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FULL RESEARCH PAPER
Air pollution and environmental science

Cardiovascular benefit of statin use against air pollutant exposure in older adults

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Aims

Little is known about the cardiovascular benefit of statin use against ambient air pollution among older adults who are at higher risk of cardiovascular disease (CVD) potentially owing to age-related declines in cardiovascular functions along with other risk factors.

Methods and results

This retrospective, population-based cohort study consisted of adults aged 60 years and older free of CVD at baseline identified from the National Health Insurance Service database linked to the National Ambient Air Monitoring Information System for average daily exposure to PM_{10} and $PM_{2.5}$ in 2015 in the major metropolitan areas in the Republic of Korea. The follow-up period began on 1 January 2016 and lasted until 31 December 2021. The Cox proportional hazards model was used to evaluate the association of cardiovascular benefit with statin use against different levels of air pollutant exposure. Of 1 229 444 participants aged 60 years and older (mean age, 67.4; 37.7% male), 377 076 (30.7%) were identified as statin users. During 11 963 322 person-years (PYs) of follow-up, a total of 86 018 incident stroke events occurred (719.0 events per 100 000 PYs). Compared to statin non-users exposed to high levels of PM_{10} (>50 μg/m^3) and $PM_{2.5}$ (>25 μg/m^3), statin users had 20% [adjusted hazard ratio (HR), 0.80; 95% confidence intervals (CI), 0.75–0.85] and 17% (adjusted HR, 0.80; 95% CI, 0.80–0.86) lower adjusted risk of incident stroke for PM_{10} and $PM_{2.5}$, respectively. A similar risk reduction for incident CVD was also found among statin users exposed to low or moderate levels of PM_{10} (≤50 μg/m^3) and $PM_{2.5}$ (≤25 μg/m^3) exposure.

Conclusion

Among adults aged 60 years and older with high and low or moderate levels of exposure to PM_{10} and $PM_{2.5}$, statin use was associated with a significantly lower risk of stroke.

Lay summary

- In a retrospective cohort study of older adults exposed to high and low or moderate levels of PM_{10} and $PM_{2.5}$, statin use was associated with a significantly lower risk of incident stroke.

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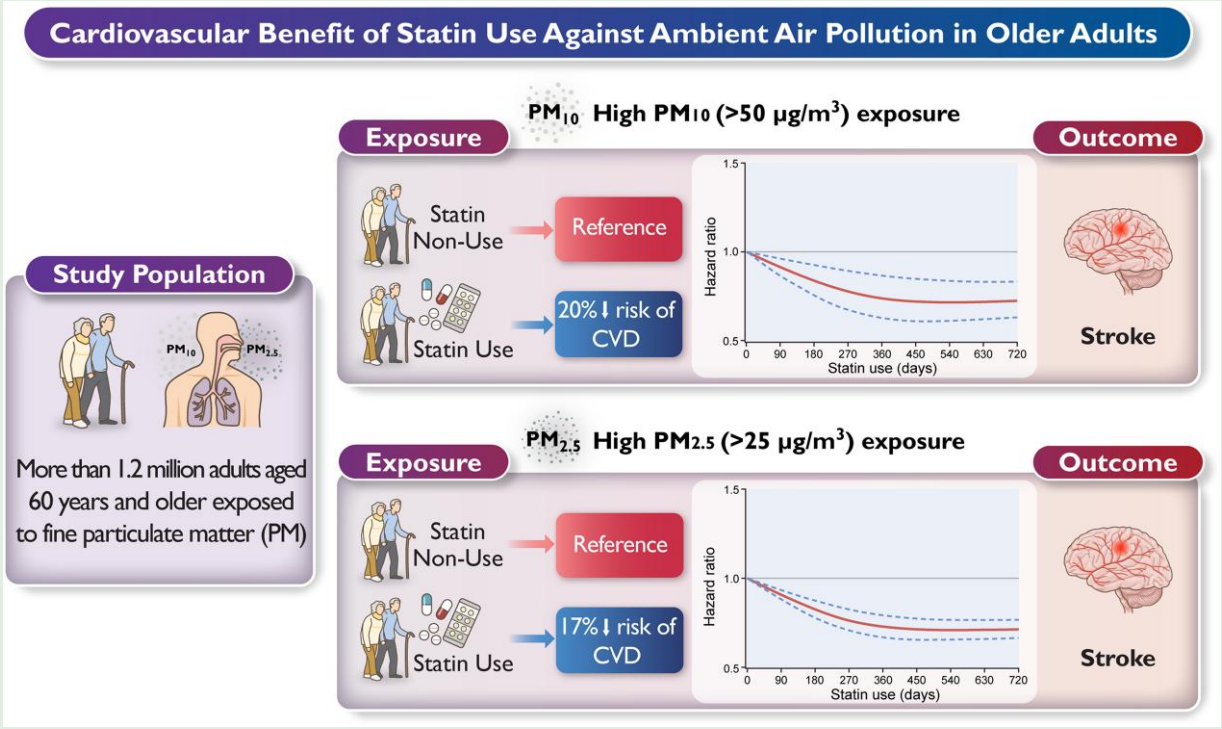
Graphical Abstract



Keywords Hydroxymethylglutaryl-CoA reductase inhibitors • Air pollutants • Particulate matter • Cardiovascular diseases • Older adults

Introduction

According to the Global Burden of Disease study, cardiovascular disease (CVD), mainly coronary heart disease (CHD) and stroke, is the leading cause of morbidity and mortality worldwide responsible for nearly 523 million prevalent cases and 18.6 million deaths in 2019, which have steadily increased in the past two decades.[1] In the US alone, the number of deaths from CHD and stroke is projected to increase more than 18% by 2030.[2] Burden of CVD rises with age and continues to remain as one of the leading causes of morbidity and mortality among older adults in the USA and elsewhere in the world.[3–5] Along with other well-established traditional and emerging risk factors for CVD, ambient air pollution is a serious public health concern associated with increased risk of CVD.[6] Expert position paper from the European Society of Cardiology (ESC) and updated American Heart Association (AHA) scientific statement on particulate matter (PM) air pollution and CVD underline the detrimental effects of PM on cardiovascular health.[7–9] Also, older adults are particularly vulnerable to the adverse effects of PM potentially owing to age-related declines in cardiovascular and pulmonary function.[10–14]

