Night-shift work is associated with poorer glycaemic control in patients with type 2 diabetes

AREESA MANODPITIPONG[1], SUNEE SAETUNG[1], HATAIKARN NIMITPHONG[1], NANTAPORN SIWASARANOND[1], THANAWAT WONGPHAN[2], CHOTIMA SORNSIRIWONG[3], PRANEE LUCKANAJANTACHOTE[4], PRASITCHAI MANGJIT[5], PRASIT KEESUKPHAN[1], STEPHANIE J. CROWLEY[6], MEGAN M. HOOD[6] and SIRIMON REUTRAKUL[1]

[1]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [2]International Health Policy Progeam (IHPP), Ministry of Public Health, Nonthaburi, Thailand; [3]Rayong Provincial Hospital, Rayong, Thailand; [4]Samutsakhon Provincial Hospital, Samutsakhon, Thailand; [5]Kaengkhoi Hospital, Saraburi, Thailand; [6]Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL, USA;

Keywords
sleep apnea, Thailand

Correspondence
Sirimon Reutrakul, MD, CDE, Division of Endocrinology and Metabolism, Department of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Rd, Ratchathewi, Bangkok, Thailand 10400.
Tel.: +6622011647;
fax: +6622011647;
e-mail: sreutrak10800@gmail.com

Accepted in revised form 1 April 2017; received 12 December 2016

DOI: 10.1111/jsr.12554

SUMMARY

The circadian system plays a role in regulating metabolism. Night-shift work, a form of circadian misalignment, is associated with increased type 2 diabetes risk. This study aimed to determine if night-shift workers with type 2 diabetes experience poorer glycaemic control than non-shift workers. Patients with type 2 diabetes (104 unemployed, 85 day workers and 60 night-shift workers) participated. Sleep duration, sleep quality, morningness–eveningness preference, depressive symptoms and dietary intake were assessed using standardized questionnaires. Haemoglobin A1c levels were measured. Night-shift workers had significantly higher haemoglobin A1c levels compared with others, while there were no differences between day workers and unemployed participants (median 7.86% versus 7.24% versus 7.09%, respectively). Additionally, night-shift workers were younger, had a higher body mass index, and consumed more daily calories than others. Among night-shift workers, there were no significant differences in haemoglobin A1c levels between those performing rotating versus non-rotating shifts ($P = 0.856$), or those with clockwise versus counterclockwise shift rotation ($P = 0.833$). After adjusting for age, body mass index, insulin use, sleep duration, morningness–eveningness preference and percentage of daily intake from carbohydrates, night-shift work, compared with day work, was associated with significantly higher haemoglobin A1c ($B = 0.059$, $P = 0.044$), while there were no differences between unemployed participants and day workers ($B = 0.016$, $P = 0.572$). In summary, night-shift work is associated with poorer glycaemic control in patients with type 2 diabetes.

INTRODUCTION

The circadian system is known to play a role in tissue metabolism and hormonal secretions (Marcheva *et al.*, 2013). The central clock, located in the hypothalamus, is synchronized to the light–dark cycle and relays the information to peripheral organs, which contain 'peripheral clocks', to modulate daily rhythms of sleep/wake and other organ functions. In addition, environmental factors, such as temperature, meal timing and exercise, are 'zeitgebers' or 'time givers', and play a role in entraining the circadian system. There is growing evidence that desynchrony between the circadian system and environmental time givers or 'circadian misalignment' is detrimental to human health. Several well-controlled laboratory experiments employing different protocols (forced desynchrony or simulated shift work or circadian misalignment protocols) in which participants slept and ate out of phase to the usual timing revealed

that circadian misalignment resulted in reduced glucose tolerance (Buxton *et al.*, 2012; Leproult *et al.*, 2014; McHill *et al.*, 2014; Scheer *et al.*, 2009), alterations in appetite-regulating hormones (Buxton *et al.*, 2012), elevated inflammatory markers (Leproult *et al.*, 2014), increased blood pressure (Scheer *et al.*, 2009), and decreased energy expenditure (McHill *et al.*, 2014).

Night-shift workers, estimated to be approximately one-fifth of the work force (McMenamin, 2007), typically eat during their circadian night and sleep during their circadian day, and therefore are exposed to an extreme form of chronic circadian misalignment. Observational studies revealed that night-shift work is associated with increased risk of metabolic syndrome (Wang *et al.*, 2014), dyslipidaemia (Karlsson *et al.*, 2003), prevalent diabetes (Ghazawy *et al.*, 2014; Ika *et al.*, 2013) and incident diabetes (Pan *et al.*, 2011; Suwazono *et al.*, 2006). In addition, there was a relationship between longer duration of night-shift work and increasing diabetes risk (Pan *et al.*, 2011). In shift workers without diabetes, glycated haemoglobin (a reflection of overall glucose levels) was reported to be higher than day workers in one study (Cesana *et al.*, 1985), although no differences in glucose levels were found in another study (Karlsson *et al.*, 2003).

There are multiple factors that may predispose night-shift workers to increased diabetes risk, including unhealthy diet, overweight/obesity and sleep disturbances. In a study of 2254 workers, those aged 30 years and older performing midnight shifts (00:15–06:30 hours) consumed higher daily calories than fixed-day workers (Morikawa *et al.*, 2008). Data from NHANES 2005–2010 revealed that shift workers, especially those with rotating shifts, consumed an unhealthier diet as measured by a dietary inflammatory index, compared with day workers (Wirth *et al.*, 2014). A smaller study, however, did not find differences in dietary patterns among shift work status (Lennernas *et al.*, 1993). Shift work was also a predictor of abdominal obesity (Guo *et al.*, 2015). Both sleep duration and sleep quality, known to be risk factors for incident diabetes, are often reduced in shift workers (Reutrakul and Knutson, 2015). These factors likely interact with each other and shift work status, and may modify the risk of developing abnormal glucose metabolism or diabetes.

