



Particulate matter air pollution, physical activity and systemic inflammation in Taiwanese adults

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ABSTRACT

Background: The protective effects of physical activity (PA) against chronic disease can be partially ascribed to its anti-inflammatory effects. On the other hand, long-term exposure to particulate matter with an aerodynamic diameter less than 2.5 μm ($\text{PM}_{2.5}$) may induce systemic inflammation.

Objective: To investigate the joint effects of habitual PA and long-term exposure to $\text{PM}_{2.5}$ on systemic inflammation in a large cohort of Taiwanese adults.

Methods: We studied 359,067 adult participants from a cohort consisting of Taiwanese residents who participated in a standard medical examination program from 2001 to 2014. Peripheral white blood cell (WBC) and differential counts were measured as indicators of systemic inflammation. Two-year average concentration of $\text{PM}_{2.5}$ was estimated at each participant's address using a satellite-based spatio-temporal model. Habitual PA level was assessed by questionnaire (inactive, low, moderate and high). Mixed-effects linear regression model was used to examine the associations of WBC counts with $\text{PM}_{2.5}$ and PA.

Results: Compared with inactive participants, those with low, moderate or high PA levels had 0.36% [95% confidence interval (CI): 0.31%, 0.41%], 0.70% (95%CI: 0.65%, 0.76%) and 1.16% (95%CI: 1.11%, 1.22%) lower WBC counts, respectively, after adjusting for $\text{PM}_{2.5}$ exposure and a wide range of confounders. Long-term $\text{PM}_{2.5}$ exposure was associated with increased WBC counts at all PA levels. Analyses for differential counts generated similar results. No significant interaction was observed between PA and $\text{PM}_{2.5}$ exposure (P for interaction = 0.59).

Conclusions: Habitual PA was associated with statistically significant lower markers of systemic inflammation across different levels of $\text{PM}_{2.5}$. Effects of PA and $\text{PM}_{2.5}$ exposure on systemic inflammation are independent.

1. Introduction

The health benefits of regular physical activity (PA) have been well documented (Warburton et al., 2006). Even low-volume habitual PA (15 min a day or 90 min a week of moderate-intensity exercise) is associated with reduced mortality from cardiovascular disease, diabetes and cancer (Wen et al., 2011). In contrast to PA, particulate matter

(PM) air pollution poses a significant risk to health. According to the Global Burden of Disease Study, ambient PM air pollution was the ninth leading cause of mortality in 2010, responsible for more than 3.2 million deaths (Lim et al., 2013).

Worldwide, 31.1% of adults are estimated to be physically inactive (Hallal et al., 2012). Public health campaigns promoting PA are increasingly being used in an attempt to combat the pandemic of physical

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inactivity. However, enhanced exposure to air pollutants in the lungs due to higher minute ventilation during PA may amplify the adverse health effects of air pollution (Giles and Koehle, 2014). The results of a cross-over experimental study in Barcelona, Spain showed that the beneficial effects of PA on blood pressure and heart rate variability were reduced by exposure to higher traffic-related air pollution, indicating an interaction between PA and short-term exposure to air pollution (Kubesch et al., 2015a; Cole-Hunter et al., 2016). However, such interaction was not found for lung function and inflammatory markers (Kubesch et al., 2015b). Data from epidemiological studies are scarce: A cross-sectional study in Hong Kong reported habitual PA may prevent premature death attributable to short-term exposure to air pollution (Wong et al., 2007); the Danish Diet, Cancer and Health Cohort study that examined the effects of leisure-time PA and long-term exposure to nitrogen dioxide (NO₂) on mortality and incidence of asthma and chronic obstructive pulmonary disease (COPD) found no PA-air pollution interactions (Andersen et al., 2015; Fisher et al., 2016).

Balancing the benefits of PA and the potential detrimental effects of enhanced exposure to air pollution during PA has become an important public concern, especially in those regions with significant air pollution. As air pollution is ubiquitous, people need to be clearly aware whether they can benefit from PA despite inhaling a larger amount of air pollution because of the higher minute ventilation during PA.

Systemic inflammation has been recognized as an underlying mechanism for many chronic diseases including cancer and cardiovascular disease. Inflammation induced by PM with an aerodynamic diameter less than 2.5 µm (PM_{2.5}) is hypothesized as a biological link between air pollution and increased morbidity and mortality of chronic diseases, especially for cardiovascular disease (Brook et al., 2010; Pope and Dockery, 2006). On the other hand, the protective effects of PA against chronic disease can be partially ascribed to its anti-inflammatory effects (Nimmo et al., 2013; Beavers et al., 2010). We therefore investigated the joint effects of habitual PA and long-term exposure to PM_{2.5} on systemic inflammation in a large prospective cohort.

