University of Birmingham
Research at Birmingham

Cardiovascular mortality, habitual exercise, and particulate matter 2.5 exposure

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

DOI:
10.1016/j.amepre.2022.09.004

License:
Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version
Peer reviewed version

Citation for published version (Harvard):
Bo, Y, Yu, T, Guo, C, Lin, C, Yang, HT, Chang, L-Y, Thomas, GN, Tam, T, Lau, AKH & Lao, XQ 2023, 'Cardiovascular mortality, habitual exercise, and particulate matter 2.5 exposure: a longitudinal cohort study', *American journal of preventive medicine*, vol. 64, no. 2, pp. 250-258. https://doi.org/10.1016/j.amepre.2022.09.004

Link to publication on Research at Birmingham portal

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.
•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
•User may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
•Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 20. Apr. 2024

Cardiovascular Mortality, Habitual Exercise, and $PM_{2.5}$ Exposure: A Longitudinal Cohort Study

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

From the [1]School of Public Health, Zhengzhou University, Zhenghzou, China; [2]Department of Public Health, College of Medicine, National Cheng Kung University, Taiwan; [3]Jockey Club School of Public Health and Primary Care, the Chinese University of Hong Kong, Hong Kong; [4]Division of Environment and Sustainability, the Hong Kong University of Science and Technology, Hong Kong; [5]Institute of Sociology, Academia Sinica, Taiwan; [6]Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, United Kingdom; [7]Department of Sociology, the Chinese University of Hong Kong, Hong Kong; [8]Department of Civil and Environmental Engineering, the Hong Kong University of Science and Technology, Hong Kong; and [9]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 ($PM_{2.5}$) 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 $PM_{2.5}$. The beneficial effects of habitual exercise on cardiovascular mortality were not modified by chronic exposure to $PM_{2.5}$. Compared with high exercise group participants exposed to low levels of $PM_{2.5}$, those inactive ones with high $PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ 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.[1] Physical activity is an effective means for preventing cardiovascular disease. The 2019 ACC/AHA guideline recommends ≥150 minutes of accumulated moderate-intensity aerobic physical activity or ≥75 minutes of vigorous physical activity per week for reducing the risk of atherosclerotic cardiovascular disease.[2] 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 ($PM_{2.5}$) has shown to be a well-known risk factor for cardiovascular mortality.[3–6] 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[7] and the Hong Kong Elderly Health Service Cohort Study.[8] 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

Commented [FJ1]: Subheadings in Methods have been modified to better align with AJPM Style.

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.[9–11] 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.[11,12] 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–I71.

Information on participants' leisure time habitual exercise was collected using a validated self-administered questionnaire that has been described in previous studies.[13–16] 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^{-1} [kg bodyweight]$^{-1}$) 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[17] and findings from a previous study.[18] 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,[19,20] only the categorical exercise were used in data analysis.

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

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/m³), 'moderate' (22.23–25.94 μg/m³), and 'high'

(≥25.94 μg/m³) according to the tertile cut-off points] and continuous data (i.e., per 10 μg/m³) were used.

Details on the collection of covariate data have been described elsewhere.[9,10,15,23,24] 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],[25] vegetable intake [<1, 1–2, or >2 servings/day],[25] 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^2). 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 within-city clustering effects. The interaction was detected using a multiplicative interaction term 'continuous $PM_{2.5}$ (every 10 μg/m³) × 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 $PM_{2.5}$ at each $PM_{2.5}$ or exercise stratum. The combined effects were examined by classifying participants into nine groups, which were based on the categories of $PM_{2.5}$ and exercise with reference to the participants who had high exercise and exposed to low level of ambient $PM_{2.5}$.

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 ≥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), and self-reported physician-diagnosed cardiovascular disease and cancer. Second, using the annual average $PM_{2.5}$ in the year of the medical examination to proxy exposure to $PM_{2.5}$. Third, restricting the analyses to participants who were followed up for ≥2 years to account for chronic effects of $PM_{2.5}$ and exercise on cardiovascular death. Fourth, restricting participants aged 65 years or older to examine whether the combined effects of $PM_{2.5}$ and exercise on the mortality differed by age. Finally, Restricting participants aged ≥60 years to investigate whether the combined effects of $PM_{2.5}$ and exercise on cardiovascular death were different.

