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Original Article

The Magnitude of Mortality from Ischemic Heart Disease Attributed to Occupational Factors in Korea - Attributable Fraction Estimation Using Meta-analysis

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Objectives: Ischemic heart disease (IHD) is a major cause of death in Korea and known to result from several occupational factors. This study attempted to estimate the current magnitude of IHD mortality due to occupational factors in Korea.
Methods: After selecting occupational risk factors by literature investigation, we calculated attributable fractions (AFs) from relative risks and exposure data for each factor. Relative risks were estimated using meta-analysis based on published research. Exposure data were collected from the 2006 Survey of Korean Working Conditions. Finally, we estimated 2006 occupation-related IHD mortality.
Results: For the factors considered, we estimated the following relative risks: noise 1.06, environmental tobacco smoke 1.19 (men) and 1.22 (women), shift work 1.12, and low job control 1.15 (men) and 1.08 (women). Combined AFs of those factors in the IHD were estimated at 9.29% (0.3-18.51%) in men and 5.78% (-7.05-19.15%) in women. Based on these fractions, Korea's 2006 death toll from occupational IHD between the age of 15 and 69 was calculated at 353 in men (total 3,804) and 72 in women (total 1,246).
Conclusion: We estimated occupational IHD mortality of Korea with updated data and more relevant evidence. Despite the efforts to obtain reliable estimates, there were many assumptions and limitations that must be overcome. Future research based on more precise design and reliable evidence is required for more accurate estimates.

Key Words: Attributable fraction, Cardiovascular disease, Korea, Mortality, Occupation

Introduction

In 2007, the number of deaths was 244,874 in South Korea, with 23.5% from circulatory disease [1]. This proportion has continued for the last 10 years. In particular, hypertensive disease, ischemic heart disease (IHD), and cerebrovascular disease account for 86.3% of circulatory disease mortality [1], which could occur or be aggravated by several occupational and environmental risk factors.

Deaths or disease from occupational factors place heavy burdens on society in terms of economic costs and human suffering [2]. The World Health Organization is a research leader in the study of disease burden from exposure to occupational risk factors [3]. Results have suggested lower back pain, hearing loss, chronic obstructive pulmonary disease, asthma, lung cancer, leukemia, and injury. However, other extensive diseases, including circulatory disease, have not yet been reported, probably due to the uncertainty of inaccurate measurement of oc-

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Table 1. Population attributable fraction (PAF) of occupational factors for cardiovascular disease in previous studies

Country	PAF (%)	Exposure included	Outcome included	Age range	Reference
United States	6.3-18.0	Noise, low job control, shiftwork, ETS	Coronary heart disease	< 70 years	Steenland et al., 2003 [2]
Finland	18.9 (men) 9.1 (women) 16.9 (all)	Noise, shiftwork, ETS, engine exhausts	Ischemic heart disease	24-74 years	Nurminen and Karjalainen, 2001 [4]
United states	5-10	Chemical exposures (lead, carbon monoxide and solvents, etc), job strain, psychosocial stress	Cardiovascular and cerebrovascular disease	< 65 years	Leigh et al., 1997 [5]
Denmark	16 (male) 22 (female)	Monotonous, high-paced work, shiftwork, noise, chemical exposures, ETS	Cardiovascular disease	< 70 years	Olsen and Kristensen, 1991 [6]
United States	1-3	All potential exposures	Ischemic heart disease, hypertension, atherosclerosis, cerebrovascular disease	25-64 years	Markowitz et al., 1989 [7]

ETS: environmental tobacco smoke.

cupational risk factors and their relatively lower risks.

Several studies have estimated the magnitude of cardiovascular disease due to occupational risk factors in the US and in European countries (Table 1) [2,4-7]. Due to insufficient scientific data and exposure prevalence, most studies in the initial stage (1980-1990s) were dependent on narrative estimation rather than systematic analysis [5,7]. In addition, chemical exposure, which has a direct influence on the cardiovascular system, was the main consideration. Because other occupational risk factors, such as noise, shift work, job stress, and environmental tobacco smoke have recently been suggested, earlier estimates might be somewhat lower than actual risk. Two previous studies have shown more reliable and conservative attributable fraction estimates with systematic design and a mathematical approach [2,4].

As for Korean working conditions, exposure data on some physicochemical factors could be obtained by working environmental measurement or investigation. However, previous Korean data were not representative and excluded psychosocial factors. Fortunately, exposure data covering known cardiovascular risk factors were collected in the 2006 Korean Working Conditions Survey, which was a nationwide, large-scale, representative survey [8]. Therefore, we attempted to estimate the current magnitude of IHD mortality due to occupational factors in Korea.