Substantial body of evidence from observational and clinical studies suggest cardiovascular benefit of statins (hydroxymethylglutaryl-CoA reductase inhibitors) in diverse populations, including older adults.[15–17] In addition, the US Preventive Services Task Force statement released in 2022 recommends prescription of statin for primary prevention of CVD for adults between ages of 40 and 75 years based on the presence of CVD risk factors and 10-year CVD risk estimation.[18] Although experimental data suggest that statin may attenuate PM-induced myocardial inflammation through the reduction of lipid levels and inflammatory biomarkers, cardiovascular benefit of statin use against air pollutant exposure is not well understood, especially in population-based studies.[19] Epidemiologic data of US women with chronic exposure to PM showed that statin use was associated with the reduced level of C-reactive protein, an inflammatory biomarker associated with the development of CVD.[20] Despite these studies, evidence on the cardiovascular benefit of statin use as measured by cardiovascular outcomes with respect to PM exposure in older adults remains limited.

To address this evidence gap, we investigated the association of cardiovascular benefit with statin use against air pollutants using a population-based study of older adults linked to publicly available data on PM exposure.

Methods

Study population

Adults aged 60 years and older residing in the metropolitan area of the Republic of Korea (Seoul, Incheon, and Busan) who participated in the biennial national health screening programme (2014–15) free of CVD and without previous statin use were identified through the National Health Insurance Service (NHIS) data warehouse ($n = 1\,236\,341$). The NHIS offers compulsory healthcare coverage to nearly all Korean citizens with a high enrolment rate of 98%.[21] The NHIS collects standardized information on its enrolees including hospitalization and outpatient visit records, prescriptions of medications, and results from the national health screening.[22] Some well-established epidemiologic studies have used the NHIS database, and details are described elsewhere.[23–26] To create a cohort of older adults with complete information, those with missing information on national health screening ($n = 1474$) were excluded. Additionally, those who died before the follow-up period were also excluded ($n = 5423$) to minimize survival bias and to reflect the fact that statin is not typically recommended for those

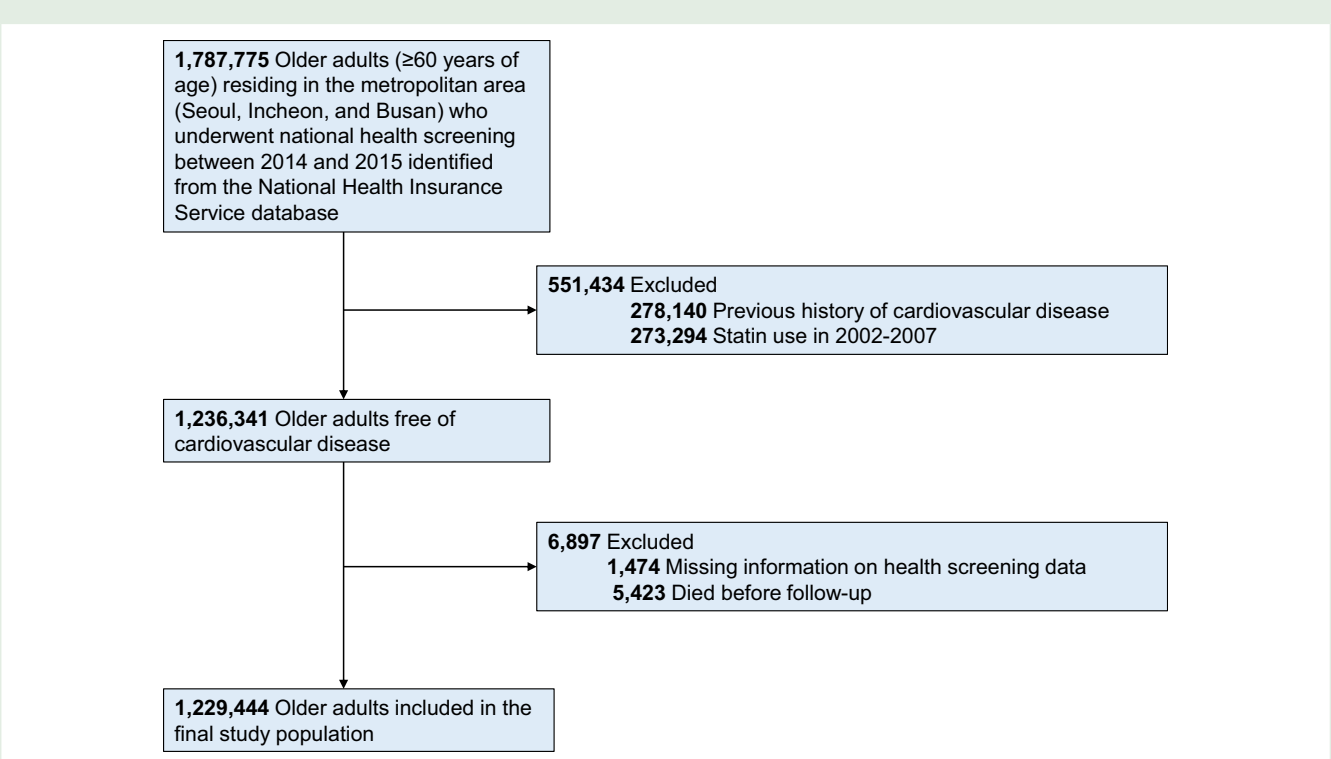


Figure 1 Study population flowchart.

with limited life expectancy (*Figure 1*). This study was approved by the Institutional Review Board (IRB) at the Seoul National University Hospital (IRB No.: E-2204-038-1314).

