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Exposure to ambient air pollution and blood lipids in adults: The 33 Communities Chinese Health Study

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ABSTRACT

Background: Little information exists on the lipidemic effects of air pollution, particularly in developing countries. We aimed to investigate the associations of long-term exposure to ambient air pollutants with lipid levels and dyslipidemias in China.

Methods: In 2009, a total of 15,477 participants aged 18–74 years were recruited from the 33 Communities Chinese Health Study conducted in three Northeastern China cities. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured in participants' blood specimens. Three year (2006–08) average air pollution concentrations were assessed using data from 33 communities (particles with diameters ≤1.0 μm (PM_1) and ≤2.5 μm ($PM_{2.5}$) were predicted using a spatial statistical model) or 11 air monitoring stations (particles with diameters ≤10 μm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3)). Associations were evaluated by two-level logistic and generalized linear regression models.

Results: We detected many significant associations between exposure to air pollutants (especially for PM_1 and $PM_{2.5}$) and blood lipid levels. Most of the associations suggested deleterious effects on blood lipid markers (e.g.,

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular diseases; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NO_2, nitrogen dioxide; OR, odds ratio; O_3, ozone; PM_1, particles with diameters ≤1.0 μm; $PM_{2.5}$, particles with diameters ≤2.5 μm; PM_{10}, particles with diameters ≤10 μm; $PM_{2.5-10}$, particles with diameters ranging from 2.5 to 10 μm; SEPA, the State Environmental Protection Administration of China; SO_2, sulfur dioxide; TC, total cholesterol; TG, triglycerides; 33CCHS, the 33 Chinese Community Health Study

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a 10 μg/m^3 increase in PM_1 was associated with 1.6% (95% confidence interval (CI): 1.1, 2.0), 2.9% (95% CI: −3.3, 9.3), and 3.2% (95% CI: 2.6, 3.9) higher levels of TC, TG, and LDL-C, respectively, but 1.4% (95% CI: −1.8, −0.9) lower HDL-C levels), although beneficial associations were found for O_3. In analysis with dyslipidemias, all the observed associations suggested deleterious lipidemic effects of air pollutants, and no significant beneficial association was observed for O_3. Stratified analyses showed that the associations were stronger in overweight or obese participants; sex and age modified the associations, but the pattern of effects was mixed.

Conclusions: Long-term ambient air pollution was associated with both altered lipid profiles and dyslipidemias, especially among overweight or obese participants.

1. Introduction

Cardiovascular diseases (CVD) are responsible for approximately 31% of deaths worldwide (Word Health Organization, 2017) and the results of numerous epidemiological studies have supported a causal relation for long-term air pollution exposure with CVD (Brook et al., 2010; Bourdrel et al., 2017). Inhaled air pollutants trigger inflammation, oxidative stress, autonomic imbalance, and epigenetic changes (Brook et al., 2010; Bourdrel et al., 2017). These reactions have been linked to several CVD risk factors, including atherosclerosis, hypertension, diabetes mellitus, and dyslipidemia (Brook et al., 2010; Thiering and Heinrich, 2015; Rajagopalan and Brook, 2012; Yang et al., 2018). For example, higher levels of particulate matter (PM) have been linked to increased systemic inflammation (Brook et al., 2010), which can lead to adverse lipid metabolism and lipid oxidation (Chen et al., 2013). The relationships of air pollution with hypertension and diabetes mellitus have been demonstrated by many epidemiological and experimental studies (Brook et al., 2010; Rajagopalan and Brook, 2012; Thiering and Heinrich, 2015), including our own (Dong et al., 2013; Yang et al., 2017; Yang et al., 2018).

Dyslipidemia, characterized by hypercholesterolemia, hypertriglyceridemia, hypoalphalipoproteinemia, and/or hyperbetalipoproteinemia, is the foremost cause of atherosclerosis (Stensland-Bugge et al., 2000) and is inextricably related to the development of CVD (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). The global prevalence of dyslipidemias is high and increasing (Cahalin et al., 2014). For example, a 2013 report from the American Heart Association suggested that the prevalences of hypercholesterolemia, hypoalphalipoproteinemia, and hyperbetalipoproteinemia in American adults were 43.4%, 21.8%, and 31.1%, respectively (Go et al., 2013). Several previous epidemiological studies explored relationships between ambient air pollutant exposure and dyslipidemia and blood lipid levels, yet the results were inconsistent (Bell et al., 2017; Bind et al., 2016; Cai et al., 2017; Chuang et al., 2011; Jiang et al., 2016; Poursafa et al., 2014; Shanley et al., 2016; Sørensen et al., 2015; Wallwork et al., 2017; Yeatts et al., 2007; Yitshak Sade et al., 2016) (see Table S1). Additionally, most studies investigated effects among specific populations, including asthmatics (Yeatts et al., 2007), patients with chronic diseases (Yitshak Sade et al., 2016), the elderly (Bind et al., 2016; Chuang et al., 2011; Sørensen et al., 2015; Wallwork et al., 2017), and adolescents (Poursafa et al., 2014). However, the lipidemic effects of air pollution exposure were rarely evaluated in general populations. Moreover, previous studies were mostly conducted in high-income nations or regions (Bell et al., 2017; Bind et al., 2016; Chuang et al., 2011; Shanley et al., 2016; Sørensen et al., 2015; Wallwork et al., 2017; Yeatts et al., 2007; Yitshak Sade et al., 2016). There are few data available to characterize the risks of air pollution exposure on lipid levels and dyslipidemia in low-income countries.

