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ARTICLE

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Interaction between visceral adiposity and ambient air pollution on LDL cholesterol level in Korean adults

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Abstract

Background Although previous reports have found that obesity intensifies the negative impact of long-term air pollution exposure on the low-density lipoprotein-cholesterol (LDL-C) level, few studies have examined whether the type of abdominal adiposity, such as visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), and the visceral-to-subcutaneous fat ratio (VSR) affects this relationship. We investigated the association between ambient air pollution and LDL-C in Korean adults and identified whether this association is different by the type of abdominal adiposity.

Methods A total of 2737 adults were included. Abdominal fat areas were quantified by computed tomography, and the annual average concentration of air pollutants was included in this analysis.

Results In the total sample, none of the air pollutants was associated with LDL-C level in either the crude or adjusted model (all $p > 0.05$). The association was not significant even in subgroups stratified according to the obesity status defined by body mass index, and no interaction on the LDL-C level was also found (all $p_{int} > 0.05$). In the subgroup analysis stratified according to adiposity level, particulate matter with an aerodynamic diameter of ≤10 μm (PM_{10}) [β (SE) = 3.58 (1.59); $p = 0.0245$] and sulfur dioxide (SO_2) exposures [β (SE) = 2.71 (1.27); $p = 0.0330$] in the high-VAT group were associated with the increased LDL-C level. Interactions on LDL-C level were also found between VAT level and ambient air pollutants such as PM_{10} and SO_2 (both $p_{int} < 0.05$). In the analysis of the VSR, PM_{10} exposure showed a significant interaction on LDL level ($p_{int} = 0.0032$). However, the strength of these associations was not significant across all SAT subgroup (all $p_{int} > 0.05$).

Conclusions In conclusion, we found that association between air pollution exposure and LDL-C level is different by abdominal fat distribution.

Introduction

Low-density lipoprotein-cholesterol (LDL-C), referred to as "bad" cholesterol, is a well-established key risk factor for atherosclerotic cardiovascular disease [1]. LDL-C is involved in the buildup of plaque within the arteries, which contributes to the chronic inflammatory disease such as atherosclerosis [2]. Chronic inflammatory diseases can cause various vascular complications including stroke, myocardial infarction, peripheral vascular disease, and coronary artery disease, all of which are associated with increased all-cause mortality [3, 4]. In a recent report, the number of deaths from high LDL-C level was estimated to be about 4.32 million worldwide [5].

Along with global health issues caused by air pollution, associations between air pollution and the lipid profile have been reported [6–8]. More recent reports have indicated that obese people, defined by body mass index (BMI), may be particularly vulnerable to having a high LDL-C level because of exposure to ambient air pollutants [9, 10]. However, it may be very important to distinguish the visceral and subcutaneous fat compartments in that the impact of obesity on LDL-C can differ between specific fat depots. Compared with subcutaneous fat accumulation,

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visceral fat accumulation is closely related to impairment of lipid metabolism through excess free fatty acids [11]. Visceral adipose tissue (VAT) also contributes to lipid damage and peroxidation via pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [11, 12]. Indeed, IL-6, which inhibits lipoprotein lipase activity, is released approximately 2 to 3 times more in VAT than in subcutaneous adipose tissue (SAT) [12]. In addition, VAT promotes generation of reactive oxygen species (ROS) which plays an important role in chronic inflammation to atherosclerosis as well as direct damage of the lipids [13, 14]. It is associated with oxidative stress, an imbalance between free radicals and antioxidants, which in turn leads to cellular oxidative damage and lipid peroxidation [13].

Similar to visceral fat accumulation, long-term air pollution exposure is implicated in biological pathways such as chronic inflammatory and oxidative stress responses. Continuous exposure to ambient air pollution triggers altered lipid metabolism and changes in blood lipid levels through inflammation [15]. Moreover, it induces peroxidation of lipids as well as oxidized phospholipids by TLR4/NADPH oxidase dependent signaling [16, 17]. Given these shared mechanisms of visceral fat accumulation and chronic air pollution exposure in lipids, it is possible that visceral fat, rather than subcutaneous fat, might be important to the association between air pollution and LDL-C level. Therefore, epidemiological studies of abdominal fat content quantified by specific methods, such as computed tomography (CT), are needed to understand better the link between obesity, chronic exposure to air pollution, and LDL-C level.