2. Methods

2.1. Study population

The study participants were from a large prospective cohort in Taiwan, which has been documented elsewhere (Wen et al., 2011; Wen et al., 2008; Wu et al., 2017). Briefly, the cohort consisted of more than 0.5 million Taiwanese residents who took part in a standard medical examination program provided by a private firm (MJ Health Management Institution, Taiwan) since 1996. The participants received a series of medical examinations including anthropometric measurements, physical examination, blood and urinary tests and a standard self-administered questionnaire survey during each visit. The participants were encouraged to visit the firm regularly and they gave written informed consent prior to participation. Ethical approval was obtained from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee.

In the present study, we only included participants aged 18 or above who participated in the cohort from 2001 to 2014, a period for which PM_{2.5} exposure assessment was available. During the study period, white blood cell (WBC) measurements were available for 424,047 participants with 959,280 observations. We excluded 159,733 observations with incomplete information (475 on anthropometric measurements, 44,466 on demographic information, 47,913 on blood tests, 61,667 on PA and other lifestyle factors and 5152 on PM_{2.5} exposure due to missing residential addresses). Compared with all observations, the excluded observations had similar distributions in age (mean: 42.3 vs 42.2 years), sex (male: 49.7% vs 49.8%) and WBC count (median: 5.8 vs 5.8 × 10⁹/L).

We further excluded 2735 observations with WBC count < 3.5 × 10⁹/L and 14,408 observations with WBC count ≥ 12.5 × 10⁹/

L to avoid the potential confounding bias from reduced immune function or acute infections (Tong et al., 2004). The final sample size included in the present data analysis was 359,067 participants with 782,404 observations. Of the 359,067 participants, 158,213 (44.1%) underwent more than one examination.

2.2. Medical examination

The participants received a series of medical examinations during their visits. Height and weight were measured with participants wearing light indoor clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m). Seated blood pressure was measured using an auto-sphygmomanometer (Citizen CH-5000, Tokyo, Japan). An overnight fasting blood sample was taken in the morning and Complete Blood Count (CBC) tests were conducted using ABBOTT Cell Dyn 3000/3700 hematology analyzer. Total WBC and differential (neutrophil, lymphocyte and monocyte) counts were retrieved from CBC tests. In addition to CBC, plasma glucose, total cholesterol, triglyceride and high-density lipoprotein cholesterol (HDL-C) were also measured using an automatic biochemical analyzer (7150, Hitachi, Tokyo, Japan). All blood samples were analyzed at the central laboratory of MJ Health Screening Center. All tests were performed by trained technicians and the detailed information including quality control can be accessed in the technical report released by the MJ Health Research Foundation (Chang et al., 2016).

A standard self-administered questionnaire was used to collect information on the demographic characteristics, medical history and lifestyle factors.

2.3. Physical activity

Information on habitual PA was collected by questionnaire. The method for assessing PA level has been described in previous publications (Wen et al., 2011; Wu et al., 2017). First, the participants were asked to classify the weekly PAs during the previous month into four intensity categories: light (e.g. walking), moderate (e.g. brisk walking), medium-vigorous (e.g. jogging) and high-vigorous (e.g. rope skipping). A metabolic equivalent value (MET) based on the Compendium of Physical Activities (Ainsworth et al., 2000a) was assigned to each PA category: 2.5 for light, 4.5 for moderate, 6.5 for medium-vigorous and 8.5 for high-vigorous. A weighted MET was assigned to those participants who reported activities in more than one intensity category, depending on the time spent in each category. Afterwards, MET-hour per week was calculated as the product of intensity (MET) and duration (hours) of exercise. In accordance with the guidelines for Americans from the Physical Activity Guidelines Advisory Committee (Physical Activity Guidelines Advisory Committee, 2008), the participants were classified into four groups for data analysis: inactive (< 3.75 MET-hour), low (3.75–7.49 MET-hour), moderate (7.50–16.49 MET-hour) and high (≥ 16.50 MET-hour).

2.4. Air pollution exposure assessment

The details for estimating PM_{2.5} air pollution have been described elsewhere (Zhang et al., 2017). Briefly, we used a spatio-temporal model with high resolution (1 × 1 km) based on satellite aerosol optical depth (AOD) data to retrieve ground-level PM_{2.5} concentrations. The 1-km satellite AOD data was derived from the spectral data from the two Moderate Resolution Imaging Spectroradiometer (MODIS) instruments aboard Terra and Aqua satellites from the U.S. National Aeronautics and Space Administration (Hong Kong University of Science and Technology, 2016). We recently validated the model using data from more than 70 monitoring stations in Taiwan between 2005 and 2014 (PM_{2.5} data were only available for three monitoring stations from 2001 to 2004. Validations were therefore not conducted for this period). The data used for validation were different from the data used

for model development (Lin et al., 2015). The correlation coefficients between the average satellite-retrieved and ground-level monitoring PM_{2.5} concentrations ranged from 0.79 to 0.83 in different years and the mean percentage errors were around 20%. Spatial correlation coefficient between average satellite-retrieved PM_{2.5} and ground PM_{2.5} from monitoring stations in Taiwan in 2005 is presented in Supplementary Fig. 1. The spatial correlation coefficients for each year between 2006 and 2014 have been presented in our previous publication (Zhang et al., 2017).

