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Research Article

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Modifying effect of statin use on the association between nitrogen dioxide exposure and ischemic heart disease in patients with hypertension

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ABSTRACT

Background: Air pollution, particularly nitrogen dioxide (NO_2), adversely affects cardiovascular health by inducing systemic inflammation. Evidence remains limited regarding short-term exposure to traffic-related air pollution, including NO_2, and whether statin use modifies susceptibility to pollution-related acute cardiovascular events. This study evaluated whether the short-term effects of NO_2 exposure and ischemic heart disease (IHD) hospitalization differ by statin-use status, focusing on patients with hypertension.
Methods: A time-stratified case-crossover analysis was conducted using data from National Health Insurance Service for patients hospitalized with IHD in Seoul from 2018 to 2020. The included patients had a prior diagnosis of hypertension and had used antihypertensive medication within the previous 3 years. This group was further stratified as prescription-based statin users and non-users based on whether they had received a statin prescription within 1 year before their IHD admission. The daily average NO_2 concentrations in Seoul were retrieved from Air Korea for the admission day and the preceding 7 days. Weighted conditional logistic regression models were applied separately for each subgroup after adjusting for meteorological conditions and national holidays. The risk of IHD hospitalization was presented as odds ratios (ORs) per 0.01 ppm increase in NO_2, with 95% confidence intervals (CIs). Differences in risk between statin users and non-users were tested (*P* for interaction).
Results: Of the 72,753 IHD cases analyzed, 24% were statin non-users and 76% were statin users. A 0.01 ppm increase in NO_2 at lag0 was associated with higher odds of IHD-related hospitalization (OR, 1.012; 95% CI, 1.003–1.020), with similar results for lag0–lag5 and cumulative windows (lag01, lag02). A significant interaction between NO_2 exposure and statin use was identified (*P* for interaction < 0.05). The associations differed by statin-use status, with generally lower, non-significant estimates among statin users. Among non-users, significant positive associations were observed at lag1, lag2, and lag01 (ORs > 1). In contrast, estimates among statin users were lower and non-significant.
Conclusions: Short-term NO_2 exposure was associated with an increased risk of hospitalization for IHD among patients with hypertension. However, this association differed by statin-use status, with lower estimates observed among statin users than non-users.

Keywords: Ischemic heart disease; Hypertension; Hydroxymethylglutaryl-CoA reductase inhibitors; Antihypertensive agents; Nitrogen dioxide

Abbreviations

CI, confidence interval; CVD, cardiovascular disease; ICD-10, International Classification of Diseases, 10th revision; IHD, ischemic heart disease; NHIS, National Health Insurance Service; NO_2, nitrogen dioxide; OR, odds ratio; PM, particulate matter; SD, standard deviation.

Funding

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Competing interest

The authors declare that they have no competing interests.

Availability of data and materials

The data supporting this study's findings are available through the National Health Insurance Service (NHIS) of Korea; however, due to licensing restrictions, they are not publicly accessible. Data may be available from the authors upon reasonable request and with NHIS permission.

Ethics approval and consent to participate

This study received approval from the Institutional Review Board of the Yonsei University Health System, Severance Hospital (IRB No. 4-2021-1628).

Consent for publication

Not applicable.

Authors' contributions

Conceptualization: Cho J; Supervision: Cho J; Data curation: Park H; Formal analysis: Park H; Methodology: Cho J, Jang H, Park H; Validation: Park H, Jang H; Writing - original draft: Park H; Writing - review & editing: Park H, Jang H, Lee H, Kim C, Cho J.

BACKGROUND

Ischemic heart disease (IHD) is the second leading cause of global disability-adjusted life years and remains the most common type of cardiovascular disease (CVD) worldwide [1,2]. In the Republic of Korea, both the incidence and hospitalization rates for IHD have steadily risen, adding to the national disease burden [3]. Mounting evidence suggests that IHD risk is associated with exposure to ambient air pollution, particularly nitrogen dioxide (NO_2) via pathways such as systemic inflammation and endothelial dysfunction [4,5]. A meta-analysis of 38 case-crossover and 48 time-series studies reported that NO_2 exposure (per 10 ppb) increases the risk of IHD by up to 7% [6].