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 2-sided *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 $PM_{2.5}$ concentrations by year is shown in Appendix Table 1. The level of ambient $PM_{2.5}$ 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 $PM_{2.5}$ stratum. Borderline and strong associations between $PM_{2.5}$ 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 $PM_{2.5}$ exposure, and the risk of cardiovascular mortality are shown in Figure 1. High-exercise participants who were exposed to low levels of $PM_{2.5}$ comprised the reference group. This study suggested that participants with high-exercise who were exposed to low-$PM_{2.5}$ exhibited the lowest risk of cardiovascular mortality, while those who were inactive and exposed to high-$PM_{2.5}$ 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 $PM_{2.5}$ 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 $PM_{2.5}$ and habitual exercise in a general adult population. In this longitudinal cohort study in Taiwan, where the annual $PM_{2.5}$ 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 $PM_{2.5}$ were associated with lower risks of cardiovascular death. The beneficial effects of habitual exercise were observed across all levels of ambient $PM_{2.5}$ studied. The interaction test showed that exposure to $PM_{2.5}$ 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.[26–29] 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.[30,31] 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 $PM_{2.5}$ was associated with a higher risk of cardiovascular health.[6,32–34]

It is important to determine the risk–benefit relationship between habitual exercise and exposure to ambient $PM_{2.5}$ with respect to the prevention of cardiovascular mortality, while also considering that air pollution is an obstacle to active exercise.[35,36] The findings show that the benefits of habitual exercise to cardiovascular mortality persist regardless of the level of $PM_{2.5}$ 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.[7,8]

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.[8] 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_2.[7]

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 $PM_{2.5}$ on hypertension,[10] and chronic kidney disease.[37] 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,[38] all-cause mortality,[7] and asthma/COPD hospitalizations.[35] The Hong Kong Elderly Health Service Cohort Study also observed no evidence of interaction between air pollution and leisure time exercise on dementia.[39] The Nurses' Health Study, which included 104,990 female participants, found no evidence for the modifying effects of chronic exposure to $PM_{2.5}$ on the benefits of leisure time physical activity on cardiovascular disease and all-cause mortality.[40] 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 $PM_{2.5}$ exposure (Appendix Table 6). In

Commented [FJ2]: In the U.S? You identified the country of origin with the other studies mentioned, please also do so here.

contrast, a Korean study by Kim et al.[41] 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 $PM_{2.5}$ or PM_{10}. 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 $PM_{2.5}$ 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.[42] Taken together, the $PM_{2.5}$-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,[43] 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.[7]

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 $PM_{2.5}$ 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.[44] Second, as information on other pollutants such as NO_2, SO_2, 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).[45] 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^2) was used for exposure assessment in the present study. The level of $PM_{2.5}$ 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 $PM_{2.5}$ exposure, higher levels of habitual exercise combined with lower levels of $PM_{2.5}$ exposure was associated with decreased risk of cardiovascular mortality. Habitual exercise is consistently associated with lower risk of cardiovascular mortality across all ambient $PM_{2.5}$ 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.

Commented [FJ3]: This is a little confusing. What about, “Higher levels of habitual exercise combined with lower levels of PM2.5 exposure was associated with decreased risk of CV mortality.” ?

ACKNOWLEDGMENTS

Part of the data was provided by MJ Health Research Foundation (Authorization code: MJHR2019006A). Any interpretation or conclusion described in this paper does not represent the views of MJ Health Research Foundation. We are grateful to the Health Data Science Centre, Ministry of Health and Welfare in Taiwan for assistance in mortality data linkage.

The authors declared that there was no conflict of interest.

This work was supported by RGC-General Research Fund (14603019), Environmental Health Research Fund of the Chinese University of Hong Kong (7104946), and Guangdong Basic and Applied Basic Research Foundation (2019A1515011697). Dr. Cui Guo is supported by the RGC Postdoctoral Fellowship Scheme of the University Grants Committee of Hong Kong. No other financial disclosures were reported by the authors of this paper.