The aim of this study was to investigate the association between annual air pollution exposure and LDL-C in Korean adults and to identify whether this association is different by the type of abdominal fat depot, especially in the visceral compartment.

Subjects and methods

Participants

We recruited subjects who underwent regular comprehensive health checkups from 2009 to 2015 at two health screening centers run by Seoul National University Hospital in South Korea. The study included all subjects who live in 16 administrative districts nationwide, including Seoul (Table S1). In general, adults in South Korea undergo regular comprehensive health checkups for early detection or prevention of various diseases, and many people across the country visit large hospitals, such as Seoul National University Hospital, for a more accurate comprehensive examination. For this reason, a national sample was included in our study. During the collection period, a total of 5043 individuals were enrolled, 2918 of whom had abdominal CT information such as VAT and SAT. Of these, our final analyses only included 2737 people who met the additional following criteria: (1) age ≥ 20 years; (2) postal code information that allowed the identification of each participant's exposure to air pollution; (3) phenotypic information such as LDL cholesterol level; (4) not taking any cholesterol-lowering medication; and (5) information about the variables of interest such as demographics and health-related behaviors. This study was approved by the institutional review board of the National Cancer Center. Informed consent was waived by the institutional review board because this was a retrospective study that used de-identified data.

Assessment of phenotype and variables of interest

We evaluated demographic and health-behavior factors, including age, sex, smoking status, alcohol consumption, moderate physical activity, and use of cholesterol-related medication. Information about these variables was collected in a questionnaire and categorized in the analysis as follows: smoking status (never-, ex-, or current-smoker), alcohol consumption (never-, ex-, or current-drinker), and moderate physical activity (yes or no). Anthropometric measurements, such as height and weight, were measured with the participant in light clothing. Samples for laboratory examinations, such as measurement of LDL-C level, were obtained after a 12-h overnight fast. We used direct method to determine circulating LDL levels at both two health screening center.

Assessment of obesity and abdominal adiposity

Various obesity-related parameters were included to determine obesity status. BMI was calculated as weight in kilograms (kg) divided by height in meters squared (m^2). To assess overall obesity, we classified the participants into three groups using the Asia-Pacific obesity classification of adult Asians as follows: underweight or normal (BMI < 23 kg/m^2), overweight (23 kg/m^2 ≤ BMI < 25 kg/m^2), and obese (BMI ≥ 25 kg/m^2). Abdominal adiposity was categorized as visceral, subcutaneous, and total fat, and was quantified using abdominal CT scanning (Somatom Sensation 16 CT scanner, Siemens AG, Erlangen, Germany). We calculated the cross-sectional area of each abdominal adipose tissue using the Rapidia v. 2.8 software package (threshold range −250 to −50 Hounsfield units; Infinitt Co, Ltd., Seoul, Korea). The VAT area was estimated by delineating intra-abdominal fat bound by parietal peritoneum or transversalis fascia, excluding the vertebrae and spinal

muscles. The SAT area was estimated by subtracting the visceral fat area from the total fat area. Using these fat areas, we also calculated the visceral-to-subcutaneous fat ratio (VSR). To classify further the adiposity levels, we considered two cutoff points (100 cm^2 and 150 cm^2) for VAT and SAT areas, and we sub-classified three groups according to the adiposity levels as follows: low VAT or SAT area (VAT or SAT area < 100 cm^2), intermediate VAT or SAT area (100 cm^2 ≤ VAT or SAT area < 150 cm^2), and high VAT or SAT area (VAT or SAT area ≥ 150 cm^2) [18]. We also defined three groups according to the VSR as low VSR (VSR < 0.8), intermediate VSR (0.8 ≤ VSR < 1.0), and high VSR (VSR ≥ 1.0).

Assessment of air pollution exposure

The approach to estimate individual exposure to air pollution has been described previously [19]. Briefly, we obtained the real-time atmospheric monitoring data from about 300 atmospheric monitoring stations nationwide managed by the Ministry of the Environment of Korea (https://www.airkorea.or.kr). We considered the annual average concentrations of the four air pollutants: PM_{10}, NO_2, sulfur dioxide (SO_2), and carbon monoxide (CO). Using each participant's residential postal code, we used the annual average concentrations from the closest monitoring station that corresponded to that used for the person's health screening year. We also classified the exposure groups using quartiles of each air pollution concentration as low exposure (quartile 1), intermediate exposure (quartiles 2–3), and high exposure (quartile 4).

