Shiftwork and myocardial infarction: a case-control study

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Abstract

***Objectives*—Previous studies have indicated an association between shiftwork and coronary heart disease. The increased risk could be due to job strain, which could act as a mediator of disease. There is also a possibility that interaction between shiftwork and job strain could occur that may induce or modify the development of disease. We conducted this study to explore the relation between shiftwork, job strain, and myocardial infarction.**

***Methods*—2006 cases with acute first time myocardial infarction were compared with 2642 controls without symptoms of myocardial infarction, and obtained from the same population that gave rise to the cases (population based case-control study).**

***Results*—Myocardial infarction risk was associated with shiftwork both in men (odds ratio (OR) 1.3, 95% confidence interval (95% CI)1.1 to 1.6) and women (OR 1.3, 95% CI 0.9 to 1.8). In the age group 45–55, the relative risk was 1.6 in men and 3.0 in women. The results cannot be explained by job strain, age, job education level, or smoking. No interaction was found between shiftwork and job strain.**

***Conclusions*—The findings indicate that shiftwork is associated with myocardial infarction in both men and women. The mechanism is unclear, but the relation cannot be explained by job strain, smoking, or job education level.**

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Keywords: job strain; smoking; case-referent; sex; coronary artery disease

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Established risk factors for coronary heart disease (CHD) can explain only a minor part of the variation in CHD. In searching for additional risk factors for CHD, the role of psychosocial environmental factors has attracted growing attention during recent years. Shiftwork and job strain are factors discussed in this context. Working irregular hours, including night work and shiftwork, has been found to be associated with higher incidences of CHD.[1] In a cohort study of male paper mill workers a dose-response relation was shown between years of shiftwork and CHD.[2] A recent study of female nurses in the United States gave similar results.[3] A Danish study showed that occupations with a higher proportion of workers who work odd hours had a higher risk of admission to hospital for myocardial infarction.[4] McNamee *et al*, however, found no association between shiftwork and mortality from CHD in a study of male workers at a factory producing nuclear fuel elements.[5] In a 6 year follow up of 1806 male participants in the Helsinki heart study the relative risk of CHD among shiftworkers compared with day workers was 1.4 after adjustment for lifestyle factors, blood pressure, and serum lipids.[6] Job strain explained part of the risk of CHD for blue collar workers.

To shed further light on the alleged relation between shiftwork and risk of CHD, we carried out an analysis, with data from the Stockholm heart epidemiology programme(SHEEP) and Västernorrland infarction project (VIP), a research project which was designed to test several hypotheses about risk factors for myocardial infarction. Of particular interest was the evaluation of the relation between shiftwork, job strain, and myocardial infarction. Work related stress has been discussed as an important mediator of disease in shiftworkers. Therefore, it is of importance to study whether job strain is on the aetiological pathway between shiftwork and CVD. There is also a possibility that an interaction between shiftwork and job strain could occur that may induce or modify the development of disease.

Materials and methods

STUDY DESIGN

A population based case-referent design was used. Cases were defined as all non-fatal and fatal first events of acute myocardial infarction, first episode. Data from two parallel studies (the Stockholm heart epidemiology programme, and the Västernorrland infarction project) were used for the present report. These two studies had identical design, the only exceptions being the period of case identification and the age span of the subjects, as stated below. The combined study base comprised all Swedish citizens living in the counties of Stockholm and Västernorrland, respectively, who were 45–70 years of age (calendar years) and free of previous clinically diagnosed myocardial infarction. In the Stockholm county, male cases were identified during a 2 year period (1992–3), and female cases during 3 years (1992–4). During the period January to October 1992, the upper age limit was 65 years; from 1 November 1992 and onwards, it was 70 years. In the Västernorrland county, the age span was restricted to 45–65 years, and male and female cases were identified during the period March 1993 to March 1995.