To date, data are scarce whether patients with diabetes who are night-shift workers have worse metabolic control than day workers. Only a few studies have addressed this question. Two studies (61 and 152 participants) found that patients with type 2 diabetes performing shift work had significantly worse glycaemic control, as measured by haemoglobin A1c (HbA1c), than day workers (El Tayeb *et al.*, 2014; Ghazawy *et al.*, 2014). However, another study in 95 participants found no differences in HbA1c levels between the two groups (Rodrigues and Canani, 2008). Another cross-sectional study of 240 patients found that, compared with day workers, shift workers were less likely to achieve good glycaemic control, as determined by fasting glucose levels (28.3% versus 15.8%; Chalernvanichakorn *et al.*, 2008). Lastly, a small study in 16 rotating night-shift workers and 16 day workers found no differences in HbA1c levels between the two groups, although glycaemic control (as measured by fructosamine) deteriorated in shift workers after they moved to a rapidly rotating shift pattern (Poole *et al.*, 1992). None of these studies, however, considered other potential confounders that could affect glycaemic control, including sleep duration, sleep quality and dietary intake.

Therefore, the purpose of this study was to compare glycaemic control in patients with type 2 diabetes who were performing night-shift work compared with those who were non-shift workers and those who were unemployed. Sleep duration, sleep quality and dietary intake were examined as potential confounders. In addition, morningness–eveningness preference, previously reported to be related to worse glucose control in patients with type 2 diabetes (Iwasaki *et al.*, 2013; Osonoi *et al.*, 2014), was considered. We hypothesized that night-shift work was associated with poorer glycaemic control, independently of sleep duration, morningness–eveningness preference and diet.

MATERIALS AND METHODS

Participants

Adults with type 2 diabetes being followed at six hospitals in Thailand were invited to participate. Participants who were unemployed or performed day work (defined as work hours between 06:00 and 19:00 hours) were a part of a previously reported study that was conducted between January and December 2014 at Ramathibodi Hospital (Reutrakul *et al.*, 2015). Participants who performed night-shift work reported overnight work that started between 15:00 and 24:00 hours, and ended between 03:00 and 08:00 hours for at least 3 months. Night-shift workers ($n = 60$) were enrolled from September 2015–June 2016 from six hospitals located within 200 km of each other [Ramathibodi Hospital ($n = 25$), three provincial hospitals ($n = 14$) and two sub-provincial hospitals ($n = 21$)]. Exclusion criteria included pregnancy, neurological or physical impairments that required patients to depend on others for daily activity, such as being confined to bed or needing assistance with feeding. All participants gave written informed consent. The protocol was approved by the Institutional Review Board, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Weight was measured at the time of assessment. Age, height, current medications and the most recent HbA1c values (within 3 months) were extracted from patient medical records. All HbA1c values were measured by an immunoturbidmetric method (CV of $< 2\%$). Body mass index (BMI) was calculated using the standard formula [weight (kg)/height (metre)^2]. Details of diabetes medication use were obtained, including insulin, number of non-insulin diabetes medications [sulphonylurea, metformin, thiazolidinediones, glucagon-like peptide 1 receptor agonist, dipeptidyl peptidase 4 inhibitor,

alpha-glucosidase inhibitor and sodium glucose transporter 2 (SGLT-2) inhibitor], as well as anti-anxiety/antidepressant use or use of medications that may interfere with sleep/circadian functions. Research personnel interviewed participants about their work schedule, and then categorized participants as unemployed, day workers or night-shift workers. For night-shift workers, detailed shift schedule during the past month was obtained. Night-shift work was categorized into rotating (i.e. performing other shifts in addition to night-shifts) and non-rotating shift (i.e. performing only night-shifts). Those performing rotating shifts were categorized further into clockwise or counterclockwise rotation (i.e. forward or backward rotation of the shifts). Participants were also asked about their lifetime work duration as well as duration of any previous shift work and current shift work.

Depressive symptoms were assessed using the Thai version of the Center for Epidemiologic Studies-Depression scale (Trangkasombat *et al.*, 1997). Additional validated measures are described below.

Subjective sleep assessments

The average sleep duration for non-night-shift workers was derived from the question "During the past month, how many hours of 'actual sleep' did you get at night on week nights (or work days for day workers) and weekends (or free days for day workers)?". For unemployed participants, we computed a weighted weekly average: sleep duration = [(sleep duration on weekdays*5) + (sleep duration on weekend*2)]/7. For day workers, weighted average weekly sleep duration was calculated from sleep patterns reported on their work days and free days.

For night-shift workers, a detailed shift schedule for the past month was obtained. Participants were asked about the actual sleep they got during their main sleep for each reported work schedule and on their free days, and a weighted average sleep duration was computed.

To assess sleep quality independently of sleep duration, we utilized the modified Pittsburgh Sleep Quality Index (PSQI) score (Knutson *et al.*, 2006). The PSQI score evaluates sleep duration and quality within the past month, with a higher score indicating worse sleep (Buysse *et al.*, 1989), and has been validated in a Thai population (Sitasuwan *et al.*, 2014). The modified PSQI score excludes the sleep duration component from the PSQI to assess sleep quality only (Knutson *et al.*, 2006).

Participants reported whether they had a diagnosis of obstructive sleep apnea (OSA). Those without a previous diagnosis were interviewed using the Berlin questionnaire to assess the risk of OSA, which categorizes respondents as high or low risk of having OSA (Netzer *et al.*, 1999). The questionnaire was previously validated in a Thai population (Suksakorn *et al.*, 2014). Participants who had a diagnosis of or were at high risk for OSA were grouped together as presence or high risk of OSA (OSA Risk).