Statistical analysis

All statistical analyses were performed using SAS 9.4 version (SAS Institute, Cary, NC, USA) and statistical significance was set at $\alpha = 0.05$ (two-side test). Before the analysis, we identified that the distribution of LDL-C follows a normal distribution. Univariate regression analyses were performed to determine the potential covariates for LDL-C level (Table S2). Age and smoking status, which were significantly associated with LDL-C level, were considered as the final adjustment variables. In addition, we included site of recruitment, humidity, temperature, and seasonality as potential covariates. For humidity and temperature, we used the monthly average value corresponding to the each subject's examination year and month. Based on the each subject's examination month, seasonality was classified into four seasonal categories: spring (March to May), summer (June to August), fall (September to November), and winter (December to February). We then used multiple regression analyses to assess the associations between air pollution or abdominal fat and LDL-C level. The beta coefficients (β) and standard errors (SE) of adiposity traits or ambient air pollutants for LDL-C level were estimated in both crude and adjusted models after adjusting for covariates such as site of recruitment, age, smoking status, humidity, temperature, and seasonality. We converted the statistical estimates for each adiposity measure, including VAT and SAT, according to a 10 cm^2 scale area. The estimates in air pollution exposure were also scaled to the interquartile range (IQR) according to the increase in the concentration of each air pollutant (8.9 μg/m^3 for PM_{10}, 14.0 ppb for NO_2, 1.5 ppb for SO_2, and 2.0 ppm for CO). To evaluate the impact of abdominal fat on the association between air pollution exposure and LDL-C level, we also stratified the groups according to abdominal adiposity traits (BMI, VAT and SAT areas, and VSR) and then used a multiple regression approach to test interaction of air pollution exposure and adiposity level on LDL-C level. Similarly, we performed the subgroup analyses stratified by each air pollution level on the association between adiposity traits and LDL-C. In all statistical analyses, we included term of random effects in main models for association or interaction to consider heterogeneous influences across the nation.

Results

The baseline characteristics of the study subjects ($n = 2737$) are displayed in Table 1. Most participants were men (88.9%), and the mean age was 50.8 years. For smoking status, the percentage of ex-smokers (38.0%) was highest, and the percentages of never- (30.0%) and current-smokers (32.0%) were similar. More than 70% ($n = 2029$) were classified into the current-drinking group, and the percentages of never- and ex-drinkers were 19.6% ($n = 535$) and 6.3% ($n = 173$), respectively. The mean BMI was 24.4 kg/m^2. The mean SAT area (141.2 cm^2) was slightly higher than that of the VAT area (128.3 cm^2), and the mean VSR was 1.0. The mean PM_{10}, NO_2, SO_2, and CO concentrations were 48.8 μg/m^3, 30.9 ppb, 4.9 ppb, and 0.6 ppm, respectively, and the mean temperature and relative humidity values were 12.6 °C and 63.8%, respectively. The mean LDL-C level was 130.8 mg/dL.

The results of simple and multivariate linear regression analysis for the association of long-term ambient air pollutant exposure and various adiposity traits with serum LDL-C level are presented in Table 2. In both the crude and adjusted models, BMI was significantly associated with LDL-C level (both $p < 0.05$). Abdominal adiposity traits, including VAT area ($p < 0.0001$) and SAT area ($p < 0.0001$), but not VSR ($p = 0.1466$), were significantly associated with LDL-C level. Significance in these associations was also maintained after adjustment for ambient air pollutants (Data not shown). None of the air pollutants was significantly associated with LDL-C level in either the

Table 1 Characteristics of study participants.