In recent decades, China has experienced a gradual increase in the prevalence of dyslipidemia, although it remains lower than that in many developed countries (Pan et al., 2016). For instance, the 2002 China National Nutrition and Health Survey reported that the prevalences of hypercholesterolemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, and hypertriglyceridemia were 2.9%, 2.5%, 7.4%, and 11.9%, respectively (Zhao, 2008), while the corresponding 2013–2014 China Chronic Disease and Risk Factor Surveillance prevalences were 6.9%, 8.1%, 20.4%, and 13.8% (Zhang et al., 2018). Simultaneously, air pollution has emerged as a severe environmental problem in China (Guan et al., 2016; Rohde and Muller, 2015). Given temporal increases in both ambient air pollution and the prevalence of dyslipidemia, and the scarcity of data, it is of significant public health importance to explore the relationship between the two. To begin to address the data gap, this study examined associations between long-term residential ambient air pollution and blood lipid levels in a large community-based sample of urban adults participating in the 33 Chinese Community Health Study (33CCHS).

2. Methods

2.1. Study population

The population of the 33CCHS was previously described in detail (Dong et al., 2013; Yang et al., 2017). Briefly, in 2009, we used a random-number generator coupled to a four-staged, stratified, cluster sampling strategy to recruit study participants. First, to maximize the inter-city gradients of air pollutants, we randomly selected three cities - Shenyang, Anshan, and Jinzhou - from 14 total cities in Liaoning province. There are five districts in Shenyang city and three each in the cities of Anshan and Jinzhou. Second, we randomly selected three communities from each of the districts, generating a total of 33 study communities. Each study community was approximately 0.25–0.64 km^2 in area. Third, we randomly selected 700–1000 households from each study community. Fourth, from each study household, we randomly selected one adult aged 18 to 74 years for study enrollment. To be included, individuals had to live at the study address for at least five years, have no severe pre-existing diseases (e.g., cancers), and not be pregnant. Based on the sampling frame, 28,830 participants were invited, of whom 24,845 individuals completed the survey, yielding an overall response rate of 86.2%. A total of 9368 individuals were excluded from the present analysis due to refusal to provide a blood sample, leaving a final sample of 15,477 participants (62.3% of the 33CCHS participants). All participants completed informed consent prior to study enrollment, and Sun Yat-Sen University's Human Studies Committee reviewed and approved all study procedures and protocols.

2.2. Health outcomes

After an overnight fast, peripheral venous blood samples were collected from study participants. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were determined using a Hitachi Autoanalyzer (Type 7170A; Hitachi Ltd.; Tokyo, Japan). Hypercholesterolemia was defined as TC ≥ 240 mg/dL; hypertriglyceridemia was defined as TG ≥ 200 mg/dL; hypoalphalipoproteinemia was defined as HDL-C ≤ 40 mg/dL; and hyperbetalipoproteinemia was defined as LDL-C ≥ 160 mg/dL (Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of

Dyslipidemia in Adults, 2007).

2.3. Air pollution data

A detailed description of the exposure assessment was provided in our previous publications (Dong et al., 2013; Yang et al., 2017; Chen et al., 2018). Briefly, daily concentrations of PM with diameters $\leq 1.0\,\mu m$ (PM_1) and $\leq 2.5\,\mu m$ ($PM_{2.5}$) were predicted for the 33 study communities, at a $0.1^\circ \times 0.1^\circ$ spatial resolution, using PM_1 and $PM_{2.5}$ measurements from air monitoring stations, satellite remote sensing, meteorology, and land use characteristics. Aerosol optical depth data was combined from two types of Moderate Resolution Imaging Spectroradiometer algorithms—Dark Target and Deep Blue. A generalized additive model was developed to link ground-monitored PM_1 and $PM_{2.5}$ data with aerosol optical depth data and other spatial and temporal predictors. In each of the study districts, there was one air monitoring station, which was located within a 1-km distance from the centroid of the community of each study participant's home address (Fig. S1). We collected data for PM with diameters $\leq 10\,\mu m$ (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and ozone (O_3) concentrations from 11 air monitoring stations, according to standardized procedures set by the State Environmental Protection Administration of China (SEPA) (SEPA, 1992). These air monitoring stations were mandated to be away from main traffic roads, industry sources, or residential sources of emissions from the combustion of coal, waste, or oil. Thus, air pollution measurements from these stations were more likely to reflect mixtures from different sources and background levels in urban areas. Daily average concentrations of PM_{10}, SO_2, NO_2, and an eight-hour average of O_3 were calculated using measurements from days with at least 75.0% of one-hour values available. PM_{coarse} ($PM_{2.5–10}$) was calculated by subtracting $PM_{2.5}$ from PM_{10}. The three-year (2006–08) average concentrations of air pollutants were calculated for the 33 communities and 11 districts (or air monitoring stations), and then assigned to each participant based on proximity of the community or district to his/her residential address, as surrogates of long-term air pollution exposure.

