Chronic fine particulate matter exposure, habitual exercise, and dyslipidemia: A longitudinal cohort study

Yi Qian Zeng\textsuperscript{a}, Ly-yun Chang\textsuperscript{b}, Cui Guo\textsuperscript{c}, Changqing Lin\textsuperscript{d}, Yacong Bo\textsuperscript{a,d}, Martin C. S. Wong\textsuperscript{a}, Tony Tam\textsuperscript{a}, Alexis K. H. Lau\textsuperscript{e}, Xiang Qian Lao\textsuperscript{a,g}*

\textsuperscript{a}Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China; \textsuperscript{b}Institute of Sociology, Academia Sinica, Taipei, Taiwan; \textsuperscript{c}Division of Environment and Sustainability, The Hong Kong University of Science and Technology, Hong Kong, SAR, China; \textsuperscript{d}Shenzhen Research Institute of the Chinese University of Hong Kong, Shenzhen, Guangdong, China.

\textsuperscript{e}Department of Nutrition and Food Hygiene, School of Public Health, Zhengzhou University, Zhengzhou, Henan, China; \textsuperscript{f}Department of Sociology, The Chinese University of Hong Kong, Hong Kong SAR, China; \textsuperscript{g}Department of Civil and Environmental Engineering, The Hong Kong University of Science and Technology, Hong Kong SAR, China; and \textsuperscript{h}Shenzhen Research Institute of the Chinese University of Hong Kong, Shenzhen, Guangdong, China.

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Introduction

Cardiovascular disease contributed to 17.8 million deaths globally and was the leading cause of death in 2017.\textsuperscript{1} Cardiovascular-related deaths have increased by 21.1\% over the last 10 years.\textsuperscript{1} Dyslipidemia, which refers to abnormal levels of blood lipids, is regarded as one of the crucial risk factors that can be modified to prevent cardiovascular disease, especially atherosclerotic cardiovascular disease.\textsuperscript{2}

At least 30 minutes of exercise per day is recommended to improve the lipid abnormalities of dyslipidaemic patients.\textsuperscript{3} Previous studies have also shown that habitual exercise is associated with a better lipid profile in the general population.\textsuperscript{4,5} Habitual exercise is, therefore, important to improve lipid profiles and prevent cardiovascular disease. However, approximately 1 in 4 adults worldwide do not meet the World Health Organization (WHO) recommendations for physical activity.\textsuperscript{6} The WHO has proposed a global action plan to reduce the prevalence of insufficient physical activity by 15\% by 2030.\textsuperscript{6}

What this study adds

- This is the first large-scale cohort study investigating the combined effects of habitual exercise and chronic exposure to fine particulate matter (PM\textsubscript{2.5}) on dyslipidemia.
- Increased levels of exercise and reduced exposure to PM\textsubscript{2.5} are associated with a lower incidence of dyslipidemia.
- Although the association between habitual exercise and dyslipidemia is slightly attenuated by PM\textsubscript{2.5} exposure, the negative associations between dyslipidemia and habitual exercise remains, regardless of the level of PM\textsubscript{2.5} exposure.
- Habitual exercise is beneficial for dyslipidemia prevention, even for people residing in polluted areas.
However, air pollution may discourage people from exercising because the higher ventilation rate during exercise may increase the inhalation and deposition of air pollutants. An increasing number of studies have shown that exposure to air pollution is associated with a poor lipid profile and a higher incidence of dyslipidemia.\(^5,6\) More than 91% of the global population lives in areas where air pollution levels exceed the WHO guidelines.\(^10\) Exposure to air pollution seems unavoidable to most people in the world. Balancing the beneficial health effects of exercise with the potentially harmful effects of the excess inhalation of air pollutants during exercise has become an important public health concern.

There is a lack of evidence for the combined effects of exercise and air pollution on dyslipidemia. We only identified one cross-sectional study in rural Chinese adults that reported no significant interaction effects of exercise and air pollution on metabolic syndrome,\(^11\) which includes dyslipidemia as a component. It is necessary to understand whether habitual exercise is beneficial to the lipid profile of people with exposure to high levels of air pollution. Therefore, we conducted a longitudinal cohort study consisting of 121,948 adults with 407,821 medical examination records to investigate the combined effects of habitual exercise and chronic fine particulate matter (PM\(_{2.5}\)) exposure on the development of dyslipidemia in Taiwan, where the annual PM\(_{2.5}\) concentration is 2.6 times as high as the WHO guideline.\(^12\)

**Methods**

**Study design and population**

This study was based on an ongoing cohort in Taiwan. Details of this cohort have been described in our previous publications.\(^7,13–15\) In brief, since 1994, a private firm, the MJ Health Management Institution, has recruited residents across Taiwan who have paid the membership fees to join the standard medical screening programme.\(^16\) Participants were encouraged to visit the institution periodically to receive a series of medical examinations, including anthropometric measurements, blood glucose/lipids measurements, and liver/kidney/lung functions tests during each medical visit. In addition, they were required to complete a standard self-administered questionnaire survey, consisting of questions about demographic information, family medical history, current health status, life style, and dietary habits. Information collected during each medical examination has been computerized since 1996 and has been deidentified for research use.\(^17\) From 1996 to 2016, approximately 600,000 Taiwan residents were recruited in the programme and 44% of those recruited had at least two medical visits. Each participant signed an informed consent form before each medical visit authorizing MJ Health Management Institution to release the data for research purposes. Ethical approval for this study has been obtained from the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