REFERENCES

1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76(25):2982-3021. https://doi.org/10.1016/j.jacc.2020.11.021.
2. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646. https://doi.org/10.1161/cir.0000000000000678.
3. Crouse DL, Peters PA, van Donkelaar A, et al. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environ Health Perspect*. 2012;120(5):708-714. https://doi.org/10.1289/ehp.1104049.
4. Pope CA, 3rd, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*. 2004;109(1):71-77. https://doi.org/10.1161/01.CIR.0000108927.80044.7F.
5. Cao J, Yang C, Li J, et al. Association between long-term exposure to outdoor air pollution and mortality in China: a cohort study. *J Hazard Mater*. 2011;186(2-3):1594-1600. https://doi.org/10.1016/j.jhazmat.2010.12.036.
6. Ostro B, Broadwin R, Green S, Feng WY, Lipsett M. Fine particulate air pollution and mortality in nine California counties: results from CALFINE. *Environ Health

Perspect. 2006;114(1):29-33. https://doi.org/10.1289/ehp.8335.

7. Andersen ZJ, de Nazelle A, Mendez MA, et al. A study of the combined effects of physical activity and air pollution on mortality in elderly urban residents: the Danish Diet, Cancer, and Health Cohort. *Environ Health Perspect*. 2015;123(6):557-563. https://doi.org/10.1289/ehp.1408698.
8. Sun S, Cao W, Qiu H, et al. Benefits of physical activity not affected by air pollution: a prospective cohort study. *Int J Epidemiol*. 2020;49(1):142-152. https://doi.org/10.1093/ije/dyz184.
9. Guo C, Zhang Z, Lau AKH, et al. Effect of long-term exposure to fine particulate matter on lung function decline and risk of chronic obstructive pulmonary disease in Taiwan: a longitudinal, cohort study. *Lancet Planet Health*. 2018;2(3):e114-e125. https://doi.org/10.1016/S2542-5196(18)30028-7.
10. Guo C, Zeng Y, Chang LY, et al. Independent and Opposing Associations of Habitual Exercise and Chronic PM(2.5) Exposures on Hypertension Incidence. *Circulation*. 2020;142(7):645-656. https://doi.org/10.1161/CIRCULATIONAHA.120.045915.
11. Guo C, Chan TC, Teng YC, et al. Long-term exposure to ambient fine particles and gastrointestinal cancer mortality in Taiwan: A cohort study. *Environ Int*. 2020;138:105640. https://doi.org/10.1016/j.envint.2020.105640.
12. Ministry of Health and Welfare. Cause of Death Data. https://www.mohw.gov.tw/mp-1.html. Accessed May 2019.
13. Lao XQ, Deng H-B, Liu X, et al. Increased leisure-time physical activity associated with lower onset of diabetes in 44 828 adults with impaired fasting glucose: a

population-based prospective cohort study. *Br J Sports Med*. 2018;53(14):895-900. https://doi.org/10.1136/bjsports-2017-098199.

14. Guo C, Tam T, Bo Y, Chang L-y, Lao XQ, Thomas GN. Habitual physical activity, renal function and chronic kidney disease: A cohort study of nearly 200,000 adults. *Br J Sports Med*. 2020;54(20):1225-1230. https://doi.org/10.1136/bjsports-2019-100989.
15. Guo C, Bo Y, Chan T-C, et al. Does fine particulate matter (PM2.5) affect the benefits of habitual physical activity on lung function in adults: a longitudinal cohort study. *BMC Med*. 2019;18(1):134. https://doi.org/10.1186/s12916-020-01570-5.
16. Wen CP, Cheng TY, Tsai MK, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *Lancet*. 2008;371(9631):2173-2182. https://doi.org/10.1016/S0140-6736(08)60952-6.
17. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32(9):S498-S504. https://doi.org/10.1097/00005768-200009001-00009.
18. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol*. 2011;40(5):1382-1400. https://doi.org/10.1093/ije/dyr112.
19. Egan BM. Physical Activity and Hypertension Knowing Is Not Enough; We Must Apply. Willing Is Not Enough; We Must Do-von Goethe. *Hypertension*. 2017;69(3):404-406. https://doi.org/10.1161/HYPERTENSIONAHA.116.08508.
20. Andersen K, Mariosa D, Adami HO, et al. Dose-response relationship of total and

leisure time physical activity to risk of heart failure: a prospective cohort study. *Circ Heart Fail*. 2014;7(5):701-708. https://doi.org/10.1161/CIRCHEARTFAILURE.113.001010.