Table 1
Study population characteristics (n = 15,477).

	Value (mean ± SD, n (%), or median (Q1, Q3))		
Characteristics	Total (n = 15,477)	Men (n = 8156)	Women (n = 7321)
Age (years)[a]	44.97 ± 13.45	44.44 ± 14.20	45.56 ± 12.55
Ethnicity			
Han	14,554 (94.0%)	7670 (94.0%)	6884 (94.0%)
Other	923 (6.0%)	486 (6.0%)	437 (6.0%)
Education[a]			
Junior college or higher	3579 (23.1%)	2250 (27.6%)	1329 (18.2%)
Middle school	9554 (61.7%)	5008 (61.4%)	4546 (62.1%)
Primary school	1863 (12.0%)	782 (9.6%)	1081 (14.8%)
No school	481 (3.1%)	116 (1.4%)	365 (5.0%)
Annual family income[a]			
≤5000 Yuan	1167 (7.5%)	618 (7.6%)	549 (7.5%)
5001–10,000 Yuan	1977 (12.8%)	846 (10.4%)	1131 (15.5%)
10,001–30,000 Yuan	7869 (50.8%)	4198 (51.5%)	3671 (50.1%)
≥30,000 Yuan	4464 (28.8%)	2494 (30.6%)	1970 (26.9%)
Tobacco smoking status[a]			
Nonsmoker	10,837 (70.0%)	4004 (49.1%)	6833 (93.3%)
Smoker	4640 (30.0%)	4152 (50.9%)	488 (6.7%)
Alcohol drinking status[a]			
Nondrinker	11,668 (75.4%)	4562 (55.9%)	7106 (97.1%)
Drinker	3809 (24.6%)	3594 (44.1%)	215 (2.9%)
Regular exercise[a]			
Yes	4932 (31.9%)	2724 (33.4%)	2208 (30.2%)
No	10,545 (68.1%)	5432 (66.6%)	5113 (69.8%)
Control diet with low calorie and fat[a]			
Yes	3861 (24.9%)	1828 (22.4%)	2033 (27.8%)
No	11,616 (75.1%)	6328 (77.6%)	5288 (72.2%)
Sugar-sweetened soft drink intake[a]			
≤1 day per week	13,621 (88.0%)	6996 (85.8%)	6625 (90.5%)
2–4 days per week	1286 (8.3%)	818 (10.0%)	468 (6.4%)
≥5 days per week	570 (3.7%)	342 (4.2%)	228 (3.1%)
BMI[a]			
≥25 kg/m^2	6271 (40.5%)	3660 (44.9%)	2611 (35.7%)
< 25 kg/m^2	9206 (59.5%)	4496 (55.1%)	4710 (64.3%)
Family history of dyslipidemia[a]			
Yes	1228 (7.9%)	492 (6.0%)	736 (10.1%)
No	14,249 (92.1%)	7664 (94.0%)	6585 (89.9%)
Blood lipids & dyslipidemias			
TC (mg/dL)	179.92 (155.98, 205.41)	180.70 (157.53, 204.83)	179.15 (154.44, 206.18)
TG (mg/dL)[a]	118.58 (81.42, 176.99)	130.09 (88.50, 200.89)	106.19 (75.22, 160.18)
HDL-C (mg/dL)[a]	50.97 (43.63, 60.61)	48.26 (40.84, 58.30)	54.05 (47.10, 62.93)
LDL-C (mg/dL)	98.60 (75.67, 122.31)	98.60 (75.87, 122.29)	98.74 (75.50, 122.41)
Hypercholesterolemia	1717 (11.1%)	910 (11.2%)	807 (11.0%)
Hypertriglyceridemia[a]	3494 (22.6%)	2336 (28.6%)	1158 (15.8%)
Hypoalphalipoproteinemia[a]	2836 (18.3%)	2064 (25.3%)	772 (10.6%)
Hyperbetalipoproteinemia	1333 (8.6%)	698 (8.6%)	635 (8.7%)

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation; TC, total cholesterol; TG, triglycerides.

[a] Statistically significant difference between men and women ($p < .05$).

