Original Article

Shift Work and Diabetes Mellitus among Male Workers in Japan: Does the Intensity of Shift Work Matter?

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The purpose of this study was to examine the association between shift work and diabetes mellitus by separating shift workers according to the intensity of their shift work (seasonal shift work and continuous shift work). Between May and October 2009, we collected data from annual health checkups and questionnaires at a manufacturing company in Shizuoka, Japan. Questionnaires were returned by 1,601 workers (response rate: 96.2%, men/women = 1,314/287). Diabetes mellitus was defined as hemoglobin A1c $\geq 6.5\%$ and fasting blood sugar ≥ 126 mg/dl. After exclusions, which included all the women and clerical workers because they did not work in shifts, we analyzed 475 skilled male workers. After adjusting for age, smoking status, frequency of alcohol consumption, and cohabitation status, odds ratios for diabetes mellitus were 0.98 (95% confidence interval [CI]: 0.28–4.81) and 2.10 (95% CI: 0.77–5.71) among seasonal shift workers and continuous shift workers, respectively, compared with non-shift workers. In an age-stratified analysis (< 45 years vs. ≥ 45 years), the association between continuous shift work and diabetes mellitus was more pronounced among older participants. Compared with non-shift workers, the risk of diabetes mellitus was increased among continuous shift workers, whereas its effect is limited among seasonal shift workers.

S hift work is an essential system in modern society and is found mainly in manufacturing industries, medical institutions, and retail outlets that are open around the clock. According to the 2007 *Survey on State of Employees' Health* from the Ministry of Health, Labour and Welfare, in Japan, 16.4% of working men and 21.9% of working women are shift workers [http://www.e-stat.go.jp/SG1/estat/List.do?bid=000001020613&cycode=0 (Japan Ministry of Health, Labour and Welfare, Survey on State of Employees' Health, 2007) accessed October 16, 2012]. In Europe and the United States, shift workers account for about a sixth of the entire work force [http://monographs.iarc.fr/ENG/Monographs/vol98/mono98-8.pdf (International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 98, 2010) accessed October 16, 2012; http://www.eurofound.europa.eu/pubdocs/2010/74/en/3/EF1074EN.pdf (European Foundation for the Improvement of Living and Working Conditions (EUROFOUND), Changes over time − First findings from the fifth European Working Conditions Survey, 2010) accessed October 16, 2012)].

Despite the global spread of shift work, there is a growing concern over its adverse health effects, including the negative effects of accumulated fatigue on immune function, particularly from being engaged

in long-term continuous shift work [1, 2]. Moreover, shift work has been shown to be a risk factor for various chronic diseases [3–5] including cardiovascular disease [6, 7] as well as for malignant tumors such as breast cancer [8, 9] and prostate cancer [10]. Indeed, the International Agency for Research on Cancer (IARC) recognizes the association between shift work and breast cancer in women. According to the Carcinogenicity Criteria of the IARC, shift work involving disturbed circadian rhythms is assigned to Group 2A, which implies that it is probably carcinogenic to humans [http://monographs.iarc.fr/ENG/Monographs/vol98/mono98-8.pdf (International Agency for Research on Cancer, 2010) accessed October 16, 2012].

Although genetic factors often contribute to the onset of diabetes mellitus, the work environment, such as shift work employment, is also known to play an important role in the onset of diabetes mellitus [4, 11, 12]. In line with this, several studies have also reported that shift work is associated with an increased risk of obesity [13, 14] and metabolic syndrome [15, 16]. However, there are some issues to be addressed. First, most of those studies examined the effect of shift work on diabetes mellitus without taking into account the type of occupation (e.g., "white collar" work vs. "blue collar" work). For example, in a recent study from Japan, Oyama et al. [17] examined the association between shift work and impaired glucose tolerance in men. Although the results of this study suggested a significant increase in the risk of impaired glucose tolerance among shift workers, their analysis was based on a comparison between shift workers and non-shift workers without taking into account the types of occupation. Considering the mounting evidence that manual work is associated with worse health-related behaviors in Japan [18, 19], further studies are warranted to solely examine the association between shift work and diabetes mellitus taking into account health disparities across occupations [20, 21].