Morningness–eveningness assessment

Morningness–eveningness preference was assessed using the validated Thai version of the Composite Score of Morningness (CSM; Pornpitakpan, 1998; Smith *et al.*, 1989). The CSM consists of 13 questions regarding the preferred time individuals would like to wake up and go to bed, preferred time for physical and mental activity, and subjective alertness. The total score ranges from 13 (extreme eveningness) to 55 (extreme morningness).

Dietary assessments

Participants were interviewed regarding their dietary intake on the previous day (24-h dietary recall). Calories and macronutrient (percentage of daily intake from carbohydrate, fat and protein) consumption was calculated by dieticians using a Thai food database, Inmucal Nutrition Software (Institute of Nutrition, 2016).

Statistical analysis

Data are expressed as mean (SD), median [inter-quartile range (IQR)] or frequency (%). HbA1c values were not normally distributed; therefore, the natural logarithm transformation of HbA1c (lnHbA1c) was used for the analyses. One-way ANOVAs and chi-square statistics were computed to test group differences in demographics, sleep outcomes, diet and HbA1c. *Post hoc* analyses were performed using Tukey's method.

To determine the factors associated with glycaemic control, univariate regression analyses were used to explore the associations between the lnHbA1c and demographic, work status, sleep and diet variables. To determine whether night-shift work was independently associated with poorer glycaemic control, a multiple regression analysis with lnHbA1c as the outcome was performed, adjusting for factors shown to be associated with lnHbA1c in the univariate analysis ($P < 0.1$). Analyses were performed using SPSS 18.0 software (Chicago, Illinois, USA). A P-value of < 0.05 was considered statistically significant.

RESULTS

There were a total of 249 participants; 104 were unemployed, 85 performed day work and 60 performed night-shift work. Demographic, glycaemic, sleep, morningness–eveningness preference and diet outcomes are shown in Table 1. Night-shift workers reported a median (IQR) duration of performing current night work of 192 months (85–318 months), and a total lifetime duration of night work of 240 months (123–354 months). There were significant age differences among the groups, with night-shift workers being the youngest. Night-shift workers had higher BMIs than unemployed participants. Insulin use, the number of non-insulin diabetes medications and anti-anxiety/

Table 1 Characteristics of all participants and comparisons among work status

	All (n = 249)	Unemployed (n = 104)	Day work (n = 85)	Night work (n = 60)	P*
Demographic and glycaemic parameters					
Age (years)	56.4 (11.4)	64.6 (8.3)	52.7 (9.1)	47.1 (8.9)	< 0.001*,†,‡
Female (n) (%)	144 (57.8)	65 (62.5)	49 (57.6)	30 (50.0)	0.295
BMI (kg m^{-2})	28.4 (5.0)	27.5 (4.2)	28.6 (5.0)	29.6 (6.1)	0.030†
College education	117 (46.9)	45 (43.2)	56 (65.8)	16 (26.6)	< 0.001*,†,‡
Diabetes duration (years)	10.8 (9.2)	14.4 (10.0)	8.6 (7.8)	7.8 (7.4)	< 0.001†,‡
Insulin use (n) (%)	91 (36.5)	44 (42.3)	30 (35.3)	17 (28.3)	0.193
Number of non-insulin diabetes medications	1.76 (0.97)	1.64 (0.94)	1.85 (1.00)	1.85 (0.97)	0.241
Types of non-insulin diabetes medications (n) (%)					
Sulphonylurea	116 (46.5)	40 (38.4)	41 (48.2)	35 (58.3)	
Metformin	214 (85.9)	86 (82.7)	73 (85.9)	55 (91.7)	
Thiazolidinediones	51 (20.5)	20 (19.2)	18 (21.1)	13 (21.6)	
Glucagon-like peptide 1 receptor agonist	6 (2.4)	1 (1.0)	3 (3.5)	2 (3.3)	
Dipeptidyl peptidase 4 inhibitor	52 (20.8)	24 (23.0)	23 (27.0)	5 (8.3)	
α-Glucosidase inhibitor	9 (3.6)	1 (1.0)	6 (7.0)	2 (3.3)	
SGLT-2 antagonist	1 (0.4)	0 (0)	0 (0)	1 (1.7)	
Anti-anxiety/antidepressant use (n) (%)	16 (6.4)	10 (6.9)	5 (5.9)	1 (1.6)	0.132
HbA1c (%)	7.35 (6.62, 8.28)	7.09 (6.61, 8.08)	7.24 (6.61, 8.05)	7.86 (6.87, 9.60)	0.015*,†
Sleep, morningness–eveningness preference and depression parameters					
Average sleep duration (h)	5.4 (1.5)	5.3 (1.5)	5.6 (1.5)	5.1 (1.6)	0.093
Work days/weekdays sleep duration (h)	5.2 (1.6)	5.3 (1.5)	5.5 (1.5)	4.6 (1.9)	0.005*,†
Free days/weekends sleep duration (h)	5.9 (1.8)	5.4 (1.5)	6.0 (1.6)	6.6 (2.3)	< 0.001†,‡
Modified PSQI	5.9 (2.9)	5.9 (2.7)	5.6 (3.1)	6.4 (2.9)	0.318
OSA risk (n) (%)	93 (37.3)	38 (36.5)	36 (42.3)	19 (31.6)	0.377
CSM score	43.6 (6.0)	44.9 (5.5)	44.8 (5.5)	40.7 (7.2)	< 0.001*,†
Center for Epidemiologic Studies-Depression	11.9 (6.5)	11.6 (6.5)	11.4 (5.9)	13.2 (7.0)	0.207
Dietary parameters					
Total calories per day	1188 (505)	1099 (485)	1124 (408)	1434 (584)	< 0.001*,†
% Carbohydrate	59.3 (10.7)	60.6 (12.7)	58.4 (9.5)	58.2 (8.1)	0.266
% Fat	25.4 (8.8)	24.3 (10.2)	25.7 (8.0)	26.7 (7.1)	0.205
% Protein	15.2 (4.7)	15.0 (5.6)	15.8 (3.8)	14.8 (4.4)	0.445

