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Original article

Association with Combined Occupational Hazards Exposure and Risk of Metabolic Syndrome: A Workers' Health Examination Cohort 2012–2021

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ABSTRACT

Background: This study aimed to evaluate the association between exposure to occupational hazards and the metabolic syndrome. A secondary objective was to analyze the additive and multiplicative effects of exposure to risk factors.

Methods: This retrospective cohort was based on 31,615 health examinees at the Pusan National University Yangsan Hospital in Republic of Korea from 2012–2021. Demographic and behavior-related risk factors were treated as confounding factors, whereas three physical factors, 19 organic solvents and aerosols, and 13 metals and dust were considered occupational risk factors. Time-dependent Cox regression analysis was used to calculate hazard ratios.

Results: The risk of metabolic syndrome was significantly higher in night shift workers (hazard ratio = 1.45: 95% confidence interval = 1.36–1.54) and workers who were exposed to noise (1.15:1.07–1.24). Exposure to some other risk factors was also significantly associated with a higher risk of metabolic syndrome. They were dimethylformamide, acetonitrile, trichloroethylene, xylene, styrene, toluene, dichloromethane, copper, antimony, lead, copper, iron, welding fume, and manganese. Among the 28 significant pairs, 19 exhibited both positive additive and multiplicative effects.

Conclusions: Exposure to single or combined occupational risk factors may increase the risk of developing metabolic syndrome. Working conditions should be monitored and improved to reduce exposure to occupational hazards and prevent the development of the metabolic syndrome.

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1. Introduction

Metabolic syndrome, a condition characterized by hypertension, insulin intolerance, central obesity, and dyslipidemia, is a significant public health concern with a high global prevalence. Considering that metabolic syndrome has prevalence three times higher than that of diabetes mellitus (DM), around 1 billion people worldwide might be afflicted with it [1]. In the US, the overall prevalence of metabolic syndrome was 37.3% from 2011 to 2018 [2], while among Korean adults, the prevalence of metabolic syndrome ranged from 19.4% to 22.9% from 2007 to 2018 [3]. Additionally, the prevalence of metabolic syndrome is high among workers in the US (20.6% overall, 20.2% for males, and 21.4% for females) [4], and comparable rates were reported among Korean workers (21.8%

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overall, 25.5% for males, and 15.9% for females) [5]. Metabolic syndrome is known to increase the risk of cardio-cerebrovascular diseases (CVDs) by 2.35 times and the corresponding mortality by 2.4 times [6]. According to a report on occupational diseases in The Republic of Korea in 2020, work-related CVDs accounted for 4.8% (704 of 14,816) of adverse events, while 39.2% of occupational fatalities were due to CVD (463 of 1,180) [7].

Occupational exposures, such as working conditions, organic solvents, and heavy metals, namely noise [8], night-shift work [9], mercury [10,11], and metalworking fluids [12], have been reported as risk factors for metabolic syndrome. Because most previous studies on occupational risk factors for metabolic syndrome were cross-sectional, dealing with a few risks [13–15], elucidating the causal relationship between metabolic syndrome and comprehensive occupational risk factors is difficult. Additionally, most occupational exposures involve simultaneous exposure to two or more risk factors. To the best of our knowledge, no studies have investigated the relationship between multiple exposures to occupational hazards and the metabolic syndrome.

In The Republic of Korea, workers are obligated to participate in the workers' health examination, comprising a workers' general health examination (WGHE) and a workers' special health examination (WSHE), in accordance with the Industrial Safety and Health Act as part of efforts to protect workers' health [16]. The WSHE is performed for workers who are regularly exposed to some of the 181 hazardous substances and physical environments specified in the act, whereas the WGHE is administered to all regular workers regardless of exposure status.

This study aimed to evaluate the relationship between exposure to occupational risk factors and the metabolic syndrome. The secondary aim was to analyze the additive and multiplicative effects of being exposed to two risk factors simultaneously.

2. Materials and methods

2.1. Study design and participants

A retrospective cohort was built based on all health examinees who underwent the WGHE and WSHE at the Pusan National University Yangsan Hospital (PNUYH) in The Republic of Korea from 2012 to 2021. Fig. 1 shows the screening process for the examinees. During this period, 76,665 people were examined, excluding examinees who underwent student health checkups. First, 11,833 individuals were excluded because they had been diagnosed with metabolic syndrome at the first health examination. Next, 33,217 individuals were excluded due to missing data for the diagnostic components of metabolic syndrome, health behaviors such as smoking status, and a lack of follow-up due to a single examination. Thus, among the 76,665 examinees in the PNUYH health examination database, 31,615 fulfilled the eligibility criteria. Finally, 6,666 participants (21.1%) were diagnosed with metabolic syndrome at the end of the follow-up period. We used 124,609 examination results from 31,615 examinees for the statistical analysis. This study was an analytical study using existing hospital data and was exempt from deliberation by the Institutional Review Board of PNUYH (IRB No. 04-2019-030, 05-2022-069).