Materials and Methods

Since IHD is a multifactorial disease, it is difficult to determine work-relatedness in individual IHD mortality. Attributable fraction (AF) estimation is one epidemiologic method for estimation of the relative contribution of certain risk factors to the mortality in a population. AF depends on the exposure prevalence of risk factor and its relative risks (RR) of disease.

Selecting occupational risk factors and determining their RRs

A literature investigation was performed to identify occupational risk factors for cardiovascular disease. According to a review study, work schedule (shift work, long-hour work, overtime work), chemical factors (carbon monoxide, carbon disulfide, methylene chloride, nitrate esters), physical factors (cold, heat, noise, vibration, environmental tobacco smoke, physical activity), and psychosocial factors (job strain) are possible risk factors for cardiovascular disease [9]. For quantitative analysis, we selected factors widely distributed in the workplace and enough to exhibit reliable RRs epidemiologically. Several factors were excluded for the following reasons: unknown or unstable RR (long-hour work, overtime work, cold, heat, vibration); small proportion of exposed workers and considerable environmental improvement (chemical factors); uncertainty of risk, compensable by leisure-time activity, and difficulty with quantification (physical activity). Finally, we selected noise, environmental tobacco smoke (ETS), shift work, and low job control as main occupational risk factors of IHD.

Most studies investigating the effect of noise on IHD have used environmental noise exposure rather than occupational noise. In case of ETS, the majority of studies were also based on non-occupational exposure such as spousal smoking. Since those environmental exposures could differ from occupational

ones in terms of intensity and duration of exposure, we investigated the studies on occupational exposure and applied them in meta-analysis. As for shift work, studies that included 'rotating' shift work and adjusted socioeconomic status (SES) or relevant factors (education, job group, etc) were selected, as recent studies suggested that previous positive results may be confounded by factors related to SES [10]. Lastly, job control, one axis of job strain, has been more consistently linked to coronary heart disease than job strain across most studies [2]. Korean studies have shown similar patterns that job control was significantly associated with cardiovascular disease, while other subscales of job stress had no significant relationship [11,12]. Therefore, we considered job control in estimating attributable fraction. As the RR estimates were much higher in case-control studies, possibly due to recall bias, only prospective studies adjusted SES or relevant factors (education, job group, etc) were selected and applied in meta-analysis.

We performed a literature search with MEDLINE electronic database (January 1980 to December 2009) using a script, cardiovascular diseases [MeSH] AND (occupational OR work environment OR noise OR environmental tobacco smoke OR ETS OR passive smoking OR shift work OR job strain OR job control OR decision latitude). References from articles were also reviewed. We included original articles for analysis that were written in English and reported quantitative estimates (RRs or odds ratio (OR)) and their confidence intervals using cohort or case-control design based on workplace setting. When studies had the same cohort or an updated follow-up, more relevant and recent articles were chosen. In selecting literatures on job control and shift work, those tried to adjust for socioeconomic variables were chosen.

As random effects model provides more conservative summary estimates than a fixed effects model assuming that the inter-study differences are due to chance, RRs of each risk factor were summarized by means of a random effect method using inverse variance weighting. For each summary estimate, we assessed heterogeneity between the studies. We used the funnel plot to assess publication bias, and applied the adjusted value by Duval and Tweedie's trim and fill method, in case of biased results. The analytic program was CMA (Comprehensive Meta-Analysis).

Determining the exposure prevalence of each occupational risk factor

Exposure prevalence of occupational risk factors was collected from the 2006 Survey of Korean Working Conditions [8]. The nationwide, questionnaire-based survey was carried out from the 26th of June, 2006 to the 26th of September, and 10,043 interviews (42.1% women) out of 46,498 visited households were carried out. A representative sample of economically active population aged 15 to 64 years was chosen. The enumeration district of Population Census 2005 provided the sampling frame and stratification by region, population, and urbanization level. The questionnaire was based on the fourth European Working Condition Survey 2005 [13] and contains issues regarding working time, physical risk factors, work organization, satisfaction with working conditions, and so on. Despite low response rate due to the difficulties in reaching the respondent, this survey provided an overview of recent Korean working condition reliably for the first time.