The participant's addresses were geo-coded into latitude and longitude data and address-specific yearly average PM_{2.5} concentrations were then calculated. We estimated the annual average PM_{2.5} concentrations for the calendar year of the medical examination and for the previous year. The mean of these two averages (2-year average) was used as an indicator of long-term exposure to ambient PM_{2.5} air pollution.

2.5. Statistical analysis

We used mixed-effects linear regression models to investigate the effects of PM_{2.5}/PA on WBC and differential counts with a person-level random intercept added to account for within-person clustering. The WBC and differential counts were log-transformed because of the skewed distribution. Three models were developed: Crude Model: without adjustment; Model 1: adjusted for age, sex, educational level [lower than high school (< 10 years), high school (10–12 years), college or university (13–16 years), or postgraduate (> 16 years)], smoking status (never, former and current), alcohol drinking (< once/week, 1–3 times/week, and > 3 times/week), occupational exposure (exposure to dust or organic solvents in workplace: yes vs no) and season (calendar season) of each medical examination; Model 2: further adjusted for BMI, hypertension (defined as systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or self-reported physician-diagnosed hypertension), diabetes (defined as fasting blood glucose ≥ 126 mg/dl, or self-reported physician-diagnosed diabetes), hyperlipidemia (defined as total cholesterol ≥ 240 mg/dl, or triglyceride ≥ 200 mg/dl, or HDL-C ≤ 40 mg/dl), self-reported any cardiovascular disease or stroke (yes vs no) and self-reported any form of cancer (yes vs no).

PA and PM_{2.5} were examined separately using the aforementioned three models, and then they were introduced into the fully adjusted model simultaneously to adjust for each other. Effect estimates were calculated as percentage differences in WBC or differential counts with the inactive group, or participants with 2-year PM_{2.5} levels in the 1st quartile as reference. We also conducted subgroup analyses stratified by PM_{2.5} quartiles or PA levels. In addition, we classified the participants into 16 groups based on their PA levels and PM_{2.5} quartiles, and those of inactive PA level and PM_{2.5} in the highest quartile served as the reference group for comparison.

To investigate whether beneficial effects of PA on WBC count were offset with extremely high exposure to PM_{2.5}, we categorized the participants into two groups based on their PM_{2.5} exposure (i.e. participants with exposure of lower 90 percentile and participants with exposure of upper 10 percentile). We evaluated the health effects of PA in the participants with PM_{2.5} exposure of upper 10 percentile using Model 2. An interaction term “PM_{2.5} group (continuous variable) × PA levels (continuous variable)” was subsequently introduced in the model to detect the potential interactions in analysis among all participants.

A series of sensitivity analyses were performed. 1) As the study participants were not randomly selected from the whole Taiwanese population, the characteristics of the study population could differ across the study period. Therefore, we added the year of medical examination into the regression models to control for possible time trend; 2) We used 1-year (year of the medical examination) average PM_{2.5} instead of 2-year average; 3) We restricted study population to the participants with multiple measurements and those with single

Table 1
Characteristics of participants at baseline and over all visits.

Characteristics	Baseline (N = 359,067)	All Visits (N = 782,404)
Age (year)	39.9 (13.0)	42.2 (12.7)
Male	174,902 (48.7%)	393,525 (50.3%)
Education		
Lower than high school (< 10 years)	58,525 (16.3%)	114,010 (14.6%)
High school (10–12 years)	72,829 (20.3%)	152,413 (19.5%)
College or university (13–16 years)	185,477 (51.7%)	414,425 (53.0%)
Postgraduate (> 16 years)	42,336 (11.8%)	101,556 (13.0%)
Cigarette smoking		
Never	265,124 (73.8%)	589,561 (75.4%)
Former	20,758 (5.8%)	47,317 (6.0%)
Current	73,185 (20.4%)	145,526 (18.6%)
Alcohol drinking		
< once/week	308,052 (85.8%)	668,621 (85.5%)
1–3 times/week	33,817 (9.4%)	76,450 (9.8%)
> 3 times/week	17,198 (4.8%)	37,333 (4.8%)
Physical activity		
Inactive	183,772 (51.2%)	363,682 (46.5%)
Low	70,427 (19.6%)	154,313 (19.7%)
Moderate	58,818 (16.4%)	144,687 (18.5%)
High	46,050 (12.8%)	119,722 (15.3%)
Occupational exposure		
Dust	13,493 (3.8%)	27,782 (3.6%)
Organic solvent	17,606 (4.9%)	37,129 (4.7%)
Body mass index (kg/m ²)	23.1 (3.7)	23.2 (3.6)
WBC (10 ⁹ /L) ^a	6.0 (1.3)	5.9 (1.3)
Neutrophil (10 ⁹ /L) ^a	3.3 (1.4)	3.3 (1.4)
Lymphocyte (10 ⁹ /L) ^a	1.9 (1.3)	1.9 (1.3)
Monocyte (10 ⁹ /L) ^a	0.4 (1.3)	0.4 (1.3)
Hypertension	45,596 (12.7%)	95,715 (12.2%)
Diabetes	14,136 (3.9%)	32,359 (4.1%)
Hyperlipidemia	82,978 (23.1%)	180,901 (23.1%)
Self-reported cancer	4117 (1.1%)	11,253 (1.4%)
Self-reported CVD	10,771 (3.0%)	25,305 (3.2%)
Address		
Residential address	296,526 (82.6%)	664,137 (84.9%)
Company address	62,541 (17.4%)	118,267 (15.1%)

