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Original Article

Association between shift rotation and 30-year Framingham risk of cardiovascular disease among male workers in a medium-sized manufacturing factory

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Abstract: Rotating shift work is associated with an increased risk of cardiovascular disease (CVD). This study compared the CVD risk score in 129 male line workers aged 22–49 years on different shifts in a medium-sized metal production factory from 2017 to 2020. We classified workers into four groups: permanent day shift, weekly rotation involving five consecutive nights, weekly rotation involving 3–4 consecutive nights, and monthly rotation involving two consecutive nights. We used the Framingham Risk Score to estimate the 30-yr risks of general and hard CVD (CVD risk estimates). We investigated the differences in CVD risk estimates between different groups using linear mixed models. The average 30-yr Framingham CVD risk estimates of each group ranged from 17.5% to 31.2% for general CVD and from 10.5% to 20.5% for hard CVD. Workers on weekly rotations involving 3–5 consecutive nights had 5%–10% significantly higher CVD risk estimates than workers on the permanent day shift. Workers on weekly rotations also had 6%–8% higher BMI-based CVD risk estimates than those on the monthly rotation involving two consecutive nights. While 24-h shift rotations are unavoidable, our findings underscored the potential CVD risk among workers on weekly rotations involving more consecutive nights.

Key words: Shift work, Shift rotation, Night shift, Cardiovascular disease, Framingham Risk Score, Medium-sized enterprise

Introduction

Rotating shifts, i.e., working alternatively between day, evening, and night shifts, are common in the manufacturing industry and operate for 24 hours (h) to reduce the high cost of turning machines on and off after long intervals. Workers rotate between day and night shifts to accommodate continuous manufacturing operations, typically three 8-h shifts or two 12-h shifts[1)]. Shift rotation has been reported to be an important occupational risk factor for several chronic diseases[2, 3)]. Among these, cardiovascular disease (CVD) has been a focus of occupational health in East Asia in recent years due to the relaxation of disease recognition

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criteria and the enforcement of prevention regulations for overwork-related CVD[4–7].

Rotating shift work increases CVD risk through diverse pathways, such as disturbing circadian and social rhythms and changing lifestyles[8–12]. The degree of health effects of shift rotations may vary with different shift schedules[13]. Shift schedule types can be categorized by the presence/absence of night work, the duration of shifts (the number of working hours per shift), the length of shift cycle (the number of days between two shifts or identical sequences, which is usually expressed in days, weeks, or months), and the speed of rotation (the number of consecutive night shifts, e.g., a fast speed of rotation involves fewer consecutive night shifts than a slow speed of rotation)[14, 15]. Among these shift arrangements, working at night and long hours has been widely studied and commonly pointed out as a risk factor of CVD[16–18]. For example, a 24-year (yr) prospective cohort study of 189,158 healthy nurses in the United States reported that women on longer durations of night shift work had a significantly increased risk of coronary heart disease (hazard ratio = 1.12 for duration of 5–9 yr and 1.18 for ≥10 yr) than women with no history of rotating night shift work[16]. A meta-analysis of 603,838 workers found that those working long hours (≥55 h per week [w]) had a 13% higher risk of incident coronary heart disease and 33% higher risk of incident stroke than workers whose standard working hours were 35–40 h per w[17].

In practice, when a rotating shift is unavoidable, shift arrangements should balance the production needs and worker health. In particular, different lengths of shift cycle, speeds of rotation, and number of working hours may complicate the CVD risk[19]. However, the combined effects of shift rotation speed and cycle length on CVD risk remain inconclusive. For example, some European studies recommend a fast shift rotation (i.e., fewer consecutive night shifts) because it is associated with reduced disruption and readjustment of circadian rhythms, a long sleep period, improved work-life balance, and enhanced alertness at work[20–22]. In contrast, some Asian studies recommend a slow shift rotation (i.e., more consecutive night shifts) because it allows workers to adapt to changes in body rhythms gradually[23, 24]. Therefore, this research aimed to compare the CVD risk among workers working in different rotating shifts (i.e., more, fewer, and no consecutive night shifts) using a retrospective cohort study design. Considering that preventing CVD risk has become an important task for occupational health professionals in Taiwan in recent years and to assist employers in complying with regulations[6], understanding the characteristics of different shift types and identifying the population at high risk may contribute to CVD prevention.

