Interaction between Shift Work and Established Coronary Risk Factors

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Abstract

Background: Shift work is associated with increased risk of cardiovascular disease, but the causes have not yet been fully established. It has been proposed that the coronary risk factors are more hazardous for shift workers, resulting in a potential interaction effect with shift work.

Objective: To analyse interaction effects of work schedule and established risk factors for coronary artery disease on the risk of myocardial infarction.

Methods: This analysis was conducted in SHEEP/VHEEP, a case-control study conducted in two counties in Sweden, comprising all first-time cases of myocardial infarction among men and women 45–70 years of age with controls stratified by sex, age, and hospital catchment area, totalling to 4648 participants. Synergy index (SI) was used as the main outcome analysis method for interaction analysis.

Results: There was an interaction effect between shift work and physical inactivity on the risk of myocardial infarction with SI of 2.05 (95% CI 1.07 to 3.92) for male shift workers. For female shift workers, interaction effects were found with high waist-hip ratio (SI 4.0, 95% CI 1.12 to 14.28) and elevated triglycerides (SI 5.69, 95% CI 1.67 to 19.38).

Conclusion: Shift work and some established coronary risk factors have significant interactions.

Keywords: Cardiovascular diseases; Epidemiology; Risk factors; Shift work schedule; Synergy

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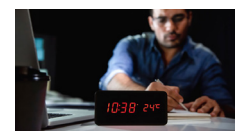
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Introduction

Several studies have shown that shift work is associated with a higher risk of cardiovascular disease (CVD). A meta-analysis published in 2012 concluded that shift work is associated with an increased risk of myocardial infarction (MI).[1]

Several hypotheses have so far attempted to explain possible causal mechanisms between shift work and CVD. These include higher prevalence of behavioral risk factors such as smoking, low physical activity and poor dietary choices, low socioeconomic status, adaptation problems of the circadian rhythm, and social stress related to the divergent working hours.[2]

An interaction occurs when two or more factors together are associated with an effect on an outcome that is greater than their individual effects alone.[3] Interactions between shift work and other risk factors that contribute to CVD have not been widely examined. One study found

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the effect of an interaction between a family history of CVD and diabetes in males on coronary heart disease risk;[4] another found that parental history of CVD interacted with shift work as a risk factor for MI among males.[5] Only a few studies have so far been concerned with studying interaction effects of shift work and cardiovascular risk factors on coronary heart disease.

Interaction between shift work and established risk factors for MI is not extensively studied and may further elucidate the association between shift work and MI; the value of such studies may be increased by the use of interaction measures such as synergy index (SI).

We conducted this study to analyze if shift work interacts with elevated body mass index (BMI), high waist-hip ratio (WHR), tobacco smoking, physical inactivity, elevated blood pressure, elevated blood lipids, and type II diabetes to increase the risk of MI.

Materials and Methods

Data Source

The analyses were conducted in a case-referent study based on two parallel studies, the Stockholm Heart Epidemiology Programme (SHEEP), and the Västernorrland Heart Epidemiology Program (VHEEP). They were identical in design, except for the period of case identification and the age span of the subjects, as described below. The combined dynamic study database contained all Swedish citizens in the counties of Stockholm and Västernorrland, who were free from previous clinically diagnosed MI and aged between 45 and 70 years. In Stockholm County, male cases were identified during 1992–93, and female cases during 1992–94. During January to October 1992, the upper age limit was 65 years. From November 1, 1992 and onwards, the upper age limit was 70 years. In Västernorrland County, the age span was restricted to 45–65 years, and cases were identified during March 1993 to March 1995.

Cases were defined as all non-fatal and fatal first ever events of acute MI. Case identification was made from coronary and intensive care units, discharge registers, and death certificates from the Swedish National Register of Causes of Death. Each case was randomly paired with one referent selected from the study database after stratification for sex, age and hospital catchment area. In this study, we had more controls than cases, as all selected controls remained in the dataset, regardless of whether the case did or not. Health information from both cases and controls were obtained through questionnaires. For deceased cases, a close relative completed the questionnaire.