Calculating attributable fraction and estimating occupation-related IHD mortality

The population attributable fraction (PAF) is the proportion of the total burden of disease that is related to a given risk factor in a population. It estimates the proportional amount by which disease risk would be reduced if all factors were to be eliminated from the population. PAF is calculated using the population prevalence of exposure (p) and the RR (or rate ratio, or OR) associated with exposure (r) as followed formula [14]:

$$PAF = \frac{p(r - 1)}{p(r - 1) + 1}$$

AF can also be estimated for simultaneously considered groups of factors. Assuming the independence of exposures, combined AF for n exposures can be calculated by the following formula [15].

$$AF_{combined} = 1 - [1 - AF_1] [1 - AF_2] \cdots [1 - AF_n]$$

Finally, we estimated the occupation-related IHD mortality of South Korea by applying the AFs to the official cause-of-death statistics. We applied statistics of certain year (2006) to show general picture of the overall burden of work-related mortality rather than to show exact mortality based on temporal relationship between exposure and outcome. Korean cause-of-death statistics provides yearly numbers of causes of deaths by gender and age (5-year group), and uses the 10th revision of the International classification of diseases (ICD-10). We restricted our estimates to the IHD (I20-I25), which includes angina pectoris (I20), myocardial infarction, and its complications (I21-23), and other acute IHD and chronic IHD (I24-25). AFs were applied to IHD deaths in the 15-69 year age range, as outcomes are expected to be the short-term effect of occupational risk factors [2,16,17].

Brief description of basic assumptions within estimation

Our estimation of AF and mortality magnitude was based on followed main assumptions. (i) There are causal relation between the exposure considered and IHD. (ii) Each occupational risk factor would be distributed independently. (iii) Foreign data on RRs of disease and exposure condition would not significantly differ from Korean population, although it is expected some differences in biological characteristics and working conditions. It is reasonable to assume that RR is the same among populations with similar exposure profiles, and it is possible to estimate the AF in a target population [18]. (vi) The effect of occupational risk factors on IHD would be short-term less than 5 years. If this assumption is not correct, the estimates of AFs and IHD deaths in this study may be conservative, as the number of IHD increase after 69 years of age [2].

Results

RRs and exposure prevalence of occupational risk factors

Noise

Table 2 summarizes studies on the association between occupational noise exposure and IHD, and shows estimated RRs for IHD [19-22]. Although statistically insignificant in general, the results are consistent in that point estimates of RRs range from 0.9 to 1.3.

As studies are few, gender differences were not considered in meta-analysis. We applied the RR in exposed above 70 dBA in the study of Willich et al. [19], and applied the RR in 13 year follow-up in the study by Virkkunen et al. [21]. In the study by Davies et al. [22], we applied the RR of 1.04 (95% CI = 0.97-1.12), which is the weighted mean of inverse variance. The summary point estimate was 1.12 (95% CI 1.01-1.23) with little evidence of heterogeneity [Q = 4.37, df(Q) 3, p = 0.224 on the Q test, I_2 = 31.3]. However, funnel plot showed some evidence for publication bias and the adjusted RR was 1.06 (95% CI = 0.95-1.18), which was applied to both genders in the final analysis.

Based on the Survey of Korean Working Conditions, 8.8% of male workers and 4.7% of female workers were exposed to noise ("need to make vocal efforts to overcome background noise levels for speech communication required") for most of their working time. Although this subjective exposure assessment is too inaccurate to be classified and interpreted as an exposed group above 85 dBA, those levels that interfere with speech communication are expected to be nearly the same.

ETS

Table 3 summarizes studies on the relation between ETS in

Table 2. Studies on occupational noise exposure and cardiovascular disease

Study (Country)	Design	Subjects	Outcome	Exposure	RR or OR	95% CI	Controlled variables
Willich et al., 2006 (Germany) [19]	Case-control	4,115 cases and matched controls (1 : 1 in men, 1 : 2 in women)	MI	> 70 dBA	1.25 (men) 1.11 (women)	0.97-1.60 0.54-2.26	DM, HTN, smoking, family history of MI, hyperlipidemia, obesity, education, living alone, employment status, working hour, shift work
McNamee et al., 2006 (UK) [20]	Nested case-control 1950-98	Male industrial workers 1,220 IHD deaths and 1,220 controls	Fatal IHD	≥ 85 dBA	1.13	0.92-1.39	BP, BMI, smoking, height, employment duration
Virkkunen et al., 2005 (Finland) [21]	Cohort 1982-99	6,005 male industrial workers	Fatal/nonfatal IHD	Continuous noise ≥ 80 dBA or impulse noise	1.16 (9 yr F/U) 1.26 (13 yr F/U) 1.35 (17 yr F/U)	0.88-1.54 1.01-1.58 1.12-1.62	Age, SBP, total cholesterol, smoking, BMI
Davies et al., 2005 (Canada) [22]	Cohort 1950-95	27,464 blue-collar workers from 14 lumber mills	Fatal MI	≥ 85 dBA	1.1 (< 3 yr) 0.94 (3-9 yr) 1.1 (10-19 yr) 1.1 (20-29 yr) 0.98 (> 29 yr)	0.94-1.3 0.81-1.1 0.94-1.2 0.93-1.2 0.83-1.2	Age, calendar year