P-values from one-way ANOVA or chi-square. Analyses on HbA1c were performed on natural logarithm transformed values.
*Significant difference between night work versus day work.
†Significant difference between night work versus unemployed.
‡Significant differences between day work versus unemployed.
BMI, body mass index; CSM, Composite Score of Morningness; HbA1c, haemoglobin A1c; OSA, obstructive sleep apnea; PSQI, Pittsburgh Sleep Quality Index; SGLT-2, sodium glucose transporter 2.

antidepressant use did not differ among groups. HbA1c level in night-shift workers was significantly higher than the others, while there were no significant differences between the unemployed and day workers. Sleep quality, OSA risk and depressive symptoms did not differ among groups. There was a trend toward shorter average sleep duration in night-shift workers compared with day workers [mean (SD) 5.1 (1.6) h versus 5.6 (1.5) h, P = 0.079), while their work day sleep duration was shorter than others, and free day sleep duration was longer than unemployed participants. Night-shift workers had more evening preference than others, as indicated by lower CSM scores. Lastly, night-shift workers consumed more daily calories than others. Dietary recall information was obtained from weekdays in all unemployed participants, and from work days in 73 (85.8%) day workers and in 56 (93%) night-shift workers. There were no significant differences in total daily calories between the recall from work days versus free days in day workers [mean (SD) 1106 (420) versus 1221 (339) calories per day, P = 0.411], or in night-shift workers [mean (SD) 1429 (593) versus 1493 (503) calories per day, P = 0.836]. There were also no differences in percentages of macronutrient intake obtained from work days or free days in both groups.

Among the night-shift workers, there were no significant differences in HbA1c levels between those performing rotating versus non-rotating shifts [7.82% (6.77, 9.66), n = 49 versus 8.17% (7.19, 9.22), n = 11, P = 0.856]. In those performing rotating shifts, there were no differences in HbA1c levels between clockwise versus counterclockwise shifts (7.69% (6.77, 9.76), n = 29, versus 8.06% (6.71, 9.37), n = 20, P = 0.833). Additional characteristics of night-shift

Table 2 Characteristics of shift workers according to the type of shifts

		Rotating workers				
	Non-rotating workers (n = 11)	All rotating workers (n = 49)	P-value (compared with non-rotating workers)	Counterclockwise workers (n = 20)	Clockwise workers (n = 29)	P-value (counterclockwise versus clockwise)
Demographic and glycaemic parameters						
Age (years)	57.6 (5.9)	44.9 (7.9)	<0.001	44.1 (6.5)	45.2 (8.9)	0.531
Female (n) (%)	3 (27.3)	27 (55.1)	0.095	10 (50.0)	18 (58.6)	0.551
BMI (kg•m^{-2})	28.5 (6.1)	29.9 (6.1)	0.504	28.6 (6.1)	30.8 (5.9)	0.206
College education	0 (0.0)	16 (32.6)	0.027	1 (5.0)	15 (51.7)	0.001
Diabetes duration (years)	14.9 (7.2)	6.2 (6.5)	< 0.001	6.2 (7.7)	6.3 (5.6)	0.948
Insulin use (n) (%)	6 (54.5)	11 (22.4)	0.033	4 (25.0%)	7 (24.1)	0.733
Number of non-insulin diabetes medications	2.01 (0.97)	1.81 (0.99)	0.575	1.50 (0.76)	2.01 (1.08)	0.063
HbA1c (%)	8.17 (7.19, 9.22)	7.82 (6.77, 9.66)	0.856	8.06 (6.71, 9.37)	7.69 (6.77, 9.76)	0.833
Sleep, morningness–eveningness preference and depression parameters						
Average sleep duration (h)	4.2 (2.1)	5.3 (1.5)	0.045	5.6 (1.7)	5.0 (1.2)	0.177
Work days sleep duration (h)	4.2 (2.3)	4.7 (1.8)	0.391	5.3 (1.9)	4.4 (1.6)	0.613
Free days sleep duration (h)	5.3 (2.5)	6.8 (2.2)	0.065	7.0 (2.4)	6.7 (2.1)	0.613
Modified PSQI	7.4 (2.9)	6.1 (2.2)	0.216	6.1 (2.9)	6.2 (2.9)	0.933
OSA risk (n) (%)	4 (36.6)	15 (31.2)	0.743	5 (25.05)	10 (34.5)	0.430
CSM	38.8 (9.8)	41.1 (6.6)	0.470	39.2 (6.5)	42.4 (6.4)	0.090
Center for Epidemiologic Studies-Depression	19.8 (9.2)	11.7 (5.4)	<0.001	13.7 (6.3)	10.3 (4.4)	0.026
Dietary parameters						
Total calories per day	1195 (551)	1487 (583)	0.135	1466 (471)	1502 (657)	0.837
% Carbohydrate	57.7 (4.7)	58.3 (8.6)	0.829	59.7 (8.8)	57.3 (8.6)	0.353
% Fat	25.9 (6.1)	26.9 (7.4)	0.693	26.6 (7.7)	27.1 (7.2)	0.828
% Protein	16.3 (3.5)	14.5 (4.5)	0.211	13.5 (3.0)	15.1 (5.3)	0.256

P-values from independent t-test or chi-square. Analyses on HbA1c were performed on natural logarithm transformed values.
BMI, body mass index; CSM, Composite Score of Morningness; HbA1c, haemoglobin A1c; OSA, obstructive sleep apnea; PSQI, Pittsburgh Sleep Quality Index.

workers are shown in Table 2. Non-rotating shift workers were older, less likely to be college educated, had longer diabetes duration, more likely to be using insulin, reported shorter average sleep duration and had more depressive symptoms than rotating shift workers, although this should be interpreted cautiously due to the small number of non-rotating shift workers. Characteristics of counterclockwise shift workers were comparable to those of clockwise shift workers, with the exception of lower educational level and more depressive symptoms.