2.4. Covariates

All potential covariates were selected a priori. An interviewer administered questionnaire was used to collect information on age (years), sex (male/female), nationality (Han/others), household annual income (≤5000 Yuan/5001–10,000 Yuan/10001–30,000 Yuan/≥30,000 Yuan), highest educational attainment (no school/primary school/middle school/junior college or higher), current smoking (yes/no), alcohol drinking (yes/no), regular exercise (yes/no), controlled diet with low calories and low fat (yes/no), sugar-sweetened soft drink consumption (≤1 day per week/2–4 days per week/≥5 days per week), family history of dyslipidemia, and district (or community). Height (cm) and weight (kg) were measured without heavy clothes and shoes, and body mass index (BMI, kg/m^2) was calculated. Data on temperature, humidity, and wind speed for the 11 districts were obtained from Liaoning Provincial Meteorological Bureau. Per-capita gross domestic product and population density in each district were obtained from Shenyang, Jinzhou, and Anshan cities' Statistical Yearbooks. Season at the time of blood sampling was also included as a potential cofounder.

2.5. Statistical analysis

The Shapiro-Wilk and the Bartlett tests were used to examine data normality and homogeneity, respectively. Differences in basic characteristics between men and women, and between participants with and without blood sampling, were tested using Student's *t*-test, or the Wilcoxon rank sum or chi-square tests. We used the Spearman rank correlation test to assess the relationship between air pollutants.

We applied linear regression models to assess associations between individual air pollutants (per 10 $\mu g/m^3$ increase) and blood lipid levels (TC, TG, HDL-C, and LDL-C), which were naturally log-transformed to achieve normal distributions. Effect estimates were then back-transformed from the log scale using $100 \times [\exp(\beta) - 1]$ and presented as percent differences with corresponding 95% confidence intervals (CI). We also used two-level binary logistic regression models to investigate associations of ambient air pollutants (per 10 $\mu g/m^3$ increase) with hypercholesterolemia, hypertriglyceridemia, hypoalphalipoproteinemia and hyperbetalipoproteinemia, where participants were treated as first-level units and districts or communities as second-level units. Detailed descriptions of the two-stage binary logistic regression models were provided in our previous publications (Dong et al., 2013; Yang et al., 2017) and in the supplemental material (detailed information on two-level binary logistic regression model). These results are presented as odds ratio (OR) with corresponding 95% CI. All regression models were adjusted for the variables listed in the Covariates section. District or community was incorporated as a random effect, and the remaining covariates were incorporated as fixed effects. Multi-pollutant models could not be applied, as all air pollutants were correlated moderately to highly (except NO_2 and SO_2). Therefore, highly correlated pollutants were regressed against each other and the residuals were then incorporated into the models for associations between air pollutants and lipid outcomes (Flexeder et al., 2017).

We performed subgroup analyses by sex (men, women), age group (≥50 years, < 50 years), and BMI category ($\geq 25\ kg/m^2$, $< 25\ kg/m^2$), and a cross-product term was incorporated into regression models to evaluate the statistical significance of their interactions. Additionally, we repeated the regression analyses of air pollution and lipid levels by excluding participants who took lipid lowering drugs, or those had cardiovascular diseases or diabetes mellitus. Also, we applied multi-annual average concentrations of air pollutants (i.e., one-year average (2008), two-year average (2007–08), and three-year average (2006–08)) as long-term exposures, in order to exclude possible exposure fluctuations over shorter periods. Furthermore, 30-day average air pollutant concentrations before the blood draw were additionally adjusted to explore the potential impact of short-term air pollution exposure on lipids. Similarly, for pollutants in which long-term and short-term levels were highly correlated, they were regressed against each other and the individual residuals were then incorporated into the regression models.

Data analysis was performed using SAS 9.4 (SAS Institute, Cary, NC) with a p value < 0.05 considered as statistically significant for a two-tailed test.

3. Results

3.1. Descriptive statistics

The mean age of study participants was 45.0 years, and 52.7% were men (Table 1). Most participants had a middle school or higher education (84.8%). Thirty percent and 24.6% of them were smokers and drinkers, respectively. Approximately 31.9% reported engaging in regular exercise and 7.9% had a family history of dyslipidemia. The prevalences of hypercholesterolemia, hypertriglyceridemia, hypoalphalipoproteinemia, and hyperbetalipoproteinemia were 11.1%, 22.6%, 18.3%, and 8.6%, respectively. The median concentrations of TC, TG, HDL-C, and LDL-C were 179.92 mg/dL, 118.58 mg/dL, 50.97 mg/dL, and 98.60 mg/dL, respectively. Men and women differed for all sociodemographic and lifestyle variables, with the exception of nationality. The distribution of the main characteristics was similar between the analytical sample and those who were excluded from this analysis (Table S2).

The PM_1, $PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3 concentrations varied greatly across study districts (or communities) with a median of 62 $\mu g/$

Table 2
Summary statistics and pairwise Spearman correlations of air pollutants.