Subjects and Methods

Study design and setting

We conducted a 4-yr retrospective cohort study of participants who underwent a health examination, and the selection period started in 2017 (baseline year) lasting until 2020. Our cohort included the production workers of a metal product manufacturing factory in central Taiwan. In practice, companies used Framingham Risk Score to estimate the CVD risk, rather than waiting for actual CVD onset, as their basis for preventive actions. Therefore, we collected variables to estimate CVD risk rather than observing the onset of CVD. This study was reviewed and approved by the Central Regional Research Ethics Committee of China Medical University, Taiwan, in September 2020 (CRREC 109-135).

Participants

We first estimated the expected number of participants in each group. A previous cross-sectional study showed that the average Framingham Risk Score of Taiwanese male workers was 6.1 ± 5.0%, with 83% of participants at low risk (score = 10%), 16% at moderate risk (score = 20%), and 1% at high risk (score = 30%)[25]. We expected that the largest relative difference in CVD risk scores between two shifts was only half of the risk levels (i.e., half of 10% = 5%). A sample size of 16 participants in each group should be sufficient using a two-tailed test with 80% power and a 5% level of significance[26].

A total of 335 workers had completed the baseline examination in 2017. The inclusion criteria for the workers was completion of the baseline and following 3-yr examinations. A total of 150 participants who fulfilled the criteria remained in the company in 2020. In the first stage, we recruited 150 potential participants in October 2020. In the second stage, we explained our study to these potential participants and requested informed consent. In the third stage, the participants who provided signed informed consent were assessed for eligibility. The participants who had self-reported diseases such as hypertension, diabetes, and cardiovascular disease in the baseline year were excluded from our study.

Work schedules

In this cohort, information on the types of work schedules was obtained via the Human Resources Information

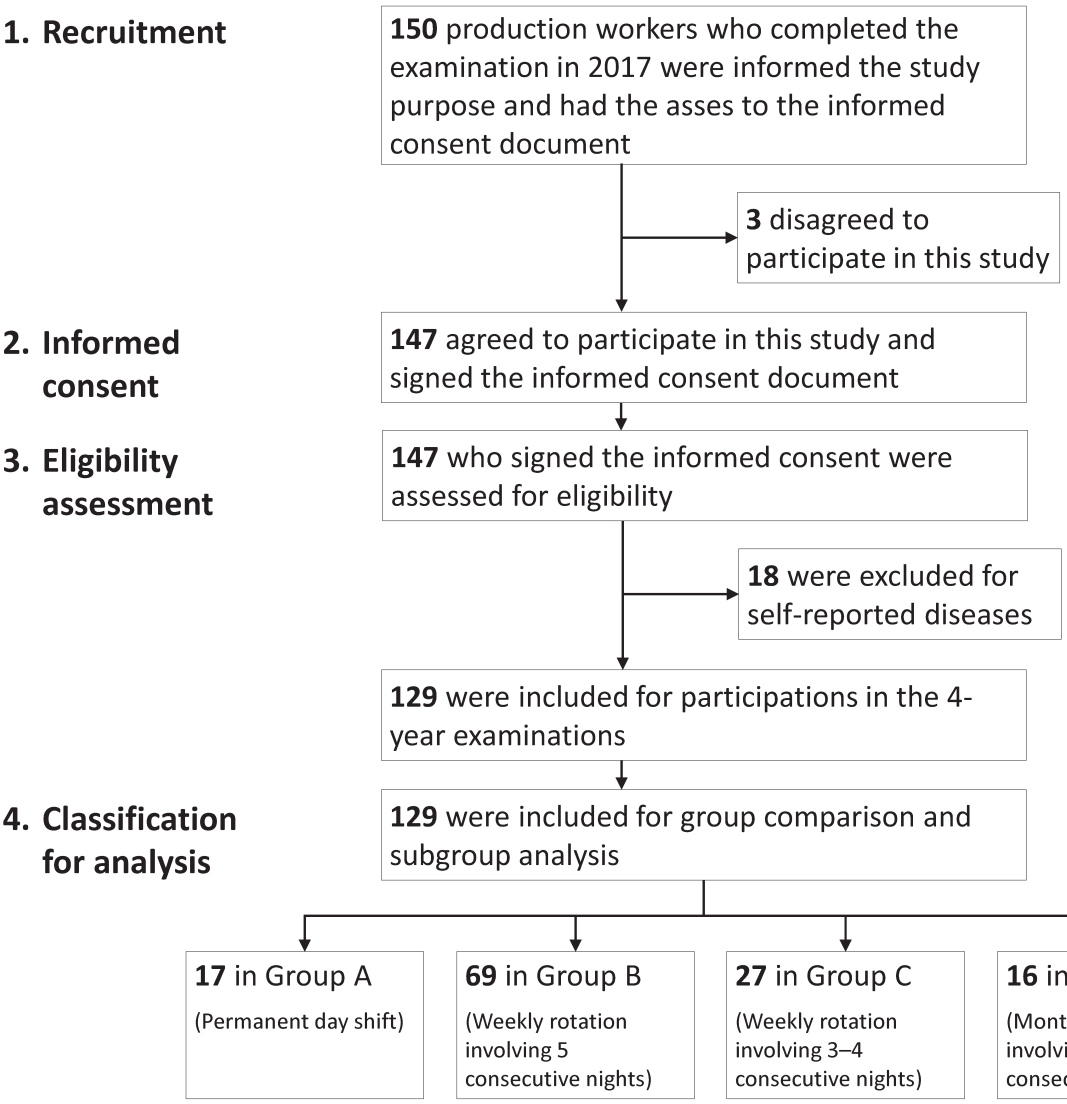
System in the metal product manufacturing factory and characterized by shift rotation (yes or no), number of working hours per shift, and length of each rotation period. Shift rotation is defined as a rotating shift that continued consistently from 2017 to 2020. Individual exposure to the type of shift schedule from 2017 to 2020 was determined. We classified participants into four groups based on their baseline shift schedule type: permanent day shift (Group A), weekly rotation involving five consecutive nights (Group B), weekly rotation involving 3–4 consecutive nights (Group C), and monthly rotation involving two consecutive nights (Group D). It should be noted that workers in Group C interchangeably rotated three or four consecutive nights for compliance with the Labor Standards Act, which regulates the regular working time ≤40 hours a week and the extension of working hours ≤46 hours a month. The characteristics of each shift are shown in Fig. 1.

