Long-term air pollution exposure and serum lipids and blood sugar: A longitudinal cohort study from the electricity generating authority of Thailand study

Kanawat Paoin[1], Kayo Ueda[1,2,] *, Prin Vathesatogkit[3], Thammasin Ingviya[4], Suhaimee Buya[5], Arthit Phosri[6], Xerxes Tesoro Seposo[7], Nisakron Thongmung[8], Teerapat Yingchoncharoen[3], Akiko Honda[1,2], Hirohisa Takano[1,2], Piyamitr Sritara[3]

[1] Department of Environmental Engineering, Graduate School of Engineering, Kyoto University, Kyoto, Japan

[2] Graduate School of Global Environmental Sciences, Kyoto University, Kyoto, Japan

[3] Department of Internal Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[4] Department of Family and Preventive Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

[5] Medical Data Center for Research and Innovation, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

[6] Department of Environmental Health Sciences, Faculty of Public Health, Mahidol University, Bangkok, Thailand

[7] School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan

[8] Research Center, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

*Corresponding author; C1-3-366, Kyoto Daigaku-Katsura, Nishikyo-ku, Kyoto 615-8540, Japan. Tel.: +81 7 5383 3341; Fax: +81 7 5383 3344; E-mail: uedak@health.env.kyoto-u.ac.jp

Abstract

Only a few studies have investigated the association between long-term exposure to air pollution and alterations of serum lipids and blood sugar level in developing countries. The present longitudinal study examined associations between long-term air pollution exposure and serum lipids [total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)] and fasting glucose (FG) in workers of the Electricity Generating

Authority of Thailand (EGAT) in the Bangkok metropolitan region (BMR) of Thailand. We performed secondary analyses using the data obtained from 1,839 participants (mean age, 58.3 years as of 2002) of the EGAT1 cohort study (2002-2012). The average concentration of each air pollutants (PM_{10}, O_3, NO_2, SO_2, and CO) at the district level in BMR from 2002 to 2012 were estimated using the ordinary kriging method. Exposure periods were averaged to 3 months prior to laboratory testing. Linear mixed effects models were used to estimate associations between air pollution and serum lipids and blood sugar. After controlling for potential confounders, an interquartile range increment of PM_{10}, SO_2, and CO was associated with elevated LDL-C [6.6% (95%CI: 4.3, 9.0), 11.1% (7.2, 15.2), and 1.9% (1.1, 2.7), respectively] and FG [2.8% (1.5, 4.2), 6.8% (4.5, 9.1), and 1.1% (0.6, 1.5), respectively]. In addition, PM_{10}, SO_2, and CO were inversely associated with HDL-C [-1.8% (-3.7, 0.1), -3.3% (-6.2, -0.3), and -1.1 (-1.7, -0.5), respectively]. O_3 was negatively associated with TC, LDL-C, TG, and FG. These findings suggest inhalation of air pollutants may increase the risk of impaired metabolism of glucose and lipids.

Key words: Long-term exposure, air pollution, longitudinal study, serum lipids, blood sugar

1. Introduction

The prevalence of impaired serum lipids and elevated blood glucose, which are the risk factors for cardiovascular disease (CVD), is rapidly increasing worldwide over the past decades (O'Neill & Driscoll, 2015). Previous studies have shown that environmental factors, especially air pollutants, are associated with CVD risk factors (i.e., obesity, diabetes mellitus, hypertension, dyslipidemia) (Brook et al., 2004, 2010; Rajagopalan & Brook, 2012). Inhaled air pollutants can trigger CVD through various mechanisms, including systemic physiological responses such as oxidative stress, inflammation (Brook et al., 2004, 2010; Pope et al., 2004), insulin resistance (Rajagopalan & Brook, 2012), and altered autonomic nervous system activity (Brook et al., 2010; Rajagopalan & Brook, 2012). These

mechanisms are related to CVD risk factors, including atherosclerosis, elevated blood pressure, abnormal serum lipid levels, and high plasma glucose (Brook et al., 2010; Rajagopalan & Brook, 2012; Yang et al., 2018). Exposure to particulate matter (PM) has been linked to impaired metabolism of glucose and lipids and mediated by insulin resistance, which can lead to the development of CVD (Brook et al., 2010; Chen et al., 2013; Rajagopalan and Brook, 2012; Sade et al., 2016).

Long-term exposure to PM less than 2.5 μm in diameter ($PM_{2.5}$) and PM less than 10 μm in diameter (PM_{10}) is reportedly associated with elevated serum lipids (Chuang et al., 2011; Gaio et al., 2019; Mao et al., 2020; Poursafa et al., 2017; Shanley et al., 2016; Yang et al., 2018; Zhang et al., 2021) and blood sugar (Cai et al., 2019; Chuang et al., 2011; Yu et al., 2019). Changes in serum lipids and fasting glucose (FG) are also related to average air concentrations of nitrogen dioxide (NO_2) and ozone (O_3) (Chuang et al., 2011; Gaio et al., 2019; Kim et al., 2019; Zhang et al., 2021). However, longitudinal studies on associations between air pollutants and serum lipids and blood sugar (A. Li et al., 2019; Sade et al., 2016; Zhang et al., 2021) are still somewhat limited, especially in Southeast Asian countries, with most such studies being cross-sectional in design (Cai et al., 2019; Chuang et al., 2011; Mao et al., 2020; Poursafa et al., 2017; Shanley et al., 2016; Yang et al., 2018; Yu et al., 2019). Therefore, the present study longitudinally examined associations between long-term exposure to air pollutants and serum lipids and blood sugar using data from an ongoing cohort study targeting workers of the Electricity Generating Authority of Thailand (EGAT) in the Bangkok metropolitan region (BMR) of Thailand.

2. Methods

2.1 Study design and participants

The population of the EGAT cohort study has been described previously (Vathesatogkit et al., 2012a). The present longitudinal study analyzed data obtained from workers of the EGAT in BMR from 2002

to 2012. Health data were obtained from the EGAT1 study, which began recruiting participants in 1985. The initial survey of the EGAT1 study mainly covered the details of established CVD risk factors, including factors related to nutrition and toxicological mechanisms (Vathesatogkit et al., 2012a). The EGAT1 cohort was surveyed with follow-up questionnaires in 1997, 2002, 2007, and 2012. The protocol of the EGAT cohort study was approved by the Ethics Committee of Ramathibodi Hospital.

