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Long-term exposure to ambient particulate matter ($PM_{2.5}$) is associated with platelet counts in adults☆

Zilong Zhang [a], Ta-Chien Chan [b], Cui Guo [a], Ly-yun Chang [c, d], Changqing Lin [e, f], Yuan Chieh Chuang [c], Wun Kai Jiang [c], Kin Fai Ho [a], Tony Tam [g], Kam S. Woo [h], Alexis K.H. Lau [e, f], Xiang Qian Lao [a, i, *]

[a] Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong
[b] Research Center for Humanities and Social Sciences, Academia Sinica, Taiwan
[c] MJ Health Research Foundation, MJ Group, Taiwan
[d] Institute of Sociology, Academia Sinica, Taiwan
[e] Department of Civil and Environmental Engineering, The Hong Kong University of Science and Technology, Hong Kong
[f] Division of Environment and Sustainability, The Hong Kong University of Science and Technology, Hong Kong
[g] Department of Sociology, The Chinese University of Hong Kong, Hong Kong
[h] Institute of Future Cities, The Chinese University of Hong Kong, Hong Kong
[i] Shenzhen Research Institute of the Chinese University of Hong Kong, Shenzhen, China

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ABSTRACT

Background: The prothrombotic effects of particulate matter (PM) may underlie the association of air pollution with increased risks of cardiovascular disease. This study aimed to investigate the association between long-term exposure to PM with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and platelet counts, a marker of coagulation profiles.

Methods: The study participants were from a cohort consisting of 362,396 Taiwanese adults who participated in a standard medical examination program between 2001 and 2014. Platelet counts were measured through Complete Blood Count tests. A satellite-based spatio-temporal model was used to estimate 2-year average ambient $PM_{2.5}$ concentration at each participant's address. Mixed-effects linear regression models were used to investigate the association between $PM_{2.5}$ exposure and platelet counts.

Results: This analysis included 175,959 men with 396,248 observations and 186,437 women with 397,877 observations. Every 10-μg/m^3 increment in the 2-year average $PM_{2.5}$ was associated with increases of 0.42% (95% CI: 0.38%, 0.47%) and 0.49% (95% CI: 0.44%, 0.54%) in platelet counts in men and women, respectively. A series of sensitivity analyses, including an analysis in participants free of cardiometabolic disorders, confirmed the robustness of the observed associations. Baseline data analyses showed that every 10-μg/m^3 increment in $PM_{2.5}$ was associated with higher risk of 17% and 14% of having elevated platelet counts (≥90th percentile) in men and women, respectively.

Conclusions: Long-term exposure to $PM_{2.5}$ appears to be associated with increased platelet counts, indicating potential adverse effects on blood coagulability.

1. Introduction

Exposure to air pollution, especially particulate matter (PM), has been associated with increased risks of cardiovascular morbidity and mortality (Pope III and Dockery, 2006; Brook et al., 2010; Hoek et al., 2013). However, the mechanisms underlying this association remain unclear. Previous studies hypothesized that the PM-induced production of reactive oxygen species (ROS) is a major mechanism underlying the cardiotoxic effects of PM air pollution (Gurgueira et al., 2002; Rhoden et al., 2005). Increases in ROS can activate both pro-inflammatory and pro-thrombotic pathways, resulting in endothelial dysfunction, increased blood coagulability and atherosclerosis progression, all of which are important

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* Corresponding author. 4/F School of Public Health, Prince of Wales Hospital, Sha Tin, N.T., Hong Kong SAR, China.
E-mail address: xqlao@cuhk.edu.hk (X.Q. Lao).

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contributors to the development of cardiovascular disease (Simkhovich et al., 2009; Libby, 2001; Libby et al., 2002; Poursafa and Kelishadi, 2010).

Findings from animal studies suggest that acute exposure to exhaust particles can rapidly induce platelet activation and experimental thrombosis (Nemmar et al., 2003). Human panel and cross-over studies have also noted an association of acute/short-term exposure to PM with increased levels of coagulation markers (Jacobs et al., 2010; Ruckerl et al., 2006; Chuang et al., 2007; Rudez et al., 2009; Delfino et al., 2009; Wu et al., 2012). It is also important to investigate the long-term effects because people generally suffer from prolonged exposure to air pollution. However, only a few epidemiological studies have investigated the association between long-term exposure to PM air pollution and blood coagulation, and the results are inconsistent (Hoffmann et al., 2009; Forbes et al., 2009; Lanki et al., 2015; Hajat et al., 2015; Dabass et al., 2016; Green et al., 2016; Viehmann et al., 2015). Furthermore, most of these studies were conducted in North America and Europe and there is limited evidence from other regions such as East Asia, where air pollution is relatively more serious. Meanwhile, there is evidence showing that the distribution of coagulability and inflammation markers could be different in Western and Asian populations (Kelley-Hedgepeth et al., 2008; Lutsey et al., 2006). Platelet count is a universally and routinely measured marker of hematologic and hemostatic changes that has been previously shown to be a valuable predictor of cardiovascular and total mortality (Thaulow et al., 1991). We therefore investigated the association between long-term exposure to PM with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) and platelet counts in a large cohort of Taiwanese adults.