^aGeometric mean (SD).

Results are presented as mean (SD) for continuous variables and number (percentage) for categorical variables.

Abbreviations: CVD, cardiovascular disease.

measurement were excluded; 4) We excluded participants who used a company address rather than a residential address.

Because 55.9% of the study participants visited the medical center only once, we also performed a baseline cross-sectional analysis using multivariable linear regression.

Statistical analyses were performed using R 3.2.5 (R Core Team, Vienna, Austria). A two-tailed *P* value < 0.05 defined statistical significance.

3. Results

The general characteristics of the study participants are presented in Table 1. The mean age was 39.9 years (SD: 13.0) at baseline and there were fewer males (48.5%) than females. Most participants were never smokers (73.9%) and seldom alcohol drinkers (85.8%). More than half of the participants (51.3%) were classified as physically inactive. The majority provided a residential address (82.6%) and only a small proportion used a company address (17.4%). Overall, the characteristics were similar at baseline and over all visits.

The locations of the participants are presented in Fig. 1. The distribution of PM_{2.5} concentrations is presented by year in Fig. 2. The spatial distribution of PM_{2.5} was generally stable over the study period.

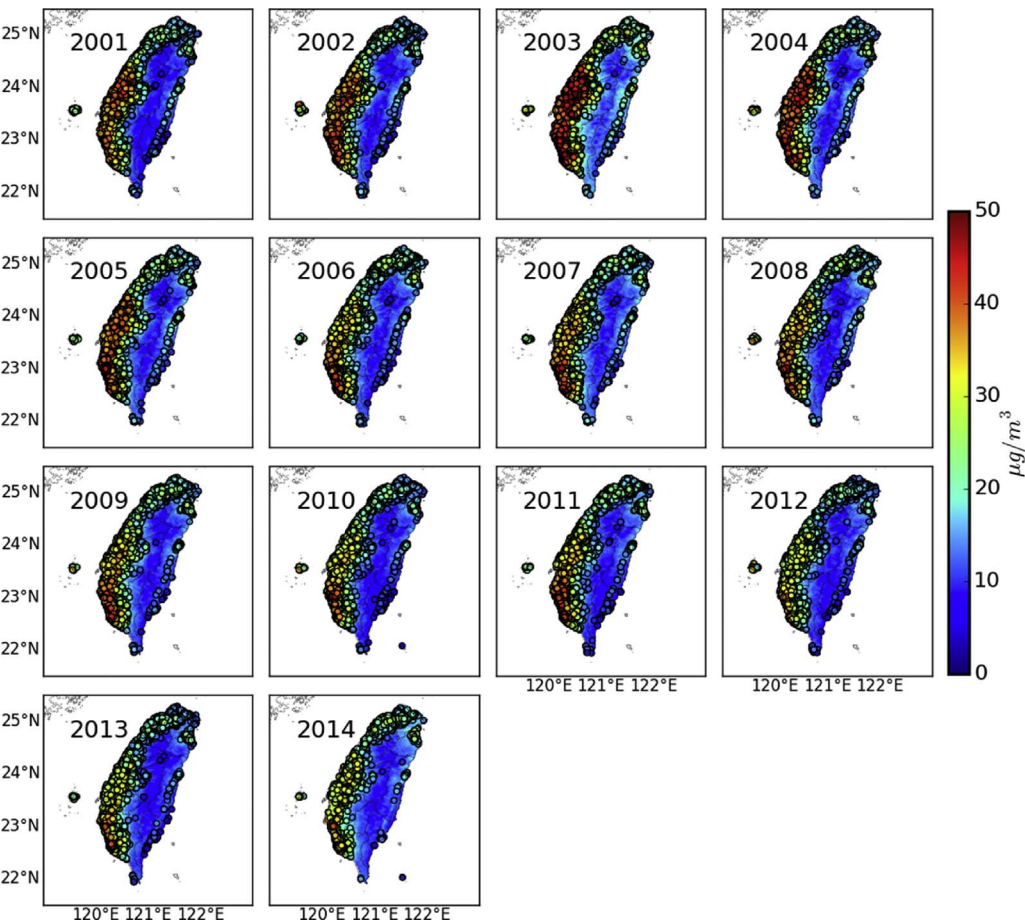


Fig. 1. Location map of the study participants by year. Circles represent locations of the participants.