We extracted data for 2,129 participants (age 52-71 years as of 2002) who lived in BMR in 2002 and met the following criteria: (1) participated in follow-up surveys at least twice (2002 and 2007) or three times (2002, 2007, and 2012) (Adar et al., 2013; Duan et al., 2019; Kaufman et al., 2016; A. Li et al., 2019; Wang et al., 2019; Wilker et al., 2013; Zhang et al., 2021), and (2) lived in Bangkok, Nonthaburi, Samut Prakan, or Pathum Thani during the study period. We excluded 290 participants who died or were lost to follow-up before 2007, or who moved from the study area in 2007.

2.2 Data collection and physical examination

Physical examinations were performed by clinicians at the time of each survey. Data on physical examinations and sociodemographic characteristics such as sex, age, blood pressure, heart rate, weight, height, waist and hip circumferences, body mass index (BMI), waist/hip ratio, smoking status, alcohol drinking, exercise habits, education level, income, prevalence of disease (e.g., hypertension, diabetes, and hypercholesterolemia), treatment status, and medication use were collected (Vathesatogkit et al., 2012a).

2.3 General chemistry

All blood samples were collected in a fasting state during the surveys. Laboratory tests were subsequently carried out and included the following: total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and FG (Vathesatogkit et al., 2012a).

2.4 Exposure assessment

Hourly PM_{10} and other gaseous pollutant concentrations, including sulfur dioxide (SO_2), NO_2, O_3, and carbon monoxide (CO), were obtained from the Pollution Control Department, a governmental agency responsible for air quality in Thailand. Meteorological data including daily average temperature (ºC) and relative humidity (%) were obtained from the Thai Meteorological Department throughout the study period. We used meteorological data from only one meteorological station located in Bangkok, where complete data on temperature and relative humidity from 2002 through 2012 were available. In addition, almost all study participants lived in Bangkok and Nonthaburi, with the latter having no meteorological station. Hence, we applied meteorological data from the methodological station in Bangkok to represent environmental conditions for all participants.

Exposure to daily average PM_{10}, SO_2, NO_2, and CO and daily maximum 8-hr average O_3 were estimated using the ordinary kriging method (Geniaux et al., 2017; Leem et al. 2006; Liu et al. 1996). Air pollutant concentrations were measured at 22 background and 7 traffic monitoring sites in BMR from 2002 to 2012, and daily average values of all discontinuous site-specific measurements were calculated. For prediction, grids of 100x100 meters were generated, and the average concentration of each air pollutant at the sub-district level was estimated based on concentrations from the grids closest to the centroid of each sub-district (Paoin et al., 2021). For each air pollutant, a separate model was developed and validated to estimate grid-specific air pollutant concentrations.

Good model performance from 2002 to 2012 was achieved, with a leave-one-out cross validation R^2 value of 0.99 for PM_{10}, O_3, NO_2, and SO_2, and 0.98 for CO (Paoin et al., 2021). Model predictions had little bias, with cross-validated slopes (predicted vs. observed) of 0.99 for PM_{10}, O_3, NO_2, and SO_2, and 0.98 for CO (Paoin et al., 2021). Long-term exposure to air pollution was determined as a 3-month average concentration preceding laboratory testing according to previous studies (Bell et al., 2017; Sade et al., 2016; Zhang et al., 2021).

2.5 Covariates

All potential covariates were selected a priori, including age (years), sex (male/female), BMI (kg/m^2), smoking status (never smokers/former smokers/current smokers), alcohol drinking (non-users/former users/occasional users/current users), exercise habits (<3 times per week/≥3 times per week), education level (0^{th}-8^{th}, 9^{th}-12^{th}, >12^{th} Grade), income (<10,000 Thai baht/10,000-20,000 Thai baht/20,000-50,000 Thai baht/>50,000 Thai baht), hypertension (yes/no), diabetes (yes/no), hypercholesterolemia (yes/no), hypertensive medication use (yes/no), and antidiabetic medication use (yes/no).

2.6 Statistical Analysis

We analyzed associations between long-term air pollution exposure (PM_{10}, O_3, NO_2, SO_2, and CO) and outcome variables, i.e., serum lipids (TC, TG, LDL-C, and HDL-C) and plasma FG, using linear mixed effects models. Variability over time within each participant was defined as a random effect. Values of outcome variables were log-transformed to stabilize the variances.

A wide range of covariates were selected according to previous reports (Cai et al., 2019; Chuang et al., 2011; Curto et al., 2019; Mao et al., 2020; McGuinn et al., 2019; Yang et al., 2018; Zhang et al., 2021). The missing data of all covariates was less than 10%. The following five models were generated by gradually including these covariates: a crude model (Model I); Model II, adjusted for age and sex only; Model III, adjusted for age, sex, BMI, hypertension, diabetes, hypercholesterolemia, hypertensive medication use, antidiabetic medication use, exercise habits, smoking status, and alcohol drinking; a main model (Model IV), adjusted for all covariates in Model III, education level, and income. We assumed that participants with treatment status may have more severity of diseases than participants without treatment status (Joseph & Schuna 1990). Owing to these reasons, we controlled the treatment status in the main model.

As a sensitivity analysis, the main models were tested by different exposure window using 1-month average of air pollution concentrations. We also adjusted for 3-month average temperature, relative humidity and short-term exposure to each air pollutant (averaged from the current day to 1 day before) (Model V) since some previous studies observed the associations between short-term exposure

to air pollution and serum lipids and blood sugar (Kim et al., 2019; A. Li et al., 2019; Wu et al., 2020). If more than one pollutant had a significant effect on an outcome, two pollutant models were applied for each pollutant to evaluate the robustness of the single pollutant model. We also added natural cubic spline with 3 degrees of freedom to each pollutant in our main model, and then plotted the residuals of fitted values against observed values of all pollutants and all serum lipids and blood sugar to check non-linear associations.

The main models (Model IV) were also stratified by income group, including high income (> 50,000 Thai baht per month, n = 876) and low to middle income (=< 50,000 Thai baht per month, n = 815) at the baseline in 2002 to check whether the associations remain or not. Values of outcome variables are presented as percentage change per interquartile range (IQR) increment for PM_{10}, O_3, NO_2, SO_2, and CO, with 95% confidence intervals (CIs). All statistical analyses were performed using the R Program (version 3.6.1). A P-value less than 0.05 was considered statistically significant.

