


Increased Risk Of Type 2 Diabetes And Abnormal FPG Due To Shift Work Differs According To Gender: A Retrospective Cohort Study Among Thai Workers In Bangkok, Thailand

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Purpose: The gender differential evidence of the association between shift work and type 2 diabetes risk remains scarce. This longitudinal study determines whether the association between shift-work exposure and type 2 diabetes risk and abnormal fasting plasma glucose (FPG) differs according to gender; the study aims to find the association between shift work and changes in physiological, behavioral, and psychosocial stress.

Patients and methods: This retrospective cohort study was conducted among 5947 workers (4647 female and 1300 male) aged ≤ 60 years old in Bangkok, Thailand. Participants required a normal FPG level (< 100 mg/dL) at baseline and at least two health check-up results from 2009 to 2016. Shift-work exposure history was assessed using a self-administered questionnaire; FPG levels were measured annually. Cox proportional hazard models were used to assess the aforementioned association.

Results: During the follow-up period, 1470 new abnormal FPG and 154 new type 2 diabetes cases developed. Stratified analysis of male workers' data revealed an association was significant in the unadjusted model, which tended to be stronger after adjustment for demographic data and the baseline values of anthropometric and biochemical parameters. This was the case both for type 2 diabetes [Hazard Ratio (HR) (95% Confidence Interval (CI))=2.98 (1.58–5.62)] and abnormal FPG [HR (95% CI)=1.86 (1.43–2.41)]; this association was less obvious among women.

Conclusion: Shift work is a risk factor for type 2 diabetes and abnormal FPG; this risk is gender differential, being more pronounced in men. Preventive measures aiming at ameliorating shift work induced type 2 diabetes risk should pay more attention to men.

Keywords: shift-work exposure, diabetes, abnormal fasting plasma glucose, gender difference, behavioral stress, retrospective cohort study, Cox proportional hazard models

Introduction

Type 2 diabetes is a chronic disease with serious long-term complications, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease;¹ it accounts for 5.0 million annual deaths worldwide.^{2,3} The global burden on public health from this disease is rapidly increasing. The International Diabetes Federation (IDF) reports that the global prevalence of diabetes increased from 151 million cases in 2000⁴ to 451 million cases in 2017,² a number estimated to increase to 693 million by 2045.² Almost half of these figures concern undiagnosed diabetics, who were at a particularly high risk of developing complications.²

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Studies undertaken in the last few decades report an association between shift work and multiple chronic diseases, one of which is type 2 diabetes.^{5–13} Shift work remains a common working schedule in certain sectors, including in the healthcare, utilities, food services, manufacturing, and transportation sectors. Approximately 21% of all workers in the European Union^{14,15} are engaged in shiftwork, as are 28.7% of workers in the United States,¹⁶ and 15–36% of workers worldwide.¹⁷

While epidemiological evidence of the association between shift work and type 2 diabetes risk is relatively sound, evidence pertaining to the gender differential of this association remains scarce and controversial. Based on the baseline data of a Brazilian Longitudinal Study of Adult Health (ELSA-Brazil) comprising 15,105 civil servants, a recent study by Silva-costa et al,¹¹ reported that the association between night work and diabetes was stronger among women [(odds ratio (OR) (1.42 95% confidence interval (CI)) (1.39–1.45)] than men [OR (95% CI)=1.06 (1.04–1.08)]. In addition, a 2013 population-based cohort study by Eriksson et al,¹⁸ involved 3205 women and 2227 men in Sweden, and used patients aged 35–56 years. All participants had normal glucose tolerance (NGT) at baseline. The study found that shift work is significantly associated with the increased risk of type 2 diabetes in women [OR (95% CI) 2.2 (1.0–4.7)]. However, after adjusting for confounding factors, this risk was found not to be statistically significant [OR (95% CI)=1.9 (0.8–4.4)]. The same study found no such association—both in the unadjusted and adjusted models [OR (95% CI)=0.9 (0.5–1.7)] and [OR (95% CI)=0.8 (0.4–1.7), respectively—among male participants. These findings were contrary to those of the recent meta-analysis conducted by Gan et al in 2015.¹⁰ This meta-analysis included 12 studies with 28 independent reports involving 226,652 participants, and demonstrates that shift work was associated with an increased risk of type 2 diabetes; this increase was found to be significantly higher among men [OR (95% CI)=1.37 (1.20–1.56)] than women [OR (95% CI)=1.09 (1.04–1.14)].

It was hypothesized that shift work may be related to increased diabetes risk because of its physiological (inflammation, blood coagulation, cardiac autonomic function, hypothalamus-pituitary-adrenal or HPA-axis, blood pressure), behavioral (sleep quality and length, cigarette smoking, nutrition, weight gain, physical inactivity), and psychosocial (work stress, work–life balance, recovery from work) consequences; these may appear differently in men than in women, resulting in a differential diabetes risk

between these two groups when exposed to shift work.¹⁹ Additionally, it was reported that risk factors such as weight gain and reduced physical activity may unequally affect men and women in terms of later diabetes risk.^{20,21} It is therefore likely that shift-work induces weight gain and physical inactivity, and that it may result in a higher diabetes risk in men than women, though no epidemiological evidence currently exists to verify this claim.

Epidemiological data pertaining to this issue may provide an initial insight into the possible biological mechanisms of shift work and type 2 diabetes risk, and how these mechanisms are affected by gender. Therefore, further investigations on the gender differential of such association in studies using a longitudinal research design—those concerning both men and women and that have sufficient statistical power—are needed.

This study has multiple aims: (a) to determine the association between shift work and the risk of type 2 diabetes and abnormal fasting plasma glucose (FPG); (b) to examine whether such an association, if it exists, differences between men and women; and (c) to explore whether the association between shift work and changes in physiological, behavioral, and psychosocial stress among shift-worker groups differ according to gender. This study was undertaken in the context of a longitudinal research involving workers in two large organizations in Bangkok, Thailand.