The overall mean and median of 2-year average $PM_{2.5}$ concentration was $26.5 \mu g/m^3$ (SD: 7.4) and $24.0 \mu g/m^3$ (inter quartile range: 6.4), respectively. In each year there was a large spatial contrast in exposure. Higher PA levels were associated with lower WBC counts, with a significant concentration–response trend. The association was stable after adjustment for potential confounders. Introducing $PM_{2.5}$ concentration into the regression model had little effect on PA effect estimates. Compared with the inactive group, participants with low, moderate and high PA levels had 0.36% [95% confidence interval (CI): 0.31%, 0.41%], 0.70% (95%CI: 0.65%, 0.76%) and 1.16% (95%CI:

1.11%, 1.22%) lower WBC counts, respectively. (Table 2)

$PM_{2.5}$ was positively associated with WBC counts. The results were robust after adjusting for potential confounders and PA level. In the fully adjusted model, participants with 2-year average $PM_{2.5}$ exposure levels in the highest quartile had 0.64% (95% CI: 0.57%, 0.71%) higher WBC counts compared with those in the lowest quartile. A significant concentration–response trend was also observed, despite the very small but significantly lower WBC counts in the second compared to the first quartile. When $PM_{2.5}$ was treated as continuous variable, each $5 \mu g/m^3$ increment in 2-year average $PM_{2.5}$ was associated with 0.19% (95% CI:

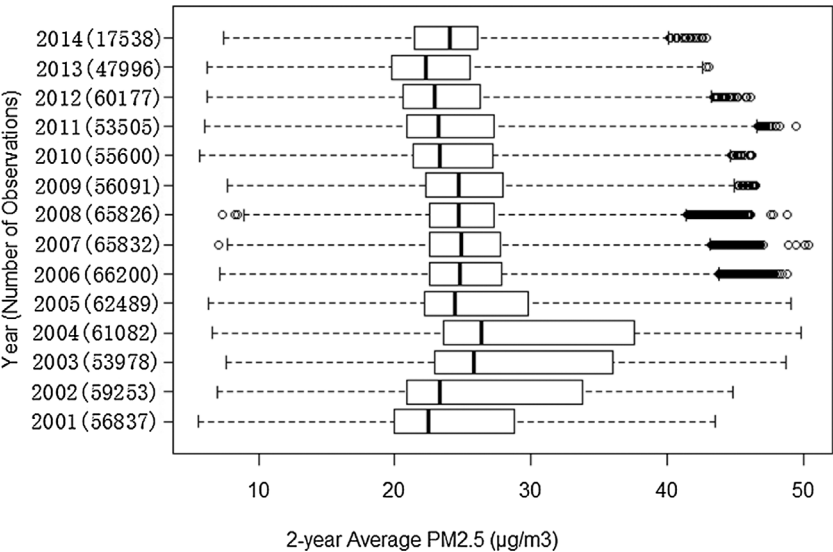


Fig. 2. Distribution of 2-year average $PM_{2.5}$ concentrations over all observations of Taiwanese adults by year. 2-year refers to the year of visit and the year before the visit. Boxes cover the 25–75th percentile (IQR) with a center line for the median concentration. Whiskers extend to the highest observation within 3 IQR of the box, with more extreme observations shown as circles. Abbreviation: $PM_{2.5}$, particulate matter with an aerodynamic diameter less than $2.5 \mu m$.

Table 2
Associations of white blood cell counts with physical activity and PM_{2.5} exposure in Taiwanese adults

N = 782,404	Crude Model ^a		Adjusted Model 1 ^a		Adjusted Model 2 ^a		PM _{2.5} and PA Together ^b	
	% Difference	P	% Difference	P	% Difference	P	% Difference	P
Physical Activity								
Inactive	Ref	–	Ref	–	Ref	–	Ref	–
Low	–0.45 (–0.50, –0.40)	< 0.001	–0.40 (–0.45, –0.35)	< 0.001	–0.36 (–0.41, –0.31)	< 0.001	–0.36 (–0.41, –0.31)	< 0.001
Moderate	–1.00 (–1.06, –0.95)	< 0.001	–0.77 (–0.82, –0.72)	< 0.001	–0.70 (–0.75, –0.65)	< 0.001	–0.70 (–0.76, –0.65)	< 0.001
High	–1.56 (–1.62, –1.50)	< 0.001	–1.31 (–1.37, –1.25)	< 0.001	–1.17 (–1.22, –1.11)	< 0.001	–1.16 (–1.22, –1.11)	< 0.001
Trend Test	–	< 0.001	–	< 0.001	–	< 0.001	–	< 0.001
PM _{2.5}								
1 st Quartile	Ref	–	Ref	–	Ref	–	Ref	–
2nd Quartile	–0.13 (–0.18, –0.07)	< 0.001	–0.18 (–0.24, –0.13)	< 0.001	–0.15 (–0.20, –0.10)	< 0.001	–0.16 (–0.22, –0.11)	< 0.001
3rd Quartile	0.13 (0.07, 0.19)	< 0.001	–0.01 (–0.07, 0.05)	0.08	0.04 (–0.02, 0.10)	0.23	0.01 (–0.05, 0.07)	0.69
4th Quartile	0.82 (0.75, 0.90)	< 0.001	0.62 (0.55, 0.69)	< 0.001	0.66 (0.59, 0.73)	< 0.001	0.64 (0.57, 0.71)	< 0.001
Trend Test	–	< 0.001	–	< 0.001	–	< 0.001	–	< 0.001
5 µg/m ³ increment	0.25 (0.23, 0.27)	< 0.001	0.18 (0.16, 0.20)	< 0.001	0.20 (0.18, 0.21)	< 0.001	0.19 (0.17, 0.21)	< 0.001