Individuals with hypertension are known to be a susceptible population to the cardiovascular impacts of air pollution [7-9]. In case-crossover analyses of acute myocardial infarction hospitalizations, short-term NO_2 exposure was associated with increased risk, with evidence of stronger effects in older adults with hypertension [7,8]. A large-scale time-series study in China reported stronger associations between NO_2 exposure and IHD admissions among individuals with hypertension [9].

A few population-based studies have shown that statin use may modify the association between air pollution and cardiovascular risk [10-12]. Statin use was associated with a lower cerebrovascular risk even under high particulate matter exposure in a large Korean cohort [11]. Similarly, in a large population-based study of older adults in Canada, statin users had weaker associations between particulate matter exposure and cardiovascular and cerebrovascular mortality compared with non-users [12]. However, current knowledge on statins as potential effect modifiers has largely focused on particulate matter exposure and the effects of long-term exposure. Evidence remains limited regarding the effects of short-term exposure to traffic-related air pollution, including NO_2, on acute cardiovascular events and the potential modifying role of statin use. In line with this literature, we used statin-use status not to estimate a pharmacologic protective effect, but as a clinically meaningful stratification variable to assess whether population-level susceptibility to short-term NO_2 exposure differs between the subgroups.

Therefore, this study aimed to evaluate whether the short-term effect of NO_2 exposure on IHD hospitalization differs between statin users and non-users, focusing on patients with hypertension.

METHODS

Time-stratified case-crossover design

A time-stratified case-crossover study was used to investigate the relationship between air pollution exposure and IHD hospitalization among patients with hypertension. The time-stratified case-crossover design is a well-established epidemiological method for evaluating the short-term impact of brief exposure on acute health outcomes [13,14]. In this design, each subject served as their own control, which naturally accounts for confounders that do not vary over time. A symmetric bidirectional design was applied, selecting control days that matched the same day of the week within the same month as the case day to avoid overlap bias.

Data source

We retrieved healthcare utilization data for patients with IHD in Seoul from 2015 to 2020 using the National Health Insurance Service (NHIS) database of the Republic of Korea. The NHIS database contains comprehensive healthcare utilization records, including dates of medical visits, codes of the International Classification of Diseases, 10th revision (ICD-10), types of visits, prescription information; and demographic details such as birth date, sex, and place of residence. Since the NHIS is the sole insurer managing Korea's universal health coverage, which includes approximately 97% of the population (with the remaining 3% covered through medical aid programs), the NHIS database is regarded as nationally representative [15].

Hospitalization for IHD among patients with hypertension

To compare the effectiveness of medications, the analysis was limited to individuals with the same medication indication to ensure a similar likelihood of exposure [16]. Therefore, we focused on patients with hypertension among those hospitalized for IHD. Hospitalizations for IHD were identified using primary or secondary diagnoses coded with ICD-10 codes I20, I21, I22, I23, I24, or I25. Hypertension was defined as having at least one medical claim with ICD-10 codes I10, I11, I12, I13, or I15, along with more than 180 days of antihypertensive prescriptions during the 3 years preceding hospitalization (**Supplementary Fig. 1**). Of the 145,770 IHD admission cases, 44,518 without a diagnosis of hypertension and 28,499 with no history of antihypertensive medication use or with cumulative prescriptions of fewer than 180 days were excluded. Consequently, 72,753 IHD cases were included in the final analysis.

Antihypertensive medication and statin use

Patients with hypertension who were on antihypertensive therapy were stratified into statin users and non-users according to whether they had a statin prescription within 1 year before their IHD hospitalization. Statin users were defined as individuals prescribed medications containing statin compounds, including both single-agent statins and combination products that contain statins together with other active ingredients, such as antihypertensive, antidiabetic, or other lipid-lowering drugs. Because both antihypertensive medications and statins require ongoing use, the duration of medication use was determined by calculating the period between the prescription start date and the final day of supply during the observation period [17]. Prescription records were grouped by active ingredients according to NHIS policies. The drug classes and specific agents are detailed in **Supplementary Table 1**.

Exposure assessment and meteorological covariates

This study was conducted in Seoul, Korea, where hourly NO_2 levels were continuously monitored through an automated air pollution telemetry system at 25 fixed-site monitoring stations. Data were sourced from the Ministry of Environment via the Air Korea Platform (www.airkorea.or.kr). Hourly NO_2 concentrations were aggregated into 24-hour average values to construct daily exposure metrics. Daily average temperature (°C) and relative humidity (%) were obtained from the Korea Meteorological Administration Open MET Data Portal (https://data.kma.go.kr/). Temperature and relative humidity were modeled using natural cubic splines to control for possible confounding by meteorological conditions. Based on previous studies, the degrees of freedom were set to 18 (6 per year × 3 years) for temperature and 9 (3 per year × 3 years) for relative humidity [18].