CASE IDENTIFICATION

Cases were identified from three sources and included at the time of incidence of disease. The sources were (*a*) the coronary and intensive care units at the internal medicine departments at all the emergency hospitals within the counties of Stockholm and Västernorrland, (*b*) the hospital discharge register for the same counties, and (*c*) death certificates from the National Register of Causes of Death at Statistics Sweden. Criteria for myocardial infarction were those accepted by the Swedish Association of Cardiologists in 1991.[7] The criteria included (*a*) certain symptoms according to information on case history, (*b*) specified changes in blood concentrations of the enzymes creatine kinase and lactate dehydrogenase, (*c*) specified electrocardiographic changes, and (*d*) necropsy findings. The diagnosis of acute myocardial infarction required two of the criteria *a–c* to be met, or that necropsy findings showed myocardial necrosis of an age compatible with the time of onset of disease. The medical inclusion and exclusion criteria for the cases in hospital were assessed by a few cardiologists only; thus, the same diagnostic criteria were applied for all cases in hospital. Cases who died before admission to hospitals were identified by special routines at the Statistics Sweden. Among these cases that were not in hospital, 72% were necropsied and had signs of recent myocardial infarction. For the remaining 28% of cases in this group, the diagnosis was made by the doctor issuing the death certificate, from information on disease history and death circumstances. In the present study 21% of cases among shiftworkers and 19% among day workers were fatal. Cases that were not admitted to hospital were checked for previous hospital admissions for myocardial infarction from 1975 in the Stockholm heart epidemiology programme and from 1985 in the Västernorrland infarction programme and onward in the hospital discharge registers (ninth revision of the international classification of diseases (ICD-9) codes 410 or 412 or corresponding codes in previous ICD revisions). If such an episode was found, the person was excluded from the study base. Subjects with previous "silent" infarctions, as judged from necropsy findings only of previous myocardial infarction (ICD-9 412), were not excluded from the study base as silent infarctions could not be ascertained among the referents within the frames of the present study.

IDENTIFICATION OF REFERENTS

One referent per case was randomly selected from the study base after stratification for sex, age, and hospital catchment area. The referents were selected within 2 days of case incidence from the computerised registers of the Stockholm and the Västernorrland county populations. Each referent candidate was also checked for history of myocardial infarction since 1975 in the hospital discharge register for Stockholm and since 1985 for Västernorrland counties, (ICD-9 codes 410 or 412 or corresponding codes in previous ICD revisions). Five referent candidates per case were sampled at the same time, so that a potentially non-responding referent could be substituted by another referent, who belonged to the study base at the time of case incidence. This substitution was done to maintain the power of the study and does not affect the non-participation rate. Before finally including a referent in the study, case history information on previous myocardial infarction was also requested. All referents were alive, regardless of whether the cases survived the myocardial infarction. The maximum difference in age between cases and controls was 3 months.

EXPOSURE INFORMATION

Information on a large set of potential risk factors was collected by questionnaires and by a complementary telephone interview. Hospital cases and their referents were also invited for a brief health examination. Unless the subject explicitly declined to participate, up to four reminders could be given if necessary. All questionnaires were returned by post. On receipt, the questionnaires were checked and missing information was completed during a telephone interview. Those subjects who stated previous myocardial infarction in the questionnaire were contacted and carefully interviewed on symptoms and treatment. If the information implied a previous clinically diagnosed myocardial infarction, the subject was excluded from the study.

Shiftwork

Previous studies on shiftwork vary in how shiftwork is defined. In general, shiftwork is defined as a work schedule which includes work hours beyond the standard daytime schedule. Standard day time, however, is an arbitrary determination, and consequently the definition of evening, morning, and night shifts varies from study to study. In the present study we have defined night as the time between 10 00 pm and 6 00 am, and day as the time between 6 00 am and 6 00 pm. Thus a shiftworker is a person whose work schedule includes hours beyond daytime. A night worker is a person who has a work schedule that always or often includes the time between 22 00 and 06 00. Thus, in the present study, "night workers" is a subgroup of shiftworkers. Shiftwork experience was assessed through the following questions (1) Did you undertake shiftwork (during the most recent 5 years of work)? If the answer was yes, the respondent was asked to add information about the type of shift schedule—for example, two shift or three shift, roster schedule, or other specified type of work schedule. (2) Another question asked when the major part of the work hours was scheduled. The response alternatives were (*a*) 06 00–18 00, (*b*) 18 00–22 00, (*c*) 22 00–06 00, (*d*) a combination of (*a*) and (*b*), (*e*) a combination of (*b*) and (*c*), (*f*) a combination of (*a*) and (*c*), and (*g*) a combination of (*a*), (*b*) and (*c*).