3. Results

Basic characteristics of study participants at baseline are shown in Table 1. Among 1839 participants analyzed, more than 70% of EGAT1 participants were male (age range, 52 - 71 years as of 2002), roughly 95% lived in Bangkok and Nonthaburi, and more than 45% were high-income earners (>50,000 baht/month) with high education levels (>12th Grade). All participants had been retired since 2007 (age >55 years). As of 2002, more than 45% of participants had hypertension and hypercholesterolemia, and roughly 20% had diabetes. The missing data of each variable was less than 1%, except income (8%). The excluded participants (N = 290), who died or were lost to follow-up before 2007, or who moved from the study area in 2007, had higher mean age and prevalence of hypertension and diabetes than study participants (Table S1).

The median follow-up period was 5 years. 1839 participants with 4415 TC, HDL, TG, FG recorded, and 4388 LDL recorded were included.

< INSERT TABLE 1 >

Daily concentrations of environmental variables are presented as mean with standard deviation (SD), range, and IQR in Table 2. The average concentration of PM_{10} during the study period nearly exceeded the annual PM_{10} standard limit in Thailand (PM_{10} <50 μg/m^3), while those of NO_2 and SO_2 were lower than the respective annual standard limits. No annual standard limits have been set for O_3 and CO in Thailand. The temperature range was 18.9ºC to 33.7ºC, and the range of relative humidity was 45.0% to 97.0% (Table 2). Air pollutants were positively correlated with one another ($P<0.05$) and negatively correlated with temperature and relative humidity ($P<0.05$) (Table 3).

< INSERT TABLE 2 >

< INSERT TABLE 3 >

Table 4 presents estimated percent changes in outcome variables for an increment of IQR increase in 3-month average PM_{10}, O_3, NO_2, SO_2, and CO in the main model (Models IV). PM_{10} was associated with higher levels of TC, LDL-C, TG, and FG (5.6% (95%CI: 4.0, 7.2), 6.6% (95%CI: 4.3, 9.0), 2.9% (95%CI: -0.9, 6.8) and 2.8% (95%CI: 1.5, 4.2), per 16.3 μg/m^3, respectively), but lower HDL-C levels (-1.8% (95%CI: -3.7, 0.10)). SO_2 was related to increase in TC, LDL-C, TG, and FG

198 (10.2% (95%CI: 7.5, 13.0), 11.1% (95%CI: 7.2, 15.2), 4.3% (95%CI: -1.8, 10.7), 6.8% (95%CI: 4.5,
199 9.1), per 5.3 ppb, respectively), and decrease in HDL-C (3.3% (95%CI: 0.3, 6.2)). CO was also
200 associated with TC, LDL-C, TG, and FG (1.8% (95%CI: 1.3, 2.3), 1.9% (95%CI: 1.1, 2.7), 1.1%
201 (95%CI: -0.2, 2.3) and 1.1% (95%CI: 0.6, 1.5) per 0.2 ppm, respectively), and a decrease in HDL-C
202 (1.1% (95%CI: 0.5, 1.7)). In contrast, TC, LDL-C, TG, and FG, but not HDL-C, were inversely
203 associated with O_3.

204

205 < INSERT TABLE 4 >

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207 The results of 1-month average air pollution concentrations were not substantially different
208 from our main results (3-month average air pollution concentrations) (Table S2). After adjusting for
209 short-term air pollution exposure and 3-month average temperature and relative humidity in Model V
210 (Table S3), most of the observed associations between serum lipids/blood sugar and 3-month average
211 concentration of each pollutant became weaker. Associations between all air pollutants and outcome
212 variables were essentially unchanged in two-pollutant models (Table S4). We did not observe any
213 departure from the linear assumption, especially for air pollutants and serum lipids (Figure S1 to Figure
214 S5).

215 After stratifying by income groups, the associations remained the same, except for PM_{10} and
216 FG which showed a stronger association in the group of low-middle income (Table 5).

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219

4. Discussion

In this study, we examined associations between long-term exposure to air pollution and serum lipids and blood sugar in EGAT workers in BMR. PM_{10}, SO_2, and CO were associated with increases in TC, LDL-C, TG, and FG, and with a decrease in HDL-C levels. In contrast, O_3 was negatively associated with TC, LDL-C, TG, and FG. We did not observe any association of NO_2 with any of these.

4.1 Comparison with other studies and interpretations

Consistent with our current findings, previous studies have reported that long-term exposure to $PM_{2.5}$ and PM_{10} is associated with altered lipid levels, including elevated TC, LDL-C, TG, and decreased HDL-C levels (Chuang et al., 2011; Shanley et al., 2016, Gaio et al., 2019; Poursafa et al., 2017; Yang et al., 2018; Zhang et al., 2021). One hypothesis is that inhalation of air pollutants, especially for PM may induce systemic inflammatory response and oxidative stress (Brook et al., 2004, 2010; Pope et al., 2004), leading to altered lipid metabolism (Araujo et al., 2008; Chen et al., 2013; Sun et al., 2005; Zhang et al., 2003), lipid oxidation (Brucker et al., 2013; Chen et al., 2013; Soares et al., 2009), and lower HDL-C levels (J. Li et al., 2019). Another plausible mechanism is PM may cause abnormalities of DNA methylation at specific genes which related to lipid metabolism and inflammation pathways (Bind et al., 2014; Chen et al., 2016; H. Li et al., 2018). All of these could contribute to exacerbated atherosclerosis (Shanley et al., 2016).

Only a few studies have reported the associations between long-term exposure to gaseous pollutants (i.e., NO_2, O_3, and SO_2) and serum lipids (Chuang et al., 2011; Kim et al., 2019; Zhang et al., 2021). In the present study, we found that long-term exposure to SO_2 and CO is associated with increased TC, LDL-C, TG, and decreased HDL-C. Wu et al. (2017) observed long-term exposure to SO_2 was also associated with decreases in HDL-C and apolipoprotein A1 although CO was not associated with lipid markers. Long-term exposure to gaseous pollutants (i.e., CO and SO_2) has the

243 potential to disrupt cholesterol balance and increase the risk of inflammation and thrombosis,
244 contributing to decrease the HDL-C levels and increase the LDL-C and TG levels (Wu et al., 2017).