Statistical analysis

We used weighted conditional logistic regression to estimate the association between NO_2 exposure and IHD hospitalization among patients with hypertension [19]. To control for time-dependent confounding, stratification by case date was applied, and the number of events within each stratum was included as frequency weights. We adjusted for holidays and major time-varying meteorological factors (temperature and relative humidity), which may vary across case and control days and confound short-term associations between NO_2 and IHD hospitalization. Because each individual served as their own control, the time-invariant risk factors for IHD (e.g., sex, chronic comorbidities, and stable lifestyle characteristics) were inherently controlled by design. We examined single-day lag models from lag0 to lag7 and developed cumulative lag models using lags that were statistically significant in the single-lag analysis to consider possible lagged effects. For temperature and relative humidity, lag structures matching those used for air pollution exposure were applied in the analysis to ensure consistency. Stratified analyses were conducted to examine the impact of statin use. Differences between strata were evaluated by calculating *P*-values for interactions using the method described by Altman and Bland [20] to compare the 2 odds ratios (ORs). When a statistically significant difference was observed and the OR for statin users was lower than that for non-users, this was interpreted as evidence of a differential association by statin-use status. Because CVD risk is generally low among younger adults in their 20s and 30s, we conducted a sensitivity analysis restricted to individuals 40 years and older, a population more relevant to IHD. The risk of IHD hospitalization is reported as ORs with 95% confidence intervals (CIs) per 0.01 ppm increase in NO_2 concentration. A significance level of 0.05 was used for all analyses and interaction tests. All statistical analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA), and R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) with RStudio (RStudio, PBC, Boston, MA, USA) was used to create the figures.

RESULTS

Characteristics of hospitalized IHD cases and environmental exposure

Of the 72,753 IHD cases, 24% were not using statins, while 76% were statin users (**Table 1**). There were 30,006 cases (41.2%) in 2018, 28,543 cases (39.2%) in 2019, and 14,204 cases (19.5%) in 2020. The median (25th–75th percentile) duration of antihypertensive medication use was 364 days in both groups (non-statin users: 355–364 days; statin users: 360–364 days). Among statin users, the median duration of statin treatment was 364 days (332–364). Significant differences were found between statin users and non-users for all variables analyzed. Throughout the study period, the mean NO_2 concentration, mean temperature, and mean relative humidity were 0.028 ppm (standard deviation [SD], 0.012), 13.3°C (SD, 10.9), and 57.1% (SD, 15.3), respectively (**Table 2**).

Association between NO_2 exposure and the risk of hospitalization for IHD in patients with hypertension

Short-term exposure to NO_2 was associated with increased odds of IHD-related hospitalization among patients with hypertension, with an OR of 1.012 (95% CI, 1.003–1.020) per 0.01 ppm increase in daily mean NO_2 concentration on the day of admission (**Fig. 1**). The single-lag analysis indicated that NO_2 exposure from 1 to 5 days before admission was positively associated with higher odds of IHD-related hospitalization. Cumulative lag analysis showed that cumulative NO_2 exposure from the day of admission to 1 day before (OR, 1.015; 95%