If a person answered yes to question 1 or chose response alternatives *b–f* of question 2 he or she was regarded as being exposed to shiftwork. If the respondent answered no to question 1 and did not choose alternatives *b–f*

of questions 2 he or she was regarded as being not exposed to shiftwork (day workers). We also defined a category called night workers—for example, people who reported a work schedule that included nights. A night worker was a person who reported options (*c*), (*e*), (*f*), or (*g*) of question 2.

Smoking

Smoking habits were recorded as type of tobacco and average smoking quantity during successive 10 year periods covering lifetime from 15 years of age up to present time and included information on year of starting and stopping smoking (if applicable). In this paper the following categorisation of smoking habits was used: non-smokers had never smoked regularly for at least 1 year; ex-smokers had previously smoked regularly but stopped more than 2 years before inclusion in the Stockholm heart epidemiology programme or Västernorrland infarction project studies; current smokers smoked at the time of inclusion or had stopped less than 2 years before inclusion.

Job strain

Job strain was measured by means of the Swedish version of the demand-control measurement questionnaire. It was introduced in 1988[8] and its psychometric properties were described later.[9 10] It has five questions about psychological demands and six questions about decision latitude, each one of them with four graded responses ranging from 1=never to 4=always or almost always. The work experience during 5 years preceding inclusion in the study was considered. Population studies in Sweden have shown that both for men and women the two factors psychological demands and decision latitude are statistically clustered in a meaningful way. For men and women the two factors had acceptable Cronbach α coefficients. The psychological demand index was summed with each question scored 1–4, with higher scores (5–20) corresponding to higher demands. Similarly, the decision latitude was summed on the basis of the six questions, with higher scores (4–24) corresponding to higher decision latitude. The ratio between demands and latitude was calculated for each person. Subjects who had ratios above the 75th percentile for the referent group were operationally defined as being exposed to job strain.

Job education level

Educational demands associated with occupation were categorised as no formal education needed, high school (2 years), high school (3–4 years), college (1–2 years), and other.

STATISTICAL ANALYSES

Unconditional logistic regression modelling was used (conditional logistic regression yielded similar results). Inclusion of age and region changed the regression coefficients for shiftwork and night work only marginally, and were therefore excluded from the final model. Smoking and educational level were included in the models as indicator variables. Smoking was coded in three categories (never smoker, ex-smoker, current smoker), and education in five. Results are reported for men and women separately. Interaction was measured based on an additive model, and the synergy index was calculated as proposed by Rothman.[11] The additive model could be explained in the following way. If the relative risk for factor a=RR(a) and for factor b=RR(b) there is positive interaction when RR(ab)>RR(a)+RR(b). Synergy index=(RR(ab)−1)/(RR(a)+RR(b)−2). The synergy index will be equal to unity if there is no interaction, and will exceed unity when positive interaction is present. SPSS-pc software was used for logistic regression, and SAS-pc for assessment of interaction.[12]

Table 1 Number of day workers and shiftworkers among cases and referents

	Men		*Women*	
	Day workers	*Shift-workers*	*Day workers*	*Shift-workers*
Cases	1165	252	492	97
Referents	1584	224	749	85

Results

Seventy seven subjects were omitted due to missing data on work schedules. The total number of cases of myocardial infarction included in the present analysis were 1417 men and 589 women. Of the cases, 252 men and 97 women were exposed to shiftwork. Of those, 61 men and 25 women reported experience of night work (table 1).

A higher proportion of shiftworkers than day workers in the referent group (which reflects the study base) were current smokers (table 2). Shiftworkers also reported more common exposure to high job strain than day workers. The educational level of dayworkers and shiftworkers associated with the job was different. Shiftworkers had a tendency toward a lower educational level.

Exposure characteristics for cases and controls are presented in table 3.

The crude odds ratio (OR) for shiftwork was 1.5 in men and 1.7 in women.

