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Bo, Yacong; Yu, Tsung ; Guo, Cui; Lin, Changqing ; Yang, Hsiao Ting ; Chang, Ly-Yun; Thomas, G Neil; Tam, Tony; Lau, Alexis K.H. ; Lao, Xiang Qian

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## Cardiovascular Mortality, Habitual Exercise, and PM<sub>2.5</sub> Exposure: A Longitudinal Cohort Study

Yacong Bo, PhD,<sup>1</sup> Tsung Yu, PhD,<sup>2</sup> Cui Guo, PhD,<sup>3</sup> Changqing Lin, PhD,<sup>4</sup> Hsiao Ting Yang, MSc,<sup>3</sup> Ly-yun Chang, PhD,<sup>5</sup> GN Thomas, PhD,<sup>6</sup> Tony Tam, PhD,<sup>7</sup> Alexis K.H. Lau, PhD,<sup>4,8</sup> Xiang Qian Lao, PhD<sup>3,9</sup>

From the <sup>1</sup>School of Public Health, Zhengzhou University, Zhenghzou, China; <sup>2</sup>Department of Public Health, College of Medicine, National Cheng Kung University, Taiwan; <sup>3</sup>Jockey Club School of Public Health and Primary Care, the Chinese University of Hong Kong, Hong Kong; <sup>4</sup>Division of Environment and Sustainability, the Hong Kong University of Science and Technology, Hong Kong; <sup>5</sup>Institute of Sociology, Academia Sinica, Taiwan; <sup>6</sup>Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, United Kingdom; <sup>7</sup>Department of Sociology, the Chinese University of Hong Kong, Hong Kong; <sup>8</sup>Department of Civil and Environmental Engineering, the Hong Kong University of Science and Technology, Hong Kong; and <sup>9</sup>Shenzhen Research Institute of The Chinese University of Hong Kong, Shenzhen, China

Address correspondence to: Xiang Qian Lao, MD, PhD, Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, 4/F School of Public Health, Prince of Wales Hospital, Sha Tin, N.T., Hong Kong SAR, China. E-mail: xqlao@cuhk.edu.hk.

**Introduction:** Habitual exercise may amplify the respiratory uptake of air pollutants in the lung, exacerbating the adverse effects of air pollution. However, it is unclear whether this can reduce the health benefits of habitual exercise (referred to as leisure time exercise). Thus, the combined effects of habitual exercise and chronic exposure to ambient fine particulate matter (PM<sub>2.5</sub>) on cardiovascular mortality was examined among adults in Taiwan.

**Methods:** A total of 384,128 adults were recruited between 2001 and 2016, and followed up to May 31, 2019. Participants' vital status was obtained by matching their unique identification numbers with records of cardiovascular death in the National Death Registry of Taiwan. A time-varying Cox regression model was used to analyze the data. Analyses were conducted in 2021.

**Results:** Cardiovascular death risks were inversely associated with habitual exercise and positively associated with chronic exposure to PM<sub>2.5</sub>. The beneficial effects of habitual exercise on cardiovascular mortality were not modified by chronic exposure to PM<sub>2.5</sub>. Compared with high exercise group participants exposed to low levels of PM<sub>2.5</sub>, those inactive ones with high PM<sub>2.5</sub> exposure exhibited a 123% higher risk of cardiovascular death (95% CI=89%, 163%).

**Conclusions:** High level of habitual exercise combined with low exposure level of ambient PM<sub>2.5</sub> is associated with the lowest risk of cardiovascular death. A higher level of habitual exercise is associated with a lower risk of cardiovascular death at all levels of PM<sub>2.5</sub> exposure studied. The results indicate that habitual exercise is a safe health promotion strategy even for people residing in relatively polluted regions.

#### INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide and has been recognized as a major contributor to disability.<sup>1</sup> Physical activity is an effective means for preventing cardiovascular disease. The 2019 ACC/AHA guideline recommends  $\geq$ 150 minutes of accumulated moderate-intensity aerobic physical activity or  $\geq$ 75 minutes of vigorous physical activity per week for reducing the risk of atherosclerotic cardiovascular disease.<sup>2</sup> However, an increase in ventilation rate during physical activity may also cause individuals to inhale more air pollutants. In particular, exposure to air pollutants such as fine particulate matter (PM<sub>2.5</sub>) has shown to be a well-known risk factor for cardiovascular mortality.<sup>3–6</sup> The risk–benefit relationship between physical activity and air pollution exposure has become an important public health concern.

There is limited evidence for the combined effects of physical activity and chronic exposure to air pollution on cardiovascular mortality. To the best of the authors' knowledge, only 2 cohort studies have investigated the competing effects of physical activity and air pollution on cardiovascular mortality: the Danish Diet, Cancer and Health Cohort Study<sup>7</sup> and the Hong Kong Elderly Health Service Cohort Study.<sup>8</sup> However, both of these studies targeted older adults and had relatively small sample sizes. Furthermore, Denmark has relatively good air quality. Therefore, there is an urgent need for studies on the relationships between physical activity, air pollution, and cardiovascular mortality in general populations living in areas with relatively high air pollution. To address this knowledge gap, a longitudinal cohort study was conducted to investigate the combined effects of habitual exercise (a common form of

physical activity) and chronic exposure to ambient  $PM_{2.5}$  on the risk of cardiovascular mortality in Taiwan.