Materials And Methods

Study Population

This retrospective cohort study was conducted using workers of the Thai Red Cross Society (a humanitarian agency that consists of a large tertiary hospital, as well as a number of other health and humanitarian agencies within its jurisdiction) and Chulalongkorn University, Bangkok, Thailand. Working patterns varied among workers, who comprised healthcare professionals, academic personnel, manual workers, and general administration officers, among others. Both organizations have provided annual health check-ups for their workers since 2002, though this study focuses on the 2009–2016 period. In 2016, Thai Red Cross Society and Chulalongkorn University employed 7419 and 7749 workers, respectively, providing a total number of 15,168 employees. Only 10,309 (67.8%) of these workers underwent an annual health check-up in 2016. Just 10,079 (66.5%) individuals agreed to participate in the current study, had completed the self-administered questionnaires in 2016, and had health check-up results

from 2009 to 2016. Of these, the 7039 workers with at least two health check-up results from the 2009–2016 period were included in the study. At baseline, 1092 workers were excluded for this study due to them having a FPG level of ($n=618$), self-reported type 1 diabetes ($n=15$), self-reported type 2 diabetes ($n=156$), their use of diabetes medication ($n=125$), and being aged ≥ 60 years ($n=178$). The numbers of eligible workers that could be used in the current study for each year within the 2009–2015 period (open cohort) were 3866 (65.0%), 139 (2.3%), 207 (3.5%), 790 (13.3%), 344 (5.8%), 286 (4.8%), and 315 (5.3%), respectively. Accordingly, a total of 5947 workers (4647 women and 1300 men) without impaired fasting plasma glucose (IFG) (FPG <100 mg/dL, 5.6 mmol/L) or type 2 diabetes at baseline were followed-up until they had the onset of abnormal FPG or type 2 diabetes (Figure 1).

This study was granted ethical approval by the Ethical Review Board of the Faculty of Medicine at Chulalongkorn University (IRB.No. 282/59). Written informed consent was obtained from each participant after they had provided information for the study. Participant identity data were kept confidential and deleted before analysis. The databases did not hold any identifiable patient data.

The Definition Of Shift Work

History of shift-work exposure among the study participants was also assessed retrospectively through use of a questionnaire survey in 2016. This questionnaire contained a set of work-related questions on the occupation and type of respondents' previous and current jobs. The questions therein offered several possible alternatives: day only, night only, rotating two shifts (day/night, 12 hrs/shift), and rotating three shifts (day/evening/night, 8 hrs/shift). These work schedules were defined accordingly: (a) day workers (working hours between 06:00 and 18:00 hrs); (b) rotating two-shift workers (working hours comprising a 12 hrs/shift, a day shift between 06:00 and 18:00 hrs, and a night shift between 18:00 and 06:00 hrs); (c) rotating three-shift workers (working hours comprising a 8 hrs/shift, a day shift between 07:30 and 16:30 hrs, an evening shift between 16:30 and 23:30 hrs, and a night shift between 23:30 and 07:30 hrs); (d) permanent night shift or night only (working hours between 18:00 and 06:00 hrs for at least 8 hrs/night). Additional data were collected on the intensities of the day, evening, and night shiftwork (times/month), total working durations (in years), and shiftwork starting and end dates; these data were then

used to retrospectively assess shift workers status at a baseline year. As a few workers only worked during night-shifts (7.5% of men and 4.2% of women), type of job schedule was therefore redefined into three groups. Day workers were defined as including those who: (a) had never done shift work or else who rotated between two or three shifts or; (b) had completed shiftwork, though with fewer than three night shifts per month until the baseline year. Current shift workers were those who: (a) did permanent night shifts only for at least three night shifts per month or; (b) who rotated between two or three shifts with at least three night shifts per month until the baseline year. Former shift workers were those who had been shift workers in the past, but who had since stopped doing shiftwork before the baseline year.

Health Outcomes

Two health outcomes were of interest in the current study: [1] type 2 diabetes (DM) defined as including at least one out of three following components: FPG level ≥ 126 mg/dL or 7.0 mmol/L; physician-diagnosed diabetes (self-reported); or use of antidiabetic medication²² and, [2] abnormal FPG was defined as having IFG (FPG level ≥ 100 mg/dL or 5.6 mmol/L)²² plus DM.

Follow-Up And Person-Years

Concerning the study's abnormal FPG outcome, 5947 workers with normal FPG level at baseline were followed-up until they displayed the onset of abnormal FPG, turned 60, became lost to follow-up, or until the end of the follow-up period (December 2016), whichever came first. Concerning the type 2 diabetes outcome, workers were also followed-up until the onset of type 2 diabetes, they became 60, became lost to follow-up, or until the end of the follow-up period (December 2016), whichever came first.

Person-time of follow-up for each worker was calculated (in years) and continued from the baseline annual health examination year until the outcome onset year (abnormal FPG or type 2 diabetes diagnosis), they turned 60, became lost to follow-up, or until the end of the follow-up period. The interval between the two consecutive health examinations was one year; accordingly, the person-time for those with abnormal FPG or type 2 diabetes outcomes were calculated from the first follow-up year until the mid-point between the last health examination year, and the first health examination year per the aforementioned outcomes.

