 h of TSD with sedentary activity vs. physical activity

Table 5 continued

First author (year)	Sample/country	Study design	Sleep measure	Diabetes measure	Covariates	Findings
Buxton (2010) [117]	20 healthy men; aged 20–35 years; US	Experimental sleep study with 2 conditions	PSG	IVGTT and hyperinsulinemic-euglycemic clamp	None	Insulin sensitivity reduced by 11–20% after sleep restriction; glucose tolerance decreased

PSG polysomnography, *SWS* slow wave sleep, *IVGTT* intravenous glucose tolerance test, *IGT* impaired glucose tolerance, *OGTT* oral glucose tolerance test, *IDM* incident diabetes mellitus, *WHO* World Health Organization, *HR* hazard ratio, *TIB* time in bed, *T2DM* type 2 diabetes mellitus, *CGM* continuous glucose monitoring, *TSD* total sleep deprivation

*$p < 0.05$

Spiegel and colleagues [31]. No significant associations were discovered between sleep condition and insulin resistance. There are various explanations, possibly from differences between study protocols, that may account for these observed discrepancies. First, volunteers were permitted to increase caffeine intake during sleep restriction to promote wakefulness [32]. Second, sleep restriction strategies were discussed between the volunteer and researcher to ensure facilitation, which may have resulted in different approaches to different individuals according to circadian preference that were not obtained and therefore not adjusted for within the analyses [32]. Third, a number of individuals completed the OGTT 2–5 days after the end of the 8-week manipulation [32]. These volunteers were instructed to continue with the allocated TIB until the OGTT had been performed, but reporting on continued compliance was not documented and may have biased the findings. Furthermore, extended time periods beyond the experimental period may have resulted in differences, although comparisons were not made in the analyses for these subjects. Fourth, a reduction of 90 min in Zielinski's protocol [32] may be inadequate to observe a significant effect and is less extreme than Spiegel's 4-h TIB [31]. Finally, the study recruited older individuals with a prolonged amount of TIB (9 h) versus total sleep time (7.4 h) [32], as compared to young healthy men in Spiegel's study [31].

Recent detailed study of hepatic and peripheral insulin sensitivity, as well as substrate utilization, in response to sleep restriction has been investigated. Rao and colleagues have revealed that an acute bout of extreme sleep reduction can result in profound metabolic alterations [33]. Participants received 2 nights of laboratory acclimatization followed

by two conditions in a randomized crossover approach undertaking 5 nights of sleep restriction (4 h TIB) and normal sleep (8 h TIB), monitored using ambulatory PSG. At the end of the 5-night sleep restriction period, peripheral and whole-body insulin sensitivity significantly decreased by 29% and 25%, respectively. No changes were noted for hepatic insulin sensitivity using the gold-standard hyperinsulinemic-euglycemic clamp technique [33]. An OGTT was also administered and HOMA-IR calculated, which revealed a 20% increase in insulin secretion following sleep restriction [33]. The authors of other experimental studies have reported comparable findings [34–37]. Similar effect sizes have also been reported following just 1 night of sleep reduction (4-h TIB) [38], suggesting that acute, extreme sleep restriction may result in metabolic disruption and a predisposition to diabetes.

The advantages of experimental sleep studies are that they usually benefit from the gold-standard measure to monitor sleep and incorporate accurate diabetes outcomes under very tightly controlled conditions, thereby removing the effect of known confounders. However, laboratory attendance may interfere with the natural sleep patterns and/or architecture, thereby introducing potential biases including environmental change (room temperature, altered noise/lighting, different bed comfort and more) and equipment to monitor sleep and diabetes (PSG wiring, catheters for repeated blood sampling). While laboratory studies are usually conducted under strictly controlled conditions, this may alter naturally occurring behaviors during attendance and objectively determined retrospective aspects of participant lifestyles and/or previous related events may not be considered but are crucial and may influence the findings. Furthermore, extreme sleep restriction is usually enforced but is not representative of voluntary small amounts of sleep loss experienced in societal behaviors. Finally, the majority of experimental work has been performed in healthy, young and male participants; therefore, the findings may not extend to other groups. That said, results of experimental sleep studies coupled with findings from large observational studies suggest a definitive association between sleep loss and diabetes. PSG monitoring confirms adherence to sleep manipulation by determining the total sleep time, but the authors do not usually report on other sleep features, despite the availability of output. Although the majority have focused on sleep duration and/or sleep loss, other sleep characteristics have also emerged to be important.

