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The joint association of physical activity and fine particulate matter exposure with incident dementia in elderly Hong Kong residents

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ABSTRACT

Objective: The evidence for the beneficial effects of physical activity (PA) and potentially detrimental effects of long-term exposure to fine particulate matter ($PM_{2.5}$) on neurodegeneration diseases is accumulating. However, their joint effects remain unclear. We evaluated joint associations of habitual PA and $PM_{2.5}$ exposure with incident dementia in a longitudinal elderly cohort in Hong Kong.

Methods: A total of 57,775 elderly participants (≥65 years) without dementia were enrolled during 1998–2001 and followed up till 2011. Their information on PA and other relevant covariates were collected at baseline (1998–2001) by a standard self-administered questionnaire, including PA volumes (high, moderate, low, and inactive) and types (aerobic exercise, traditional Chinese exercise, stretching exercise, walking slowly, and no exercise). Their annual mean $PM_{2.5}$ exposures at the residential address were estimated using a satellite-based spatiotemporal model. We then adopted the Cox proportional hazards model to examine the joint associations with the incidence of all-cause dementia, Alzheimer's diseases, and vascular dementia on additive and multiplicative scales.

Results: During the follow-up period, we identified 1,157 incident cases of dementia, including 642 cases of Alzheimer's disease and 324 cases of vascular dementia. A higher PA level was associated with a lower risk of incident all-cause dementia (hazard ratio (HR) for the high-PA volume was 0.59 (95% CI, 0.47, 0.75), as compared with the inactive-PA), whereas a high level of $PM_{2.5}$ was related to the higher risk with an HR of 1.15 (95%CI: 1.00, 1.33) compared with the low-level of $PM_{2.5}$. No clear evidence was observed of interaction between habitual PA (volume and type) and $PM_{2.5}$ inhalation to incident dementia on either additive or multiplicative scale.

Conclusion: Habitual PA and long-term $PM_{2.5}$ exposure were oppositely related to incident dementia in the Hong Kong aged population. The benefits of PA remain in people irrespective of exposure to air pollution.

1. Introduction

Dementia, characterized by deterioration in cognition, function, and behavior, creates a great burden on families, communities, and the whole society. In 2016, more than 43.8 million people suffered from dementia, and the number is projected to double by 2030 and triple by 2050 (Nichols et al., 2019; Prince et al., 2015). Dementia accounted for 2.4 million deaths and contributed to 28.8 million disability-adjusted life-years (DALYs), being the third contributors to neurological DALYs (Feigin et al., 2019; Nichols et al., 2019). The economic burden caused

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by dementia is also enormous. The total estimated worldwide cost of dementia was over a trillion-dollar by 2018 (Prince et al., 2015).

Prevention is an attractive strategy to limit the burdens of dementia since there is no effective treatment. Sedentary behavior is a well-documented risk factor of all-cause dementia and potentially modifiable (Falck et al., 2017). In contrast, physical activity (PA) is a promising non-pharmacological strategy to reduce its risk of onset or progression in later life, probably because of lowering lipids and inflammatory markers in circulation, promoting vascular or cerebral health, and involving effects on brain plasticity and cognitive reserve (Bennett et al., 2009; Cotman and Berchtold, 2002; Kivipelto et al., 2005; Kramer and Colcombe, 2018). Leisure-time PA is becoming an important line of scientific inquiry and public interest. However, frequent PA can increase the intake of air pollutants due to an elevated respiratory rate and ventilation volume. Mounting evidence indicates the detrimental impacts of fine particulate matter ($PM_{2.5}$) on neurodegeneration illness in a dose–response manner (Chen et al., 2017a; Lee et al., 2019; Oudin et al., 2016; Ran et al., 2021). Potential mechanisms include the increase of neuroinflammation and oxidative stress, disruption of the blood–brain barrier (BBB), and microglial activation (Block et al., 2007; Block and Calderón-Garcidueñas, 2009; Calderon-Garciduenas et al., 2002).

Previous studies suggested that the amplified air pollution inhalation during exercise might override PA's benefits to cardiovascular and respiratory systems (Sinharay et al., 2018), although not always consistently so (Andersen et al., 2015; Cole-Hunter et al., 2018; Fisher et al., 2016; Guo et al., 2020b, 2020a; Kubesch et al., 2018; Sun et al., 2019). However, the risk–benefit relationship of PA and $PM_{2.5}$ to the onset and progression of dementia or Alzheimer's disease would also be an important public concern but receives less attention yet. Hong Kong is one of the heavily polluted cities in Asian, where the annual mean $PM_{2.5}$ concentration is much higher than the recommended level based on the World Health Organization (WHO) air quality guideline (Hong Kong Environmental Protection Department, 2019). In this study, we took advantage of the Chinese Elderly Health Service (EHS) cohort in Hong Kong and sought to investigate the joint associations of habitual PA and long-term $PM_{2.5}$ exposure with the incidence of all-cause dementia, Alzheimer's disease, and vascular dementia.

2. Methods

2.1. Study population

The Chinese EHS cohort is a prospective cohort, into which the elderly Hong Kong residents (≥65 years old) were eligible to enrol. The cohort data are identified routine clinical records from the health assessments of the elderly enrolled in Elderly Health Centers of the Department of Health, the Government of the Hong Kong Special Administrative Region. The initial cohort enrolled 66,820 residents aged ≥65 years during 1998–2001, forming about 9% of the aged population (≥65 years) in Hong Kong (Schooling et al., 2016). Participants were voluntarily enrolled and were followed up to 2011. Standardized field interviews were conducted by registered doctors and nurses to collect their information at baseline, containing demographic characteristics, socioeconomic status (SES), lifestyle, and pre-existing chronic conditions. Details are shown in previously published papers (Qiu et al., 2017; Ran et al., 2020; Wong et al., 2015). Ethics approval was accessed from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster and the ethics committee of the Department of Health.

