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Role of low-density lipoprotein in mediating the effect of air pollution on coronary heart disease: a two-step multivariate Mendelian randomization study

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Abstract. – OBJECTIVE: Air pollution is affecting the health of millions of people all over the world. The causal correlations of PM2.5, PM10, and nitrogen dioxide (NOx), as the main fine particulate matter, and coronary heart disease (CHD) are yet to be explored. Low-density lipoprotein (LDL) has been a principal factor in the pathogenesis of CHD. It is an interesting issue to consider whether LDL mediates the effect of air pollutants in CHD pathogenesis.

MATERIALS AND METHODS: A genome-wide association study (GWAS) on the European population, followed up from 2010 to 2018, involving over 400,000 participants, was based on a land-use regression model. The annual mean concentrations of major air pollutant particles, PM2.5 (n=423,796), PM10 (n=423,796), and NOx (n=456,380), were recorded. The large GWAS database of CHD covered over ten million SNPs with independent single nucleotide polymorphisms (SNPs). LDL database collected major biochemical blood parameters from over 400,000 patients (n=440,546). Taken together, we conducted independent two-sample Mendelian randomization (MR) analyses for the causality between air pollutants (PM2.5, PM10, and NOx) and CHD. Multivariate MR analysis was conducted using causal relationships to determine the direct effects of exposure on outcome. The fixed-effect inverse variance weighted (IVW2) method was mainly employed to assess this relationship, with a confidence interval of 95% for the odds ratio (OR). Also, MR-Egger, weighted median, maximum likelihood ratio method, and random-effects inverse variance-weighted (IVW1) method were adopted as supplementary methods.

RESULTS: Two-sample MR results based on the IVW2 method suggested positive correlations between PM2.5 and CHD [OR 1.875 (1.279-2.748), *p*=0.001], PM10 and CHD [OR 2.586 (1.479-4.523), *p*=0.001], and NOx and CHD [OR 2.991 (2.021-4.427), *p*=4.37E-08]. The direct effect and mediating proportion were calculated using multivariable Mendelian randomization (MVMR). Lastly, the mediating proportions of LDL in the regulatory roles of PM2.5, PM10, and NOx in CHD were 2.82%, 4.73%, and 9.54%, respectively.

CONCLUSIONS: PM2.5, PM10, and NOx share direct causal associations with CHD, and LDL performs a mediating role in this pathogenic process. Early prevention against air pollution (such as increasing green areas and reducing large-scale industrial dust emissions) and early lipid-lowering treatment can effectively prevent the occurrence of CHD.

Key Words:
Air pollution, Low-density lipoprotein, Coronary heart disease, Mendelian randomization, Mediation.

Introduction

Coronary atherosclerotic heart disease is the dominating cause of death in the world, leading to approximately 0.36 million deaths in the United States and 1.78 million deaths in Europe annually[1]. The well-known risk factors for coronary heart disease (CHD) involve smoking, obesity, age, gender (male), diabetes, etc. Prevention against the aforementioned risk factors significantly reduces the incidence of CHD and has a favorable prognosis. In addition to traditional risk factors, recent studies[2] have illustrated that the incidence of CHD may be relevant to long-term exposure to air pollutants such as PM2.5, PM10, and NO_2.

The air pollutants generated by solid fuel combustion, such as fine particulate matter (PM2.5/PM10) and nitrogen dioxide (NOx), augment the risk of obesity and cardiometabolic diseases in

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children and adults. Long-term exposure to the above two air pollutants remarkably increases low-density lipoprotein (LDL) levels in most obese and several non-obese individuals[3]. Oxidized LDL is regarded as the core pathogenic mechanism for CHD[4]. Additionally, multiple cohort studies and meta-analyses[5] have elucidated that fine PM in the air environment is linked to the occurrence of CHD.

The pathogenic process of CHD is extremely complicated, and its progression is determined by the interaction between the environment and susceptible polygenic hosts. Recent genome-wide association studies[6] have improved our understanding of the genetic basis of CHD and provided fundamental data for the Mendelian randomization (MR) method. MR explores the relationship between exposure and outcome, relying on genetic variants as instrumental variables (IVs).

The randomly assigned genetic variants eliminate confounding biases and reverse causality in observational studies[7]. Meanwhile, as a large-scale prospective cohort study[8], the UK Biobank provides extensive information about air pollutants such as PM2.5, PM10, and NO_2. Therefore, we sought to comprehensively evaluate the causality between common air pollutants and CHD and further probed into the role of LDL in mediating the impact of air pollutants on CHD.