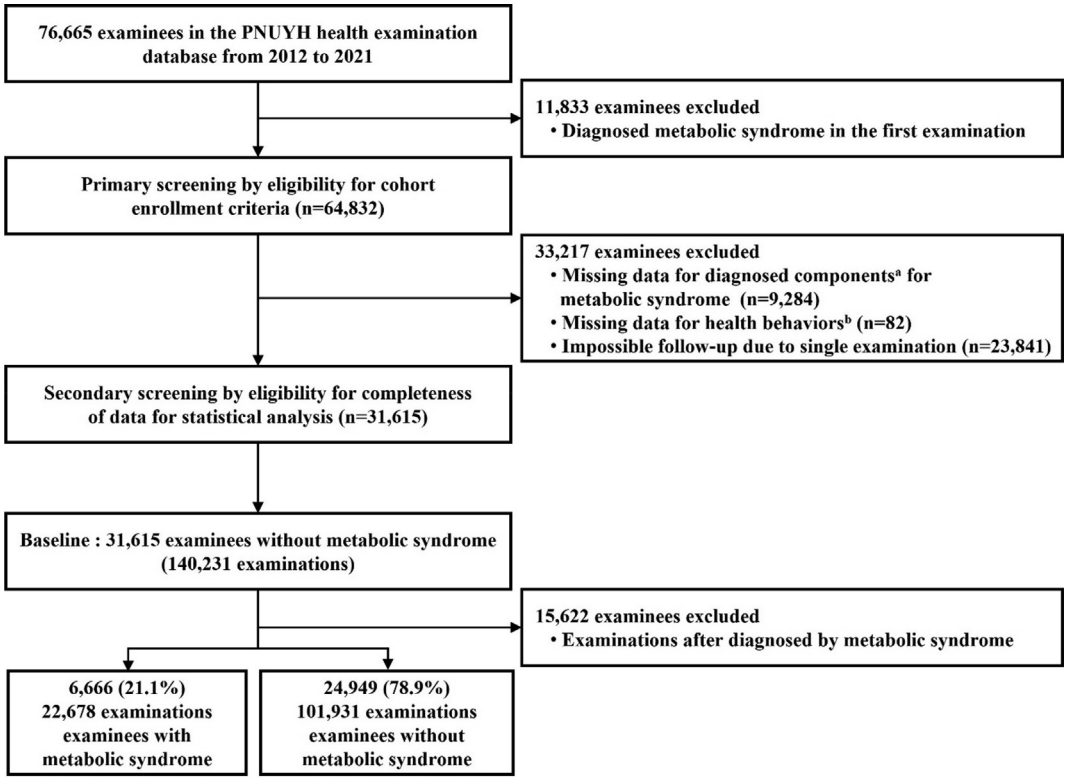

Fig. 1. Flow chart of cohort screening of study. (**a**) Diagnostic components of metabolic syndrome were "a waist circumference of ≥90 cm for men or ≥85 cm for women", "serum triglyceride concentration of ≥150 mg/dL "serum HDL-cholesterol concentration of <40 mg/dL for men, <50 mg/dL for women" "systolic blood pressure (SBP) of ≥130 mmHg or diastolic blood pressure of ≥85 mmHg or under hypertension medication", and "fasting serum glucose concentration of ≥100 mg/dL or under diabetes mellitus medication". (**b**) Data for behaviors included information about smoking status, alcohol intake, exercise frequency, and family history (stroke, heart disease, hypertension, and diabetes mellitus).

2.2. Definition of the metabolic syndrome

Metabolic syndrome was defined as the presence of any three or more of the following five components based on the criteria of the modified US National Cholesterol Education Programme Adult Treatment Panel III [17]: (1) abdominal obesity, defined as a waist circumference ≥90 cm or ≥ 85 cm for males and females, respectively (following Korean-specific cutoffs defined by the Korean Society for the Study of Obesity [18]; (2) hypertriglyceridemia, defined as a serum triglyceride concentration ≥150 mg/dL; (3) low high-density lipoprotein (HDL) cholesterol level, defined as a serum HDL cholesterol concentration <40 mg/dL and <50 mg/dL for males and females, respectively; (4) high blood pressure, defined as a systolic blood pressure of ≥130 mmHg or diastolic blood pressure of ≥85 mmHg, or treatment with antihypertensive agents; (5) high fasting glucose level, defined as a fasting serum glucose level ≥100 mg/dL or the current use of antidiabetic medication.

2.3. Behavior and occupational exposure variables

During the health examination, participants provided information about health behaviors, including smoking status, alcohol intake, exercise frequency, and family history (stroke, heart disease, hypertension, and DM) via a questionnaire. We regarded the following metabolic syndrome risk factors as confounders for the hazard ratio (HR) of exposure to occupational hazards: age, sex (male), and behavioral factors, including alcohol consumption, low exercise frequency [19], and family history of CVD, hypertension, and DM [20,21]. Smoking status, alcohol intake, and exercise frequency were categorized according to lifestyle.

We identified the occupational risk factors to which all cohort participants were exposed using the WSHE data. Occupational exposure variables varied with time. The variables were recorded as either exposure or non-exposure dichotomous variables. Exposure intensity was not linked to the measurement data for each worker.