**PM\(_{2.5}\) exposure assessment**

The relevant details about the assessment of ambient PM\(_{2.5}\) concentration have been described in previous studies.\(^20,21\) Briefly, an atmospheric optical depth (AOD)-PM\(_{2.5}\) model was developed to estimate ground-level PM\(_{2.5}\) concentration based on satellite data at a 1-km spatial resolution combined with ground-level measurements (i.e., meteorological and particulate matter data).\(^20,21\) The AOD data were derived from Terra and Aqua, the two moderate resolution imaging spectroradiometer (MODIS) instruments aboard the National Aeronautics and Space Administration Earth Observing System satellites.\(^20,21\) This method also accounted for the effects of aerosol characteristics (hygroscopic growth, particle mass extinction efficiency, and size distribution) on the AOD-PM\(_{2.5}\) relationship, which were generally not considered in previous observation-based methods.\(^20,21\) To validate our AOD-PM\(_{2.5}\) model, we obtained ground-based PM\(_{2.5}\) concentrations from more than 70 ground stations across Taiwan from 2005 to 2014 and compared them with the satellite-retrieved PM\(_{2.5}\) concentrations.\(^15\) The correlation coefficients for the two measurements ranged from 0.72 to 0.83.\(^15\)

The address of each participant was geocoded into latitudinal and longitudinal data, and the estimated PM\(_{2.5}\) concentrations were matched with individuals’ addresses to determine their exposure to ambient PM\(_{2.5}\). We calculated the 2-year average PM\(_{2.5}\) concentrations based on the yearly average of PM\(_{2.5}\) concentrations for the year of the medical examination and the previous year. This value was then used as the indicator of long-term exposure to ambient PM\(_{2.5}\) air pollution. Both continuous (per 10 \(\mu\)g/m\(^3\)) and categorical (participants were grouped into three categories based on the tertile cutoff points of PM\(_{2.5}\), i.e. low: \(<22.37\); moderate: 22.37–25.96; and high: \(\geq 25.96\) \(\mu\)g/m\(^3\)) PM\(_{2.5}\) concentration data were used for data analysis.

**Habitual exercise assessment**

Information on habitual leisure-time exercise was collected and assessed as described elsewhere.\(^13,14,22,23\) Briefly, information on habitual exercise was collected using a standard self-administered questionnaire, in which participants were asked about the intensity level and duration of weekly exercise they completed in the previous month. The intensity level of weekly exercise was
classified into the following four categories, with an example list of the types of exercise for each category, respectively: light (e.g., walking), moderate (e.g., brisk walking), medium-vigorous (e.g., jogging), and high-vigorous (e.g., rope skipping). Each level of exercise was assigned one of the following specific metabolic equivalent of task (MET; 1 MET = 1 kcal per hour per kilogram of bodyweight) values: 2.5 (light), 4.5 (moderate), 6.5 (medium-vigorous), and 8.5 (high-vigorous). If participants engaged in more than one intensity level of exercise, a weighted MET was assigned based on the time spent at each level. Therefore, the weekly exercise volume (MET-h) of each participant was calculated as the product of the intensity (MET) and duration (hours) of exercise. The participants were then classified into three physical activity groups for data analysis, based on the following rough tertile cutoff points of exercise-volume (MET-h): inactive (0 MET-h), moderate (0.01–8.75 MET-h), and high (> 8.75 MET-h). We did not use the continuous MET-h variable for data analysis because 0 MET-h was assigned to all participants in the inactive group.

**Outcome ascertainment**

Participants without dyslipidemia at baseline (n = 121,948) were followed up, and incident dyslipidemia was identified at subsequent follow-up visits for medical examinations. Incident dyslipidemia was defined as a TC concentration ≥ 240 mg/L, a TG concentration ≥ 200 mg/dL, an HDL-C concentration < 40 mg/dL, or an LDL-C concentration ≥ 160 mg/dL.2,18,19 Overnight fasting blood samples were drawn in the morning, and lipid profiles and fasting plasma glucose concentration were measured using an automated biochemical analyzer (HITACHI 7150 [Hitachi, Tokyo, Japan] before 2005 or TOSHIBA C8000 [Toshiba, Tokyo, Japan] since 2005). The end point was defined as the first occurrence of dyslipidemia or the final visit if dyslipidemia was not detected over the study period.