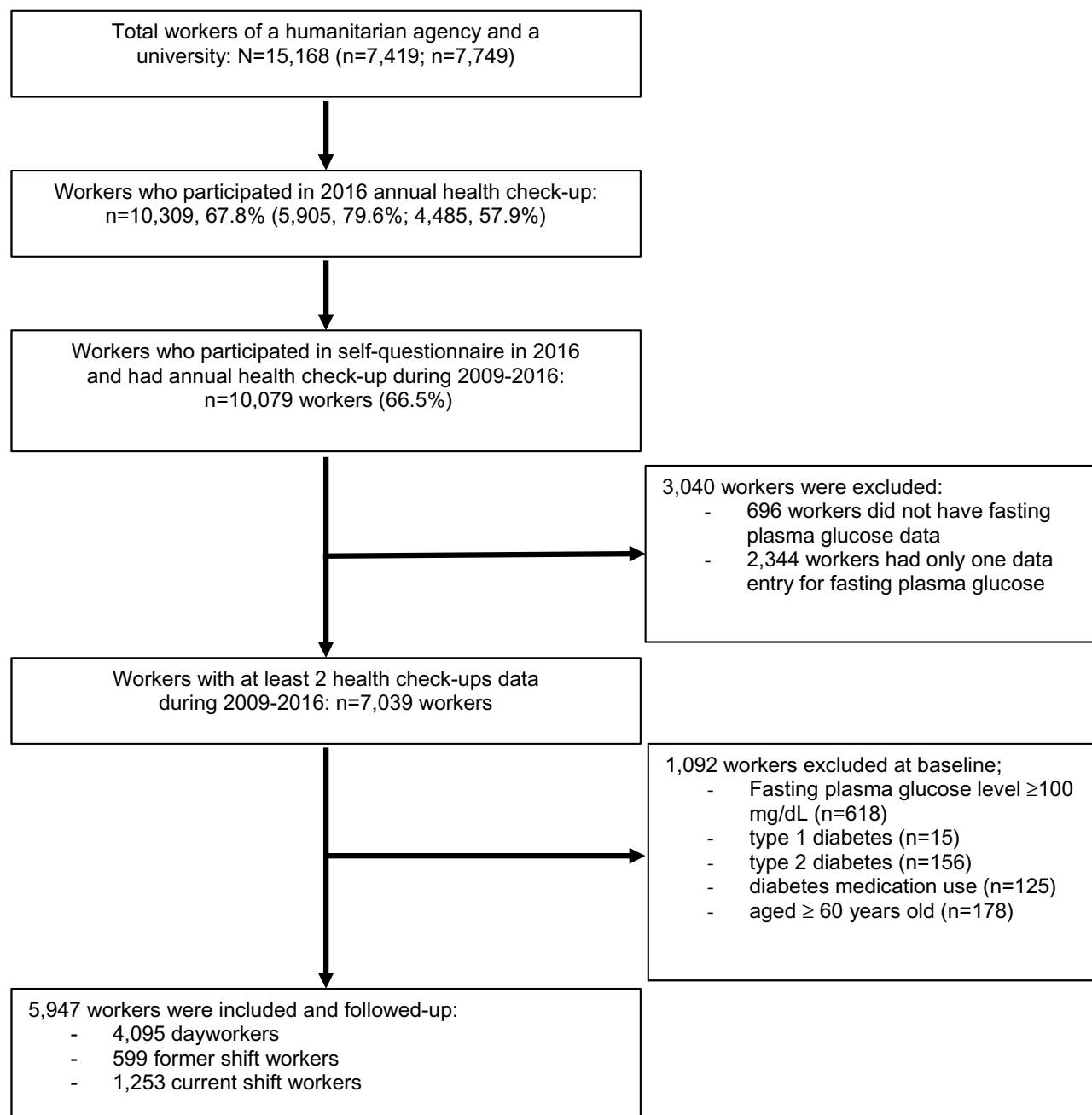


Figure 1 Flow chart showing the participant selection and exclusion and inclusion details.

Covariate Data Collection

The study questionnaire also collected personal characteristic data, such as data concerning the gender, age, educational level, marital status, income per month, and the personal and family health histories of workers. Baseline physiological and biochemical parameters, such as anthropometric measurements and blood samples, were collected by annual health examinations data from the 2009–2015 period. Individuals' weight, height, body mass index (BMI),

waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) (in the sitting position) were measured by nursing staff. BMI categorizations included 'underweight' ($<18.5 \text{ kg/m}^2$), 'normal' ($18.5\text{--}22.9 \text{ kg/m}^2$), and "overweight/obese" ($\geq 23.0 \text{ kg/m}^2$);^{2,3} while hypertension was defined as SBP ≥ 140 and/or DBP ≥ 90 mmHg. Fasting plasma glucose (FPG), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), white blood cell count (WBC), were measured in a standardized

manner at the University's biomedical laboratory. Metabolic syndrome (MetS) was defined as including four out of five following components: 1) elevated TG (≥ 150 mg/dL); 2) a low HDL-C (< 40 mg/dL in men and < 50 mg/dL in women); 3) an elevated BP (SBP ≥ 130 or a DBP ≥ 85 mmHg); 4) an elevated FPG level (≥ 100 mg/dL); 5) a BMI ≥ 23 kg/m²,²⁴ or a WC with a cut-off point for Asian populations (≥ 90 cm in men and ≥ 80 cm in women).²⁵ Similar procedures were utilized in the follow-up annual health examinations. Additional data were also collected, including alcohol consumption (no/former/current), cigarette smoking (no/former/current); physical exercise, such as walking, cycling and sport (yes/no); meals eaten per day (3 times/1–2 times/ > 3 times), fruit and vegetable consumption of at least 0.5 kg per day (no or low consumption/occasional consumption (1–3 days per week)/everyday consumption (4–7 days per week), sleep duration (< 5 hrs/5–6.9 hrs/ ≥ 7 hrs); sleep quality, which was defined with a cut-off for Thai-PSQI²⁶ for good sleep (score < 5 points) and poor sleep (score ≥ 5 points), working hours per day (6–8 hrs/ > 8 –12 hrs/ > 12 hrs) and working hours per week (≤ 48 hrs/week/ > 48 hrs/week).

Statistical Analysis

Descriptive statistics was used to describe the workers' characteristics. Baseline characteristics were compared among the worker groups (day, former, and current shift workers) and stratified by gender. Frequencies (as a percentage) were calculated for categorical variables and means (standard deviation: SD) or medians (interquartile ranges) for continuous variables with normal or skewed distributions, respectively. Skew data were log-transformed and ANOVA was used to assess the significant group difference, while the Chi-square test was used for categorical data. The incidence rates (IRs) and 95% confidence intervals (CIs) of abnormal FPG and type 2 diabetes outcomes were calculated as number of new IFG+DM and DM cases divided by person-years of follow-up and reported as rate per 1000 person-years. The association between shift-work exposure with abnormal FPG or type 2 diabetes was examined by Cox proportional hazard models to estimate hazard ratios (HR), with a 95% confidence interval (95% CI). Potential confounders from previous literature^{27,28} were managed by adding them into the existing equation for the main factor (shift-work exposure status) and outcome (abnormal FPG or diabetes) association. Proportional hazards assumption was tested using a time-dependent variable. Effect modification (interaction term) of the association between shift work and

gender regarding the study outcomes was tested for all models. Following the objective of this study, the analysis was performed both overall and stratified by gender. Finally, The estimated hazard ratios (HR) were constructed as three models: an unadjusted model; Model 1, adjusted for well-established confounders,^{27,28} such as baseline values of age, family history of diabetes, BMI, and baseline status of hypertension; and Model 2, variables in Model 1 plus adjustment for other potential confounders such as educational level, marital status, baseline value of FPG, WBC, TG, HDL-C, and WC.

Missing data at baseline for personal characteristics—such as educational level, and marital status ($< 0.5\%$), as well as physiological (BMI, WC, SBP, DBP and hypertension, 2.9–4.2%) and blood-chemistry parameters—such as white blood cell count (WBC), TG, and HDL-C (1.9–5.9%) were managed by gender-specific mean imputation²⁹ before multivariate hazard ratios (HR) were performed. Sensitivity analysis was performed to compare the main results between imputed and unimputed datasets.