245 FG is primarily used to assess plasma glucose levels after overnight fasting. Chuang et al.
246 (2011) suggested that the close relationship between high blood sugar and an elevated atherosclerotic
247 risk may be associted with exposures to PM. Most of previous studies have consistently found similar
248 results that long-term exposure to $PM_{2.5}$ and PM_{10} is associated with elevated FG (Cai et al., 2019;
249 Chuang et al., 2011; Yu et al., 2019). Particulate air pollution may cause an imbalance in the
250 autonomic nervous system, which directly affects insulin resistance (Andersen et al., 2012; Liu et al.,
251 2016; Rajagopalan & Brook, 2012). Systemic inflammatory response is another potential mechanism
252 underlying the association between long-term $PM_{2.5}$ exposure and FG (Yu et al., 2019).

253 Chuang et al. 2011 reported that long-term exposure to NO_2 and O_3 were positively associted
254 with FG, but not for SO_2 and CO. On the other hand, our results showed the positive associations
255 between long-term exposure to SO_2 and CO with FG. Previous animal study observed that SO_2 induced
256 alterations in glycogen metabolism of rats in liver resulting in the increase of glucose-6-phosphatase
257 (Fatma et al., 2015), which lead to higher concentration of blood glucose level (Argaud et al., 1997).
258 Additionally, elevated blood glucose was also observed in the CO-poisoned rat (Penney et al., 1990).
259 Two hours after CO exposure (post-CO-exposure) induced hyperglycemia even in the presence of
260 elevated plasma insulin activity, suggests the lack of the insulin control of blood glucose in rats
261 (Penney et al., 1990). Nevertheless, the evidence of long-term CO exposure and blood glucose is still
262 limited in both epidemiological and toxicological studies.

263 In our study, O_3 was negatively associated with TC, LDL-C, TG, and FG. There are
264 inconsistent results of the associations between O_3 with serum lipids and blood sugar (Chuang et al.,
265 2011; Kim et al., 2019; A. Li et al., 2019; Yang et al., 2018; Zhang et al., 2021). Some studies
266 observed the adverse effects of O_3 on serum lipids (A. Li et al., 2019; Zhang et al., 2021) and FG

(Chuang et al., 2011). Other studies observed beneficial (Yang et al., 2018) and no associations (Kim et al., 2019) between long-term O_3 exposure and serum lipids and FG. Furthermore, our results of NO_2 are also inconsistent with some previous studies (Chuang et al., 2011; Kim et al., 2019; Zhang et al., 2021). The possible reasons of inconsistent results may be due to the difference in study designs (cross-sectional and longitudinal studies), groups of the population, and a lack of adjustment for potential confounders such as education level, income, disease prevalence, medication use, and exercise habit in previous studies (Chuang et al., 2011; Zhang et al., 2021). Further epidemiological studies are needed to examine the association between gaseous pollutants (i.e., O_3, NO_2, SO_2, and CO) with serum lipids and blood sugar in different locations and characteristics of population.

4.2 Exposure window

Results of previous studies have been inconsistent as to why long-term exposure to air pollutants is associated with serum lipids and blood sugar. Bell et al. (2017) found no association between 1-year average $PM_{2.5}$ and HDL-C, although 3-month average $PM_{2.5}$ was associated with HDL-C. Sade et al. (2016) also reported a strong association between 3-month average $PM_{2.5}$ exposure and decreased HDL-C. Hemoglobin A1c (HbA1c) reflects variations in plasma glucose levels over roughly 3 months; short-term air pollution exposure was not associated with HbA1c (Sade et al., 2016). As for serum lipids and blood sugar, no or weak associations with short-term exposure to air pollution have been reported (Kim et al., 2019; A. Li et al., 2019; Wu et al., 2020). In the present longitudinal study, we focused on long-term exposure (i.e., 3 months) to assess whether exposure to air pollutants over a longer period of time might play a more prominent role in altering serum lipids and blood sugar.

4.3 Model adjustment

Vathesatogkit et al. (2012b) revealed long-term effects of income and education level on cardiovascular risk factors. Therefore, we adjusted for them in our main model (Model IV). We further adjust for short-term exposure to each air pollutant and 3-month average temperature and relative

humidity (Model V) because some previous studies reported the short-term associations between air pollution exposure and serum lipids and blood sugar (Kim et al., 2019; A. Li et al., 2019; Wu et al., 2020). Short-term air pollution exposure may trigger the daily variation while long-term exposure contributes to the chronic change in the variables examined. Hence, we controlled the short-term associations to focus only long-term associations in this study. While the values of serum lipids and blood sugar decreased after these adjustments, associations between air pollutants and serum lipids/blood sugar essentially remained the same. Hence, the alterations in serum lipids and blood sugar were not affected by long-term air pollution exposure alone, but also affected by other factors that we controlled in the models.

4.4 Strengths and limitations

In the present study, we collected a large amount of data including BMI, education level, income, exercise habits, alcohol consumption, and smoking status, and controlled for these variables in our models. Furthermore, we used the ordinary kriging method, which allowed us to evaluate the spatial representativeness of monitoring stations and improve the accuracy of air pollution exposure estimates.

Our study has several limitations. First, due to data restrictions in Thailand, we could not include traffic variables or land use data in ordinary kriging. However, data from traffic monitoring stations were used to assess exposures to traffic-related air pollutants such as NO_2 and CO. In addition, the average air pollution concentrations longer than 6-month preceding laboratory testing in 2002 would be difficult to generate according to a very few numbers of monitoring stations in Thailand before 2002. Second, participants of this study were EGAT workers aged 50 years and older (as of 2002), whose lifestyles may have differed from the general Thai population given their higher income and education levels. Therefore, our study population does not represent the general population. Moreover, the results of the present study may underestimate the effects of air pollutants on serum

lipids and blood sugar, as people with low SES are more likely to suffer greater health effects from air pollutants due to higher exposure to air pollution and compromised health status due to material deprivation and environmental equity. Third, we included only participants who had been followed-up at least 2 times during study period. The study participants might be healthier than the participants who had been excluded because they were lost followed-up or dead. Therefore, the results of this study might be underestimated. Finally, data on food consumption, a potential confounder, were not available. However, we adjusted for other covariates related to SES, lifestyle, and eating habits, such as income, education level, BMI, hypertension, diabetes, and hypercholesterolemia using linear mixed models.