Risk of cardiovascular disease assessment

We used the Framingham Risk Score to estimate the CVD risk for each male participant in each year. The Framingham Risk Score was developed from the results of the Framingham Heart Study by using specific CVD risk factors to estimate future CVD event rates in percent, i.e., out of 100 subjects with such CVD risk factors, how many would have a CVD event[27]. The Framingham Heart Study provided formulas to calculate 10-yr and 30-yr CVD risks[27]. The 10-yr risk of CVD was designed for the population aged 30–74 yr, and the estimated risk was typically low in the young population[28]. The 30-yr risk of CVD was designed for the population aged 20–59 yr. Our participants were aged 22–46 yr at baseline, with 31% younger than 30 yr of age. Therefore, we calculated the 30-yr general and hard CVD risks for our study population[29]. The Framingham Heart Study provided two methods to estimate the 30-yr risk of the two types of CVD outcomes: lipids-based estimation and body mass index (BMI)-based estimation[27]. The two types of CVD outcomes were general CVD (i.e., coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure) and hard CVD (i.e., coronary death, myocardial infarction, and stroke)[27]. Sources of data used for the risk score calculation were health examination reports and self-administered questionnaires. The variables obtained from health examination reports were BMI, total serum cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP), glycated hemoglobin or hemoglobin A1c (HbA1c), and fasting serum glucose levels. Subjects with HbA1c ≥6.5% and/or fasting blood glucose concentration ≥126 mmol/L (%) were defined as having diabetes. Subjects with SBP ≥160 mmHg and/or DBP ≥100 mmHg as well as using antihypertensive treatment were defined as hypertension patients. The variables obtained from the self-administered questionnaires were age and smoking habits. Other potential covariates, such as sleeping hours and health promotion, were also obtained from the questionnaire. In total, four types of CVD risks were calculated: 30-yr general CVD risk using lipid-based estimation, 30-yr hard CVD risk using lipid-based estimation, 30-yr general CVD risk using BMI-based estimation, and 30-yr hard CVD risk using BMI-based estimation.