1) Therefore, the presence or absence of occupational risk factor exposure was identified for each worker. All risk factors to which each worker was exposed during the cohort follow-up period were recorded.
2) Approximately 130 exposure substances were identified; among them, 35 substances for which the sum of the number of exposures in all examinees was >100 were analyzed (e.g., if a worker was exposed to the same substance three times during the cohort follow-up period, three exposures were recorded).

2.4. Cohort follow-up

Observations were terminated when diseases occurred after enrollment. The presence or absence of exposure was considered from baseline to the end of follow-up. Additionally, this was a limited-period cohort, and data on exposure prior to 2012 were unknown. Therefore, we did not consider an incubation period because defining exposure by considering the incubation period itself can lead to bias.

2.5. Statistical analysis

Time-dependent Cox regression analysis was used to calculate HRs. We established an unadjusted model (simple regression) that did not include confounders (sex, age, smoking status, alcohol intake, exercise frequency, and family history). Then, we adjusted for confounders in the model (multiple regression). To evaluate the effect of exposure to two different risk factors at the same time, a new variable was created that consisted of "not exposed", "exposed to only one hazardous substance (exposed to hazard A)", "exposed to only the other (exposed to hazard B)", and "doubly exposed (exposed to hazard A and B)". However, it should be noted that most workers were exposed to complex hazards in their working environments. Therefore, exposure to hazard A is defined as exposure to substances that contain hazard A but do not contain hazard B. Conversely, exposure to hazard B is defined as exposure to substances that contain hazard B but do not contain hazard A. "Doubly exposed" is defined as exposure to substances that include both hazards (A and B). We chose occupational exposure variables when the multiple regression was significant. The indexes for measuring additive and multiplicative effects are as follows [22]: the delta method was used to calculate the confidence interval (CI) for each interaction measure, as described by Hosmer and Lemeshow [23].

λ_{11}, λ_{10}, λ_{01}, and λ_{00} are the hazard rates in the Cox regression given that individuals have been exposed to two substances, one substance, the other substance, or neither.

$$\text{Hazard ratio}_{11}\ (HR_{11}) = \lambda_{11}/\lambda_{00}$$

$$\text{Hazard ratio}_{10}\ (HR_{10}) = \lambda_{10}/\lambda_{00}$$

$$\text{Hazard ratio}_{01}\ (HR_{01}) = \lambda_{01}/\lambda_{00}$$

- Additive effect: Relative excess risk due to interaction (RERI) = HR_{11}-HR_{10}-HR_{01}+1
- Multiplicative effect: Multiplicative Interaction (MI) = $HR_{11}/(HR_{01} \times HR_{10})$

If the RERI >0, we evaluated whether the two substances had an additive effect. If MI > 1, it was regarded as having a multiplicative effect. We tested the effect of double exposure on risks in more than 100 cases.

All analyses were performed using R software (version 4.0; R Project for Statistical Computing, Vienna, Austria). R-packages "survival", "epiR", "data.table", and "ggplot2" were utilized for survival analysis, interaction analysis, preprocessing, and visualization, respectively.

3. Results

3.1. Incidence of metabolic syndrome according to participant characteristics

The risk of metabolic syndrome according to the demographic and health behavior-related characteristics of the participants is shown in Table 1. In multiple time-dependent Cox regression analyses, after adjusting for all confounders by gender, males had a significantly higher risk of metabolic syndrome (HR = 2.46 [95% CI: 2.28−2.66]) than females. The risk of metabolic syndrome increased with increasing age at the time of enrollment (Ref: <30, 30−50: HR = 1.72 [95% CI: 1.61−1.84], >50: HR = 1.95 [95% CI: 1.81−2.11]). The risk of metabolic syndrome was also significantly higher among current smokers (HR = 1.36 [95% CI: 1.25−1.43]) and people who had an alcohol intake of eight drinks per week (HR = 1.22 [95% CI: 1.15−1.30]) than among never smokers and non-drinkers, respectively. According to family history, participants with hypertension (HR = 1.25 [95% CI: 1.18−1.33]) and diabetes (HR = 1.17 [95% CI: 1.10−1.25]) had a significantly higher risk of developing metabolic syndrome. However, there were no significant risks associated with having a family history of stroke or heart disease.

Table 1
Time-dependent Cox regression analysis of metabolic syndrome according to demographic and behavior-related variables at the time of entry (n = 31,615)