After the gender differential in shift-work exposure and risk of abnormal FPG and diabetes had been calculated, we further examined the possible pathways that may explain this phenomenon by conducting shift-work group comparisons—separately for men and women—on those parameters relating to the physiological (incidence of hypertension, overweight/obesity, and MetS), behavioral (prevalence of alcohol consumption, cigarette smoking, physical exercise and adequate level physical activity, and frequency of fruit and vegetable consumption), and psychosocial (sleep duration and quality, daily and weekly working hours, and number of days off per week) stresses. The incidence rates of hypertension, overweight/obesity, and MetS used in these comparisons were calculated in a similar manner as those for abnormal FPG and diabetes. All statistical analyses were performed using STATA/IC version 14 (StataCorp. 2015. Stata Statistical Software: release 14, College Station, TX: StataCorp LP.)

Results

Participants Characteristics

The mean age of all workers was 40.5 ± 7.4 years. Concerning female participants, current shift workers used in this study were younger than both day and former shift workers; concerning male participants, the ages of current, day, and former shift workers were comparable (Table 1). The educational level of current

Table 1 Comparison Of Baseline Demographics And Work-Related Data Of The Three Groups Of Workers, Stratified By Gender

Characteristics	Female (n=4647)						Male (n=1300)					
	Day Workers		Former Shift Workers		Current Shift Workers		Day Workers		Former Shift Workers		Current Shift Workers	
	(n=3049)		(n=491)		(n=1107)		(n=1046)		(n=108)		(n=146)	
	N	%	N	%	N	%	N	%	N	%	N	%
Age at baseline (years old)												
<35	478	15.7	43	8.8 ^b	304	27.5 ^{c,d}	115	11.0	12	11.1	20	13.7
35–45	1697	55.6	264	53.8	603	54.4	654	62.5	64	59.3	80	54.8
46–59	874	28.7	184	37.4	200	18.1	277	26.5	32	29.6	46	31.5
Age (years; mean ± SD)	40.8 ± 7.4		43.0 ± 7.8 ^b		38.2 ± 7.4 ^{c,d}		40.9 ± 6.6		41.2 ± 7.3		41.1 ± 7.5	
Educational level ^a												
6–12 years	721	23.8	86	17.6 ^b	422	38.3 ^{c,d}	282	27.0	50	46.7 ^b	115	78.8 ^{c,d}
>12 years	2311	76.2	403	82.4	681	61.7	762	73.0	57	53.3	31	21.2
Marital status ^a												
Single/Divorce	1446	47.6	212	43.3	567	51.5 ^{c,d}	341	32.6	31	29.0	47	32.2
Married	1589	52.4	278	56.7	534	48.5	704	67.4	76	71.0	99	67.8
Income per month ^a												
<20,000 Baht	734	24.2	19	18.5 ^b	279	25.3 ^d	258	24.7	41	38.3 ^b	88	60.3 ^{c,d}
20,000–30,000 Baht	1062	35.0	130	26.5	409	37.0	279	26.7	36	33.6	46	31.5
>30,000 Baht	1241	40.8	270	55.0	417	37.7	507	48.6	30	28.1	12	8.2
Family history of Diabetes												
No/Unknown	1945	63.8	302	61.5	737	66.6	709	67.8	71	65.7	99	67.8
Yes	1104	36.2	189	38.5	370	33.4	337	32.2	37	34.3	47	32.2
Occupation												
Healthcare professional	569	18.7	334	68 ^b	887	80.2 ^{c,d}	95	9.1	23	21.3 ^b	54	37.0 ^{c,d}
Academic personnel	412	13.5	15	3.1	9	0.8	316	30.2	8	7.4	1	0.7
Security guards, drivers and maintenance technicians	5	0.2	0	0.0	7	0.6	126	12.0	22	20.4	47	32.2
Fulfilled other roles	2063	67.6	142	28.9	204	18.4	509	48.7	55	50.9	44	30.1
Type of shift work												
Fixed shift work					47	4.2					11	7.5
Rotated shift work					1060	95.8					135	92.5
Work duration (years)												
Mean ± SD	19.9 ± 9.4		23.3 ± 8.8		21.5 ± 8.0		18.8 ± 8.9		18.3 ± 9.7		21.3 ± 8.1	

(Continued)

Table 1 (Continued).

Characteristics	Female (n=4647)						Male (n=1300)					
	Day Workers		Former Shift Workers		Current Shift Workers		Day Workers		Former Shift Workers		Current Shift Workers	
	(n=3049)		(n=491)		(n=1107)		(n=1046)		(n=108)		(n=146)	
	N	%	N	%	N	%	N	%	N	%	N	%
Shift work duration (years)												
Mean ± SD		10.8 ± 8.3		20.4 ± 8.1		7.7 ± 6.7		20.6 ± 8.3				
Shift work intensity (days/month)												
Median ± IQR				8 ± 4				9 ± 5				
Quitting shift work (years)												
Mean ± SD		9.5 ± 7.5				10.8 ± 7.2						

Notes: ^aMissing data <0.5%. ^bsignificant difference between former shift workers and day workers at p-value <0.05; ^csignificant difference between current shift workers and day workers at p-value <0.05; ^dsignificant difference between current shift workers and former shift workers at p-value <0.05.

Abbreviations: N, Number; SD, Standard Deviation; IQR, Interquartile range.

shift workers was higher than that of the other two groups, as indicated by their higher proportion of those having 6–12 years of education. The proportion of female workers who were not in a partnership (single or divorced) was higher among current shift workers than the other two groups, while the reverse was true regarding male workers. Proportions pertaining to a family history of diabetes did not differ among the three groups. A majority of female current shift workers worked as healthcare professionals (80.2%), while the majority of male current shift workers worked as healthcare professionals (37.0%) and security guards, drivers, and maintenance technicians (32.2%). The mean durations of current shift workers were 20.4±8.1 years for women, and 20.6±8.3 years for men. Concerning the group of former shift workers, the mean duration spent before workers quit their shift work was 10.8±8.3 years for women and 7.7±6.7 years for men (Table 1).

Concerning baseline physiological and biochemical parameters for both male and female current shift workers, WBC counts were significantly higher than those of the other two groups, while FPG levels were significantly lower than those of the other two groups. Most of the parameters concerning male current shift workers were lower than those of the other two groups; however, did not significantly differ among the three groups (Table 2).