Table 1. Characteristics of hospitalizations for ischemic heart disease cases

Variable	Total	Statin		*P*-value
		Non-user	User	
Year				< 0.001
2018	30,006 (41.2)	7,722 (44.3)	22,284 (40.3)	
2019	28,543 (39.2)	7,116 (40.8)	21,427 (38.7)	
2020	14,204 (19.5)	2,603 (14.9)	11,601 (21.0)	
Season				0.009
Spring	18,751 (25.8)	4,439 (25.5)	14,312 (25.9)	
Summer	18,160 (25.0)	4,326 (24.8)	13,834 (25.0)	
Fall	17,338 (23.8)	4,074 (23.4)	13,264 (24.0)	
Winter	18,504 (25.4)	4,602 (26.4)	13,902 (25.1)	
Sex				0.016
Male	43,740 (60.1)	10,350 (59.3)	33,390 (60.4)	
Female	29,013 (39.9)	7,091 (40.7)	21,922 (39.6)	
Age group				< 0.001
20–39	433 (0.6)	198 (1.1)	235 (0.4)	
40–59	11,254 (15.5)	2,924 (16.7)	8,330 (15.1)	
60–79	43,728 (60.1)	9,247 (52.9)	34,481 (62.3)	
≥ 80	17,338 (23.8)	5,072 (29.0)	12,266 (22.2)	
Household income				< 0.001
Quartile 1 (0–4)	12,575 (17.3)	3,122 (17.9)	9,453 (17.1)	
Quartile 2 (5–9)	10,657 (14.6)	2,746 (15.7)	7,911 (14.3)	
Quartile 3 (10–14)	13,487 (18.5)	3,293 (18.9)	10,194 (18.4)	
Quartile 4 (15–20)	28,348 (39.0)	6,489 (37.2)	21,859 (39.5)	
Unknown	7,686 (10.6)	1,791 (10.3)	5,895 (10.7)	
Comorbidities (dyslipidemia)				< 0.001
No	66,950 (92.0)	14,819 (85.0)	52,131 (94.2)	
Yes	5,803 (8.0)	2,622 (15.0)	3,181 (5.8)	

Values are presented as number (%).
Group characteristics based on statin use were compared using the χ^2 test.

Table 2. Characteristics of environmental exposure and meteorological variables in Seoul, Korea, 2018–2020

Variable	Mean	Min	25% percentile	Median	75% percentile	Max
NO_2 (ppm)	0.028	0.0018	0.018	0.025	0.037	0.096
Temperature (℃)	13.3	−14.8	4.3	14.35	22.8	33.7
Relative humidity (%)	57.1	22.9	46.1	56.4	66.9	97.0

CI, 1.006–1.024) and 2 days before (OR, 1.014; 95% CI, 1.005–1.023) was also significantly associated with higher odds of IHD-related hospitalization. Detailed ORs and their CIs for all lag periods are provided in **Supplementary Table 2**.

Effect modification by statin use on the association between NO_2 exposure and the risk of hospitalization for IHD in patients with hypertension

To determine whether statin use alters the association between NO_2 exposure and the risk of IHD hospitalization in patients with hypertension, stratified analyses were performed based on statin use status (**Fig. 2**, **Supplementary Table 3**). A statistically significant difference in the effect of NO_2 exposure on the risk of hospitalization for IHD was observed between statin users and non-users at lag1 (*P* for interaction = 0.019). Specifically, each 0.01 ppm increase in mean NO_2 concentration was associated with higher odds among non-users (OR, 1.039; 95% CI, 1.019–1.061) compared with that among users (OR, 1.011; 95% CI, 0.999–1.023). Similar trends were observed at lag2 (non-users: OR, 1.046; 95% CI, 1.022–1.070; statin users: OR, 1.016; 95% CI, 1.003–1.030; *P* for interaction = 0.032). The OR for cumulative exposure from lag 0–1 days (lag0–1) was 1.036 (95% CI, 1.018–1.055) among non-users and 1.008 (95%