2.2. Definition of habitual physical activity (PA)

Habitual PA was measured by question lists: type, weekly frequency, and duration of each session. Five types of PA were usually taken, including no exercise, walking slowly, stretching exercise, traditional Chinese exercise (TCE; Luk Tung Kuen, Tuen Kam, and Tai Chi), and aerobic exercise (playing ball games, walking uphill, swimming, cycling, and jogging). According to the Ainsworth compendium (Ainsworth et al., 2000), the intensity of each type was assigned by the standard metabolic equivalent of task (MET) value: no exercise (<1.0), walking slowly (2.0), stretching exercise (2.5), TCE (4.0), and aerobic exercise (6.0). We calculated MET-hours per week (MET-h/wk) by multiplying MET value, weekly frequency, and duration of each session. The habitual PA volume was then categorized into inactive (<1.00 MET-h/wk), low-PA (1.00–3.75 MET-h/wk), moderate-PA (3.75–7.50 MET-h/wk), and high-PA (>7.50 MET-h/wk) (Guo et al., 2020b, 2020a).

2.3. PM2.5 exposure assessment

The annual $PM_{2.5}$ concentration during 1998–2011 at each participant's residential address was assessed by a satellite-based model. In brief, we retrieved aerosol optical depth (AOD) recordings at a resolution of 10×10 km^2 from two National Aeronautics and Space Administration (NASA) satellites. It was refined into a resolution of 1×1 km^2 after adjusting for humidity and rainy days (Wong et al., 2015). We collected annual ground-level $PM_{2.5}$ records from four general monitoring stations in Hong Kong. We regressed annual surface extinction coefficients (SEC), for measuring AOD, on annual $PM_{2.5}$ from the four general monitoring stations. We estimated the annual mean $PM_{2.5}$ for participants based on the same regression equation. The satellite-based method for long-term $PM_{2.5}$ assessment was validated and widely used in previous cohort studies in Hong Kong (Qiu et al., 2017; Sun et al., 2019; Wong et al., 2015). Annual $PM_{2.5}$ mean concentrations were linked to each participant based on geocoded anonymized address, and we categorized them into low and high levels with a cutoff at the median (34.6 μg/m^3). The $PM_{2.5}$ exposure period was identified from the time of enrollment to the end of follow-up for each participant.

2.4. Prospective follow-up

Participants were followed until the year of dementia diagnosed, the death year, or the end of 2011, whichever came first. We obtained all hospitalization records from the electronic health record system administrated by the Hong Kong Hospital Authority that is a statutory body responsible for all local public hospitals. We ascertained the date of the first occurrence of hospitalization for dementia during the follow-up period as the date of incidence since we excluded prevalent dementia cases at baseline ahead of the following. The diagnosis of hospitalization was coded with the International Classification of Diseases 9th version (ICD-9). We used the principle diagnosis code at discharge to identify the incident cases of all-cause dementia (ICD-9: 290.0–290.9, 291.2, 294.1, 294.2, 331.0–331.9), Alzheimer's disease (ICD-9: 290.0, 290.2, 290.3, 331.0), and vascular dementia (ICD-9: 290.4), based on previous studies (Frain et al., 2017; Pippenger et al., 2001).

2.5. Covariates

Covariates were mainly selected according to literature (Chen et al., 2017b; Floud et al., 2020; Reitz et al., 2011), including age (65–74, 75–84, and ≥ 85), sex (female and male), BMI (<18.5, 18.5–23.9, 24.0–26.9, and >27.0), education attainment (below primary, primary, and secondary or above), monthly expenditure (<1000 HKD, 1000–2999 HKD, and ≥3000 HKD), smoking status (never, quit, and current), alcohol consumption (never, quit, social, and regular), social contact (one or more caregivers, anybody in regular contact, social activities participated, and subjective feeling of social isolated), and comorbidities (hypertension, heart disease, diabetes, and mental illness). All selected covariates were collected at baseline and were considered time-independent. Healthcare access for each participant is equitable because public hospitals dominate the local healthcare system and are easy to access for residents.

2.6. Statistical analysis

We adopted Cox proportional hazards regression models to explore and examine associations of habitual PA (volume and type) and dichotomous $PM_{2.5}$ exposure (the cut-off point is the median: 34.6 μg/m^3) with the incidence of all-cause dementia and its major subtypes. The follow-up time was selected as the underlying time scale. The time under risk for each participant was from the enrollment to the year of dementia diagnosed, the death year, or the end of 2011, whichever came first. The assumptions for the proportional hazard model setting were verified by the plot of Schoenfeld residuals before analysis. The estimation of regression coefficients is implemented by maximizing the partial likelihood profile of the regression model. We estimate the hazard ratio (HR) as well as its corresponding 95% confidence interval (CI) after controlling for the potential confounders, including age, sex, BMI, education attainment, monthly expenditure, smoking status, alcohol consumption, social contact, and pre-existing chronic conditions, as mentioned above.

Then, we examined the interaction effects of habitual PA and air pollution on both additive and multiplicative scales to test if the potential effects of habitual PA remained in the less or more polluted areas (Berrington De González and Cox, 2005; Knol and VanderWeele, 2012). Interaction on an additive scale or a multiplicative scale indicates that the joint effect of the two exposures is larger/smaller than the sum or product of their individual effects (Knol et al., 2011; Knol and VanderWeele, 2012). We created two new variables by combining $PM_{2.5}$ categories and habitual PA. One had eight categories representing eight (2×4) combinations of $PM_{2.5}$ exposure (low, and high) and habitual PA volume (inactive, low-PA, moderate-PA, and high-PA). The other had ten (2×5) categories representing ten combinations of $PM_{2.5}$ exposure (low and high) and habitual PA type (no exercise, walking slowly, stretching exercise, TCE, and aerobic exercise). We calculated the relative excess risk due to interaction (RERI) to estimate the additive interaction (Knol et al., 2011). Since RERI is recommended to encode factors from the lower risk to higher risk, we set participants with low $PM_{2.5}$ exposure and high-PA (low $PM_{2.5}$ exposure and aerobic exercise) as the combined reference subgroups (Knol et al., 2011). A RERI of less than, equal to, or more than 0 indicates negative additive interaction (joint excess risk $<$ sum of individual excess risks), no additive interaction (joint excess risk $=$ sum of individual excess risks), or positive additive interaction (joint excess risk $>$ sum of individual excess risks), respectively. A positive value of RERI illustrated that the effect of $PM_{2.5}$ exposure would significantly modify the effects of habitual PA on dementia. After the interaction in the additive scale, we further evaluated the interaction effect in the multiplicative scale. The P-value for interaction less than 0.05 indicates the existence of multiplicative interaction (Knol and VanderWeele, 2012).