5. Conclusions

Long-term exposure to air pollutants, especially for PM_{10}, SO_2, and CO was associated with impaired serum lipids and elevated blood sugar in participants of the EGAT cohort study. A further study will be necessary to elucidate mechanisms underlying these associations.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

This study was supported by the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok; the National Research Council; the Thailand Research Fund; the Thai Heart Association; the Thai Health Foundation; the Electricity Generating Authority of Thailand and the Praman Chansue

Foundation; the Environment Research and Technology Development Fund (S12); and Kyoto University Internal Grant ISIZUE.

Acknowledgements

The authors would like to express their sincere gratitude to the EGAT and Ramathibodi Hospital and their staff, the Pollution Control Department of the Ministry of Natural Resources and Environment, and Thai Meteorological Department for providing useful data for analyses in this study, with special thanks to Ms. Krittika Saranburut and Mr. Puchong Inchai for guiding us through the complex data processing. The authors would also like to thank Dr. Suphanat Wongsanuphat, Mr. Thatkiat Meema, Dr. Vera Ling Hui Phung, and Dr. Kraiwuth Kallawicha for their guidance and encouragement.

Ethics and Consent

Approval for the study was obtained from the ethics committee of Ramathibodi Hospital and the Graduate School of Engineering, Kyoto University.

Reference

Adar, S. D., Sheppard, L., Vedal, S., Polak, J. F., Sampson, P. D., Diez Roux, A. V., Kaufman, J. D., et al., 2013. Fine Particulate Air Pollution and the Progression of Carotid Intima-Medial Thickness: A Prospective Cohort Study from the Multi-Ethnic Study of Atherosclerosis and Air Pollution. *PLoS Medicine*, *10*(4). https://doi.org/10.1371/journal.pmed.1001430

Andersen, Z. J., Raaschou-Nielsen, O., Ketzel, M., Jensen, S. S., Hvidberg, M., Loft, S., Sørensen, M., et al., 2012. Diabetes Incidence and Long-Term Exposure to Air Pollution. *Diabetes Care*, *35*, 92–98. https://doi.org/10.2337/dc11-1155

Araujo, J. A., Barajas, B., Kleinman, M., Wang, X., Bennett, B. J., Gong, W., Geffen, D., et al., 2008. Ambient Particulate Pollutants in the Ultrafine Range Promote Early Atherosclerosis and

Systemic Oxidative Stress. *Circ Res.*, *102*(5), 589–596. https://doi.org/10.1016/j.jmb.2009.08.044

Argaud, D., Kirby, T.L., Newgard, C.B., Lange, A.J., 1997. Stimulation of glucose-6-phosphatase gene expression by glucose and fructose-2, 6-biphosphate. *J Biol Chem*, *272*, 12854–12861.

Bell, G., Mora, S., Greenland, P., Tsai, M., Gill, E., & Kaufman, J. D., 2017. Association of air pollution exposures with high-density lipoprotein cholesterol and particle number: The multi-ethnic study of atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *37*(5), 976–982. https://doi.org/10.1161/ATVBAHA.116.308193

Bind, M., Lepeule, J., Zanobetti, A., Gasparrini, A., Baccarelli, A. A., Coull, B. A., Schwartz, J., et al., 2014. Air pollution and gene-specific methylation in the Normative Aging Study. *Epigenetics*, *9*(3), 448–458. https://doi.org/10.4161/epi.27584

Brook, R. D., Franklin, B., Cascio, W., Hong, Y., Howard, G., Lipsett, M., Tager, I., et al., 2004. Air Pollution and Cardiovascular Disease A Statement for Healthcare Professionals From the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation*, *109*(21), 2655–2671. https://doi.org/10.1161/01.CIR.0000128587.30041.C8

Brook, R. D., Rajagopalan, S., Pope, C. A., Brook, J. R., Bhatnagar, A., Diez-Roux, A. V., Kaufman, J. D., et al., 2010. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the american heart association. *Circulation*, *121*(21), 2331–2378. https://doi.org/10.1161/CIR.0b013e3181dbece1

Brucker, N., Moro, A. M., Charão, M. F., Durgante, J., Freitas, F., Baierle, M., Garcia, S. C., et al., 2013. Biomarkers of occupational exposure to air pollution, inflammation and oxidative damage in taxi drivers. *Science of the Total Environment*, *463–464*, 884–893. https://doi.org/10.1016/j.scitotenv.2013.06.098

Cai, L., Wang, S., Gao, P., Shen, X., Jalaludin, B., Bloom, M. S., Huang, C., et al., 2019. Effects of ambient particulate matter on fasting blood glucose among primary school children in Guangzhou, China. *Environmental Research*, *176*, 108541. https://doi.org/10.1016/j.envres.2019.108541

Chen, T., Jia, G., Wei, Y., & Li, J., 2013. Beijing ambient particle exposure accelerates atherosclerosis in ApoE knockout mice. *Toxicology Letters*, *223*, 146–153. https://doi.org/10.1007/s12192-014-0499-2

Chen, R., Meng, X., Zhao, A., Wang, C., Yang, C., Li, H., Kan, H., et al., 2016. DNA hypomethylation and its mediation in the effects of fine particulate air pollution on cardiovascular biomarkers: A randomized crossover trial. *Environment International*, *94*, 614–619. https://doi.org/10.1016/j.envint.2016.06.026

Chuang, K. J., Yan, Y. H., Chiu, S. Y., & Cheng, T. J., 2011. Long-term air pollution exposure and risk factors for cardiovascular diseases among the elderly in Taiwan. *Occupational and Environmental Medicine*, *68*(1), 64–68. https://doi.org/10.1136/oem.2009.052704

Curto, A., Ranzani, O., Milà, C., Sanchez, M., Marshall, J. D., Kulkarni, B., Tonne, C., et al., 2019. Lack of association between particulate air pollution and blood glucose levels and diabetic status in peri-urban India. *Environment International*, *131*, 105033. https://doi.org/10.1016/j.envint.2019.105033

Duan, C., Talbott, E. O., Broadwin, R., Brooks, M., Matthews, K., & Barinas-Mitchell, E., 2019. Residential Exposure to PM2.5 and Ozone and Progression of Subclinical Atherosclerosis Among Women Transitioning Through Menopause: The Study of Women's Health Across the Nation. *Journal of Women's Health*, *28*(6), 802–811. https://doi.org/10.1089/jwh.2018.7182

