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Long-term exposure to air pollution and the blood lipid levels of healthy young men

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ABSTRACT

Background: There is insufficient evidence of an association between long-term exposure to air pollution and changes in blood lipid levels, and assessments may be influenced by residual confounding factors, such as socioeconomic status.
Objectives: To investigate the associations between long-term exposure to air pollution and blood lipid profiles while controlling for the risk of residual confounding factors.
Methods: We conducted a study involving conscripted Korean soldiers to assess the associations between air pollution and blood lipid levels. The soldiers, who were randomly distributed among military units throughout the country, led homogenous lives and were subjected to health checkups 8–12 months post-enlistment. We analyzed data pertaining to those who enlisted and underwent health checkups in 2019 ($n = 12{,}778$) using linear mixed models. Additionally, we evaluated quantile-specific associations using quantile regression models. We also assessed interactions based on body mass index (BMI) at the time of enlistment ($\geq$25.0 vs. $<$ 25.0 kg/m^2).
Results: The linear mixed models revealed that a 10-μg/m^3 increase in fine particulate matter $\leq$ 2.5 μm ($PM_{2.5}$) decreased high-density lipoprotein cholesterol (HDL-C) levels by −0.66% (95% confidence interval [CI]: −1.21, −0.10), and a 10-ppb increase in nitrogen dioxide (NO_2) increased total cholesterol (TC) levels by 1.04% (95% CI: 0.24, 1.84). In the quantile regression models, associations were also found at specific deciles. $PM_{2.5}$ exposure contributed to higher TC, NO_2 resulted in higher triglycerides and lower HDL-C, and ozone (O_3) led to lower HDL-C. The association between O_3 and TC differed according to BMI (p-value for interaction = 0.03); among those with a BMI $\geq$ 25.0 kg/m^2, a 10-ppb increase in O_3 increased TC by 1.09% (95% CI: 0.20, 1.09).
Discussion: These results shed new light on the importance of controlling air pollution, which can contribute to abnormal blood lipid levels, an independent risk factor for cardiovascular disease.

1. Introduction

Lipid profile abnormality is one of the most significant contributing factors affecting disability-adjusted life years globally (GBD 2015 Risk Factors Collaborators, 2016). It is an established risk factor for cardiovascular disease (Bays et al., 2021; Byrne and Targher, 2021), which is the number one cause of mortality worldwide (accounting for approximately 32% of deaths globally), and it is also responsible for most instances of air pollution-related mortality (GBD 2017 Causes of Death Collaborators 2018).

Air pollution has been associated with abnormal blood lipid levels in animal models (Ge et al., 2017; Umezawa et al., 2018); however, evidence from human studies remains insufficient and inconclusive. In a recent systematic review that assessed the association between air pollution and blood lipid levels in humans, the authors concluded that the current level of evidence is low, and due to the small number of

Abbreviations: AFMC, Armed Forces Medical Command; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NO_2, nitrogen dioxide; O_3, ozone; PM2.5, particulate matter with an aerodynamic diameter $\leq$ 2.5 μm; ROK, Republic of Korea; SES, socioeconomic status; TC, total cholesterol; TG, triglycerides; UMND, unit under the direct control of the Ministry of National Defense.

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studies published to date, the only identified associations were between particulate matter with an aerodynamic diameter $\leq$ 10.0 μm (PM_{10}) and higher triglyceride (TG) concentrations and between nitrogen dioxide (NO_2) and higher TG levels (Gaio et al., 2019).

Air pollution, especially long-term exposure (longer than a month), is closely related to multiple facets of socioeconomic status (SES), affecting the health of individuals through various pathways, such as diet, physical activity, occupation, and indoor environment (Hajat et al., 2021). Therefore, SES can act as a confounding variable when assessing the association between long-term exposure to air pollution and blood lipid levels; for example, individuals with a lower SES may be more likely to live in areas with higher air pollution levels, and they may also have abnormal blood lipid profiles (Iscan et al., 1996). However, simple methods, such as model adjustment for a single SES factor, are reportedly insufficient for controlling the confounding effects due to the multidimensional features of SES (Hajat et al., 2021).

Therefore, we performed this study to investigate the associations between long-term exposure to air pollution and blood lipid profiles while attempting to lower the potential impact of residual confounding factors (including unknown and unmeasured factors, especially those related to SES). We conducted this study using data from conscripted Korean soldiers who were randomly distributed among military units and led homogeneous lives in terms of diet, physical activity, occupation, and the indoor environment in which they worked and lived. We expect that this study, which randomly assigned exposure levels to homogeneous groups, will provide strong evidence for the associations between air pollution and lipid metabolism in humans.

2. Methods

2.1. Study population and design

All men of Korean nationality are expected to undergo a conscription physical examination at 19 years of age. Those who meet the criteria established by the Military Manpower Administration are expected to perform full-time military service for 18–22 months between the ages of 20 and 28 years, usually in the early 20 s (Yeom et al., 2020). The proportion of individuals deemed fit for active duty was 82.5% in 2019. After enlistment, all soldiers who are not commissioned or noncommissioned officers are randomly assigned to units located throughout the Republic of Korea (ROK) by a computerized random number lottery witnessed by their family members. They work and live within the units during the course of their military service. Regardless of the units they are assigned to, these soldiers lead a homogenous life in terms of diet, physical activity, occupation, and the indoor environment in which they work and live, in conformance with the guidelines of the ROK Armed Forces.