We performed subgroup analysis to explore the stratification between $PM_{2.5}$ exposure and habitual PA to dementia varied by sex. Three sensitivity analyses were conducted to test the robustness of the results. First, to test the suitability of annual mean $PM_{2.5}$, we used the baseline mean $PM_{2.5}$ (1998–2001) as a proxy for long-term $PM_{2.5}$ exposure. Second, to avoid potential healthy survivor bias, we excluded participants who died or dropped out during the follow-up period. Third, to rule out the residual confounding due to cardiovascular conditions, we did another sensitivity analysis by excluding participants who had pre-existing cardiovascular conditions at baseline. A two-tailed P value <0.05 was considered as statistical significance.

2.7. Data availability statement

The cohort data will be shared upon reasonable request. The data are identified as participant data, which are available from the Hong Kong Department of Health upon reasonable request.

3. Results

A total of 57,775 old individuals (out of 66,820 in the initial cohort) with 599,396 observations were included for analysis after excluding 5,373 participants without correct address record or other demographic information, 3,327 without estimates of physical activity or $PM_{2.5}$ exposure, and 345 diagnosed with dementia when enrolling. During the follow-up, 1,157 incident cases of dementia were identified, including 642 cases of Alzheimer's disease and 324 cases of vascular dementia (Fig. 1). Fig. 2 shows the spatial distributions of dementia or non-dementia cases with varied habitual PA volumes.

Of those included (57,775 participants) at baseline, 28.3% were 75 years or older, 65.6% were female, 51.7% were identified as overweight or obese, 17.3% had secondary education degree or above, and 14.6% had a relatively higher salary. The majority of participants had no smoking (71.0%) or drinking (72.2%) habits. Regarding social contact, 75.8% had one or more regular caregivers, and 97.3% had regular social contacts, 59.6% participated in social activities, and only 5.9% had subjective feelings of social isolation. In terms of pre-existing chronic conditions, there were 35.9% participants with hypertension, 12.3% with diabetes, 12.3% with heart disease, and 3.2% with potential mental illness (especially depression and anxiety). The incident cases of all-cause dementia were more likely to be older, lower BMI, had a lower education level, and higher monthly expenditure. They might have fewer regular contacts and feel more socially isolated. And they were more likely to have had pre-existing diabetes, stroke, or mental illness (Table 1).

Participants residing in high $PM_{2.5}$ areas might have a higher risk of all-cause incident dementia than those exposed to low $PM_{2.5}$ concentration. The HR per 10 μg/m^3 increase in $PM_{2.5}$ was 1.20 (95%CI: 1.02, 1.41) for the incidence of all-cause dementia. A higher habitual PA volume was related to a lower risk of incident dementia. Especially, compared with inactive participants ($<$1.00 MET-h/wk), the HRs of all-cause incident dementia were 0.77 (95% CI: 0.66, 0.91), 0.64 (95% CI: 0.54, 0.77), and 0.59 (95% CI: 0.47, 0.75) for participants with low-PA, moderate-PA, and high PA, respectively. The beneficial effects of physical activity on the incident dementia were more pronounced for TCE and aerobic exercise, with the HRs of 0.52 (95% CI: 0.42, 0.65) and 0.50 (95% CI: 0.38, 0.66). We also found moderate benefits of walking slowly (HR: 0.74; 95% CI: 0.61, 0.90) and stretching exercise (HR: 0.81; 95% CI: 0.69, 0.95), comparing those without exercise. Comparable results were observed for both Alzheimer's disease and vascular dementia (Table 2).

Table 3 shows the joint associations of habitual PA volume and $PM_{2.5}$ exposure with incident dementia, selecting participants with high-PA and low $PM_{2.5}$ level as the reference subgroup. The HRs of all-cause dementia were 1.98 (95% CI: 1.37, 2.84) and 2.06 (95% CI: 1.45, 2.92) for inactive participants (0 MET-h/wk) residing in low and high $PM_{2.5}$ areas, respectively. Similarly, the HRs of Alzheimer's disease were 2.11 (95% CI: 1.32, 3.37) for those in low $PM_{2.5}$ area and 1.92 (95% CI: 1.21, 3.05) for those in high $PM_{2.5}$ area. We observed no clear interaction between the two variables on either additive or multiplicative scales on the main analyses (Table 3) and gender-specific subgroup analyses (Table S1).

Table 4 represents the joint effects of habitual PA type and long-term $PM_{2.5}$ exposure on incident dementia, where participants with aerobic exercise and low $PM_{2.5}$ level as the reference subgroup. A lower-intensity type of habitual PA was associated with a higher incidence risk of all-cause dementia, Alzheimer's disease, and vascular dementia, irrespective of $PM_{2.5}$ levels. For example, the HRs of all-cause dementia from no exercise were 2.09 (95% CI: 1.38, 3.16) and 2.18 (95% CI: 1.45, 3.26) for participants residing in low and high $PM_{2.5}$ areas, respectively. We also found little evidence of joint associations between habitual PA type and $PM_{2.5}$ exposure (Table 4 and Table S2).