Statistical analyses

We performed the Kruskal-Wallis test to compare four groups with regard to age, total cholesterol level, HDL level, SBP, BMI, sleeping hours, and four types of CVD risks. We performed Fisher's exact test to compare the distribution of binary variables (i.e., hypertension, diabetes, smoking, and engagement of health consultation) among the groups. We used linear mixed models to analyze the trends in CVD risks over the 4 years and associations between shift work types and CVD risks adjusted for the interaction between year and shift, baseline age, number of sleeping hours per day, engagement of health promotion, and variables used to calculate the CVD risks. Fixed-effects models can provide unbiased estimates, but some of our models violated the assumption of normality and homogeneity of variance[30]. However, we still log-transformed all CVD risk variables to mitigate their influence. We used the restricted maximum likelihood method to estimate all the unknown parameters in each model. The Akaike information criterion was applied to compare models and select the Toeplitz structured and unstructured as the best covariance structures for lipid-based and BMI-based models, respectively, to consider the autocorrelation among repeated measures. In particular, to solve some divergence problems in some models, we applied the Kenward-Roger method to compute the denominator degrees of freedom for the tests of fixed effects. The post hoc test was further applied to make pairwise comparisons between the two shift types in each type of CVD risk over the 4 years. There was no multicollinearity among the main effects because all tolerances were less than 1. In particular, the estimated changes in each type of CVD risk from the baseline year and between two shift rotations were computed by transforming the estimated coefficient $\hat{\beta}$ using the formula $(\exp(\hat{\beta})-1)\times 100\%$.



Permanent or rotating	Permanent	Rotating	Rotating	Rotating
Shift cycle and length of each duty shift	No shift rotation • Repatedly work 5 days and rest 2 days	Weekly rotation (more frequent) • Work 5 days, rest 2 days, and then switch to the next shift (clockwise)	Weekly rotation (more frequent) • Work 4 days, rest 2 days (or work 3 days, rest 3 days), and then swith to the next shfit	Monthly rotation (less frequent) • Repatedly work 2 days and rest 2 days for a month, and then swith to the next shfit
Start and end time (duration) of each duty shift	• 08:00–17:00 (8 hours)	• 08:00–16:00 (8 hours) • 16:00–00:00 (8 hours) • 00:00–08:00 (8 hours)	• 08:00–20:00 (12 hours) • 20:00–08:00 (12 hours)	• 08:00–20:00 (12 hours) • 20:00–08:00 (12 hours)
Average weekly working hours	40 hours	40 hours	42–56 hours	42 hours
Night work and number of consecutive night shifts	No • 0 night	Yes • 5 consecutive nights	Yes • 3–4 consecutive nights	Yes • 2 consecutive nights

Fig. 1. Study flow and number of subjects in each stage.

Table 1. Baseline characteristics in 2017, by groups

Characteristics	Total (n=129)	Group A (n=17)	Group B (n=69)	Group C (n=27)	Group D (n=16)	*p*-value[a]
Mean age (SD), years	32.5 (4.9)	35.8 (5.3)	31.5 (4.4)	30.7 (4.2)	36.5 (4.3)	<0.001
Mean total cholesterol (SD), mg/dL	191.8 (37.1)	191.0 (36.5)	185.1 (36.1)	201.6 (39.2)	205.2 (34.3)	0.001
Mean high density lipoprotein cholesterol (HDL) (SD), mg/dL	46.1 (9.1)	47.5 (11.0)	46.3 (10.1)	44.5 (6.5)	46.4 (6.2)	0.944
Mean systolic blood pressure (SBP), mmHg	128.4 (10.9)	127.1 (11.7)	128.8 (10.5)	127.3 (10.6)	130.1 (12.8)	0.585
Mean BMI (SD)	24.8 (4.7)	25.2 (6.4)	24.1 (3.8)	25.5 (5.4)	26.4 (4.3)	0.002
Mean sleeping hours per day (SD), hours	7.0 (1.0)	7.0 (1.2)	7.0 (1.0)	7.0 (1.1)	6.9 (0.9)	0.765
Hypertension[b] (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Diabetes[c] (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Smoking habits (%)	89 (69.0%)	13 (76.5%)	40 (58.0%)	21 (77.8%)	15 (93.8%)	0.018
Engaged in health consultation (%)	23 (17.8%)	6 (35.3%)	9 (13.0%)	6 (22.2%)	2 (12.5%)	0.171
Mean 30-year Framingham general CVD risk, estimated using lipids (SD), %	20.3 (10.5)	25.1 (14.6)	17.5 (8.9)	19.6 (9.7)	28.6 (6.9)	<0.001
Mean 30-year Framingham hard CVD risk, estimated using lipids (SD), %	12.6 (7.8)	16.4 (11.5)	10.5 (6.3)	12.1 (7.1)	18.6 (5.3)	<0.001
Mean 30-year Framingham general CVD risk, estimated using BMI (SD), %	21.2 (10.5)	26.9 (14.2)	18.0 (7.8)	20.0 (10.5)	31.2 (8.4)	<0.001
Mean 30-year Framingham hard CVD risk, estimated using BMI (SD), %	13.2 (7.9)	17.7 (11.4)	10.7 (5.4)	12.3 (7.7)	20.5 (6.7)	<0.001