#### METHODS

#### **Study Population**

The participants of this study were part of a dynamic (open) cohort study with no end date. Details of the cohort have been described elsewhere.<sup>9–11</sup> In short, participants who purchased the memberships of the MJ Health Management Institution were encouraged to visit the institution periodically for a series of medical examinations. Each participant provided signed, written informed consent prior to each medical examination. The study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (2018.388) and the National Cheng Kung University Research Ethics Committee (A-ER-108-081).

#### Measures

Each participant's vital status up to May 31, 2019 was determined by matching their unique personal identification number with the National Death Registry maintained by the Ministry of Health and Welfare of Taiwan.<sup>11,12</sup> The case of cardiovascular mortality was identified as the underlying cause of death based on the ICD-9 codes 390–440 and the ICD-10 codes I01–171.

Information on participants' leisure time habitual exercise was collected using a validated

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self-administered questionnaire that has been described in previous studies.<sup>13-16</sup> Exercise intensity was classified into 4 levels by asking the question "Which types of exercise did you usually take in the previous month?" with several examples given under each type: 'light' (e.g., walking), 'moderate' (e.g., 'brisk walking'), 'medium-vigorous' (e.g., jogging), and 'high-vigorous' (e.g., running). A specific MET (1 MET=1 kJ h<sup>-1</sup> [kg bodyweight]<sup>-1</sup>) of 2.5, 4.5, 6.5, and 8.5 was assigned to each corresponding exercise intensity, respectively, based on the Compendium of Physical Activities<sup>17</sup> and findings from a previous study.<sup>18</sup> The participants were categorized into the following 3 categories based on the tertile cut-off values of the weekly MET-h: inactive (MET-h=0), moderate (0 < MET-h ≤8.75), and high (MET-h >8.75), respectively. As approximately a third of the participants did not engage in habitual exercise (i.e., MET-h=0) and previous studies showed a non-linear relationship between habitual exercise and non-communicable disease,<sup>19,20</sup> only the categorical exercise were used in data analysis.

The annual average ambient PM<sub>2.5</sub> exposure during this study period was estimated using a satellite-derived spatial-temporal model at a resolution of  $1 \text{ km}^{2}$ .<sup>9,21,22</sup> A model was developed using aerosol optical depth (AOD) and meteorological data to evaluate the concentration of PM<sub>2.5</sub>.<sup>22</sup>

The 2-year average  $PM_{2.5}$  concentration was used as the indicator of long-term ambient  $PM_{2.5}$  exposure, which was calculated based on the concentrations during the year of the medical examination and the preceding year. In the analysis, both categorical data on ambient  $PM_{2.5}$  concentrations [defined as 'low' (<22.23 µg/m<sup>3</sup>), 'moderate' (22.23–25.94 µg/m<sup>3</sup>), and 'high'

 $(\geq 25.94 \ \mu g/m^3)$  according to the tertile cut-off points] and continuous data (i.e., per 10  $\mu g/m^3$ ) were used.

Details on the collection of covariate data have been described elsewhere.<sup>9,10,15,23,24</sup> Briefly, questions were adopted from the validated questionnaires used in previous studies to collect information on participants' demographic characteristics (age [years], sex [male or female]), SES (educational level [<10, 10–12 years, 13–16 or >16 years]), lifestyle factors (smoking [never, former, or current], alcohol drinking [<1, 1–3, or >3 times/week], fruit intake [<1, 1–2, or >2 servings/day],<sup>25</sup> vegetable intake [<1, 1–2, or >2 servings/day],<sup>25</sup> occupational exposure to dust/organic solvents [yes or no]), and physical labor at work (i.e., intensity of physical labor that each participant experienced at work.). BMI was calculated as weight (kg) divided by height squared (m<sup>2</sup>). Seated blood pressure was measured in the morning using an auto-sphygmomanometer (Citizen CH-5000, Tokyo, Japan).

#### **Statistical Analysis**

A time-varying Cox regression model was used with random participant intercepts to investigate the combined effects of  $PM_{2.5}$  and habitual exercise on cardiovascular mortality. The variable 'habitual exercise', ambient  $PM_{2.5}$ , and all covariates (except for sex) were treated as time-dependent variables in the analysis to account for the changes in these variables throughout the study period. A city-level random intercept (including Taipei, Keelong, Taoyuan, Hsinchu, Ilan, Miaoli, Taichung, Changhua, Nantou, Hualien, Yunlin, Chiayi, Tainan, Kaoshiung, Taitung and Pingtung) was also included to control for withincity clustering effects. The interaction was detected using a multiplicative interaction term 'continuous  $PM_{2.5}$  (every 10  $\mu$ g/m<sup>3</sup>) × category of exercise' in. All analyses were conducted in 2021.

The stratified analyses were conducted to investigate the specific relationship between cardiovascular mortality and exercise or PM<sub>2.5</sub> at each PM<sub>2.5</sub> or exercise stratum. The combined effects were examined by classifying participants into nine groups, which were based on the categories of PM<sub>2.5</sub> and exercise with reference to the participants who had high exercise and exposed to low level of ambient PM<sub>2.5</sub>.