Characteristics	*n* (%) or mean (SD)
n	2737
Sampling site, *n* (%)	
Site A	2,182 (79.7)
Site B	555 (20.3)
Female, *n* (%)	305 (11.1)
Age (years), mean (SD)	50.8 (8.2)
Smoking, *n* (%)	
Never	821 (30.0)
Former-smokers	1039 (38.0)
Current-smokers	877 (32.0)
Alcohol drinking, *n* (%)	
Never	535 (19.6)
Former-drinkers	173 (6.3)
Current- drinkers	2029 (74.1)
Physical activity, *n* (%)	
Yes	1415 (51.7)
No	1322 (48.3)
Height (cm), mean (SD)	169.1 (7.2)
Weight (kg), mean (SD)	69.9 (10.9)
BMI(kg/m^2), mean (SD)	24.4 (2.9)
Adiposity measures, mean (SD)	
VAT (cm^2)	128.3 (58.5)
SAT (cm^2)	141.2 (53.2)
TAT (cm^2)	269.5 (98.6)
VSR	1.0 (0.8)
Air pollutants, mean (SD)	
PM_{10} (μg/m^3)	48.8 (7.2)
NO_2 (ppb)	30.9 (12.8)
SO_2 (ppb)	4.9 (1.3)
CO (ppm)	0.6 (0.1)
Temperature (°C), mean (SD)	12.6 (9.9)
Temperature (°C), median (min ~ max)	13.1 (−7.2 ~ 28.7)
Relative Humidity (%),mean (SD)	63.8 (9.3)
Relative Humidity (%), median (min ~ max)	62.0 (35 ~ 87.7)
LDL-C (mg/dL), mean (SD)	130.8 (33.3)

SD standard deviation, *BMI* body mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue, *TAT* total adipose tissue, *VSR* visceral-to-subcutaneous fat ratio, *PM_{10}* particulate matter ≤10 μm in diameter, *NO_2* nitrogen dioxide, *SO_2* sulfur dioxide, *CO* carbon monoxide, *LDL-C* low-density lipoprotein cholesterol.

Table 2 Linear regression results for the association between air pollution, adiposity-related traits, and LDL-C.

	LDL-C (mg/dL)			
	Crude model		Adjusted model[a]	
	β (SE)	*p* value	*β* (SE)	*p* value
Adiposity trait				
BMI (kg/m^2)	0.98 (0.22)	<0.0001	0.92 (0.22)	<0.0001
VAT (cm^2)	0.66 (0.11)	<0.0001	0.68 (0.11)	<0.0001
SAT (cm^2)	0.75 (0.11)	<0.0001	0.73 (0.11)	<0.0001
VSR	1.07 (0.79)	0.1730	1.16 (0.80)	0.1466
Air pollution				
PM_{10} (μg/m^3)	1.18 (0.86)	0.1706	1.21 (0.88)	0.1684
NO_2 (ppb)	0.47 (0.91)	0.6055	0.37 (0.92)	0.6902
SO_2 (ppb)	−0.19 (0.75)	0.8008	−0.15 (0.75)	0.8396
CO (ppm)	1.42 (0.97)	0.1464	1.30 (0.98)	0.1879

The beta coefficient and standard error in adiposity measures including VAT and SAT was converted by scale to the 10 cm^2 area.

The beta coefficient and standard deviation in each air pollutant was scaled to the interquartile range for each pollutant, respectively (8.9 μg/m^3 for PM_{10}, 14.0 ppb for NO_2, 1.5 ppb for SO_2, and 2.0 ppm for CO).

LDL-C low-density lipoprotein cholesterol, *BMI* Body mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue, *VSR* visceral-to-subcutaneous fat ratio, *PM_{10}* particulate matter ≤10 μm in diameter, *NO_2* nitrogen dioxide, *SO_2* sulfur dioxide, *CO* carbon monoxide, *SE* standard error.

[a]Adjusted model was adjusted for site of recruitment, age, smoking status (never-, ex-, or current-smokers), humidity, temperature, and seasonality.

crude or adjusted model (all $p > 0.05$). In addition, we assessed whether the associations between air pollution and LDL levels could be confounded by obesity status prior to the subgroup analysis, but there was no significant difference in the association results before and after adjusting for obesity status (Data not shown).

To investigate the association between air pollutant exposure and LDL-C level according to each adiposity trait, we performed a subgroup analysis based on the three adiposity levels (Table 3). The association between air pollution exposure and LDL-C level did not differ significantly between groups stratified according to BMI (all $p > 0.05$), and no interaction on the LDL-C level was also found (all $p_{int} > 0.05$). Interestingly, the relationship between ambient air pollution exposure and LDL-C level was different by visceral adiposity level. In the low-VAT (VAT area ≤ 100 cm^2) and intermediate-VAT (100 cm^2 ≤ VAT area < 150 cm^2) adiposity groups, air pollutant exposure was not significantly related to LDL-C level (both $p > 0.05$). By contrast, in the high-VAT group (VAT area ≥ 150 cm^2) air pollutant exposure was significantly associated with increased LDL-C level. Exposure to the ambient air pollutants PM_{10} and SO_2 was significantly related to LDL-C level. Each increase in the IQR of these pollutants was associated with a 3.58 mg/dL and 2.71 mg/dL increase in LDL-C level, respectively. These pollutants also showed significant interactions by higher VAT area on the LDL-C level (p_{int} for $PM_{10} = 0.0027$ and p_{int} for $SO_2 = 0.0388$). These associations on VAT area remained significant after adjusting for BMI (data not shown). In the analysis of the VSR, PM_{10} exposure showed a significant interaction on