21. Lin C, Li Y, Yuan Z, Lau AK, Li C, Fung JC. Using satellite remote sensing data to estimate the high-resolution distribution of ground-level PM2.5. *Remote Sens Environ*. 2015;156:117-128. https://doi.org/10.1016/j.rse.2014.09.015.
22. Zhang Z, Chang L-y, Lau AK, et al. Satellite-based estimates of long-term exposure to fine particulate matter are associated with C-reactive protein in 30 034 Taiwanese adults. *Int J Epidemiol*. 2017;46(4):1126-1136. https://doi.org/10.1093/ije/dyx069.
23. Ly-Yun Chang, Shan Pou Tsai , Myron Li Wang, Ting-Ting Liu, Jing-Yun Jhao, Yuan-Chieh Chuang, Hsin-Jung Chiang, Yao-Mao Chang, Yaw-Tang Shih, Chwen-Keng Tsao, MJ Health Database (MJHD), a large health database in Taiwan, MJ Health Research Foundation Technical Report, MJHRF-TR-01, August, 2016.
24. Lao XQ, Guo C, Chang LY, et al. Long-term exposure to ambient fine particulate matter (PM2.5) and incident type 2 diabetes: a longitudinal cohort study. *Diabetologia*. 2019;62(5):759-769. https://doi.org/10.1007/s00125-019-4825-1.
25. Chiu YF, Hsu CC, Chiu TH, Lee CY, Liu TT, Tsao CK, et al. Cross-sectional and longitudinal comparisons of metabolic profiles between vegetarian and non-vegetarian subjects: a matched cohort study. *Br J Nutr*. 2015;114(8):1313-1320. https://doi.org/10.1017/S0007114515002937.
26. Zhao M, Veeranki SP, Li S, Steffen LM, Xi B. Beneficial associations of low and large doses of leisure time physical activity with all-cause, cardiovascular disease and

cancer mortality: a national cohort study of 88,140 US adults. *Br J Sports Med*. 2019;53(22):1405-1411. https://doi.org/10.1136/bjsports-2018-099254.

27. Cheng W, Zhang Z, Cheng W, Yang C, Diao L, Liu W. Associations of leisure-time physical activity with cardiovascular mortality: A systematic review and meta-analysis of 44 prospective cohort studies. *Eur J Prev Cardiol*. 2018;25(17):1864-1872. https://doi.org/10.1177/2047487318795194.
28. DeFina LF, Radford NB, Barlow CE, Willis BL, Leonard D, Haskell WL, et al. Association of All-Cause and Cardiovascular Mortality With High Levels of Physical Activity and Concurrent Coronary Artery Calcification. *JAMA Cardiol*. 2019;4(2):174-181. https://doi.org/10.1001/jamacardio.2018.4628.
29. Pedisic Z, Shrestha N, Kovalchik S, et al. Is running associated with a lower risk of all-cause, cardiovascular and cancer mortality, and is the more the better? A systematic review and meta-analysis. *Br J Sports Med*. 2020;54(15):898-905. https://doi.org/10.1136/bjsports-2018-100493.
30. Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet*. 2017;390(10113):2643-2654. https://doi.org/10.1016/S0140-6736(17)31634-3.
31. Dempsey PC, Strain T, Khaw KT, Wareham NJ, Brage S, Wijndaele K. Prospective Associations of Accelerometer-Measured Physical Activity and Sedentary Time With Incident Cardiovascular Disease, Cancer, and All-Cause Mortality. *Circulation*. 2020;141(13):1113-1115. https://doi.org/10.1161/CIRCULATIONAHA.119.043030.

32. Thurston GD, Ahn J, Cromar KR, et al. Ambient Particulate Matter Air Pollution Exposure and Mortality in the NIH-AARP Diet and Health Cohort. *Environ Health Perspect*. 2016;124(4):484-490. https://doi.org/10.1289/ehp.1509676.

33. Kim H, Byun G, Choi Y, Kim S, Kim SY, Lee JT. Effects of long-term exposure to air pollution on all-cause mortality and cause-specific mortality in seven major cities of South Korea: Korean national health and nutritional examination surveys with mortality follow-up. *Environ Res*. 2021;192:110290. https://doi.org/10.1016/j.envres.2020.110290.