Fatma, F., Begum, N., & Pandey, R. S., 2015. Sulphur Dioxide Induced Alterations in Glycogen Metabolism in Rattus norvegicus. *Natl. Acad. Sci. Lett.*, *38*(4), 311–313. https://doi.org/10.1007/s40009-014-0323-7

Gaio, V., Roquette, R., Dias, C. M., & Nunes, B., 2019. Ambient air pollution and lipid profile: Systematic review and meta- analysis. *Environmental Pollution*, *254*, 113036. https://doi.org/10.1016/j.envpol.2019.113036

Geniaux, G., Martinetti, D., Gabriel, E., Parent, E., Desassis, N., Allard, D., Romary, T., et al., 2017. Analyzing spatio-temporal data with R: Everything you always wanted to know-but were afraid to ask. *Journal de la Société Française de Statistique*, *158*(3), 124-158.

Joseph, J.C., Schuna A.A., 1990. Management of hypertension in the diabetic patient. *Clin Pharm.*, 9(11), 864-73.

Kaufman, J. D., Adar, S. D., Barr, R. G., Budoff, M., Burke, G. L., Cynthia, L., Watson, K. E., et al., 2016. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi- Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. *Lancet*, *388*(10045), 696–704. https://doi.org/10.1016/S0140-6736(16)00378-0.Association

Kim, J. S., Chen, Z., Alderete, T. L., Toledo-corral, C., Lurmann, F., Berhane, K., & Gilliland, F. D., 2019. Associations of air pollution, obesity and cardiometabolic health in young adults: The Meta-AIR study. *Environment International*, *133*, 105180. https://doi.org/10.1016/j.envint.2019.105180

Leem, J. H., Kaplan, B. M., et al., 2006. Exposures to air pollutants during pregnancy and preterm delivery. *Environ Health Perspect*., *114*(6), 905–910.

Li, H., Chen, R., Cai, J., Cui, X., Huang, N., & Kan, H., 2018. Short-term exposure to fine particulate air pollution and genome-wide DNA methylation: A randomized, double-blind, crossover trial. *Environment International*, *120*, 130–136. https://doi.org/10.1016/j.envint.2018.07.041

Li, A., Pei, L., Zhao, M., Xu, J., Mei, Y., Li, R., & Xu, Q., 2019. Investigating potential associations between O3 exposure and lipid profiles: A longitudinal study of older adults in Beijing. *Environment International*, *133*, 105135. https://doi.org/10.1016/j.envint.2019.105135

Li, J., Zhou, C., Xu, H., Brook, R. D., Liu, S., Yi, T., Pan, B., et al., 2019. Ambient Air Pollution Is Associated With HDL (High- Density Lipoprotein) Dysfunction in Healthy Adults. *Arterioscler Thromb Vasc Biol.*, *39*, 513–522. https://doi.org/10.1161/ATVBAHA.118.311749

Liu, L.J.S., Rossini, A., 1996. Use of kriging models to predict 12-hour mean ozone concentrations in metropolitan Toronto—a pilot study. *Environ. Int.*, *22*, 677–692.

Liu, C., Yang, C., Zhaoc, Y., Mad, Z., Bid, J., Liue, Y., Kan, H., et al., 2016. Associations between long-term exposure to ambient particulate air pollution and type 2 diabetes prevalence, blood glucose and glycosylated hemoglobin levels in China. *Environ Int.*, *92–93*, 416–421.

Mao, S., Chen, G., Liu, F., Li, N., Wang, C., Liu, Y., Li, S., et al., 2020. Long-term effects of ambient air pollutants to blood lipids and dyslipidemias in a Chinese rural population. *Environmental Pollution*, *256*, 113403. https://doi.org/10.1016/j.envpol.2019.113403

McGuinn, L. A., Schneider, A., McGarrah, R. W., Ward-Caviness, C., Neas, L. M., Di, Q., Devlin, R. B., et al., 2019. Association of Long-term PM2.5 Exposure with Traditional and Novel Lipid Measures Related to Cardiovascular Disease Risk. *Environ Int.*, *122*, 193–200. https://doi.org/10.1016/j.hal.2017.06.001.

O'Neill, S., & Driscoll, L. O., 2015. Metabolic syndrome: a closer look at the growing epidemic and its

associated pathologies. *Obesity Reviews*, *16*, 1–12. https://doi.org/10.1111/obr.12229

Paoin, K., Ueda, K., Ingviya, T., Buya, S., Phosri, A., Seposo, X. T.,Takano, H., et al., 2021. Long-term air pollution exposure and self-reported morbidity: a longitudinal analysis from the Thai cohort study (TCS). *Environmental Research*, *192*. https://doi.org/10.1016/j.envres.2020.110330

Penney, D. G., Helfman, C. C., Hull, J. A., Dunbar, J. C., & Verma, K., 1990. Elevated blood glucose is associated with poor outcome in the carbon-monoxide-poisoned rat. *Toxicol Lett.*, *54*, 287–298.

Pope, C. A., Burnett, R. T., Thurston, G. D., Thun, M. J., Calle, E. E., Krewski, D., & Godleski, J. J., 2004. Cardiovascular Mortality and Long-Term Exposure to Particulate Air Pollution: Epidemiological Evidence of General Pathophysiological Pathways of Disease. *Circulation*, *109*(1), 71–77. https://doi.org/10.1161/01.CIR.0000108927.80044.7F

Poursafa, P., Amin, M. M., Mansourian, M., Hajizadeh, Y., Sadeghian, B., & Kelishadi, R., 2017. Association of Exposure to Fine Particulate Matter and Risk Factors of Non-Communicable Diseases in Children and Adolescents. *International Journal of Pediatrics*, *5*(10), 5863–5870. https://doi.org/10.22038/ijp.2017.22739.1900

Rajagopalan, S., & Brook, R. D., 2012. Air pollution and type 2 diabetes: Mechanistic insights. *Diabetes*, *61*(12), 3037–3045. https://doi.org/10.2337/db12-0190

Sade, M. Y., Kloog, I., Liberty, I. F., Schwartz, J., & Novack, V., 2016. The association between air pollution exposure and glucose and lipids levels. *Journal of Clinical Endocrinology and Metabolism*, *101*(6), 2460–2467. https://doi.org/10.1210/jc.2016-1378