Sensitivity analyses did not materially change our findings, including using the baseline mean $PM_{2.5}$ (1998–2001) as a proxy for long-term

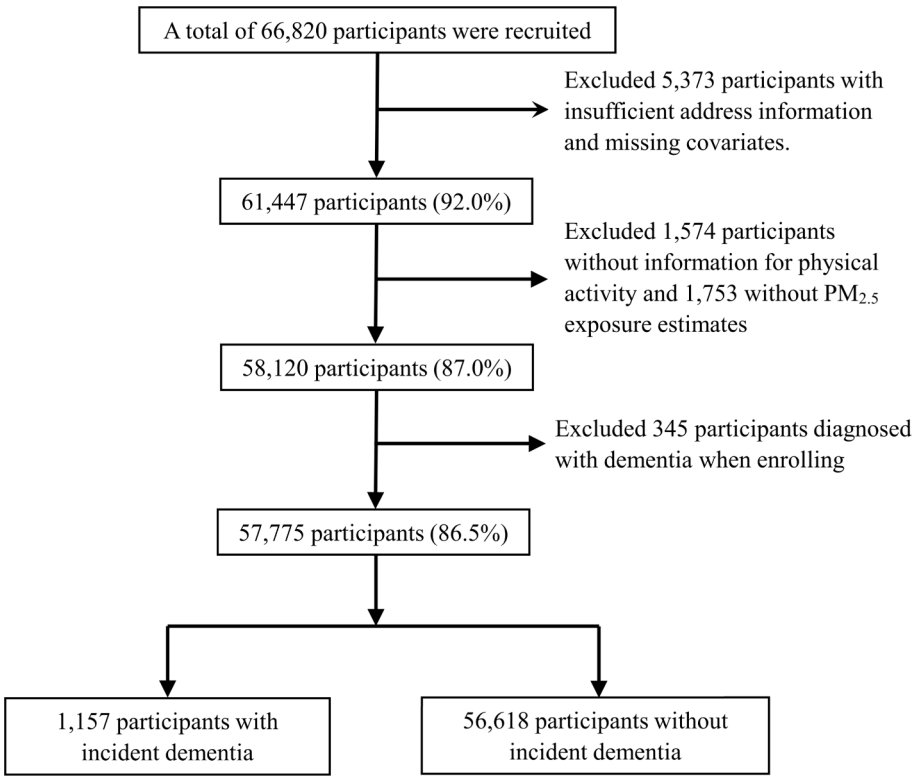

Fig. 1. Flowchart describing the inclusion of participants in the analysis.

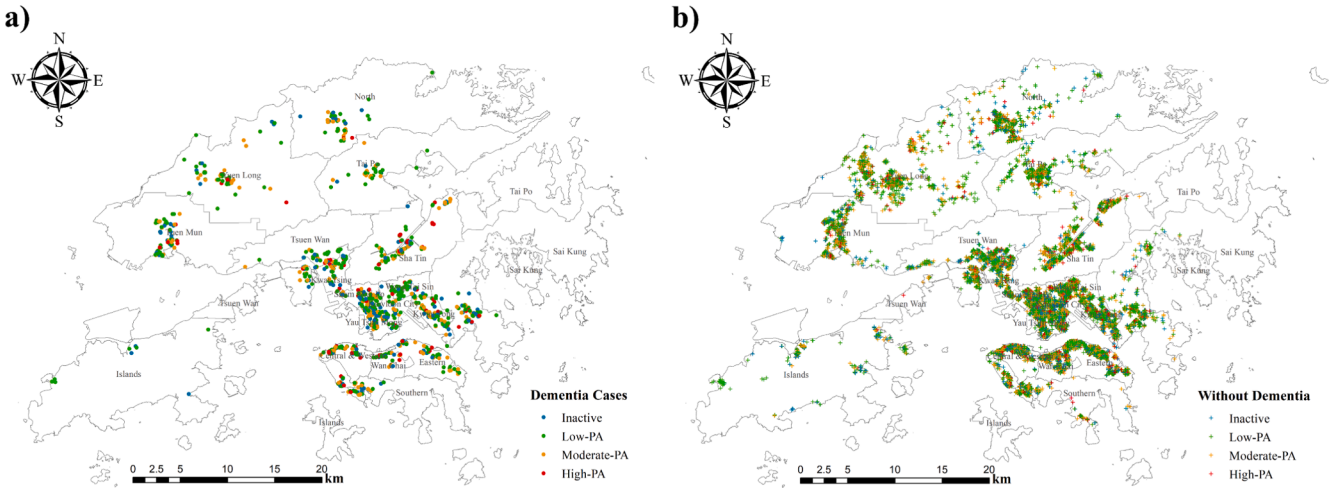

Fig. 2. Spatial distribution of participants with different habitual physical activity (PA) volumes in Hong Kong. The blue, green, yellow, and red points indicate participants with inactive, low-PA, moderate-PA, and high-PA volumes. The left panel shows the distribution of participants with all-cause dementia, and the right penal shows the distribution of those without all-cause dementia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

exposure (Table S3 and Table S4), excluding participants who died or dropped out during the follow-up period (Table S5 and Table S6), and excluding participants who had pre-existing cardiovascular conditions at baseline (Table S7 and Table S8). The beneficial effects of habitual PA on all-cause dementia or its main subtypes were still clear and robust, irrespective of residing in areas of low or high $PM_{2.5}$ concentrations.