Table 3 Results of stratified analyses by abdominal adiposity traits for the association between LDL-C and exposure to air pollution.

		LDL-C (mg/dL)						
		Low adiposity		Intermediate adiposity		High adiposity		
Adiposity	Exposure	β (SE)	p value	β (SE)	p value	β (SE)	p value	P_{int}
BMI (kg/m^2)	Sample n	BMI < 23 (n = 864)		23 ≤ BMI < 25 (n = 799)		BMI ≥ 25 (n = 1074)		
	PM_{10} (μg/m^3)	1.07 (1.51)	0.4754	−0.04 (1.67)	0.9791	0.69 (1.31)	0.5972	0.8241
	NO_2 (ppb)	1.86 (1.58)	0.2383	−2.06 (1.45)	0.1567	−0.25 (1.20)	0.8332	0.9793
	SO_2 (ppb)	0.62 (1.25)	0.6236	−1.18 (1.37)	0.3920	0.46 (1.18)	0.6969	0.9852
	CO (ppm)	0.67 (1.67)	0.6878	0.81 (1.86)	0.6637	1.17 (1.47)	0.4255	0.4753
VAT (cm^2)	Sample n	VAT < 100 (n = 900)		100 ≤ VAT < 150 (n = 944)		VAT ≥ 150 (n = 893)		
	PM_{10} (μg/m^3)	**−1.85 (1.48)**	**0.2135**	**0.18 (1.41)**	**0.8984**	**3.58 (1.59)**	**0.0245**	**0.0027**
	NO_2 (ppb)	0.19 (1.52)	0.8982	−1.56 (1.34)	0.2445	0.74 (1.46)	0.6143	0.2911
	SO_2 (ppb)	**−1.21 (1.21)**	**0.3195**	**−1.61 (1.30)**	**0.2161**	**2.71 (1.27)**	**0.0330**	**0.0388**
	CO (ppm)	−0.54 (1.63)	0.7396	−0.75 (1.63)	0.6480	2.88 (1.67)	0.0850	0.0746
SAT (cm^2)	Sample n	SAT < 100 (n = 602)		100 ≤ SAT < 150 (n = 1092)		SAT ≥ 150 (n = 1043)		
	PM_{10} (μg/m^3)	1.01 (1.64)	0.5366	1.33 (1.37)	0.3322	0.09 (1.40)	0.9497	0.6736
	NO_2 (ppb)	1.86 (1.62)	0.2509	−1.62 (1.29)	0.2104	−0.19 (1.28)	0.8840	0.4996
	SO_2 (ppb)	0.70 (1.32)	0.5945	−0.10 (1.21)	0.9346	0.15 (1.22)	0.8993	0.9764
	CO (ppm)	−0.49 (1.79)	0.7828	1.39 (1.55)	0.3724	1.65 (1.57)	0.2945	0.4281
VSR	Sample n	VSR < 0.8 (n = 1054)		0.8 ≤ VSR < 1.0 (n = 615)		VSR ≥ 1.0 (n = 1068)		
	PM_{10} (μg/m^3)	**−1.24 (1.49)**	**0.4051**	**2.08 (1.62)**	**0.2014**	**2.69 (1.41)**	**0.0559**	**0.0032**
	NO_2 (ppb)	−1.01 (1.52)	0.5082	0.44 (1.66)	0.7905	0.57 (1.35)	0.6731	0.3905
	SO_2 (ppb)	−1.78 (1.29)	0.1688	−0.49 (1.40)	0.7284	1.75 (1.16)	0.1331	0.1264
	CO (ppm)	−0.24 (1.69)	0.8858	1.04 (1.82)	0.5695	2.17 (1.54)	0.1594	0.2022

The result was adjusted for site of recruitment, age, smoking status (never-, ex-, or current-smokers), humidity, temperature, and seasonality.