Sleep Quality in Relation to Insulin Resistance and Diabetes

Severely short sleep, defined by some as $\leq$5 h per night, as well as insomnia has been previously linked to a significantly increased risk of T2DM [18] and increased insulin resistance [39] through validated sleep measures. Lack of self-reported sleep [40] as well as sleep debt [41] has also been linked to the condition. These sleep outcomes (insomnia, lack of sleep and sleep debt) may be due to poor-quality sleep, which has resulted in researchers investigating this in relation to diabetes.

The most commonly used validated sleep quality questionnaire is the Pittsburgh Sleep Quality Index (PSQI). It is 24-item survey with 7 subcategories (sleep duration, disturbance, medication, latency, quality and efficiency as well as daytime dysfunction) that can be totaled

to provide an overall score [42]. A combined score of more than five is suggestive of poor sleep quality. Some have investigated the prevalence of sleep quality, as determined by the PSQI, among T2DM. Fiorentini and colleagues reported a higher prevalence of T2DM in those with poor-quality sleep (19.4%) compared to those with good quality sleep (8.8%) [43]. Similarly, another study reported 33.3% of 50 participants with an HbA1c level of >7% had poor quality sleep [44]. Another reported 55% of 300 T2DM patients had poor-quality sleep [45]. Further, a sample of 551 patients in China revealed that the prevalence of poor sleep quality was significantly greater in those with poorer glycemic control and that average insulin resistance was higher among those with poorer sleep quality [16]. A larger effect size was observed by Tsai et al. using HbA1c levels to compare sleep quality using the PSQI [46]. After adjustment for age, gender and BMI in a sample of 46 T2DM patients, poor sleep quality was associated with poorer glycemic control OR 6.94, $p = 0.002$ [46]. Small studies with subjective sleep quality measures may be the result of chronic complications or 'side effects' of T2DM. In an attempt to disentangle the chronic impact of diabetes on sleep, Rajendran and colleagues administered the PSQI to investigate the relationship between sleep quality and duration of T2DM in 120 patients. Diabetes duration was negatively associated with the global PSQI score ($\beta = -020$, $p = 0.02$), independent of age, gender, BMI, HbA1c and medication [47]. This association is consistent with another larger study ($n = 614$ older patients with T2DM) [48].

Aside from the existing data from diabetic populations, the relationship between sleep quality and insulin resistance has also been investigated in healthy individuals as well as those at risk of developing T2DM. Hung et al. examined 1805 participants, of whom 1217 had normal glucose tolerance (healthy) and 118 had impaired fasting glucose (IFG), impaired glucose tolerance (IGT) was present in 287, a total of 80 had both IFG and IGT, and 103 had newly diagnosed T2DM [49]. Comparisons among these groups were made according to sleep quality using the PSQI. The IGT group, compared to the healthy group, was positively associated with global PSQI when assessed through linear regression after adjustment for a range of confounders including self-reported physical activity, BMI, demographics, lipids, blood pressure and lifestyle factors, $\beta = 0.63$ (95% CI 0.33–0.94). A similar observation was reported for individuals with IFG and IGT, compared to the healthy group, where $\beta = 0.61$ (95% CI 0.06–1.15). The greatest effect size for poorer sleep quality was present in those with T2DM versus healthy individuals, $\beta = 0.86$ (95% CI 0.37–1.35). PSQI was then dichotomized into poor quality (>5) and good quality (≤5) was used as the referent category. Comparing all groups to the healthy group, only those with an existing diagnosis of T2DM showed a significant effect of poor sleep quality, OR 2.27 (95% CI 1.39–3.70), after adjustment [49]. Although cross sectional, this study partly controls for the potential chronic and psychological impact of diabetes on sleep given that those with diabetes were unaware of their diagnosis.