Four sensitivity analyses were conducted to examine the robustness of the estimates. First, to investigate the potential modifying effect of co-morbidities, further adjusting the analyses for diabetes (defined as fasting blood glucose  $\geq$ 126 mg/dL, or self-reported physician-diagnosed diabetes), hypertension (defined as SBP  $\geq$ 140 mmHg or DBP  $\geq$ 90 mmHg, or self-reported physician-diagnosed hypertension), and self-reported physician-diagnosed cardiovascular disease and cancer. Second, using the annual average PM<sub>2.5</sub> in the year of the medical examination to proxy exposure to PM<sub>2.5</sub>. Third, restricting the analyses to participants who were followed up for  $\geq$ 2 years to account for chronic effects of PM<sub>2.5</sub> and exercise on cardiovascular death. Fourth, restricting participants aged 65 years or older to examine whether the combined effects of PM<sub>2.5</sub> and exercise on the mortality differed by age. Finally, Restricting participants aged  $\geq$ 60 years to investigate whether the combined effects of PM<sub>2.5</sub> and exercise on the mortality differed by age. Finally, Restricting participants aged  $\geq$ 60 years to investigate whether the combined effects of PM<sub>2.5</sub> and exercise on the mortality differed by age. Finally, Restricting participants aged  $\geq$ 60 years to investigate whether the combined effects of PM<sub>2.5</sub> and exercise on the mortality differed by age. Finally, Restricting participants aged  $\geq$ 60 years to investigate whether the combined effects of PM<sub>2.5</sub> and exercise on the mortality differed by age.

A stratified analysis was conducted to examine whether the effect of habitual exercise was modifier by pre-existing disease at baseline.

All statistical analyses were conducted using the statistical software R (version 4.0.3). A 2sided p-value <0.05 was taken to indicate statistical significance.

#### RESULTS

The procedure for participants selection is shown in Appendix Figure 1. The general characteristics of the participants are shown in Table 1. In brief, a total of 384,128 participants with a mean age of 39.2 (SD=12.7) years at baseline were included. A total of 2,493 cardiovascular-related deaths were identified, with a median follow-up duration of 13.4 years (IQR=9.4–16.5 years). The number of medical examinations ranged from 1 to 26 with a mean value of 2.2. The distribution of 2-year mean ambient PM<sub>2.5</sub> concentrations by year is shown in Appendix Table 1. The level of ambient PM<sub>2.5</sub> peaked approximately in 2004 and gradually decreased thereafter.

The main associations between cardiovascular mortality risk and habitual exercise or chronic exposure to  $PM_{2.5}$  are shown in Table 2. A lower volume of habitual exercise was consistently associated with a higher risk of cardiovascular mortality. In contrast, the exposure to a higher level of ambient  $PM_{2.5}$  was consistently associated with an increased risk of cardiovascular mortality. Further mutual adjustment generally resulted in little changes in these associations. The interaction test showed no significant interactive effect between habitual exercise and  $PM_{2.5}$  on cardiovascular mortality (p=0.990).

The results of the stratified analyses are shown in Table 3. A low level of habitual exercise was associated with a higher risk of cardiovascular mortality in each PM<sub>2.5</sub> stratum. Borderline and strong associations between PM<sub>2.5</sub> and cardiovascular mortality were observed in the inactive stratum and high-exercise stratum, respectively. No significant associations were observed in the moderate-exercise stratum.

The combined associations between habitual exercise, long-term PM<sub>2.5</sub> exposure, and the risk of cardiovascular mortality are shown in Figure 1. High-exercise participants who were exposed to low levels of PM<sub>2.5</sub> comprised the reference group. This study suggested that participants with high-exercise who were exposed to low-PM<sub>2.5</sub> exhibited the lowest risk of cardiovascular mortality, while those who were inactive and exposed to high-PM<sub>2.5</sub> had the highest risk of cardiovascular mortality.

The sensitivity analyses also generally yielded similar results with the main findings (Appendix Tables 2–5). The results of the analysis stratified by pre-existing disease at baseline are shown in Appendix Table 6. There were no significant modifying effects of pre-existing disease for the association between habitual exercise and cardiovascular mortality. Further adjustment for PM<sub>2.5</sub> yielded similar results. The corresponding HRs were comparable between participants with and without pre-existing disease.

#### DISCUSSION

To the authors' knowledge, this is the largest study to investigate the risk-benefit relationship of cardiovascular mortality with chronic exposure to PM<sub>2.5</sub> and habitual exercise in a general adult population. In this longitudinal cohort study in Taiwan, where the annual PM<sub>2.5</sub> concentration was 5.3 times as high as that stipulated in the WHO guideline, the results of this study suggested that higher levels of habitual exercise and lower chronic exposure to ambient PM<sub>2.5</sub> were associated with lower risks of cardiovascular death. The beneficial effects of habitual exercise were observed across all levels of ambient PM<sub>2.5</sub> studied. The interaction test showed that exposure to PM<sub>2.5</sub> did not modify the beneficial effects of habitual exercise on cardiovascular death.