Association Between Shift-Work Exposure With The Occurrence Of Abnormal FPG And Type 2 Diabetes

Throughout 32,534 person-years (min 0.5, mean 5.4, max 7 years) of follow-up for type 2 diabetes, 154 new type 2 diabetes cases had developed. Overall, 1470 new abnormal FPG cases had developed throughout 28,155.5 person-years (min 0.5, mean 4.7, max 7 years) of follow-up. The overall incidence rates of abnormal FPG and type 2 diabetes did not differ significantly among the three worker groups. However, analysis according to gender revealed that, for male workers, incidence rates (IR) of both outcomes were significantly higher for current shift workers (IR=116.10 per 1000 person-years for abnormal FPG and 17.42 per 1000 person-years for DM) than they were for the other two groups [IR of abnormal FPG=79.85 and 55.50 per 1000 person-years for day and former shift workers, respectively and IR of DM=6.37 and 5.28 per 1000 person-years, respectively]. Incidence rates among female workers did not differ significantly among the three shift-worker groups (Tables 3 and 4).

Association between shift-work exposure and health outcomes was further analyzed using the Cox proportional hazard model, wherein day workers were treated as the reference group. The unadjusted results showed that, overall, the current shift workers group was not significantly associated with increased type 2 diabetes risk HR [95% CI]=1.33 (0.94–1.89)] and abnormal FPG outcomes [0.96 (0.85–1.09)]

Table 2 Comparison Of Baseline Physiological And Biochemical Of The Three Groups Of Workers, Stratified By Gender

Parameter at Baseline	Female (n=4647)			Male (n=1300)		
	Day Workers	Former Shift Workers	Current Shift Workers	Day Workers	Former Shift Workers	Current Shift Workers
	(n=3049)	(n=491)	(n=1107)	(n=1046)	(n=108)	(n=146)
	(mean ± SD)	(mean ± SD)	(mean ± SD)	(mean ± SD)	(mean ± SD)	(mean ± SD)
FPG (mg/dL)	85.7 ± 6.5	85.8 ± 6.2	84.8 ± 6.4 ^{c,d}	88.5 ± 6.3	88.1 ± 5.9	86.7 ± 6.4 ^c
BMI (kg/m ²) ^a	23.3 ± 4.1	22.6 ± 3.3 ^b	22.9 ± 3.8 ^c	24.4 ± 3.4	24.6 ± 3.8	24.4 ± 3.7
WC (cm) ^a	74.5 ± 9.5	73.2 ± 8.0 ^b	73.5 ± 8.7 ^c	84.5 ± 8.6	84.1 ± 9.7	83.1 ± 9.8
SBP (mmHg) ^a	116.1 ± 13.2	114.3 ± 13.7 ^b	112.4 ± 12.3 ^{c,d}	124.53 ± 13.5	125.8 ± 14.4	122.9 ± 12.7
DBP (mmHg) ^a	74.5 ± 9.5	73.3 ± 10.0 ^b	72.4 ± 9.1 ^c	79.6 ± 9.8	79.5 ± 9.6	78.6 ± 8.8
Hypertension (%) ^a	13.6	13.9	8.4 ^{c,d}	29.1	26.2	22.5
WBC (10 ³ cells/μL) ^a	6.5 ± 1.6	6.3 ± 1.6 ^b	6.8 ± 1.7 ^{c,d}	6.7 ± 1.7	6.6 ± 1.5	7.1 ± 1.6 ^c
TG (mg/dL) ^{a, f}	80 ± 50	78 ± 47	74 ± 49.5 ^c	113 ± 86	107 ± 71	110 ± 69
HDL-C (mg/dL) ^{aa, f}	61 ± 20	62 ± 19	61 ± 18	49 ± 16	51 ± 15	47 ± 15

Notes: ^aMissing data <5%. ^{aa}Missing data 5–10.9%. ^bSignificant difference between former shift workers and day workers at p-value <0.05. ^cSignificant difference between current shift workers and day workers at p-value <0.05. ^dSignificant difference between current shift workers and former shift workers at p-value <0.05. ^fMedian ± IQR was shown instead of Mean ± SD.

Abbreviations: FPG, fasting plasma glucose; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cell count; SD, Standard Deviation; IQR, Interquartile range.

(Tables 3 and 4). After adjustment for potential confounders, the association between the current shift worker group with increased health risk was found to be both stronger and significant for both type 2 diabetes [HR (95% CI)=1.82 (1.27–2.60) and 1.85 (1.27–2.69) for Models 1 and 2, respectively], as well as abnormal FPG outcomes [HR (95% CI) =1.20 (1.06–1.36) and 1.28 (1.13–1.46), respectively].

Stratified analysis by gender showed that the association between current shift workers and abnormal FPG and type 2 diabetes risks were more pronounced among men but less obvious among women (*p*-interaction <0.05 for all model of abnormal FPG and *p*-interaction >0.05 for all model of type 2 diabetes). For men, such associations were only significant for the unadjusted model [HR (95% CI) =2.66 (1.45–4.87 and 1.44 (1.12–1.85) for type 2 diabetes and abnormal FPG, respectively] and tended to be stronger for the adjusted models for both type 2 diabetes [HR (95% CI)=2.77 (1.51–5.08) and 2.98 (1.58–5.62) for Model 1 and 2, respectively] and abnormal FPG outcomes [HR (95% CI)=1.46 (1.14–1.88) and 1.86 (1.43–2.41), respectively]. These associations were found to be not statistically significant for all models regarding both type 2 diabetes and abnormal FPG outcomes among women.

Overall and gender-specific analysis revealed that former shift workers were not significantly associated with increased abnormal FPG and type 2 diabetes risk when compared with day workers (Tables 3 and 4). Finally, the sensitivity analysis revealed that the magnitude of the

association between shift work and abnormal FPG and type 2 diabetes did not materially alter, and that it still associated with the increased risk of type 2 diabetes and abnormal FPG (Tables 3 and 4).

Distribution Of Physiological, Behavioral, And Psychosocial Stress Among Shift-Worker Groups

Further analysis was undertaken to examine a possible pathway explaining the gender differential in shift work-diabetes risk, as described above. Accordingly, we targeted those parameters with a gender discrepancy regarding the differences between current shift and day workers. It was found that, among male workers, the incidence rates of hypertension (27.9 versus 18.4, *p*=0.024), and MetS (29.6 versus 19.4, *p*=0.018) were significantly higher for current shift than day workers, and that the prevalence rate of physical exercise (50.0 versus 66.2, *p*<0.001) was significantly lower for current shift than day workers; these findings were not the case for female workers (Table 5). Patterns of shift-work group differences for the remaining parameters between males and female workers were not dissimilar.