A broad range of characteristics can be used to measure sleep quality. Sleep efficiency, sleep fragmentation, number of wake episodes, wake after sleep onset and length of awakenings are all indicators. Sleep efficiency (the percentage of time spent in bed sleeping) has been used to explore the relationship with diabetes. The Coronary Artery Risk Development in young Adults (CARDIA) study recruited young

individuals (aged 18–30 years) with ($n = 40$) and without ($n = 115$) T2DM [39]. A fasting blood sample was drawn, and insulin resistance was measured using HOMA-IR. A wrist actigraphy device was worn for 3 consecutive days/nights and repeated around 2 years later to estimate sleep fragmentation, an indicator of sleep quality. Insulin resistance was positively and significantly associated with sleep fragmentation in those with T2DM only before and after adjustment, where $\beta = 0.36$, $p < 0.001$ and $\beta = 0.35$, $p < 0.001$, respectively. Insomnia, but not sleep duration, was positively associated with insulin resistance in those with T2DM but not those without [39]. The relationship between sleep fragmentation and insulin sensitivity has been confirmed by others in case-control studies [50, 51] as well as experimental manipulation [52]. Two nights of induced sleep fragmentation in controlled laboratory conditions has been shown to significantly decrease insulin sensitivity by 25.2% and glucose effectiveness by 20.9% [52]. Sleep fragmentation is a common feature of sleep-disordered breathing (SDB), specifically obstructive sleep apnea (OSA), a condition closely linked to T2DM (for brief discussion, see the section titled "The role of other sleep features upon insulin resistance and diabetes").

The majority of studies highlighting a relationship between indicators of sleep quality and diabetes are based on cross-sectional data [10, 16, 39, 41, 43–49, 53–57], and while just one found no association [56], causality remains the main issue. A small number of case-control studies have aided comparisons of differences in sleep quality between those with and without T2DM [50, 51, 58]. There are, however, limited convincing prospective data. Early work by Nilsson et al. used a non-validated questionnaire (two questions) to determine the difficulty of initiating sleep and use of hypnotics along with subjectively reported T2DM with a mean follow-up of 15 years, reporting a 52% and 78% increased risk of incident T2DM in those with one or both sleep features, respectively [59]. Similar findings have been reported by those with difficulty maintaining sleep [53]. Conversely, another group found no association between difficulties initiating sleep and objectively confirmed incident T2DM [26]. Thus, recruitment of initially healthy, young populations incorporating regular prospective follow-ups paired with objective sleep/activity monitoring in the natural environment is required to confirm or refute the relationship between sleep quality and diabetes.

The Emerging Effect of Sleep-Wake Misalignment Upon Insulin Resistance and Diabetes

While the majority of focus has been on sleep quantity and quality relative to diabetes, there is now emerging evidence suggesting that circadian rhythms, chronotype and sleep-wake timings play an important role in diabetes onset, development and management. It is well established that shift workers have a higher prevalence of metabolic disorders [60]. In particular, night-shift workers and rotating shift workers are among those worst affected as they not only experience circadian disruption but also sleep loss. These extreme patterns are in conflict with human evolution and challenge our internal circadian pacemakers, regulated by the hypothalamic suprachiasmatic nucleus. Recent evidence suggests that extreme sleep-wake timings are not necessary to cause metabolic alteration, but that even slightly shifted changes and/or circadian preferences can influence diabetes.

Buxton and colleagues examined the effects of sleep restriction combined with gradual circadian misalignment (eventually simulating shift-work patterns) upon glucose metabolism. A total of 21 healthy participants were examined across a 39 consecutive day/night period in a strictly controlled laboratory setting [61]. A 32% reduction in insulin response to a standardized meal was reported, resulting in inadequate glucose regulation. The resting metabolic rate was also reduced following experimental manipulation of sleep restriction and circadian desynchrony, although levels reverted back to baseline subsequent to 9 days/nights of recovery sleep [61].