The beta coefficient and standard deviation in each air pollutant was scaled to the interquartile range for each pollutant, respectively (8.9 μg/m^3 for PM_{10}, 14.0 ppb for NO_2, 1.5 ppb for SO_2, and 2.0 ppm for CO).

Significant interaction effects are marked in bold ($p_{int} < 0.05$).

LDL-C low-density lipoprotein cholesterol, *BMI* body mass index, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue, *VSR* visceral-to-subcutaneous fat ratio, *PM_{10}* particulate matter ≤10 μm in diameter, *NO_2* nitrogen dioxide, *SO_2* sulfur dioxide, *CO* carbon monoxide, *SE* standard error.

LDL level ($p_{int} = 0.0032$), even though the association between PM_{10} and LDL-C level in the high VSR group was not significant ($p = 0.0559$). This interaction was not observed for other air pollutants such as NO_2, SO_2, and CO (all $p_{int} > 0.05$). However, unlike VAT-related characteristics, the association between air pollutant exposure and LDL-C level did not differ significantly according to the SAT level (all $p_{int} > 0.05$). In other words, compared with BMI or SAT area, the abdominal visceral-related variables quantified using CT, including VAT area and VSR, were more strongly related to LDL-C level. The patterns of air pollution exposure on LDL-C level in two adiposity groups (low to intermediate vs high groupings for VAT and SAT areas, and VSR) are shown in Fig. 1. For PM_{10} exposure, the group with high visceral fat-related indicators, such as VAT area and VSR, showed a clear pattern of increase in LDL-C level but no distinct pattern according to the SAT area. A pattern similar to that for PM_{10} exposure was also observed for SO_2 exposure. For NO_2 and CO exposures, the differences in pattern between the two adiposity groups for LDL-C were not apparent in VAT and VSR, compared to SAT.

We performed subgroup analysis of groups stratified according to the air pollutant concentrations, and the results are shown in Table S3. Notably, the associations between visceral fat-related traits and LDL-C level differed according to the concentrations of ambient PM_{10}. Similar to the results of the analysis of groups stratified according to adiposity level, the association between VAT area and LDL-C level was strongest in the high-PM_{10} exposure group [β (SE) = 1.07 (0.22); $p < 0.0001$], although an interaction was not observed ($p_{int} = 0.1704$). For PM_{10} exposure, the pattern for the VSR was similar to that of VAT area. Compared with the low- and intermediate-exposure groups, the association between the VSR and LDL-C level was greatest in the high-PM_{10} exposure group [β (SE) = 10.87 (3.37); $p = 0.0013$], and an interaction was not observed ($p_{int} = 0.1559$). Although no significant interaction was found, similar patterns as those found for PM_{10} exposure were found for the associations with all other pollutants, including NO_2, SO_2, and CO. These findings indicate that the strongest associations between VAT area and the VSR with LDL-C level were in the high-exposure group.