Exposure	Summary statistics						Spearman correlation coefficients					
	Mean	Median	Minimum	Maximum	IQR	> WHO guideline (%)[c]	PM_1	$PM_{2.5}$	PM_{10}	SO_2	NO_2	O_3
PM_1 ($\mu g/m^3$)[a]	65.97	62	50	82	15	None[d]	1.00	0.99[e]	0.73[e]	0.52	0.67[e]	0.47
$PM_{2.5}$ ($\mu g/m^3$)[a]	82.02	73	64	104	26	100		1.00	0.72[e]	0.51	0.63[e]	0.45[e]
PM_{10} ($\mu g/m^3$)[b]	123.06	123	93	145	19	100			1.00	0.81[e]	0.65[e]	0.81[e]
SO_2 ($\mu g/m^3$)[b]	54.42	48	36	78	20	100				1.00	0.25	0.84[e]
NO_2 ($\mu g/m^3$)[b]	35.28	33	27	45	9	18.2					1.00	0.45
O_3 ($\mu g/m^3$)[b]	49.40	50	27	71	22	0.0						1.00

Abbreviations: IQR, interquartile range; NO_2, nitrogen dioxide; O_3, ozone; PM_1, particle with aerodynamic diameter ≤1.0 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤2.5 μm; PM_{10}, particle with aerodynamic diameter ≤10 μm; SD, standard deviation; SO_2, sulfur dioxide.

[a] Based on values from 33 communities.

[b] Based on values from 11 districts.

[c] World Health Organization (WHO) air quality guidelines (2005).

[d] No guideline for PM_1.

[e] Statistically significant correlation ($p < .05$).

m^3, 73 μg/m^3, 123 μg/m^3, 48 μg/m^3, 33 μg/m^3, and 50 μg/m^3, respectively (Table 2). Except for SO_2 and NO_2, moderate to high correlations between air pollutants were detected (Spearman correlations ranged from 0.45 to 0.99). In particular, NO_2 and O_3 were positively correlated, which might be caused by high air pollutants levels, especially NO_x and volatile organic compounds (Shi et al., 2015; Zong et al., 2017), at the study site.

3.2. Associations between air pollutants and lipid levels

The associations of air pollutants with blood lipid levels are summarized in Tables 3 and S3. For all participants, higher concentrations of PM_1 and $PM_{2.5}$ consistently showed significant associations with higher levels of TC, TG, and LDL-C, as well as with lower levels of HDL-C. However, associations of PM_{10} with blood lipids were less consistent, and $PM_{2.5–10}$ was associated only with TG levels (Table S3). Higher NO_2 levels were significantly associated with higher levels of TC and TG and with lower levels of HDL-C. SO_2 was positively associated with TG, but not with the remaining lipid markers. Higher O_3 concentrations were significantly associated with higher levels of TG and HDL-C, but with lower levels of TC and LDL-C. The results remained materially unchanged in sensitivity analyses where 263 individuals taking lipid lowering drugs (Table S4) or 2222 individuals with CVD or diabetes mellitus (Table S5) were excluded, where multi-annual average concentrations of air pollutants were used (Table S6), and where the models were additionally adjusted for short-term air pollutant levels (Table S7). The only exception in the latter case was the statistical insignificance of the association between O_3 and HDL-C (Table S7).

We detected statistically significant interactions between air pollutant concentrations and sex on blood lipids; however, the pattern of effects was mixed in stratified analyses (Fig. 1; Table S8). For example, while associations of all six air pollutants with HDL-C were stronger for men, in the case of TG they were stronger for women. In addition, the positive associations of LDL-C with PM_1 and $PM_{2.5}$ were stronger in women than in men, and were stronger yet negative for PM_{10}, SO_2, NO_2 and O_3. In stratified analysis by age, the associations between air pollutants and lipid levels were similarly complex, although most interaction terms were not statistically significant (Table S8). In another stratified analysis, BMI significantly modified the associations of PM_1 and $PM_{2.5}$ with HDL-C and LDL-C, with stronger associations among overweight/obese participants (Table S8).

3.3. Associations between air pollutants and dyslipidemias

For all participants, we detected statistically significant associations between: (1) higher PM_1, and $PM_{2.5}$ concentrations with higher odds for hypercholesterolemia, hypoalphalipoproteinemia, and hyperbetalipoproteinemia; (2) higher PM_{10}, SO_2, and O_3 concentrations with higher odds for hypertriglyceridemia; and (3) higher NO_2 concentrations with higher odds for hypercholesterolemia (Table 4). In stratified analyses by sex and age, we detected statistically significant interactions of air pollutant concentrations with sex and age for several dyslipidemia associations, but the pattern was mixed (Table S9). In stratified analyses by BMI, associations of air pollutants with dyslipidemias (particularly for hypoalphalipoproteinemia) were consistently greater in participants who were overweight or obese (Table S9).

4. Discussion

4.1. Key findings

To our knowledge, this is the largest population-based epidemiological study to date, to explore associations between ambient air pollution and blood lipids in a developing country. We detected many statistically significant associations between exposure to long-term ambient air pollutants (particularly PM_1 and $PM_{2.5}$) and blood lipid levels and the prevalence of dyslipidemias. Most of the associations suggested deleterious effects on blood lipid levels (i.e., associated with higher levels of TC, TG, and LDL-C, and lower HDL-C levels), though beneficial associations were detected for O_3. However, all observed associations suggested deleterious effects of air pollutants on dyslipidemias; no beneficial significant association was observed for O_3 with dyslipidemias. Stratified analyses showed that associations between air pollutants and lipids were generally stronger among overweight and obese participants; sex and age also modified associations, but the pattern of effects was complicated.