Abbreviation: n = number of subjects, SD = standard deviation, BMI = body mass index, CVD = cardiovascular disease.
Group A: permanent day shift; Groups B: weekly rotation involving five consecutive nights; Group C: weekly rotation involving 3–4 consecutive nights; Group D: monthly rotation involving two consecutive nights.
a We performed the Kruskal-Wallis test to compare the group differences for continuous variables and Fisher's exact test for binary variables.
b Number of subjects with SBP ≥160 mmHg and/or DBP ≥100 mmHg and using antihypertensive treatment (%)
c Number of subjects with HbA1c ≥6.5% and/or fasting blood glucose concentration ≥126 mmol/L (%)

All data management and analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA). Type I error was set to 0.05.

Results

Fig. 1 shows the study flow, including the number of subjects in each stage. A total of 147 out of 150 workers agreed to participate in this study and signed an institutional review board-approved informed consent document. The participation rate was high (98%). Of these, 129 were eligible for inclusion. All 129 participants worked in the same type of work schedule throughout the 4 years. They were classified into four groups with 17 participants in group A, 69 participants in group B, 27 participants in group C, and 16 participants in group D.

All production workers were men. The general characteristics of the study population at baseline are summarized in Table 1. The study subjects were young and middle-aged adults with a mean age of 32.5 yr (standard deviation [SD] = 4.9) and mean total cholesterol level of 191.8 mg/dL (SD=37.1), HDL level of 46.1 mg/dL (SD=9.1), SBP of 128.4 mmHg (SD=10.9), BMI of 24.8 (SD=4.7), and sleeping hours of 7.0 per day (SD=1.0). None had hypertension or diabetes in the baseline year, but the prevalence of cigarette smoking was high (69%). BMI-based estimations of