Discussion

This study demonstrated that current shift work is associated with increased risk of abnormal FPG or type 2

Table 3 Hazard Ratios Of Association Between Shift Work And Abnormal FPG For The Imputed And Unimputed Datasets, Stratified By Gender

Shift Work Status	Case/N	PYs	IRs/ 1000 PYs	95% CI	Abnormal FPG vs Normal					
					Unadjusted		Adjusted Model 1		Adjusted Model 2	
					HR	95% CI	HR	95% CI	HR	95% CI
IMPUTED DATASET										
Overall	1470/5947	28,155.5	52.21	49.57–54.95						
Day workers	994/4095	18,605	53.43	50.16–56.85	1.00		1.00		1.00	
Former shift workers	141/599	2948.5	47.82	40.25–56.40	0.90	0.76–1.08	0.93	0.78–1.12	0.97	0.81–1.16
Current shift workers	335/1253	6602	50.74	45.45–56.48	0.96	0.85–1.09	1.20	1.06–1.36	1.28	1.13–1.46
Female	1015/4647	22,592.5	44.93	42.22–47.73						
Day workers	641/3049	14184	45.19	41.76–48.83	1.00		1.00		1.00	
Former shift workers	113/491	2444	46.24	38.10–55.59	1.03	0.84–1.26	1.03	0.84–1.26	1.06	0.86–1.29
Current shift workers	261/1107	5964.5	43.76	38.61–49.40	0.98	0.84–1.13	1.14	0.98–1.32	1.17	1.01–1.36
Male	455/1300	5563	81.79	74.45–89.66						
Day workers	353/1046	4421	79.85	71.73–88.63	1.00		1.00		1.00	
Former shift workers	28/108	504.5	55.50	36.88–80.21	0.70	0.48–1.03	0.68	0.47–1.00	0.72	0.49–1.06
Current shift workers	74/146	637.5	116.10	91.15–145.73	1.44	1.12–1.85	1.46	1.14–1.88	1.86	1.43–2.41
			p-interaction		0.0033		0.0271		0.0008	
UNIMPUTED DATASET										
Overall	1470/5947	28,155.5	52.21	49.57–54.95						
Day workers	994/4095	18,605	53.43	50.16–56.85	1.00		1.00		1.00	
Former shift workers	141/599	2948.5	47.82	40.25–56.40	0.90	0.76–1.08	0.90	0.75–1.00	0.95	0.79–1.15
Current shift workers	335/1253	6602	50.74	45.45–56.48	0.96	0.85–1.09	1.21	1.06–1.37	1.34	1.16–1.54
Female	1015/4647	22,592.5	44.93	42.22–47.73						
Day workers	641/3049	14184	45.19	41.76–48.83	1.00		1.00		1.00	
Former shift workers	113/491	2444	46.24	38.10–55.59	1.03	0.84–1.26	0.99	0.80–1.23	1.04	0.84–1.29
Current shift workers	261/1107	5964.5	43.76	38.61–49.40	0.98	0.84–1.13	1.15	0.99–1.34	1.23	1.06–1.44
Male	455/1300	5563	81.79	74.45–89.66						
Day workers	353/1046	4421	79.85	71.73–88.63	1.00		1.00		1.00	
Former shift workers	28/108	504.5	55.50	36.88–80.21	0.70	0.48–1.03	0.67	0.45–1.00	0.70	0.46–1.06
Current shift workers	74/146	637.5	116.10	91.15–145.73	1.44	1.12–1.85	1.44	1.11–1.87	1.84	1.40–2.41
			p-interaction		0.0033		0.0529		0.0049	

Notes: Model 1, Adjusted for age at baseline (years), family history of DM (no/yes), BMI at baseline (kg/m²), hypertension at baseline (yes; SBP ≥140 mmHg and/or DBP ≥90 mmHg/no). Model 2, model 1 additional adjusted for FPG at baseline (mg/dL), WBC at Baseline (cells/μL), TG at baseline (mg/dL), HDL-C at baseline (mg/dL), WC at baseline (cm), marital status (single or divorce/married), education level (≤12 years/>12 years).

Abbreviations: N, Number; PYs, person-years; IR, incidence rates; 95% CI, 95% confidence intervals; HR, hazard ratio.

diabetes. Stratified analysis by gender revealed that the association between current shift workers and abnormal FPG and type 2 diabetes risks was more pronounced among men, but less obvious among women. These findings confirm the association between current shift work and risk of abnormal FPG and type 2 diabetes, indicating that such an association is stronger in men than in women. In addition, we also provide evidence that this gender

discrepancy may be mediated via the differential effect shift work has regarding the behavioral (physical exercise) and physiological (incidence of hypertension and MetS) consequences for both genders.

The results of this study are consistent with those of the recent meta-analysis conducted by Gan et al.¹⁰ However, the magnitudes of association and gender disparity were much more pronounced in the current study: [OR (95%

Table 4 Hazard Ratios Of Association Between Current Shift Workers And Type 2 Diabetes For The Imputed And Unimputed Datasets, Stratified By Gender