Second, although 2 previous studies from Japan examined the effects of the pattern of shift work (i.e., 2- or 3-shift work) [17, 22], no studies have investigated the differential effects (if any) of the intensity of the shift work (e.g., regular vs. seasonal shift work) [23]. Even in a recent large study of female nurses in the U.S. [24], differences in working conditions in hospitals were not addressed, and the differential effects of the intensity of shift work were not examined. Given the diversified patterns of shift work in modern society, there is interest in examining the differential health effects of various domains of shift work [4, 23].

Accordingly, in the present study we sought to examine the association between shift work and diabetes mellitus among male skilled workers using data from a large manufacturing company in Japan. We attempted to investigate the possible differential effects of shift work by separating shift workers according to the intensity of their shift work (i.e., seasonal shift work and continuous shift work).

Materials and Methods

Study design and participants.   The study subjects were skilled workers aged 19 to 70 years employed at a large manufacturing company in Shizuoka Prefecture, Japan. In late May 2009, we collected data from a questionnaire that included items on sociodemographic factors, working conditions, and health-related behaviors. We also collected the health-outcome data from the workers' annual health checkup between May and October 2009. Fig. 1 is a flow diagram describing how the participants were selected for/excluded from the present study. Of the 1,664 workers, 1,601 returned the questionnaire (response rate: 96.2%, 1,314 men and 287 women), and we excluded all of the women respondents because the proportion of the women engaged in shift work was considerably low (i.e., 0.9%). Of the remaining 1,314 men, we excluded subjects who could not be linked to their annual health checkup data for administrative reasons (e.g., unavailability of electronic data of health checkup) (n = 360). Subsequently, we excluded clerical workers, all of whom were non-shift workers, from the analysis to solely examine the effect of shift work by increasing the comparability between non-shift workers and shift workers. The employees who worked more than 10h a day were also excluded from the analysis in reference to a previous study, which showed a 3.7 times higher risk for diabetes mellitus in those who worked overtime more than 50h a month (or 10h a day on average), compared to those who worked 0–25h a month [25]. The final population for analysis was 475 male skilled workers.

Fig. 1   The inclusion and exclusion of the participants, all of whom were employed at a large manufacturing company in Shizuoka Prefecture, Japan.

The study was reviewed and approved by the Ethics Committee on the Research of Epidemiology at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences.

Measurements.   Shift work at the time of the study was assessed by questionnaire. The schedule for skilled workers at this company consisted mainly of the following 3 working patterns: (1) non-shift work (only day shift), (2) continuous shift work, and (3) seasonal shift work. Non-shift workers were required to work on the 5-weekdays (8 : 00–16 : 45 including a 1-h break; 7h and 45min of actual working hours per day) and take 2 days off on weekends. Continuous shift workers are divided into 2 groups and work on a rotating 14-day cycle. The cycle consists of a pattern in which the employees work 5-weekday day shifts (8 : 00–16 : 45 including a 1-h break; 7h and 45min of actual working hours per day) and take 2 days off on the weekend and then work 5-weekday night shifts (21 : 15–6 : 00 including a 1-h break; 7h and 45min of actual working hours per day) and take 2 days off on the weekend. Seasonal shift workers work in the same pattern as the continuous shift employees during the busy season, and work in the same pattern as the non-shift workers during off-peak times. The busy season varies depending on the sales situation but is a consecutive period mainly from spring to summer and lasts, on average, about 5 months. Average working hours were ascertained from the following question on the questionnaire: "How many hours did you work per day for the past month on average?"

As a primary health outcome, based on the blood test data from the workers' annual health checkup, we defined diabetes mellitus as hemoglobin A1c (HbA1c) $\geq 6.5\%$ (converted to the international standard) and fasting blood sugar (FBS) $\geq 126\,\mathrm{mg/dl}$, which is one of the diagnostic criteria for diabetes mellitus [26]. In accordance with the recommendation from the Japan Diabetes Society [27], the HbA1c values were converted to the international standard using the following formula: National Glycohemoglobin Standardization Program $(\%) = 1.02 \times$ Japan Diabetes Society $(\%) + 0.25\%$. In addition, to enhance the comparability with some previous studies, we also used the following 2 definitions as supplementary health outcomes: (1) HbA1c $\geq 6.5\%$ (converted to the international standard), and (2) FBS $\geq 126\,\mathrm{mg/dl}$. To minimize the possibility of misclassification, all employees were required to observe an overnight fast after 21 : 00 on the previous day, and the annual health checkup was carried out during the morning.