**Covariates**

The details of the data collection and quality-control measures have been described in the Technical Reports of the MJ Health Research Foundation and in previous studies. The weight and height of each participant were measured by trained staffs using an autoanthropometer (KN-5000A; Nakamura, Tokyo, Japan). Body mass index (BMI) was then calculated as the weight (kg) divided by the square of the height (m). Seated blood pressure including systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a computerized automercury sphygmomanometer (CH-5000; Citizen, Tokyo, Japan). In addition, the participants’ demographic characteristics, behavioral and lifestyle factors, and medical history were collected through a standard self-administered questionnaire. The following covariates were selected based on previous studies: age (years); sex (male or female); education status (lower than high school [<10 years], high school [10–12 years], college or university [13–16 years], or postgraduate [>16 years]); smoking status (never, ever [smoked at least once but quit later] or current [more than once a week]); alcohol consumption (seldom [<once/week], occasional [1–3 times/week], or regular [>3 times/week]); vegetable intake (seldom [<1 serving/day], moderate [1–2 servings/day], or frequent [>2 servings/
day); fruit intake (seldom [<1 serving/day], moderate [1–2 servings/day], or frequent [≥ 2 servings/day]); occupational exposure to dust or solvents in the workplace (yes or no); physical labor at work (sedentary jobs [e.g., clerk], jobs that require approximately half sedentary and half standing/walking [e.g., nurse], jobs that mostly require walking and standing [e.g., retail salesperson], or jobs that require vigorous physical activity [e.g., porter]); BMI (kg/m²); diabetes (defined as fasting blood glucose concentration ≥ 126 mg/dL or self-reported physician-diagnosed diabetes); hypertension (defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or self-reported physician-diagnosed hypertension); self-reported cardiovascular disease, including stroke (yes or no); any self-reported form of cancer (yes or no); and the season (spring [March to May], summer [June to August], autumn [September to November], or winter [December to February]) and calendar year of baseline visit.

**Data analysis**

A time-varying Cox regression model with a random participant-level intercept was used to investigate the associations between exercise or PM$_{2.5}$ concentration and incident dyslipidemia. A city-level random intercept was added to the model to adjust for the correlation between individuals living within the same city. The follow-up time was used as the time scale in the model. The model of habitual exercise, PM$_{2.5}$ concentration, and all the covariates (except for sex and baseline year) were treated as time-varying variables in the analysis, to account for changes in the variables during the study period. Three models with the gradual addition of the aforementioned covariates were developed to investigate the main effects of exercise or PM$_{2.5}$ exposure level. The Crude Model had no adjustments for covariates. Model 1 was adjusted for age, sex, educational level, season, baseline year, smoking status, alcohol consumption, vegetable intake, fruit intake, occupational exposure, and physical labor at work. Model 2 was further adjusted for BMI, diabetes, hypertension, self-reported cardiovascular disease, and self-reported cancer. A trend test was performed across exercise and PM$_{2.5}$ concentration categories, with the corresponding category treated as a non-integer variable (an ordinal variable code of 1–3). HRs with 95% CIs for exercise with the inactive-exercise group as the reference. HRs with 95% CIs for PM$_{2.5}$ were estimated for every 10 μg/m$^3$ increase in PM$_{2.5}$ concentration or with the low-PM$_{2.5}$ exposure group as the reference.

Mutual adjustments for exercise and PM$_{2.5}$ concentration were performed for comparison (i.e., we further included PM$_{2.5}$ concentration in the model to assess the main effect of exercise, or exercise in the model to assess the main effect of PM$_{2.5}$ concentration). The interaction term, “exercise (inactive, moderate, and high) × continuous PM$_{2.5}$ concentration (every 10 μg/m$^3$)” was added to Model 2 to examine the potential interaction effects of exercise and PM$_{2.5}$ concentration. We also used a likelihood ratio test to explore the potential interaction effect for comparison.

In addition, subgroup analyses were performed through the stratification of PM$_{2.5}$ concentration or exercise categories, separately. Finally, to examine the combined effects of exercise and PM$_{2.5}$ exposure, the participants were classified into nine groups based on their exercise and PM$_{2.5}$ concentration categories, and those who were inactive and had a high level of PM$_{2.5}$ exposure served as the reference group.

A series of sensitivity analyses were performed. First, we excluded participants with baseline diabetes, hypertension, obesity (defined as BMI ≥ 30), cardiovascular diseases, or cancer and those using lipid-lowering, antidiabetic or antihypertensive drugs to eliminate potential comorbidity effects. Second, we used the annual average PM$_{2.5}$ concentration from the year before the medical visit to examine the stability of the PM$_{2.5}$ exposure effects. Third, we excluded participants who enrolled before 2005, whose lipid profiles were measured using the HITACHI 7150 analyzer, to eliminate potential measurement bias due to the use of different equipment. Fourth, we excluded the participants who were followed-up for less than 2 years in the analysis, as dyslipidemia is a chronic disease. Fifth, we grouped the participants into four categories using the following exercise cutoff values: inactive (≤ 3.75 MET-h), low (3.75–7.49 MET-h), moderate (7.49–16.49 MET-h), and high (> 16.49 MET-h) based on the Physical Activity Guidelines for Americans, to determine whether using different cutoff points would result in different findings from the main findings. Sixth, we further examined the interaction of habitual exercise and PM$_{2.5}$ exposure in different types of dyslipidemia (hypercholesterolemia, defined as a TC concentration ≥ 240 mg/dL; hypertriglyceridemia, defined as a TG concentration ≥ 200 mg/dL; hypoaipophiliaiproteinemia, defined as an HDL-C concentration < 40 mg/dL; and hyperbetalipoproteinemia, defined as an LDL-C concentration ≥ 160 mg/dL). Seventh, we compared the results of the association between PM$_{2.5}$ exposure and incident dyslipidemia using model 2 with the results obtained using the same model, but with the city-level random intercept excluded.

Statistical analyses were performed using R 3.2.5 (R Core Team, Vienna, Austria). A two-tailed P < 0.05 was used to define statistical significance.