Univariate analyses

Univariate regression analyses were used to examine the relationship between glycaemic control and other variables (Table 3). In addition to being night-shift workers, younger participants, those with higher BMI and those using insulin had poorer glycaemic control, while sex, educational level, the number of non-insulin diabetes medications and anti-anxiety/antidepressant use were not predictive of glycaemic control. OSA risk and sleep quality were not associated with HbA1c levels. There was an association between shorter sleep duration and higher HbA1c ($P = 0.039$), and more evening preference and higher HbA1c ($P = 0.004$). A higher percentage of daily fat and lower percentage of carbohydrate intake but not total calories was associated with poorer glycaemic control. The percentage of daily carbohydrate intake was inversely related to percentages of daily fat and protein intake (correlation coefficients -0.891, $P < 0.001$ and -0.589, $P < 0.001$, respectively).

Table 3 Univariate regression analyses with lnHbA1c as an outcome

	B	*P*
Demographics and work status		
Age	−0.002	0.020
Female	−0.029	0.244
BMI	0.005	0.028
College education	−0.015	0.489
Diabetes duration	0.002	0.171
Insulin use	0.127	< 0.001
Number of non-insulin diabetes medications	0.015	0.204
Anti-anxiety/antidepressant use	−0.056	0.235
*Work status**		
Night work	0.075	0.015
Unemployed	−0.006	0.825
Sleep and depressive parameters		
Average sleep duration	−0.016	0.039
Modified PSQI	0.006	0.163
OSA risk	0.021	0.374
CSM score	−0.006	0.004
Center for Epidemiologic Studies-Depression	−0.001	0.754
Dietary parameters		
Total calories	0.00003	0.155
% Carbohydrate	−0.004	< 0.001
% Fat	0.004	0.001
% Protein	0.005	0.060

B = unstandardized coefficient.
*Day work = reference.
BMI, body mass index; CSM, Composite Score of Morningness; OSA, obstructive sleep apnea; PSQI, Pittsburgh Sleep Quality Index.

Table 4 Multivariate regression analysis with lnHbA1c as an outcome

	B	*P*
Age	−0.002	0.178
BMI	0.003	0.163
Insulin use	0.128	< 0.001
Sleep duration	−0.009	0.220
CSM score	−0.002	0.279
% Carbohydrate intake	−0.003	0.002
*Work status**		
Night-shift	0.059	0.044
Unemployed	0.016	0.572
Adjusted R^2	0.166	

*Day work = reference.
BMI, body mass index; CSM, Composite Score of Morningness.

Multivariate analysis

To determine whether there was an independent association between night-shift work and lnHbA1c, a multivariate analysis was performed adjusting for age, BMI, insulin use, average sleep duration, CSM scores and percentage of daily carbohydrate intake (Table 4). This revealed that, compared with day work, night-shift work was associated with poorer glycaemic control ($B = 0.059$, $P = 0.044$). The unemployed participants had no significant differences in their glycaemic control compared with day workers.

DISCUSSION

This study demonstrated that patients with type 2 diabetes who performed overnight work had significantly worse glycaemic control as assessed by HbA1c than those not working or performing day work, after adjusting for multiple factors including sleep duration, morningness–eveningness preference and diet. Night-shift work was associated with a 5.9% increase in HbA1c of its original value. For example, two individuals who only differ by their work status, a HbA1c value of a night-shift worker would be approximately 7.4% compared with 7.0% in a non-shift worker. This difference is clinically significant as it is comparable to the effect of some diabetes medications (American Diabetes Association, 2016). In addition, night-shift workers had shorter sleep duration, higher BMI and consumed more daily calories, though these factors were not independent predictors of glycaemic control. These results further extend previous findings in non-diabetic populations, and are in agreement with earlier findings in patients with type 2 diabetes (El Tayeb *et al.*, 2014; Ghazawy *et al.*, 2014). Collectively, these data support the detrimental effects of night-shift work on metabolic control in patients with diabetes.

Experimental forced desynchrony protocols in healthy volunteers help elucidate the mechanisms of circadian disruption on metabolism. In a 3-week protocol, 21 participants underwent a 28-h day schedule with concurrent sleep restriction of 5.6 h per day to simulate shift work (Buxton *et al.*, 2012). At the end of the experiment, glucose levels increased both at fasting (by 8%) and after standardized breakfast (by 14%), along with decreased insulin levels indicating inadequate β-cell function. These changes returned to baseline following a 9-day recovery period. In addition, the resting metabolic rate decreased by 8%, leptin profile slightly decreased, and free ghrelin slightly increased. In another experiment, a parallel design compared 8 days of sleep restriction (5 h) and sleep restriction combined with circadian misalignment (8.5 h sleep-onset delay; Leproult *et al.*, 2014). The misaligned group had twice as large a reduction in insulin sensitivity as assessed by intravenous glucose tolerance test compared with the aligned group, along with inadequate β-cell response and increased high-sensitivity C-reactive protein levels. This indicated detrimental effects of circadian misalignment independently of sleep loss. Our study, conducted in a natural setting, found that night-shift work is associated with poorer glucose control even after adjusting for sleep duration, which is in line with these experimental data.