4. Discussion

To our knowledge, this is the first study to evaluate the risk–benefit relationship of habitual PA and $PM_{2.5}$ exposure to neurodegeneration diseases. The study was conducted in Hong Kong, where the dementia prevalence is estimated to be at 7.2% among old people (≥65 years old) (Wu et al., 2018) and the annual mean $PM_{2.5}$ concentration during the study period is much higher than the WHO air quality guideline (35 μg/m^3 *vs* 10 μg/m^3). In our study, we ascertained the first occurrence of hospital admission for dementia as the incidence since we excluded all participants diagnosed with dementia at baseline. We found that habitual PA was related to a reduced incidence risk of all-cause dementia, Alzheimer's disease, and vascular dementia. The benefits were sounder for a higher PA volume or higher-intensity PA types (TCE and aerobic exercise). Long-term $PM_{2.5}$ exposure was independently linked

Table 1
Demographics and baseline characteristics of the included subjects at enrollment (1998–2000) by the incidence of all-cause dementia during the follow-up period.

	All subjects	Incidence of all-cause dementia		P-value
		Yes	No	
	(n = 57,775)	(n = 1,157)	(n = 56,618)	
Habitual PA volume, n (%)				<0.001
Inactive (=0 MET-h/wk)	9047 (15.7%)	224 (19.4%)	8823 (15.6%)	
Low-PA (0–3.75 MET-h/wk)	25,674 (44.4%)	536 (46.3%)	25,138 (44.4%)	
Moderate-PA (3.76–7.50 MET-h/wk)	16,424 (28.4%)	289 (25.0%)	16,135 (28.5%)	
High-PA (>7.50 MET-h/wk)	6630 (11.5%)	108 (9.33%)	6522 (11.5%)	
Habitual PA type, n (%)				<0.001
No exercise	9047 (15.7%)	224 (19.4%)	8823 (15.6%)	
Walking slowly	10,621 (18.4%)	213 (18.4%)	10,408 (18.4%)	
Stretching exercise	22,003 (38.1%)	510 (44.1%)	21,493 (38.0%)	
Traditional Chinese exercise	10,320 (17.9%)	143 (12.4%)	10,177 (18.0%)	
Aerobic exercise	5784 (10.0%)	67 (5.79%)	5717 (10.1%)	
$PM_{2.5}$ level, n (%)				<0.001
Low (<34.6 μg/m^3)	29,205 (50.5%)	458 (39.6%)	28,747 (50.8%)	
High (≥34.6 μg/m^3)	28,570 (49.5%)	699 (60.4%)	27,871 (49.2%)	
Age, n (%)				<0.001
65–74	41,466 (71.8%)	551 (47.6%)	40,915 (72.3%)	
75–84	14,708 (25.5%)	516 (44.6%)	14,192 (25.1%)	
≥85	1601 (2.77%)	90 (7.78%)	1511 (2.67%)	
Sex, n (%)				0.075
Female	37,903 (65.6%)	788 (68.1%)	37,115 (65.6%)	
Male	19,872 (34.4%)	369 (31.9%)	19,503 (34.4%)	
BMI, n (%)				<0.001
<18.5	3049 (5.28%)	94 (8.12%)	2955 (5.22%)	
18.5–23.9	24,865 (43.0%)	550 (47.5%)	24,315 (42.9%)	
24.0–26.9	17,546 (30.4%)	319 (27.6%)	17,227 (30.4%)	
≥27.0	12,315 (21.3%)	194 (16.8%)	12,121 (21.4%)	
Education attainment, n (%)				<0.001
Below primary	26,221 (45.4%)	622 (53.8%)	25,599 (45.2%)	
Primary	21,575 (37.3%)	391 (33.8%)	21,184 (37.4%)	
Secondary or above	9979 (17.3%)	144 (12.4%)	9835 (17.4%)	
Monthly expenditure, n (%)				<0.001
<1000 HKD	9429 (16.3%)	149 (12.9%)	9280 (16.4%)	
1000–2999 HKD	39,927 (69.1%)	799 (69.1%)	39,128 (69.1%)	
≥3000 HKD	8419 (14.6%)	209 (18.1%)	8210 (14.5%)	
Smoking status, n (%)				0.008
Never	41,048 (71.0%)	798 (69.0%)	40,250 (71.1%)	
Quit	11,100 (19.2%)	261 (22.6%)	10,839 (19.1%)	
Current	5627 (9.74%)	98 (8.47%)	5529 (9.77%)	
Alcohol consumption, n (%)				0.004
Never	41,733 (72.2%)	847 (73.2%)	40,886 (72.2%)	
Quit	5635 (9.75%)	139 (12.0%)	5496 (9.71%)	
Social	8107 (14.0%)	132 (11.4%)	7975 (14.1%)	
Regular	2300 (3.98%)	39 (3.37%)	2261 (3.99%)	
Social contact, n (%)				
Cared by a regular carer	43,776 (75.8%)	844 (72.9%)	42,932 (75.8%)	0.026
Anybody in regular contact	56,195 (97.3%)	1091 (94.3%)	55,104 (97.3%)	<0.001
Social activities participated	34,393 (59.5%)	738 (63.8%)	33,655 (59.4%)	0.003
Subjective feeling of social isolated	3396 (5.88%)	112 (9.68%)	3284 (5.80%)	<0.001
Pre-existing chronic conditions, n (%)				
Hypertension	20,743 (35.9%)	432 (37.4%)	20,311 (35.9%)	0.308
Diabetes	7079 (12.3%)	166 (14.4%)	6913 (12.2%)	0.031
Heart disease	7111 (12.3%)	162 (14.0%)	6949 (12.3%)	0.082
Stroke	1678 (2.9%)	60 (5.19%)	1618 (2.86%)	<0.001
Mental disease	1848 (3.2%)	87 (7.52%)	1761 (3.11%)	<0.001

Abbreviations: PA, physical activity; MET-h/wk, hours of the metabolic equivalent of task per week; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; BMI, body mass index.

to an increased risk of dementia onset. With the same habitual PA type or volume, participants exposing to high $PM_{2.5}$ seemed to have a higher HR than those exposed to low $PM_{2.5}$ concentration. However, the observed differences were slight and not of statistical significance, indicating little evidence of joint associations between habitual PA and $PM_{2.5}$ exposure with incident dementia. This suggests that the benefits of habitual PA for the Hong Kong aged population remain in the less or more polluted areas.