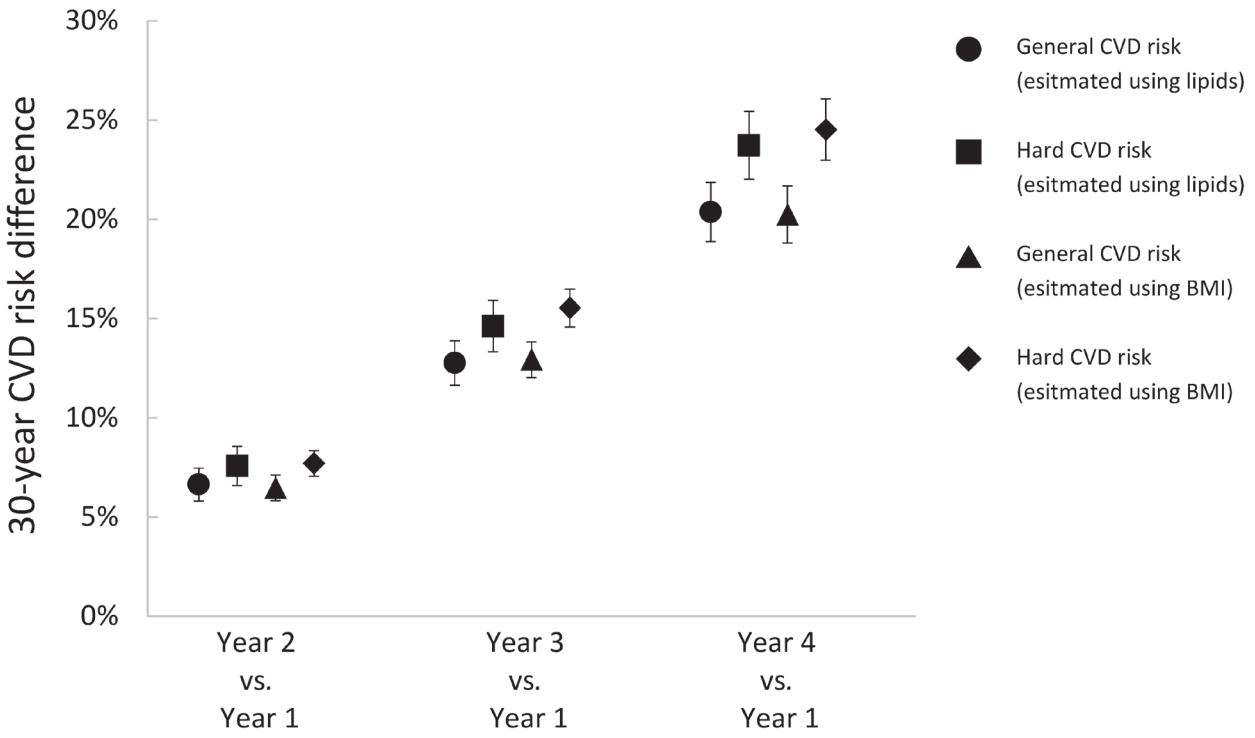


Fig. 2. Risk differences in 30-yr Framingham risk of cardiovascular disease (CVD) between different years.

30-yr CVD risks (general CVD, 21.2% [SD=10.5]; hard CVD, 13.2% [SD=7.9]) were slightly higher than the lipid-based estimations (general CVD, 20.3% [SD=10.5]; hard CVD, 12.6% [SD=7.8]). There were significant differences between the groups in baseline age ($p<0.001$), cholesterol level ($p=0.001$), BMI ($p=0.002$), smoking habit ($p=0.018$), and CVD risk ($p<0.001$), where Group D was the oldest group with an average age of 36.5 yr (SD=4.3), the highest mean total cholesterol level of 205.2 mg/dL (SD=34.3), highest average BMI of 26.4 (SD=4.3), the highest proportion of smokers (94%), and the highest CVD risks of all four types.

Fig. 2 shows adjusted changes in CVD risks of the 129 subjects over the 4 years by estimated linear mixed models revealing significant elevations in all CVD risks over time. Compared with the CVD risk in the baseline period, the BMI-based general CVD risk was significantly high by 6.5% (95% confidence interval [CI]: 5.8%–7.1%; $p<0.001$) in the second year and the BMI-based hard CVD risk, by 24.5% (95% CI: 23.0%–26.1%; $p<0.001$) in the fourth year. We took the 30-yr general CVD risk estimated using BMI as an example to interpret the risk difference of 6.5%. As shown Table 1, the average CVD risk of 129 subjects in the first year was 21.2%. After adjusting for covariates, the risk increase of 6.5% suggests a CVD risk that is 6.5% higher in the second year than in the first year, which becomes 21.2% + 21.2%×6.5% = 22.6%.

Fig. 3 shows the risk differences for CVD risk between groups using the estimated linear mixed models after adjusting for covariates. Compared with the CVD risks of Group A (permanent day shift), Groups B (weekly rotation involving five consecutive nights) and Group C (weekly rotation involving 3–4 consecutive nights) had significantly and positively changed percentages in four types of 30-yr CVD risks (Panels a and b). The significant risk differences in panels a and b ranged from 4.9% (95% CI: 0.3%–9.7%, $p=0.037$) for the general CVD risk estimated using lipids between Groups B and A to 10.5% (95% CI: 5.1%–16.1%, $p<0.001$) for the hard CVD risk estimated using BMI. Groups B and C also had higher BMI-based CVD risks than Group D (monthly rotation involving two consecutive nights), with risk differences ranging from 6.1% (95% CI: 0.3%–12.9%, $p=0.040$) for the general CVD risk (Panel e) to 8.0% (95% CI: 2.5%–13.7%, $p=0.004$) for the hard CVD risk (Panel d).

Discussion

Our retrospective cohort study examined the association of rotating shift work with the 30-yr CVD risk over a 4-yr