With reference to a previous study [12], we considered the following variables as potential confounders: age (continuous), cohabitation status (cohabitating vs. non-cohabitating), smoking status (current vs. never/former), and frequency of alcohol consumption. The frequency of alcohol consumption was categorized into the following 3 groups: none/rarely, sometimes (1–3 days a month/1–3 days a week), and often (4–6 days a week/daily). We also examined the prevalence of hypertension and proteinuria. We defined hyperten-

sion as systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg, which is diagnostic criteria for grade I hypertension [28]. Proteinuria categories were defined as No ($-/\pm$) and Yes ($+/2+/3+$); these are diagnostic criteria for positive proteinuria [http://www.jsn.or.jp/guideline/pdf/CKDguide2012.pdf (Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012, Japanese Society of Nephrology, 2012) accessed October 16, 2012]. Although the information about body mass index (BMI) and sleeping hours were obtained, we decided *a priori* not to adjust for these variables as confounders because they could act as mediators between shift work and diabetes mellitus, being affected by disturbed circadian rhythms or working hours [29].

Statistical analysis.   We first examined the prevalence of diabetes mellitus and other sociodemographic characteristics by the different intensity of shift work. Then, we examined the association between shift work and diabetes mellitus by using a crude logistic regression model (Model 1). Subsequently, we adjusted for age (continuous) as a covariate (Model 2), and finally, we additionally adjusted for smoking status, frequency of alcohol consumption, and cohabitation status as covariates (Model 3). To further evaluate the effect of the duration of shift work on diabetes mellitus, we conducted an age-stratified analysis by splitting the group of subjects roughly in half (*i.e.*, < 45 years vs. $\geq$ 45 years). Throughout the analysis, we used the non-shift workers as a reference. We did not adjust for working hours as a covariate due to a significant correlation with shift work ($p < 0.001$, Kruskal-Wallis rank sum test).

Odds ratios (ORs) and 95% confidence intervals (CIs) for each health outcome were calculated, and *p*-values < 0.05 (two-sided test) were considered statistically significant. All analyses were performed using STATA/SE 11.1 (StataCorp, College Station, TX, USA).

Results

Table 1 shows the sociodemographic characteristics of the subjects based on the intensity of their shift work. Of the 475 subjects analyzed, 252 were engaged in non-shift work, 67 in seasonal shift work, and 156 in continuous shift work. Working hours among continuous shift workers were longer, compared with the non-shift workers and seasonal shift workers.

Table 2 lists the ORs and 95% CIs for diabetes mellitus and related health outcomes. Of all 475 subjects, 21 (4.4%) met the criteria for diabetes mellitus. The crude ORs for diabetes mellitus among the 67 seasonal shift workers and the 156 continuous shift workers were 0.74 (95% CI: 0.16–3.48) and 1.48 (95% CI: 0.59–3.73), respectively (Model 1). When we adjusted for age in Model 2, the OR for diabetes mellitus among the continuous shift workers increased. In Model 3, the point estimate of OR among the seasonal shift workers was close to 1.0, although its precision was low (OR: 0.98, 95% CI: 0.20–4.81). In contrast, the OR among the continuous shift workers was 2.10 (95% CI: 0.77–5.71). When we additionally adjusted for BMI, the OR among the seasonal shift workers was 1.18, (95% CI: 0.23–6.00), whereas the OR among the continuous shift workers was 1.93 (95% CI: 0.68–5.46). When only HbA1c or FBS was used to define the health outcome, similar patterns were observed, with the exception of relatively lower point estimates of ORs among the continuous shift workers when the outcome was defined as HbA1c $\geq$ 6.5%. In addition, when the 20 subjects who worked more than 10 h a day were included in the analysis, we observed no substantial changes (data not shown).

Table 3 shows the results of the age-stratified analysis. The association between continuous shift work and diabetes mellitus was more pronounced among the 221 older subjects – the point estimates of ORs were 1.91 and 2.24 among the younger and older continuous shift workers, respectively. The pattern was reversed for the seasonal shift workers – the point estimates of ORs were 2.24 and 0.61 among the younger and older subjects, respectively. However, the precision of these estimates is considerably low.