2. Material and methods

2.1. Study population

Study participants were drawn from a large cohort in Taiwan, which was documented in previous publications (Chang et al., 2018; Wen et al., 2011; Zhang et al., 2017). In brief, over 0.5 million participants from all over Taiwan joined a standard medical examination program that was provided by a private company (MJ Health Management Institution, Taipei, Taiwan) from 1996 to 2014. All participants visited the health institution and received a series of health examinations including anthropometric measurements, general physical examinations and biochemical tests of blood and urine. A standard self-administered questionnaire was also used to collect information on demographics, lifestyle and medical history. Participants were encouraged to visit the medical center regularly (on a yearly basis). All participants provided written informed consent prior to their participation. The proposal of this study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

In the present study, we included adult participants (age $\geq$ 18 years) who visited the medical institution from 2001 to 2014, the period for which $PM_{2.5}$ exposure data were available. During this period, platelet counts were available for 431,372 participants with 974,698 observations. We excluded 160,815 observations because of missing information on key variables (455 on anthropometric measurements, 41,857 on demographic information, 45,095 on blood tests, 68,171 on lifestyle factors and 5237 on $PM_{2.5}$ exposure data due to missing address). To minimize the possible confounding effects of thrombocytosis or thrombocytopenia, we further excluded 3410 and 16,348 observations with platelet counts higher than 450×10^9/L and lower than 150×10^9/L, respectively (Giles, 1981). The data analysis included a final sample of 362,396 participants (48.6% men) with 794,125 observations. Compared with the participants excluded, those included were slightly younger, more educated and healthier with a healthier lifestyle (e.g. lower prevalence of smoking and alcohol drinking) and lower prevalence of cardiovascular factors such as hypertension, diabetes and hyperlipidemia (Supplementary Table 1). Among the 362,396 participants included in data analysis, 160,154 (44.2%) visited the medical center more than once and the average number of visits was 3.7 (SD: 2.2).

2.2. Air pollution exposure assessment

To estimate $PM_{2.5}$ exposure, we used a spatio-temporal model with a resolution of resolution 1×1 km, which was described in detail in our previous studies (Zhang et al., 2017, 2018; Lin et al., 2015). In brief, the model was developed based on aerosol optical depth data derived from spectral data obtained by two Moderate Resolution Imaging Spectroradiometer (MODIS) instruments aboard the Terra and Aqua satellites of the U.S. National Aeronautics and Space Administration. We recently validated this model using ground-measured $PM_{2.5}$ data from more than 70 monitoring stations around Taiwan. The correlation coefficients between estimated and ground-measured yearly average $PM_{2.5}$ concentrations ranged from 0.72 to 0.83.

Participants' addresses were transformed into latitude and longitude data through geo-coding. Then, address-specific yearly average $PM_{2.5}$ concentration was calculated for each participant. In the present study, we estimated annual average $PM_{2.5}$ concentrations for the year of each medical examination and for the previous year. Then, the mean of these two averages (2-year average concentration) was used as an indicator of long-term exposure to ambient $PM_{2.5}$ air pollution.

2.3. Health examination

The main health outcome of interest was the platelet count. For each participant, an overnight fasting blood sample was collected in the morning. Participants failing to adhere to fasting were rescheduled for another medical examination. Complete blood count (CBC) tests were performed using an ABBOTT Cell Dyn 3000/3700 hematology analyzer. Platelet count data were retrieved from the CBC test results. In addition to the CBC tests, plasma glucose, total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels were measured using an automatic biochemical analyzer (7150, Hitachi, Tokyo, Japan). Each participant's barefoot height and weight were measured, and body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m). Seated blood pressure was measured using an auto-sphygmomanometer (Citizen CH-5000, Tokyo, Japan). All procedures were performed by trained technicians. The detailed examination procedures and relevant quality control measures can be accessed from the technical report of the MJ Health Research Foundation (Chang et al., 2018).

2.4. Statistical analysis

We used mixed-effects linear regression models to investigate the associations between $PM_{2.5}$ exposure and platelet counts. A person-level random intercept was added to account for within-person clustering. Platelet count was log-transformed to achieve normal distribution. Because our preliminary analysis suggested an effect modification by sex, we performed regression analysis in the men and women separately. Because 55.2% of the participants (54.6% of the males and 57.0% of the females) had only one measurement, a baseline cross-sectional analysis was performed using multivariable linear regression models. We also used Logistic