The effects of ambient fine particulate matter exposure and physical activity on heart failure: a risk-benefit analysis of a prospective cohort study

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Abstract

Background: Evidence supporting the adverse effects of air pollution and the benefits of physical activity (PA) on heart failure (HF) has continued to grow. However, their joint effects remain largely unknown.

Methods: Our investigation included a total of 321,672 participants free of HF at baseline from the UK Biobank. Participants were followed up till March 2021. Information on participants' PA levels and additional covariates was collected by questionnaire. The annual fine particulate matter ($PM_{2.5}$) concentration was estimated using a Land Use Regression (LUR) model. Cox proportional hazards models were used to assess the associations of PA and $PM_{2.5}$ exposure with incident HF, as well as their interaction on both additive and multiplicative scales.

Results: During a median follow-up of 12.0 years, 8,212 cases of HF were uncovered. Compared with participants with low PA, the hazard ratios (HRs) were 0.69 (95% CI: 0.65, 0.73) and 0.61 (95% CI: 0.58, 0.65) for those with moderate and high PA, respectively. $PM_{2.5}$ was associated with an elevated risk of incident HF with an HR of 1.11 (95% CI: 1.08, 1.14) per interquartile range (IQR) increment. The synergistic additive interaction between low PA and high $PM_{2.5}$ exposure on HF was observed. Compared with participants with high PA and low $PM_{2.5}$ exposure, those with low PA and high $PM_{2.5}$ exposure had the highest risk of HF [HR (95% CI): 1.90 (1.76, 2.06)].

Conclusions: Our findings indicate that PA might still be an appropriate strategy to prevent HF for those living in areas with relatively high air pollution. Individuals with low PA may pay more attention to air pollution.

Keywords: Fine particulate matter; Physical activity; Heart failure; Prospective cohort study

1. Introduction

Heart failure (HF), characterized as a clinical syndrome caused by the impairment of cardiac structure or function, has become a critical health concern with high prevalence and mortality rate (Ambrosy et al., 2014; Bragazzi et al., 2021; Ziaeian and Fonarow, 2016). In 2017, there were 64.3 million HF cases worldwide, which attributed to 9.9 million years lived with disability (YLDs) (James et al., 2018). Additionally, HF imposes substantial economic burden with an estimated $108 billion globally per annum (Cook et al., 2014). Given the heavy disease burden, it's essential to formulate appropriate and effective public health policies for the prevention of HF.

Physical activity (PA) has been widely recognized as one significant lifestyle-related protective factor of HF (Aune et al., 2021). Previous studies have indicated that the risk of the HF would reduce progressively as PA levels increase (deFilippi et al., 2012; Kraigher-Krainer et al., 2013; Pandey et al., 2015; Patel et al., 2013; Young et al., 2014). In contrast, ambient air pollution, a serious threat to health worldwide, has been associated with the risk of HF, especially particulate matter with aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$) (Bai et al., 2019a; de Aguiar Pontes Pamplona et al., 2020; Huschmann et al., 2020; Liu et al., 2018). With an increased respiratory rate and ventilation volume during PA, it is possible that the elevated inhalation of air pollutants might reduce the beneficial effects of PA. Prior studies have reported that increased levels of air pollution could reduce and potentially override the benefits of PA on cardiovascular and respiratory health (Laeremans et al., 2018; McCreanor et al., 2007; Sinharay et al., 2018). However, the relationship between air pollution and PA

to HF has not yet been disclosed. Previous studies typically focused on the individual association of PA or air pollution with HF and have neglected their combined effect (Aune et al., 2021; Shah et al., 2013). The identification of the risk-benefit relationship between air pollution and PA would be relevant and valuable for HF prevention.

We therefore conducted this study in a large prospective cohort with the aim to assess the joint association of PA and long-term exposure to $PM_{2.5}$ with incident HF. The potential interaction effects of PA and $PM_{2.5}$ on HF were further investigated.

2. Methods

2.1 Study design and participants

Participants were drawn from the UK Biobank, a large population-based prospective study. The details of this cohort and study procedures have been reported previously (Sudlow et al., 2015). In brief, over half a million residents across the UK aged 37-73 years were enrolled across 2006 and 2010. Participants provided extensive health-related information via touchscreen questionnaires and physical measurements. The UK Biobank study was approved by the North West Multicenter Research Ethics Committee. Each participant provided written informed consent.