Many studies have investigated the effect of either physical activity or chronic air pollution exposure on the risk of cardiovascular death. The inverse relationship between habitual exercise and cardiovascular mortality risk observed in the current study aligns with the existing evidence.<sup>26–29</sup> In addition, the results of the beneficial effects of exercise in this study are also in line with previous studies investigating the cardiovascular effects of total physical activity calculated as a total of occupation, transportation, house work, and recreational activity.<sup>30,31</sup> Nonetheless, it is difficult to compare the findings of the current study because the differences in physical activity category, and method of physical activity assessment. The results also corroborate previous reports that chronic exposure to PM<sub>2.5</sub> was associated with a higher risk of cardiovascular health.<sup>6,32–34</sup>

It is important to determine the risk–benefit relationship between habitual exercise and exposure to ambient PM<sub>2.5</sub> with respect to the prevention of cardiovascular mortality, while also considering that air pollution is an obstacle to active exercise.<sup>35,36</sup> The findings show that the benefits of habitual exercise to cardiovascular mortality persist regardless of the level of PM<sub>2.5</sub> exposure. These findings align with those of 2 previous cohort studies, which also reported that physical activity benefits outweighed the harmfulness of air pollution on cardiovascular mortality.<sup>7,8</sup>

The interaction test in this study did not show significant modifying effects of  $PM_{2.5}$  on the association between cardiovascular mortality and habitual exercise. In addition, the stratified analysis by exercise level showed that the association between  $PM_{2.5}$  and cardiovascular mortality in the high-exercise stratum was significant, with larger HRs relative to the

associations in the inactive- and moderate-exercise strata (Table 3b). The relatively smaller sample size of the stratified analysis might contribute to this inconsistency across the strata. The Hong Kong Elderly Health Service Cohort Study, which targeted 58,643 adults aged 65 years or older, also did not observe significant interactions between air pollution and leisure time exercise.<sup>8</sup> Likewise, the Danish Diet, Cancer, and Health Cohort Study found that the benefits of physical activity, which included leisure time and transport-related, on cardiovascular mortality outweighed the detrimental effects of chronic exposure to NO<sub>2</sub>.<sup>7</sup>

Most previous studies that examined other health outcomes also have reported the lack of a modifying effect of air pollution on the health benefits of physical activity. Previous studies on the same Taiwanese cohort have suggested that the benefits of habitual exercise were not modified by the harmful effects of ambient PM<sub>2.5</sub> on hypertension,<sup>10</sup> and chronic kidney disease.<sup>37</sup> In the Danish Diet, Cancer, and Health Cohort Study, no interaction was observed between air pollution and physical activity in association with incident and recurrent myocardial infarction,<sup>38</sup> all-cause mortality,<sup>7</sup> and asthma/COPD hospitalizations.<sup>35</sup> The Hong Kong Elderly Health Service Cohort Study also observed no evidence of interaction between air pollution and leisure time exercise on dementia.<sup>39</sup> The Nurses' Health Study, which included 104,990 female participants, found no evidence for the modifying effects of chronic exposure to PM<sub>2.5</sub> on the benefits of leisure time physical activity on cardiovascular disease and all-cause mortality.<sup>40</sup> The present study also suggested that there were no significant modifying effects of pre-existing disease for the association between habitual exercise and cardiovascular mortality after considering the PM<sub>2.5</sub> exposure (Appendix Table 6). In

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contrast, a Korean study by Kim et al.<sup>41</sup> found a modifying effect of air pollution on the relationship and reported that an increased level of physical activity was associated with an increased risk of cardiovascular disease among young adults with an exposure to high levels of PM<sub>2.5</sub> or PM<sub>10</sub>. The inconsistency might be due to the differences among the studies including study design, health outcome, age group of participants, and chemical component contained in the pollutants.

The precise mechanisms accounting for the minor or lack of modifying effects of air pollution on the association between habitual exercise and various health outcomes are unclear. A previous study suggested that PM<sub>2.5</sub> is associated with a higher level inflammation and oxidative stress. Conversely, habitual exercise may activate the anti-inflammatory signaling pathways and simultaneously constrains the production of inflammatory markers.<sup>42</sup> Taken together, the PM<sub>2.5</sub>-related inflammation might be partially offset by exercise. Moreover, the additional volume of air pollutants inhaled during exercise may account for only a small fraction of the total air pollutants inhaled,<sup>43</sup> and therefore exercise does not increase the risk of cardiovascular mortality significantly. Another hypothesis is that the temporary pathophysiological changes caused by short-term exposure to air pollution during exercise may not attenuate the long-term benefits of habitual exercise.<sup>7</sup>

The comprehensive data analysis was the major strength of this study. The large sample size allowed for conducting a series of stratified and sensitivity analyses to test the robustness of the relationships. This study also collected more extensive information on physical activity,

such as exercise type and duration, and details of participants' physical labor at work. Another strength of the study was the longitudinal study design, which made it possible to account for changes in  $PM_{2.5}$  exposure, habitual exercise, and other covariates throughout the study period.