Leproult et al. examined a healthy population of young (21–39 years) individuals ($n = 26$). Wrist actigraphy was used to monitor standardized sleep-wake schedules 1 week prior to the circadian misalignment intervention [36]. Upon laboratory attendance, sleep was monitored using PSG and volunteers underwent 3 baseline days/nights, then 8 days/nights of 5 h TIB (centered around 03:00: circadian alignment). Half of the sample experienced an 8.5-h delay in bedtimes (09:00–14:00) for 4 of the 8 nights (circadian misalignment), followed by 3 nights of sleep recovery. All participants encountered the same amount of sleep opportunity (24 h over 8 days/nights), ensuring the effect of circadian misalignment per se was examined. An IVGTT was performed following an overnight fast on the 2nd baseline day as well as on the 2nd to last day of the intervention, and multiple blood samples were obtained. Insulin sensitivity was decreased in 96% of the sample, which was unaccompanied by an increase in responsiveness of β-cell function. The decrease in insulin sensitivity was almost double in the misaligned group (−58%) versus the controls (−32%), $p = 0.011$. Similarly, a greater effect was observed in the experimental group where C-reactive protein (an indicator of systemic inflammation) increased by 146% from baseline compared to the control group (+64%).

Taken together, findings from enforced circadian misalignment concurrent with sleep loss provide clues about metabolic alterations that arise from sleep changes, which challenge human physiology. It is well known that physical activity is crucial for preventing diabetes onset and progression. If sleep loss paired with circadian misalignment results in decreases in basal metabolic rate then a greater amount of energy expenditure will be required for energy homeostasis. Additional energy expenditure is less likely when in a sleep-deprived state. Furthermore, sleep-wake timings that are inconsistent with human evolution may result in decreased insulin sensitivity as well as increased systemic inflammation, which is associated with cardiovascular disease. Forced desynchronization is extreme and simulates shift work but is not necessarily representative of societal behaviors or day workers. Other groups have investigated less radical approaches of circadian misalignment by examining circadian preferences (morningness-eveningness). A number of studies have investigated circadian preference in T2DM patients with cross-sectional data [12, 62–65].

One group highlighted a significant association between HbA1c and self-reported circadian preference, where $\beta = -1.54$, $p = 0.03$ after adjustment for age and high-density lipoprotein cholesterol in 101 Japanese men [65]. Lower scores on the morningness-eveningness questionnaire (MEQ) indicate evening types, suggesting that 'night owls' had poorer glycemic control [65]. Another study included 725 Japanese mixed-gender

T2DM patients and found a dose-dependent effect of circadian preference on HbA1c levels. HbA1c was significantly higher in those with evening preference (7.3%) compared to morning types (6.7%), and linear regression revealed $\beta = -2.94$, $p < 0.01$ after adjustment for a range of established potential confounders including physical activity, dietary intake and demographics [64]. One further study that recruited a random sample of 6,258 Finnish adults, aged 25–74 years, revealed that evening types (determined from MEQ) predicted increased odds of T2DM (OR 2.6, $p < 0.0001$), after adjustment [12]. Two more studies by the same group, and possibly data analysis from the same sample, demonstrated significant evening chronotype associations with diabetes [62, 63]. A total of 194 T2DM patients were assessed using the midpoint of sleep, calculated from self-reported estimated sleep-wake times in order to determine circadian preference (chronotype). Glycemic control (HbA1c) was obtained from medical records, and the relationship was assessed with circadian preference. The midpoint of sleep on free days was positively correlated ($r = 0.34$, $p < 0.001$) with glycemic control. In hierarchial regression analysis, the association remained, where $\beta = 0.03$, $p = 0.001$ after adjustment [63]. Similar findings were reported in the other study where it was proposed that chronotype mediated the association between skipping breakfast and glycemic control [62].

Aside from experimental work, insulin sensitivity in relation to circadian misalignment/preference has not been extensively examined, although it is a growing area of study. The existing evidence indicates that extreme misalignment of sleep-wake timings in healthy individuals may promote pre-diabetes. Furthermore, evening types with T2DM may have poorer glycemic control, although causality remains undetermined, and further investigation is required for confirmation.

The Role of Other Sleep Features Upon Insulin Resistance and Diabetes

When sleep occurs, highly complex physiological processes ensue including hormone release, information processing, cellular restoration and more. Previously, sleep was believed to be a phenomenon for and by the brain. Undoubtedly, the brain regulates sleep, but evidence now indicates clear peripheral effects on metabolic outcomes. This is representative of gradual sleep alterations that have occurred within contemporary society, concomitant with the rising prevalence of metabolic diseases. Much of the research focus has been on sleep quantity; however, there are many other significant sleep characteristics that have been liked to T2DM.