Assessment of statin use and exposure to air pollutants

The NHIS prospectively collects all drug prescription records from primary, secondary, and tertiary healthcare institutions using a highly reliable and comprehensive electronic drug claims system. Among the participants, statin use was defined with a new-user design, excluding those with previous prescribed from 2002–07. We collected statin prescription records between 1 January 2008 and 31 December 2015 from the NHIS records. All participants were categorized as statin non-users (never use of statin or <90 days of prescription) and users (≥90 days of prescription) using the pharmacy claims database according to a previous study.[27] Statin users were further categorized according to prescription days (90–180 days, 181–364 days, 365–729 days, and ≥730 days). In addition, daily defined dose (DDD) for average daily consumption of statin was computed using Anatomical Therapeutic Chemical codes of statins (atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, and pitavastatin) along with records on dose, number of pills, and prescription days. The NHIS data of each participant were linked to the National Ambient Air Monitoring Information System (NAMIS) database to identify daily average of air pollutant (fine particulate matter with different aerodynamic diameter sizes; PM_{10} and $PM_{2.5}$) exposure of the participants between 1 January 2015 and 31 December 2015 using the residential district code. In brief, the NAMIS database provides information on daily air quality from atmospheric monitoring devices installed in each administrative districts in metropolitan areas in the Republic of Korea.[28] We defined high and low or moderate levels of exposure to average daily air pollutant adopted from the interim target for PM_{10} and $PM_{2.5}$ from the 2021 World Health Organization global air quality guidelines.[29] Validity of the NAMIS database linked to the NHIS data has been described in detail elsewhere.[30,31]

Outcome assessment

The primary endpoint was incident stroke ascertained with the International Classification of Diseases, Tenth Revision (ICD-10) with at least 48 h of hospitalization records from the NHIS database.[24,26,30,32] The main outcomes for incident stroke were identified as the total stroke (ICD-10: I60–I69) and stroke subtypes (ICD-10: I63 for ischaemic stroke and I60–I62 for haemorrhagic stroke).[33] Prior investigations have used the diagnosis codes in combination with hospital admission records from the NHIS database to identify incident CVD and the positive predictive value is ~95%.[34]

Covariates

The NHIS insurance eligibility assessment database provided participant information such as age, sex, residential area, and insurance premium as a proxy for income status. Anthropometric measurements and self-reported responses from the national health screening programme provided data on cigarette smoking, physical activity, and body mass index (BMI). Hypertension, type 2 diabetes, hyperlipidaemia (total cholesterol ≥ 240 mg/dL), and LDL-cholesterol level were identified using national health screening and medication claims records. The use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelet (without acetylsalicylic acid), and anticoagulants was defined as a prescription of over 30 days as recorded in medication claims. The presence of cardiac arrhythmias [paroxysmal tachycardia (ICD-10: I47), atrial fibrillation and flutter (ICD-10: I48), and other cardiac arrhythmias (ICD-10: I49)] was defined by the outpatient or hospitalization records with the medical claims.[35] The Charlson Comorbidity Index[36] was calculated from comorbid conditions, assigning specific weights from medical claims records (categorized as 0, 1, and ≥2).

Statistical analysis

Using inverse distance weighting approach, we imputed missing values of measurement data on PM_{10} and $PM_{2.5}$ on certain days in the NAMIS database. Each missing value was imputed with the average of nearest stations weighted by the inverse distance to account for change of concentration

level and composition of air pollutant over time. We used the Bland–Altman plot to assess the agreement between the actual measurement and imputed data of missing values on air pollutants derived from inverse distance weighting interpolation.

Participants were followed up from 1 January 2016 (index date) until the earliest date of incident stroke, death from CVD or other causes, or 31 December 2021 (end of the follow-up period), whichever came first. If no stroke events or deaths occurred, the participants were followed up until the end of the follow-up period (31 December 2021). We developed a multivariable Cox proportional hazards regression model to explore the association of cardiovascular benefit with statin use against air pollutant exposure among the participants. The model was adjusted for sociodemographic factors (age, sex, insurance premium, residential area), health status (BMI, hypertension, type 2 diabetes hyperlipidaemia), health behaviour (cigarette smoking, physical activity), clinical characteristics (aspirin, NSAIDs, antiplatelet, anticoagulants, cardiac arrhythmias, and Charlson Comorbidity Index). The multicollinearity of the variables used in the regression model was tested with variance inflation factor (VIF). Proportional hazards assumption was verified using Schoenfeld residuals. Using the multivariable model, we computed adjusted hazard ratio (HR) and 95% confidence intervals (CI) for incident CVD in statin user as compared to statin non-user exposed to different levels of air pollutant. To further investigate this association, we utilized restricted cubic splines with four knots placed at the 5th, 33th, 67th, and 95th percentiles of days of statin use. Stratified analyses were performed to assess whether the association remained consistent in subgroups and interaction tests were conducted with the likelihood ratio test. Furthermore, we used DDD to define statin use and assessed ischaemic and haemorrhagic stroke events as separate events in sensitivity analyses. We used a Kruskal–Wallis test, analysis of variance, and χ^2 test to compare median, mean, and percentage of PM_{10} and $PM_{2.5}$ levels as well as sociodemographic, health behaviour, and clinical characteristics of the participants across the residential area, respectively.

All data collection, analyses, and visualization were conducted with SAS Enterprise Guide 7.1 and R version 3.5.3. We considered $P < 0.05$ (two-sided) as statistically significant.

Results

The NHIS cohort of adults aged 60 years and older consisted of 1 229 444 participants including 852 368 statin non-users (69.3%) and 377 076 statin users (30.7%). After imputation, the Bland–Altman plot demonstrated a high level of agreement between imputed and actual values for air pollutant exposure (Pearson correlation coefficient > 0.9 for both PM_{10} and $PM_{2.5}$) (eFigure 1 in the Supplement). Among statin non-users, median values for high level of average daily air pollutant exposure were 51.8 μg/m^3 [interquartile range (IQR), 51.2–52.4] for PM_{10} and 26.0 μg/m^3 (IQR, 25.4–27.5) for $PM_{2.5}$. Similar degree of average daily air pollutants was observed in statin users exposed to high level of air pollutants. Level of low or moderate exposure of average daily air pollutant was also similar in the two groups. *Table 1* shows sociodemographic factors, health status and behaviour, and clinical characteristics of the participants at baseline stratified by statin use.