All referents and all surviving cases were invited for a physical examination approximately three months after the MI. The study has been described in detail elsewhere.[6]

Study Variables

Shift work was defined as either fixed work between 18:00 and 6:00 or rotating shift work in the same period, concerning the last five years before the inclusion in the study.[6] If the participant was on long-term sick leave, had retired or otherwise was

TAKE-HOME MESSAGE

- Interaction between shift work and risk factors for coronary heart disease is not widely studied.

- Shift work and some established coronary risk factors interact to increase the risk of myocardial infarction.

- More research is needed to analyze if interactions play a role in the association between shift work and myocardial infarction.

not working, the questions concerned the last five years of their occupational career. Smoking habits were divided into current smokers including ex-smokers who had stopped smoking within the last two years before inclusion, and non-smokers included ex-smokers quitting more than two years ago.[6]

Height, weight, hip, and waist measurements were collected at the physical examination. From this information BMI (weight/height[2]), and WHR (waist measurement divided by hip measurement) was calculated. A BMI was considered high if it was ≥28 kg/m^{2}; WHR was considered high if it exceeded 0.875 for women under 60 years of age, 0.9 for women over 60 years, and 1.0 for men.[6] For those who failed to attend the physical examination, but who had answered the questionnaire, only information on height and weight were used. For those with both self-reported and measured height and weight, the correlation between the two was high ($r^2 = 0.9$). Spare time physical activity was considered for the last 10 years before inclusion in the SHEEP/VHEEP study. Participants who answered that they never or only occasionally were physically active in their spare time were considered physically inactive; those who did not meet this criterion were used as reference.[6]

The cut-off value for elevated triglycerides was set at ≥2.3 mmol/L; that for total cholesterol was ≥6.5 mmol/L. The samples were based on fasting levels of blood lipids. Pharmacological treatment for blood lipid-related disorders was also included as an indicator of elevated blood lipids.[6] High blood pressure was considered if a participant had either a systolic blood pressure of ≥170 mm Hg or diastolic pressure of ≥95 mm Hg, or reported pharmacological treatment for diseases consistent with ICD-9 code 40, or earlier pharmacological treatment for hypertension that ended less than five years before

inclusion in the database.[6] Type II diabetes was considered if a participant had a fasting glucose level of >6.7 mmol/L (120 mg/dL) or if the question of known type II diabetes in the questionnaire was reported, or the participant required insulin, or if the participant regularly medicated for diseases consistent with ICD-9 code 250, or if a participant mentioned pharmacological treatment against type II diabetes in the questionnaire.[6]

Statistical Analysis

Differences in population characteristic were analyzed using χ^2 analysis. A p value <0.05 was considered statistically significant. All analyses were performed separately for men and women and all odds ratios (ORs) were adjusted for age.

Interaction on an Additive Scale

The interaction analyses aimed to determine whether the presence of both component causes increased the risk of MI using Rothman's SI,[7] presented as ORs. OR_{10} and OR_{01} denote OR among those exposed to one of the analyzed risk factors; OR_{11} denotes OR among those exposed to both. The equation presented here is aimed to provide an overview of how SI is calculated, the full SI equation and calculation of its 95% CI is presented elsewhere.[8]

SI = 1 means no interaction (the sum of effects due to multiple causes). SI > 1 reflects to a positive interaction; SI < 1, a negative interaction.

χ^2 and logistic regression analysis were calculated with SPSS® for Windows® ver 17.0; SI and its 95% CI were calculated with SAS® 9.1 for Windows® using a published SAS program.[8]

Results

We studied 4648 participants—1417 (44%) men and 589 (41%) women with MI. Shift work was significantly more common

Table 1: Relative frequency (%) of exposure to various characteristics for the shift work and day work participants stratified by sex

Parameters	Men (n=1417)			Women (n=589)		
	Shift workers (%)	Day workers (%)	p value	Shift workers (%)	Day workers (%)	p value
BMI* ≥28 kg/m^2	33.5	21.4	<0.01	24.2	32.9	0.08
Current smoker	40.2	28.5	<0.01	24.7	32.9	0.1
High WHR†	27.3	16.6	<0.01	24.1	24.6	0.94
Physical inactivity	33.8	34.2	0.9	40.4	38.8	0.78
Elevated triglycerides‡	21.5	25.2	0.15	28.6	18.1	0.05
Elevated cholesterol§	34.2	36.3	0.47	45.7	43.7	0.66
Hypertension¶	31.3	28.8	0.29	32.7	28.8	0.31
Type II diabetes‖	12.3	16.8	0.05	17.6	12.1	0.03