Among the 502,461 participants with available data, we excluded 2,741 individuals with HF at baseline based on self-reported information and medical record review. Participants with any missing data for covariates, PA, or $PM_{2.5}$ exposure were also excluded, the remaining 321,672 participants were included in the current analysis

(Figure 1).

2.2 Ambient $PM_{2.5}$ exposure assessment

The annual average concentration of $PM_{2.5}$ was estimated using a Land Use Regression (LUR) model developed by the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (Eeftens et al., 2012). The LUR model was based on ESCAPE monitoring done between 26 January 2010 - 18 January 2011, and $PM_{2.5}$ estimates were representative for the year 2010. Based on predictor variables (e.g. traffic intensity, population and land use) generated from the Geographic Information System (GIS), the LUR model was used to evaluate the spatial variation of annual average concentrations at geo-coded residential addresses of participants given at the baseline visit. Leave-one-out cross-validation displayed a good model performance for $PM_{2.5}$ (cross-validation R^2=77%) in the southeast England area (London/Oxford). Details on the development and validation of the ESCAPE LUR models have been described elsewhere (Eeftens et al., 2012). The ESCAPE estimates of $PM_{2.5}$ are valid up to 400 km from the monitoring area in Greater London. Thus, all addresses that are more than 400 km away from Greater London have missing data for the $PM_{2.5}$ measures (number of records: 33,935). The available $PM_{2.5}$ data in 2010 was used as a proxy of long-term $PM_{2.5}$ exposure, as the fluctuation of temporal trend of $PM_{2.5}$ concentrations remained generally stable during study period (Sheridan et al., 2022). Participants were further classified into two groups based on median cut-off of the $PM_{2.5}$ concentration distribution: low exposure (<9.9μg/m^3) and high exposure

(≥9.9μg/m^3).

2.3 Physical activity (PA) measurement

PA was measured using the self-reported short-form International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). Participants were asked about the frequency and duration of their engagement in three types of activity (walking, moderate and vigorous activities). The total PA was calculated in total Metabolic Equivalent Task (MET) minutes per week following the rules of IPAQ (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/ipaq_analysis.pdf). Based on IPAQ guidelines, we categorized PA into three groups: high PA (vigorous activity on at least 3 days/week achieving a minimum total PA of at least 1500 MET-minutes/week OR ≥ 7 days/week of any combination of walking, moderate or vigorous activities achieving a minimum total PA of at least 3000 MET-minutes/week), moderate PA (≥ 3 days/week of vigorous activity of at least 20 minutes per day OR ≥ 5 days/week of moderate activity and/or walking of at least 30 minutes per day OR ≥ 5 days of any combination of walking, moderate or vigorous activities achieving a minimum total physical activity of at least 600 MET-minutes/week), and low PA (no activity is reported OR some activity is reported but not enough to meet the criteria of moderate or high).

2.4 Follow-up and outcomes

Participants were followed until the date of incident HF, death, loss to follow-up, or

31 March 2021, whichever came first. HF cases were identified through self-reported information and linkages to a range of health-related records, including primary care, hospital inpatient, and death registry records in the UK Biobank. Details of these records are accessible on the UK Biobank website (https://www.ukbiobank.ac.uk). We defined incident HF based on the International Classification of Diseases, 10th revision (ICD-10: I50). The date of the first occurrence of the records for HF during the follow-up was used as the date of incident HF in our study.

2.5 Covariates

We developed a directed acyclic graph (DAG) to identify potential covariates that need to be adjusted in our multivariate analyses (Greenland et al., 1999). Based on the priori knowledge and existing literature, (Djoussé and Gaziano, 2008; Rautiainen et al., 2015; Uijl et al., 2019), we included a set of covariates in the DAG that should be considered in the analyses. Potential adjustment was considered for the variables: age, sex, ethnicity, education attainment, household income, smoking status, alcohol consumption, body mass index (BMI), fruit and vegetable intake. A minimally sufficient adjustment set was identified to account for confounding effects in the exposure-outcome relationship and included in our final model (Figure S1), including age (continuous), sex (female or male), ethnicity (White, Black, Asian, mixed or other), education attainment (higher degree, any school degree, vocational qualifications or other), household income (less than 18,000£, 18,000 to 30,999£, 31,000 to 51999£, 52,000 to 100,000£ or greater than 100,000£) and smoking status

158 (never, previous or current smoker).