Materials and Methods

Study Design

To explore the genetic association between air pollutants and CHD, we conducted a two-sample MR analysis using the GWAS database with a large amount of data. The total effect of each exposure on the outcome can be categorized into direct effects and indirect effects. The direct effect of air pollutants on CHD could be identified through multivariate MR after the adjustment of LDL. The indirect effect mediated by LDL is also known as the mediating effect. Firstly, we probed into the impact of air pollutants on LDL. Eventually, after adjustment of the potential mediator (LDL), multivariate MR was conducted to determine the direct impact of exposure on outcomes. The mediating effect was assessed by subtracting the direct effect from the total effect. The ratio of the mediating effect to the total effect was calculated to determine the mediating role of LDL in the pathogenic process further (Figure 1).

Data Resources for MR Analysis

Tabulate statistics of fine particulates in air pollution were sourced from (GWAS) UK Biobank, and the annual mean concentrations of PM2.5, PM10, NO_2, and NOx were estimated using a land-use regression (LUR) model developed by the ESCAPE research team. This model uses estimated variables obtained from geographic in-

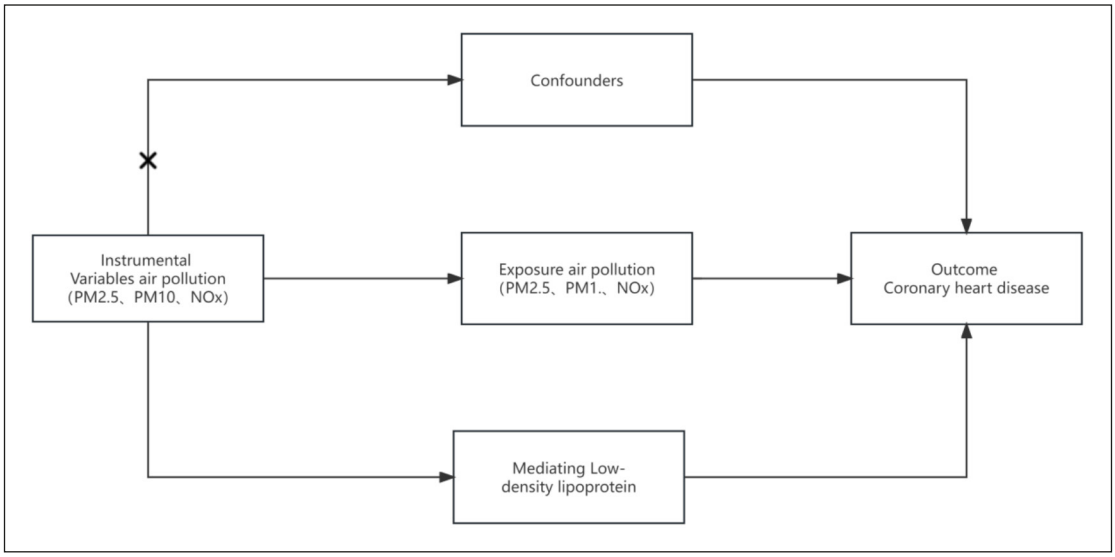

Figure 1. Schematic diagram of MR Hypothesis based on MR Analysis of the relationship between low-density lipoprotein mediating air pollutants and coronary heart disease.

formation systems (GIS) and is linked to the residential addresses provided by participants during baseline access to the UK Biobank. Exposure data from 2010 to 2018 were measured individually. We calculated the annual mean air pollutant concentrations of PM with diameters (D) ≤2.5 (PM2.5) and D ≤10 (PM10) and nitrogen oxides (NO2 and NOx) and linked them to the residential addresses of the participants[8,9]. The patients with missing participant information, patients without air pollution measurement data, and patients with medical records of cancer or a history of cardiovascular diseases were excluded. The final main analysis (N=423,796) involved approximately 400,000 participants.

FinnGen Biobank is a large-scale public-private partnership aimed at collecting and analyzing genetic and health data from 500,000 participants in the FinnGen Biobank (https://www.finngen.fi/en), which provides CHD GWAS tabulate statistics data, including more than 10 million SNPs[10]. The CHD data in participants were analyzed.

LDL data were acquired from the IEU Open GWAS project, and biochemical parameters were collected from approximately 400,000 patients (Table I). The blood lipid concentrations were recorded, and patients with primary hyperlipidemia were eliminated.

We are using a public database; therefore, ethics approval is not required.