Frequent and longer daytime sleep (napping/siesta) has been linked to a higher risk of T2DM prevalence/incidence [66–68]. It has been suggested that napping may be a consequence of poor sleep quality and/or insufficient sleep duration. In the studied populations, however, napping is habitual and believed to have beneficial health effects. Napping after lunch reflects the human circadian rhythm (post-lunch dip) although, according to the two-process model of sleep [1], there is insufficient prior wakefulness to warrant sleep initiation. Some have therefore considered daytime napping and combined this with nocturnal sleep duration (calculating total sleep time) to investigate the relationship between total sleep and metabolic outcomes [69, 70]. Experimental sleep studies, however, usually prohibit napping in study protocols and thus may not capture crucial information.

There are many documented metabolic consequences of daytime sleep/circadian misalignment [36, 61, 71], with some linking this to diabetes complications [72]. Sleep debt is usually accumulated across the week and repaid during weekends. Recent experimental data in 19 healthy males with at least a 6-month history of voluntary sleep curtailment were recruited. When 'catch-up' sleep was not permitted and short sleep persisted across a 7-day period for 3 weeks, insulin sensitivity decreased and HOMA-IR increased compared to those with compensatory weekend catch-up sleep [73].

Snoring may also be a risk factor for T2DM [74], possibly as a consequence of OSA. Undoubtedly, OSA is strongly linked to diabetes, although which develops first is to be determined, given that they are both noncommunicable. Obstructive sleep apnea (OSA), as well as concomitant intermittent nocturnal hypoxemia, is common in patients with T2DM [75, 76]. Several studies have reported an association between OSA, glycemic control and diabetes microvascular complications [77–81]. OSA appears to be more common in ethnicities where T2DM is more common [82]. Many studies have not been able to address the confounding effect of OSA in the relationship between sleep and metabolism. Interestingly, continuous positive airway pressure (CPAP), used to treat OSA, has also been shown to improve glycemic control prospectively [75]. Thus, improving sleep can in turn improve metabolic profiles. While SDB certainly disrupts metabolic regulation and extensive data have recently emerged in relation to insulin resistance and other features of diabetes, this is beyond the scope of the current review. Clearly, the extent of other sleep aspects on metabolic health is slowly emerging, although a better understanding of all characteristics is still required, along with mechanistic explanations.

Significant changes in sleep architecture have also been noted in a retrospective case-control study [58]. T2DM patients had 4.5% less slow wave sleep (SWS) and 10.3% more rapid eye movement (REM) sleep compared to those without the condition. Differences in sleep architecture between those with and without diabetes have also been investigated in the Sleep Heart Healthy Study but detected different results [83]. Differences in SWS between diabetic and non-diabetic volunteers diminished after adjustment, and REM sleep accounted for a significantly reduced proportion of total sleep time in those with diabetes [83]. Tasali and colleagues attempted to disentangle this relationship by suppressing SWS for 3 consecutive nights using an acoustic stimulus in nine healthy, young volunteers [84]. SWS suppression was achieved and resulted in significant reductions in insulin sensitivity (~25%) and glucose tolerance (~23%) compared to baseline. SWS is considered to have a restorative effect; thus, a reduction in this deep phase of sleep may induce metabolic alterations that can promote diabetes as well as other related comorbidities. SWS declines with age and diabetes risk increases with age; thus, age may mediate this relationship, and future studies need to investigate the strength of such associations in older individuals as well as those with T2DM.