At 8–12 months following enlistment, all soldiers undergo a health checkup, consisting of physical examination, anthropometric measurements, blood tests (including those for blood lipids and liver enzymes), urine tests, chest radiography, and dental assessments at military hospitals or division medical units. The present study population comprised soldiers who were not commissioned or noncommissioned officers who underwent a health checkup in 2019 and whose health checkup data were available to access from the Defense Medical Statistics Information System (n = 12,778). For a subset of the study population, we obtained additional information on total cholesterol (TC) levels (n = 9,055) and anthropometric factors (n = 4,010) measured at the time of enlistment from the Defense Medical Statistics Information System.

A randomized controlled trial, which is a gold standard for inferring causal relationships, ensures comparability between groups of participants, not only with respect to known and measured factors, but also to those that are unknown or unmeasured; this involves randomly assigning exposure levels to the individuals included in the trial. However, randomized controlled trials are difficult to conduct when the assignment and maintenance of exposure levels are unethical or unfeasible (as is the case in the assessment of the effects of long-term exposure to air pollution). Therefore, to accurately estimate the associations between long-term exposure to air pollution and blood lipid profiles, we leveraged the random allocation of military units to randomly assign individual air pollution exposure levels. We also confirmed comparability between groups based on the homogenous lifestyles and environmental conditions among members of the ROK Army.

The study protocol was approved by the Institutional Review Board of the Armed Forces Medical Command (AFMC) (AFMC-19102-IRB-072), and the study was conducted according to the tenets of the Declaration of Helsinki. The need for informed consent was waived because we used de-identified secondary health checkup data provided by the AFMC (i.e., by excluding personal information, such as the individual's name, age, personal identification number, and sensitive disease information).

2.2. Measurement of blood lipid levels

Peripheral venous blood samples were collected after 12 h of fasting, and blood lipid concentrations were measured using an enzymatic colorimetric method at military and non-military health institutions that met the strict quality standards of the AFMC. Specifically, the blood lipid parameters measured included TC, TG, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels at the health checkup and TC levels at the time of enlistment.

2.3. Assessment of air pollution and meteorological factors

We obtained information on the hourly concentrations of particulate matter with an aerodynamic diameter $\leq$ 2.5 μm ($PM_{2.5}$), NO_2, and ozone (O_3) measured at 318 fixed-site monitoring stations throughout the country from the National Ambient Air Monitoring Information System. Air pollution monitoring is conducted under strict quality control conditions (Ministry of Environment. 2021), and the proportion of missing values was less than 5%. Missing values were excluded from the present analyses. For security reasons, the locations of the military units were only known at the municipality ("si-gun-gu") level. The ROK consists of 226 municipalities with a median area of 443.24 km^2 (minimum, 2.83 km^2; 5th percentile, 16.35 km^2; 25th percentile, 53.99 km^2; 75th percentile, 676.32 km^2; 95th percentile, 1,127.29 km^2; and maximum, 1,820.31 km^2). Therefore, we determined the individual exposures by averaging the daily mean $PM_{2.5}$ and NO_2 levels and the daily 8-h maximum O_3 levels of the municipalities where the units were located, from the day of enlistment to the day of the health checkup. In cases in which there were multiple monitoring stations in a municipality, we used the averaged values from all the stations in the municipality as the exposure level.

Data on temperature (°C) and relative humidity (%) were obtained from the Korean National Meteorological Administration. Because the meteorological data existed at the provincial level (the ROK consists of 17 provinces), we determined individual exposures by averaging the daily mean temperature and relative humidity of the provinces where the units were located, from the day of enlistment to the day of the health checkup.

2.4. Measurement of anthropometric factors

Within 7 days after enlistment, trained medical personnel measured each individual's height without shoes (to the nearest 0.1 cm) and weight with light clothes and without shoes. The body mass index (BMI) at the time of enlistment was calculated by dividing the weight (kg) by the square of the height (m).

2.5. Statistical analysis

Because the concentrations of blood lipids, with the exception of

LDL-C (Fig. S1), followed a log-normal distribution, we natural log-transformed the raw values of the blood lipid measurements for use in the subsequent analyses. We first checked whether air pollution levels (as a proxy for military units) were allocated randomly by testing the associations of factors measured at the time of enlistment (weight, BMI, and TC) and factors not expected to be affected by air pollution (height and liver enzymes) with air pollution levels using bivariate linear regression models. We then evaluated the associations between long-term exposure to certain air pollutants ($PM_{2.5}$, NO_2, and O_3) and blood lipids (TC, TG, HDL-C, and LDL-C) using separate unadjusted linear regression models and linear mixed models in which the military branch (Army, Navy, Air Force, and the unit under the direct control of the Ministry of National Defense [UMND]) was considered to have a random effect. Regression assumptions, such as linearity of the associations and normality of residuals, were visually inspected and assessed to be generally satisfied, except those for LDL-C. The linear mixed models were also adjusted for the following covariates: month of enlistment, exposure period (from enlistment to health checkup) in months, average temperature and relative humidity (from enlistment to health checkup), and air pollutant levels on lag day 1 of the health checkup. These covariates were selected based on previous studies because they could act as potential confounders or affect health outcomes (He et al., 2021; Kim et al., 2015; Zhang et al., 2021). In analyzing the associations between air pollution and TC levels, we additionally constructed models that were further adjusted for log-transformed TC levels at the time of enlistment. We also investigated the associations between air pollution and changes in TC levels during the study period with the same linear mixed models using changes in TC levels from enlistment to health checkup as outcomes.