Genetic IVs

To construct an effective genetic variation model, three assumptions required for the MR analysis must be met. (1) The genetic variations of PM2.5, PM10, and NOx are significantly correlated with the exposure levels of PM2.5, PM10, and NOx. (2) The correlations of PM2.5, PM10, and NOx genetic IVs with CHD are not affected by confounding factors. (3) PM2.5, PM10, and NOx genetic IVs only affect the incidence of CHD through their exposure. This study followed the Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR). We selected applicable single nucleotide polymorphisms (SNPs) from the GWAS database to explore the causal relationship between exposure and outcomes at the genetic level. We used the R software package "TwoSampleMR" to select the corresponding SNPs (p<5E-6) for PM2.5, PM10, and nitrogen oxide exposures with genome-wide significance thresholds (Kb=5,000 and the linkage disequilibrium r^2<0.001) This approach was adopted to ensure that the selected SNPs are not in linkage disequilibrium and represent independent genetic variants[11,12]. Meanwhile, factors such as age, gender, blood lipid, diabetes, etc., were deleted to limit the influence of confounding factors.

TSMR and Mediation Analysis

TSMR

MR-Egger, weighted median, random-effects inverse variance-weighted (IVW1) method, maximum likelihood ratio method, linear weighted median, and fixed-effect inverse variance weighted (IVW2) method were employed to determine the causality between air pollutants (PM2.5, PM10, NOx) and CHD. For the preliminary analysis, we used the IVW2 method and assumed that all genetic variants in the analysis were valid IVWs. Afterwards, a sensitivity analysis was conducted. Firstly, the weighted median method was chosen because it provides a reliable estimation of causal relationships. It was assumed that over 50% of IVs were valid. Thirdly, we calculated the p-values derived from Cochrane's Q and Q statistics to evaluate heterogeneity (p<0.05 was considered statistically significant). Ultimately, we conducted MR-Egger regression analysis to reveal possible horizontal pleiotropy by calculating p-values (p>0.05)[13].

Table I. Details of GWAS included in Mendelian randomization analyses.

Trait	Consortium	No. of samples	No. of SNPs	Ethnicity
PM2.5	UK Biobank	423,796	44	European
PM10	UK Biobank	423,796	23	European
NOx	UK Biobank	456,380	40	European
LDL	IEU OpenGWAS project	440, 546	163	European
CHD	FinnGen Biobank	/	/	European

PM2.5, particulate matter air pollution; PM10, particulate matter air pollution; NOx, nitrogen dioxide air pollution; LDL, low-density lipoprotein; CHD, coronary heart disease.

Mediation Analysis

The total effect of any exposure on the outcome was classified into direct and indirect effects. To determine the indirect effect of LDL on mediating the contribution of air pollutants to CHD, the following formula was applied to calculate the percentage of potential mediating effects (mediating proportion)[14].

After adjusting LDL, the direct effects of air pollutants (such as PM2.5, PM10, NO_2) on CHD were obtained through multivariate MR analysis. In this analysis, the regression coefficient β1 is the MR effect of air pollutants on mediators (such as LDL), β2 is the MR effect of the mediator (LDL) on CHD after adjustment of genetically determined air pollutants, and β3 represents the MR effect of air pollutants on CHD after adjusting the genetically determined potential mediator.

Sensitivity Analysis

The "leave-one-out method" was adopted for sensitivity analysis to identify SNPs with more significant correlations. In the meantime, SNPs were excluded one by one, and the correlations among all SNPs, except for that one, were evaluated.

Statistical Analysis

All data analysis was implemented using R Studio 4.2.1 with the "Two-Sample-MR (version 0.5.6, Bristol, UK)". The statistical significance level chosen was $p<0.05$.

Results

Selection of IVs

For the selection of IVs for air pollutants, we selected SNPs with significant genome-wide significance (p=5e-6, $r^2<0.001$ KB<5,000), PM2.5 (64), PM10 (29), and NOx (84). Several SNPs were deleted because they were strongly linked to age, obesity, hyperlipidemia, diabetes, and other confounding factors. The following SNPs served as IVs: PM2.5 (44), PM10 (23), and NOx (40).

For the selection of the mediator (LDL), we selected SNPs with significant genome-wide significance (p=5e-8, $r^2<0.001$ KB<10,000) and finally obtained LDL (163) after excluding confounding factors.

Total Effect of Air Pollution on CHD

A positive correlation was identified between genetically determined air pollutant PM2.5 and increased risk of CHD [IVW2: odds ratio (OR) 1.875 (1.279-2.745), p=0.001 ($p<0.05$ suggested statistical significance)]. There existed a positive correlation between PM10 and CHD risk [IVW2: OR 2.586 (1.479-4.523), p=0.001 ($p<0.05$ denoted statistical significance)]; NOx was positively linked to an increased risk of CHD [IVW2: OR 2.991 (2.021-4.427), p=4.37E-08 ($p<0.05$ showed statistical significance)]. The method used is presented in Figure 2. This result was consistent with other evaluation methods. No horizontal pleiotropy was found between fine particulate matter (PM2.5, PM10, and NOx) and CHD, but heterogeneity existed (Figure 2) (Table II).