Our findings that night-shift workers had higher BMI than unemployed participants are also consistent with previous data (Morikawa *et al.*, 2008). Although caloric intake from a

24-h recall was not related to glucose control in this study, night-shift workers had significantly higher daily caloric intake than other groups. This could contribute to higher BMI if continued in the long term. Energy expenditure may also play a role, as an experiment in healthy volunteers found that energy expenditure decreased by 3% following a 6-day in-patient-simulated night-shift protocol (3-day daytime schedule followed by 3-day night-shift schedule; McHill *et al.*, 2014). The combination of these factors poses an increased obesity risk in shift workers.

There are additional factors that could play a role in glucose metabolism in shift workers, including exposure to light at night, sleep disturbances and alterations in meal timing. Light is the most potent synchronizer of the central clock and can modulate the circadian gene expression (Fonken and Nelson, 2014). Mice kept in bright light or dim light at night had significantly higher body weight and reduced glucose tolerance compared with those kept in a standard light–dark environment (Fonken *et al.*, 2010). In humans, increased ambient light exposure at night ($\geq$ 3 lux) in the elderly was associated with a 51.2% increase in prevalent diabetes (Obayashi *et al.*, 2014), and with increases in obesity parameters in a longitudinal follow-up (Obayashi *et al.*, 2016). Melatonin may be one of the mediators between light at night and abnormal glucose metabolism. Light can significantly suppress melatonin production, and low urinary melatonin level has been shown to be associated with incident diabetes (McMullan *et al.*, 2013). Sleep quality and duration, especially during main sleep, are often reduced in shift workers (Chan *et al.*, 1989; Guo *et al.*, 2013). These sleep disturbances have been shown to be associated with insulin resistance and poor glycaemic control in patients with type 2 diabetes (Knutson *et al.*, 2006). Lastly, exposure to food at an inappropriate time of the day could lead to misalignment between central and peripheral clocks, resulting in altered metabolism. In animals, feeding at the wrong circadian time led to more weight gain despite similar caloric intake during the appropriate feeding timing (Arble *et al.*, 2009). In those with type 2 diabetes, night eating was associated with poor glycaemic control, possibly due to the fact that insulin sensitivity is worse in the evening (Hood *et al.*, 2014; Van Cauter *et al.*, 1997). This is supported by another study in which patients with type 2 diabetes who consumed two larger meals (breakfast and lunch) had a greater reduction in hepatic fat content and fasting glucose, and higher insulin sensitivity after 12 weeks compared with those consuming six small meals throughout the day (Kahleova *et al.*, 2014). Collectively, these factors may contribute to abnormal glucose metabolism in night-shift workers.

Several interventions have been shown to improve health status in shift workers, although none has been specifically conducted in patients with diabetes (Neil-Sztramko *et al.*, 2014). These interventions included adjusting shift schedules, controlled light exposure (with use of bright light or light-blocking glasses or the combination to promote circadian adaptation), behavioural and pharmacological interventions. Fast-forward rotating shifts have shown benefits on sleep (Neil-Sztramko *et al.*, 2014). Lifestyle interventions with exercise and weight loss helped improve body composition, sleep duration and diet quality (Harma *et al.*, 1988; Morgan *et al.*, 2011). Medications including melatonin, hypnotics and wake-promoting agents (modafinil or armodafinil) have shown mixed results on sleep (Neil-Sztramko *et al.*, 2014). There are a few studies addressing glucose metabolism and cardiovascular risk factors after interventions, although none was specifically conducted in workers with diabetes. In one study of 40 workers, changing from backward-rotating shift system to a rapidly forward-rotating shift system resulted in a significant decrease in systolic blood pressure, but not glucose, HbA1c or lipid levels (Viitasalo *et al.*, 2008). In another study of 40 policemen, 4 weeks of clockwise rotation, compared with counterclockwise rotation, resulted in decreased glucose, triglycerides, systolic blood pressure and urine catecholamines levels, along with improved sleep (Orth-Gomer, 1983). Because sleeping at the wrong time is generally associated with changes in sleep (quality or duration), it remains to be investigated if a circadian intervention alone has an effect on glucose metabolism independently of that resulting from changes in sleep duration/quality.

A strength of this study is the evaluation of multiple factors (glycaemic, sleep and diet) in patients with type 2 diabetes with different work statuses. However, there are limitations. Sleep and dietary assessments were subjective, naps were not available, data on exercise and medication compliance were not available, and light exposure at night was not measured. We also do not have information on whether non-night-shift workers ever performed shift work. The night-shift workers were recruited from different hospitals, and there are possibly other confounders not controlled for that could affect glycaemic control. HbA1c levels, however, did not differ between the clinics (data not shown). In addition, night-shift workers were not recruited at the same time as the others. However, during this period, only one additional diabetes medication (SGLT-2 antagonist) became available in Thailand, and was used by only one night-shift worker. Lastly, this study focused on patients with type 2 diabetes only. One previous study suggested that shift work was associated with poor glycaemic control in patients with type 1 diabetes (Young *et al.*, 2013). Because the pathogenesis of type 1 differs from that of type 2 diabetes, whether shift work has detrimental effects on glycaemic control of patients with type 1 diabetes as well as the mechanisms linking such a relationship should be further explored. Nonetheless, this study demonstrated a suboptimal glycaemic control in night-shift workers with type 2 diabetes, indicating that special attention should be made in optimizing their medications, exercise and diet. Whether interventions directly addressing circadian misalignment will improve glycaemic control in this population remain to be investigated.

In summary, night-shift work is associated with poorer glycaemic control in patients with type 2 diabetes. Reducing the adverse metabolic effects of circadian misalignment may help improve glycaemic control in this patient group.

ACKNOWLEDGEMENT

This study was funded by The Endocrine Society of Thailand and Mahidol University, Bangkok, Thailand.

CONFLICT OF INTEREST

SR received a grant from Merck, and speaker fees from Sanofi, Novo Nordisk and Medtronic. These are not related to the subject matter of the manuscript. All other authors disclose no conflict of interest.