4.2. Comparison with other studies and interpretations

Several previous studies investigated associations between air pollution exposure and blood lipid levels or dyslipidemias, but the findings have been inconsistent (Bell et al., 2017; Bind et al., 2016; Cai et al., 2017; Chuang et al., 2011; Jiang et al., 2016; Poursafa et al., 2014; Shanley et al., 2016; Sørensen et al., 2015; Wallwork et al., 2017; Yeatts et al., 2007; Yitshak Sade et al., 2016). Consistent with our current findings, a cross-sectional study from the USA revealed that an 11.1 μg/m^3 increase in PM_{10} was associated with 2.42% higher TG levels (Shanley et al., 2016). Another cross-sectional study, from Denmark, reported positive association for $PM_{2.5}$ exposure with TC levels. Similarly, a retrospective cohort study of Israeli adults reported a statistically significant association between higher $PM_{2.5}$ concentrations and lower HDL-C levels (Yitshak Sade et al., 2016). Chuang et al. (2011) found that PM_{10} and NO_2 were significantly associated with higher TC levels in Taiwan, but there were no associations with TG or HDL-C levels. In addition, a panel study among American adults showed no significant association between $PM_{2.5}$ exposure and TC levels (Yeatts et al., 2007). The specific reasons for the inconsistent results across studies of ambient air pollution exposure and blood lipid levels are not clear. They may be related to the differences in population characteristics (e.g., age, genetic background, lifestyles, and health status) and/or local or regional differences in the physical and chemical properties of the air pollutants (e.g., concentrations, chemical constituents, and sources).

Table 3
Associations between per 10-μg/m^3 increment in air pollutants and blood lipid levels (n = 15,477).

Pollutant	% changes (95% confidence interval)[a]			
	TC	TG	HDL-C	LDL-C
PM_1	1.6 (1.1, 2.0)[b]	2.9 (−3.3, 9.3)	−1.4 (−1.8, −0.9)[b]	3.2 (2.6, 3.9)[b]
$PM_{2.5}$	1.1 (0.8, 1.4)[b]	1.1 (0.4, 1.8)[b]	−1.1 (−1.4, −0.8)[b]	2.9 (2.4, 3.5)[b]
PM_{10}	−0.2 (−0.5, 0.1)	4.7 (3.6, 5.9)[b]	−0.2 (−0.7, 0.2)	−0.9 (−1.3, −0.4)[b]
SO_2	−0.2 (−0.7, 0.1)	5.1 (3.9, 6.3)[b]	−0.1 (−0.6, 0.4)	−0.1 (−0.7, 0.5)
NO_2	0.7 (0.0, 1.4)[b]	6.0 (3.5, 8.6)[b]	−1.6 (−2.3, −1.0)[b]	−0.1 (−1.2, 1.1)
O_3	−1.2 (−1.6, −0.8)[b]	5.6 (4.5, 6.7)[b]	0.6 (0.2, 1.0)[b]	−2.7 (−3.2, −2.2)[b]

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NO_2, nitrogen dioxide; O_3, ozone; PM_1, particle with aerodynamic diameter ≤1.0 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤2.5 μm; PM_{10}, particle with aerodynamic diameter ≤10 μm; SO_2, sulfur dioxide; TC, total cholesterol; TG, triglycerides.

[a] Adjusted for age, sex, body mass index, education, family income, smoking, alcohol drinking, exercise, diet, sugary drink intake, family history of dyslipidemia, temperature, humidity, wind speed, season, gross domestic product, population density, residuals from regression model of highly correlated pollutants, and study district (or community).

[b] Statistically significant association (p < .05).