34. Kim OJ, Lee SH, Kang SH, Kim SY. Incident cardiovascular disease and particulate matter air pollution in South Korea using a population-based and nationwide cohort of 0.2 million adults. *Environ Health*. 2020;19(1):113. https://doi.org/10.1186/s12940-020-00671-1.

35. Fisher JE, Loft S, Ulrik CS, et al. Physical Activity, Air Pollution, and the Risk of Asthma and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2016;194(7):855-865. https://doi.org/10.1164/rccm.201510-2036OC.

36. An R, Zhang S, Ji M, Guan C. Impact of ambient air pollution on physical activity among adults: a systematic review and meta-analysis. *Perspect Public Health*. 2018;138(2):111-121. https://doi.org/10.1177/1757913917726567.

37. Zeng Y, Lin C, Guo C, et al. Combined effects of chronic PM(2.5) exposure and habitual exercise on renal function and chronic kidney disease: A longitudinal cohort study. *Int J Hyg Environ Health*. 2021;236:113791. https://doi.org/10.1016/j.ijheh.2021.113791.

38. Kubesch NJ, Therming Jørgensen J, Hoffmann B, et al. Effects of Leisure-Time and Transport-Related Physical Activities on the Risk of Incident and Recurrent Myocardial Infarction and Interaction With Traffic-Related Air Pollution: A Cohort Study. *J Am Heart Assoc*. 2018;7(15). https://doi.org/10.1161/JAHA.118.009554.

39. Ran J, Zhang Y, Han L, et al. The joint association of physical activity and fine particulate matter exposure with incident dementia in elderly Hong Kong residents. *Environ Int*. 2021;156:106645. https://doi.org/10.1016/j.envint.2021.106645.

40. Elliott EG, Laden F, James P, Rimm EB, Rexrode KM, Hart JE. Interaction between Long-Term Exposure to Fine Particulate Matter and Physical Activity, and Risk of Cardiovascular Disease and Overall Mortality in U.S. Women. *Environ Health Perspect*. 2020;128(12):127012. https://doi.org/10.1289/EHP7402.

41. Kim SR, Choi S, Kim K, et al. Association of the combined effects of air pollution and changes in physical activity with cardiovascular disease in young adults. *Eur Heart J*. 2021;42(25):2487-2497. https://doi.org/10.1093/eurheartj/ehab139.

42. Clarkson PM, Thompson HS. Antioxidants: what role do they play in physical activity and health? *Am J Clin Nutr*. 2000;72(2 Suppl):637s-646s. https://doi.org/10.1093/ajcn/72.2.637S.

43. Rojas-Rueda D, de Nazelle A, Tainio M, Nieuwenhuijsen MJ. The health risks and benefits of cycling in urban environments compared with car use: health impact assessment study. *BMJ*. 2011;343:d4521. https://doi.org/10.1136/bmj.d4521.

44. Department of Physical Education Ministry of Education. Report of Active Cities, Taiwan, 2019.

https://isports.sa.gov.tw/Apps/TIS08/TIS0801M_01V1.aspx?MENU_CD=M07&ITEM_CD=T01&MENU_PRG_CD=12&LEFT_MENU_ACTIVE_ID=26. Accessed July 1, 2022.

45. Mazidi M, Katsiki N, Mikhailidis DP, Sattar N, Banach M. Lower carbohydrate diets and all-cause and cause-specific mortality: a population-based cohort study and pooling of prospective studies. *Eur Heart J*. 2019;40(34):2870-2879. https://doi.org/10.1093/eurheartj/ehz174.

LIST OF FIGURES

PM, particulate matter.

Table 1. Baseline Characteristics of the Participants According to $PM_{2.5}$ and Exercise Level

Characteristics	All participants (n=384,128)	Stratified by $PM_{2.5}$ level			Stratified by exercise level		
		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)	/	/	/

$PM_{2.5}$ 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^2)	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.

Table 2. Adjusted HRs (95% CIs) for Cardiovascular Mortality in Relation to Habitual Exercise and $PM_{2.5}$ Exposure

Exposure	**Model 1**	**Model 1 + $PM_{2.5}$/ Exercise**	**Model 2**	**Model 2+ $PM_{2.5}$/ 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)
$PM_{2.5}$ 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 $\mu g/m^3$	1.27 (1.16, 1.39)	1.22 (1.12, 1.33)	1.10 (1.04, 1.17)	1.10 (1.04, 1.17)

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+$PM_{2.5}$/Exercise or Model 2+$PM_{2.5}$/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) in the respective model. P=0.990 for the interaction term between habitual exercise and $PM_{2.5}$ exposure.