Causal Effect of LDL on CHD

We notified a positive correlation of genetically determined LDL with an increased risk of CHD [IVW2: OR 1.752 (1.632-1.882), p=1.31E-53 ($p<0.05$ was considered statistically significant)], without heterogeneity or horizontal pleiotropy (Table II).

Causal Effect of Air Pollution on LDL

A positive association was observed between genetically determined air pollutant PM2.5 and the risk of elevated LDL [IVW2: OR 1.108 (1.045-1.175), p=0.001 ($p<0.05$ denoted statistical significance)], without horizontal pleiotropy or heterogeneity. Additionally, PM10 was positively relevant to the risk of elevated LDL [IVW2: OR 1.151 (1.054-1.258), p=0.002 ($p<0.05$ was regarded statistically significant)], without horizontal pleiotropy or heterogeneity. NOx was also positively linked to the risk of elevated LDL [IVW2: OR 1.093 (1.038-1.512), p=0.001 ($p<0.05$ signified statistical significance)], without horizontal pleiotropy or heterogeneity (Table II).

Mediating Effect and Proportion of LDL

In the PM2.5-LDL-CHD multivariate MR analysis, the direct effect of PM2.5 on CHD was calculated after adjusting LDL, and the mediating proportion of LDL was 2.82%. In the PM10-LDL-CHD multivariate MR analysis, the direct effect of PM10 on CHD was calculated after adjusting LDL, and the mediating proportion of LDL was 4.73%. In the NOx-LDL-CHD multivariate MR analysis, the direct effect of NOx on CHD was calculated after adjusting LDL, and the mediating proportion of LDL was 9.54% (Table III).

Discussion

Fine particulate matter PM2.5, PM10, and NOx are recognized as the main global pollutants. In

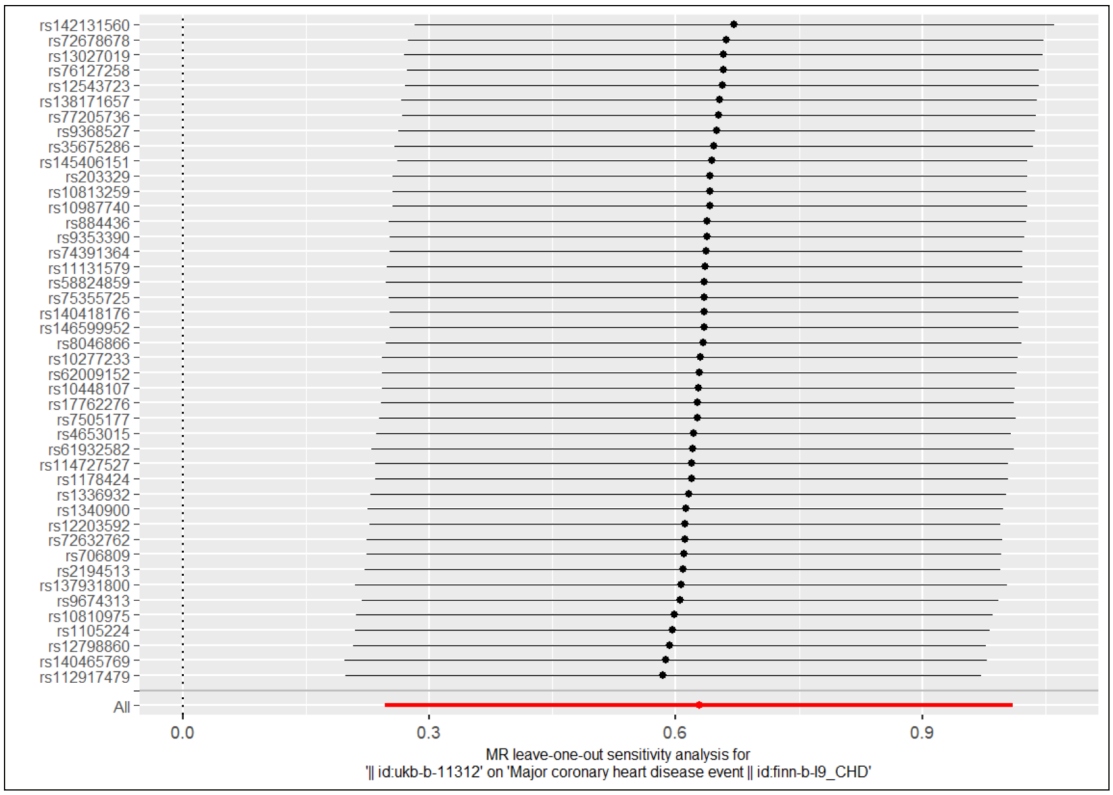

Figure 2. MR leave-one-out sensitivity analysis for air pollution PM2.5 on CHD.