During 11 963 322 person-years of follow-up, a total of 86 018 incident stroke events occurred in the NHIS cohort of 1 229 444 participants. Compared to statin non-user exposed to high level of PM_{10} (>50 μg/m^3) and $PM_{2.5}$ (>25 μg/m^3), statin users had 18% (adjusted HR, 0.82; 95% CI, 0.77–0.87) and 15% (adjusted HR, 0.85; 95% CI, 0.82–0.88) lower adjusted risk of incident stroke for PM_{10} and $PM_{2.5}$, respectively. Similar degree of the risk reduction for incident stroke was found among statin users exposed to low or moderate level of PM_{10} (≤50 μg/m^3) and $PM_{2.5}$ (≤25 μg/m^3) exposure (adjusted HR, 0.84; 95% CI, 0.82–0.86 for PM_{10} and adjusted HR, 0.84; 95% CI, 0.81–0.86 for $PM_{2.5}$, respectively). The association of statin use with incident stroke stratified by different levels of cumulative air pollutant exposure is shown in *Table 2*. The cardiovascular benefit of statin use against air pollution appeared to be dose-dependent when the study participants were further categorized into statin non-user (never use of statin or <90 days) and statin user (90–180 days, 181–364 days, 365–729 days, and ≥730 days). As compared to statin non-user exposed to high level of PM_{10} and $PM_{2.5}$, the risk of incident stroke was not significantly lower in statin user with 90–180 days (adjusted HR, 0.93; 95% CI, 0.82–1.06 for PM_{10} and adjusted HR, 0.99; 95% CI, 0.93–1.05 for $PM_{2.5}$). However, the risk of stroke was significantly lower in statin user with 181–364 days (adjusted HR, 0.83; 95% CI, 0.72–0.93 for PM_{10} and adjusted HR, 0.84; 95% CI, 0.79–0.90 for $PM_{2.5}$), 365–729 days (adjusted HR, 0.84; 95% CI, 0.75–0.94 for PM_{10} and adjusted HR, 0.85; 95% CI, 0.80–0.91 for $PM_{2.5}$), and more than 730 days (adjusted HR, 0.77; 95% CI, 0.71–0.84 for PM_{10} and adjusted HR, 0.80; 95% CI, 0.77–0.84 for $PM_{2.5}$) (P value for trend < 0.001). Similar results were found for low or moderate exposure to air pollutant (*Table 3*). The restricted cubic spline model showed the cardioprotective association of statin use across different levels of exposure to average daily air pollutant exposure (*Figure 2*). Stratified analyses demonstrated that the association of cardiovascular benefit with statin use against different levels of cumulative air pollutant remained generally consistent, although statistical significance was attenuated in participants with hypercholesterolaemia (total cholesterol ≥ 240 mg/dL), without hypertension, and anticoagulant use. Statistically significant interactions were not found in most of the subgroups ($P > 0.05$ for all interactions) except for total cholesterol level, LDL-cholesterol level, hypertension, type 2 diabetes, NSAIDs use, antiplatelet use, and anticoagulant use (*Figure 3*). Participant characteristics based on statin dosage and residential area are presented in the Supplementary material online, *Tables S1* and *S2*. In sensitivity analyses, the association between statin use, as defined by DDD, and cardioprotective association against cumulative exposure to different levels of air pollutants remained consistent, demonstrating a 15–17% lower risk in statin users compared to non-users. The overall results were consistent with the primary analysis when CHD and total stroke were separately examined as outcomes (see Supplementary material online, *Tables S1–S8*). The multicollinearity test with VIF showed that all variables used in the regression model exhibited low levels of multicollinearity (VIF < 5 for all variables) (see Supplementary material online, *Table S9*).

Discussion

In this cohort of adults aged 60 years and older free of CVD at baseline exposed to high and low or moderate levels of PM_{10} and $PM_{2.5}$, statin use was associated with significantly lower risk of stroke. The cardiovascular benefit of statin use against air pollutant exposure among older adults appeared to be dose-dependent, and the results remained generally consistent across clinically important subgroups.

Comparison with other studies

Our observation of the CVD risk reduction among statin users as compared to statin non-users exposed to different levels of air pollutants is consistent with well-established evidence on primary prevention of CVD with statin therapy. A network meta-analysis of 76 randomized controlled trials (RCTs) including more than 170 000 participants demonstrated a 14%–26% risk reduction of non-fatal myocardial infarction and stroke [pooled relative risk (RR), 0.74; 95% CI, 0.67–0.81 and RR, 0.86; 95% CI, 0.78–0.95, respectively] in participants randomly allocated to receive statin as compared to the placebo groups.[37] However, in that study, only one RCT [i.e. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)] comprised of 5804 participants aged 70–82 years conducted nearly two decades ago was included for evidence synthesis.[38] In addition to the findings from the PROSPER trial, a subgroup of 1263 UK adults aged between 75 and 80 from the Heart Protection Study (HPS) and a cohort of 7 242 193

Table 1 Characteristics of the older adults aged 60 years and older residing in metropolitan areas according to statin use in the National Health Insurance Service cohort