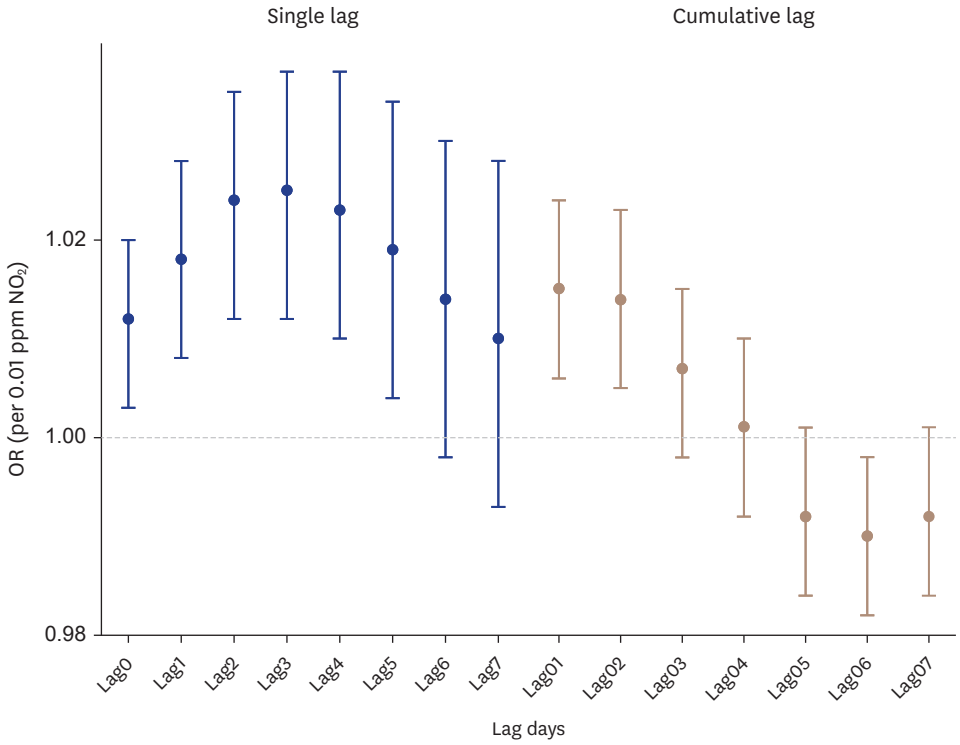

Fig. 1. Association between NO_2 exposure and hospitalization for IHD in patients with hypertension. ORs and 95% CIs for IHD per 0.01 ppm increase in daily mean NO_2 were estimated using a time-stratified case-crossover design with weighted conditional logistic regression after adjusting for national holidays, daily mean temperature, and relative humidity. Single-day lags (lag0–lag7) represent NO_2 on the admission day through 7 days prior; cumulative lags (lag01–lag07) represent moving-average NO_2 from lag0 through each lag day.
NO_2, nitrogen dioxide; IHD, ischemic heart disease; OR, odds ratio; CI, confidence interval.

CI, 0.998–1.018) among statin users, with a significant interaction between groups (*P* for interaction = 0.008).

In the sensitivity analysis restricted to individuals aged 40 years and older, the association between short-term NO_2 exposure and IHD hospitalization remained similar to the main findings (**Supplementary Table 4**). For cumulative lag exposure, the ORs for lag0–1 were 1.039 (95% CI, 1.019–1.061) among non-users and 1.011 (95% CI, 0.999–1.023) among statin users (*P* for interaction, 0.019). Similarly, for lag0–2, the ORs were 1.046 (95% CI, 1.022–1.070) for non-users and 1.016 (95% CI, 1.003–1.030) for statin users (*P* for interaction = 0.032).

DISCUSSION

In this time-stratified case-crossover study, we examined whether statin use modified the association between short-term NO_2 exposure and IHD-related hospital admissions among patients with hypertension in Seoul, Republic of Korea. Short-term NO_2 exposure was associated with a statistically significant increase in the risk of IHD-related admissions. Notably, the stratified analyses indicated that the association differed by statin-use status, with consistently lower estimates among statin users than non-users, especially for cumulative exposure over lag0–2 days. These results suggest that short-term NO_2 exposure was associated with higher odds of IHD-related hospital admission, potentially reflecting worsening of acute symptoms among susceptible individuals.