*BMI: body mass index
†Waist hip ratio >0.875 for women <60 years of age, >0.9 for women >60 years of age, and >1.0 for men
‡Triglycerides ≥2.3 mmol/L
§Total cholesterol ≥6.5 mmol/L
¶Systolic blood pressure of ≥170 mm Hg in systolic or diastolic blood pressure of ≥95 mm Hg or pharmacological treatment for hypertension
‖Disease consistent with ICD-9 code 250 or having established type II diabetes or pharmacological treatment for type II diabetes

among those with MI in both men (17.8% *vs* 12.4%, p <0.001) and women (16.5% *vs* 10.2%, p<0.001).

Male shift workers more often had elevated BMI, were current smokers, and had high WHR and type II diabetes compared with male day workers. Female shift workers more often had elevated triglycerides and type II diabetes compared with female day workers. The rest of the analyzed risk factors did not show any difference between shift and day workers (Table 1).

Table 2 shows the calculated SI, a measure of interaction effect between shift work and certain risk factors. The results showed that physical inactivity and shift work had an interaction effect on the risk of MI for males. Both high WHR and shift work and elevated triglycerides together with shift work had an interaction effect for females.

Discussion

This analysis showed that shift work and physical inactivity had an interaction effect for males, and that shift work and high WHR or elevated triglycerides had an interaction effect for females on the risk factors of MI.

The results indicated that the negative consequences of physical inactivity were more hazardous for male shift workers compared with male day workers regarding the risk of MI. It has been previously reported that leisure-time physical activity is associated with decreased risk of CVD[9] and lower prevalence of CVD risk factors, such as hypertension[10] and dyslipidemia[11]. An increase in physical activity for male shift workers may therefore normalize their risk of MI. There is also a possibility that physical inactivity acting as a proxy variable for other CVD risk factors; physical inactivity may be associated with other

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Table 2: Interaction effects between shift work and analyzed risk factors on the MI for male and female shift workers compared with day workers, expressed as synergy index (SI) and their confidence interval (95 % CI). OR_{00} (reference), OR_{10} and OR_{01} denote OR among those exposed to one of the analyzed risk factors; OR_{11} denotes OR among those exposed to both adjusted for age.

Risk factors	Men		Women	
	OR (95% CI)	SI (95% CI)	OR (95% CI)	SI (95% CI)
BMI*≥28 kg/m^2 (n=4593)				
BMI<28 and day work	1		1	
BMI≥28 and day work	1.67 (1.41 to 1.99)		1.52 (1.18 to 1.96)	
BMI<28 and shift work	1.77 (1.39 to 2.25)		1.70 (1.14 to 2.52)	
BMI≥28 and shift work	1.65 (1.19 to 2.29)	0.45 (0.19 to 1.07)	2.31 (1.38 to 3.84)	0.70 (0.37 to 3.08)
Current smoker (n=4648)				
Non-smoker and day work	1		1	
Current smoker and day work	2.33 (1.99 to 2.74)		3.36 (2.62 to 4.29)	
Non-smoker and shift work	1.48 (1.12 to 1.94)		1.33 (0.84 to 2.11)	
Current smoker and shift work	3.06 (2.31 to 4.06)	1.14 (0.71 to 1.83)	5.73 (3.57 to 9.19)	1.76 (0.94 to 3.31)
WHR† (n=3311)				
Non-WHR and day work	1		1	
WHR and day work	1.75 (1.41 to 2.17)		1.41 (1.04 to 1.92)	
Non-WHR and shift work	1.38 (1.05 to 1.81)		1.38 (0.86 to 2.22)	
WHR and shift work	1.47 (0.97 to 2.24)	0.42 (0.11 to 1.61)	4.17 (2.19 to 7.92)	4.00 (1.12 to 14.28)
Physically inactivate (PI) (n=4614)				
Non PI and day work	1		1	
PI and day work	1.52 (1.30 to 1.78)		2.33 (1.84 to 2.95)	
Non PI and shift work	1.33 (1.03 to 1.73)		1.84 (1.18 to 2.85)	
PI and shift work	2.74 (2.03 to 3.71)	2.05 (1.07 to 3.92)	3.85 (2.42 to 6.14)	1.32 (0.65 to 2.67)
Elevated triglycerides (ET)‡ (n=3076)				
Non-ET and day work	1		1	
ET and day work	2.32 (1.85 to 2.90)		2.46 (1.7 to 3.55)	
Non-ET and shift work	1.38 (1.04 to 1.83)		1.37 (0.88 to 2.15)	
ET and shift work	3.22 (1.97 to 5.25)	1.32 (0.6 to 2.9)	9.40 (3.85 to 22.92)	5.69 (1.67 to 19.38)