	Statin non-user (<90 days)	Statin user (≥90 days)	*P* value
No. of participants	852 368	377 076	
Air pollutant, median (IQR), μg/m^3			
PM_{10}			
High (>50 μg/m^3)	51.8 (51.2–52.4)	51.8 (51.2–52.4)	
Moderate/low (≤50 μg/m^3)	45.5 (44.9–46.3)	45.5 (44.9–46.3)	
$PM_{2.5}$			
High (>25 μg/m^3)	26.0 (25.4–27.5)	26.0 (25.4–27.3)	
Moderate/low (≤25 μg/m^3)	23.2 (22.9–24.2)	23.2 (22.9–24.2)	
Age, mean (SD)	67.2 (6.2)	67.4 (6.0)	<0.001
Sex			<0.001
Male	455 034 (53.4)	142 333 (37.7)	
Female	397 334 (46.6)	234 743 (62.3)	
Insurance premium[a]			<0.001
Upper half	492 072 (57.7)	224 648 (59.6)	
Lower half	360 296 (42.3)	152 428 (40.4)	
Residential area (city)			<0.001
Seoul	500 608 (58.7)	227 048 (60.2)	
Incheon	132 259 (15.5)	55 413 (14.7)	
Busan	219 501 (25.8)	94 615 (25.1)	
Cigarette smoking			<0.001
Past smoker	192 787 (22.6)	68 504 (18.2)	
Never smoker	540 213 (63.4)	271 868 (72.1)	
Current smoker	119 368 (14.0)	36 704 (9.7)	
Body mass index, mean (SD), kg/m^2	23.8 (3.0)	24.5 (3.0)	<0.001
Physical activity			<0.001
Inactive	418 496 (49.1)	190 982 (50.6)	
Active[b]	433 872 (50.9)	186 094 (49.4)	
Hypertension[c]	622 735 (73.1)	314 930 (83.5)	<0.001
Type 2 diabetes[d]	109 418 (12.8)	102 380 (27.2)	<0.001
Hyperlipidaemia[e]	85 016 (10.0)	72 030 (19.1)	<0.001
LDL-cholesterol, mean (SD), mg/dL	119.2 (33.4)	116.1 (57.1)	<0.001
High (>160 mg/dL)	73 385 (8.6)	64 976 (17.2)	
Borderline (130–159 mg/dL)	224 596 (26.3)	74 927 (25.0)	
Normal (<130 mg/dL)	554 387 (65.0)	237 173 (62.9)	
Medication use			
Aspirin	101 138 (11.9)	100 319 (26.6)	<0.001
NSAIDs	655 715 (76.9)	312 883 (83.0)	<0.001
Antiplatelet[f] (without acetylsalicylic acid)	42 623 (5.0)	47 708 (12.7)	<0.001
Anticoagulants[g]	7773 (0.9)	5141 (1.4)	<0.001
Cardiac arrhythmias			
Paroxysmal tachycardia	4168 (0.5)	2654 (0.7)	<0.001
Atrial fibrillation and flutter	10 821 (1.3)	6366 (1.7)	<0.001
Other cardiac arrhythmias	20 571 (2.4)	12 603 (3.3)	<0.001
Charlson Comorbidity Index			<0.001
0	356 759 (41.9)	89 367 (23.7)	
1	242 036 (28.4)	104 434 (27.7)	
≥2	253 573 (29.)	183 275 (48.6)	

Presented as *N* (%) unless otherwise specified.
PM, particulate matter; IQR, interquartile range; SD, standard deviation; MVPA, moderate to vigorous physical activity; SBP, systolic blood pressure; DBP, diastolic blood pressure; FSG, fasting serum glucose; NSAIDs, non-steroidal anti-inflammatory drugs.
[a]Proxy for socioeconomic status.
[b]More than one time of MVPA per week based on the self-reported questionnaire.
[c]Defined as SBP ≥ 130 mmHg or DBP ≥ 80 mmHg or prescription of antihypertensive drugs.
[d]Defined as FSG ≥ 126 mg/dL or prescription of antidiabetic drugs.
[e]Defined as total cholesterol ≥ 240 mg/dL.
[f]Includes clopidogrel, ticagrelor, ticlopidine, abciximab, tirofiban, prasugrel, cilostazol, and others.
[g]Includes warfarin, heparin, enoxaparin, dabigatran, rivaroxaban, apixaban, fondaparinux, and others.

Table 2 Hazard ratio for risk of incident stroke according to statin use stratified by different levels of average daily air pollutant exposure in older adults aged 60 years and older residing in metropolitan areas in the National Health Insurance Service cohort

	Statin non-user (<90 days)	Statin user (≥90 days)
PM_{10}		
High PM_{10} (>50 μg/m^3)		
No. of participants	109 245	45 492
Event	4120	1552
Person-year (PY)	623 713	262 251
Crude rate/100 000 PY	660.6	591.8
HR (95% CI)	1 (reference)	0.80 (0.75–0.85)*
Low/moderate PM_{10} (≤50 μg/m^3)		
No. of participants	743 123	331 584
Event	26 209	11 128
Person-year (PY)	4 265 997	1 917 441
Crude rate/100 000 PY	614.4	580.4
HR (95% CI)	1 (reference)	0.83 (0.81–0.85)*
$PM_{2.5}$		
High $PM_{2.5}$ (>25 μg/m^3)		
No. of participants	381 077	162 905
Event	14 899	5982
Person-year (PY)	2 175 482	938 818
Crude rate/100 000 PY	684.9	637.2
HR (95% CI)	1 (reference)	0.83 (0.80–0.86)*
Low/moderate $PM_{2.5}$ (≤25 μg/m^3)		
No. of participants	471 291	214 171
Event	15 430	6698
Person-year (PY)	2 714 227	1 240 875
Crude rate/100 000 PY	568.5	539.8
HR (95% CI)	1 (reference)	0.83 (0.80–0.85)*

Hazard ratio is computed from the multivariable Cox proportional hazards model adjusted for age, sex, insurance premium, residential area, body mass index, cigarette smoking, physical activity, hypertension, type 2 diabetes, LDL-cholesterol, aspirin, NSAIDs, antiplatelet (without acetylsalicylic acid), anticoagulants, cardiac arrhythmias (paroxysmal tachycardia, atrial fibrillation and flutter, and other cardiac arrhythmias), and Charlson Comorbidity Index.
PM, particulate matter; PYs, person-years; HR, hazard ratio; CI, confidence intervals; LDL, low-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs.
*$P < 0.001$.

US veterans aged 75 years and older showed a significant CVD risk reduction associated with statin use.[39,40] However, neither PROSPER trial nor HPS addressed the cardiovascular benefit of statin use against chronic exposure to air pollutants in older adults possibly due to lack of data on environmental risk factors for CVD in RCTs. Such data are usually available in observational cohort studies linked to aerial-level environmental data through geocoded residential addresses.