Shanley, R. P., Hayes, R. B., Cromar, K. R., Ito, K., Gordon, T., & Ahn, J., 2016. Particulate Air Pollution and Clinical Cardiovascular Disease Risk Factors. *Epidemiology*, *27*(2), 291–298. https://doi.org/10.1097/EDE.0000000000000426

Soares, S. R. C., Carvalho-Oliveira, R., Ramos-Sanchez, E., Catanozi, S., da Silva, L. F. F., Mauad, T., Garcia, M. L. B., et al., 2009. Air pollution and antibodies against modified lipoproteins are associated with atherosclerosis and vascular remodeling in hyperlipemic mice. *Atherosclerosis*, *207*(2), 368–373. https://doi.org/10.1016/j.atherosclerosis.2009.04.041

Sun, Q., Wang, A., Jin, X., Natanzon, A., Duquaine, D., & Brook, R. D., 2005. Long-term Air Pollution Exposure and Acceleration of Atherosclerosis and Vascular Inflammation in an Animal Model. *JAMA*, *294*(23), 3003–3010. https://doi.org/10.1001/jama.294.23.3003

Vathesatogkit, P., Woodward, M., Tanomsup, S., Hengprasith, B., Aekplakorn, W., Yamwong, S., & Sritara, P., 2012b. Long-term effects of socioeconomic status on incident hypertension and progression of blood pressure. *Journal of Hypertension*, *30*(7), 1347–1353. https://doi.org/10.1097/HJH.0b013e32835465ca

Vathesatogkit, P., Woodward, M., Tanomsup, S., Ratanachaiwong, W., Vanavanan, S., Yamwong, S., & Sritara, P., 2012a. Cohort profile: The electricity generating authority of Thailand study. *International Journal of Epidemiology*, *41*(2), 359–365. https://doi.org/10.1093/ije/dyq218

Wang, M., Sampson, P. D., Sheppard, L. E., Stein, J. H., Vedal, S., & Kaufman, J. D., 2019. Long-term exposure to ambient ozone and progression of subclinical arterial disease: The multi-ethnic study of atherosclerosis and air pollution. *Environmental Health Perspectives*, *127*(5), 1–8. https://doi.org/10.1289/EHP3325

Wilker, E. H., Mittleman, M. A., Coull, B. A., Gryparis, A., Bots, M. L., Schwartz, J., & Sparrow, D., 2013. Long-term exposure to black carbon and carotid intima-media thickness: The normative

aging study. *Environmental Health Perspectives*, *121*(9), 1061–1067. https://doi.org/10.1289/ehp.1104845

Wu, X., Basu, R., Malig, B., Broadwin, R., Ebisu, K., Gold, E. B., Green, R. S., et al., 2017. Association between gaseous air pollutants and inflammatory, hemostatic and lipid markers in a cohort of midlife women. *Environment International*, *107*, 131–139. https://doi.org/10.1016/j.envint.2017.07.004

Wu, Y., Tian, Y., Wang, M., Wang, X., Wu, J., Wang, Z., & Hu, Y., 2020. Short-term exposure to air pollution and its interaction effects with two ABO SNPs on blood lipid levels in northern China: A family-based study. *Chemosphere*, *249*, 126120. https://doi.org/10.1016/j.chemosphere.2020.126120

Yang, B. Y., Bloom, M. S., Markevych, I., Qian, Z. (Min), Vaughn, M. G., Cummings-Vaughn, L. A., Dong, G. H., et al., 2018. Exposure to ambient air pollution and blood lipids in adults: The 33 Communities Chinese Health Study. *Environment International*, *119*, 485–492. https://doi.org/10.1016/j.envint.2018.07.016

Yu, W., Caturini, D., Gasevic, D., Xu, R., Julia, M., Kartika, I., Guo, Y., et al., 2019. Long-term exposure to PM2.5 and fasting plasma glucose in non-diabetic adolescents in Yogyakarta, Indonesia. *Environmental Pollution*. https://doi.org/10.1016/j.envpol.2019.113423

Zhang, K., Wang, H., He, W., Chen, G., Lu, P., Xu, R., Guo, Y., et al., 2021. The association between ambient air pollution and blood lipids: A longitudinal study in Shijiazhuang, China. *Science of the Total Environment*, *752*, 141648. https://doi.org/10.1016/j.scitotenv.2020.141648

Zhang, Y., Zanotti, I., Reilly, M. P., Glick, J. M., Rothblat, G. H., & Rader, D. J., 2003. Overexpression of apolipoprotein A-I promotes reverse transport of cholesterol from macrophages to feces in vivo. *Circulation*, *108*(6), 661–663. https://doi.org/10.1161/01.CIR.0000086981.09834.E0

529 Table 1. Basic characteristics of study participants at baseline (in 2002) (N = 1,839)

Variables	**Number (%)**
Sex, n (%)	
Male	1,357 (73.8)
Female	482 (26.2)
Age, years	
Mean ± SD	58.9 ± 4.7
Range	52 – 71
Body mass index, kg/m^2	
Mean ± SD	24.6 ± 3.4
Smoking status, n (%)	
Never smokers	890 (48.4)
Former smokers	691 (37.5)
Current smokers	253 (13.8)
Missing data	5 (0.3)
Alcohol drinking, n (%)	
Non-users	584 (31.8)
Former users	310 (16.9)
Occasional users (<1 day/week)	460 (25.0)
Current users	479 (26.0)
Missing data	6 (0.3)
Exercise, n (%)	
<3 times/week	766 (41.6)
≥ 3 times/week	1066 (58.0)
Missing data	7 (0.4)
Education levels, n (%)	
0 – 8th Grade	444 (24.2)
9th – 12th Grade	570 (31.0)
>12th Grade	819 (44.5)
Missing data	6 (0.3)
Income (monthly), n (%)	
<10000 Baht	135 (7.3)
10000 – 20000 Baht	151 (8.2)
20000 – 50000 Baht	529 (28.8)
>50000 Baht	876 (47.6)
Missing data	148 (8.1)
Prevalence of disease, n (%)	
Hypertension	838 (45.6)
Diabetes	382 (20.8)