RR: relative risk, OR: odds ratio, CI: confidence interval, MI: myocardial infarction, DM: diabetes mellitus, HTN: hypertension, IHD: ischemic heart disease, BP: blood pressure, BMI: body mass index, SBP: systolic blood pressure.

the workplace and IHD [23-32]. In men, the summary point estimate was 1.19 (95% CI 1.05-1.35) with little evidence of heterogeneity [Q = 5.31, df(Q) 6, p = 0.505 on the Q test, I^2 = 0]. In women, the summary point estimate was 1.22 (95% CI 0.95-1.56) with marginal evidence of heterogeneity [Q = 15.44, df(Q) 8, p = 0.051 on the Q test, I^2 = 48.2]. Accordingly, RR of 1.19 (1.05-1.35) for male workers and 1.22 (0.95-1.56) for female workers was applied in the final analysis.

Based on the Survey of Korean Working Conditions, 19.0% of male and 11.3% of female nonsmoking workers were exposed to ETS for more than 1/4 of their working time. A nonsmoker was defined as anyone whose total amount of smoked cigarettes was less than 100 during their lifetime. Considering that the RRs of coronary artery disease due to ETS are 1.2, 1.6, and 1.7 when exposed to 0-2 hours, 3-5 hours, and more than 6 hours in a day, respectively, it may be appropriate to regard "more than 1/4 of working time (2 hour a day)" as an exposure to ETS [33].

Shift work

Table 4 summarizes studies on the association between shift work and IHD [10,34-40]. The summary point estimate was 1.17 (95% CI 1.00-1.37). We observed heterogeneity between studies [Q = 17.85, df(Q) 7, p = 0.013 on the Q test, I^2 =60.8] and found some evidence for publication bias by funnel plot. The adjusted RR was 1.12 (95% CI = 0.94-1.33) and applied to both genders in the final analysis.

According to the Survey of Korean Working Conditions, 8.6% of male and 5.4% of female workers worked a rotating schedule. The proportion of those working in two shifts, three

Table 3. Studies on ETS exposure in the workplace and cardiovascular disease among non-smokers

Study (Country)	Design	Subjects	Outcome	RR or OR	95% CI	Controlled variables
Wen et al., 2006 (China) [23]	Cohort	66,520 female workers	Fatal CVD	0.92	0.64-1.32	Age, education, occupation, family income, physical activity, BMI, intake of meat/vegetables/fruit
Pitsavos et al., 2002 (Greece) [24]	Case-control	847 patients and 1,078 controls	Nonfatal ACS	1.97	1.16-3.34	Age, gender, HTN, DM, hypercholesterolemia, family history of premature CHD, physical inactivity, diet, alcohol, education, income, BMI, depression
Rosenlund et al., 2001 (Sweden) [25]	Case-control	334 patients and 677 controls	Nonfatal MI	1.14 (men) 0.94 (women)	0.78-1.67 0.59-1.50	Age, hospital/catchment area, BMI, SES, job strain, HTN, diet, DM
McElduff et al., 1998 (Australia) [26]	Case-control	953 patients and 3,189 controls	MI or fatal CHD	1.31 (men) 0.58 (women)	0.95-1.80 0.27-1.24	Age, education, history of heart disease, BMI
Kawachi et al., 1997 (US) [27]	Cohort	32,046 female nurses	MI and fatal CHD	1.68	0.81-3.47	Age, BMI, HTN, DM, hyperlipidemia, exercise, saturated-fat intake, vitamin E intake, alcohol, use of aspirin, parental history of MI
Steenland et al., 1996 (US) [28]	Cohort	479,680 persons	Fatal CHD	1.10 (men) 1.09 (women)	0.82-1.31 0.78-1.52	Age, gender, education, heart disease, BMI, HTN, DM, aspirin/diuretic/estrogen use, alcohol, exercise
Muscat and Wynder, 1995 (US) [29]	Case-control	114 patients and 158 controls	MI	1.2 (men) 1.0 (women)	0.6-2.2 0.4-2.5	Age, ethnicity, education, hypertension, calendar year
He et al., 1994 (China) [30]	Case-control	59 female cases and 126 controls	Nonfatal CHD event	1.85	0.86-4.00	Age, history of HTN, type A personality, total and HDL cholesterol levels
Butler, 1988 (US) [31]	Cohort 1976-82	1,489 men, 3,488 women	Fatal IHD	1.02 (men) 1.85 (women)	0.61-1.70 1.13-3.02	Age
Svendsen et al., 1987 (US) [32]	Cohort 1973-82	1,245 men	MI or fatal CHD	1.4	0.8-2.5	Age, blood pressure, serum cholesterol, weight, alcohol consumption, education

RR: relative risk, OR: odds ratio, CI: confidence interval, CVD: cardiovascular disease, BMI: body mass index, ACS: acute coronary syndrome, HTN: hypertension, DM: diabetes mellitus, CHD: coronary heart disease, MI: myocardial infarction, SES: socioeconomic status.