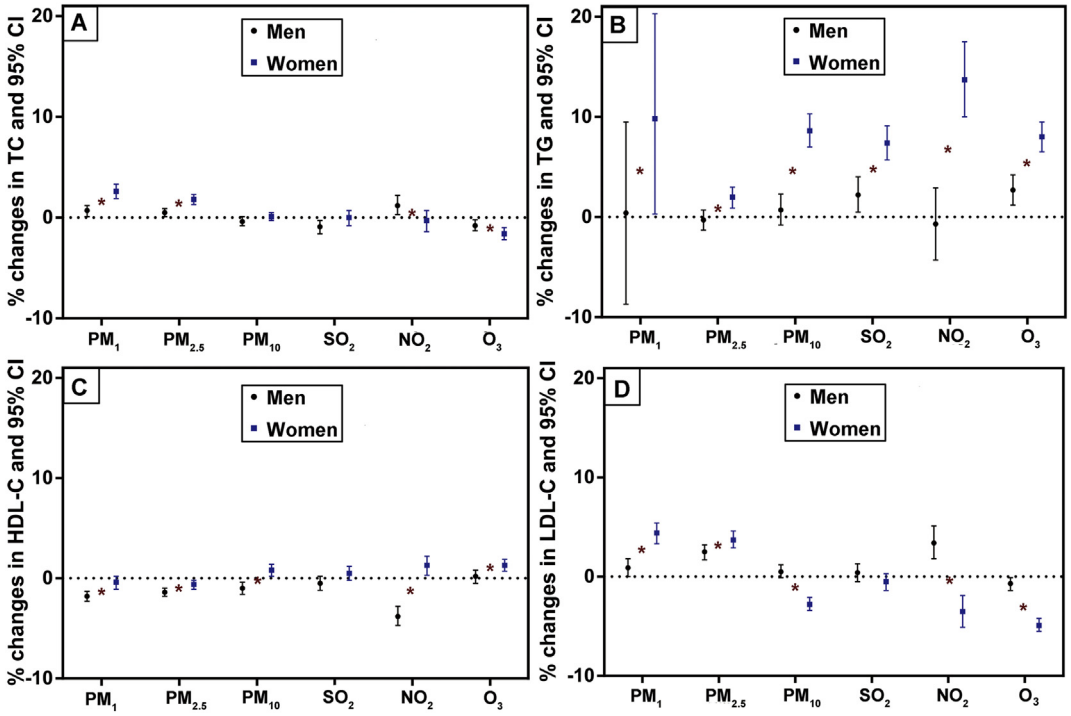

Fig. 1. Associations between air pollutants and blood lipid levels (A: total cholesterol, TC; B: triglycerides, TG; C: high-density lipoprotein cholesterol, HDL-C; D: low-density

The biological mechanisms underlying links between air pollutants and lipid metabolism are not fully understood. However, several possible biological pathways have been proposed. One hypothesis is that inhaled air pollution elicits systemic inflammation and oxidative stress (Lodovici and Bigagli, 2011; Shanley et al., 2016; Thompson et al., 2010), which can induce adverse lipid metabolism and lipid oxidation (Chen et al., 2013). Air pollutants could also cause aberrant DNA methylation by decreasing activity of DNA methyltransferases. Several studies have linked air pollution exposure to abnormalities in global DNA methylation as well as to methylation at specific genes related to lipid metabolism (Chen et al., 2016; Bind et al., 2014). The associations between air pollutant concentrations, PM in particular, and blood lipid levels in our current study are consistent with these hypothesized biological mechanisms.

In stratified analyses, we found stronger associations between air pollutants and blood lipids among overweight and obese participants, which are partially consistent with Sørensen et al. (2015). Existing evidence shows that both air pollution exposure and overweight/obesity are associated with higher systemic inflammation (Bastard et al., 2006; Rajagopalan and Brook, 2012). Overweight and obese participants might therefore be more vulnerable to adverse health effects from air pollution, which act in part through an inflammation pathway. We also found that sex and age modified the effects of air pollution on lipid levels and dyslipidemias, but the pattern was mixed. To the best of our knowledge, only two prior studies (Shanley et al., 2016; Sørensen et al., 2015) investigated sex- and age- specific associations between air pollutants and blood lipids. In line with our linear regression findings, Shanley et al. (2016) reported that age did not significantly modify the associations of PM_{10} with TC and TG. However, they also observed a stronger association between PM_{10} and TC among women, whereas for PM_{10} and TG a stronger association was observed among men, which contradicts our results. In another study, Sørensen et al. (2015) observed that both age and sex did not modify the associations of NO_2 and $PM_{2.5}$ with TC. Collectively, there is limited and inconsistent epidemiological evidence to characterize the role of age and sex in modifying air pollution-lipid associations at present, and so

Table 4
Associations between per 10-μg/m^3 increment in air pollutants and dyslipidemias (n = 15,477).

Pollutant	Odds ratio (95% confidence interval)[a]			
	Hypercholesterolemia	Hypertriglyceridemia	Hypoalphalipoproteinemia	Hyperbetalipoproteinemia
PM_1	1.26 (1.02, 1.57)[b]	1.03 (0.91, 1.17)	1.27 (1.06, 1.52)[b]	1.29 (1.02, 1.64)[b]
$PM_{2.5}$	1.18 (1.01, 1.37)[b]	1.07 (0.95, 1.19)	1.15 (1.02, 1.30)[b]	1.28 (1.05, 1.57)[b]
PM_{10}	1.05 (0.92, 1.22)	1.14 (1.01, 1.29)[b]	1.08 (0.88, 1.32)	1.06 (0.89, 1.27)
SO_2	1.11 (0.79, 1.55)	1.16 (1.00, 1.39)[b]	1.01 (0.79, 1.29)	0.98 (0.77, 1.25)
NO_2	1.23 (1.02, 1.48)[b]	1.21 (0.76, 1.90)	1.27 (0.68, 2.38)	1.25 (0.74, 2.11)
O_3	0.95 (0.77, 1.19)	1.17 (1.01, 1.36)[b]	0.97 (0.78, 1.20)	0.98 (0.84, 1.15)

Abbreviations: NO_2, nitrogen dioxide; O_3, ozone; PM_1, particle with aerodynamic diameter ≤1.0 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤2.5 μm; PM_{10}, particle with aerodynamic diameter ≤10 μm; SO_2, sulfur dioxide.