Previous studies have suggested that the effects of air pollution on blood lipid levels may differ among those with different levels of blood lipids (McGuinn et al., 2019; Wang et al., 2021). Therefore, we constructed quantile regression models to assess the associations between air pollution and each decile of the blood lipid concentrations (Staffa et al., 2019). This method is superior to conventional regression models in that it can provide comprehensive information on quantile-specific associations by using the full distributions of outcomes instead of only the means. In addition, it can effectively deal with data that violate the assumptions of conventional regression methods, such as normality of distributions (which is the case for LDL), lending further credibility to the results obtained from the afore-mentioned models. We constructed the quantile regression models adjusted for the same covariate set (including the military branch), while using variables that were not log-transformed as outcomes, as this method of analysis does not depend on the data distribution (Bind et al., 2016).

Previous studies have suggested that individuals with a higher BMI may be more susceptible to the effects of air pollution on blood lipid levels (Mao et al., 2020b; Wang et al., 2021; Wu et al., 2020). Therefore, to assess the heterogeneity of the associations between air pollution and blood lipid levels based on BMI, we tested the interaction terms between air pollution levels and BMI, which was categorized as either ≥ 25.0 kg/m^2 ($n = 1{,}563$) or < 25.0 kg/m^2 ($n = 2{,}447$). The interaction terms were added to the linear mixed models adjusted for the same covariates and BMI. We used the BMI at the time of enlistment because an individual's BMI at the time of the health checkups may have acted as a mediating factor rather than an effect modifier, considering the temporal relevance. A p-value < 0.05 was considered to indicate an interaction. We also conducted stratified analyses by BMI at the time of enlistment ($\geq$25.0 kg/m^2 vs. $<$ 25.0 kg/m^2). The interaction tests and stratified analyses were conducted among individuals with information on BMI at the time of enlistment ($n = 4{,}010$).

We conducted the following sensitivity analyses: First, we conducted analyses without adjusting for air pollution levels on lag day 1 to directly compare the results to those of previous studies that assessed the associations between long-term air pollution exposure and blood lipid concentrations, as those studies did not consider short-term exposure to air pollution as a confounder (He et al., 2021; Kim et al., 2015). Second, we constructed multi-pollutant models, including the air pollutants that affected blood lipid levels based on the single-pollutant models, to control for possible confounding effects resulting from the presence of other air pollutants. Third, because the medians (and distributions) of the LDL-C concentrations from individuals in the Navy were substantially different from those of individuals in the other military branches (Table 1; Fig. S1), we evaluated the associations between air pollution and blood lipid levels after excluding participants from the Navy ($n =$ 1,493). Even after excluding those participants and conducting a log transformation, the LDL-C levels were not normally distributed. Therefore, we used the quantile regression models in these analyses.

Data management and statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC), and plots were drawn using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). We presented the association estimates for increments of 10 μg/m^3 for $PM_{2.5}$, and 10 ppb for NO_2 and O_3.

3. Results

In total, 12,778 study participants were enrolled between January 2 and May 20, 2019; these individuals were randomly distributed among 275 military units (Army, 128; Navy, 76; Air Force, 49; and UMND, 22) across the ROK. They underwent health checkups between August 22 and December 31, 2019, with a mean duration of 9.5 months from the time of enlistment to a health checkup. The medians (1st quartile, 3rd quartile) of the TC, TG, HDL-C, and LDL-C levels of the study participants were 169.0 (150.0, 190.0) mg/dL, 72.0 (54.0, 97.0) mg/dL, 57.8 (49.3, 67.0) mg/dL, and 61.0 (12.0, 84.0) mg/dL, respectively. The means (±standard deviations) of the daily average $PM_{2.5}$ and NO_2 levels and the 8-h maximum O_3 levels were 19.6 (±7.3) μg/m^3, 11.6 (±4.1) ppb, and 29.3 (±9.8) ppb, respectively. The means (±standard deviations) of the BMI were 23.8 (±4.1) kg/m^2 at the time of enlistment and 23.3 (±3.0) kg/m^2 at the health checkup (Table 1). Factors measured at the time of enlistment (weight, BMI, and TC) and those not expected to be affected by air pollution (height and liver enzymes) were not related to air pollution levels (Table S1).

In the unadjusted linear regression models, a 10-μg/m^3 increase in $PM_{2.5}$ levels was associated with higher TC (0.53% increase; 95% confidence interval [CI]: 0.07, 0.99) and lower HDL-C concentrations (-0.58%; 95% CI: −1.12, −0.03), and a 10-ppb increase in NO_2 levels was associated with higher TC concentrations (1.63%; 95% CI: 0.82, 2.44). In the linear mixed models that were adjusted for potential confounders, the association remained between higher $PM_{2.5}$ and lower HDL-C levels (−0.66%; 95% CI: −1.21, −0.10), as did the association between higher NO_2 and higher TC levels (1.04%; 95% CI: 0.24, 1.84) (Table 2). In analyses further adjusted for TC levels at the time of enlistment, NO_2 (1.14%; 95% CI: 0.32, 1.97), but not $PM_{2.5}$ (0.34%; 95% CI: −0.12, 0.81) and O_3 (0.01%; 95% CI: −0.32, 0.34), were associated with higher TC levels. When we investigated the associations between air pollution and changes in TC levels during the study period, NO_2 (1.69 mg/dL; 95% CI: 0.07, 3.30), but not $PM_{2.5}$ (0.47 mg/dL; 95% CI: −0.45, 1.39) and O_3 (0.05 mg/dL; 95% CI: −0.61, 0.71), were associated with an increase in TC levels from enlistment to health checkup.

We performed quantile regression analyses and found that the associations between air pollution and blood lipid levels were heterogenous across the quantiles of lipid concentrations (Fig. 1).