Table 4. Studies on shift work and cardiovascular disease

Study (Country)	Design	Subjects	Outcome	Exposure	RR or OR	95% CI	Controlled variables
Yadegarfar and McNamee, 2008 (UK) [10]	Nested case-control 1950-98	Male industrial workers 635 IHD deaths and 635 controls	Fatal IHD	Various patterns of shift work ≥ 1 month	1.04	0.83-1.30 (90% CI)	Pre-employment SBP, DBP, BMI, smoking, height, social status, employment duration (restricted to workers survived ≥ 10 yr after hire)
Fujino, et al., 2006 (Japan) [34]	Cohort 1988-2003	17,649 men	Fatal IHD	Rotating or fixed night shift work	2.32	1.37-3.95	Age, smoking, alcohol, education, perceived stress, BMI, past medical history, hours of exercise/walking, job type
Karlsson and Knutsson, 2005 (Sweden) [35]	Cohort 1952-2001	5,442 men in two pulp/paper plants	Fatal IHD	Mainly rotating 3 shift	1.11	0.95-1.30	Age
Bøggild, and Knutsson, 1999 (Denmark) [36]	Cohort 1971-1993	5,249 men from 14 companies	Fatal/nonfatal IHD	Shift work or irregular work hours	0.9	0.7-1.1	Social class, sleep deviation, smoking, age, weight, height, fitness value
Knutsson et al., 1999 (Sweden) [37]	Case-control	2,006 patients and 2,642 community controls	Fatal/nonfatal AMI	Shift or night work last 5 years	1.3 (men) 1.3 (women)	1.1-1.6 0.9-1.8	Age, smoking, job strain, education, region
Tenkanen et al., 1997 (Finland) [38]	Cohort 1987-1993	1,806 men from several industries	Fatal/nonfatal IHD	Mainly continuous, slowly rotating 3-shift	1.33	0.89-1.99	Age, smoking, BMI, physical activity, alcohol, BP, lipid, job strain, restricted to blue collar
Steenland and Fine, 1996 (US) [39]	Nested case-control	Male industrial workers 163 IHD deaths and 781 controls	Fatal IHD	Night shift	0.64	0.28-1.47	Age, race, plant
Kawachi, et al., 1995 (US) [40]	Cohort 1988-1992	79,109 female nurses	Fatal/nonfatal AMI	> 1 yr of 3 nights, 1 month (rotating)	1.31	1.02-1.68	Age, smoking, BMI, alcohol, physical activity, HTN, DM, hyperlipidemia, other medical status

RR: relative risk, OR: odds ratio, CI: confidence interval, IHD: ischemic heart disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, AMI: acute myocardial infarction, BP: blood pressure, HTN: hypertension, DM: diabetes mellitus.

shifts, and an alternating day system was 50.4%, 33.7%, and 14.0%, respectively.

Job control

Results from studies on the association between job control and cardiovascular disease are summarized in Table 5 [41-50]. In men, the summary point estimate was 1.19 (95% CI 1.05-1.34) with little evidence of heterogeneity [Q = 11.87, df(Q) 7, p = 0.105 on the Q test, I^2 = 41.0]. However, funnel plot showed some evidence for publication bias and the adjusted RR was 1.15 (95% CI = 1.01-1.32). In women, the summary point estimate was 1.08 (95% CI 0.83-1.41) with little evidence of heterogeneity [Q = 5.03, df(Q) 3, p = 0.170 on the Q test, I^2 = 40.3]. Accordingly, RR of 1.15 (1.01-1.32) for male workers and 1.08(0.83-1.41) for female workers was applied in the final analysis.

In the Survey of Korean Working Conditions, 31.7% of male workers and 32.5% of female workers responded that they do not make decisions in their working order, method, and pace. Because the RRs of most studies are based on the classification by quartile, tertile, or median on the questionnaire score, this exposure measure is not in accordance with them.