Mechanisms

There is now clear evidence linking sleep to the onset and development of pre-diabetes and T2DM. Understanding the mechanisms involved is of great importance. It has been suggested that insufficient sleep and/or poor quality sleep can result in oxidative stress as

well as overactivation of the sympathetic nervous system, and some have used heart rate variability to support this notion [31]. Others have shown that changes in the appetite-regulating hormones leptin (related to satiety) and ghrelin (related to hunger) have been observed in response to short/insufficient sleep duration [85, 86]. Disruption of the regulation of these hormones from sleep loss has also been linked to an increased appetite for carbohydrate-dense foods [85, 86] and intake of calories from sweet foods (snacks) [87]. Poor dietary habits are well known to promote T2DM; thus, the effects of sleep loss may contribute to these unhealthy behaviors through metabolic disruption. Sleep deprivation is associated with activation of the hypothalamic orexin (hypocretin) neuropeptide system [88–90]. Orexin (hypocretin) neurons are located in the lateral hypothalamus and project throughout the central nervous system and particularly to areas important in wakefulness. Orexin activation is associated with increased sympathetic nervous system activation, increased cortisol and suppressed growth hormone secretion, which can all predispose to hyperglycemia. Orexin receptor antagonists are currently under investigation for use in insomnia, and it would be of interest to study their impact on metabolism. The importance of the central nervous system in the regulation of glucose metabolism has been further highlighted by the use of bromocriptine in the treatment of T2DM. Bromocriptine is a dopamine D2 receptor agonist, primarily used in the treatment of prolactinoma. Bromocriptine has received United States Food and Drug administration approval for the treatment of T2DM. Its use is supported by more recent randomized controlled trials (RCTs) in those with diabetes [91, 92]. The precise site of action of bromocriptine in regulating metabolism is unknown, but dopamine acts at several levels including the hypothalamus and pineal gland [93], which are key areas for the regulation of circadian rhythms, sleep and metabolism. The timing of bromocriptine administration in glycemic regulation appears to be important with greater effects in the morning when endogenous dopaminergic drive is at its peak. A side effect of bromocriptine for diabetes treatment is sleepiness. Dopamine receptor antagonism by anti-psychotic drugs has been observed to be associated with obesity and subsequent insulin resistance and diabetes.

Key Limitations

Some observational data highlight a U-shaped relationship between sleep and diabetes prevalence, and while much of the focus has been on short sleepers, long sleep may also be problematic and has shown a greater effect size compared to short sleep in a recent meta-analysis of prospective studies [94]. Previously, conclusions suggested that long sleepers possibly have underlying health issue(s) that result in sleep lengthening. Of course, this may not always be true; thus, there is a need to identify general cut points for when sleep may become harmful, given that sleep extension studies are underway in an attempt to address metabolic dysregulation. Definitions of short/long sleep are also inconsistent, meaning comparisons can be difficult and conclusions misconstrued. There is a need for reliable cut points that can be applied across all studies to ensure uniformity.

Most of the sleep-diabetes evidence is consistent although not completely homogeneous. Of particular concern is the lack of prospective evidence for sleep quality

and diabetes onset/progression. Other prospective discrepancies exist from a powerful 32-year follow-up study [27] finding no association between sleep and incident diabetes. There are some potential explanations for this including (1) the possibility of OSA as a hidden confounder, an unrecognized sleep disorder at the time the study commenced; (2) lack of an objective sleep measure; (3) gender differences, given that the study was only conducted in women; (4) dietary habits were not considered.

Sleep perceptions are subject to several biases; thus, objective measures in natural environments are preferable. Participants should be regularly monitored with validated wrist actigraphy to ensure sleep-wake information is captured. However, that said, sleep is not static, making it incredibly difficult to capture an accurate picture and study its effects. Furthermore, there is no gold-standard measure of dietary intake, an important confounder of the sleep-diabetes relationship. Capturing full and accurate information about food selection, micro-/macronutrients, portion sizes, methods of cooking, unknown ingredients in takeaway food and more is near impossible to reliably measure in a natural setting. Food diaries are a reasonable compromise but require specific programs to analyze the data, are time consuming to administer, complete and analyze, may not be completed, are subjective and can therefore introduce bias. An improved alternative that is accurate is urgently needed, given that energy intake/selection can dramatically alter metabolic regulation and hormone release. The majority of the work, whether observational, case-control, prospective or experimental, has not ascertained or adjusted for the combination of the three factors known to promote diabetes (energy intake, energy expenditure, familial history). This is a major limitation in the existing literature, and consistency across studies of all potential confounding factors is urgently needed.