#### Limitations

This study was not without several limitations. First, information on whether the participants were engaged in exercise indoors or outdoors was not available. Thus, it is difficult to exclusively examine the joint associations of outdoor habitual exercise and ambient PM2.5 with cardiovascular mortality. However, a national survey among Taiwanese residents in 2015 revealed that only a small proportion (7.3%) of residents undertook indoor exercise as their most frequent form of leisure time exercise.<sup>44</sup> Second, as information on other pollutants such as NO<sub>2</sub>, SO<sub>2</sub>, and ozone were not available, the analyses could not account for the effects of these pollutants. Third, as the participants were generally well-educated and had a better SES (they were recruited to the study through a paid membership), care should be taken in generalizing the results to other populations. However, other main characteristics of the participants such as age and sex of the cohort members were similar to those of the general Taiwan population in 2009, which was approximately the median year of enrolment (2001–2016), (48.7% vs 50.0% for males and 36.0 years vs 36.8 years for median age).<sup>45</sup> The authors thus speculate that this limitation should not affect the study conclusion. Fourth, only the habitual exercise was considered, further studies considering broader physical activity such as transportation-related physical activity and work-related physical activity is

warranted to verify these associations. Fifth, a high resolution (1 km<sup>2</sup>) was used for exposure assessment in the present study. The level of PM<sub>2.5</sub> might still differ over a short distance (<1 km) due to the uneven distribution of emission sources, dilution, and physicochemical conversions. In addition, the air pollution exposure was estimated at residential addresses but the exercise might not have taken place at that location. However, there is no evidence showing that this kind of misclassification is systematic. A non-systematic (random) misclassification might be expected to make it more difficult to detect true associations, but the large sample size in this study will help offset this. Finally, as the study was performed in a moderately polluted area, additional studies in areas exposed to more severe air pollution are needed to further corroborate the findings.

#### CONCLUSIONS

This study suggested that compared with lower levels of habitual exercise combined with higher levels of PM<sub>2.5</sub> exposure, higher levels of habitual exercise combined with lower levels of PM<sub>2.5</sub> exposure was associated with decreased risk of cardiovascular mortality. Habitual exercise is consistently associated with lower risk of cardiovascular mortality across all ambient PM<sub>2.5</sub> concentrations studied. The findings suggest that habitual exercise is a safe means for preventing premature death caused by cardiovascular disease, even for individuals residing in moderately polluted areas. This study also underscores the importance of mitigating air pollution. Further studies considering more broad physical activity such as transportation-related physical activity and work-related physical activity is warranted to verify these combined relationships.

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The authors declared that there was no conflict of interest.

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#### LIST OF FIGURES

Figure 1. Combined effects of habitual exercise and  $PM_{2.5}$  on cardiovascular mortality in

adults in Taiwan.

PM, particulate matter.

Characteristics	All participants	Str	Stratified by PM <sub>2.5</sub> level			Stratified by exercise level		
	(n=384,128)	Low (n=127,437)	Moderate (n=126,413)	High (n=130,278)	Inactive (n=173,945)	Moderate (n=113,668)	High (n=96,515)	
Age, years	39.2 (12.7)	39.5 (12.9)	38.5 (12.3)	39.6 (13)	37.5 (11.6)	39 (12.4)	42.4 (14.4)	
Male, n (%)	186,984 (48.7)	62,090 (48.7)	60,916 (48.2)	63,978 (49.1)	74,753 (43.0)	55,574 (48.9)	56,657 (58.7)	
Education, n (%)								
Below high school	56,860 (14.8)	19,200 (15.1)	15,846 (12.5)	21,814 (16.7)	25,274 (14.5)	14,074 (12.4)	17,512 (18.1)	
High school	75,247 (19.6)	24,860 (19.5)	22,497 (17.8)	27,890 (21.4)	37,777 (21.7)	19,882 (17.5)	17,588 (18.2)	
College or university	204,730(53.3)	66,243 (52.0)	70,265 (55.6)	68,222 (52.4)	93,773 (53.9)	63,366 (55.7)	47,591 (49.3)	
Postgraduate	47,291 (12.3)	17,134 (13.5)	17,805 (14.1)	12,352 (9.5)	17,121 (9.8)	16,346 (14.4)	13,824 (14.3)	
Cigarette smoking, n (%)								
Never	284,310 (74.0)	93,935 (73.7)	93,472 (73.9)	96,903 (74.4)	126,105 (72.5)	86,568 (76.2)	71,637 (74.2)	
Former	21,944 (5.7)	7,804 (6.1)	6,889 (5.5)	7,251 (5.6)	8,386 (4.8)	6,117 (5.4)	7,441 (7.7)	
Current	77,874 (20.3)	25,698 (20.2)	26,052 (20.6)	26,124 (20.1)	39,454 (22.7)	20,983 (18.5)	17,437 (18.1)	
Alcohol consumption, n (%)								
Never/seldom	330,177 (86.0)	109,492 (85.9)	109,222 (86.4)	111,463 (85.6)	151,659 (87.2)	98,166 (86.4)	80,352 (83.3)	
Former	36,063 (9.4)	12,033 (9.4)	11,680 (9.2)	12,350 (9.5)	14,164 (8.1)	11,057 (9.7)	10,842 (11.2)	
Current	17,888 (4.7)	5,912 (4.5)	5,511 (4.4)	6,465 (5.0)	8,122 (4.7)	4,445 (3.9)	5,321 (5.5)	
Physical labor at work, n (%)								
Sedentary jobs	242,746 (63.2)	82,329 (64.6)	84,254 (66.7)	76,163 (58.5)	105,687 (60.8)	76,008 (66.9)	61,051 (63.3)	
Jobs that equally comprised sedentary activities and standing or walking	100,314 (26.1)	31,974 (25.1)	30,592 (24.2)	37,748 (29.0)	47,223 (27.1)	28,246 (24.8)	24,845 (25.7)	
Jobs that mostly require standing and walking	33,123 (8.6)	10,495 (8.2)	9,352 (7.4)	13,276 (10.2)	16,761 (9.6)	7,880 (6.9)	8,482 (8.8)	
Jobs that require vigorous physical activity	7,945 (2.1)	2,639 (2.1)	2,215 (1.8)	3,091 (2.4)	4,274 (2.5)	1,534 (1.3)	2,137 (2.2)	
Habitual exercise, n (%)								
Inactive	173,945 (45.3)	54,915 (43.1)	58,635 (46.4)	60,395 (46.4)	/	/	/	
Moderate	113,668 (29.6)	37,940 (29.8)	37,831 (29.9)	37,897 (29.1)	/	/	/	
High	96,515 (25.1)	34.582 (27.1)	29.947 (23.7)	31,986 (24,6)	/	/	/	