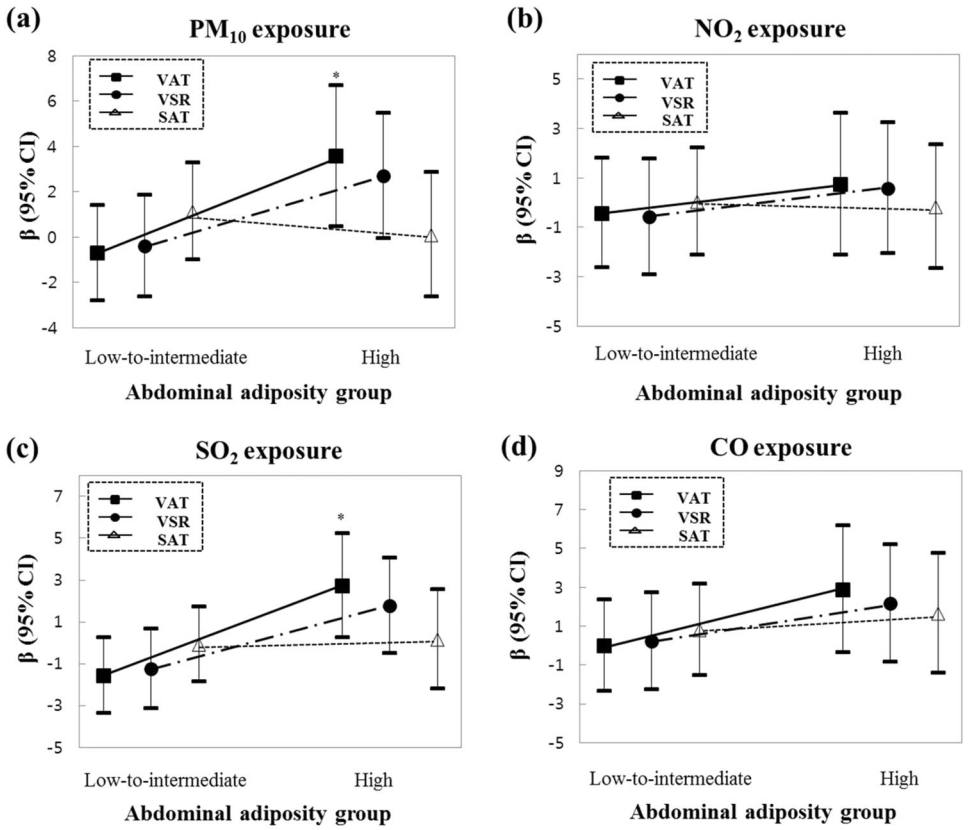

Fig. 1 The patterns between two abdominal adiposity groups in the association of each air pollution exposure with LDL-C level. The effect size of air pollution exposures such as (**a**) PM_{10}, (**b**) NO_2, (**c**) SO_2, and (**d**) CO in LDL-C according to VAT, VSR, and SAT binary groups (low or intermediate adiposity vs high adiposity) (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). The black square and circle indicate VAT and VSR, respectively. White triangle represents SAT.

Discussion

This study comprehensively investigated the relationships between the annual average concentration of ambient air pollutants, abdominal adiposity, and LDL-C level in Korean adults. In the total sample, adiposity traits, including BMI, VAT and SAT areas, were significantly and positively associated with LDL-C level. By contrast, the average annual exposure to ambient air pollutants, such as PM_{10}, NO_2, SO_2, and CO, was not significantly related to LDL-C level. Notably, the significant interactions of air pollution and adiposity traits on LDL-C level were observed only for abdominal visceral fat-related traits such as VAT area and the VSR. In the subgroup analysis stratified according to adiposity level, the associations between LDL-C level and most air pollutants were much stronger in the high-VAT group than in the low- or intermediate-VAT group. The subgroup analysis of the VSR showed a similar pattern as that for VAT area, especially for PM_{10} exposure. By contrast, air pollution exposure and LDL-C level did not differ significantly between the three subgroups of SAT area. Our findings provide the first evidence that, in people with persistent exposure to air pollution, a larger VAT area compared to SAT area is more strongly related to an increased LDL-C level.

Previous epidemiological studies have identified significant associations between air pollution exposure and the lipid profile [6–8]. One study found that long-term PM_{10} exposure was closely related to increased serum triglyceride and total cholesterol levels, and increases of 2.42% and 1.43% in serum triglyceride and total cholesterol levels, respectively, per one IQR width increase in PM_{10} exposure (11.1 μg/m^3) were reported [7]. Another association study reported that intermediate-term exposure rather than short-term exposure to PM_{10} or $PM_{2.5}$ was clearly associated with changes in the levels of lipids such as LDL-C and high-density lipoprotein cholesterol (HDL-C) [8]. A multiethnic study of atherosclerosis also identified an inverse association between HDL-C level and air pollution, including black carbon and $PM_{2.5}$ [6].

More recent evidence suggests that obesity, primarily defined as BMI, influences on the relationship between air pollution exposure and changes in the lipid profile [9, 10, 20]. One study of Chinese adults living in large communities reported that the associations between long-term exposure to air pollution with an altered lipid profile and dyslipidemia were strongest among overweight or obese people [20]. Another epidemiological study of a Chinese rural population also reported that the significant association between air pollution exposure and LDL-C level

was more pronounced in overweight individuals [9]. Kim et al. (2019) assessed the associations of short- and long-term air pollution exposure, obesity, and cardiometabolic risk indicators in young adults aged 17–22 years [10]. They found that the associations of the preceding 1-year average ambient NO_2 exposure with total cholesterol and LDL-C levels were 4.5 and 9 times greater, respectively, in the obese group compared with the nonobese group ($p_{int} =$ 0.008 and 0.03, respectively). However, in the present results, the association between air pollution exposure and LDL-C level did not differ significantly according to the overall obesity status, as defined by BMI. Rather, the interaction was stronger for visceral fat when measured accurately by CT than for BMI, which is an indirect measurement of obesity. Our results highlight the importance of using precise indicators, such as CT-measured abdominal fat distribution, when quantifying the relationships between air pollution exposure, obesity, and LDL-C level.