**Results**

In total, 121,948 participants with 407,821 medical records were included in the data analysis. The mean follow-up duration was 4.6 years with a standard deviation of 3.4 years. During the study period, 26,669 participants developed dyslipidemia, leading to an incidence rate of 4.7 per 100 person-years. The baseline characteristics of all participants and the 26,669 participants who developed dyslipidemia during the study period are shown in Table 1. The mean age of the participants at baseline was 37.8 years, and 43.4% of them were male. Most of the participants were well educated, nonsmokers, and light drinkers. More than half of the participants had a sedentary job and approximately 45% of them were physically inactive. The PM$_{2.5}$ concentrations were similar across different exercise groups. The temporal distribution of PM$_{2.5}$ concentration by year is presented in Figure 2. PM$_{2.5}$ concentration peaked in 2004 and then declined gradually.

Table 2 shows the main effects of habitual exercise and PM$_{2.5}$ on incident dyslipidemia. A higher level of habitual exercise was associated with a lower incidence of dyslipidemia, with fully adjusted HRs (95% CI) of 0.91 (0.88, 0.94) and 0.73 (0.71, 0.75) for moderate and high levels of exercise, respectively (Model 2). In contrast, a higher level of PM$_{2.5}$ exposure was associated with a higher incidence of dyslipidemia, with fully adjusted HRs (95% CI) of 1.36 (1.32, 1.40) and 1.90 (1.81, 1.99) for moderate and high levels of PM$_{2.5}$ exposure, respectively (model 2). Mutual adjustment for PM$_{2.5}$ concentration or exercise did not affect the associations. We also found significant exposure-response associations for the categories of exercise and PM$_{2.5}$ exposure level. The interaction between habitual exercise and ambient PM$_{2.5}$ concentration was statistically significant, with HRs (95% CI) of 1.09 (1.05, 1.14) and 1.16 (1.11, 1.21) for interactions of PM$_{2.5}$ concentration with moderate- and high-level of exercise, respectively (results not shown). The HR (95% CI) for the overall interaction test was 1.08 (1.05, 1.10), and the likelihood ratio test also showed that the interaction effect was significant (P < 0.001; results not shown).

Subgroup analyses revealed that a higher level of habitual exercise was significantly associated with a lower incidence of dyslipidemia in all PM$_{2.5}$ categories, although the associations were slightly attenuated for higher concentrations of PM$_{2.5}$. Positive associations between PM$_{2.5}$ exposure and incident
dyslipidemia were observed for each exercise level, with stronger associations seen for higher levels of exercise (Table 3). Figure 3 shows the combined effects of exercise and PM$_{2.5}$ concentration on incident dyslipidemia. Participants with a high level of exercise and a low level of PM$_{2.5}$ exposure had the lowest incidence of dyslipidemia, whereas physically inactive participants with a high level of exposure to PM$_{2.5}$ had the highest incidence of dyslipidemia. The trend patterns of associations of dyslipidemia with PM$_{2.5}$ and exercise were prominent in each PM$_{2.5}$ concentration and exercise stratum. The corresponding estimated HRs are shown in eTable 2; http://links.lww.com/EE/A172.

The results of sensitivity analyses showed that the associations remained robust after excluding participants with baseline chronic conditions (eTable 3; http://links.lww.com/EE/A172), using the average annual PM$_{2.5}$ concentration of the year before