We identified the following associations between air pollution and blood lipid profiles, some of which were not observed in either the unadjusted linear regression models or the linear mixed models that were adjusted for potential confounders. A 10-μg/m^3 increase in $PM_{2.5}$ levels was associated with higher TC levels at the 1st decile (1.11 mg/dL; 95% CI: 0.17, 2.05) and lower HDL-C levels at the 7th (-0.51 mg/dL; 95% CI: −0.93, −0.09), 8th (-0.85 mg/dL; 95% CI: −1.31, −0.38), and 9th deciles (-0.82 mg/dL; 95% CI: −1.50, −0.15). A 10-ppb increase in NO_2 levels was associated with higher TC levels at the 1st (2.85 mg/dL; 95%

Table 1
Characteristics of the study participants.

	Total (n = 12,778)	Army (n = 10,390)	Navy (n = 1,493)	Air Force (n = 780)	UMND (n = 115)
TC (mg/dL)	169.0 (40.0)	165.0 (39.0)	194.0 (47.0)	175.0 (39.5)	161.0 (28.0)
TG (mg/dL)	72.0 (43.0)	72.0 (43.0)	69.0 (42.0)	69.0 (42.0)	72.0 (49.0)
HDL-C (mg/dL)	57.8 (17.7)	57.5 (17.7)	59.7 (16.8)	57.0 (18.2)	54.0 (17.0)
LDL-C (mg/dL)	61.0 (72.0)	64.0 (73.0)	14.0 (62.0)	70.0 (72.0)	71.5 (74.0)
$PM_{2.5}$ ($\mu g/m^3$)[a]	19.6 (7.3)	19.6 (7.2)	19.4 (7.3)	20.7 (7.7)	19.3 (7.3)
NO_2 (ppb)[a]	11.6 (4.1)	11.5 (4.1)	12.0 (4.2)	12.6 (4.0)	11.4 (3.9)
O_3 (ppb)[a]	29.3 (9.8)	29.3 (9.9)	29.0 (9.9)	29.1 (8.2)	30.4 (10.2)
Exposure period (months)	9.5 (1.0)	9.5 (1.0)	9.4 (0.9)	9.8 (1.2)	9.6 (1.0)
Temperature (°C) [a]	14.4 (1.4)	14.3 (1.3)	15.1 (1.5)	14.4 (1.8)	14.3 (1.4)
Relative humidity (%)[a]	68.2 (2.5)	68.1 (2.2)	69.5 (2.9)	68.2 (3.8)	67.8 (4.4)
BMI (kg/m^2)	23.3 (3.0)	23.3 (3.0)	23.7 (3.5)	22.7 (2.7)	23.1 (2.5)
TC at enlistment (mg/dL)	170.0 (40.0)	170.0 (40.0)	170.0 (40.0)	.	160.0 (50.0)
BMI at enlistment (kg/m^2)	23.8 (4.1)	23.8 (4.1)	.	.	25.1 (3.8)

Abbreviations: UMND, the unit under the direct control of the Ministry of National Defense; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; $PM_{2.5}$, particulate matter with an aerodynamic diameter $\leq$ 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; BMI, body mass index.
Values are presented as median (interquartile range) for TC, TG, HDL-C, and LDL-C concentrations, and as mean (standard deviation) for the other factors.
[a] Averages of the daily mean $PM_{2.5}$, NO_2, temperature, and relative humidity levels and of the 8-hour maximum O_3 levels from the day of enlistment to the day of the health checkup.

Table 2
Associations between air pollutants and blood lipid levels, estimated from unadjusted linear regression models and linear mixed models adjusted for potential confounders.[a]

		$PM_{2.5}$		NO_2		O_3	
		Percent difference (%)	95% CI	Percent difference (%)	95% CI	Percent difference (%)	95% CI
TC	Unadjusted	0.53	(0.07, 0.99)	1.63	(0.82, 2.44)	−0.14	(−0.48, 0.20)
	Adjusted	0.15	(−0.30, 0.59)	1.04	(0.24, 1.84)	−0.10	(−0.43, 0.23)
TG	Unadjusted	0.16	(−0.92, 1.25)	1.60	(−0.31, 3.55)	−0.10	(−0.90, 0.70)
	Adjusted	−0.15	(−1.24, 0.96)	1.60	(−0.38, 3.61)	−0.09	(−0.90, 0.73)
HDL-C	Unadjusted	−0.58	(−1.12, −0.03)	0.03	(−0.93, 0.99)	−0.27	(−0.68, 0.13)
	Adjusted	−0.66	(−1.21, −0.10)	−0.37	(−1.35, 0.62)	−0.37	(−0.78, 0.05)
LDL-C	Unadjusted	−2.20	(−4.45, 0.11)	−3.73	(−7.58, 0.27)	−0.09	(−1.80, 1.65)
	Adjusted	−2.06	(−4.34, 0.27)	−3.86	(−7.80, 0.24)	−0.17	(−1.90, 1.59)

Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter $\leq$ 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; CI, confidence interval; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Values are presented as percent differences in blood lipid levels induced by exposure to air pollutants in increments of 10 $\mu g/m^3$ for $PM_{2.5}$ and 10 ppb for NO_2 and O_3.
[a] Evaluated with linear mixed models using the military branch as a random effect and adjusted for month of enlistment, exposure period, average temperature and relative humidity, and air pollution levels on lag day 1 of the health checkup.