Shift-work status	Case/N	PYs	IRs/ 1000 PYs	95% CI	Type 2 Diabetes Vs Normal					
					Unadjusted		Adjusted Model 1		Adjusted Model 2	
					HR	95% CI	HR	95% CI	HR	95% CI
IMPUTED DATASET										
Overall	154/5947	32,534	4.73	4.02–5.54						
Day workers	97/4095	21,642	4.48	3.63–5.47	1.00		1.00		1.00	
Former shift workers	10/599	3289	3.04	1.46–5.59	0.67	0.35–1.29	0.82	0.42–1.57	0.72	0.37–1.40
Current shift workers	47/1253	7603	6.18	4.54–8.22	1.33	0.94–1.89	1.82	1.27–2.60	1.85	1.27–2.69
Female	101/4647	25,611	3.94	3.21–4.79						
Day workers	62/3049	16,148.5	3.84	2.94–4.92	1.00		1.00		1.00	
Former shift workers	7/491	2720.5	2.57	1.03–5.30	0.66	0.30–1.45	0.81	0.37–1.78	0.59	0.26–1.36
Current shift workers	32/1107	6742	4.75	3.25–6.70	1.20	0.78–1.83	1.50	0.97–2.33	1.52	0.98–2.36
Male	53/1300	6923	7.66	5.73–10.01						
Day workers	35/1046	5493.5	6.37	4.44–8.86	1.00		1.00		1.00	
Former shift workers	3/108	568.5	5.28	1.09–15.42	0.83	0.25–2.69	0.80	0.25–2.61	1.02	0.31–3.34
Current shift workers	15/146	861	17.42	9.75–28.73	2.66	1.45–4.87	2.77	1.51–5.08	2.98	1.58–5.62
			<i>p</i> -interaction		0.1067		0.2666		0.1960	
UNIMPUTED DATASET										
Overall	154/5947	32,534	4.73	4.02–5.54						
Day workers	97/4095	21,642	4.48	3.63–5.47	1.00		1.00		1.00	
Former shift workers	10/599	3289	3.04	1.46–5.59	0.67	0.35–1.29	0.79	0.40–1.58	0.72	0.35–1.45
Current shift workers	47/1253	7603	6.18	4.54–8.22	1.33	0.94–1.89	1.91	1.33–2.75	2.05	1.40–3.02
Female	101/4647	25,611	3.94	3.21–4.79						
Day workers	62/3049	16,148.5	3.84	2.94–4.92	1.00		1.00		1.00	
Former shift workers	7/491	2720.5	2.57	1.03–5.30	0.66	0.30–1.45	0.75	0.32–1.76	0.57	0.24–1.37
Current shift workers	32/1107	6742	4.75	3.25–6.70	1.20	0.78–1.83	1.58	1.01–2.45	1.68	1.07–2.63
Male	53/1300	6923	7.66	5.73–10.01						
Day workers	35/1046	5493.5	6.37	4.44–8.86	1.00		1.00		1.00	
Former shift workers	3/108	568.5	5.28	1.09–15.42	0.83	0.25–2.69	0.85	0.26–2.77	1.13	0.34–3.73
Current shift workers	15/146	861	17.42	9.75–28.73	2.66	1.45–4.87	2.93	1.59–5.41	3.32	1.73–6.35
			<i>p</i> -interaction		0.1067		0.2691		0.1845	

Notes: Model 1, Adjusted for age at baseline (years), family history of DM (no/yes), BMI at baseline (kg/m²), hypertension at baseline (yes; SBP ≥140 mmHg and/or DBP ≥90 mmHg/no). Model 2, model 1 additional adjusted for FPG at baseline (mg/dL), WBC at Baseline (cells/μL), TG at baseline (mg/dL), HDL-C at baseline (mg/dL), WC at baseline (cm), marital status (single or divorce/married), education level (≤12 years/>12 years).

Abbreviations: N, Number; PYs, person-years; IR, incidence rates; 95% CI, 95% confidence intervals; HR, hazard ratio.

CI)=1.09 (1.04–1.14) for women, and 1.37 (1.20–1.56) for men in Gan et al's report versus 1.52 (0.98–2.36) for women and 2.98 (1.58–5.62) for men in our study]. This was true even after adjustment for various confounding demographic, anthropometric, and biochemical parameters effects (age, gender, family history of diabetes, marital status and educational level, the baseline value of BMI, WC, hypertension, FPG, WBC, TG, HDL-C). However, as almost all of the working shifts with which our study was

concerned were of the rotating-shift type, we were therefore unable to compare the magnitude of association among different types of shift work. Comparatively, these findings were contrary to those of a recent study by Silva-costa et al,¹¹ based on the baseline data of the Brazilian Longitudinal Study of Adult Health (ELSA-Brazil), which reported that the association between night work and diabetes was stronger among women [OR (95% CI)=1.42 (1.39–1.45)] than among men [OR (95% CI)

Table 5 Distribution Of Physiological, Behavioral And Psychosocial Stress Among Shift Workers Group Separate By Gender

Parameter	Female						Male					
	Day Workers		Former Shift Workers		Current Shift Workers		Day Workers		Former Shift Workers		Current Shift Workers	
	N	%	N	%	N	%	N	%	N	%	N	%
Physiological stress												
Hypertension incidence (n=4740)												
Yes	297	11.9	41	10.6	101	10.4	130	18.4	16	21.6	29	27.9 ^b
Overweight + obesity (n=3001)												
BMI ≥23 kg/m ²	341	20.7	59	20.9	134	21.6	95	26.5	9	22.5	20	36.4
Metabolic Syndrome incidence (MetS)												
MetS; WC (n=4780)	342	14.2	56	14.4	131	14.8	160	20.5	13	15.9	26	26.5
MetS; BMI ≥ 23 kg/m ² (n=4631)	341	14.0	53	13.8	123	13.9	145	19.4	11	13.9	29	29.6 ^{b,c}
Behavioral stress												
Alcohol consumption (n=5947)												
No	2637	86.8	672	91.8	777	88.8 ^a	603	57.7	54	41.8	63	50.0 ^a
Former	171	5.6	22	3.0	45	5.1	104	10.0	17	13.2	12	9.5
Current	232	7.6	38	5.2	53	6.1	338	32.3	58	45.0	51	40.5
Cigarette Smoking (n=5947)												
No	3007	98.9	728	99.5	869	99.3	873	83.5	92	71.3	95	75.4 ^a
Former	23	0.8	4	0.5	2	0.2	78	7.5	20	15.5	15	11.9
Current	10	0.3	0	0.0	4	0.5	94	9.0	17	13.2	16	12.7
Physical Exercise (n=5947)												
Yes	1384	45.5	341	46.6	381	43.5	692	66.2	85	65.9	63	50.0 ^{b,c}
Meal frequency (n=5947)												
3 times/day	2310	76.0	566	77.3	567	64.8 ^{b,c}	798	76.4	96	74.4	98	77.8
1–2 times/day	571	18.8	117	16.0	218	24.9	186	17.8	28	21.7	17	13.5
> 3 times/day	159	5.2	49	6.7	90	10.3	61	5.8	5	3.9	11	8.7
Fruit and Vegetable dietary intake (n=5947)												
No or low	472	15.5	96	13.1	133	15.2	187	17.9	21	16.3	29	23.0
Occasional consumption (1–3 days/week)	1193	39.3	309	42.2	351	40.1	445	42.6	65	50.4	46	36.5
Everyday consumption (4–7 days/week)	1375	45.2	327	44.7	391	44.7	413	39.5	43	33.3	51	40.5
Sleep duration (hours/night) (n=5925)												
<5 hrs	85	2.8	18	2.5	88	10.0 ^{b,c}	32	3.1	5	3.9	12	9.6 ^b
5–6.9 hrs	1653	54.6	411	56.2	550	62.9	560	53.9	64	49.6	64	51.2
≥7 hrs	1289	42.6	302	41.3	237	27.1	446	43.0	60	46.5	49	39.2
Sleep quality (Thai-PSQI) (n=5947)												
Good (≤5 points)	2053	67.5	487	66.5	483	55.2 ^{b,c}	723	69.2	83	64.3	76	60.3 ^b
Poor (>5 points)	987	32.5	245	33.5	392	44.8	322	30.8	46	35.7	50	39.7
Psychosocial stress												
Working hours per day (n=4019)												
6–8 hrs	1855	62.1	384	54.1	423	48.7	653	63.3	80	63.0	69	54.8 ^{b,c}
>8–12 hrs	1022	34.2	282	39.8	220	25.4	335	32.4	43	33.9	26	20.6
>12 hrs	110	3.7	43	6.1	225	25.9	44	4.3	4	3.1	31	24.6
Working hours per week (n=4019)												
≤48 hrs week	1972	66.0	404	57.0	428	49.3	691	67.0	86	67.7	66	52.4 ^{b,c}
>48 hrs/week	1015	34.0	305	43.0	440	50.7	341	33.0	41	32.3	60	47.6