 Table 1. Baseline Characteristics of the Participants According to PM2.5 and Exercise Level

PM <sub>2.5</sub> level							
Low	127,437 (33.2)	/	/	/	54,915 (31.6)	37,940 (33.4)	34,582 (35.8)
Moderate	126,413 (32.9)	/	/	/	58,635 (33.7)	37,831 (33.3)	29,947 (31.0)
High	130,278 (33.9)	/	/	/	60,395 (34.7)	37,897 (33.3)	31,986 (33.1)
Vegetable intake, n (%)							
Seldom	54,198 (14.1)	18,105 (14.2)	18,502 (14.6)	17,591 (13.5)	31,737 (18.2)	12,861 (11.3)	9,600 (9.9)
Moderate	226,734 (59.0)	74,853 (58.7)	74,983 (59.3)	76,898 (59.0)	103,850 (59.7)	68,655 (60.4)	54,229 (56.2)
Frequent	103,196 (26.9)	34,479 (27.1)	32,928 (26.1)	35,789 (27.5)	38,358 (22.1)	32,152 (28.3)	32,686 (33.9)
Fruit intake, n (%)							
Seldom	132,707 (34.6)	44,632 (35.0)	44,960 (35.6)	43,115 (33.1)	74,826 (43)	33,960 (29.9)	23,921 (24.8)
Moderate	206,112 (53.7)	67,930 (53.3)	67,227 (53.2)	70,955 (54.5)	84,532 (48.6)	65,689 (57.8)	55,891 (57.9)
Frequent	45,309 (11.8)	14,875 (11.7)	14,226 (11.3)	16,208 (12.4)	14,587 (8.4)	14,019 (12.3)	16,703 (17.3)
Occupational exposure, n (%)	31,145 (8.1)	9,901 (7.8)	9,076 (7.2)	12,168 (9.3)	15,406 (8.9)	8,475 (7.5)	7,264 (7.5)
BMI (kg/m <sup>2</sup> )	23.0 (3.7)	23.1 (3.7)	23.9 (1.0)	35.1 (6.5)	22.8 (3.9)	23 (3.6)	23.5 (3.5)

Notes: The statistics are shown as means (SDs) for continuous variables and counts (percentages) for categorical variables.

PM, particulate matter.

Exposure	Model 1	Model 1 + PM <sub>2.5</sub> / Exercise	Model 2	Model 2+ PM <sub>2.5</sub> / Exercise
Habitual exercise				
High	ref (1.00)	ref (1.00)	ref (1.00)	ref (1.00)
Moderate	1.40 (1.25, 1.54)	1.37 (1.24, 1.52)	1.33 (1.20, 1.48)	1.32 (1.19, 1.47)
Inactive	1.88 (1.71, 2.06)	1.86 (1.69, 2.04)	1.68 (1.53, 1.86)	1.69 (1.51, 1.84)
PM <sub>2.5</sub> exposure				
Low	ref (1.00)	ref (1.00)	ref (1.00)	ref (1.00)
Moderate	1.19 (1.08, 1.32)	1.17 (1.06, 1.30)	1.20 (1.09, 1.33)	1.19 (1.07, 1.31)
High	1.12 (1.02, 1.24)	1.11 (1.01, 1.22)	1.19 (1.07, 1.31)	1.19 (1.07, 1.31)
Per 10 $\mu$ g/m <sup>3</sup>	1.27 (1.16, 1.39)	1.22 (1.12, 1.33)	1.10 (1.04, 1.17)	1.10 (1.04, 1.17)

Table 2. Adjusted HRs (95% CIs) for Cardiovascular Mortality in Relation to Habitual Exercise and PM<sub>2.5</sub> Exposure

*Notes*: Model 1 was adjusted for age, sex, education, and city. Model 2 was further adjusted for BMI, physical labor at work, cigarette smoking, alcohol drinking, vegetable intake, fruit intake, occupational exposure, season, and year of enrolment. Model 1+PM<sub>2.5</sub>/Exercise or Model 2+PM<sub>2.5</sub>/Exercise refers to further adjustment for PM<sub>2.5</sub> (for the association between exercise and cardiovascular mortality) or exercise (for the association between PM<sub>2.5</sub> and cardiovascular mortality) in the respective model. *P*=0.990 for the interaction term between habitual exercise and PM<sub>2.5</sub> exposure.

PM, particulate matter.