CI: 1.10, 4.60), 2nd (2.18 mg/dL; 95% CI: 0.78, 3.58), 3rd (1.88 mg/dL; 95% CI: 0.30, 3.46), 4th (1.77 mg/dL; 95% CI: 0.39, 3.14), 5th (1.56 mg/dL; 95% CI: 0.07, 3.05), and 9th deciles (2.70 mg/dL; 95% CI: 0.01, 5.39). Higher NO_2 levels were also associated with higher TG concentrations at the 9th decile (6.07 mg/dL; 95% CI: 0.74, 11.40) and lower HDL-C levels at the 8th decile (-0.94 mg/dL; 95% CI: −1.84, −0.05). A 10-ppb increase in O_3 levels was associated with lower HDL-C levels at the 8th decile (−0.45 mg/dL; 95% CI: −0.82, −0.08) (Fig. 1; Table S2).

The association between O_3 and TC concentrations differed according to BMI (p-value for interaction = 0.03). Among the study participants with a BMI $\geq$ 25.0 kg/m^2, a 10-ppb increase in O_3 levels was associated with higher TC concentrations (1.09%; 95% CI: 0.20, 1.09), whereas, among those with a BMI < 25.0 kg/m^2, no corresponding association was found (-0.22%; 95% CI: −0.87, 0.45). In the stratified analyses, we additionally detected an association between higher $PM_{2.5}$ and lower HDL-C levels (-1.49%; 95% CI: −2.65, −0.31) among study participants with a BMI < 25.0 kg/m^2; a similar outcome was observed among those with a BMI $\geq$ 25.0 kg/m^2 (p-value for interaction = 0.91), although the CI was wider (−1.53%: 95% CI: −3.13, 0.10) (Fig. 2; Table S3).

The results of the sensitivity analyses were robust. First, the results were similar to those of the analyses in which there was no adjustment for the air pollution levels on lag day 1, confirming the association between $PM_{2.5}$ and HDL-C levels and the association between NO_2 and TC levels (Table S4). Second, consistent results were observed in the multi-pollutant models that included both $PM_{2.5}$ and NO_2, which were found to be associated with blood lipid concentrations in the single-pollutant models. In the multi-pollutant models, we also detected the association between $PM_{2.5}$ and HDL-C levels and the association between NO_2 and TC levels (Table S5). Third, the results did not change appreciably after excluding the study participants from the Navy (Table S6).

4. Discussion

This study involving healthy young men revealed that long-term exposure to air pollution was associated with blood lipid levels. In the linear mixed models, $PM_{2.5}$ exposure decreased HDL-C levels, whereas NO_2 exposure increased the concentrations of TC. In the quantile regression models, we additionally found that, at specific deciles, $PM_{2.5}$ increased TC, NO_2 increased TG and decreased HDL-C, and O_3 decreased HDL-C levels. We identified an interaction between O_3 and BMI in terms of TC levels, and, when we stratified the analyses, the association between O_3 and higher TC levels was only observed among individuals with a BMI $\geq$ 25.0 kg/m^2. Abnormal blood lipid profiles are an