^aCrude model: no adjustment; Adjusted model 1: adjusted for age, sex, educational level, smoking, drinking, occupational exposure to dust & organic solvent and season; Adjusted model 2: further adjusted for body mass index, hypertension, diabetes, hyperlipidemia, self-reported cardiovascular disease and self-reported cancer.

^bPM_{2.5} and PA were introduced into fully adjusted models together to adjust for each other.

Results are presented as percentage differences in WBC counts.

Abbreviation: PM_{2.5}, particulate matter with an aerodynamic diameter less than 2.5 µm; PA, physical activity.

0.17%, 0.21%) increase in WBC counts. (Table 2)

In subgroup analyses stratified by PM_{2.5} quartile, the negative concentration-response trend for PA level and WBC counts was generally observed in all four PM_{2.5} quartiles. (Table 3) On the other hand, PM_{2.5} exposure was associated with increased WBC counts at all PA levels. (Table 4) Every 5 µg/m³ increment in PM_{2.5} exposure was associated with 0.22%, 0.18%, 0.16%, and 0.23% increased WBC counts in the inactive, low, moderate and high PA groups, respectively. (Table 4)

Compared with the participants with inactive PA level and PM_{2.5} in the highest quartile, participants in all other groups had lower WBC counts. Generally, the participants with a higher level of PA and a lower level of PM_{2.5} had a lower level of WBC. (Fig. 3; Supplementary Table 1)

Analyses on differential counts yielded similar results. (Supplementary Tables 2–4 and Supplementary Fig. 2 are for neutrophil; Supplementary Tables 5–7 and Supplementary Fig. 3 are for lymphocyte; Supplementary Tables 8–10 and Supplementary Fig. 4 are for monocyte)

The 90th percentile cutoff point for PM_{2.5} exposure was 39.8 µg/m³ in the present study. Among the participants with an exposure of greater than 39.8 µg/m³ (upper 10 percentile), participants with low, moderate and high PA levels had 0.54% (95% CI: 0.38%, 0.69%), 1.06% (95%CI: 0.89%, 1.23%) and 1.11% (95%CI: 0.91%, 1.31%) lower WBC counts (all *p* values < 0.001) when compared with the inactive participants, respectively. Interaction was tested but no significant modification effect was observed (*P* = 0.59).

Table 3
Associations between physical activity and white blood cell counts in Taiwanese adults exposed to different PM_{2.5} levels.

PA Levels (N = 782,404)	1 st Quartile (< 21.7 µg/m ³)		2nd Quartile (21.7–24.0 µg/m ³)		3rd Quartile (24.0–28.1 µg/m ³)		4th Quartile (≥ 28.1 µg/m ³)	
	% Difference	P	% Difference	P	% Difference	P	% Difference	P
Inactive	Ref	–	Ref	–	Ref	–	Ref	–
Low	–0.29 (–0.39, –0.19)	< 0.001	–0.34 (–0.44, –0.23)	< 0.001	–0.39 (–0.49, –0.29)	< 0.001	–0.45 (–0.55, –0.36)	< 0.001
Moderate	–0.73 (–0.84, –0.62)	< 0.001	–0.76 (–0.87, –0.65)	< 0.001	–0.79 (–0.89, –0.68)	< 0.001	–0.75 (–0.86, –0.65)	< 0.001
High	–1.27 (–1.38, –1.15)	< 0.001	–1.41 (–1.54, –1.29)	< 0.001	–1.24 (–1.37, –1.11)	< 0.001	–1.06 (–1.18, –0.94)	< 0.001
Trend Test	–	< 0.001	–	< 0.001	–	< 0.001	–	< 0.001

Results are presented as percentage differences in WBC counts.

Results were fully adjusted for age, sex, educational level, smoking, drinking, occupational exposure to dust & organic solvent, season, body mass index, hypertension, diabetes, hyperlipidemia, self-reported cardiovascular disease and self-reported cancer.