AUTHOR CONTRIBUTIONS

AM, SS, HN, NS, TW, CS, PL, PM researched data, reviewed and edited the manuscript. PK planned the study, reviewed and edited the manuscript. SJC and MM conceptualized the study, contributed to the discussion, reviewed and edited the manuscript. SR conceptualized the study, researched and analysed the data, wrote the manuscript, contributed to the discussion, and reviewed/edited the manuscript.

REFERENCES

American Diabetes Association. Standards of Medical Care in Diabetes–2016. *Diabetes Care*, 2016, 39: S1–S109.

Arble, D. M., Bass, J., Laposky, A. D., Vitaterna, M. H. and Turek, F. W. Circadian timing of food intake contributes to weight gain. *Obesity (Silver Spring)*, 2009, 17: 2100–2102.

Buxton, O. M., Cain, S. W., O'Connor, S. P. *et al.* Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. *Sci. Transl. Med.*, 2012, 4: 129ra43.

Buysse, D. J., Reynolds, C. F. III, Monk, T. H., Berman, S. R. and Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.*, 1989, 28: 193–213.

Cesana, G., Panza, G., Ferrario, M., Zanettini, R., Arnoldi, M. and Grieco, A. Can glycosylated hemoglobin be a job stress parameter? *J. Occup. Med.*, 1985, 27: 357–360.

Chalernvanichakorn, T., Sithisarankul, P. and Hiransuthikul, N. Shift work and type 2 diabetic patients' health. *J. Med. Assoc. Thai.*, 2008, 91: 1093–1096.

Chan, O. Y., Phoon, W. H., Gan, S. L. and Ngui, S. J. Sleep-wake patterns and subjective sleep quality of day and night workers: interaction between napping and main sleep episodes. *Sleep*, 1989, 12: 439–448.

El Tayeb, I. M., El Saghier, E. O. A. and Ramadan, B. K. Impact of shift work on glycemic control in insulin treated diabetics Dar El Chefa Hospital, Egypt 2014. *Int J Diabetes Res*, 2014, 3: 15–21.

Fonken, L. K. and Nelson, R. J. The effects of light at night on circadian clocks and metabolism. *Endocr. Rev.*, 2014, 35: 648–670.

Fonken, L. K., Workman, J. L., Walton, J. C. *et al.* Light at night increases body mass by shifting the time of food intake. *Proc. Natl Acad. Sci. USA*, 2010, 107: 18664–18669.

Ghazawy, E. R., Kamel, S. M., Gamal, H. M. and Ewis, A. A. Night shift working and its Impact on development and control of diabetes mellitus in workers of Abo Korkas Sugar Factory, El-Minia. *Egypt. Egypt. J. Occup. Med.*, 2014, 38: 197–211.

Guo, Y., Liu, Y., Huang, X. *et al.* The effects of shift work on sleeping quality, hypertension and diabetes in retired workers. *PLoS ONE*, 2013, 8: e71107.

Guo, Y., Rong, Y., Huang, X. *et al.* Shift work and the relationship with metabolic syndrome in Chinese aged workers. *PLoS ONE*, 2015, 10: e0120632.

Harma, M. I., Ilmarinen, J., Knauth, P., Rutenfranz, J. and Hanninen, O. Physical training intervention in female shift workers: I. The effects of intervention on fitness, fatigue, sleep, and psychosomatic symptoms. *Ergonomics*, 1988, 31: 39–50.

Hood, M. M., Reutrakul, S. and Crowley, S. J. Night eating in patients with type 2 diabetes. Associations with glycemic control, eating patterns, sleep, and mood. *Appetite*, 2014, 79: 91–96.

Ika, K., Suzuki, E., Mitsuhashi, T., Takao, S. and Doi, H. Shift work and diabetes mellitus among male workers in Japan: does the intensity of shift work matter? *Acta Med. Okayama*, 2013, 67: 25–33.

Institute of Nutrition (2016) M. U. B. Inmucal-Nutrients V.3. 2016. Available at http://www.inmu.mahidol.ac.th/inmucal/last updated 2016. Accessed 20 February 2016.

Iwasaki, M., Hirose, T., Mita, T. *et al.* Morningness-eveningness questionnaire score correlates with glycated hemoglobin in middle-aged male workers with type 2 diabetes mellitus. *J. Diabetes Investig.*, 2013, 4: 376–381.

Kahleova, H., Belinova, L., Malinska, H. *et al.* Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: a randomised crossover study. *Diabetologia*, 2014, 57: 1552–1560.

Karlsson, B. H., Knutsson, A. K., Lindahl, B. O. and Alfredsson, L. S. Metabolic disturbances in male workers with rotating three-shift work. Results of the WOLF study. *Int. Arch. Occup. Environ. Health*, 2003, 76: 424–430.

Knutson, K. L., Ryden, A. M., Mander, B. A. and Van Cauter, E. Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus. *Arch. Intern. Med.*, 2006, 166: 1768–1774.

Lennernas, M. A., Hambraeus, L. and Akerstedt, T. Nutrition and shiftwork: the use of meal classification as a new tool for qualitative/quantitative evaluation of dietary intake in shiftworkers. *Ergonomics*, 1993, 36: 247–254.

Leproult, R., Holmback, U. and Van Cauter, E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes*, 2014, 63: 1860–1869.

Marcheva, B., Ramsey, K. M., Peek, C. B., Affinati, A., Maury, E. and Bass, J. Circadian clocks and metabolism. *Handb. Exp. Pharmacol.*, 2013, 127–155.

McHill, A. W., Melanson, E. L., Higgins, J. *et al.* Impact of circadian misalignment on energy metabolism during simulated nightshift work. *Proc. Natl Acad. Sci. USA*, 2014, 111: 17302–17307.