Abdominal adiposity, especially visceral fat, is implicated as a primary risk factor for metabolic abnormalities [21]. Studies have reported higher LDL-C levels in people with abdominal obesity, especially those with an excess of visceral fat compared with subcutaneous fat, independently of BMI [22–24]. Sam et al. found that visceral fat was positively associated with very-low-density lipoprotein size or particle number and LDL particle number [24]. However, neither SAT nor BMI was significantly associated with lipoprotein indicators. Sadeghi et al. also reported a positive association of visceral fat with LDL-C level in patients with stable angina without coronary heart disease (CHD). These findings suggest that visceral fat, as measured by CT, may provide the best indicator for dyslipidemia in participants without CHD [23]. An epidemiological study in a Chinese nondiabetic population found that serum LDL-C level was significantly higher in people with greater VAT (≥ 80 cm^2) than in those with a similar BMI but with low VAT (< 80 cm^2) [22]. These findings support the hypothesis that excess visceral fat, rather than a high BMI, may play an important role in increase in LDL-C level related to exposure to ambient air pollution.

Although the mechanisms underlying the interaction between visceral fat and ambient air pollution exposure on LDL-C level remain unclear, this may be inferred through the shared biological mechanisms. One of the most likely mechanisms is the inflammatory response, one of the major biological pathways underlying cholesterol accumulation [25]. Excessive accumulation of visceral fat promotes the inflammatory response through the secretion of proinflammatory adipokines including IL-6, macrophage chemoattractant protein-1, TNF-α, resistin, and C-reactive protein [26, 27]. Such inflammatory responses seem to be related more to visceral fat than to subcutaneous fat [28]. Similarly, some evidence suggests that exposure to air pollution leads to changes in blood lipids and altered lipid metabolism via systemic inflammation [10, 29]. Macrophages are a crucial source of proinflammatory cytokines in adipose tissue [27, 30]. Exposure to ambient PM increases macrophage infiltration in adipose tissue and amplifies adipose inflammation and visceral adiposity [31]. Presumably, considering that macrophages play an important role in processing inhaled dust and air particles [32], VAT hypertrophy may be the price paid to maintain homeostasis when breathing contaminated air. In our study, the strong association of air pollution exposure with LDL-C level in participants with high visceral adiposity level may be explained in part by the interactions of air pollution and visceral fat on activation of the inflammatory response. Another potential explanation is the role of oxidative stress, which is involved in the pathogenesis of dyslipidemia. Both ambient air pollutants and visceral adiposity are closely related to systemic oxidative stress, such as the overproduction of ROS, which may trigger cholesterol accumulation in smooth muscle cells [33–35]. However, more studies are needed to understand the full spectrum of mechanisms underlying the associations between visceral fat, ambient air pollution, and lipid metabolism.

To our knowledge, this study is the first to demonstrate that the link between ambient air pollution exposure and LDL-C level is more closely related to visceral fat accumulation than to subcutaneous fat accumulation. However, our study has some limitations. First, the study design was cross-sectional, which does not allow us to infer a causal relationship between adiposity traits, ambient air pollution exposure, and LDL-C level. Second, we assessed the concentrations of air pollutants for each participant using only postal codes because of the lack of relevant data to estimate an individual's exact exposure concentration. However, this approach does not reflect other factors such as workplace exposure level, outdoor exposure time, proximity to major roads, and residence period; thus, we may have over- or underestimated each participant's exposure level.

Conclusion

In conclusion, we found that the subjects with high abdominal visceral fat, rather than subcutaneous fat, may be more susceptible to an increased LDL-C level induced by air pollution exposure. Additional research on other populations is needed to understand more clearly the relationships between ambient air pollution exposure, abdominal adiposity, and LDL-C level.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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