### Table 1: Baseline characteristics of the participants

| Characteristic                        | All participants at baseline* | Dyslipidemia case* |
|---------------------------------------|-------------------------------|--------------------|
|                                       | (n = 121,948)                | (n = 26,669)       |
| Age (year)                            | 37.8 (11.7)                  | 40.6 (11.8)        |
| Male (n, %)                           | 52,967 (43.4)                | 11,095 (41.6)      |
| Educational level (n, %)              |                               |                    |
| Lower than high school                | 14,161 (11.6)                | 4,170 (15.6)       |
| High school                           | 23,760 (19.5)                | 5,402 (20.3)       |
| College or university                 | 68,754 (56.4)                | 13,993 (52.5)      |
| Postgraduate                          | 15,273 (12.5)                | 3,104 (11.6)       |
| Smoking status (n, %)                 |                               |                    |
| Never                                 | 96,474 (79.1)                | 19,101 (71.6)      |
| Former                                | 5,934 (4.9)                  | 1,613 (6.1)        |
| Current                               | 19,540 (16.0)                | 5,955 (22.3)       |
| Alcohol consumption (n, %)            |                               |                    |
| Seldom                                | 106,825 (87.6)               | 22,326 (83.7)      |
| Occasional                            | 10,390 (8.5)                 | 2,915 (10.9)       |
| Regular                               | 4,733 (3.9)                  | 1,428 (5.4)        |
| Physical labor at work (n, %)         |                               |                    |
| Sedentary job                         | 79,247 (65.0)                | 16,598 (62.2)      |
| Job that requires approximately half sedentary and half standing/walking | 31,392 (25.7) | 7,290 (27.3) |
| Job that mostly requires walking and standing | 9,355 (7.1) | 2,241 (8.4) |
| Job that requires vigorous physical activity | 1,954 (1.6) | 540 (2.0) |
| Habitual exercise (n, %)              |                               |                    |
| Inactive (0 MET-h)                    | 55,299 (45.4)                | 11,581 (43.4)      |
| Moderate (0.01—8.75 MET-h)           | 36,867 (30.2)                | 8,051 (30.2)       |
| High (>8.75 MET-h)                   | 29,782 (24.4)                | 7,037 (26.4)       |
| Vegetable intake (n, %)               |                               |                    |
| Seldom                                | 16,216 (13.3)                | 3,548 (13.3)       |
| Moderate                              | 72,744 (60.3)                | 16,079 (60.3)      |
| Frequent                              | 32,988 (27.1)                | 7,042 (26.4)       |
| Fruit intake (n, %)                   |                               |                    |
| Seldom                                | 39,508 (32.4)                | 8,302 (31.1)       |
| Moderate                              | 67,081 (55.0)                | 14,951 (56.1)      |
| Frequent                              | 15,359 (12.6)                | 3,416 (12.8)       |
| Occupational exposure$^{c}$ (n, %)    | 9,791 (8.0)                  | 2,424 (9.1)        |
| BMI (kg/m$^2$)                        | 22.3 (3.4)                   | 23.5 (3.3)         |
| Total cholesterol concentration (mg/dL) | 182.6 (26.6) | 196.3 (26.4) |
| Triglyceride concentration (mg/dL)    | 86.2 (37.3)                  | 109.5 (40.7)       |
| High-density lipoprotein cholesterol concentration (mg/dL) | 59.8 (13.6) | 54.9 (13.1) |
| Low-density lipoprotein cholesterol concentration (mg/dL) | 105.8 (24.6) | 119.7 (23.4) |
| Diabetes (n, %)                       | 2,819 (2.3)                  | 942 (3.5)          |
| Hypertension (n, %)                   | 12,990 (10.7)                | 4,116 (15.4)       |
| Cardiovascular disease (n, %)         | 2,688 (2.2)                  | 704 (2.6)          |
| Cancer (n, %)                         | 1,235 (1.0)                  | 331 (1.2)          |
| PM$_{2.5}$ concentration (μg/m$^3$)   | 26.7 (7.7)                   | 26.7 (7.8)         |
| PM$_{2.5}$ by exercise category (μg/m$^3$) |                     |                    |
| Inactive (0 MET-h)                    | 26.8 (7.8)                   | 26.8 (7.8)         |
| Moderate (0.01—8.75 MET-h)           | 26.7 (7.7)                   | 26.8 (7.8)         |
| High (>8.75 MET-h)                   | 26.6 (7.7)                   | 26.6 (7.8)         |
| Season (n, %)                         |                               |                    |
| Spring                                | 30,380 (24.9)                | 6,704 (25.1)       |
| Summer                                | 34,017 (27.9)                | 7,326 (27.5)       |
| Autumn                                | 32,602 (26.7)                | 7,134 (26.8)       |
| Winter                                | 24,949 (20.5)                | 5,505 (20.6)       |

Values are presented as mean (standard deviation) for continuous variables and count (%) for categorical variables.

*$^a$Baseline characteristics of the 121,948 participants without dyslipidemia at baseline.

*$^b$Baseline characteristics of the 26,669 participants who developed dyslipidemia during the study period.

*$^c$Classified as exposure to dust or organic solvents in the workplace, as established by asking, 'Are there any occupational hazards in your workplace?'

*Refers to the average PM$_{2.5}$ concentration levels of the year of the visit and the year before the visit.

BMI, body mass index; MET, metabolic equivalent of task.
the medical examinations (eTable 4; http://links.lww.com/EE/A172); excluding participants who enrolled before 2005 (eTable 5; http://links.lww.com/EE/A172); excluding participants who were followed up for less than 2 years (eTable 6; http://links.lww.com/EE/A172); and using the exercise categories listed in the Physical Activity Guidelines for Americans (eTable 7; http://links.lww.com/EE/A172). The associations between habitual exercise and PM$_{2.5}$ concentration were also robust among the four types of dyslipidemias (see eTable 8; http://links.lww.com/EE/A172). The association between PM$_{2.5}$ exposure and incident dyslipidemia was slightly stronger after including a city-level random intercept in the model (eTable 9; http://links.lww.com/EE/A172).

Discussion

We found that a higher level of habitual exercise was associated with a lower incidence of dyslipidemia at all levels of PM$_{2.5}$ exposure, although the negative associations with habitual exercise were slightly attenuated at higher levels of PM$_{2.5}$ exposure. However, a higher level of PM$_{2.5}$ exposure was associated with a higher incidence of dyslipidemia at different levels of habitual exercise. This association was slightly stronger when participants engaged in a higher level of exercise. We detected a statistically significant, but minor, interaction effect of PM$_{2.5}$ exposure and exercise on the development of dyslipidemia, with an overall HR (95% CI) of 1.08 (1.05, 1.10), which indicates that an incremental level of exercise was associated with an 8% increase in the risk of dyslipidemia associated with every 10 μg/m$^3$ increase in PM$_{2.5}$ exposure.