multiple epidemiological studies[15], they are associated with the risk of cardiovascular diseases, respiratory diseases, and some cancers. In aerodynamics, exposure to fine particulate matter with a diameter of less than 2.5 μm is often related to elevated incidences of myocardial infarction (MI), ischemic encephalopathy, and arrhythmia. The most significant finding is that the risk of all-cause mortality is increased by 2% with every 1 mg/m^3 increase in PM2.5 concentration[16]. In contrast to all-cause mortality, air pollutants dominated by PM2.5 are more significantly associated with the morbidity and mortality of cardiovascular diseases, especially CHD. A large prospective study[17] has revealed a strong correlation between maternal exposure to high PM2.5 concentrations and the presence of CHD subtypes and morbidity in their offspring. Meanwhile, solid combustion and tobacco combustion produce a large amount of smoke, and the fine particles in the smoke are dominated by PM2.5, similar to the fine particles produced by tobacco combustion. Therefore, smokers and passive smokers have a higher risk of CHD[18,19]. This also confirms that smoking is one of the risk factors for CHD. Three types of air pollutants can induce oxidative stress, autonomic dysfunction, and endothelial cell dysfunction, thereby accelerating the initiation of CHD[20,21].

As is well known, LDL exerts a critical role in the onset of CHD[22]. The pro-atherosclerotic of LDL and anti-atherosclerotic effect of high-density lipoprotein (HDL) have been reported by many experts[23]. Zebrafish is a common animal model for cytotoxicity tests and hyperlipidemia[24]. In a large-scale animal experiment[3] on zebrafish and its embryos, a micro solution containing PM2.5 was injected into the experimental subjects. It was observed that zebrafish died in a short period, accompanied by developmental skeletal disorders. It was mainly because PM2.5 extract resulted in HDL degradation and LDL aggregation, inducing oxidative stress, cardiovascular toxicity, skin aging, and embryotoxicity. Based on the above experimental facts, PM2.5 is inhaled into the lungs through the respiratory tract and dissolved in the circulatory system after material exchange through pulmonary capillaries[25]. Due to the amphiphilic nature, PM2.5D binds to LDL and produces oxidized low-density lipoprotein (OX-LDL), accelerating the occurrence of hyperlipidemia and CHD[26].

Table II. Association between different air pollution, LDL and coronary heart disease in Mendelian randomization analysis.

Exposure	Outcome	MR methods	OR (95% CI)	*p* for association	*p* for heterogeneity test	*p* for MR-Egger intercept
PM2.5	CHD	MR Egger	1.703 (0.729-3.974)	0.225	0.997	0.804
		IVW1	1.875 (1.279-2.748)	0.001	0.997	
		Weighted median	1.938 (1.146-3.276)	0.014		
		Maximum likelihood	1.895 (1.285-2.792)	0.001		
		Penalized weighted median	1.938 (1.131-3.320)	0.016		
		IVW2	1.875 (1.279-2.748)	0.001		
PM10	CHD	MR Egger	4.591 (1.337-15.765)	0.025	0.916	0.319
		IVW1	2.586 (1.479-4.523)	0.001	0.907	
		Weighted median	2.134 (1.003-4.544)	0.049		
		Maximum likelihood	2.683 (1.509-4.771)	0.001		
		Penalized weighted median	2.134 (0.958-4.758)	0.064		
		IVW2	2.586 (1.479-4.523)	0.001		
NOx	CHD	MR Egger	0.577 (0.037-9.110)	0.698	3.37E-21	0.225
		IVW1	2.991 (1.236-7.236)	0.015	3.82E-23	
		Weighted median	1.902 (1.145-3.158)	0.013		
		Maximum likelihood	3.639 (2.328-5.689)	1.46E-08		
		Penalized weighted median	1.898 (1.110-3.245)	1.92E-02		
		IVW2	2.991 (2.021-4.427)	4.37E-08		
LDL	CHD	MR Egger	2.273 (1.828-2.826)	8.25E-12	5.51E-65	0.002
		IVW1	1.752 (1.505-2.040)	5.03E-13	4.58E-72	
		Weighted median	1.982 (1.742-2.255)	2.73E-25		
		Maximum likelihood	1.762 (1.639-1.895)	5.17E-53		
		Penalized weighted median	1.987 (1.749-2.258)	6.79E-26		
		IVW2	1.752 (1.632-1.882)	1.31E-53		
PM2.5	LDL	MR Egger	1.127 (0.962-1.320)	0.147	0.034	0.821
		IVW1	1.108 (1.034-1.187)	0.004	0.041	
		Weighted median	1.046 (0.961-1.138)	0.301		
		Maximum likelihood	1.045 (0.959-1.138)	0.317		
		Penalized weighted median	1.113 (1.048-1.187)	0.001		
		IVW2	1.108 (1.045-1.175)	0.001		
PM10	LDL	MR Egger	1.163 (0.943-1.435)	0.175	0.37	0.917
		IVW1	1.151 (1.053-1.259)	0.002	0.433	
		Weighted median	1.090 (0.957-1.241)	0.194		
		Maximum likelihood	1.077 (0.951-1.219)	0.245		
		Penalized weighted median	1.156 (1.055-1.267)	0.002		
		IVW2	1.151 (1.054-1.258)	0.002		
NOx	LDL	MR Egger	1.022 (0.880-1.186)	0.78	0.652	0.347
		IVW1	1.093 (1.038-1.151)	0.001	0.655	
		Weighted median	1.061 (0.986-1.142)	0.116		
		Maximum likelihood	1.059 (0.984-1.139)	0.127		
		Penalized weighted median	1.094 (1.038-1.153)	0.001		
		IVW2	1.093 (1.038-1.512)	0.001		
LDL	CHD	MR Egger	2.273 (1.828-2.826)	8.25E-12	5.51E-65	0.002
		IVW1	1.752 (1.505-2.040)	5.03E-13	4.58E-72	
		Weighted median	1.982 (1.742-2.255)	2.73E-25		
		Maximum likelihood	1.762 (1.639-1.895)	5.17E-53		
		Penalized weighted median	1.987 (1.749-2.258)	6.79E-26		
		IVW2	1.752 (1.632-1.882)	1.31E-53		