PM, particulate matter.

Table 3a. Adjusted HRs (95% CIs) for Cardiovascular Mortality Associated With Habitual Exercise, Stratified by $PM_{2.5}$ Levels

$PM_{2.5}$ 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)

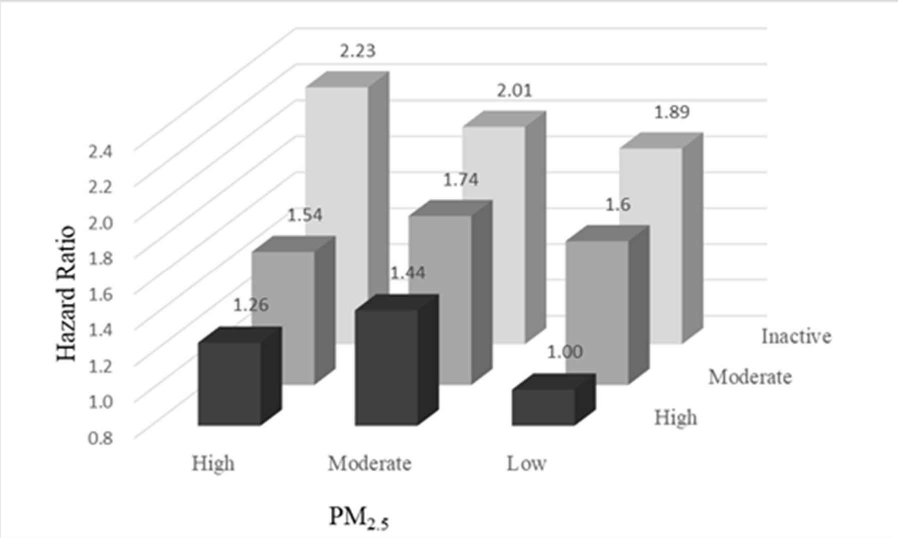
Table 3b. Adjusted HRs (95% CIs) for Cardiovascular Mortality Associated With $PM_{2.5}$ Exposure, Stratified by Habitual Exercise Levels

Exercise level	**$PM_{2.5}$ Level**			
	Low	**Moderate**	**High**	**10 $\mu g/m^3$ 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.

1



Chart's data source:

Exercise Level	$PM_{2.5}$ 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 [FJ4]: Please provide a figure with the text in a sans-serif font (e.g., Arial).

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

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

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

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 $PM_{2.5}$ further adjusting for hypertension, diabetes, cardiovascular diseases, and cancer

Exposure	Model 2	Model 2+ $PM_{2.5}$/ 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)
$PM_{2.5}$ 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).

Appendix Table 3. Adjusted HRs (95% CIs) for cardiovascular mortality in relation to habitual exercise and annual $PM_{2.5}$ in the year of medical examination

Exposure	**Model 2**	**Model 2+ $PM_{2.5}$/ 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)
$PM_{2.5}$ 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 $\mu g/m^3$	1.37 (1.26, 1.50)	1.34 (1.22, 1.46)

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).

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

Exposure	**Model 2**	**Model 2+ $PM_{2.5}$/ 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)
$PM_{2.5}$ 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 $\mu g/m^3$	1.24 (1.14, 1.36)	1.20 (1.10, 1.31)

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).

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

Exposure	Hazard Ratio [a]	Hazard Ratio [b]
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)
$PM_{2.5}$ 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 $\mu g/m^3$	1.16 (1.05, 1.27)	1.11 (1.02, 1.22)

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 $PM_{2.5}$ 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).

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

Models	Hazard Ratio [a]	P_{inter}	Hazard Ratio [b]	P_{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 disease 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)	

Abbreviations: PM: particulate matter
The effects were presented as hazard ratio with 95% confidence level, with physically inactive participants as the reference group
[a] 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.
[b] Further adjusted for $PM_{2.5}$.

Appendix Figure 1. Flow chart of participant selection