Table 2 Exposure characteristics (%) in referent group

	Men		*Women*	
	Day workers	*Shift-workers*	*Day workers*	*Shift-workers*
Smokers:				
Never	37	27	52	41
Current	29	40*	25	33†
Ex-smokers	35	33	24	26
Job strain:				
Low	80	70	70	44
High	20	31‡	30	56§
Educational demands:				
No formal education	40	51¶	51	66**
High school (2–3 y)	9.2	8.5	8.7	9.5
High school (3–4 y)	12	4.5	5.1	0
College (1–2 y)	16	9.0	11	2.4
Other	23	27	24	23

*Difference current-never among men $\chi^2(1)=13.9$, p=0.0002.
†Difference current-never among women $\chi^2(1)=3.7$, p=0.054.
‡Difference among men $\chi^2(1)=15.9$, p=0.00021.
§Difference among women $\chi^2(1)=22.8$, p<0.0001.
¶Difference among men $\chi^2(4)=23.2$, p=0.0001.
**Difference among women $\chi^2(4)=12.7$, p=0.01.

Table 3 Prevalence of exposure characteristics (%) for cases and controls

	Men		*Women*	
Characteristic	*Cases*	*Controls*	*Cases*	*Controls*
Work schedule:				
Day work	82	88	84	90
Shiftwork	18	12	17	10
Night work	4.3	3.3	4.2	2.0
Smoking:				
Never	22	35	32	52
Current	50	30	54	25
Ex-smokers	28	35	14	23
Job strain:				
Low	72	79	54	67
High	28	21	46	33
Educational demands:				
No formal education	53	42	63	53
High school (2 y)	9.4	9.1	6.0	8.8
High school (3–4 y)	9.0	11	2.9	4.6
College (1–2 y)	8.7	15	6.8	9.9
Other education	20	23	21	24

Table 4 Predictors of myocardial infarction

	Men		*Women*	
Predictor	*OR**	*95% CI*	*OR**	*95% CI*
Shiftwork/day work†	1.5	1.3 to 1.9	1.7	1.3 to 2.4
Shiftwork/day work‡	1.5	1.2 to 1.8	1.5	1.1 to 2.1
Shiftwork/day work§	1.3	1.1 to 1.6	1.3	0.9 to 1.8
Nightwork/day work†	1.4	1.0 to 2.0	2.2	1.2 to 4.2
Nightwork/day work§	1.3	0.9 to 1.8	1.6	0.8 to 3.1
Shiftwork/day work§, age group:				
45–55	1.6	1.1 to 2.4	3.0	1.4 to 6.5
45–60	1.5	1.1 to 2.0	1.7	1.0 to 3.0
45–65	1.3	1.0 to 1.6	1.3	0.9 to 2.0

*Odds ratio obtained through multiple logistic regression.
†Crude odds ratio.
‡Odds ratio adjusted for job strain.
§Odds ratio adjusted for smoking, job strain, and educational level.

Table 5 Odds ratios for the combined effect of shiftwork and job strain (men and women combined)

	*Odds ratio for myocardial infarction**	
	Low job strain	*High job strain*
Day work (n)	1.0 (2906)	1.5 (1044)
Shiftwork (n)	1.5 (386)	1.7 (257)

*Odds ratios obtained through logistic regression, with adjustment for smoking and educational level.
Synergy index 0.7 (95% CI 0.3 to 1.4).

Table 4 shows the results of the logistic regression. Inclusion of job strain did not change the results. The crude OR for shiftwork changed only from 1.5 to 1.3 among men and from 1.7 to 1.3 in women after adjustment for smoking, job strain, and job education level. Isolating the night work component did not increase the relative risk in men, but a small increase was found in women. To explore whether a recent exposure to shiftwork was associated with a higher relative risk of myocardial infarction, a series of restrictions were made. When the data set was restricted to only age group 45–55 the relative risk was 1.6 in men and 3.0 in women.

The potential interaction between shiftwork and job strain is evaluated in table 5. The synergy index was <1.0 indicating antagonism. However, the 95% confidence interval (95% CI) included 1.0. Thus, there was no significant interaction.

When computing synergy indexes for shiftwork and job strain in different age categories, the synergy indexes (95% CI) were: age group 45–55, 1.33 (0.51 to 3.51); age group 56–60, 1.12 (0.32 to 3.93); age group 61–65, 0.58 (0.09 to 3.85), and age group 66–70, 0.06 (0.00 to 64.52). Thus, the synergy index was not significantly increased in any of the age groups.