PM2.5, particulate matter air pollution; PM10, particulate matter air pollution; NOx, Nitrogen dioxide air pollution; LDL, Low-density lipoprotein; CHD, Coronary heart disease, inverse variance weighted (IVW2).

Table III. Multivariate MR analysis of the direct effect of LDL on CHD.

Exposure/Outcome	Adjusted Factors	nSNP	OR (95% CI)	*p*-value	Mediation Effect (%)
PM2.5/CHD	LDL	148	1.875 (1.279-2.748)	0.001	2.82%
PM10/CHD	LDL	150	2.586 (1.479-4.523)	0.001	4.73%
NOx/CHD	LDL	147	2.991 (2.021-4.427)	4.37E-08	9.54%

PM2.5, particulate matter air pollution; PM10, particulate matter air pollution; NOx, nitrogen dioxide air pollution; LDL, low-density lipoprotein; CHD, coronary heart disease; SNPs, single nucleotide polymorphisms.

In the context of the aforementioned studies, this article conducted the most comprehensive MR analysis to explore the relationships among air pollutants (PM2.5, PM10, NOx), LDL, and CHD. We provided additional evidence to demonstrate a direct relationship between exposure to air pollutants and the morbidity of CHD and suggest a regulatory role of LDL in its progression.

Firstly, we retrieved the corresponding sample size from the GWAS database, eliminated confounding factors, and collected relevant SNPs to explore the actual causation between air pollutants and CHD. Furthermore, the total effects of genetically determined PM2.5, PM10, and NOx on CHD were estimated with the TSMR design. With the results of 95% CI (1.279-2.748), 95% CI (1.479-4.523), and 95% CI (2.021-4.427), we demonstrated a direct causation between three types of air pollutants and the incidence of CHD. We also adopted IVW2 for preliminary analysis and then performed MR-Egger regression analysis to assess the potential horizontal pleiotropy of IVs, as the presence of horizontal pleiotropy can affect the value of the analysis results. Fortunately, horizontal pleiotropy was not found in our analysis. Secondly, the causation between LDL and CHD was evaluated using TSMR, and a value of 95% CI (1.632-1.882) validated a direct causation between LDL and CHD. The success of the analysis with the two samples laid a solid foundation for future research. After investigating the direct causal correlations between air pollutants and LDL, we found 95% CI values of (1.045-1.175), (1.054-1.258), and (1.038-1.512). Multivariable Mendelian randomization (MVMR) was utilized to calculate the direct effects more accurately and estimate the mediating proportion. The final results showed that the mediating proportion of LDL was 2.82%, 4.73%, and 9.54%, respectively, in the effect of PM2.5, PM10, and NOx on CHD.

LDL is the main carrier of cholesterol. Upon endothelial cell damage, LDL is accumulated in the arterial intima, which stimulates the expression of endothelial cell adhesion factors and chemokines, evoking the migration of monocytes to the damaged region and their differentiation into macrophages. Macrophages phagocytose cholesterol, eventually forming the characteristic foam cells for atherosclerosis (AS) after daily accumulation[16,27]. Atherosclerosis (AS), as the pathological basis, leads to clinical CHD when 50% of the lumen is blocked by atherosclerotic plaques[28]. Most studies[29] are limited to the impact of short-term exposure to air pollutants on the hospitalization rate of CHD. Short-term high exposure increases hospitalization rates, and our MR study also supported the aforementioned findings and improved relevant studies at the genetic level.