The inverse association between habitual PA and dementia, observed in our study, was in line with previous findings. Mounting evidence indicated the beneficial effects of habitual or leisure-time PA on cognitive function, reduced risk of neurodegeneration diseases, and sustained executive function in Alzheimer-type dementia (Krell-Roesch et al., 2018; Najar et al., 2019; Sabia et al., 2017; Scarmeas et al., 2009). Habitual PA is protective against cognitive decline probably through several potential bio-mechanisms: One main pathway is by preventing or limiting cardiovascular and metabolic risk factors, such as hypertension, diabetes, and hyperlipidemia (Kivipelto et al., 2005; Rosendorff et al., 2007). These factors are highly related to the onset or progress of neurodegeneration and can be modified or restricted by appropriate exercises. Habitual PA improves cerebral circulation by enhancing blood flow and oxygen supply, which can effectively prevent vascular-related mild cognitive impairment (MCI) (Hamer and Chida, 2008). Other

Table 2
Hazard ratio (HR) and 95% confidence interval (CI) of incident dementia associated with the volume and type of physical activity and long-term exposure to fine particulate matter air pollution in Hong Kong aged population (n = 57,775).

	All-cause dementia			Alzheimer's disease			Vascular dementia		
	No. events	HR (95% CI)	P-value	No. events	HR (95% CI)	P-value	No. events	HR (95% CI)	P-value
$PM_{2.5}$ level (μg/m^3)									
Low	458	1.00 [reference]		276	1.00 [reference]		113	1.00 [reference]	
High	699	1.15 (1.00, 1.33)	0.043	366	1.01 (0.84, 1.21)	0.939	211	1.38 (1.05, 1.80)	0.020
Continuous (per 10)	1157	1.20 (1.02, 1.41)	0.027	642	1.09 (0.87, 1.38)	0.457	324	1.29 (0.96, 1.72)	0.078
Habitual PA volume (MET-h/wk)									
Inactive	224	1.00 [reference]		129	1.00 [reference]		63	1.00 [reference]	
Low-PA	536	0.77 (0.66, 0.91)	0.001	301	0.75 (0.61, 0.93)	0.008	143	0.75 (0.56, 1.01)	0.062
Moderate-PA	289	0.64 (0.54, 0.77)	<0.001	153	0.60 (0.47, 0.76)	<0.001	86	0.70 (0.51, 0.98)	0.039
High-PA	108	0.59 (0.47, 0.75)	<0.001	59	0.55 (0.40, 0.76)	<0.001	32	0.62 (0.40, 0.96)	0.034
Habitual PA type									
No exercise	224	1.00 [reference]		129	1.00 [reference]		63	1.00 [reference]	
Walking slowly	213	0.74 (0.61, 0.90)	0.002	127	0.77 (0.60, 0.99)	0.039	59	0.73 (0.51, 1.04)	0.086
Stretching exercise	510	0.81 (0.69, 0.95)	0.009	278	0.75 (0.60, 0.92)	0.007	143	0.83 (0.62, 1.13)	0.236
TCE	143	0.52 (0.42, 0.65)	<0.001	78	0.51 (0.38, 0.67)	<0.001	41	0.55 (0.37, 0.82)	0.004
Aerobic exercise	67	0.50 (0.38, 0.66)	<0.001	30	0.41 (0.27, 0.61)	<0.001	18	0.48 (0.28, 0.81)	0.006

The effects are presented as the hazard ratio with 95% CI, with the participants who had high-PA volume and exposed to the low level of $PM_{2.5}$ as the reference group. The models were fully adjusted for age, sex, BMI, education attainment, monthly expenditure, smoking status, alcohol consumption, social contact, and pre-existing chronic conditions.
Abbreviations: PA, physical-activity, MET-h/wk, hours of the metabolic equivalent of task per week, PM2.5, particles with aerodynamic diameter ≤ 2.5 μm, RERI, relative excess risk due to interaction

Table 3
Additive and multiplicative interaction effects between habitual PA volume (MET-h/wk) and long-term exposure to $PM_{2.5}$ on the incident dementia in Hong Kong aged population.

	Low $PM_{2.5}$ (<34.6 μg/m^3)		High $PM_{2.5}$ (≥34.6 μg/m^3)		RERI	P for interaction
	No. events	HR (95% CI)	No. events	HR (95% CI)		
All-cause dementia						0.569
High-PA	44	1.00 [reference]	64	1.40 (0.95, 2.07)		
Moderate-PA	115	1.17 (0.83, 1.66)	174	1.41 (1.00, 1.99)	−0.16 (−2.40, 2.08)	
Low-PA	208	1.49 (1.07, 2.06)	328	1.62 (1.17, 2.24)	−0.27 (−2.75, 2.22)	
Inactive	91	1.98 (1.37, 2.84)	133	2.06 (1.45, 2.92)	−0.32 (−3.59, 2.96)	
Alzheimer's disease						0.681
High-PA	26	1.00 [reference]	33	1.21 (0.72, 2.04)		
Moderate-PA	65	1.13 (0.72, 1.79)	88	1.25 (0.80, 1.95)	−0.09 (−1.96, 1.77)	
Low-PA	128	1.57 (1.03, 2.40)	173	1.46 (0.95, 2.23)	−0.32 (−2.34, 1.70)	
Inactive	57	2.11 (1.32, 3.37)	72	1.92 (1.21, 3.05)	−0.40 (−3.25, 2.46)	
Vascular dementia						0.323
High-PA	9	1.00 [reference]	23	2.33 (1.06, 5.10)		
Moderate-PA	31	1.58 (0.75, 3.32)	55	2.17 (1.06, 4.45)	−0.74 (−4.40, 2.92)	
Low-PA	47	1.65 (0.81, 3.39)	96	2.30 (1.14, 4.62)	−0.69 (−4.64, 3.27)	
Inactive	26	2.72 (1.27, 5.85)	27	2.71 (1.28, 5.71)	−1.35 (−5.23, 2.54)	