Currently, evidence on cardiovascular benefit of statin use against air pollutant exposure is limited to experimental and observational studies on cardiovascular biomarkers. Two investigators in China used animal models exposed to $PM_{2.5}$ and found that exposure to $PM_{2.5}$ increased atherosclerotic risk in 32 Wistar rats by inducing elevated levels of cholesterol, oxidative stress, and inflammation.[19] In this experiment, administration of atorvastatin to the rats was effective in attenuating myocardial inflammation caused by $PM_{2.5}$ exposure and led to improved levels of CVD-associated biomarkers such as triglyceride, HDL-cholesterol, interlukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), high sensitivity-C-reactive protein. While this experimental study demonstrated biologically plausible mechanisms on cardiovascular benefit of statin use in the animal models exposed to $PM_{2.5}$, the evidence is limited to the animal model of human diseases. Meanwhile, investigators of the Study of Women's Health Across the Nation (SWAN), a multi-ethnic cohort of mid-life US women, examined vulnerable subgroups with chronic exposure to $PM_{2.5}$ among 1923 participants.[20] In the SWAN cohort, the significant association between $PM_{2.5}$ exposure and elevated level of C-reactive protein was observed, especially among the elderly individuals with diabetes, and those who smoke cigarettes or were single. Moreover, this association was attenuated among those with statin use measured by per cent change in C-reactive protein due to 10.0 μg/m^3 annual change in $PM_{2.5}$. Our analyses of the NHIS cohort further extend evidence on cardiovascular benefit of statin use against chronic exposure to PM_{10} and $PM_{2.5}$ with large, population-level data with ascertained CVD events in older adults.

Implications

The potential mechanisms beyond the association of cardiovascular benefit with statin use against ambient air pollutants found in this study are multifactorial. Chronic exposure to PM_{10} or $PM_{2.5}$ is known to have an adverse impact on cardiovascular health by inducing inflammation, oxidative stress, and endothelial dysfunction, especially in the elderly

Table 3 **Hazard ratio for risk of incident stroke according to statin use stratified by different levels of average daily air pollutant exposure in older adults aged 60 years and older residing in metropolitan areas in the National Health Insurance Service cohort**

	Statin non-user (<90 days)	Statin user (90–180 days)	Statin user (181–364 days)	Statin user (365–729 days)	Statin user (≥730 days)	*P* value for trend
PM_{10}						
High PM_{10} (>50 μg/m^3)						
No. of participants	109 245	7341	7185	9113	21 853	
Event	4120	265	238	319	730	
Person-year (PY)	623 713	42 316	41 360	52 468	126 108	
Crude rate/100 000 PY	660.6	626.2	575.4	608.0	578.9	
HR (95% CI)	1 (reference)	0.90 (0.80–1.03)	0.79 (0.69–0.90)*	0.82 (0.73–0.92)*	0.77 (0.71–0.83)*	<0.001
Low/moderate PM_{10} (≤50 μg/m^3)						
No. of participants	743 123	54 986	50 324	64 941	161 333	
Event	26 209	1994	1748	2138	5248	
Person-year (PY)	4 265 997	317 647	290 874	385 531	933 390	
Crude rate/100 000 PY	614.4	627.7	600.9	554.6	562.3	
HR (95% CI)	1 (reference)	0.98 (0.94–1.03)	0.88 (0.84–0.93)*	0.81 (0.77–0.85)*	0.78 (0.75–0.80)*	<0.001
$PM_{2.5}$						
High $PM_{2.5}$ (>25 μg/m^3)						
No. of participants	381 077	30 111	26 904	32 918	72 972	
Event	14 899	1167	948	1216	2651	
Person-year (PY)	2 175 482	173 528	155 048	189 624	420 618	
Crude rate/100 000 PY	684.9	672.5	611.4	641.3	630.3	
HR (95% CI)	1 (reference)	0.95 (0.90–1.01)	0.82 (0.76–0.87)*	0.83 (0.78–0.88)*	0.79 (0.75–0.82)*	<0.001
Low/moderate $PM_{2.5}$ (≤25 μg/m^3)						
No. of participants	471 291	32 216	30 605	41 136	110 214	
Event	15 430	1092	1038	1241	3327	
Person-year (PY)	2 714 227	186 434	177 186	238 374	638 880	
Crude rate/100 000 PY	568.5	585.7	585.8	520.6	520.8	
HR (95% CI)	1 (reference)	0.99 (0.93–1.05)	0.93 (0.87–0.99)*	0.79 (0.75–0.84)*	0.76 (0.73–0.79)*	<0.001

Hazard ratio is computed from the multivariable Cox proportional hazards model adjusted for age, sex, insurance premium, body mass index, residential area, cigarette smoking, physical activity, hypertension, type 2 diabetes, LDL-cholesterol, aspirin, NSAIDs, antiplatelet (without acetylsalicylic acid), anticoagulants, cardiac arrhythmias (paroxysmal tachycardia, atrial fibrillation and flutter, and other cardiac arrhythmias), city (residential area), and Charlson Comorbidity Index.
PM, particulate matter; PYs, person-years; HR, hazard ratio; CI, confidence intervals; LDL, low-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs.
*$P < 0.001$.