Table 3a. Adjusted HRs (95% CIs) for Cardiovascular Mortality Associated With Habitual Exercise, Stratified by PM<sub>2.5</sub> Levels

PM <sub>2.5</sub> level		Exercise Level				
	High	Moderate	Inactive			
Low	ref (1.00)	1.60 (1.32, 1.92)	1.84 (1.54, 2.19)			
Moderate	ref (1.00)	1.19 (1.00, 1.43)	1.39 (1.17, 1.65)			
High	ref (1.00)	1.23 (1.03, 1.47)	1.82 (1.54, 2.15)			

Table 3b. Adjusted HRs (95% CIs) for Cardiovascular Mortality Associated With PM2.5 Exposure, Stratified by Habitual Exercise Levels

Exercise level	PM <sub>2.5</sub> Level					
	Low	Moderate	High	10 μg/m <sup>3</sup> elevation		
High	ref (1.00)	1.45 (1.22, 1.72)	1.42 (1.16, 1.74)	1.59 (1.36, 1.87)		
Moderate	ref (1.00)	1.09 (0.90, 1.31)	0.95 (0.78, 1.15)	0.96 (0.87, 1.07)		
Inactive	ref (1.00)	1.06 (0.91, 1.25)	1.18 (1.01, 1.37)	1.09 (1.00, 1.18)		

*Notes*: The models were fully adjusted for age, sex, education, city, BMI, physical labor at work, cigarette smoking, alcohol drinking, vegetable intake, fruit intake, occupational exposure, season, and year of enrolment.

PM, particulate matter.



#### Chart's data source:

Evension Level	PM <sub>2.5</sub> Level	PM <sub>2.5</sub> Level					
Exercise Level	High	Moderate	Low				
High	1.26 (1.07, 1.51)	1.44 (1.21, 1.71)	Referent (1.00)				
Moderate	1.54 (1.28, 1.85)	1.74 (1.45, 2.08)	1.60 (1.33, 1.92)				
Inactive	2.23 (1.89, 2.63)	2.01 (1.70, 2.39)	1.89 (1.60, 2.24)				

**Commented [FJ5]:** Does this table need to be included with the figure? Typically figures stand alone.

Year	N	Mean (SD)	P25th	P50th	P75th
2001	60,631	25.0 (7.3)	20.1	22.5	27.5
2002	62,588	26.3 (8.1)	21	23.3	32.9
2003	58,288	28.8 (8.4)	23.1	25.8	35.6
2004	65,766	29.7 (8.7)	23.6	26.5	36.7
2005	66,761	27.4 (8.0)	22.2	24.4	28.0
2006	68,122	26.9 (6.9)	22.6	24.7	27.7
2007	67,678	26.9 (6.7)	22.6	24.9	27.8
2008	67,318	26.8 (6.7)	22.6	24.7	27.3
2009	53,383	26.8 (6.9)	22.3	24.7	27.8
2010	55,701	25.7 (7.1)	21.4	23.3	26.7
2011	54,465	25.5 (7.1)	20.9	23.2	26.6
2012	62,345	24.9 (6.5)	20.6	23.0	26.1
2013	49,629	23.7 (5.9)	19.8	22.3	25.4
2014	15,410	24.3 (4.4)	21.4	24.0	26.1
2015	19,337	22.8 (4.8)	19.4	21.4	26.5
2016	14,962	18.7 (4.8)	15.4	16.7	21.4
All	842,384	26.3 (7.4)	21.6	23.9	27.8

Appendix Table 1. Distribution of the 2-year average concentrations of  $PM_{2.5}$  (µg/m<sup>3</sup>)

PM: particulate matter; SD, standard deviation; P, percentile

**Appendix Table 2.** Adjusted HRs (95% CIs) for cardiovascular mortality in relation to habitual exercise and annual PM<sub>2.5</sub> further adjusting for hypertension, diabetes, cardiovascular diseases, and cancer

Exposure	Model 2	Model 2+ PM <sub>2.5</sub> / Exercise
Habitual exercise		
High	Referent (1.00)	Referent (1.00)
Moderate	1.32 (1.19, 1.47)	1.31 (1.18, 1.46)
Inactive	1.69 (1.53, 1.87)	1.68 (1.52, 1.86)
PM <sub>2.5</sub> exposure		
Low	Referent (1.00)	Referent (1.00)
Moderate	1.19 (1.08, 1.32)	1.07 (1.10, 1.31)
High	1.16 (1.05, 1.29)	1.03 (1.15, 1.28)
Per 10 $\mu g/m^3$	1.22 (1.12, 1.33)	1.18 (1.09, 1.28)

Abbreviations: PM: particulate matter

384,128 participants with 842,384 medical examinations

Model 2 was adjusted for age, sex, education, city, body mass index, physical labour at work, cigarette smoking, alcohol drinking, vegetable intake, fruit intake, occupational exposure, season, and year of enrolment.

Model 2+PM2.5/Exercise refers to further adjustment for  $PM_{2.5}$  (for the association between exercise and cardiovascular mortality) or exercise (for the association between  $PM_{2.5}$  and cardiovascular mortality).