The effects are presented as the hazard ratio with 95% CI, with the participants who had high-PA volume and exposed to the low level of $PM_{2.5}$ as the reference group. The models were fully adjusted for age, sex, BMI, education attainment, monthly expenditure, smoking status, alcohol consumption, social contact, and pre-existing chronic conditions. A RERI of less than, equal to, or more than 0 indicates negative additive interaction (joint excess risk < sum of individual excess risks), no additive interaction (joint excess risk = sum of individual excess risks), or positive additive interaction (joint excess risk > sum of individual excess risks), respectively; The P-value for interaction<0.05 indicates the existence of multiplicative interaction.
Abbreviations: PA, physical-activity; MET-h/wk, hours of the metabolic equivalent of task per week; $PM_{2.5}$, particles with aerodynamic diameter ≤ 2.5 μm.

mechanisms involve contributions to synaptic plasticity, neurogenesis, angiogenesis, synaptogenesis, and generation of brain-derived neurotrophic factors (BDNFs), which mediate the benefits of exercise on brain function (Cotman et al., 2007; Håkansson et al., 2017).

Besides the loss of life expectancy (Qi et al., 2020), exposure to $PM_{2.5}$ would result in a cognitive decline or impairment and the incidence of dementia and Alzheimer's disease, which was observed in western populations, and even those living in the Ontario of Canada, one of the territories with the best air quality (Chen et al., 2017a; Lee et al., 2019; Oudin et al., 2016). $PM_{2.5}$ can contribute to neurodegeneration probably through particle-induced systemic inflammation and direct neurodamage of particle components. $PM_{2.5}$ inhalation elevates and mobilizes plasma cytokines into circulation. The circulating cytokines (especially IL-1β and TNFα) can deteriorate the blood–brain barrier (BBB), activate microglia, and stimulate neuroinflammation and neurotoxicity when accessing the brain (Calderón-Garcidueñas et al., 2008). Neuroinflammation, BBB disruption, and microglia activation are widely accepted as biomechanism of neurodegeneration (Block and Calderón-Garcidueñas, 2009). Moreover, a recent study also found that ischemic heart disease and heart failure seemed to enhance the association between air pollution and dementia, and stroke could be a potential mediator (Grande et al., 2020). The role of cardiovascular diseases played in the pathway from air pollution exposure and dementia incidence demands further disentanglement.

No clear interaction between habitual PA and $PM_{2.5}$ exposure to dementia was observed in our study, which is partially in line with previous studies about the non-joint effects on cardiovascular and respiratory diseases. Although there are conflicting lines of evidence, the

Table 4
Additive and multiplicative interaction effects between habitual PA type and long-term exposure to PM2.5 on the dementia incidence in Hong Kong aged population.

	Low $PM_{2.5}$ (<34.6 μg/m^3)		High $PM_{2.5}$ (≥34.6 μg/m^3)		RERI	P for interaction
	No. events	HR (95% CI)	No. events	HR (95% CI)		
All-cause dementia						0.965
Aerobic exercise	30	1.00 [reference]	37	1.12 (0.69, 1.83)		
TCE	55	1.01 (0.64, 1.57)	88	1.21 (0.79, 1.84)	0.08 (−2.63, 2.79)	
Stretching exercise	195	1.59 (1.08, 2.34)	315	1.82 (1.24, 2.67)	0.10 (−4.19, 4.41)	
Walking slowly	87	1.44 (0.95, 2.19)	126	1.70 (1.14, 2.55)	0.14 (−3.89, 4.16)	
No exercise	91	2.09 (1.38, 3.16)	133	2.18 (1.45, 3.26)	−0.03 (−5.05, 4.99)	
Alzheimer's disease						0.781
Aerobic exercise	17	1.00 [reference]	13	0.66 (0.31, 1.39)		
TCE	33	1.00 (0.56, 1.80)	45	1.04 (0.59, 1.83)	0.38 (−1.93, 2.68)	
Stretching exercise	112	1.46 (0.87, 2.44)	166	1.55 (0.93, 2.58)	0.43 (−3.26, 4.12)	
Walking slowly	57	1.56 (0.90, 2.68)	70	1.56 (0.91, 2.68)	0.35 (−3.29, 3.98)	
No exercise	57	2.13 (1.23, 3.68)	72	1.94 (1.13, 3.34)	0.15 (−4.27, 4.58)	
Vascular dementia						0.362
Aerobic exercise	4	1.00 [reference]	14	3.20 (1.04, 9.78)		
TCE	14	2.02 (0.66, 6.14)	27	2.81 (0.97, 8.11)	−1.40 (−7.96, 5.15)	
Stretching exercise	49	3.16 (1.14, 8.78)	94	4.17 (1.52, 11.48)	−1.18 (−11.34, 9.03)	
Walking slowly	20	2.53 (0.86, 7.41)	39	3.89 (1.38, 10.99)	−0.83 (−10.95, 9.28)	
No exercise	26	4.54 (1.58, 13.05)	37	4.50 (1.58, 12.76)	−2.24 (−11.74, 7.27)	

The effects are presented as hazard ratio with 95% CI, with the participants who took aerobic exercise and exposed to low level of $PM_{2.5}$ as the reference group. The models were fully adjusted for age, sex, BMI, education attainment, monthly expenditure, smoking status, alcohol consumption, social contact, and pre-existing chronic conditions. The effects are presented as the hazard ratio with 95% CI, with the participants who had high-PA volume and exposed to the low level of $PM_{2.5}$ as the reference group. The models were fully adjusted for age, sex, BMI, education attainment, monthly expenditure, smoking status, alcohol consumption, social contact, and pre-existing chronic conditions. RERI, relative excess risk due to interaction. A RERI of less than, equal to, or more than 0 indicates negative additive interaction (joint excess risk < sum of individual excess risks), no additive interaction (joint excess risk = sum of individual excess risks), or positive additive interaction (joint excess risk > sum of individual excess risks), respectively; The P-value for interaction<0.05 indicates the existence of multiplicative interaction.
Abbreviations: PA, physical-activity; MET-h/wk, hours of the metabolic equivalent of task per week; $PM_{2.5}$, particles with aerodynamic diameter ≤ 2.5 μm; TCE, traditional Chinese exercise.