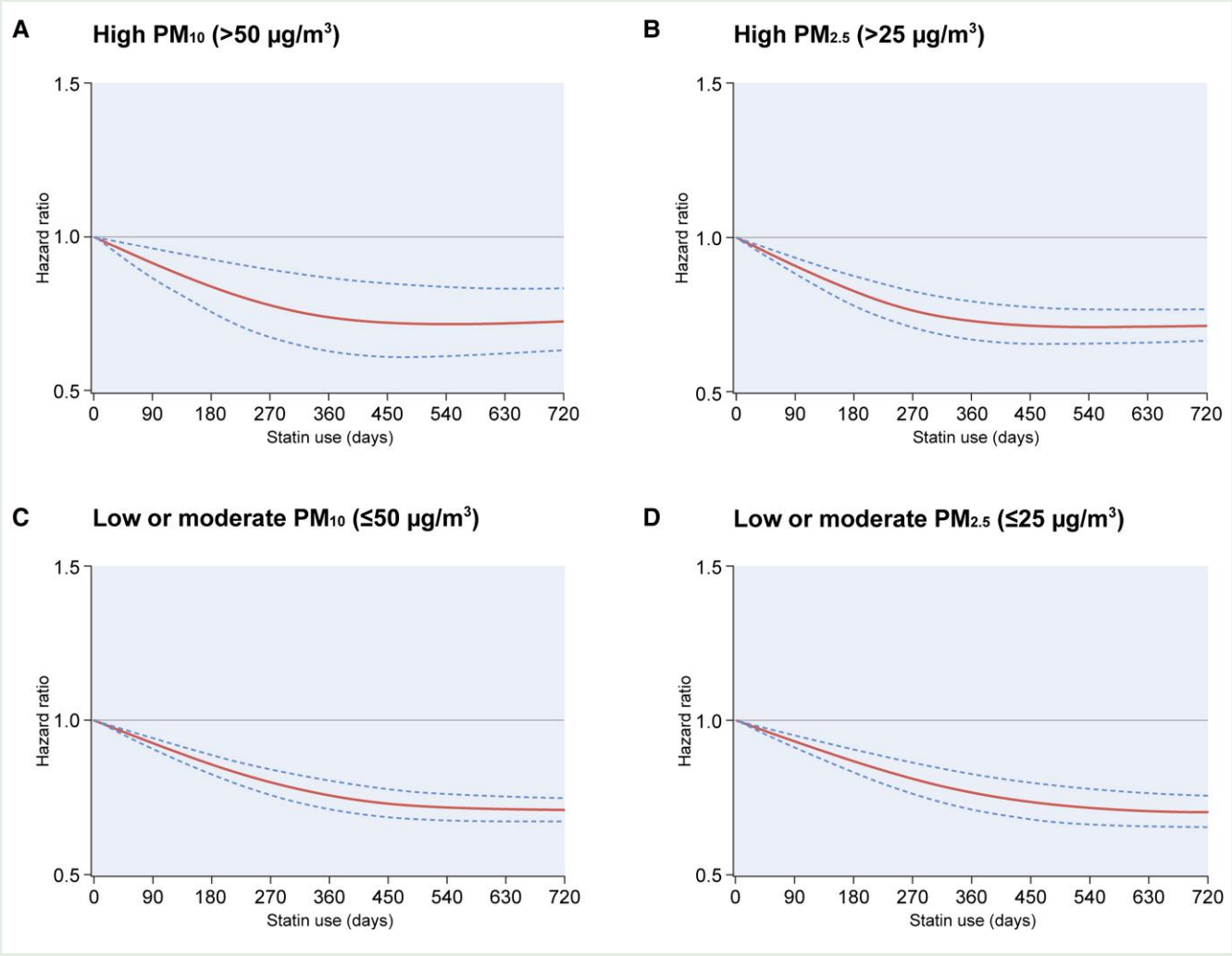


Figure 2 Restricted cubic spline plots of the association between cumulative days of statin use and incident cardiovascular risk among adults aged 60 years and older exposed to different levels of air pollutants. Reference level is no statin use, and the knots were placed at the 5th, 33th, 67th, and 95th percentiles of days of statin medication. The curves were adjusted for age, sex, insurance premium, residential area, body mass index, cigarette smoking, physical activity, hypertension, type 2 diabetes, LDL-cholesterol, aspirin, NSAIDs, antiplatelet (without acetylsalicylic acid), anticoagulants, cardiac arrhythmias (paroxysmal tachycardia, atrial fibrillation and flutter, and other cardiac arrhythmias), and Charlson Comorbidity Index using the multivariable Cox proportional hazards model. PM, particulate matter; NSAIDS, non-steroidal anti-inflammatory drugs; LDL, low-density lipoprotein.

population.[41] Air pollutants could also damage the endothelium and promote the development of atherosclerosis through systemic inflammation.[42] Among individuals chronically exposed to PM_{10} or $PM_{2.5}$, statin use may reduce the expression of pro-inflammatory cytokines (e.g. IL-6 and TNF-α) and adhesion molecules, which may be helpful in prevention of the activation of inflammatory pathways in response to air pollutant exposure.[43] Also, statins could potentially increase the activity of antioxidant enzymes and reduce vascular oxidative stress caused by exposure to air pollutants.[43] In addition, statins have been shown to improve endothelial function by promoting the production of endothelial nitric oxide, a molecule that helps to dilate blood vessels and improve blood flow.[44] Overall, the cardiovascular benefit of statin use against air pollutants is likely to involve multiple mechanisms including their anti-inflammatory, antioxidant, and endothelial protective effects.

A recent joint opinion from the World Heart Federation, American College of Cardiology, AHA, and the ESC emphasizes the importance of structural actions for reducing air pollution emissions and minimizing exposure to air pollutant for substantial cardiovascular health benefits.[45,46] While drugs are not originally intended to protect individuals against harmful effects of air pollutants, our study suggests the association of cardiovascular benefit with statin use against chronic exposure to PM_{10} and $PM_{2.5}$ in older adults. The observational nature of our study prevents any definitive conclusion on the causality of the cardioprotective association with statin use against air pollutant exposure. Therefore, the evidence on safety and efficacy of statin use to mitigate the harmful effects of air pollutant exposure should be further supported by controlled, randomized studies.

Strengths and limitations

Notable strengths of our study include analyses of a large and representative study population with linkage to cumulative average of air pollutant data collected from reliable environmental database to address the time-varying nature of PM_{10} and $PM_{2.5}$. Moreover, we were able to account for a wide range of confounders on sociodemographic factors, health status, health behaviour, and clinical characteristics for adjustment and stratified analyses to minimize potential bias in the analyses.