Variables			N (%)	Simple	Multiple*
				HR_S (95% CI)	HR_S (95% CI)
Gender		Female	12,607 (39.88)	Ref	Ref
		Male	19,008 (60.12)	3.24 (3.05-3.45)	2.46 (2.28-2.66)
Age (years)		<30	10,645 (33.67)	Ref	Ref
		30∼50	13,447 (42.53)	2.27 (2.12-2.42)	1.72 (1.61-1.84)
		50≤	7,523 (23.80)	2.09 (1.94-2.25)	1.95 (1.81-2.11)
Smoke		Never	17,830 (56.40)	Ref	Ref
		Former	5,107 (16.15)	2.21 (2.08-2.36)	1.10 (1.02-1.19)
		Current	8,678 (27.45)	2.48 (2.35-2.62)	1.36 (1.25-1.43)
Alcohol intake (drinks/week)†		No drink	14,893 (47.11)	Ref	Ref
		<8	8,037 (25.42)	1.07 (1.00-1.13)	0.99 (0.93-1.06)
		≥8	8,685 (27.47)	1.80 (1.70-1.90)	1.22 (1.15-1.30)
Exercise (exercise/week)‡		≥5	6,930 (21.9)	Ref	Ref
		≤4	12,703 (40.2)	0.93 (0.86-0.99)	0.96 (0.90-1.02)
		No Exercise	11,982 (37.9)	0.89 (0.84-0.95)	0.98 (0.92-1.05)
Family history	Stroke	No	28,728 (90.87)	Ref	Ref
		Yes	2,887 (9.13)	1.18 (1.10-1.28)	1.03 (0.95-1.11)
	Heart Disease	No	28,993 (91.71)	Ref	Ref
		Yes	2,622 (8.29)	1.12 (1.03-1.21)	1.01 (0.93-1.09)
	Hypertension	No	24,498 (77.49)	Ref	Ref
		Yes	7,117 (22.51)	1.12 (1.06-1.18)	1.25 (1.18-1.33)
	Diabetes	No	26,643 (84.27)	Ref	Ref
		Yes	4,972 (15.73)	1.18 (1.11-1.26)	1.17 (1.10-1.25)

Abbreviations: HR, Hazard ratio; CI, confidence interval.
* adjustment for all variables (sex, age, smoking, alcohol intake, exercise frequency, and family history).
† 1 drink = 14 g alcohol.
‡ Combined number of medium- and high-strength exercises.

3.2. Occupational exposures

The results of the multiple time-dependent Cox regression analysis of occupational exposure are shown in Table 2. Among physical agents, after adjusting for all confounders (sex, age, smoking, alcohol intake, exercise frequency, and family history), the risk of metabolic syndrome was significantly higher for night-shift workers (HR = 1.45, [95% CI: 1.36−1.54]) and workers exposed to noise (HR = 1.15, [95% CI: 1.07−1.24]). Among organic solvents and aerosols, after adjusting for all confounders, workers had a

Table 2
Time-dependent Cox regression analysis of metabolic syndrome according to occupational exposure

Category	Risk factor	N (%)	UnAdjusted	Adjusted*
			HR_S (95% CI)	HR_S (95% CI)
Physical	Night shift work	18,763 (20.18)	1.30 (1.22-1.38)	1.45 (1.36-1.54)
	Noise	9022 (9.70)	1.61 (1.50-1.73)	1.15 (1.07-1.24)
	Radiation	639 (0.69)	0.55 (0.34-0.90)	0.94 (0.58-1.51)
	Toluene	1182 (1.27)	1.80 (1.50-2.16)	1.42 (1.18-1.71)
Organic solvents, Aerosols	Xylene	492 (0.53)	2.38 (1.85-3.06)	1.67 (1.29-2.15)
	Styrene	184 (0.20)	2.32 (1.58-3.41)	1.52 (1.03-2.24)
	Phenol	296 (0.32)	1.30 (0.81-2.09)	1.23 (0.77-1.98)
	Dichloromethane	643 (0.69)	1.96 (1.55-2.47)	1.41 (1.11-1.78)
	TCM(Chloroform)	158 (0.17)	0.31 (0.08-1.22)	0.51 (0.13-2.05)
	Trichloroethylene	316 (0.34)	2.55 (1.90-3.41)	1.86 (1.38-2.51)
	2-Butoxyethanol	604 (0.65)	1.39 (1.04-1.87)	1.23 (0.92-1.66)
	Formaldehyde	128 (0.14)	1.39 (0.70-2.75)	1.16 (0.59-2.28)
	Acetone	353 (0.38)	1.32 (0.89-1.96)	1.03 (0.69-1.53)
	Methyl ethyl ketone	369 (0.40)	1.20 (0.80-1.80)	0.88 (0.59-1.32)
	Methyl isobutyl ketone	489 (0.53)	1.73 (1.31-2.30)	1.20 (0.90-1.60)
	Dimethylformamide	217 (0.23)	3.03 (1.84-4.97)	2.10 (1.26-3.49)
	Methylene Bisphenyl Diisocyanate	170 (0.18)	0.91 (0.47-1.76)	0.70 (0.36-1.35)
	Acetonitrile	159 (0.17)	1.72 (0.99-2.99)	2.00 (1.14-3.50)
	Oil mist	494 (0.53)	1.71 (1.30-2.25)	1.30 (0.98-1.72)
	HCl	130 (0.14)	0.58 (0.21-1.57)	0.50 (0.18-1.36)
	Sulfuric acid	122 (0.13)	0.84 (0.37-1.91)	0.70 (0.31-1.58)
	Nitrogen dioxide	118 (0.13)	1.65 (0.87-3.13)	1.62 (0.82-3.21)
	Fe	1365 (1.47)	1.90 (1.61-2.23)	1.28 (1.08-1.50)
Metals, Dust	Mn	839 (0.90)	1.85 (1.50-2.29)	1.24 (1.01-1.53)
	Al	789 (0.85)	1.57 (1.24-1.99)	1.12 (0.88-1.42)
	Cr	573 (0.62)	1.45 (1.08-1.94)	1.03 (0.76-1.38)
	Ni	457 (0.49)	1.60 (1.17-2.18)	1.14 (0.83-1.56)
	Pb	445 (0.48)	1.76 (1.30-2.38)	1.38 (1.02-1.86)
	Cu	439 (0.47)	2.81 (2.21-3.56)	1.87 (1.47-2.37)
	Zn	343 (0.37)	0.84 (0.52-1.34)	0.60 (0.37-0.96)
	Sn	165 (0.18)	1.45 (0.86-2.43)	1.46 (0.88-2.41)
	Sb	140 (0.15)	2.58 (1.61-4.14)	1.83 (1.08-3.10)
	Welding fume	607 (0.65)	1.91 (1.50-2.43)	1.27 (1.00-1.62)
	Mineral dust	684 (0.74)	1.63 (1.27-2.10)	1.14 (0.89-1.47)
	Fibrous glass dust	141 (0.15)	1.89 (1.08-3.31)	1.58 (0.91-2.76)