McMenamin, T. M. A time to work: recent trends in shift work and flexible schedules. 1-15.2007. Office of Employment and Unemployment Statistics, Bureau of Labor Statistics. Available at: http://www.bls.gov/opub/mlr/2007/12/art1full.pdf Accessed 8-1-2016.

McMullan, C. J., Schernhammer, E. S., Rimm, E. B., Hu, F. B. and Forman, J. P. Melatonin secretion and the incidence of type 2 diabetes. *JAMA*, 2013, 309: 1388–1396.

Morgan, P. J., Collins, C. E., Plotnikoff, R. C. *et al.* Efficacy of a workplace-based weight loss program for overweight male shift workers: the Workplace POWER (Preventing Obesity Without Eating like a Rabbit) randomized controlled trial. *Prev. Med.*, 2011, 52: 317–325.

Morikawa, Y., Miura, K., Sasaki, S. *et al.* Evaluation of the effects of shift work on nutrient intake: a cross-sectional study. *J. Occup. Health*, 2008, 50: 270–278.

Neil-Sztramko, S. E., Pahwa, M., Demers, P. A. and Gotay, C. C. Health-related interventions among night shift workers: a critical review of the literature. *Scand. J. Work Environ. Health*, 2014, 40: 543–556.

Netzer, N. C., Stoohs, R. A., Netzer, C. M., Clark, K. and Strohl, K. P. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann. Intern. Med.*, 1999, 131: 485–491.

Obayashi, K., Saeki, K., Iwamoto, J., Ikada, Y. and Kurumatani, N. Independent associations of exposure to evening light and nocturnal urinary melatonin excretion with diabetes in the elderly. *Chronobiol. Int.*, 2014, 31: 394–400.

Obayashi, K., Saeki, K. and Kurumatani, N. Ambient light exposure and changes in obesity parameters: a longitudinal study of the HEIJO-KYO cohort. *J. Clin. Endocrinol. Metab.*, 2016, 101: 3539–3547.

Orth-Gomer, K. Intervention on coronary risk factors by adapting a shift work schedule to biologic rhythmicity. *Psychosom. Med.*, 1983, 45: 407–415.

Osonoi, Y., Mita, T., Osonoi, T. *et al.* Morningness-eveningness questionnaire score and metabolic parameters in patients with type 2 diabetes mellitus. *Chronobiol. Int.*, 2014, 31: 1017–1023.

Pan, A., Schernhammer, E. S., Sun, Q. and Hu, F. B. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Med.*, 2011, 8: e1001141.

Poole, C. J., Wright, A. D. and Nattrass, M. Control of diabetes mellitus in shift workers. *Br. J. Ind. Med.*, 1992, 49: 513–515.

Pornpitakpan, C. Psychometric properties of the composite scale of morningness. *Person. Individ. Diff.*, 1998, 25: 699–709.

Reutrakul, S. and Knutson, K. L. Consequences of circadian disruption on cardiometabolic health. *Sleep Med. Clin.*, 2015, 10: 455–468.

Reutrakul, S., Siwasaranond, N., Nimitphong, H. *et al.* Relationships among sleep timing, sleep duration and glycemic control in Type 2 diabetes in Thailand. *Chronobiol. Int.*, 2015, 32: 1469–1476.

Rodrigues, T. C. and Canani, L. H. The influence of the work shift in patients with type 2 diabetes. *Rev. Assoc. Med. Bras. (1992)*, 2008, 54: 160–162.

Scheer, F. A., Hilton, M. F., Mantzoros, C. S. and Shea, S. A. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc. Natl Acad. Sci. USA*, 2009, 106: 4453–4458.

Sitasuwan, T., Bussaratid, S., Ruttanaumpawan, P. and Chotinaiwattarakul, W. Reliability and validity of the Thai version of the Pittsburgh Sleep Quality Index. *J. Med. Assoc. Thai.*, 2014, 97 (Suppl 3): S57–S67.

Smith, C. S., Reilly, C. and Midkiff, K. Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. *J. Appl. Psychol.*, 1989, 74: 728–738.

Suksakorn, S., Rattanaumpawan, P., Banhiran, W., Cherakul, N. and Chotinaiwattarakul, W. Reliability and validity of a Thai version of the Berlin questionnaire in patients with sleep disordered breathing. *J. Med. Assoc. Thai.*, 2014, 97(Suppl 3): S46–S56.

Suwazono, Y., Sakata, K., Okubo, Y. *et al.* Long-term longitudinal study on the relationship between alternating shift work and the onset of diabetes mellitus in male Japanese workers. *J. Occup. Environ. Med.*, 2006, 48: 455–461.

Trangkasombat, U., Larpboonsarp, V. and Havanond, P. CES-D as a screen for depression in adolescents. *J. Psych. Assoc. Thail.*, 1997, 42: 2–13.

Van Cauter, E., Polonsky, K. S. and Scheen, A. J. Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocr. Rev.*, 1997, 18: 716–738.

Viitasalo, K., Kuosma, E., Laitinen, J. and Harma, M. Effects of shift rotation and the flexibility of a shift system on daytime alertness and cardiovascular risk factors. *Scand. J. Work Environ. Health*, 2008, 34: 198–205.

Wang, F., Zhang, L., Zhang, Y. *et al.* A meta-analysis on night shift work and risk of metabolic syndrome. *Obes. Rev.*, 2014, 15: 709–720.

Wirth, M. D., Burch, J., Shivappa, N. *et al.* Dietary inflammatory index scores differ by shift work status: NHANES 2005 to 2010. *J. Occup. Environ. Med.*, 2014, 56: 145–148.

Young, J., Waclawski, E., Young, J. A. and Spencer, J. Control of type 1 diabetes mellitus and shift work. *Occup. Med. (Lond.)*, 2013, 63: 70–72.