Our findings of the inverse association between dyslipidemia and exercise confirm those of previous studies.$^{4,28,29}$ A positive association between PM$_{2.5}$ exposure and the incidence of dyslipidemia has also been reported in previous studies.$^{7,8,30}$ However, information on the combined effects of habitual exercise and chronic exposure to air pollution on dyslipidemia is scarce. Previous cohort studies that have investigated the combined effects of exercise and air pollutants have mainly focused on lung function, cardiovascular disease, diabetes, and mortality.$^{31-36}$ Most of these studies found no statistically significant interaction between exercise and air pollution,$^{31-34}$ but some found evidence of a reduction in the beneficial effects of exercise on specific outcomes in relatively highly polluted areas.$^{32,34-36}$ A study of the Danish Diet, Cancer, and Health Cohort found that the inverse association between exercise and respiratory mortality was more pronounced in people with low levels of NO$_2$.$^{32}$ Similar findings have been reported in a cohort study of children, showing that the development of asthma is only associated with exercise in children living in areas with high ozone levels.$^{36}$ A study of including 66,820 Hong Kong elderly individuals reported that the cardiovascular benefits of walking are attenuated in people with exposure to a higher level of exposure to air pollution.$^{34}$ In a Korean cohort, the negative association between exercise and stroke was found to be stronger in people with exposed to a low or moderate concentration of PM$_{2.5}$.$^{35}$ Although statistically significant interaction results were observed in the aforementioned studies, the magnitudes of the interactions were generally small, which is consistent with our results (HR: 1.08, 95% CI = 1.05, 1.10). Inconsistencies in the statistically significant interactions in different studies may be due to the differences in the sample sizes and outcomes measured. The heterogeneity of study populations and regions may also contribute to the inconsistent findings. Similarly, our previous studies based on the same cohort revealed a statistically significant interaction of habitual exercise and PM$_{2.5}$ exposure on lung function but not on hypertension, diabetes, and
We have previously examined the association between long-term exposure to PM$_{2.5}$ and the development of dyslipidemia previously in the same cohort. The association between dyslipidemia and PM$_{2.5}$ in this study was slightly stronger than in the previous study. This phenomena may be because our previous study did not consider the correlation between individuals living within the same city. A previous study showed that a statistical model adjusting for the correlation between individuals living within the same city may affect the associations between air pollution and mortality. However, exercise in areas with lower PM$_{2.5}$ concentrations when possible. However, exercise in a polluted area has more health benefits than staying inactive. Our study reinforces the importance of air pollution mitigation to maximize the benefits of exercise.

Indeed, habitual exercise is known to have an antiinflammatory effect by increasing the production of anti-inflammatory cytokines (e.g., IL-10) and suppressing the production of the proinflammatory cytokines (e.g., TNF-α). In addition, exercise improves lipid profiles through the activation of the enzyme, lipoprotein lipase. Conversely, exposure to PM$_{2.5}$ has been shown to induce inflammation and lipid oxidation, which increases the risk of dyslipidemia. However, the mechanism responsible for these interaction effects on dyslipidemia remains unclear. We observed significant benefits for all the PM$_{2.5}$ exposure levels and high-exercise level/high-PM$_{2.5}$ concentration, respectively.

95% CI, 95% confidence interval; HR, hazard ratio.

### Table 2. Associations of incident dyslipidemia with habitual exercise and PM$_{2.5}$ exposure in Taiwanese adults

| Model | Without mutual adjustment | Mutual adjustment$^a$ |
|-------|---------------------------|-----------------------|
|       | HR (95% CI) | P | HR (95% CI) | P |
| **Main effects of exercise** | | | | |
| Crude model | | | | |
| Inactive (0 MET-h) | Reference | – | Reference | – |
| Moderate (0.01–8.75 MET-h) | 0.96 (0.93, 0.99) | 0.008 | 0.97 (0.94, 1.00) | 0.04 |
| High (> 8.75 MET-h) | 0.87 (0.85, 0.90) | <0.001 | 0.89 (0.86, 0.91) | <0.001 |
| Test for trend$^b$ | 0.93 (0.92, 0.95) | <0.001 | 0.94 (0.93, 0.96) | <0.001 |
| Model 1 | | | | |
| Inactive (0 MET-h) | Reference | – | Reference | – |
| Moderate (0.01–8.75 MET-h) | 0.87 (0.85, 0.90) | <0.001 | 0.89 (0.86, 0.91) | <0.001 |
| High (> 8.75 MET-h) | 0.71 (0.69, 0.74) | <0.001 | 0.72 (0.70, 0.74) | <0.001 |
| Test for trend$^b$ | 0.84 (0.83, 0.86) | <0.001 | 0.85 (0.83, 0.86) | <0.001 |
| Model 2 | | | | |
| Inactive (0 MET-h) | Reference | – | Reference | – |
| Moderate (0.01–8.75 MET-h) | 0.87 (0.85, 0.90) | <0.001 | 0.89 (0.86, 0.91) | <0.001 |
| High (> 8.75 MET-h) | 0.72 (0.70, 0.75) | <0.001 | 0.73 (0.71, 0.75) | <0.001 |
| Test for trend$^b$ | 0.85 (0.84, 0.87) | <0.001 | 0.86 (0.84, 0.87) | <0.001 |
| **Main effects of PM$_{2.5}$ exposure** | | | | |
| Crude Model | | | | |
| Low (< 22.37 μg/m$^3$) | Reference | – | Reference | – |
| Moderate (22.37–25.96 μg/m$^3$) | 1.22 (1.18, 1.26) | <0.001 | 1.22 (1.18, 1.25) | <0.001 |
| High (> 25.96 μg/m$^3$) | 1.52 (1.45, 1.58) | <0.001 | 1.50 (1.44, 1.57) | <0.001 |
| Test for trend$^b$ | 1.23 (1.20, 1.25) | <0.001 | 1.22 (1.20, 1.25) | <0.001 |
| Per 10 μg/m$^3$ | 1.46 (1.41, 1.51) | <0.001 | 1.44 (1.39, 1.49) | <0.001 |
| Model 1 | | | | |
| Low (< 22.37 μg/m$^3$) | Reference | – | Reference | – |
| Moderate (22.37–25.96 μg/m$^3$) | 1.35 (1.31, 1.39) | <0.001 | 1.34 (1.30, 1.39) | <0.001 |
| High (> 25.96 μg/m$^3$) | 1.88 (1.79, 1.96) | <0.001 | 1.86 (1.77, 1.95) | <0.001 |
| Test for trend$^b$ | 1.37 (1.34, 1.40) | <0.001 | 1.36 (1.33, 1.39) | <0.001 |
| Per 10 μg/m$^3$ | 2.04 (1.96, 2.12) | <0.001 | 2.01 (1.93, 2.09) | <0.001 |
| Model 2 | | | | |
| Low (< 22.37 μg/m$^3$) | Reference | – | Reference | – |
| Moderate (22.37–25.96 μg/m$^3$) | 1.37 (1.32, 1.41) | <0.001 | 1.36 (1.32, 1.40) | <0.001 |
| High (> 25.96 μg/m$^3$) | 1.92 (1.83, 2.01) | <0.001 | 1.90 (1.81, 1.99) | <0.001 |
| Test for trend$^b$ | 1.38 (1.35, 1.41) | <0.001 | 1.37 (1.34, 1.40) | <0.001 |
| Per 10 μg/m$^3$ | 2.09 (2.01, 2.18) | <0.001 | 2.07 (1.99, 2.15) | <0.001 |