Continued

Table 2: Interaction effects between shift work and analyzed risk factors on the MI for male and female shift workers compared with day workers, expressed as synergy index (SI) and their confidence interval (95 % CI). OR_{00} (reference), OR_{10} and OR_{01} denote OR among those exposed to one of the analyzed risk factors; OR_{11} denotes OR among those exposed to both adjusted for age.

Risk factors	Men		Women	
	OR (95% CI)	SI (95% CI)	OR (95% CI)	SI (95% CI)
Elevated cholesterol (EC)§ (n=3284)				
Non-EC and day work	1		1	
EC and day work	1.56 (1.3 to 1.88)		2.14 (1.61 to 2.84)	
Non-EC and shift work	1.30 (1.0 to 1.74)		1.97 (1.19 to 3.28)	
EC and shift work	2.21 (1.51 to 3.25)	1.34 (0.6 to 3.0)	3.72 (2.12 to 6.53)	1.68 (0.6 to 5.13)
High blood pressure¶ (n=4574)				
No high blood pressure and day work	1		1	
High blood pressure and day work	0.52 (0.37 to 0.73)		1.87 (1.46 to 2.38)	
No high blood pressure and shift work	0.70 (0.49 to 1.0)		1.76 (1.20 to 2.56)	
High blood pressure and shift work	0.82 (0.55 to 1.21)	1.0 (0.45 to 2.21)	3.26 (1.81 to 5.85)	1.60 (0.56 to 4.56)
Type II diabetes‖ (n=4648)				
No type II diabetes and day work	1		1	
Type II diabetes and day work	2.27 (1.80 to 2.86)		4.25 (2.93 to 6.15)	
No type II diabetes and shift work	1.49 (1.21 to 1.86)		1.82 (1.3 to 2.56)	
Type II diabetes and shift work	3.31 (2.05 to 5.35)	1.27 (0.61 to 2.65)	4.00 (1.88 to 8.54)	0.75 (0.25 to 2.25)

*BMI: body mass index
†Waist hip ratio >0.875 for women <60 years of age, >0.9 for women >60 years of age, and >1.0 for men
‡Triglycerides ≥2.3 mmol/L
§Total cholesterol ≥6.5 mmol/L
¶Systolic blood pressure of ≥170 mm Hg in systolic or diastolic blood pressure of ≥95 mm Hg or pharmacological treatment for hypertension
‖Disease consistent with ICD-9 code 250 or having established type II diabetes or pharmacological treatment for type II diabetes

factors, say tobacco smoking. By promoting physical activity among shift workers, the prevalence of tobacco smoking, for example, is likely to decrease.

Several mediating mechanisms by which physical activity is supposed to affect the risk of CVD have been proposed. HDL-cholesterol levels have been reported to increase with physical activity; it would therefore decrease LDL-cholesterol and

triglycerides.[9] Physical activity has also been found to improve insulin sensitivity,[11] and thereby decreasing the risk of type II diabetes.

Regular physical activity lowers C-reactive protein (CRP) levels and reduces systemic inflammation and thereby decreasing the risk of CVD.[12] Some of the inflammatory lowering effects may also be mediated by the lower body weight associated with regular exercise, as obesity and adipose tissue increase the inflammatory processes in the body. The total energy expenditure incorporates occupational physical activity, household physical activity, and leisure-time physical activity. Leisure-time physical activity is only a part of the total activity or total energy expenditure. When studied separately, the results regarding occupational physical activity have not been as consistent as for leisure-time physical activity.[9,12] Physical activity, as household work, has rarely been studied as a separate factor.