Notes: ^aSignificant difference between former shift workers and day workers at p-value <0.05. ^bSignificant difference between current shift workers and day workers at p-value <0.05. ^cSignificant difference between current shift workers and former shift workers at p-value <0.05.

Abbreviations: N, Number; BMI, body mass index; WC, waist circumference; Thai-PSQI, the Thai version of the Pittsburgh Sleep Quality Index.

=1.06 (1.04–1.08)]. Due to differences in study design, it was difficult to compare the results of the ELSA-Brazil study with the results of the current study. Notably, the ELSA-Brazil study was a cross-sectional study, while the current research is a longitudinal study. Accordingly, further investigations are needed into the gender differential of such an association using a longitudinal research design comprising both men and women.

While our evidence of the gender differential regarding the association between shift work and diabetes contributes to research and findings in the field, our evidence that behavioral (physical exercise) and physiological (incidence of hypertension and MetS) consequences were the likely mediators of this differential proved to be a novel finding.

Since physical inactivity is a well-established risk factor of type 2 diabetes,³⁰ a stronger association between shift-work exposure and reduced prevalence of physical exercise among men than women may partly explain the gender differential association of shift work and type 2 diabetes risk. Furthermore, men preferentially utilize carbohydrates as a fuel source when exercising; comparatively, women oxidize a greater proportion of lipids relative to carbohydrates when exercising. This means that a reduced physical activity level will affect the utilization of carbohydrate regarding women's metabolisms. This means that the detrimental impact for men will be greater than that of women in terms of diabetes risk.³¹ However, since the association between shift-work exposure and the prevalence of physical exercise is cross-sectional, future longitudinal studies are needed in order to verify this cause–effect association.

Similarly, there is a stronger association between shift-work exposure and increased incidence of being overweight/obese (which is a strong and established type 2 diabetes risk factor) for men as compared with women. Hence, this contributes to a stronger magnitude regarding the relationship between shift work and type 2 diabetes. Furthermore, women tend to store more adipose tissue in subcutaneous areas, which compares to preferential visceral fat deposition in men. Since visceral fat deposition is generally related to increased insulin resistance and cardiometabolic risk, increased body weight, therefore, carries more adverse health impacts (including type 2 diabetes risk) for men as compared with women.^{31,32} This is supported by evidence showing that men are diagnosed as having diabetes with a BMI 1–3 kg/m² lower than that of women.²¹

Additionally, stronger associations are demonstrated between shift-work exposure and increased incidence of established type 2 diabetes co-morbidities—such as hypertension and MetS—among men than among women. Since both of these conditions are supposed to be consequences of insulin resistance, this may imply that gender disparity regarding the association between shift work and later type 2 diabetes risk is also mediated via the insulin-resistance pathway.

Since data relating to the psychosocial consequences of shift work (such as work stress, work–life balance, and recovery from work) were not collected, we are unable to examine their potential role as mediators of the gender disparity regarding the association between shift work and future type 2 diabetes.

The strengths of this study include its longitudinal design, which used a relatively large study population incorporating a sufficient number of males and female workers. Moreover, our ascertainment of diabetes based on FPG level as well as other biochemical parameters is more valid than self-reported since they were measured in standardized manner at the University's biomedical laboratory. Finally, the potential confounding effect of many demographic, anthropometric, and biochemical parameters at baseline (such as age, gender, family history of diabetes, marital status and educational level, the baseline value of BMI, WC, hypertension, FPG, WBC, TG, HDL-C) were all considered in the statistical analysis.

However, this study also has several limitations. First, follow-up time was relatively short (the longest follow-up time was seven years), rendering a small number of new type 2 diabetes cases to limited statistical power in providing firm evidence for the difference of associations between shift-work exposure and type 2 diabetes risk between genders. We compensated this limitation by incorporating abnormal FPG. Second, most participants were healthcare workers, presumably with better-than-average health consciences, and so the generalizability of this study's findings to other occupations with different shift-work pattern may be limited. Third, shift-work exposure data were retrospectively collected using self-reported questionnaires, potentially leading to incomplete recall data and misclassifications of the exposure; however, this is part of the nature of a retrospective cohort study. Finally, this study was unable to control for the confounding effect of lifestyle factors (cigarette smoking, alcohol consumption, physical activity, and diet quality) in the multivariate modeling, nor was it able to verify whether gender

discrepancy may be mediated via the differential effect shift work on these factors because data relating to these factors were obtained from recent questionnaire surveys, rather than at baseline and during the follow-up period. Furthermore, this limitation also hindered us in examining the joint effect of shift work and lifestyle factors on the increased type 2 diabetes and abnormal FPG risk, as suggested by recent evidence.³³

Conclusion

This study suggests that shift work is a risk factor for abnormal FPG and type 2 diabetes and, furthermore, that this is a gender differential risk because the exposure and outcome association was more pronounced in men than in women. In addition, we also provide novel evidence that this gender differential might be mediated behaviorally (physical exercise) and psychologically (hypertension, and MetS incidence). The results suggest that preventive measures aiming at ameliorating shift work induced type 2 diabetes risk should pay more attention to men by targeting intervention measures pertaining to these potential mediators. Many potential mediators (such as work stress, work–life balance, recovery from work) are not sufficiently included in this investigation, accordingly, future longitudinal studies are needed for further examination into the possible role of this gender differential regarding the association between shift work and future type 2 diabetes.

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Author contributions

All authors contributed towards data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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