Table 5. Studies on low job control and cardiovascular disease

Study (Country)	Design	Subjects	Outcome	Exposure	RR or OR	95% CI	Controlled variables
Kuper et al., 2006 (Sweden) [41]	Cohort 1991-2002	48,066 women	Fatal CHD or nonfatal MI	Lowest compared to highest (cut by tertile)	0.7 (full-time) 1.1 (part-time)	0.4-1.2 0.5-2.6	Age, SES, smoking, BMI, alcohol, diabetes, HTN, exercise
Netterstrøm et al., 2006 (Denmark) [42]	Cohort 1986-99	659 men	Fatal/nonfatal IHD	Low compared to high (cut by median)	1.1	0.9-1.3	Age, SES, marital status, social network, job demand
Hemmingsson and Lundberg, 2006 (Sweden) [43]	Cohort 1990-2003	49,323 men	Fatal/nonfatal CHD	Lowest compared to highest (cut by quartile)	0.99	0.82-1.19	Socioeconomic position of father, crowded housing in childhood, income, short stature, low education, alcohol, smoking, overweight
De Bacquer et al., 2005 (Belgium) [44]	Cohort 1994-99	13,337 men	Cornary events including fatal MI	Lowest compared to highest (cut by tertile)	0.83	0.48-1.43	Age, education, BMI, smoking, DM, SBP, total cholesterol, job title, company
Andersen et al., 2004 (Denmark) [45]	Cohort 1974-1996	16,214 employees (44% women)	Fatal/nonfatal MI	Lowest compared to highest (cut by quartile)	1.26	1.04-1.54	Cohort of investigation, age, gender, cohabitation, smoking, alcohol, exercise, BMI, SBP, cholesterol, SES
Kivimäki et al., 2002 (Finland) [46]	Cohort 1973-2001	812 employees	Cardio- and cerebrovascular mortality	Lowest compared to highest (cut by tertile)	1.42	0.72-2.82	Age, gender, occupational group, smoking, physical activity, SBP, cholesterol, BMI
Lee et al., 2002 (US) [47]	Cohort 1992-96	35,038 female nurses	Nonfatal MI and fatal CHD	Lowest compared to highest (cut by tertile)	0.97	0.65-1.45	Age, F/U period, smoking, alcohol, BMI, history of HTN, DM, hypercholesterolemia, diet, physical activity, parental history of MI (< 60 years), (husband's) education, marital status
Steenland et al., 1997 (US) [48]	Cohort 1971-87	3,575 men	Fatal/nonfatal heart disease	Lowest compared to highest (cut by quartile)	1.41	1.07-1.85	Age, BP, education, BMI, cholesterol, smoking, DM
Johnson et al., 1996 (Sweden) [49]	Nested case-control	Male workers 521 CVD deaths and 2422 controls	Fatal CVD	Lower three groups compared to highest (cut by quartile)	1.83	1.19-2.82	Age, year last worked, survey year, smoking, exercise, education, social class, nationality
Alterman et al., 1994 (US) [50]	Cohort 1957-83	1,683 men	Fatal/nonfatal IHD	Decision lattitude (per 20 point in scale, score ranged 33-92)	1.18	0.97-1.43	Age, SBP, cholesterol, smoking, alcohol, family history of CVD, education, occupational class

RR: relative risk, OR: odds ratio, CI: confidence interval, CHD: coronary heart disease, SES: socioeconomic status, BMI: body mass index, HTN: hypertension, IHD: ischemic heart disease, MI: myocardial infarction, DM: diabetes mellitus, SBP: systolic blood pressure, F/U: follow up, BP: blood pressure, CVD: cardiovascular disease.

Table 6. Attributable fraction for each occupational risk factor and estimates of IHD mortality in Korea (2006)

Risk factor	Exposure (%)		Summary estimate of RR	Attributable fraction (%)		Estimates of IHD mortality	
	Male	Female		Male	Female	Male	Female
Noise	8.8	4.7	1.06 (0.95-1.18)	0.53 (-0.44-1.56)	0.28 (-0.24-0.84)	20 (-17-59)	4 (-3-10)
ETS (nonsmoker)	19.0	11.3	1.19 (1.05-1.35, men) 1.22 (0.95-1.56, women)	3.48 (0.94-6.23)	2.43 (-0.57-5.95)	133 (36-237)	30 (-7-74)
Shift work	8.6	5.4	1.12 (0.94 -1.33)	1.02 (-0.52-2.76)	0.64 (-0.33-1.75)	39 (-20-105)	8 (-4-22)
Low job control	31.7	32.5	1.15 (1.01-1.32, men) 1.08 (0.83-1.41, women)	4.54 (0.32-9.21)	2.53 (-5.85-11.76)	173 (12-350)	32 (-73-147)
Combined				9.29 (0.30-18.51)	5.78 (-7.05-19.15)	353 (12-704)	72 (-88-239)

RR: relative risk, IHD: ischemic heart disease, ETS: environmental tobacco smoke.
Total numbers of IHD mortality in the age of 15-69 years: Male, 3,804; Female, 1,246.

However, there is little difference between our exposure prevalence and the proportion of high risk groups in previous studies, considering that many studies have assessed the RR of 33% (tertile) high risk group. On the contrary, it is preferable, as it suggested the actual proportion of workers who felt insufficient job control.