Abbreviation: PM_{2.5}, particulate matter with an aerodynamic diameter less than 2.5 µm; PA, physical activity.

The results of sensitivity analyses for WBC count are presented in Supplementary Table 11 and Supplementary Table 12. Additional adjustment for year of medical examination or replacing 2-year average PM_{2.5} with the 1-year average did not change the results materially, especially for PA. The effects of PM_{2.5} was reduced but remained significant after adding year of examination. The results were also robust to the exclusion of participants with single measurement, or who used a company address.

For PA, baseline cross-sectional analysis generated results similar to those from the analysis of all observations. (Supplementary Table 13) PM_{2.5} was still associated with increased WBC in the fourth quartile and in the linear analysis, but with reduced effect estimates. WBC counts were significantly lower in the second and third quartile compared to the first quartile.

4. Discussion

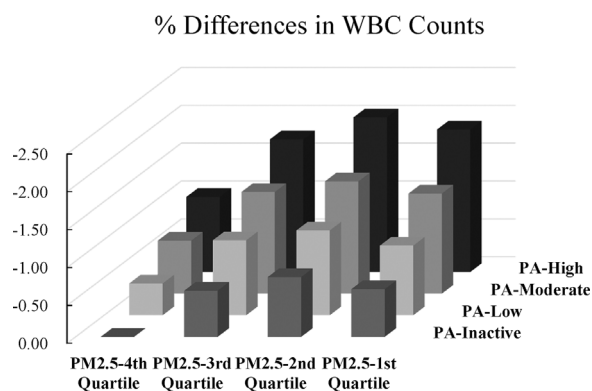
In this large prospective cohort study, we found significant health benefits of habitual PA on systemic inflammation, indicated by total and differential WBC counts, at different levels of PM_{2.5} air pollution. The WBC counts of the participants with low, moderate or high PA levels are respectively 0.36% (95% CI: 0.31%, 0.41%), 0.70% (95%CI: 0.65%, 0.76%) and 1.16% (95%CI: 1.11%, 1.22%) lower than those of the inactive participants after taking PM_{2.5} exposure into account. On the other hand, long-term exposure to PM_{2.5} is associated with increased WBC and differential counts in participants at all PA levels. No significant effect modification was observed. Our results suggest that

Table 4Associations between PM_{2.5} and white blood cell counts in Taiwanese adults with different physical activity levels.

PM _{2.5} Levels (N = 782,404)	Inactive		Low		Moderate		High	
	% Difference	P	% Difference	P	% Difference	P	% Difference	P
1st Quartile	Ref	–	Ref	–	Ref	–	Ref	–
2nd Quartile	–0.18 (–0.26, –0.10)	< 0.001	–0.20 (–0.32, –0.07)	0.002	–0.19 (–0.32, –0.06)	0.003	–0.19 (–0.33, –0.05)	0.009
3rd Quartile	0.06 (–0.03, 0.15)	0.17	–0.09 (–0.23, 0.04)	0.18	–0.09 (–0.23, 0.05)	0.21	0.00 (–0.15, 0.16)	0.98
4th Quartile	0.76 (0.66, 0.85)	< 0.001	0.57 (0.43, 0.71)	< 0.001	0.53 (0.38, 0.68)	< 0.001	0.74 (0.57, 0.91)	< 0.001
Trend Test	–	< 0.001	–	< 0.001	–	< 0.001	–	< 0.001
5 µg/m ³ increment	0.22 (0.20, 0.25)	< 0.001	0.18 (0.15, 0.22)	< 0.001	0.16 (0.12, 0.20)	< 0.001	0.23 (0.19, 0.27)	< 0.001

Results are presented as percentage differences in WBC counts.

Results were fully adjusted for age, sex, educational level, smoking, drinking, occupational exposure to dust & organic solvent, season, body mass index, hypertension, diabetes, hyperlipidemia, self-reported cardiovascular disease and self-reported cancer.

Abbreviation: PM_{2.5}, particulate matter with an aerodynamic diameter less than 2.5 µm; PA, physical activity.**Fig. 3.** Comparison on white blood cell counts of Taiwanese adults with different levels of physical activity and PM_{2.5} exposure.Participants with inactive PA level and PM_{2.5} in the highest quartile served as reference group. Results are presented as percentage differences in WBC counts.

Results were fully adjusted for age, sex, educational level, smoking, drinking, occupational exposure to dust & organic solvent, season, body mass index, hypertension, diabetes, hyperlipidemia, self-reported cardiovascular disease and self-reported cancer.

Abbreviation: PM_{2.5}, particulate matter with an aerodynamic diameter less than 2.5 µm.the beneficial effects of PA and detrimental effects of PM_{2.5} air pollution on systemic inflammation are independent from each other.