Discussion

To our knowledge, this is the first study to investigate the association between shift work and diabetes mellitus by dividing the shift workers according to the intensity of their shift work (*i.e.*, seasonal shift work and continuous shift work). We sought to examine the association by targeting all skilled male workers in a large manufacturing company in Japan, which meant

Table 1　Characteristics of the study subjects by shift work among men in Japan, 2009

| Characteristics | Non-shift workers (n = 252) | | Shift workers | | | |
| | | | Seasonal (n = 67) | | Continuous (n = 156) | |
	n	%	n	%	n	%
Age (years; mean, SD)	45.2	11.51	45.1	9.88	43.1	9.84
Body mass index						
$< 25\,kg/m^2$	185	73.4	49	73.1	109	69.9
$\geq 25\,kg/m^2$	67	26.6	18	26.9	47	30.1
Working hours per day (mean, SD)	8.05	0.58	7.95	0.51	8.80	0.88
Cohabitation status						
Cohabitating	204	81.0	54	80.6	118	75.6
Non-cohabitating	35	13.9	13	19.4	35	22.4
Missing	13	5.2	0	0.0	3	1.9
Smoking status						
Never/Former	112	44.4	26	38.8	57	36.5
Current	140	55.6	41	61.2	99	63.5
Frequency of alcohol consumption[a]						
None/Rarely	89	35.3	14	20.9	54	34.6
Sometimes	58	23.0	17	25.4	30	19.2
Often	105	41.7	36	53.7	71	45.5
Missing	0	0.0	0	0.0	1	0.6
Hypertension[b]						
No	221	87.7	57	85.1	135	86.5
Yes	31	12.3	10	14.9	21	13.5
Proteinuria[c]						
No	239	94.8	63	94.0	144	92.3
Yes	13	5.2	4	6.0	12	7.7

SD, standard deviation.
[a]The frequency of alcohol consumption categories were: none/rarely; sometimes (1–3 days a month / 1–3 days a week); and often (4–6 days a week/daily).
[b]Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg.
[c]Proteinuria categories were defined as No ($-/\pm$) and Yes ($+/2+/3+$).

Table 2　Odds ratios for diabetes mellitus associated with shift work among men in Japan, 2009

	Case	Non-case	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Diabetes mellitus[a]					
Non-shift workers	10	242	1.00	1.00	1.00
Seasonal shift workers	2	65	0.74 (0.16–3.48)	0.80 (0.17–3.81)	0.98 (0.20–4.81)
Continuous shift workers	9	147	1.48 (0.59–3.73)	1.87 (0.72–4.85)	2.10 (0.77–5.71)
HbA1c $\geq$ 6.5%					
Non-shift workers	16	236	1.00	1.00	1.00
Seasonal shift workers	3	64	0.69 (0.20–2.44)	0.75 (0.21–2.71)	0.92 (0.25–3.43)
Continuous shift workers	9	147	0.90 (0.39–2.10)	1.16 (0.49–2.77)	1.32 (0.53–3.29)
FBS $\geq$ 126 mg/dl					
Non-shift workers	16	236	1.00	1.00	1.00
Seasonal shift workers	3	64	0.69 (0.20–2.44)	0.75 (0.21–2.70)	0.79 (0.22–2.90)
Continuous shift workers	15	141	1.57 (0.75–3.27)	2.07 (0.96–4.46)	2.10 (0.95–4.66)

OR, odds ratio; CI, confidence interval; HbA1c, hemoglobin A1c; FBS, fasting blood sugar.
Model 1: Crude model. Model 2: Adjusted for age (continuous). Model 3: Adjusted for age (continuous), smoking status, frequency of alcohol consumption, and cohabitation status.
[a]Diabetes mellitus was defined as hemoglobin A1c $\geq$ 6.5% (converted to the international standard) and fasting blood sugar $\geq$ 126 mg/dl.

Table 3   Odds ratios for diabetes mellitus associated with shift work among men stratified by age in Japan, 2009