benefit-risk relationship between habitual PA and $PM_{2.5}$ exposure has been well-documented for cardiopulmonary diseases because outdoor exercises can inevitably result in personal inhalation of air pollution by increasing respiratory rate and ventilation volume. Moreover, the internal distribution of pollutants can also be accelerated during exercises by enhancing blood follow. Studies reported that the benefits of habitual PA would be diminished by concurrent air pollution exposure during exercises, especially benefits to blood pressure control, cardiac rehabilitation, and lung function recovery for patients with COPD or asthma (Giorgini et al., 2015; Kubesch et al., 2015; McCreanor et al., 2007; Sinharay et al., 2018). A few other studies, nevertheless, found that exposure to high levels of air pollution might not modify associations, which indicated benefits of habitual PA to the lung and cardiac functions might not be influenced by the amplified air pollutants (Cole-Hunter et al., 2018; Fisher et al., 2016; Guo et al., 2020b; Kubesch et al., 2018; Sun et al., 2019). Similar to cardiopulmonary diseases, neurodegeneration diseases are also independently related to both habitual PA and long-term $PM_{2.5}$ exposure, mentioned above. In our observation, the benefits of habitual PA was not statistically modified by risks of $PM_{2.5}$ exposure in the Hong Kong aged population probably because the beneficial effects from exercise might much overweigh the limited risks of air pollution. However, evidence in other cities or populations is highly warranted since the interaction effect on neurodegeneration diseases is hardly ever reported. Additionally, there seemed to be less of a $PM_{2.5}$-effect in the inactive group compared with the moderate-PA and low-PA groups. For example, the HRs of high-$PM_{2.5}$ and low-$PM_{2.5}$ exposures with all-cause dementia were 2.06 (95%CI: 1.45, 2.92) and 1.98 (95%CI: 1.37, 2.84), respectively. One possible reason was that inactive people might receive less ambient air pollution exposure since they spent less time outdoors.

This study has limitations. First, participants in the EHS cohort only accounts for approximately 9% of older people in Hong Kong (Schooling et al., 2016). Participants were voluntarily enrolled, and they were more health-conscious and in a better health condition. The relative risks of inactive PA and $PM_{2.5}$ exposure in the cohort might be less pronounced than those in the general Hong Kong aged population. Second, we were unable to control for the participants' cognitive levels at baseline because the information was not collected. We hence excluded participants who were diagnosed with dementia before or during the enrollment period in the main analysis as a remedial measure. However, our pre-analysis found that the excluding prevalent cases were more likely to be inactive or have a lower level of physical activity. But the difference of long-term $PM_{2.5}$ exposure between the two groups was not apparent (Table S9). Third, we selected $PM_{2.5}$ concentration at the participant's residential address as an indicator of long-term $PM_{2.5}$ exposure since we assumed that most older adults took exercises near their residences. However, exposure measurement error in $PM_{2.5}$ was also likely and might bias towards the null (Hart et al., 2015; Kioumourtzoglou et al., 2014). Fourth, numerous dementia incident cases were not identified because we retrieved dementia cases merely with the principal diagnosis code at discharge. However, the missing is likely independent of any risk or benefit factors because of the universal healthcare in Hong Kong. This nondifferential misclassification might also underestimate the true beneficial effects of habitual PA or the detrimental effects of $PM_{2.5}$ exposure on incident dementia. Additionally, residential information for each participant was collected at the baseline period and we did not have the update residential information during the follow-up period. Participants who lived in high air pollution areas were more likely to move due to high air pollution exposure. Thus, our results tend to be overestimated. Finally, we cannot fully control for unmeasured confounding by noise and greenness because relevant data were inaccessible. Studies found that noise might positively be associated with cognitive impairment and negatively relate to exercise habit (Foraster et al., 2016; Tzivian et al., 2016), while residential surrounding greenness was suggested to be linked to lower dementia risk and higher exercise frequency (Astell-Burt et al., 2020; Villeneuve et al., 2018). Noise and greenness might be common causes when estimating the association of dementia incidence with both air pollution and physical activity.

In this elderly cohort, we found that higher PA (higher PA volume

and higher-intensity PA type) and lower $PM_{2.5}$ were independently associated with a lower incidence of dementia. Our findings did not suggest any evidence of interaction effects between habitual PA and $PM_{2.5}$ exposure on dementia. The benefits of habitual PA overrode the detrimental effects of $PM_{2.5}$ exposure. Our findings may be in line with the guidelines on promoting physical activity for preventing the onset of dementia or Alzheimer's disease, even for residents living with relatively high air pollution. More studies in other populations and cities are highly warranted to validate these findings.

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CRediT authorship contribution statement

Jinjun Ran: Conceptualization, Formal analysis, Writing - original draft, Supervision. **Yamin Zhang:** Writing - original draft, Writing - review & editing. **Lefei Han:** Visualization, Writing - review & editing. **Shengzhi Sun:** Writing - review & editing, Supervision. **Shi Zhao:** Formal analysis, Methodology. **Chen Shen:** Validation, Methodology. **Xiaohong Zhang:** Writing - review & editing. **King-Pan Chan:** Investigation, Resources. **Ruby Siu-yin Lee:** Data curation, Project administration. **Yulan Qiu:** Writing - review & editing. **Linwei Tian:** Project administration, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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