* adjustment with all variables in Table 1 (sex, age, smoking, alcohol intake, exercise frequency, and family history).

higher risk of developing metabolic syndrome if they were exposed to dimethylformamide (DMF) (HR = 2.10, [95% CI: 1.26–3.49]), acetonitrile (HR = 2.00, [95% CI: 1.14–3.50]), trichloroethylene (TCE) (HR = 1.86, [95% CI: 1.38–2.51]), xylene (HR = 1.67, [95% CI: 1.29–2.15]), styrene (HR = 1.52, [95% CI: 1.03–2.24]), toluene (HR = 1.42, [95% CI: 1.18–1.71]), and dichloromethane (HR = 1.41, [95% CI: 1.11–1.78]). In terms of exposure to metals and dust, after adjusting for all confounders, workers had a higher risk of developing metabolic syndrome if they were exposed to copper (HR = 1.87, [95% CI: 1.47–2.37]), antimony (HR = 1.83, [95% CI: 1.08–3.10]), lead (HR = 1.38, [95% CI: 1.02–1.86]), iron (HR = 1.28, [95% CI: 1.08–1.50]), and manganese (HR = 1.24, [95% CI: 1.01–1.53]).

3.3. Combined exposure of two occupational exposures

Among the 14 significant occupational risk factors included in the multiple regression, 40 pairs wherein each risk had more than 100 cases are shown in Table 3.

There were 28 pairs of significant combined risk factors: night shift in combination with noise (HR = 1.66, n = 2499), toluene (HR = 2.43, n = 157), xylene (HR = 2.14, n = 92), TCE (HR = 17.19, n = 3), DMF (HR = 10.71, n = 7), manganese (HR = 1.73, n = 126), lead (HR = 3.33, n = 56), and copper (HR = 1.76, n = 140); noise in combination with toluene (HR = 1.65, n = 154), xylene (HR = 1.85, n = 85), TCE (HR = 2.59, n = 27), iron (HR = 1.42, n = 514), and copper (HR = 1.89, n = 127); toluene in combination with xylene (HR = 1.66, n = 380), styrene (HR = 1.91, n = 92), and copper (HR = 1.83, n = 120); xylene in combination with styrene (HR = 2.05, n = 78), iron (HR = 3.00, n = 32), and copper (HR = 1.86, n = 130); styrene in combination with lead (HR = 3.27, n = 20), copper (HR = 2.61, n = 54), and antimony (HR = 13.42, n = 2); TCE in combination with copper (HR = 9.59, n = 7); iron combined with manganese (HR = 1.28, n = 760), and copper (HR = 2.44, n = 37); manganese combined with copper (HR = 2.44, n = 30), and antimony (HR = 11.53, n = 5); and lead combined with copper (HR = 2.27, n = 45). Although there were five pairs with HRs higher than 9 (night-shift work and TCE; night-shift work and DMF; styrene and antimony; TCE and copper; manganese and antimony), it is difficult to interpret the clinical significance of these results because the pairs had fewer than 10 double-exposed cases and the 95% CIs were too wide.

Among the 28 significant pairs, 19 were both positive additive (RERI >0) and multiplicative (MI > 1): night-shift work with noise, toluene, TCE, DMF, and Pb; noise with toluene, TCE, and Fe; toluene with styrene; xylene with styrene and iron; styrene with lead, copper, and antimony; TCE with copper; iron with manganese and copper; and manganese with copper and antimony. None of the 19 pairs with positive additive and multiplicative effects had significant additive effects (RERI), while two pairs had significant multiplicative effects, namely, night-shift work with lead and manganese with antimony.

4. Discussion

We established a health examination cohort conducted at a university hospital from 2012–2021 and found an association between exposure to occupational hazards and the occurrence of metabolic syndrome through the analysis of 124,609 records of 31,615 examinees. Exposure to occupational hazards was divided into three major categories: physical factors, organic solvents and aerosols, and metals and dust.