	Case	Non-case	Model 1	Model 2	Model 3
			OR (95% CI)	OR (95% CI)	OR (95% CI)
Younger than 45 (n = 254)					
Diabetes mellitus[a]					
Non-shift workers	2	121	1.00	1.00	1.00
Seasonal shift workers	1	35	1.73 (0.15–19.63)	1.52 (0.13–17.62)	2.24 (0.18–28.28)
Continuous shift workers	2	93	1.30 (0.18–9.41)	1.18 (0.16–8.68)	1.91 (0.24–15.22)
HbA1c $\geq$ 6.5%					
Non-shift workers	3	120	1.00	1.00	1.00
Seasonal shift workers	2	34	2.35 (0.38–14.66)	2.10 (0.33–13.49)	3.00 (0.42–21.44)
Continuous shift workers	2	93	0.86 (0.14–5.25)	0.78 (0.12–4.83)	0.95 (0.14–6.27)
FBS $\geq$ 126 mg/dl					
Non-shift workers	3	120	1.00	1.00	1.00
Seasonal shift workers	1	36	1.14 (0.11–11.33)	1.04 (0.10–10.36)	1.16 (0.11–11.86)
Continuous shift workers	3	92	1.30 (0.26–6.61)	1.42 (0.24–6.22)	1.42 (0.27–7.52)
45 or older (n = 221)					
Diabetes mellitus[a]					
Non-shift workers	8	121	1.00	1.00	1.00
Seasonal shift workers	1	30	0.50 (0.06–4.19)	0.51 (0.06–4.26)	0.61 (0.07–5.02)
Continuous shift workers	7	54	1.96 (0.68–5.68)	2.04 (0.69–6.01)	2.24 (0.71–7.06)
HbA1c $\geq$ 6.5%					
Non-shift workers	13	116	1.00	1.00	1.00
Seasonal shift workers	1	30	0.30 (0.04–2.36)	0.32 (0.04–2.56)	0.41 (0.05–3.43)
Continuous shift workers	7	54	1.16 (0.44–3.06)	1.36 (0.50–3.70)	1.68 (0.58–4.88)
FBS $\geq$ 126 mg/dl					
Non-shift workers	13	116	1.00	1.00	1.00
Seasonal shift workers	2	29	0.62 (0.13–2.88)	0.64 (0.14–3.00)	0.65 (0.14–3.12)
Continuous shift workers	12	49	2.19 (0.93–5.13)	2.40 (1.00–5.73)	2.43 (0.98–6.04)

OR, odds ratio; CI, confidence interval; HbA1c, hemoglobin A1c; FBS, fasting blood sugar.
Model 1: Crude model. Model 2: Adjusted for age (continuous). Model 3: Adjusted for age (continuous), smoking status, frequency of alcohol consumption, and cohabitation status.
[a]Diabetes mellitus was defined as hemoglobin A1c $\geq$ 6.5% (converted to the international standard) and fasting blood sugar $\geq$ 126 mg/dl.

that the working environment and conditions other than the shift work were almost the same for all subjects and thus suitable for a more valid evaluation of the health effects of shift work.

Unlike previous studies [17, 25, 30], we attempted to eliminate the influence of confounding factors influenced by the subjects' type of occupation by restricting our analysis to skilled workers from the same company. Our present findings suggest that, compared to the non-shift workers, the continuous shift workers had approximately double the odds of diabetes mellitus. In contrast, no clear association was observed between seasonal shift work and diabetes mellitus. This notable discrepancy between the different intensities of shift work had not been addressed in earlier studies. In our age-stratified analysis, the association

between continuous shift work and diabetes mellitus was more pronounced among the subjects aged $\geq$ 45 years, which may indicate that the adverse health effects of continuous shift work become increasingly accentuated in long-term shift work.

We surmise that the marked discrepancies between the different intensities of shift work can be interpreted within the context of a potential biological model underlying the association between shift work and diabetes mellitus. Kivimäki *et al.* [29] proposed a potential model in which circadian rhythms may be disturbed by long-term continuous shift work, possibly leading to type 2 diabetes mellitus due to insulin resistance and weight gain, as well as negatively affect sleep [31], exercise [32, 33], dietary habits [34], and stress [35]. For example, the difference in work-

ing styles might affect various dietary habits, including total calories eaten, the types of food eaten, food style such as fast food, the duration of each mealtime, and the frequency of taking snacks. It is likely that these adverse health effects of shift work appear once workers are engaged in shift work over a prolonged period (*i.e.*, continuous shift workers) rather than for a limited duration (*i.e.*, seasonal shift workers).

Indeed, it is likely that seasonal shift workers have sufficient recovery time that would afford them the opportunity to tackle the adverse health effects of their shift work. Furthermore, in the present study, the association between continuous shift work and diabetes mellitus was more pronounced among the older subjects (aged ≥ 45 years). This finding is consistent with previous reports regarding female nurses in the U.S.; Kroenke *et al.* [36] reported that shift workers who worked for ≥ 10 years had a significantly higher risk of developing type 2 diabetes mellitus in a cohort study, and Pan *et al.* [24] reported that the risk of type 2 diabetes mellitus increased gradually depending on the number of years of continuous shift work by using the data from the Nurses' Health Study (NHS) I (1988–2008) and NHS II (1989–2007). Thus, the findings of the present study further confirm the risk of diabetes mellitus in Japanese men doing shift work.