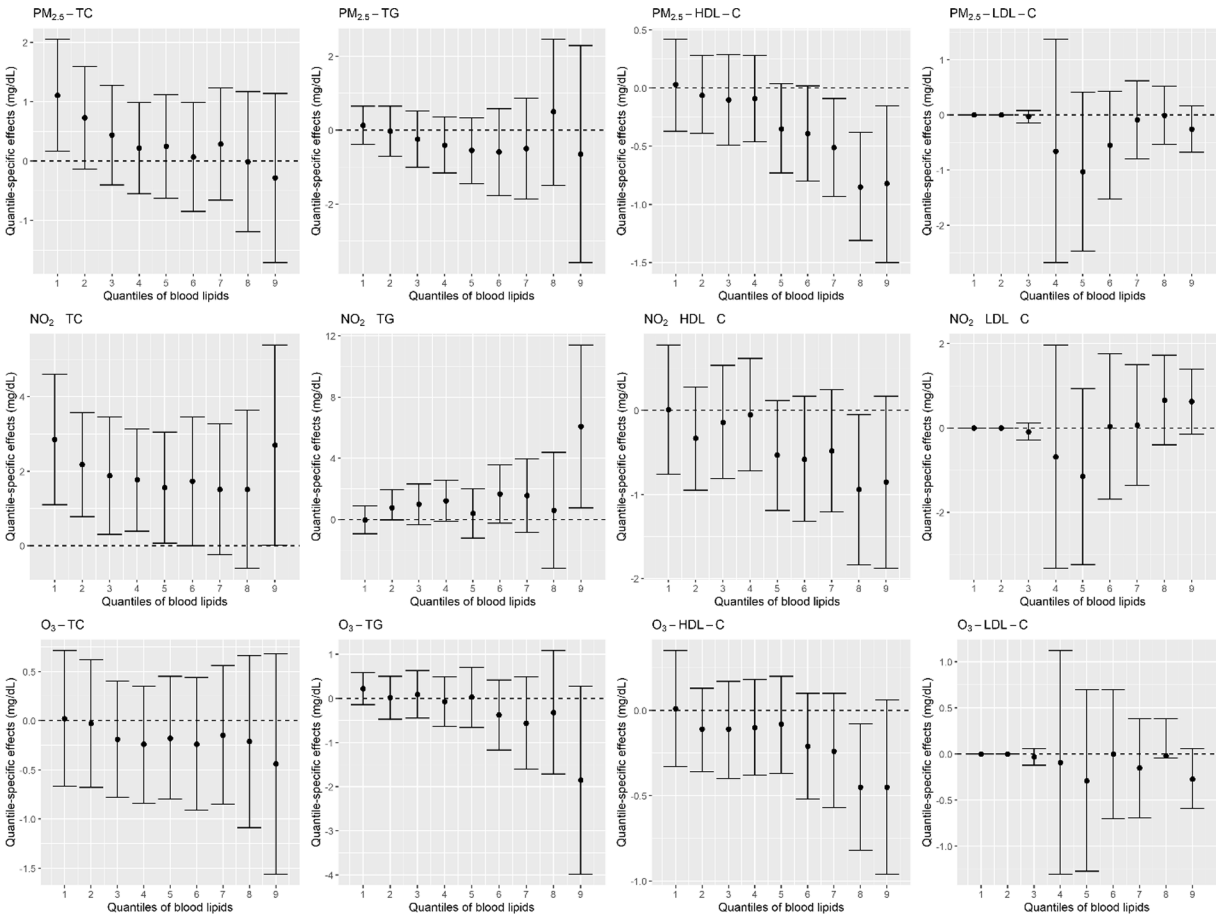

Fig. 1. Quantile-specific associations between air pollutants and blood lipid levels in the quantile regression models. The top, middle, and bottom rows show the associations of $PM_{2.5}$, NO_2, and O_3 with blood lipid levels, respectively. From left to right, the columns show data for TC, TG, HDL-C, and LDL-C levels, respectively. Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter $\leq$ 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Associations are estimated from the quantile regression models, adjusted for month of enlistment, exposure period, average temperature and relative humidity, air pollution levels on lag day 1 of the health checkup, and military branch. Values are presented as percent differences in blood lipid levels induced by air pollutants in increments of 10 μg/m^3 for $PM_{2.5}$ and 10 ppb for NO_2 and O_3.

independent risk factor for cardiovascular disease, and effective management of blood lipids can lower cardiovascular disease morbidity and mortality (Stevens et al., 2016); therefore, these results have substantial public health implications.

The results of previous studies that investigated the association between air pollution and blood lipid concentrations have been heterogeneous. For example, among middle-aged American women, annual average $PM_{2.5}$ levels were shown to be associated with lower HDL-C, but not with TC, TG, and LDL-C levels (Wu et al., 2019). Among Chinese children and adolescents, 3-year average $PM_{2.5}$ and NO_2 levels were associated with higher TC, but not with TG, HDL-C, and LDL-C levels (Gui et al., 2020). Among Chinese adults aged 30–79 years, however, 3-year average $PM_{2.5}$ levels were associated with higher TC, TG, and LDL-C and lower HDL-C levels, NO_2 levels were associated with higher TC and LDL-C and lower HDL-C levels, and O_3 levels were associated with higher TC and LDL-C and lower HDL-C levels (Wang et al., 2021). Among healthy Chinese college students, $PM_{2.5}$ levels measured within 5 days before blood collection were associated with lower HDL-C concentrations (He et al., 2021). These results are partially consistent with those of the present study, whereas the results of the following studies were less consistent: among American patients undergoing cardiac catheterization, annual average $PM_{2.5}$ levels were associated with higher TC, TG, HDL-C, and LDL-C concentrations (McGuinn et al., 2019). Among Chinese adults older than 45 years of age, annual average $PM_{2.5}$ levels were associated with higher TC and LDL-C, but not with TG and HDL-C levels (Li et al., 2021). This heterogeneity may be attributed to differences in the study populations, air pollution levels, modeling of the duration of exposure, and accuracy of the exposure and outcome measurements. These discrepancies may also be attributed to residual confounding factors inherent to observational studies (e.g., those related to diet, physical activity, occupation, and the indoor environment), which, we assumed, were controlled sufficiently in the present study.

This is one of the first studies to utilize a quantile regression method to explore the quantile-specific associations between air pollution and blood lipid profiles. In the present study, the quantile regression analyses confirmed the results derived from the conventional regression analyses (i.e., linear regression and linear mixed models) and revealed new associations between air pollution and blood lipids that were not detected using those other methods. However, although previous studies have suggested that the associations might be more pronounced among individuals who are already at higher risk, such as those with higher TC, TG, and LDL-C and lower HDL-C levels (Bind et al., 2016; Emerging Risk Factors Collaboration et al., 2009; Hu et al., 2013), these expected patterns were not observed consistently in the present study. The associations between $PM_{2.5}$ and TC concentrations were more pronounced at the lower TC deciles, the associations between NO_2 and TG concentrations were greater at higher TG deciles, and the associations of $PM_{2.5}$, NO_2, and O_3 with HDL-C levels were stronger at higher HDL-C deciles (Fig. 1). Studies investigating the quantile-specific associations between air pollution and blood lipid levels are rare and have reported