Exposure to physical factors such as night-shift work and noise increased the risk of metabolic syndrome. In our study, the risk of metabolic syndrome among night-shift workers was significant (HR = 1.45) and similar to that reported in a previous meta-analysis that included 13 studies [24]. The pooled relative risk (RR) of metabolic syndrome for night-shift work was 1.57 (95% CI: 1.24–1.98) and 1.77 (95% CI: 1.32–2.36) for longer durations with a dose-response relationship [24]. Additionally, in a systematic review and meta-analysis published in 2021, the pooled odds ratio of metabolic syndrome among night-shift versus day workers was estimated at 1.11 (95% CI: 1.06–1.17) for the adjusted model [25]. In that study, obesity (RR = 1.66), high blood sugar (RR = 1.30), and high blood pressure (RR = 1.30) had significant positive associations, but high triglyceride (RR = 1.11) and low HDL (RR = 1.15) levels were not significantly associated with obesity. Night-shift work causing circadian misalignment affects the homeostasis of blood glucose and lipids, and night-shift workers have a higher frequency of smoking, drinking, and high carbohydrate intake, which leads to increased triglyceride levels [26]. Similar to our study, previous studies on noise and metabolic syndrome showed significantly increased HRs among moderate noise (HR = 1.13) and higher noise (HR = 1.24) workers [8] and a 17% increase in HR with an 11.6 dB increase in noise (HR = 1.17) [27]. To date, the mechanisms underlying the chronic effects of noise on the metabolic system are not fully understood, and several possible pathways may have long-term metabolic consequences [28].

In the present study, monocyclic aromatic hydrocarbons (MAHs), such as styrene, toluene, and xylene, are associated with an increased risk of metabolic syndrome. In a previous study, blood sugar and triglycerides were significantly higher than the cumulative organic solvent exposure for 5 and 10 years [29]. Another study showed that total cholesterol, fasting blood glucose, fasting insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and tumor necrosis factor-α (TNF-α) were significantly higher in the MAH-exposed group than in the control group, and the total anti-oxidative capacity was significantly lower in the exposed group. Additionally, by analyzing the correlation between MAH exposure and insulin resistance index, it was found that there was a significant correlation with fasting blood glucose [30]. These results suggest that exposure to organic solvents, such as MAH, can increase the risk of metabolic syndrome through oxidative stress, resulting in insulin resistance. However, the correlation between exposure to organic solvents and the risk of metabolic syndrome remains unclear due to a lack of reliable evidence.

For metals and dust factors, heavy metals increased the risk of metabolic syndrome. In a meta-analysis of the associations between metabolic syndrome and four heavy metals (arsenic, cadmium, lead, and mercury), participants with metabolic syndrome had significantly higher levels of heavy metal exposure [31]. This synergistic effect is thought to have occurred because heavy metals may also induce excessive oxidative stress [32]. Another study showed that copper and zinc in urine were significantly related to metabolic syndrome onset in the general Chinese population, which might be caused by a systemic inflammatory response to copper and zinc exposure, as suggested by a quantitative linear relationship with plasma CRP [33].

Considering that most workers are exposed to two or more risk factors simultaneously, our study also analyzed the effects of multiple exposures to occupational risk factors. The top five pairs with the highest combined HRs were night-shift work combined with TCE, styrene with antimony, manganese with antimony, night-shift work with DMF, and TCE with copper. However, as mentioned earlier, these combined exposures were too few to be considered clinically significant. Therefore, these results require cautious interpretation. Further studies are needed to determine the magnitude and mechanisms of the relationship between combined exposure to occupational risk factors and metabolic syndrome.

This study has several limitations. First, there is the potential for exposure misclassification. Hazard exposure is stipulated as a

Table 3
Time-dependent Cox regression analysis of metabolic syndrome according to double occupational exposure after adjusting for all demographic and behavioral risk factors