In this study, we tested both HbA1c and FBS in blood to assess the health outcomes of interest to minimize the possibility of misclassification. Indeed, the combination of these 2 tests would also be clinically relevant, since it could be used to efficiently identify the individuals who are most likely to develop diabetes and to allow for early intervention [37]. Previous studies have used only either HbA1c [17, 22] or FBS [38] to define diabetes mellitus. Additionally, despite concern regarding low sensitivity [39], diabetes mellitus was defined based on a self-reported questionnaire in the 2 previous studies from the U.S. [24, 36]. Future studies should assess diabetes mellitus by testing both HbA1c and FBS. In addition, given that the clinical importance and severity of diabetes mellitus depend on the presence of its complications such as nephropathy, retinopathy, angiopathy, and neuropathy, further studies are warranted to examine the health effects of shift work by taking into account these complications.

The present study had some limitations. First, there is a possibility of selection bias caused by excluding the subjects who could not be linked to annual health checkup data. This exclusion predominantly occurred due to the unavailability of electronic data of health checkup of workers who had completed medical checkups in different hospitals on different occasions, instead of their annual health checkup. The proportions of those who had an annual health checkup varied across the groups: 68.7% for the non-shift workers, 77.0% for the seasonal shift workers, and 78.0% for the continuous shift workers. Since the likelihood of getting an annual health checkup may be influenced by employees' shift work as well as the presence of diabetes mellitus, the selection bias could be a limitation. However, even under this situation, the ORs are not biased when shift work and diabetes mellitus are noninteracting (*i.e.*, the effect of shift work on receiving an annual health checkup is independent of the effect of diabetes mellitus on receiving an annual health checkup) [40, 41].

Second, although we used the results of blood tests to define the health outcomes, information about the subjects' use of medication was unavailable. Therefore, there is a possibility that those who were treated showed good test results. This misclassification, however, would be non-differential, which may have resulted in an underestimation of the present findings.

Third, because shift work was assessed only at the time of this study, the results do not necessarily represent the history of shift work. In particular, there is a possibility that some subjects did not engage in shift work for health reasons and that others may have left continuous shift work due to health problems. Consequently, the present findings may be underestimated due to this reverse causation.

Fourth, information about dietary habits, physical activity, and job stress was not available. Since these factors potentially mediate the association between shift work and diabetes mellitus [29], a rigorous assessment of their roles would enhance our understanding of this cause-effect relationship [42–44]. Finally, we examined only 1 company, and the low statistical power resulting from the relatively small sample size is another limitation.

The findings of the present study demonstrate the importance of considering the intensity of shift work when examining its possible adverse health effects. Our data suggest that the risk of diabetes mellitus is

increased among continuous shift workers compared to non-shift workers. However, the seasonal workers did not show an increased risk of diabetes mellitus. The present findings may be useful in exploring the mechanism by which diabetes mellitus is induced by shift work. In future studies examining the health effects of shift work (including effects on cancer risk), it would be of significant importance to assess various domains of shift work (*e.g.*, direction of rotation, rate of rotation, *etc.*) [23], which would further increase our understanding of the possible health effects among those who are engaged in shift work for decades.

References

1. Nagai M, Morikawa Y, Kitaoka K, Nakamura K, Sakurai M, Nishijo M, Hamazaki Y, Maruzeni S and Nakagawa H: Effects of fatigue on immune function in nurses performing shift work. J Occup Health (2011) 53: 312–319.

2. Costa G, Haus E and Stevens R: Shift work and cancer - considerations on rationale, mechanisms, and epidemiology. Scand J Work Environ Health (2010) 36: 163–179.

3. Nazri SM, Tengku MA and Winn T: Lipid disorders among male factory shift workers in Kota Bharu, Kelantan. Med J Malaysia (2007) 62: 134–138.

4. Wang XS, Armstrong ME, Cairns BJ, Key TJ and Travis RC: Shift work and chronic disease: the epidemiological evidence. Occup Med (2011) 61: 78–89.