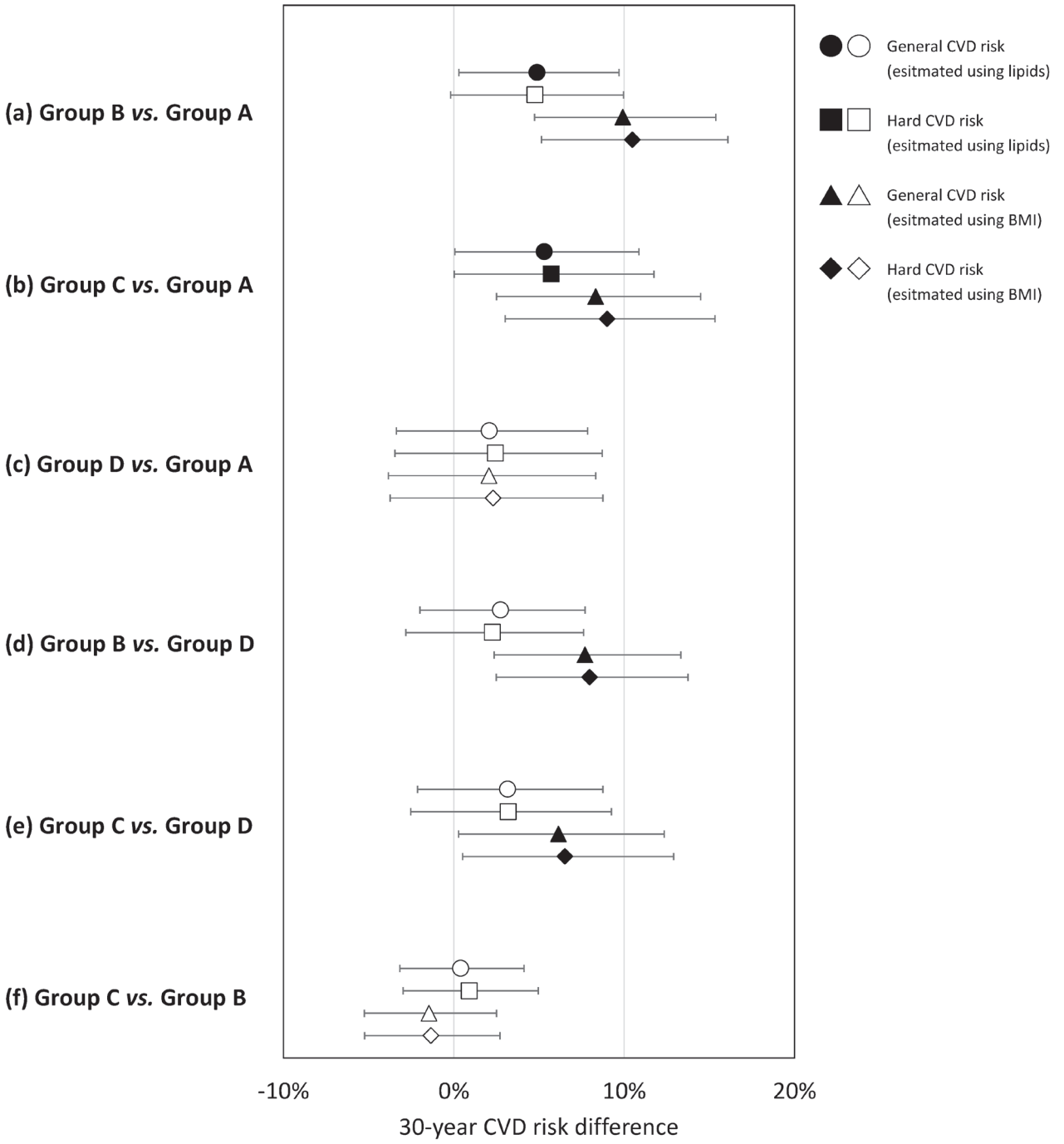


Fig. 3. Risk differences in 30-yr Framingham risk of cardiovascular disease (CVD) between different shift rotations.
Black symbols indicate statistically significant data with respect to the estimated risk differences, while white symbols indicate statistically non-significant data.
Group A: permanent day shift; Group B: weekly rotation involving five consecutive nights; Group C: weekly rotation involving 3–4 consecutive nights; Group D: monthly rotation involving two consecutive nights.

follow-up period and found that weekly rotations involving more consecutive nights were associated with significantly higher CVD risks by 5%–10% than the permanent day shift. In contrast, the monthly rotation involving two consecutive nights was associated with a statistically insignificant increase in the CVD risk of only 2%. This study also reported higher BMI-based CVD risks in workers on weekly rotations involving 3–5 consecutive nights than in those on the monthly rotation involving two consecutive nights.