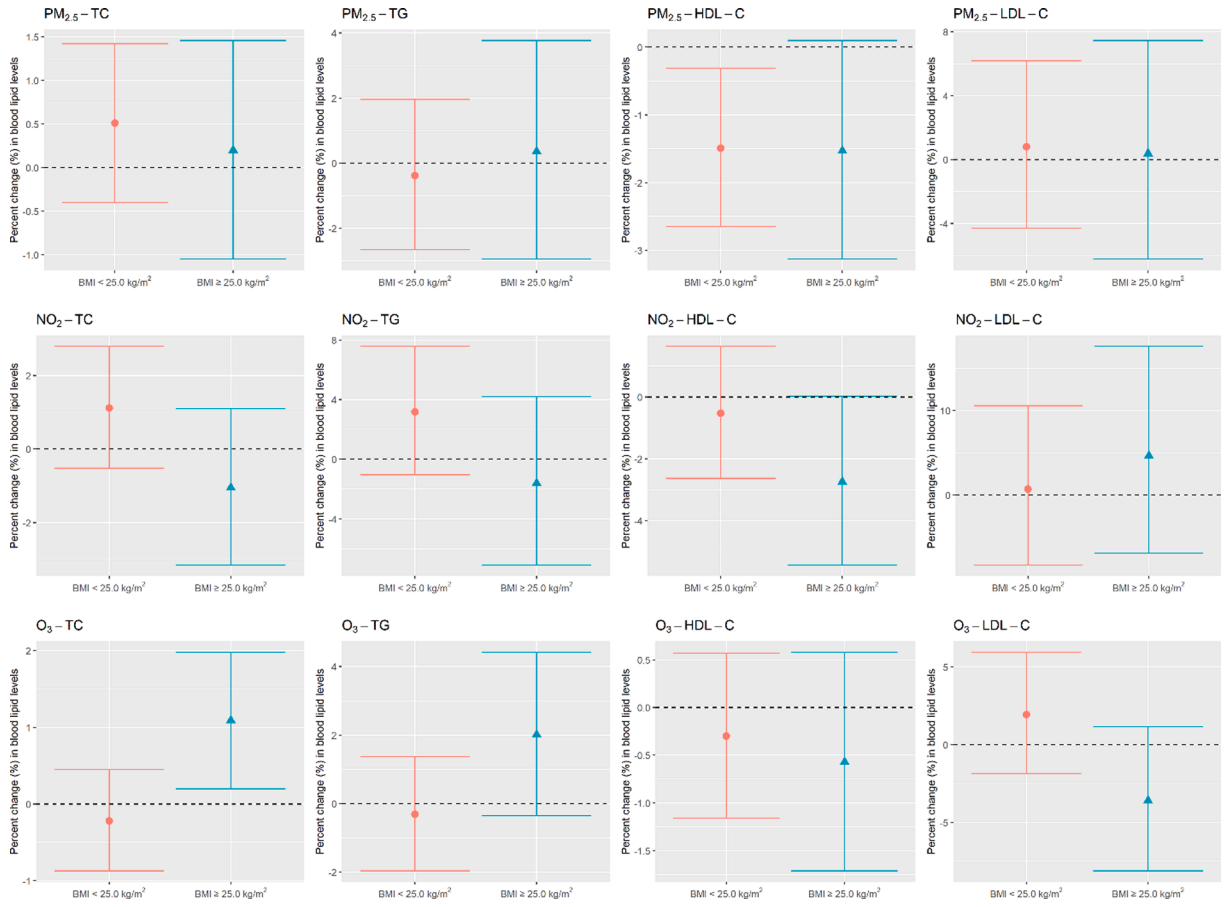

Fig. 2. Associations between air pollutants and blood lipids, stratified by BMI at the time of enlistment. The top, middle, and bottom rows show the associations of $PM_{2.5}$, NO_2, and O_3 with blood lipid levels, respectively. From left to right, the columns show data for TC, TG, HDL-C, and LDL-C levels, respectively. Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter $\leq$ 2.5 μm; BMI, body mass index; NO_2, nitrogen dioxide; O_3, ozone; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Associations are estimated from the linear mixed models, with the military branch as a random effect, adjusted for month of enlistment, exposure period, average temperature and relative humidity, and air pollution levels on lag day 1 of the health checkup. Values are presented as percent differences in blood lipid levels induced by air pollutants in increments of 10 $\mu g/m^3$ for $PM_{2.5}$ and 10 ppb for NO_2 and O_3. Circles and triangles represent point estimates of the associations between air pollution and blood lipid levels for individuals with a BMI $<$ 25.0 kg/m^2 and those with a BMI $\geq$ 25.0 kg/m^2, respectively. Error bars represent 95% confidence intervals.

inconsistent results; for example, stronger associations were reported at higher TC and lower HDL-C deciles (Wang et al., 2021), whereas another study demonstrated stronger associations at higher TG deciles (McGuinn et al., 2019). Further studies are warranted before any conclusions can be made regarding quantile-specific effects, considering the heterogeneity among various populations in terms of age, sex, race/ethnicity, and SES.

Previous studies have suggested that the effects of air pollution might be greater among individuals with a higher BMI due to the induction of increased pro-inflammatory cytokine release from adipose tissue (Li et al., 2016; Mao et al., 2020b; Wu et al., 2020). Although we found a stronger association between O_3 and TC concentrations among individuals with a BMI $\geq$ 25.0 kg/m^2 than among those with a BMI $<$ 25.0 kg/m^2 (p-value for interaction $=$ 0.03), no statistical differences were observed between those with a BMI $\geq$ 25.0 kg/m^2 and those with a BMI $<$ 25.0 kg/m^2 for any other pairs of air pollutants and blood lipids. The reason for these findings is unclear. These results may be attributable, at least in part, to the fact that the BMI may not accurately reflect the amount of adipose tissue in populations with a relatively high proportion of muscle tissue resulting from engagement in intense physical activity, as in the present study population (Etchison et al., 2011).

Several potentially interrelated mechanisms have been proposed to describe the effects of air pollution on blood lipids. Air pollution-induced oxidative stress and systemic inflammation may disrupt lipid metabolism, leading to changes in blood lipid levels (Li et al., 2013). Air pollution may also affect peroxisome proliferator-activated receptor activity in the liver as a result of circadian rhythm changes, disturbing hepatic lipid metabolism and altering the concentration of lipids in the blood (Deprince et al., 2020; Li et al., 2020b; Xu et al., 2019). Finally, air pollution may alter DNA methylation of certain genes related to lipid metabolism, which can affect blood lipid levels (Li et al., 2018). The next step would be to investigate the mechanisms underlying the differential effects of specific air pollutants on blood lipids that were observed in the present study (Gaio et al., 2019).