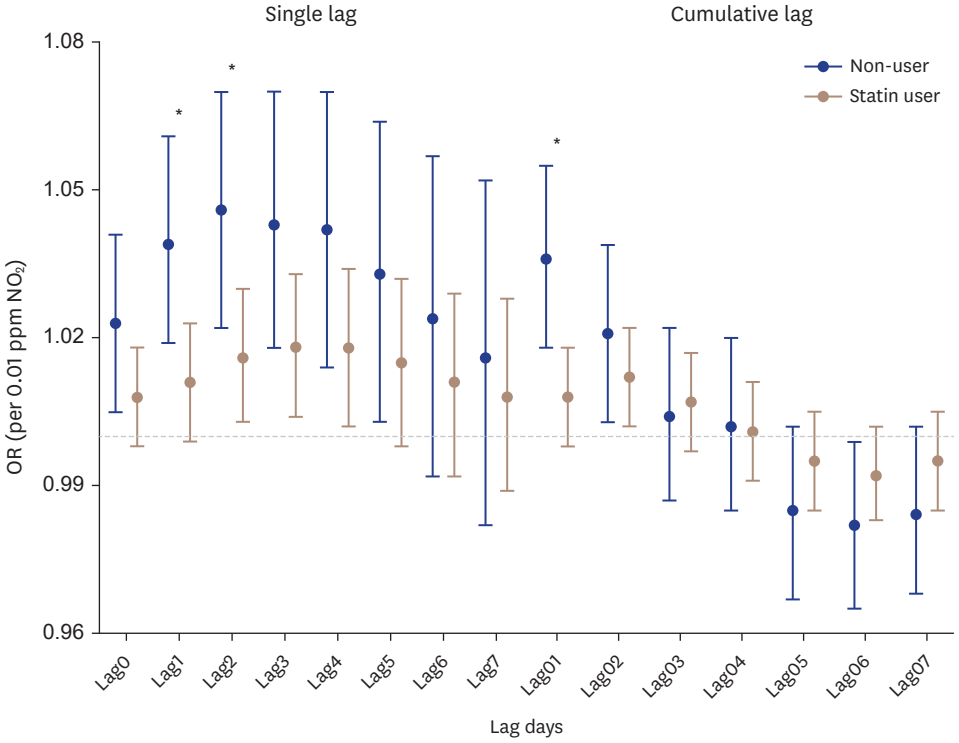

Fig. 2. Effect modification by statin use on the association between NO_2 exposure and hospitalization for IHD in patients with hypertension.
ORs and 95% CIs for ischemic heart disease per 0.01 ppm increase in daily mean NO_2 were estimated separately among non-users and statin users. Estimates are from weighted conditional logistic regression within the time-stratified case-crossover design and are adjusted for meteorological variables. Asterisks (*) indicate lag windows with statistically significant effect modification by statin use (P for interaction < 0.05). Single-day lags (lag0–lag7) represent NO_2 on the admission day through 7 days prior; cumulative lags (lag01–lag07) represent moving-average NO_2 from lag0 through each lag day.
NO_2, nitrogen dioxide; IHD, ischemic heart disease; OR, odds ratio; CI, confidence interval.

We focused on individuals with hypertension, who are known to be more susceptible to the cardiovascular effects of air pollution, and observed higher odds of IHD-related hospitalization associated with short-term NO_2 exposure in this group. This result is consistent with those of previous studies and highlights the importance of implementing targeted prevention strategies for high-risk groups, such as patients with hypertension [6,9,21].

Among those not using statins, significant positive associations between NO_2 exposure and the risk of hospitalization for IHD were detected at lag1, 2, and lag01, with all effect estimates above 1. In contrast, the associations between NO_2 exposure and the risk of hospitalization for IHD were weaker in statin users, with estimates closer to 1 and not consistently statistically significant. For example, at lag1, the OR was 1.039 in non-users versus 1.011 in statin users, indicating a difference in the association by statin-use status. Taken together, these findings suggest a differential susceptibility to NO_2-related IHD hospitalization between statin users and non-users. Such differences may still be relevant at the population level in large, high-risk groups. This is in line with the recent findings of Kim et al. [11], who showed that statin use influenced the association between long-term particulate matter $(PM)_{2.5}$ exposure and CVD risk among older adults with dyslipidemia in the Republic of Korea. Statin users exposed to elevated levels of PM_{10} (> 50 μg/m^3) and $PM_{2.5}$ (> 25 μg/m^3) had a 20% and 17% lower adjusted risk of incident stroke, respectively, compared to non-users.

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Previous randomized controlled trials have shown that combining statins with antihypertensive treatment provides greater cardiovascular benefits than using antihypertensive therapy alone [22]. Although this study did not directly examine the causal effects of combination therapy, our results indicated that statin use among patients with hypertension who were also taking antihypertensive medications was linked to a smaller increase in IHD hospitalization risk related to NO_2 exposure. These findings are consistent with earlier trial evidence demonstrating the differences in cardiovascular risk profiles between statin users and non-users in combined therapy settings.

In the sensitivity analysis restricted to individuals aged ≥ 40 years, the effect modification by statin use was consistent with the main analysis: NO_2-associated odds of IHD hospitalization were higher among non-users than among statin users, and the interaction remained statistically significant for cumulative exposure at lag0–1 and lag0–2. Notably, effect estimates for cumulative NO_2 exposure were higher among statin non-users than among statin users, with significant interactions for both lag0–1 and lag0–2 exposure windows. These findings suggest that the use of statin may modify susceptibility to short-term NO_2 exposure among middle-aged and older adults, a population at higher baseline risk of IHD.