$^a$Further adjusted for BMI, hypertension, diabetes, self-reported cardiovascular disease, and self-reported cancer.

$^b$The trend test was performed by entering 1, 2, and 3 as continuous variables in the models for inactive-exercise level/low—PM$_{2.5}$ concentration, moderate—exercise level/moderate-PM$_{2.5}$ concentration, and high-exercise level/high-PM$_{2.5}$ concentration, respectively.

HR (95% CI) also showed that the effect of PM$_{2.5}$ exposure on dyslipidemia was slightly stronger after including the city-level random intercept. In addition, the sample size in the present study was larger in the present study than in our previous study (121,948 vs. 66,702 participants at the baseline visit), which increased the robustness and stability of our results.

Our findings indicated that exercising in an area with a higher concentration of PM$_{2.5}$ may slightly attenuate the benefits of habitual exercise in the prevention of dyslipidemia, but the benefits of exercise remained. Thus, the benefits of exercise outweighed the adverse effects of excess inhalation of PM$_{2.5}$ due to the exercise. Therefore, our results suggest that people should exercise in areas with lower PM$_{2.5}$ concentrations when possible. However, exercise in a polluted area has more health benefits than staying inactive. Our study reinforces the importance of air pollution mitigation to maximize the benefits of exercise.

Indeed, habitual exercise is known to have an antiinflammatory effect by increasing the production of anti-inflammatory cytokines (e.g., IL-10) and suppressing the production of the proinflammatory cytokines (e.g., TNF-α). In addition, exercise improves lipid profiles through the activation of the enzyme, lipoprotein lipase. Conversely, exposure to PM$_{2.5}$ has been shown to induce inflammation and lipid oxidation, which increases the risk of dyslipidemia. However, the mechanism responsible for these interaction effects on dyslipidemia remains unclear. We observed significant benefits for all the PM$_{2.5}$ exposure categories and the modifying effects of PM$_{2.5}$ exposure were minor. It may be that the harmful effects of excess inhaled air pollution during exercise do not completely offset the long-term beneficial health effects of habitual exercise. Moreover, the additional air pollutants inhaled, while performing exercise may account for only a small fraction of the total inhaled air pollutants.
This study has several important strengths. First, this is the first large-scale cohort study investigating the combined effects of habitual exercise and chronic exposure to PM$_{2.5}$ on dyslipidemia. Second, the large sample size provided sufficient power to detect the combined effects of habitual exercise and PM$_{2.5}$ exposure, resulting in more stable and precise estimates. The large sample size also enabled us to conduct a series of subgroup and sensitivity analyses to test the robustness of the estimates. Third, the repeated measurements allowed us to consider the effects of the changes in exercise level, PM$_{2.5}$ exposure, and other covariates over the study period. Finally, the satellite-based spatiotemporal model used in our study enabled us to overcome the limited spatial coverage and resolution that generally occur when exclusively using data from monitoring stations.