Discussion

Our results indicate that shiftwork is a risk factor for myocardial infarction. The increased risk could not be explained by job strain, smoking, or job education level. For shiftworkers the excess risk was 30% in both men and women. Our findings are in agreement with the results from two previous studies. One of these—a cohort study of 504 papermill workers—showed an excess risk of 40% in shiftworkers compared with day workers.[2] For those who were exposed for 6 to 10 years the relative risk was 2.0, and the relative risk increased to 2.8 among those who were exposed for 16–20 years. In a prospective cohort study of female nurses from the United States (n=79 109) a relative risk of 1.38 was found for those who reported ever doing shiftwork compared with those who had never done so.[3] The relative risk was adjusted for smoking and various other cardiovascular risk factors. However, no adjustment was made for job related stress. In a recent study by McNamee *et al*, however, a decreased relative risk of mortality from CHD (OR 0.9) was reported among shiftworkers in a nested case-control study.[5] An obvious problem with that study was the different prevalences of traditional risk factors at baseline. At the time of employment the shiftworkers had a lower blood pressure and a lower prevalence of overweight workers than did the day workers, and information on smoking was missing in almost 50% of the shiftworkers.

Analysis of different age strata in this study yielded higher relative risks in younger age groups. The interpretation of this finding could be that younger people have reported more recent experience of shiftwork as the questionnaire asked for shiftwork during the past 5 years of work. In the older age groups, many were retired when the myocardial infarction occurred, and the exposure to shiftwork could have occurred more than 5 calendar years back in time.

In this study a shiftworker is defined as a worker who did shiftwork during the most recent 5 years of work. It is probable that some of those classified as day workers had been shiftworkers before the 5 year period asked for. If the latent period between shiftwork experience and disease is long (>5 years) and if shiftwork is associated with myocardial infarction this misclassification would lead to an underestimation of the relative risk.

A previous study showed that the increased risk of myocardial infarction among shiftworkers could be due to the night work component.[13] The present study could not confirm this. When night work was used as a predictor, ORs similar to those in shiftworkers were found.

A significant relation between job strain and risk of myocardial infarction has been shown in

the Stockholm part of this study (OR 1.3, 95% CI 1.0 to 1.8).[9] The present study indicates that the relation between shiftwork and myocardial infarction remains after adjustment for job strain. These results are in agreement with those reported by Tenkanen *et al*.[6]

Socioeconomic status is a potential confounder in any analysis of health outcomes in shiftworkers. Shiftwork is more prevalent among unskilled workers and lower civil servants, and cardiovascular disease is related to socioeconomic status. Adjustment for educational level, used as a marker of socioeconomic status, reduced the relative risk in the present study. Our estimate of the relative risk of myocardial infarction is similar to that reported in a study of female nurses, in which adjustment for husband's educational attainment was done.[3] However, insufficient control for socioeconomic status should be considered as a possible explanation for the increased risk of CVD in shiftworkers in the present study.

The causal pathway between shiftwork and CHD is still unclear. The results of the logistic regression models indicate that job strain is not a mediating factor and we could not show significant interaction between shiftwork and job strain. One possibility is that job strain is an invalid instrument of measuring strain associated with shiftwork. However, other possibilities should be considered. One obvious biological and psychological effect of shiftwork is disturbed circadian rhythm. Today we do not know whether disturbed circadian rhythm, in the long run, induces effects on the cardiovascular system. Two cross sectional studies, carried out in different European countries, have shown that shiftworkers, on average, have higher concentrations of serum triglycerides.[14 15] This could indicate that shiftwork is associated with metabolic effects, which in turn, might increase the risk of coronary heart disease.

To conclude, the present study has strengthened the evidence of a relation between shiftwork and coronary artery disease. As shiftwork is prevalent in the industrialised countries (the prevalence of shiftwork is estimated to be around 20% in industrialised countries), the aetiological fraction associated with shiftwork is high, despite the relatively low relative risk. Assuming a relative risk of 1.4 and an exposure prevalence of 20%, this yields an aetiological fraction of 7%. If we agree that shiftwork is inevitable in a modern society, further research on disease mechanisms is needed if we want to reduce the increased risk of myocardial infarction among shiftworkers.

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