The negative association between PA and inflammation is well documented (Geffken et al., 2001; Ford, 2002; Pitsavos et al., 2005) and we also observed that PA decreased the total/differential WBC counts with significant concentration-response trends in the present study. PM-induced inflammation has been hypothesized as one of the biological mechanisms linking air pollution and various chronic diseases (Brook et al., 2010; Pope and Dockery, 2006). We found positive associations between long-term exposure to PM air pollution and total/differential WBC counts in the present study, which supports this hypothesis. We also found that long-term exposure to PM_{2.5} may increase C-reactive protein level, another marker of systemic inflammation, in our previous study (Zhang et al., 2017).

Our results about the joint relationships among PA, PM and total/differential WBC counts are novel. To our knowledge, this is the first large cohort study to investigate the joint effects of long-term PM_{2.5} exposure and PA on systemic inflammation, the underlying pathogenesis of atherosclerosis. We found that higher levels of PA has greater beneficial effects in different PM_{2.5} levels. We speculate that PA may lead to increases in inhaled amount of air pollutants due to the increased ventilation during exercise, but this additional amount may be just a small fraction of the total inhaled dose of air pollutants (Rojas-Rueda et al., 2011). Another hypothesis is that the adverse effects induced by short-term exposure during exercise are “transient and reversible and do not abate long-term benefits of habitual PA” (Andersen et al., 2015). Further studies are warranted to clarify the underlying

mechanism.

Our findings are in line with a Danish study which reported no consistent interactions between associations of habitual PA and 1-year average NO₂ exposure on mortality (Andersen et al., 2015), or incident asthma and COPD (Fisher et al., 2016), although the pollutants and health outcomes are different. However, Denmark has relatively low levels of air pollution, whereas our participants were exposed to higher levels of air pollution (the 2-year average PM_{2.5} concentration was 26.5 µg/m³, higher by a factor of 2.65 than the WHO air quality guideline value of 10 µg/m³ for annual mean PM_{2.5}). A cross-over study in Spain also suggested that PA does not modify the acute effects of air pollution on inflammatory response (Kubesch et al., 2015b). However, our study is not directly comparable with that study, in which only a single bout of exercise (cycling) and short-term air pollution exposure were assessed. Inflammatory responses to acute and regular/chronic exercise are different, as acute exercise generally leads to activated inflammation, whereas regular/chronic exercise can lead to low-grade inflammation because of the adaptive effects of skeletal muscle (Nimmo et al., 2013). In addition, long-term exposure to air pollution generally leads to a greater health risk than acute or short-term exposure because of cumulative effect. Evidence is scarce for the relationship between detrimental effects of long-term air pollution and the beneficial effects of regular exercise. There is an urgent need for further studies to be conducted in different regions with different levels of air pollution using different health outcomes.

The present study has several important strengths. It used a longitudinal cohort design and included information on changes in a wide range of potential confounders including socioeconomic status, lifestyle factors and metabolic risk factors. The total and differential WBC counts were retrieved from standardized CBC results. The large sample size enabled us to obtain stable and precise estimates. In addition, we used a MET-based method to evaluate PA level, which took into consideration both the intensity and duration. This method was previously used in this cohort and protective effects of PA on mortality were reported (Wen et al., 2011). Another advantage is that we used a spatio-temporal model to obtain individual exposures by estimating address-specific PM_{2.5} at a fine scale (1 × 1 km). The spatial pattern of PM_{2.5} distribution was generally stable in Taiwan over the study period, therefore the 2-year average PM_{2.5} is a good indicator of long-term exposure. The large contrast in PM_{2.5} exposure makes it possible to investigate the health effects of PM_{2.5} across a wide range of concentrations.

Our study has some limitations. First, we excluded 159,733 out of 959,280 observations due to the missing information. However, the exclusion should not affect our results. There are no evidence showing that participants with missing information had different pollution exposure and habitual physical activities. Furthermore, the excluded observations were comparable to all observations in age, sex and WBC count, suggesting the excluded observations were randomly distributed. Second, as we did not know whether the reported PA took place

outdoors or indoors, we cannot evaluate outdoor PA exclusively. However, outdoor PA is a traditional practice in Taiwan. Only a small proportion (7.3%) of residents reported indoor activities as their most frequent PA in a nationwide survey (Department of Physical Education, 2015). Thus, the calculated weekly MET-hour is likely a good proxy for outdoor PA. Third, as we used self-reported PA collected by questionnaire, our results are subject to participants' recall bias. However, the recall questionnaire is considered reliable in providing a quantification of the most apparent characteristics of PA patterns in large epidemiological studies (Ainsworth et al., 2000b). Another limitation is that we only evaluated the effects of particles because of the lack of information on gaseous air pollutants, such as NO₂.

5. Conclusions

In conclusion, we found that habitual PA was associated with lower markers of systemic inflammation across different levels of air pollution. Our results suggest habitual PA and long-term PM_{2.5} exposure are independently associated with systemic inflammation, supporting the adoption of strategies to improve health through PA promotion and air pollution mitigation.

Conflict of interests

The authors declare that they have no conflicting interests related to this manuscript.

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