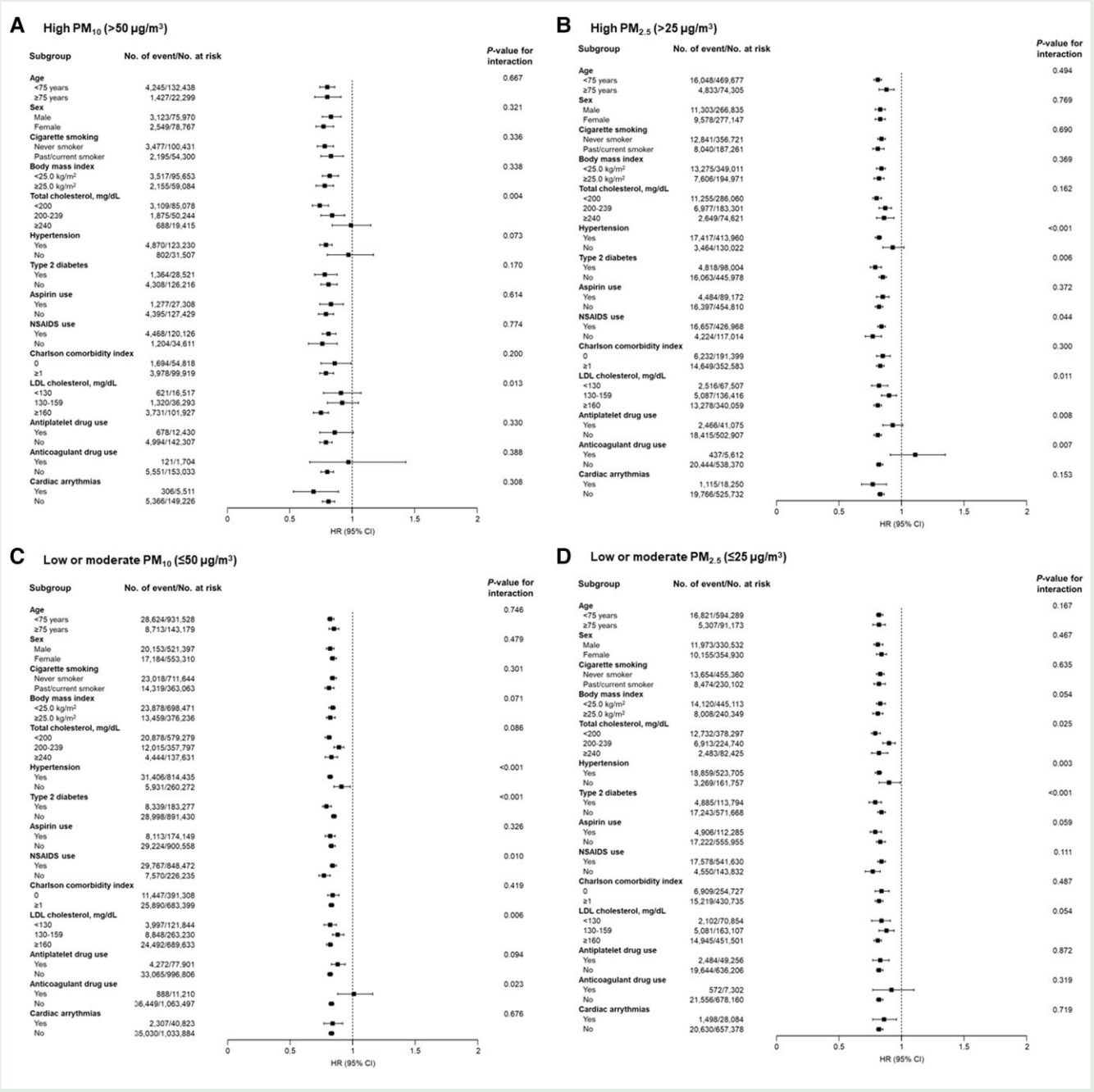


Figure 3 Subgroup analyses for the association of statin use with incident cardiovascular risk among adults aged 60 years and older with high and low or moderate levels of PM_{10} and $PM_{2.5}$ exposure. Statin use is defined as more than 90 days of prescription. Hazard ratio and 95% CI in each subgroup is derived from the Cox proportional hazards model adjusted for all of the variables listed in other subgroups. PM, particulate matter; NSAIDS, non-steroidal anti-inflammatory drug; CI, confidence intervals.

Our study has several limitations. First, we lacked individual-level data on exposure to air pollutant from personal exposure monitoring equipment. Instead, we were only able to use the data derived from outdoor monitoring stations. Nonetheless, well-established population-based studies have demonstrated that air pollutant data obtained from fixed sites could be a reliable substitute for personal-level exposure.[30,31] Second, this study did not include older adults living outside of the three major cities in the Republic of Korea. This was due to the limited data availability of PM_{10} and $PM_{2.5}$ from the NAMIS database for locations other than those cities. Thus, the generalizability of the association found in this study is limited to the metropolitan area in the country. Third, it should be noted that statin prescription records in the NHIS database were used as a proxy for statin use. Therefore, whether the older adults in the NHIS cohort took statin medication as prescribed remains uncertain.

Fourth, the ascertainment of cardiac arrhythmias among participants relied on medical claims records rather than direct electrocardiogram monitoring. Fifth, our study is limited by a lack of data on potential

socioeconomic disparities in exposure to PM_{10} and $PM_{2.5}$. This gap may be attributed to variations in indoor or outdoor activities during work hours and warrants future research.[47] Sixth, in this study, outcome event was limited to incident stroke, and additional research, including other CVD events such as CHD is imperative to enhance the generalizability of our findings. Nonetheless, our analyses showed a significant dose–response relationship between statin use and CVD risk reduction against air pollutant. This association is also supported by evidence on the CVD risk reduction among patients with high medication compliance.[48] Lastly, the observational nature of our study prevents any definitive conclusion on the causality of the cardioprotective association with statin use against air pollutant exposure. Therefore, the evidence on safety and efficacy of statin use to mitigate the harmful effects of air pollutant exposure should be further supported by controlled, randomized studies.

Conclusion

In a large cohort of adults aged 60 and older exposed to both high and low or moderate levels of air pollutants, statin use was associated with a significantly lower risk of stroke in a dose–response manner. Nonetheless, due to the observational nature of this epidemiologic study, further research is warranted to assess the precise role of statin therapy for prevention of CVD against air pollutant.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

K.K.: Conceptualization, Methodology, Writing—original draft, Visualization. S.J.: Conceptualization, Methodology, Writing—original draft, Data Curation. S.C.: Writing—review and editing. J.C.: Writing—review and editing, Data Curation, Validation. D.C.: Writing—review and editing. G.L.: Writing—review and editing. S.R.K.: Data Curation. S.M.P.: Conceptualization, Supervision, Writing—review and editing.

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Conflict of interest: none declared.

Data availability

No additional data available. Only authorized researchers were permitted access to the database at the Big Data Research Center, National Health Insurance Service (NHIS-2019-1-637), Seoul, Republic of Korea.

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