NO_2 mainly contributes to CVD by causing systemic oxidative stress, initiating inflammatory responses, raising blood pressure, and increasing adhesion molecule expression in vascular endothelial cells. These processes result in endothelial dysfunction and elevate the risk of IHD [4,5,23]. The mechanisms underlying the observed differences in the association between NO_2 exposure and IHD hospitalization by statin-use status remain uncertain. Potential explanations include differences in baseline cardiovascular risk management, healthcare utilization patterns, and residual heterogeneity between statin users and non-users. Statins have been shown to exert anti-inflammatory and endothelial-stabilizing effects in experimental and clinical studies [10,24-28], though the present findings should not be interpreted as evidence of mechanisms underlying the observed differences in the associations. Additional studies are needed to further characterize the sources of this differential susceptibility.

This study analyzed a large, clearly defined population that included all identified IHD-related hospitalizations among patients with hypertension in Seoul over several years, which increased both the generalizability and statistical strength of the results. The application of a time-stratified case-crossover design effectively adjusted for confounders that do not change over time and for temporal trends, reinforcing the observed short-term associations between NO_2 exposure and IHD hospitalization.

Despite these strengths, this study has several limitations that should be noted. First, exposure assessment was based on ambient NO_2 levels measured at fixed monitoring stations, which may not fully reflect individual exposure variations. We used comprehensive national monitoring data to minimize bias, and any resulting misclassification was likely non-differential and therefore unlikely to significantly bias the risk estimates. Second, hypertension and medication users were defined using healthcare utilization data and aggregated information on antihypertensive medications. Thus, information on hypertension severity, blood pressure control status, and specific antihypertensive regimens and dosing was not available in the present study. However, these factors are generally more time-stable over short windows in a case-crossover design; nonetheless, we could not evaluate their potential influence in greater detail due to data limitations. Such information

may be useful in future studies to further characterize heterogeneity in the association between air pollution and IHD admission. Third, statin exposure was defined from prescription records within one year prior to the index IHD admission; although the median (25th–75th percentile) duration was 364 days (332–364), claims-based coverage may not fully reflect actual adherence or persistence, and future studies incorporating adherence measures are needed. Fourth, limiting the study sample to patients who used healthcare services in Seoul may affect how broadly the findings can be applied. However, these findings offer valuable insights for this urban population as an exploratory analysis. Finally, although individual-level confounders are inherently controlled in the case-crossover study design via within-person comparisons, the observed difference in the association between NO_2 and IHD admission by statin-use status may partly reflect residual confounding related to concomitant cardiovascular medications (e.g., higher use of antiplatelet agents or other cardioprotective therapies) and unmeasured health-related behaviors (e.g., consistent mask use), which may be more prevalent in this group. Therefore, our findings should be interpreted as evidence of differential associations by statin-use status, rather than as an isolated effect of statin use alone.

CONCLUSIONS

Among patients with hypertension, short-term exposure to NO_2 was linked to a higher risk of hospitalization for IHD. However, this association was weaker in patients who were using statins, especially for cumulative exposure during the 0–2 days before admission. Stratified analyses showed that statin users had consistently lower ORs than non-users, with statistically significant interaction effects observed at several lag periods. These findings suggest that short-term NO_2 exposure was associated with higher odds of IHD-related hospital admission, potentially reflecting worsening of acute symptoms among susceptible individuals, and that this association differed by statin-use status, with lower estimates observed among statin users.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Drug classes and corresponding agents

Supplementary Table 2
Effect estimates of short-term NO_2 exposure for IHD hospitalization among patients with hypertension

Supplementary Table 3
Effect estimates for the association between short-term NO_2 exposure and IHD hospitalization by statin use among patients with hypertension

Supplementary Table 4

Effect modification by statin use on the association between NO_2 exposure and hospitalization for IHD in patients with hypertension aged ≥ 40 years

Supplementary Fig. 1

Hypertension diagnosis and medication observation timeline. Schematic illustration of the index hospitalization and exposure/eligibility windows used to define the hypertensive cohort and medication use. ① indicates the index date, defined as the date of hospital admission for ischemic heart disease. ② indicates the hypertension ascertainment window during the 3 years preceding the index admission. ③ indicates the medication exposure window during the 1 year preceding the index admission, used to classify patients receiving antihypertensive therapy into statin users vs non-users based on the presence of any statin. Case 1 and case 2 present example timelines with different index years.

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