Hypercholesterolemia	910 (49.5)
Treatment status, n (%)	
Hypertension	487 (26.5)
Diabetes	249 (13.6)
City of residence, n (%)	
Bangkok	874 (47.5)
Nonthaburi	887 (48.2)
Samut Prakan	40 (2.2)
Pathum Thani	38 (2.1)
Serum lipids & blood sugar, Mean ± SD	
TC (mg/dl)	241.9 ± 43.2
LDL-C (mg/dl)	158.2 ± 39.7
HDL-C (mg/dl)	54.7± 15.0
TG (mg/dl)	149.2 ± 97.3
FG (mg/dl)	106.8 ± 28.7

549 Table 2. Summary statistics for daily average concentration of environmental variables during the
550 study period

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Environmental Variable	Mean ± SD	Range	IQR
PM_{10} (μg/m^3)	47.5 ± 18.1	20.5 – 140.8	16.3
O_3 (ppb)	30.1 ± 5.3	7.0 – 41.5	7.0
NO_2 (ppb)	19.7 ± 4.4	12.3 – 45.0	4.6
SO_2 (ppb)	6.5 ± 3.7	1.2 – 18.9	5.3
CO (ppm)	0.7 ± 0.2	0.2 – 2.1	0.2
Temperature (℃)	29.1 ± 1.6	18.9 – 33.7	1.9
Relative humidity (%)	72.5 ± 8.4	45.0 – 97.0	11.0

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554 Table 3. Correlation coefficients between air pollutants and environmental variables during the study
555 period

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	PM_{10}	O_3	NO_2	SO_2	CO
O_3	0.27				
NO_2	0.47	0.34			
SO_2	0.1	0.08	0.08		
CO	0.3	0.16	0.57	0.11	
Temperature	-0.11	-0.06	-0.29	-0.07	-0.25
Relative humidity	-0.33	-0.46	-0.21	-0.17	-0.08

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559 Table 4. Estimated percent change (95% CI) in outcome variables for 3-month average concentrations
560 of air pollutants in the main model (Model IV)

	PM_{10} ($\mu g/m^3$)	O_3 (ppb)	NO_2 (ppb)	SO_2 (ppb)	CO (ppm)
TC (mg/dl)	5.6 (4.0, 7.2)*	-2.4 (-3.2, -1.6)*	-0.1 (-0.9, 0.7)	10.2 (7.5, 13.0)*	1.8 (1.3, 2.3)*
LDL-C (mg/dl)	6.6 (4.3, 9.0)*	-2.3 (-3.5, -1.2)*	0.1 (-1.1, 1.2)	11.1 (7.2, 15.2)*	1.9 (1.1, 2.7)*
HDL-C (mg/dl)	-1.8 (-3.7, 0.1)	-0.3 (-1.3, 0.7)	-0.7 (-1.7, 0.4)	-3.3 (-6.2, -0.3)*	-1.1 (-1.7, -0.5)*
TG (mg/dl)	2.9 (-0.9, 6.8)	-2.2 (-4.1, -0.2)*	1.0 (-1.0, 3.1)	4.3 (-1.8, 10.7)	1.1 (-0.2, 2.3)
FG (mg/dl)	2.8 (1.5, 4.2)*	-1.9 (-2.6, -1.2)*	0.4 (-0.3, 1.1)	6.8 (4.5, 9.1)*	1.1 (0.6, 1.5)*

561 Significance indicated by *P < 0.05. Model IV (main model): adjusted for age, sex, BMI, smoking status, alcohol
562 drinking, exercise habits, hypertension, diabetes, hypercholesterolemia, and treatment of hypertension and
563 diabetes, education level and income.

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576 Table 5. Estimated percent change (95% CI) in outcome variables in 3-month average air pollutants

577 stratified by income group

	PM_{10} (μg/m^3)	O_3 (ppb)	NO_2 (ppb)	SO_2 (ppb)	CO (ppm)
TC					
High	5.0 (2.9, 7.1)*	-1.7 (-2.8, -0.6)*	-0.4 (-1.5, 0.6)	8.9 (5.3, 12.7)*	1.2 (0.5, 1.9)*
Low-middle	6.1 (3.6, 8.6)*	-2.8 (-4.1, -1.6)*	0.6 (-0.7, 1.8)	10.5 (6.4, 14.7)*	2.1 (1.4, 2.9)*
LDL-C					
High	6.3 (3.3, 9.4)*	-1.7 (-3.3, -0.2)*	-0.4 (-1.8, 1.2)	10.6 (5.3, 16.2)*	1.1 (0.1, 2.2)*
Low-middle	6.5 (3.0, 10.1)*	-2.5 (-4.3, -0.7)*	0.7 (-1.1, 2.5)	9.6 (3.8, 15.7)*	2.2 (1.1, 3.2)*
HDL-C					
High	-0.9 (-3.3, 1.7)	-0.0 (-1.3, 1.3)	-0.84 (-2.1, 0.5)	-2.8 (-6.8, 1.3)	-0.9 (-1.7, -0.1)*
Low-middle	-1.9 (-4.7, 1.0)	-0.8 (-2.3, 0.8)	-0.4 (-2.0, 1.2)	-2.3 (-6.5, 2.1)	-0.8 (-1.6, 0.1)
TG					
High	4.4 (-0.7, 9.7)	-2.1 (-4.5, 0.5)	0.6 (-1.9, 3.3)	1.9 (-6.3, 10.8)	1.3 (-0.4, 3.0)
Low-middle	0.4 (-5.1, 6.2)	-1.7 (-4.7, 1.3)	2.2 (-0.9, 5.3)	4.6 (-4.1, 14.1)	0.5 (-1.2, 2.2)
FG					
High	0.66 (-1.0, 2.3)	-1.6 (-2.4, -0.7)*	0.2 (-0.7, 1.0)	5.6 (2.7, 8.6)*	0.5 (-0.1, 1.1)
Low-middle	4.8 (2.6, 7.1)*	-2.4 (-3.5, -1.2)*	0.8 (-0.3, 2.0)	7.8 (4.2, 11.5)*	1.3 (0.6, 1.9)*

578 Significance indicated by *P < 0.05. Potential covariates in the adjusted models include: age, sex, BMI, smoking

579 status, alcohol drinking, exercise habits, hypertension, diabetes, hypercholesterolemia, treatment of hypertension

580 and diabetes, education level.

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