Exposure	Model 2	Model 2+ PM <sub>2.5</sub> / Exercise
Habitual exercise		
High	Referent (1.00)	Referent (1.00)
Moderate	1.40 (1.25, 1.54)	1.37 (1.24, 1.52)
Inactive	1.88 (1.71, 2.06)	1.86 (1.69, 2.04)
PM <sub>2.5</sub> exposure		
Low	Referent (1.00)	Referent (1.00)
Moderate	1.27 (1.15, 1.40)	1.25 (1.13, 1.38)
High	1.34 (1.19, 1.51)	1.30 (1.15, 1.47)
Per 10 $\mu$ g/m <sup>3</sup>	1.37 (1.26, 1.50)	1.34 (1.22, 1.46)

**Appendix Table 3.** Adjusted HRs (95% CIs) for cardiovascular mortality in relation to habitual exercise and annual PM<sub>2.5</sub> in the year of medical examination

Abbreviations: PM: particulate matter

384,128 participants with 842,384 medical examinations

Model 2 was adjusted for age, sex, education, city, body mass index, physical labour at work, cigarette smoking, alcohol drinking, vegetable intake, fruit intake, occupational exposure, season, and year of enrolment.

Model 2+PM2.5/Exercise refers to further adjustment for  $PM_{2.5}$  (for the association between exercise and cardiovascular mortality) or exercise (for the association between  $PM_{2.5}$  and cardiovascular mortality).

Exposure	Model 2	Model 2+ PM <sub>2.5</sub> / Exercise
Habitual exercise		
High	Referent (1.00)	Referent (1.00)
Moderate	1.35 (1.21, 1.50)	1.34 (1.20, 1.49)
Inactive	1.71 (1.54, 1.89)	1.69 (1.53, 1.88)
PM <sub>2.5</sub> exposure		
Low	Referent (1.00)	Referent (1.00)
Moderate	1.20 (1.08, 1.33)	1.18 (1.07, 1.31)
High	1.17 (1.06, 1.29)	1.15 (1.04, 1.28)
Per 10 $\mu$ g/m <sup>3</sup>	1.24 (1.14, 1.36)	1.20 (1.10, 1.31)

Appendix Table 4. Adjusted HRs (95% CIs) for cardiovascular mortality with habitual exercise and  $PM_{2.5}$  in participants with  $\geq 2$  years of follow up

Abbreviations: PM: particulate matter

381,357 participants with 838,945 medical examinations.

Model 2 was adjusted for age, sex, education, city, body mass index, physical labour at work, cigarette smoking, alcohol drinking, vegetable intake, fruit intake, occupational exposure, season, and year of enrolment.

Model 2+PM2.5/Exercise refers to further adjustment for  $PM_{2.5}$  (for the association between exercise and cardiovascular mortality) or exercise (for the association between  $PM_{2.5}$  and cardiovascular mortality).

Exposure	Hazard Ratio <sup>a</sup>	Hazard Ratio <sup>b</sup>
Habitual exercise		
High	Referent (1.00)	Referent (1.00)
Moderate	1.23 (1.03, 1.47)	1.21 (1.01, 1.44)
Inactive	1.82 (1.54, 2.15)	1.78 (1.51, 2.10)
PM <sub>2.5</sub> exposure		
Low	Referent (1.00)	Referent (1.00)
Moderate	1.10 (0.97, 1.25)	1.08 (0.96, 1.23)
High	1.29 (1.11, 1.50)	1.25 (1.08, 1.46)
Per 10 $\mu$ g/m <sup>3</sup>	1.16 (1.05, 1.27)	1.11 (1.02, 1.22)

Appendix Table 5. Adjusted HRs (95% CIs) for cardiovascular mortality with habitual exercise and  $PM_{2.5}$  in participants aged 60 years or above

Abbreviations: PM: particulate matter

34,507 participants with 64,543 medical examinations.

The effects were presented as hazard ratio with 95% confidence level, with physically inactive participants or those who exposed to high level of PM<sub>2.5</sub> as the reference group. Model 2 was adjusted for age, sex, education, city, body mass index, physical labour at work, cigarette smoking, alcohol drinking, vegetable intake, fruit intake, occupational exposure, season, and year of enrolment.

Model 2+PM2.5/Exercise refers to further adjustment for  $PM_{2.5}$  (for the association between exercise and cardiovascular mortality) or exercise (for the association between  $PM_{2.5}$  and cardiovascular mortality).

Models	Hazard Ratio <sup>a</sup>	<b>P</b> inter	Hazard Ratio <sup>b</sup>	<b>P</b> inter
Without pre-existing disease at baseline		0.430		0.420
High -exercise	Referent (1.00)		Referent (1.00)	
Moderate-exercise	1.29 (1.06, 1.58)		1.29 (1.06, 1.58)	
Inactive-exercise	1.68 (1.39, 2.03)		1.67 (1.39, 2.02)	
With pre-existing di	sease at baseline			
High -exercise	Referent (1.00)		Referent (1.00)	
Moderate-exercise	1.34 (1.19, 1.51)		1.33 (1.18, 1.50)	
Inactive-exercise	1.70 (1.51, 1.90)		1.69 (1.50, 1.89)	

Appendix Table 6. Adjusted HRs (95% CIs) for the associations between habitual exercise and cardiovascular mortality stratified by pre-existing disease at baseline

Abbreviations: PM: particulate matter

The effects were presented as hazard ratio with 95% confidence level, with physically inactive participants as the reference group

<sup>a</sup> Model was adjusted for age, sex, education, city, body mass index, physical labour at work, cigarette smoking, alcohol drinking, vegetable intake, fruit intake, occupational exposure, season, and year of enrolment. <sup>b</sup> Further adjusted for PM<sub>2.5</sub>.

Appendix Figure 1. Flow chart of participant selection