High WHR and elevated triglycerides had an interaction effect in shift working women on the association with MI. Therefore, it appears that high WHR and elevated triglycerides is more harmful to female shift workers compared with female day workers regarding the risk of MI. There was an interaction effect between WHR and shift work on the risk of MI. The finding of higher prevalence of high WHR among male shift workers has previously been reported,[13] and the result is in accordance with the theory that shift work is probably associated with the metabolic syndrome.[14] High WHR can indicate visceral adipose tissue that in turn is also a component of the metabolic syndrome and associated with increased risk of CVD.[15] Promoting physical activity among female shift workers would potentially decrease their risk of CVD by reducing their visceral adipose tissue.[16] Triglyceride levels is likely to also be decreased via increased

physical activity.[9] Such efforts may counteract the interaction effects reported in this study for female shift workers. Both WHR and triglycerides are components in the metabolic syndrome and can be viewed as a pre-diabetic state. However, both male and female shift workers had a higher prevalence of type II diabetes compared with day workers. Nonetheless, we could observe no interaction effects with shift work on the association with the risk of MI. The interaction effect of high WHR and triglycerides for female shift workers and interaction between type II diabetes and shift work warrant further focus on independent datasets.

The cut-off values for hypertension and elevated blood lipids used in our study were higher than those commonly used in clinical practice in Sweden today. Given that we used higher cut-off levels, we included participants with an even higher risk; therefore, the observed interaction effects might have been overestimated. On the other hand, if the number of participants included in each analysis is low, the observed interaction effects might be underestimated. Given the sample size in our study, the risk of underestimation, however, is very unlikely.

To further study the interaction between shift workers and the risk of coronary heart disease, more attention should be paid to a number of factors. For example, if the arteries of shift workers are more affected by atherosclerosis,[17] it would be of interest to study indicators of vascular specific inflammation. If shift workers with elevated vascular inflammation have a synergy effect when exposed to physical inactivity, for example, the need for effective preventive measures would be even more highlighted.

The data used in this study were representative of the sex segregated labor market in Sweden with more women in the health care sector and more men in

the transport sector, for example,[18] meaning that the working situation for women and men in shift work compared with day work could be different. This means that shift work in different sectors of the labor market might lead to different levels of exposure to various causal components that interact differently between men and women. This may have affected the results in our study.

Epidemiological studies are often limited by the fact that the information on shift work exposure is based on questionnaire data.[19] Questions used to determine shift work exposure varies from questions not attempting to determine vital components of the shift work exposure to elaborate questions dealing with type of shift work and the exposure duration.[20] The questionnaire data regarding shift work exposure used in this study and the definition of shift work and day work derived from that question has been used in previous studies.[6]

Lifetime exposure to shift work was not possible to derive from the data obtained, representing a limitation in this study. The definition of shift work in this study was based on the last five years of work exposure. This created a potential misclassification risk where respondents might have had trouble in correctly determining their work conditions. This might have led to an underestimation or overestimation of the risk associated with shift work exposure. However, it has been proposed that questionnaire data on shift work would not be subject to recall bias in any greater extent.[21]

In the existing literature, only a limited number of studies have analyzed interaction effects for shift workers and the risk of MI. Therefore, the findings of this study should be regarded as preliminary; more research in the field is needed. It might seem as if the traditional risk factors were more hazardous for shift workers. If this is the case, ordinary confounder control such as stratification or logistic regression analysis without the use of interaction terms would not be enough to control for the traditional risk factors, and an uneven distribution would therefore not be sufficiently accounted for. Confounding control was not addressed further in this study than the inclusion of age as a covariate in the interaction analyses. Given that the potential interactions between shift work and CVD risk factors are sparsely studied, the choice of potential confounders in interaction analyses is an area where further research is needed.

In summary, the analysis showed an interaction effect between physical inactivity and an increased association with risk of MI for male shift workers. Interaction effects were found for female shift workers with elevated triglycerides, WHR, and an increased association with the risk of MI, indicating that these risk factors may be more harmful to male and female shift workers. To determine whether that is the case, more research is needed. If verified, the reported interactions suggest that focus on prevention among shift workers should aim at promoting physical activity.

Conflicts of Interest: None declared.

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