This study had several limitations that should be noted. First, we did not collect information on whether the exercises were performed indoors or outdoors. However, a series of national surveys reported that more than 86% of Taiwanese residents

### Table 3

| Subgroup | HR (95% CI) | P     | HR (95% CI) | P     | HR (95% CI) | P     |
|----------|-------------|-------|-------------|-------|-------------|-------|
| Effects of exercise: stratified by PM$_{2.5}$ concentration | Low—PM$_{2.5}$ concentration | Moderate—PM$_{2.5}$ concentration | High—PM$_{2.5}$ concentration |
| Inactive (0 MET-h) | Reference | 0.87 (0.83, 0.92) | <0.001 | 0.90 (0.86, 0.95) | <0.001 | 0.95 (0.90, 1.00) | 0.05 |
| Moderate (0.01–8.75 MET-h) | 0.68 (0.64, 0.72) | <0.001 | 0.75 (0.71, 0.80) | <0.001 | 0.77 (0.73, 0.81) | <0.001 |
| Test for trend a | 0.82 (0.80, 0.85) | <0.001 | 0.87 (0.85, 0.89) | <0.001 | 0.88 (0.86, 0.90) | <0.001 |
| Effects of PM$_{2.5}$ stratified by exercise | Low (≤22.37 μg/m$^3$) | Moderate (22.37–25.96 μg/m$^3$) | High (>25.96 μg/m$^3$) |
| Inactive | Reference | 1.27 (1.21, 1.34) | <0.001 | 1.31 (1.24, 1.39) | <0.001 | 1.42 (1.34, 1.50) | <0.001 |
| Moderate-exercise level | 1.63 (1.52, 1.75) | <0.001 | 1.83 (1.70, 1.97) | <0.001 | 2.01 (1.85, 2.18) | <0.001 |
| High—exercise level | 1.28 (1.23, 1.32) | <0.001 | 1.34 (1.30, 1.39) | <0.001 | 1.42 (1.36, 1.47) | <0.001 |
| Test for trend a | 1.74 (1.63, 1.86) | <0.001 | 1.92 (1.80, 2.05) | <0.001 | 2.16 (2.02, 2.30) | <0.001 |
| Per 10 μg/m$^3$ increment | 1.74 (1.63, 1.86) | <0.001 | 1.92 (1.80, 2.05) | <0.001 | 2.16 (2.02, 2.30) | <0.001 |

All results were fully adjusted for age, sex, educational level, season, baseline calendar year, physical labor at work, smoking status, alcohol consumption, occupational exposure, vegetable intake, fruit intake, BMI, hypertension, diabetes, self-reported cardiovascular disease, and self-reported cancer.

The trend test was performed by entering 1, 2, and 3 as continuous variables in the models for inactive exercise level/low PM$_{2.5}$ concentration, moderate exercise level/moderate PM$_{2.5}$ concentration, and high exercise level/high PM$_{2.5}$ concentration, respectively.

95% CI, 95% confidence interval; HR, hazard ratio.

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**Exercise**

Figure 3. Combined effects of habitual exercise and PM$_{2.5}$ exposure on incident dyslipidemia in adults in Taiwan. The results are fully adjusted for age, sex, educational level, season, baseline calendar year, physical labor at work, smoking status, alcohol consumption, occupational exposure, vegetable intake, fruit intake, BMI, hypertension, diabetes, self-reported cardiovascular disease, and self-reported cancer. Combined effects were analyzed with participants classified into nine groups according to exercise and PM$_{2.5}$ exposure categories, with the inactive-exercise group exposed to a high-PM$_{2.5}$ concentration comprising the reference group. The inactive, moderate, and high levels of exercise were 0, 0.01–8.75, and > 8.75 MET-h, respectively. The low, moderate, and high level of PM$_{2.5}$ were ≤22.37, 22.37–25.96, and >25.96 μg/m$^3$, respectively. MET, metabolic equivalent of task.
chose outdoor exercise as their most frequent form of exercise from 2005 to 2016.41 Therefore, the majority of habitual exercise in this study was likely to be outdoor exercise. Second, the information on habitual exercise was collected using a self-administered questionnaire, which may be imprecise at evaluating the amount of exercise. However, the validity and reliability of the questionnaire have been confirmed previously.42 The assessment of habitual exercise based on a questionnaire is commonly used in large-scale epidemiologic studies because formal exercise testing is not practical. Third, information on indoor air pollution was not available in this study. Instead, we accounted for smoking in our analysis, which is the major source of indoor air pollution in developed economies. Fourth, we did not consider the effects of other air pollutants, such as SO2 and NOx, because this information was not available. However, the collinear relationship between pollutants suggests that we should analyze the pollutants separately. Finally, the participants of this cohort study were relatively healthy and well educated. Therefore, we should be cautious when generalizing the results to other populations.

In conclusion, a high level of habitual exercise, combined with a low level of PM1 concentration, was associated with a lower incidence of dyslipidemia, whereas a low level of exercise, combined with a high level of PM1 concentration, was associated with a higher incidence of dyslipidemia. Although no significant association was found between exercise and body mass index, we found that habitual exercise reduced the incidence of dyslipidemia, regardless of the levels of chronic PM1 exposure, although the effects of exercise were slightly attenuated at high levels of PM1 exposure. Our findings suggest that people should exercise in areas with lower PM1 concentrations. However, if this is not possible, exercising in polluted areas is better than staying inactive. Our results reinforce the importance of air pollution mitigation to maximize the beneficial effects of habitual exercise. More research is warranted to confirm our findings in areas with higher air pollution levels.

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