5. Suwazono Y, Dochi M, Sakata K, Okubo Y, Oishi M, Tanaka K, Kobayashi E and Nogawa K: Shift work is a risk factor for increased blood pressure in Japanese men: a 14-year historical cohort study. Hypertension (2008) 52: 581–586.

6. Fujino Y, Iso H, Tamakoshi A, Inaba Y, Koizumi A, Kubo T and Yoshimura T: A prospective cohort study of shift work and risk of ischemic heart disease in Japanese male workers. Am J Epidemiol (2006) 164: 128–135.

7. Vyas MV, Garg AX, Iansavichus AV, Costella J, Donner A, Laugsand LE, Janszky I, Mrkobrada M, Parraga G and Hackam DG: Shift work and vascular events: systematic review and meta-analysis. BMJ (2012) 345: e4800.

8. Megdal SP, Kroenke CH, Laden F, Pukkala E and Schernhammer ES: Night work and breast cancer risk: a systematic review and meta-analysis. Eur J Cancer (2005) 41: 2023–2032.

9. Schernhammer ES, Kroenke CH, Laden F and Hankinson SE: Night work and risk of breast cancer. Epidemiology (2006) 17: 108–111.

10. Kubo T, Ozasa K, Mikami K, Wakai K, Fujino Y, Watanabe Y, Miki T, Nakao M, Hayashi K, Suzuki K, Mori M, Washio M, Sakauchi F, Ito Y, Yoshimura T and Tamakoshi A: Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. Am J Epidemiol (2006) 164: 549–555.

11. Mikuni E, Ohoshi T, Hayashi K and Miyamura K: Glucose intolerance in an employed population. Tohoku J Exp Med (1983) 141

12. Kobayashi T, Suzuki E, Takao S and Doi H: Long working hours and metabolic syndrome among Japanese men: a cross-sectional study. BMC Public Health (2012) 12: 395.

13. Suwazono Y, Dochi M, Sakata K, Okubo Y, Oishi M, Tanaka K, Kobayashi E, Kido T and Nogawa K: A longitudinal study on the effect of shift work on weight gain in male Japanese workers. Obesity (Silver Spring) (2008) 16: 1887–1893.

14. Kubo T, Oyama I, Nakamura T, Shirane K, Otsuka H, Kunimoto M, Kadowaki K, Maruyama T, Otomo H, Fujino Y, Matsumoto T and Matsuda S: Retrospective cohort study of the risk of obesity among shift workers: findings from the Industry-based Shift Workers' Health study, Japan. Occup Environ Med (2011) 68: 327–331.

15. De Bacquer D, Van Risseghem M, Clays E, Kittel F, De Backer G and Braeckman L: Rotating shift work and the metabolic syndrome: a prospective study. Int J Epidemiol (2009) 38: 848–854.

16. Ha M and Park J: Shiftwork and metabolic risk factors of cardiovascular disease. J Occup Health (2005) 47: 89–95.

17. Oyama I, Kubo T, Fujino Y, Kadowaki K, Kunimoto M, Shirane K, Tabata H, Sabanai K, Nakamura T and Matsuda S: Retrospective cohort study of the risk of impaired glucose tolerance among shift workers. Scand J Work Environ Health (2012) 38: 337–342.

18. Fukuda Y, Nakamura K and Takano T: Accumulation of health risk behaviours is associated with lower socioeconomic status and women's urban residence: a multilevel analysis in Japan. BMC Public Health (2005) 5: 53.

19. Kagamimori S, Gaina A and Nasermoaddeli A: Socioeconomic status and health in the Japanese population. Soc Sci Med (2009) 68: 2152–2160.

20. Suzuki E, Kashima S, Kawachi I and Subramanian SV: Social and geographic inequalities in premature adult mortality in Japan: a multilevel observational study from 1970 to 2005. BMJ Open (2012) 2: e000425.

21. Kondo N, Subramanian SV, Kawachi I, Takeda Y and Yamagata Z: Economic recession and health inequalities in Japan: analysis with a national sample, 1986–2001. J Epidemiol Community Health (2008) 62: 869–875.

22. Morikawa Y, Nakagawa H, Miura K, Soyama Y, Ishizaki M, Kido T, Naruse Y, Suwazono Y and Nogawa K: Shift work and the risk of diabetes mellitus among Japanese male factory workers. Scand J Work Environ Health (2005) 31: 179–183.

23. Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ, Castano-Vinyals G, Davis S, Frings-Dresen MH, Fritschi L, Kogevinas M, Kogi K, Lie JA, Lowden A, Peplonska B, Pesch B, Pukkala E, Schernhammer E, Travis RC, Vermeulen R, Zheng T, Cogliano V and Straif K: Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. Occup Environ Med (2011) 68: 154–162.

24. Pan A, Schernhammer ES, Sun Q and Hu FB: Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. PLoS Med (2011) 8: e1001141.

25. Kawakami N, Araki S, Takatsuka N, Shimizu H and Ishibashi H: Overtime, psychosocial working conditions, and occurrence of non-insulin dependent diabetes mellitus in Japanese men. J Epidemiol Community Health (1999) 53: 359–363.

26. Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, Ito C, Inagaki N, Iwamoto Y, Kasuga M, Hanafusa T, Haneda M and Ueki K: Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetol Int (2010) 1: 2–20.

Suppl: 251–256.

27. Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Ito H, Tominaga M, Oikawa S, Noda M, Kawamura T, Sanke T, Namba M, Hashiramoto M, Sasahara T, Nishio Y, Kuwa K, Ueki K, Takei I, Umemoto M, Murakami M, Yamakado M, Yatomi Y and Ohashi H: International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Invest (2012) 3: 39–40.

28. Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T and Rakugi H: The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). Hypertens Res (2009) 32: 3–107.

29. Kivimäki M, Batty GD and Hublin C: Shift work as a risk factor for future type 2 diabetes: evidence, mechanisms, implications, and future research directions. PLoS Med (2011) 8: e1001138.

30. Karlsson B, Alfredsson L, Knutsson A, Andersson E and Toren K: Total mortality and cause-specific mortality of Swedish shift- and dayworkers in the pulp and paper industry in 1952–2001. Scand J Work Environ Health (2005) 31: 30–35.

31. Cappuccio FP, D'Elia L, Strazzullo P and Miller MA: Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care (2010) 33: 414–420.

32. Endo M, Nakanishi Y and Miyatake N: The Relation between Insulin Resistance and Lifestyle in Japanese Female University Students. Acta Med Okayama (2011) 65: 199–204.

33. Thomas DE, Elliott EJ and Naughton GA: Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev (2006): CD002968.

34. Lazarou C, Panagiotakos D and Matalas AL: The role of diet in prevention and management of type 2 diabetes: implications for public health. CRC Crit Rev Food Sci Nutr (2012) 52: 382–389.

35. Kawakami N, Akachi K, Shimizu H, Haratani T, Kobayashi F, Ishizaki M, Hayashi T, Fujita O, Aizawa Y, Miyazaki S, Hiro H, Hashimoto S and Araki S: Job strain, social support in the workplace, and haemoglobin A1c in Japanese men. Occup Environ Med (2000) 57: 805–809.

36. Kroenke CH, Spiegelman D, Manson J, Schernhammer ES, Colditz GA and Kawachi I: Work characteristics and incidence of type 2 diabetes in women. Am J Epidemiol (2007) 165: 175–183.

37. Heianza Y, Hara S, Arase Y, Saito K, Fujiwara K, Tsuji H, Kodama S, Hsieh SD, Mori Y, Shimano H, Yamada N, Kosaka K and Sone H: HbA1c 5.7–6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. Lancet (2011) 378: 147–155.

38. Nagaya T, Yoshida H, Takahashi H and Kawai M: Markers of insulin resistance in day and shift workers aged 30–59 years. Int Arch Occup Environ Health (2002) 75: 562–568.

39. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ and Rodeheffer RJ: Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J Clin Epidemiol (2004) 57: 1096–1103.

40. Westreich D: Berkson's bias, selection bias, and missing data. Epidemiology (2012) 23: 159–164.

41. Tsuda T, Yamamoto E, Babazono A, Mino Y, Ogawa T, Shigemi J and Aoyama H: An epidemiologic research design using the Annual of the Pathological Autopsy Cases in Japan. Nippon Eiseigaku Zasshi (1994) 49: 753–761 (in Japanese).

42. Suzuki E, Yamamoto E and Tsuda T: Identification of operating mediation and mechanism in the sufficient-component cause framework. Eur J Epidemiol (2011) 26: 347–357.

43. VanderWeele TJ: Mediation and mechanism. Eur J Epidemiol (2009) 24: 217–224.

44. Hafeman DM: A sufficient cause based approach to the assessment of mediation. Eur J Epidemiol (2008) 23: 711–721.