In the studied factory, workers in weekly rotations

(Groups B and C) needed to readjust their daily activities every week. Given that all workers began with a shift starting at 8:00 a.m. in the first week, workers in Groups B and C needed to start working at 16:00 and 20:00, respectively, in the second week; in contrast, workers in Groups A and D had consistent schedules. Frequent changes in work schedule may increase CVD risk through unhealthy behavior, especially dietary patterns[12, 31]. Several guidelines recommend avoiding food intake between midnight and 6 a.m. or after 1 a.m. When looking at their starting and ending times, workers in Group B worked 8 h per day, but they needed to alter their meal time weekly, while other workers may not have needed to do so. Workers in Group C needed to change their main meal time every week. The timing of food intake is a key aspect of the body's metabolism[32], and associated with body fat percentage and BMI[33]. Thus, timed meal patterns can allow the digestive system to function habitually, prevent circadian desynchronization, and reduce metabolic risks. In addition, a short time interval between the last meal and timing of sleep onset was related to dyslipidemia[34]. One meta-analysis suggested that rotating shift workers had an increased risk of overweight by 21% and obesity by 16%. These studies support our findings of a high CVD risk in workers on weekly shift rotations.

The direct impact of frequent changes in work schedule involving night shifts on CVD risk could occur through a different pathway—sleep disturbance[11, 35]. A previous Chinese study found that workers on the two-shift rotation had a 1.37-fold higher risk of sleep disturbance than workers on the fixed day-shift, and the risk was even higher for workers on three-shift rotation, i.e., 2.19-fold higher risk[36]. The link between sleep duration and CVD risk was supported by previous studies in South Korea and Iran, which reported that short sleep (≤5 or ≤6 h) was associated with an individual's 10-yr CVD risk estimated using the Framingham risk score[37, 38]. In our study, we extracted data on the average number of sleeping hours per day from the questionnaire survey. However, we did not find a significant difference in sleep duration among the groups in the baseline year (Table 1). While we further analyzed the effect of sleeping hours on CVD risk in our linear mixed models, we still did not find a significant association. One possible reason for this difference is the relatively young age of our subjects. For example, the proportion of short sleeping hours (≤5) per day was 15% in a Korean study[37], but only 7% in our study. In addition, the average ages of these individuals with short sleep were 55 yr in the Korean study[37] and 34 yr in our study. The low prevalence of short sleeping hours in the young and small sample in our study may have reduced the statistical power of our calculations. A future study that applies causal mediation analysis to a large sample size with wide age composition can help us explore other reasons for the higher CVD risk among workers on different shift rotations.

Despite the small sample size, our study used a complete annual dataset. The small number of participants limits the generalizability of the results to other groups, such as female workers, senior workers, and workers in other industry sectors. However, these workers had consistent shift rotations for at least 4 years, which increased the number of workers in rotating work over a long period. A complete 4-yr follow-up dataset also allowed us to control the subjects' baseline differences and perform repeated measurements to investigate trends in annual changes. In addition, none of the participants changed their shifts during these 4 years. All these advantages provided us with a unique opportunity to analyze CVD changes over time and perform group comparisons.

A "healthy shift worker effect" is thought to be an intrinsic methodological limitation. In addition, the association between shift work and CVD risk is non-linear and seems to appear only after the first 5 years of exposure[39]. Both the "healthy shift worker effect" and a short follow-up period may have led to an underestimation of the negative health effect of rotating shifts. A study with a long follow-up period may yield a significant effect of different shift rotations on CVD risk. Other factors, such as exercise, dietary habits, and stress levels, may also be associated with CVD risk. The questions listed in our questionnaire were in line with the standardized questions provided in government guidelines, which could not comprehensively cover and address all covariates. Nevertheless, these potential confounders are highly related to the predictors that we used to estimate CVD risks, such as BMI. In addition, we obtained data on the engagement of health consultations from the factory's medical center. We noticed that the CVD risk was lower in workers who engaged in health consultation than those in who did not (range of CVD risk difference, 0.2%–0.5%); however, we did not find a significant association. Furthermore, the bias arising by not considering potential confounders in our models was low.

Conclusion

A 24-h shift rotation is expected and unavoidable in contemporary working environments. Our study compared the 30-yr Framingham CVD risk score between workers in different shifts. The highest risk was associated with more fre-

quent (weekly) rotations involving more consecutive nights, followed by the less frequent (monthly) rotation involving fewer consecutive nights and the permanent day shift. Therefore, the length of shift cycle and the number of consecutive night shifts should be considered in interventions on the prevention of CVD.

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Author Contributions

A.Y.H. contributed to idea formulation and data acquisition. L.C.C. contributed to data analysis, data interpretation, and writing of the manuscript. R.T.L. contributed to idea formulation, data analysis, reporting results, data interpretation, and writing of the manuscript. All authors participated in commenting on subsequent drafts, approved the final manuscript, and agreed to submit it for publication.

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