Risk factor A	Risk factor B	Exposure number (%)			HR (95% CI)			RERI	MI
		A	B	A&B	A	B	A&B		
Night shift work	Noise	16,264 (17.49)	6523 (7.01)	2499 (2.69)	1.42 (1.33, 1.53)	1.10 (1.01, 1.20)	1.66 (1.45, 1.90)	0.13	1.06
Night shift work	Toluene	18,606 (20.01)	1025 (1.1)	157 (0.17)	1.45 (1.36, 1.54)	1.41 (1.15, 1.72)	2.43 (1.55, 3.81)	0.58	1.20
Night shift work	Xylene	18,671 (20.08)	400 (0.43)	92 (0.1)	1.45 (1.36, 1.54)	1.71 (1.28, 2.27)	2.14 (1.18, 3.87)	-0.02	0.87
Night shift work	Dichloromethane	18,659 (20.06)	539 (0.58)	104 (0.11)	1.45 (1.36, 1.55)	1.53 (1.19, 1.97)	1.38 (0.73, 2.61)	-0.61	0.62
Night shift work	Trichloroethylene	18,760 (20.17)	313 (0.34)	3 (0)	1.45 (1.36, 1.55)	1.92 (1.42, 2.61)	17.19 (1.53, 192.73)	14.81	6.15
Night shift work	Dimethylformamide	18,756 (20.17)	210 (0.23)	7 (0.01)	1.45 (1.36, 1.54)	2.15 (1.28, 3.61)	10.71 (1.45, 79.00)	8.11	3.44
Night shift work	Fe	18,511 (19.91)	1113 (1.2)	252 (0.27)	1.46 (1.37, 1.56)	1.39 (1.16, 1.65)	1.18 (0.75, 1.85)	-0.67	0.58
Night shift work	Mn	18,637 (20.04)	713 (0.77)	126 (0.14)	1.45 (1.36, 1.55)	1.27 (1.01, 1.59)	1.73 (1.01, 2.97)	0.01	0.94
Night shift work	Pb	18,707 (20.12)	389 (0.42)	56 (0.06)	1.44 (1.35, 1.54)	1.23 (0.86, 1.76)	3.33 (2.03, 5.47)	1.66	1.88*
Night shift work	Cu	18,623 (20.03)	299 (0.32)	140 (0.15)	1.45 (1.36, 1.55)	2.10 (1.61, 2.74)	1.76 (1.08, 2.87)	-0.79	0.58
Night shift work	Sb	18,752 (20.16)	129 (0.14)	11 (0.01)	1.45 (1.36, 1.54)	1.77 (1.00, 3.12)	3.48 (0.98, 12.37)	1.27	1.36
Noise	Toluene	8868 (9.54)	1028 (1.11)	154 (0.17)	1.15 (1.07, 1.24)	1.42 (1.16, 1.74)	1.65 (1.05, 2.59)	0.08	1.01
Noise	Xylene	8937 (9.61)	407 (0.44)	85 (0.09)	1.15 (1.07, 1.24)	1.67 (1.26, 2.22)	1.85 (1.02, 3.36)	0.03	0.97
Noise	Styrene	8992 (9.67)	154 (0.17)	30 (0.03)	1.15 (1.07, 1.24)	1.51 (0.98, 2.31)	1.75 (0.69, 4.42)	0.09	1.00
Noise	Trichloroethylene	8995 (9.67)	289 (0.31)	27 (0.03)	1.15 (1.07, 1.24)	1.85 (1.35, 2.53)	2.59 (1.02, 6.57)	0.59	1.22
Noise	Fe	8508 (9.15)	851 (0.92)	514 (0.55)	1.14 (1.06, 1.23)	1.23 (0.99, 1.52)	1.42 (1.10, 1.83)	0.05	1.01
Noise	Mn	8691 (9.35)	508 (0.55)	331 (0.36)	1.15 (1.07, 1.25)	1.30 (1.00, 1.70)	1.22 (0.87, 1.70)	-0.24	0.81
Noise	Pb	8904 (9.57)	327 (0.35)	118 (0.13)	1.15 (1.07, 1.24)	1.51 (1.06, 2.14)	1.19 (0.68, 2.09)	-0.47	0.68
Noise	Cu	8895 (9.57)	312 (0.34)	127 (0.14)	1.15 (1.06, 1.24)	1.91 (1.44, 2.54)	1.89 (1.24, 2.88)	-0.17	0.86
Noise	Sb	8973 (9.65)	91 (0.1)	49 (0.05)	1.15 (1.07, 1.24)	1.65 (0.81, 3.34)	2.19 (0.96, 4.99)	0.39	1.16
Toluene	Xylene	802 (0.86)	112 (0.12)	380 (0.41)	1.28 (1.00, 1.64)	1.72 (0.92, 3.21)	1.66 (1.26, 2.19)	-0.34	0.75
Toluene	Styrene	1090 (1.17)	92 (0.1)	92 (0.1)	1.37 (1.12, 1.67)	1.12 (0.59, 2.14)	1.91 (1.19, 3.07)	0.42	1.24
Toluene	Cu	1062 (1.14)	319 (0.34)	120 (0.13)	1.38 (1.12, 1.68)	1.90 (1.44, 2.50)	1.83 (1.15, 2.91)	-0.45	0.70
Toluene	Sb	1174 (1.26)	132 (0.14)	8 (0.01)	1.42 (1.18, 1.71)	1.83 (1.04, 3.23)	1.94 (0.58, 6.54)	-0.31	0.75
Xylene	Styrene	414 (0.45)	106 (0.11)	78 (0.08)	1.58 (1.17, 2.12)	1.10 (0.59, 2.04)	2.05 (1.27, 3.32)	0.38	1.18
Xylene	Fe	460 (0.49)	1333 (1.43)	32 (0.03)	1.60 (1.23, 2.10)	1.25 (1.06, 1.48)	3.00 (1.20, 7.53)	1.15	1.50
Xylene	Pb	466 (0.5)	419 (0.45)	26 (0.03)	1.65 (1.26, 2.15)	1.34 (0.97, 1.84)	2.10 (0.79, 5.58)	0.12	0.95
Xylene	Cu	362 (0.39)	309 (0.33)	130 (0.14)	1.60 (1.17, 2.19)	1.88 (1.42, 2.49)	1.86 (1.19, 2.90)	-0.62	0.62
Styrene	Pb	164 (0.18)	425 (0.46)	20 (0.02)	1.34 (0.87, 2.07)	1.28 (0.93, 1.76)	3.27 (1.36, 7.84)	1.64	1.90
Styrene	Cu	130 (0.14)	385 (0.41)	54 (0.06)	1.10 (0.64, 1.91)	1.77 (1.36, 2.29)	2.61 (1.52, 4.49)	0.74	1.34
Styrene	Sb	182 (0.2)	138 (0.15)	2 (0)	1.47 (0.99, 2.17)	1.74 (1.01, 2.99)	13.42 (1.44, 124.94)	11.22	5.27
Dichloromethane	Trichloroethylene	533 (0 .57)	206 (0.22)	110 (0.12)	1.37 (1.05, 1.80)	2.06 (1.42, 2.99)	1.58 (0.98, 2.55)	-0.85	0.56
Dichloromethane	Cu	616 (0.66)	412 (0.44)	27 (0.03)	1.39 (1.09, 1.77)	1.86 (1.46, 2.37)	2.19 (0.76, 6.32)	-0.06	0.85
Trichloroethylene	Cu	309 (0.33)	432 (0.46)	7 (0.01)	1.81 (1.33, 2.45)	1.83 (1.44, 2.33)	9.59 (2.04, 45.05)	6.95	2.90
Fe	Mn	605 (0.65)	79 (0.08)	760 (0.82)	1.27 (0.99, 1.62)	0.78 (0.28, 2.15)	1.28 (1.03, 1.59)	0.23	1.30
Fe	Cu	1328 (1.43)	402 (0.43)	37 (0.04)	1.25 (1.06, 1.48)	1.82 (1.42, 2.35)	2.44 (1.13, 5.31)	0.37	1.07
Fe	Sb	1322 (1.42)	97 (0.1)	43 (0.05)	1.25 (1.06, 1.48)	1.68 (0.91, 3.11)	2.11 (0.86, 5.22)	0.18	1.00
Mn	Cu	809 (0.87)	409 (0.44)	30 (0.03)	1.21 (0.97, 1.50)	1.83 (1.43, 2.35)	2.44 (1.04, 5.72)	0.40	1.10
Mn	Sb	834 (0.9)	135 (0.15)	5 (0.01)	1.23 (1.00, 1.52)	1.74 (1.02, 2.98)	11.53 (2.50, 53.12)	9.56	5.38*
Pb	Cu	400 (0.43)	394 (0.42)	45 (0.05)	1.27 (0.91, 1.77)	1.83 (1.42, 2.36)	2.27 (1.13, 4.58)	0.17	0.98