This study had some limitations. First, the study population included only men. Although there are studies that have reported a lack of sex effects (Gui et al., 2020) or a stronger association among men (Mao et al., 2020a), the majority have demonstrated a stronger association between exposure to air pollution and changes in blood lipids in women (He et al., 2021; Li et al., 2019, 2020a; McGuinn et al., 2019). Therefore, the present study might underestimate the actual effects of air pollution in the real-world whole population. Second, this study only included healthy young adults, which may lead to the underestimation of the actual effects of air pollution in the entire population, given that air pollution has reportedly greater effects among older individuals and those with underlying diseases (He et al., 2021; Shin et al., 2020; Zhang et al., 2021). Third, there is no available information on the use of lipid-lowering drugs and the underlying diseases they are used to treat, which

can affect the concentrations of blood lipids (Gaio et al., 2019; Mao et al., 2020b). However, we assumed that the number of individuals taking lipid-lowering drugs would be small, considering the characteristics of the present population. Additionally, air pollution is thought to be unrelated to the use of lipid-lowering drugs; therefore, the use of such agents is not expected to act as a confounding factor that affects the association between air pollution and blood lipid levels. Fourth, personal information, such as age, education level, family income before enlistment, social class, prior dietary habit, history of hyperlipidemia, and occupational exposure to ordnance compounds and explosives, were not available. However, because the individuals were randomly distributed among units throughout the ROK, the distributions of these personal demographic factors are expected to be similar across groups exposed to different air pollution levels, and these factors were unlikely to confound the association between air pollution and blood lipid concentrations. Fifth, because this study used data retrieved from the Defense Medical Statistics Information System, any relevant data that were unavailable (data that were not computerized and/or successfully transferred to the database) could not be assessed in this study. Sixth, air pollution levels were not measured individually; instead, they were estimated at the municipality level based on ambient air pollution monitoring data (without considering indoor ventilation conditions or the existence of air purifiers). Although air pollution modeling by grids or administration divisions is common and the resolution of air pollution exposures in the present study was comparable to those of previous studies, coarse grid resolutions of air pollution (36 km or 1,296 km^2 or more) reportedly produced a larger bias for effect estimates than a fine grid resolution (12 km or 144 km^2) (Punger and West, 2013). Therefore, future studies should measure air pollution at the individual level or with finer resolution. Additionally, military units are usually stationed in suburban or remote areas away from urban centers, resulting in further non-differential measurement error that would bias the results in favor of the null hypothesis. Seventh, although exposure to air pollution before enlistment, especially during pregnancy and in early developmental periods, can cause long-term effects that last to adulthood (Gorr et al., 2014; He et al., 2019), we could not consider these possible longitudinal effects due to a lack of corresponding information. However, because air pollution levels after enlistment were randomly assigned through random allocation of military units, we assumed that air pollution levels before enlistment were comparable (similar) among groups exposed to different air pollution levels after enlistment: air pollution levels were randomly assigned to comparable groups in terms of various factors before enlistment, such as exposed air pollution levels before enlistment. Therefore, air pollution exposure before and after enlistment were unrelated to each other and an omitted variable (exposure to air pollution before enlistment in this case) would not have biased the results. Eighth, because we performed various analyses, including quantile regression analyses, some of the identified associations could have been the result of random error. However, we did not adjust for multiple comparisons because we presented all the results unselectively and the analyses conducted in the present study were correlated, not independent.

This study also has notable strengths. First, this study provided a unique opportunity to randomly allocate long-term exposure to air pollution, which is closely related to multiple facets of SES, an important confounder. Due to this random allocation of exposures, confounding factors including unknown or unmeasured factors, such as genetic polymorphisms (Wu et al., 2020), could be controlled by the study design. Second, the study population was homogeneous in terms of diet, physical activity, occupation, and the indoor environment in which the participants worked and lived, increasing the comparability among groups exposed to different air pollution levels and strengthening the causal inference (Li et al., 2021; Mao et al., 2020a, 2020b). Third, the present population engaged in many outdoor activities and worked and lived in the same place without commuting to and from work. Therefore, any air pollution measurement error would be less than that in previous studies, most of which have assigned long-term air pollution exposure levels to individuals who regularly commute (to work or school), based on their residential addresses. Fourth, due to the relatively large sample size, we were able to detect the effects of air pollution on blood lipid levels among healthy young adults, a population that is generally considered to have lower risks associated with air pollution, with sufficient self-regulatory capacity (He et al., 2021; O'Neill et al., 2012).

5. Conclusions

In this study assessing the associations between long-term exposure to air pollution and blood lipids, $PM_{2.5}$ and NO_2 decreased HDL-C and increased TC concentrations, respectively, among healthy young men. Additionally, the quantile regression analyses revealed that $PM_{2.5}$ increased TC levels, NO_2 increased TG and decreased HDL-C levels, and O_3 decreased HDL-C levels at specific deciles. We also found an interaction between O_3 exposure and BMI in terms of TC levels, with a stronger association observed among individuals with a BMI $\geq$ 25.0 kg/m^2 than among those with a BMI $<$ 25.0 kg/m^2. This study adds strong evidence that long-term exposure to air pollution affects blood lipids to the limited data from previous observational studies in humans. These findings shed new light on the importance of controlling air pollution to prevent changes leading to abnormal blood lipid profiles, which are an independent risk factor for cardiovascular disease.

CRediT authorship contribution statement

Kyoung-Nam Kim: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft. **Beomman Ha:** Data curation, Methodology, Validation, Writing – review & editing. **Woong Seog:** Data curation, Methodology, Validation, Writing – review & editing. **Il-Ung Hwang:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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