Air pollutants induce the aggregation of OX-LDL and increase the concentration of LDL in the blood circulation, leading to the initiation of AS. They can also invade through the blood-brain barrier and seem to have the same pathogenic effect on ischemic stroke[28]. However, further research is still required. Long-term exposure to air pollutants, especially PM2.5, can affect ventricular repolarization, leading to ST-segment elevation in electrocardiograms and posing a threat to cardiovascular health[30]. Therefore, long-term air quality interventions, such as green areas and the application of protective masks, can improve physical conditions[31]. It is quite indispensable to reduce deforestation in developing countries and ameliorate large-scale industrial pollution emissions[32]. When the antioxidant capacity is low, supplementation with dietary vitamins or dietary fiber-rich foods (such as green vegetables, cucumbers, and tomatoes) can effectively reduce the susceptibility to air pollutants, thereby attenuating the impact of external injuries[17]. Air temperature and humidity also have an impact on air quality. However, it is difficult to artificially adjust them, and there are significant regional differences. The specific control methods need to be investigated.

Our study has several advantages: (1) The data statistics for exposure and outcome were obtained from the largest GWAS database, and there was no overlapping sample size in the data selection. (2) Strict screening criteria for IVs enhanced statistics. (3) We excluded SNPs with confounding factors and performed sensitivity analysis with multiple methods, enhancing the reliability of the experiment.

There are also several limitations in this study: (1) The data in the GWAS database are mostly sourced from European populations, and experimental data from non-European individuals should be supplemented. (2) Due to the lack of stratification effects such as age and gender in the database, there exists certain heterogeneity. (3) There are multiple subtypes of CHD, and further research is demanded to determine whether the results of each subtype are consistent. The exploration of mediators is limited, and there are many types of lipids, which still need to be improved in the future.

Conclusions

This study indicates that LDL mediates the impact of air pollution on the incidence of CHD, and genetically related air pollutants (PM2.5, PM10, NOx) are positively linked to an increased risk of LDL. Daily protection against air pollution, dietary management, and lipid-lowering treatment for patients with hyperlipidemia are essential.

Conflict of Interest

The authors declare that no conflict of interest.

Informed Consent and Ethics Approval

We used a public database; therefore, ethics approval and informed consent were not applicable.

Authors' Contributions

All authors made contributions in writing the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Materials

Data and materials are provided in the **Supplementary file**.

References

1) Fatmi Z, Coggon D. Coronary heart disease and household air pollution from use of solid fuel: a systematic review. Br Med Bull 2016; 118: 91-109.
2) Atkinson RW, Butland BK, Anderson HR, Maynard RL. Long-term Concentrations of Nitrogen Dioxide and Mortality. Epidemiology 2018; 29: 460-472.
3) Kim JY, Lee EY, Choi I, Kim J, Cho KH. Effects of the Particulate Matter$_{2.5}$ ($PM_{2.5}$) on Lipoprotein Metabolism, Uptake and Degradation, and Embryo Toxicity. Mol Cells 2015; 38: 1096-1104.
4) Richardson TG, Sanderson E, Palmer TM, Ala-Korpela M, Ference BA, Davey Smith G, Holmes MV. Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: A multivariable Mendelian randomisation analysis. PLoS Med 2020; 17: e1003062.
5) Ma Z, Cao X, Chang Y, Li W, Chen X, Tang NJ. Association between gestational exposure and risk of congenital heart disease: A systematic review and meta-analysis. Environ Res 2021; 197: 111014.
6) Davies NM, Holmes MV, Davey Smith G: Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 2018; 362: k601.
7) Rusk N. The UK Biobank. Nat Methods 2018; 15: 1001.
8) Wang M, Zhou T, Song Q, Ma H, Hu Y, Heianza Y, Qi L. Ambient air pollution, healthy diet and vegetable intakes, and mortality: a prospective UK Biobank study. Int J Epidemiol 2022; 51: 1243-1253.
9) Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015; 12: e1001779.
10) Kurki MI, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner KM, Reeve MP, Laivuori H, Aavikko M, Kaunisto MA et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature 2023; 613: 508-518.
11) Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR, Haycock PC. The MR-Base platform supports systematic causal inference across the human phenome. Elife 2018; 7: e34408.
12) Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, Timpson NJ, Higgins JPT, Dimou N, Langenberg C et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): explanation and elaboration. BMJ 2021; 375: n2233.
13) Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol 2017; 46: 1985-1998.
14) Varbo A, Benn M, Smith GD, Timpson NJ, Tybjaerg-Hansen A, Nordestgaard BG. Remnant cholesterol, low-density lipoprotein cholesterol, and blood pressure as mediators from obesity to ischemic heart disease. Circ Res 2015; 116: 665-673.
15) Dockery DW, Pope CA, 3rd, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG, Jr., Speizer FE. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993; 329: 1753-1759.
16) Gao S, Liu J: Association between circulating oxidized low-density lipoprotein and atherosclerotic cardiovascular disease. Chronic Dis Transl Med 2017; 3: 89-94.