Relative excess risk due to interaction (RERI) = HR_{11} - HR_{10} - HR_{01} + 1.
MI (multiplicative effect) = $HR_{11}/(HR_{01} \times HR_{10})$; HR, Hazard ratio; CI, confidence interval.
* Refers to the value of statistical significance ($p < 0.05$).

harmful factor included in the WSHE, which might not represent actual exposure and is not an elaborate evaluation of exposure to harmful factors for each individual. Second, the representativeness of the cohort might be blurred because a large number of people who did not have enough information on the criteria for metabolic syndrome were excluded from the study. Third, in defining exposure in our study, only factors with multiple exposures exceeding 100 cases were analyzed; therefore, if the sample size increases, there may be a greater risk of developing other harmful factors not analyzed in this study. Fourth, in this study, qualitative occupational history information was not included owing to the possibility of increased bias as a result of the uncertainty and imprecision of retrospective large-scale health examination data. Additionally, quantitative exposure analyses were not included because our data could not be linked to exposure measurements. A precise cohort study linking measurement data will be necessary in the future. Also, the definition of exposure to a specific hazard in our study can be "exposure to a specific hazard alone" or "exposure to other hazards, including a specific hazard." The combined effect was calculated by extracting only two risk factors from workers simultaneously exposed to two or more combined risk factors. Finally, nutritional status or dietary habits are known to be closely related to metabolic syndrome [34–37]. However, nutritional status was evaluated for only specific age groups in the WGHE and WSHE; therefore, they could not be included in this analysis. In follow-up studies, additional nutrition-related evaluations are necessary.

Nevertheless, the results of this study are meaningful. Occupational risk factors, especially single and combined exposure to organic solvents and heavy metals, which had not been noticed in the past, may increase the risk of metabolic syndrome. This result has important implications because the risks emerged under very low-level exposure conditions, as can be seen from the current working environment measurements in The Republic of Korea.

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Authorship contribution statement

Conceptualization: Kang D. Data curation: Kang D, Kim TK, Lee W, Sim H. Formal analysis: Kang D, Kim TK, Lee W, Sim H. Funding acquisition: Kang D. Investigation: Kang D, Kim TK. Methodology: Kang D, Lee W, Kim SY. Project administration: Kang D. Resources: Kang D, Kim TK. Software: Kim TK, Kim YJ. Supervision: Kang D, Kim SY. Validation: Kang D, Kim SY. Visualization: Kim TK, Kim YJ, Sim H. Writing - original draft: Kang D, Lee ES, Kim TK, Kim YJ, Lee S. Writing - review & editing: Kang D, Kim SY.

Conflict of interest

All authors participated in the interpretation of results and approved the final version of the manuscript. All authors have no conflicts of interest to declare.

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