[a] Adjusted for age, sex, body mass index, education, family income, smoking, alcohol drinking, exercise, diet, sugary drink intake, family history of dyslipidemia, temperature, humidity, wind speed, season, gross domestic product, population density, residuals from regression model of highly correlated pollutants, and study district (or community).

[b] Statistically significant association ($p < .05$).

further investigation is merited.

4.3. Implications for policy makers

Dyslipidemias are well-documented risk factors for CVD (Zhang et al., 2003). Randomized trials have shown that lipid-lowering treatment could significantly decrease the risk of CVD (Fulcher et al., 2015). For example, the Asia Pacific Cohort Studies Collaboration reported 35% and 25% increased risks for coronary death and incident stroke in Asians, respectively, per 1-mmol/L higher serum TC (Zhang et al., 2003). Yet, a meta-analysis of 22 trials found that a 1-mmol/L LDL-C reduction could decrease major CVD events by 21% (Fulcher et al., 2015). In the current study, we found that a 10-μg/m^3 increase in air pollutants was associated with an approximately 1–2% increase in blood lipids levels. Although the observed difference was relatively small and thus of uncertain clinical impact, our findings have certain public health implications for helping policy makers to develop intervention policies, given the high levels of air pollution (Guan et al., 2016) and high prevalence of CVD in China (Peters et al., 2017).

4.4. Strengths and limitations

This study has several strengths. First, our analysis was based on a large sample of northeastern Chinese with a high response rate, using standardized protocols and instruments, which ensured sufficient statistical power to detect modest effects, and generalizability of our results. Second, unlike most previous studies, which focused on specific populations, our present study provides valuable evidence regarding a general population in a developing nation. Third, in addition to measuring exposure to the traditional ambient 'criteria' air pollutants (i.e., $PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3), we, for the first time, report effects for PM_1 on blood lipids. In addition, all air pollutants levels are high in our study settings, thus our results can provide a valuable reference for other developing countries, such as India. Finally, a combination of objectively measured lipid levels coupled to a rich set of covariate data allowed for a comprehensive data analysis, including adjustment for BMI, physical activity, diet, and meteorological variables to minimize the impact of confounding.

Despite the novel nature of our results, several limitations should also be acknowledged. First, the cross-sectional study design precluded assessment of temporality, and we are thus unable to infer a causal association between air pollution exposure and blood lipid levels. Second, exposure levels were assigned using data from the nearest air monitor or community rather than using personal air pollution exposure data, which means that only 33 (for PM_1 and $PM_{2.5}$) and 11 (for PM_{10}, NO_2, SO_2, and O_3) unique air pollution values were available for the 15,477 participants. The values may have misclassified some participants, by randomly underestimating exposure in some and overestimating exposure in others. Nevertheless, such exposure misclassification is likely to bias the results towards null (Hutcheon et al., 2010). This indicates that if we had individual-level data on air pollution levels, our estimated effects of air pollution on blood lipids would have been stronger than the current estimates. Furthermore, our exposure assessment did not capture specific emissions known to adversely affect health, such as traffic-related sources, that are likely to show large variation across both space and time. Third, participants' baseline characteristics differed significantly among the study districts and communities (Yang et al., 2017). Although we collected rich covariate data to adjust for confounding, it is possible that the observed significant associations were biased by unmeasured confounding factors that differed across the study districts or communities, including healthcare access, available green-space, noise, and household environments. Unfortunately, these data were not collected by the 33CCHS. In addition, conditions such as acute infection and inflammation, hyperthyroidism, and nephrotic syndrome, may affect lipid status (Nigam, 2011). These data were also not available in our current study, which may have compromised our estimates. Fourth, 62.3% of the 33CCHS participants with blood specimens were included in the current analysis, and so a selection bias was not impossible. However, the distribution of baseline characteristics was similar between participants with and without a blood specimen, and so any effect is likely to be modest. Fifth, we used a questionnaire to collect self-reported information on demographic and lifestyle characteristics; thus, recall bias and misclassification is possible. Finally, correlations between air pollutants were generally moderate or high, which limited our ability to assess the health effects of multiple pollutants simultaneously. However, we performed regression analyses on air pollutants that highly correlated with each other, and then adjusted the individual residuals in order to accommodate the co-exposures.

5. Conclusions

Our findings suggest that long-term exposure to ambient air pollution is associated with altered lipid levels and the prevalence of dyslipidemias, especially among overweight and obese people. However, considering the limitations of our study, future well-designed longitudinal studies are warranted to more definitively evaluate the effects of ambient air pollution on lipid metabolism.

Declaration of interests

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.07.016.

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