17) Yuan X, Liang F, Zhu J, Huang K, Dai L, Li X, Wang Y, Li Q, Lu X, Huang J, Liao L, Liu Y, Gu D, Liu H, Liu F. Maternal Exposure to PM(2.5) and the Risk of Congenital Heart Defects in 1.4 Million Births: A Nationwide Surveillance-Based Study. Circulation 2023; 147: 565-574.

18) Lee MS, Hang JQ, Zhang FY, Dai HL, Su L, Christiani DC. In-home solid fuel use and cardiovascular disease: a cross-sectional analysis of the Shanghai Putuo study. Environ Health 2012; 11: 18.

19) Sørensen M, Lühdorf P, Ketzel M, Andersen ZJ, Tjønneland A, Overvad K, Raaschou-Nielsen O. Combined effects of road traffic noise and ambient air pollution in relation to risk for stroke? Environ Res 2014; 133: 49-55.

20) Deng X, Rui W, Zhang F, Ding W. PM2.5 induces Nrf2-mediated defense mechanisms against oxidative stress by activating PIK3/AKT signaling pathway in human lung alveolar epithelial A549 cells. Cell Biol Toxicol 2013; 29: 143-157.

21) Atkinson RW, Carey IM, Kent AJ, van Staa TP, Anderson HR, Cook DG. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 2013; 24: 44-53.

22) Le QF, Liu J, Chen L. The value of serum lipoprotein-associated phospholipase A2, ischemia-modified albumin, and cystatin C in predicting coronary heart disease risk: a single center retrospective cohort study. Eur Rev Med Pharmacol Sci 2023; 27: 10730-10735.

23) Groop PH, Thomas MC, Rosengård-Bärlund M, Mills V, Rönnback M, Thomas S, Forsblom C, Taskinen MR, Viberti G. HDL composition predicts new-onset cardiovascular disease in patients with type 1 diabetes. Diabetes Care 2007; 30: 2706-2707.

24) Park KH, Cho KH. A zebrafish model for the rapid evaluation of pro-oxidative and inflammatory death by lipopolysaccharide, oxidized low-density lipoproteins, and glycated high-density lipoproteins. Fish Shellfish Immunol 2011; 31: 904-910.

25) Zhang PY, Xu X, Li XC. Cardiovascular diseases: oxidative damage and antioxidant protection. Eur Rev Med Pharmacol Sci 2014; 18: 3091-3096.

26) Sun Q, Yue P, Deiuliis JA, Lumeng CN, Kampfrath T, Mikolaj MB, Cai Y, Ostrowski MC, Lu B, Parthasarathy S, Brook RD, Moffatt-Bruce SD, Chen LC, Rajagopalan S. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation 2009; 119: 538-546.

27) Steinbrecher UP. Oxidation of human low density lipoprotein results in derivatization of lysine residues of apolipoprotein B by lipid peroxide decomposition products. J Biol Chem 1987; 262: 3603-3608.

28) Lucero J, Suwannasual U, Herbert LM, McDonald JD, Lund AK. The role of the lectin-like oxLDL receptor (LOX-1) in traffic-generated air pollution exposure-mediated alteration of the brain microvasculature in Apolipoprotein (Apo) E knockout mice. Inhal Toxicol 2017; 29: 266-281.

29) Zanobetti A, Schwartz J, Dockery DW. Airborne particles are a risk factor for hospital admissions for heart and lung disease. Environ Health Perspect 2000; 108: 1071-1077.

30) McCracken J, Smith KR, Stone P, Díaz A, Arana B, Schwartz J. Intervention to lower household wood smoke exposure in Guatemala reduces ST-segment depression on electrocardiograms. Environ Health Perspect 2011; 119: 1562-1568.

31) Wilkinson P, Smith KR, Davies M, Adair H, Armstrong BG, Barrett M, Bruce N, Haines A, Hamilton I, Oreszczyn T, Ridley I, Tonne C, Chalabi Z. Public health benefits of strategies to reduce greenhouse-gas emissions: household energy. Lancet 2009; 374: 1917-1929.

32) Sierra-Vargas MP, Teran LM. Air pollution: impact and prevention. Respirology 2012; 17: 1031-1038.