Studies performed in diabetes patients usually adjust for diabetes duration and medications. Details of medications are usually omitted, but specifications (name, frequency, dosage and timings) are likely to be important, particularly for medications shown to alter sleep. One further consideration is the possibility of psychological conditions, which have sometimes been adjusted for in sleep-diabetes studies. However, medication related to these conditions, which can influence sleep-wake behaviors, as well as the condition itself should be considered. Commonly used antidepressants, for example, have significant effects on sleep architecture. The impact of medications on the sleep-diabetes relationship can also be complex. For example, pregabalin enhances sleep by itself and also reduced sleep disturbance secondary to a reduction in neuropathic pain in diabetes [95]. In some patients, however, significant weight gain may occur with pregabalin and other similar drugs, which increases insulin resistance.

Finally, the majority of the experimental work has been conducted in young, healthy individuals, with more data available in men, given the complexities of the female menstrual cycle that may interfere with metabolic hormone measurements. While findings from these types of studies have highlighted important information and provided a foundation for our understanding, detailed work is required in those with T2DM as well as older individuals so that we can establish potential interventions for improving glucose control in those with long-standing disease or reverse the condition in those with new diagnoses.

Future Directions

Interventions that target those with T2DM, as well as prevention of its onset, should incorporate sleep education in addition to energy balance advice. Emerging evidence from a small study of healthy volunteers randomized to sleep extension for 40 days/nights or control has provided preliminary but promising results for improving insulin sensitivity with as little as one additional hour of time in bed [96]. Future studies should repeat this sleep extension/improvement of sleep quality in those with T2DM for further comprehensive examination and understanding. After all, making healthy food selection, controlling portion sizes and achieving the recommended minimum 30 min of daily activity require much dedication and willpower. Conversely, compliance with staying in bed for an extra hour may be easier and costs the individual little, but may greatly benefit his or her metabolic profile and could prevent the onset and/or progression of diabetes.

The majority of sleep studies in relation to diabetes mellitus have focused on T2DM. There is limited information on those with type 1 diabetes, although recent preliminary evidence has emerged suggesting that multiple sleep parameters as well as sleep staging play a role in glycemic control in this population [97, 98]. Sleep may play a key role in other types of diabetes mellitus although little is known about this, warranting further investigation.

CONCLUSION

The current evidence suggests that sleep is instrumental to metabolic regulation and disease management. Disruption of sleep homeostasis, which is comprised of multiple components (quantity, quality, timing and architecture), can result in adverse metabolic consequences. The effect of disruption of one component has been established, but disruption of multiple sleep features may worsen diabetes control, although this requires further investigation. Sleep imbalance may promote diabetes onset or hinder glucose control and insulin sensitivity in those with pre-existing diabetes. Cross-sectional studies as well as prospective cohort findings demonstrate reasonably consistent findings and implicate a role for sleep in the management of diabetes. Furthermore, acute sleep disruption under controlled laboratory conditions has shown significant and negative effects upon glucose control in healthy adults. Exposure to persistent sleep imbalance is likely to be detrimental to metabolic health/disease status. While the evidence is convincing, a number of limitations are present, including the possibility of uncontrolled major confounders, which restrict robust conclusions. Further investigation in 'at risk' populations as well as those with T2DM is needed incorporating objective and prospective sleep measures. It may be possible to prevent incident diabetes and smooth the current epidemic by improving diabetes control through sleep optimization in combination with other lifestyle advice, particularly in newly diagnosed cases. Promoting the importance of sleep for improving diabetes control/management is unlikely to result in any harmful consequences. Awareness of an additional, and easily modifiable, lifestyle behavior among healthcare professionals is therefore recommended.

ACKNOWLEDGMENTS

Both authors are funded by the Biomedical Research Program (BMRP) at Weill Cornell Medical College in Qatar, supported by the Qatar Foundation. No funding was received for the article processing charges. Teresa Arora and Shahrad Taheri designed the review. Teresa Arora drafted the initial article, and Shahrad Taheri critically revised the intellectual content. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Disclosures. Teresa Arora and Shahrad Taheri declare that they have no conflict of interest.

Compliance with ethical guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by either of the authors.

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