Estimation of AF and mortality

AFs of each considered risk factor (noise, ETS, shift work, low job control) and combined AFs were calculated using prevalence of exposure and estimated RR (Table 6). The combined AFs of those factors in IHD were estimated to be 9.29% (0.3-18.51%) in men and 5.78% (-7.05-19.15%) in women. Based on these fractions, the number of occupational IHD deaths from the age of 15 to 69 years in 2006 was calculated to be 353 (12-704) for men and 72 (-88-239) for women.

Discussion

Studies estimating mortality from occupation-related disease have been conducted mainly in US and European countries. These studies were based on accumulated evidence, including scientifically-established RR and institutionally-confirmed exposure data. Recent studies have shown estimates of magnitude for occupation-relatedness, and those estimates have been applied in several countries [2,4]. However, distribution and the effect of occupational factors may vary, as every country differs in race and culture [51]. As South Korea consists of people of the Asian race and has a special occupational climate, there would be different environment [52]. Therefore, we have tried to estimate the magnitude of occupationally-related IHD mortality that reflects actual conditions in South Korea. Although we inevitably adopted studies from other countries to summarize RRs in most estimations of AF, we made use of the best domestic data available. Exposure data was based on a Korean survey, and each investigational method should be in accord with adopted studies suggesting RR. In addition, adopted foreign studies should be consistent with results from Korean studies.

Estimation of the accurate magnitude of occupationally-related IHD mortality is hard work, because occupational risk factors are not obviously defined, and their actual effects may be much smaller than in non-occupational factors. Furthermore, results from studies conducted with workers are prone to be distorted by a healthy worker effect. Thus, this study is accompanied with many assumptions and limitations in nature. For that matter, we took a careful approach in estimation by applying interval estimates of RR rather than point estimates.

The estimated AFs in 2006 working conditions, 9.29% (0.3-18.51%) in men and 5.78% (-7.05-19.15%) in women, were relatively lower than those of previous studies: 6.3-18.0% [2]; 16.9% [4]. This is not by lower prevalence of exposure, but by lower estimates of RRs for each risk factor resulting from meta-analysis. Previous studies applied RRs relied on relatively older and few studies that tended to produce positive results without adequate adjustment [2,4]. In contrast, we selected recent studies that conducted sufficient adjustment (e.g., SES variable in shift work and low job control). Moreover, adjustments for publication bias were performed in meta-analysis, which usually leads estimates to be lower. These efforts to obtain reliable estimates of RRs would become strong points in our study rather than the sources of underestimation.

Mechanisms of each occupational factor on cardiovascular disease

Theoretical mechanisms of the effect of noise on cardiovascu-

lar disease have been suggested as stress responses by direct and indirect pathway and subsequent hemodynamic change [53-55]. Several studies have shown an association between noise exposure and hypertension or IHD. According to recent epidemiologic studies, noise exposure above 85 dBA is consistent with a 2 mmHg increase in diastolic blood pressure [53,54], and the RR estimate of coronary heart disease is known as 1.11 for every 2 mmHg increase in diastolic blood pressure in US men [55].

ETS, as well as direct smoking, is a known risk factor for IHD. Suggested mechanisms are coagulative tendency by platelet aggregation, increase in blood pressure, direct damage to arterial endothelium, decrease in oxygen supply from atherosclerosis, and increased oxygen demand by the heart, and so on [56,57].

The core issue of shift work and health problems has been the role of disturbed circardian rhythms, although there is no definite evidence of increased risk of cardiovascular disease. Suggested mechanisms are currently indirect, such as metabolic problems, arrhythmogeneity, and inflammatory response [58-60]. It has also been suggested that shift work could be acting as a proxy for other occupational factors related to heart disease, including physical factors (noise, heat, dust, ETS, standing, and monotonous repetitive tasks), and psychosocial factors (demands and control dimensions, social support, conflicts, and job insecurity) [61].

The mechanisms of cardiovascular disease due to occupational stress have been accounted for by direct pathway with the autonomic nervous system or neuroendocrine system and indirect pathway via changes in health-related behavior or psychosocial effects. High labor intensity and low job control has been shown in an experimental study to increase blood pressure by releasing catecholamine and cortisol [62]. Repetitive increases in blood pressure would result in ventricular hypertrophy, and these structural changes increase risk of IHD. As depression and anxiety is known to lead to coronary artery disease and cardiac death, negative feelings caused by occupational stress could be a component of the mechanism [11,63].

Sources of inaccurate estimation

As this study depended on several assumptions, and based on the RRs or exposure prevalence that are less likely to be measured accurately, there might be some source of under or overestimation of AF. This is especially true for components that lower accuracy and make direction unpredictable in this study, such as extrapolation of RR from foreign studies and limitation of exposure data. The former would be originated from the difference in characteristics and effects of each occupational factor by racial and cultural differences (e.g., job stress). The latter is in that exposure data was not obtained by quantified assessment but by a one-time survey based on a subjective questionnaire, with lower accuracy that does not allow prediction of continuity and change of exposure.

Suggested RRs for each study might be internally over or underestimated due to inadequate adjustments for confounders. In particular, the causal intensity of occupational factors for IHD is usually lower than in traditional occupational diseases, and it should investigate the effects of SES, individual risk factors, and their interaction. Under adjustment for confounders will yield higher RR, and inversely, over adjustment, even for intermediate variables (e.g., metabolic changes in shift work) will be an underestimation source [64]. To avoid overestimation, we made a conservative approach with an effect that ranged from 0 to a reliable level for factors still in controversy.

Application of some studies using incidence data is another source of under or overestimation. According to previous studies, the RRs of IHD for shift work were 1.2 for nonfatal IHD and 1.4 for fatal IHD [40], and the RRs by carbon disulfide were 1.4 for eletrocardiographic abnormality, 2.2 for angina, 3.7 for nonfatal MI, and 4.8 for fatal MI [65]. This suggests the possibility that using incidence data could underestimate the risk more than using mortality data. Moreover, socioeconomic factors affect those in disagreement. As the higher class tends to receive proper and frequent care, differences occur in life prolongation for the same IHD. The Whitehall Study has revealed a reverse relation between SES and mortality from IHD [66].

Since results from occupational epidemiology tend to be studied in high exposure groups, estimated RRs may be relatively higher. Therefore, overestimation could occur when we apply those RRs to the whole working population. However, it is expected to be insignificant because risk factors included in this study have been studied in a quantified manner, and we applied those values to our working conditions appropriately.

Another source of overestimation is the assumption that each occupation exposure is distributed independently, which is actually impossible. Because the close association is especially expected in shift work and low job control, it may be reliable to apply them in one factor, as in Nurminen's study [4]. Shift workers tend to be stressed from heavy workload and have lower educational levels and job control [67,68].

Exclusion of other occupational risk factors, such as long-hour work (annually about 2,500 hours, global top and most common factors for work-related cardiovascular disease approved in Korea), physical activity, and other physicochemical factors was a source of underestimation. We excluded long-hour work as an independent factor because there are few

studies suggesting RR values and currently applicable RR (1.9) showed a confidence interval that was too wide [69]. Since 30.4% of male workers and 27.8% of female workers work more than 60 hours a week, except for meal and commuting times [8], if it were included despite the uncertainty, estimates of AF would be 28.55% and 25.18% respectively in this study. Also, there is a possibility of overestimation of AF in relation to shift work and job stress.

We assumed that affected workers would be aged ≤ 69 years (4 years added on economically active age) in this study, because the effect of occupational factors on IHD is thought to be short-term [2,13,14]. However, long-term effect is also possible, and workers above 70 years are common these days. In addition, many IHD cases that occurred before 69 years, and death occurred after 70 years, since survival time from incident IHD may be prolonged by several years. These could underestimate the magnitude of total mortality.

Further consideration of socioeconomic factors

SES is one of the main confounders for cardiovascular disease and also closely related to occupational factors, including shift work and work stress [10,34,41,45,70]. Therefore, meta-analysis was done with studies adjusting for or stratifying by SES or its indicators, such as education level or occupational group. Nevertheless, this adjustment may still be incomplete and individual studies need to be interpreted in terms of SES.

In addition, the problem of non-regular workers has been an important occupational health issue in Korea. According to the survey of Korea National Statistical Office, 35.2% of total employees were non-regular workers in 2008 [71]. Most of them are contingent workers who are placed in unstable employment, and have a lower rate of social insurance (half of regular workers), and receive discriminated wages (70% of regular workers). This is a peculiar feature of Korea, different from other OECD countries, in which part-time workers are the majority of non-regular workers. It would become a kind of occupational stress when we simply regard it as job insecurity, which might be a factor for IHD [72]. However, it is appropriate to be regarded as a socioeconomic factor since the effect of occupational dissatisfaction without economic problems will be much smaller than that of economic difficulty.

In conclusions, we estimated occupational IHD mortality of South Korea with updated data and more relevant evidence. Despite the several assumptions and limitations, the study results suggest that occupational factors play a role in IHD mortality. Given conservative approaches and missing results for potential occupational risk factors such as long-working hours and job insecurity, our PAF estimates are most likely underestimated. This method has a big potential to be applied in other countries where working conditions survey and mortality registries are available. For more accurate estimates, future research based on more precise design and reliable evidence is required.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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