159

160 **2.6 Statistical analysis**

161 We utilized Cox proportional hazards regression models to examine the impacts of
162 $PM_{2.5}$ exposure and PA on HF. The hazard ratios (HRs) and 95% confidence interval
163 (CI) were used to present the associations. The time scale was the follow-up time and
164 the proportional hazards assumptions were tested using Schoenfeld residuals. Three
165 multivariable-adjusted models were performed in our analyses. Model 1 was adjusted
166 for age, sex, ethnicity. Model 2 was adjusted for covariates of Model 1 and education
167 attainment, household income and smoking status. Model 3 was further adjusted for
168 $PM_{2.5}$ (for the association with PA) and PA (for the association with $PM_{2.5}$). We also
169 conducted subgroup analyses stratified by the levels of $PM_{2.5}$ and PA separately to
170 estimate the associations of HF with PA or $PM_{2.5}$ in each stratum.

171 We then assessed the interactive effects of $PM_{2.5}$ exposure and PA on both additive
172 and multiplicative scales (Knol and VanderWeele, 2012). To test the additive
173 interaction, we created a new variable with six groups representing six combinations
174 of $PM_{2.5}$ exposure (low and high) and PA (low, moderate, and high). Individuals with
175 low $PM_{2.5}$ and high PA were treated as the reference group (Knol et al., 2011). The
176 relative excess risk due to interaction (RERI) was calculated to estimate the
177 interaction: no additive interaction (RERI = 0), negative additive interaction (RERI <
178 0), and positive additive interaction (RERI > 0) (Li and Chambless, 2007). In the
179 current analysis, a significant positive value of RERI indicated that $PM_{2.5}$ exposure

could modify the impacts of PA on HF. We further examined the multiplicative interaction by using the likelihood ratio test comparing models with and without an interaction term between $PM_{2.5}$ exposure (low and high) and PA levels (low, moderate and high). The *P*-value for interaction <0.05 indicates the existence of multiplicative interaction (Sun et al., 2020).

To examine the robustness of our results, several sensitivity analyses were conducted: (1) additionally adjusting for the residential average 24-hour sound level of noise pollution (dB) in the model; (2) excluding incident cases of HF within the first two years of follow-up; (3) excluding participants who had pre-existing coronary heart disease or atrial fibrillation at baseline.; (4) restricting the analysis to individuals who had a fixed home address throughout the follow-up; (5) restricting incident HF cases to the source of hospital inpatient data.

All analyses were performed using R (version 4.1.2) and all statistical tests were two sides. A *P*-value of <0.05 was considered statistically significant.

3. Results

3.1 Descriptive analysis

A total of 8,212 cases of incident HF were identified during a median of 12.0 years of follow-up. Table 1 displays baseline characteristics of the participants. The mean age for those included in the study was 56.0 years, 51.0% were females, and 54.6% were never smokers. Compared with those without incident HF, the incident cases were older, mainly males and more likely to be current smokers. Additionally,

participants with incident HF had a lower PA and higher $PM_{2.5}$ exposure than those without incident HF. Compared with the included participants, individuals excluded in the current study. had similar distributions in major baseline characteristics, such as age (mean: 57.5 years [excluded participants] vs 56.0 years [included participants]), PA (low: 18.8% vs 19.0%), and $PM_{2.5}$ concentration (median: 10.0 $\mu g/m^3$ vs 9.9 $\mu g/m^3$).

3.2 Separate association of PA or $PM_{2.5}$ with incident HF

The association of PA or $PM_{2.5}$ exposure with the risk of HF is shown in Table 2. Higher PA was associated with a lower risk of incident HF. Compared with low PA, the HRs after fully adjusting for the covariates, including $PM_{2.5}$, were 0.69 (95% CI: 0.65, 0.73) and 0.61 (95% CI: 0.58, 0.65) for moderate PA and high PA, respectively. In contrast, elevated $PM_{2.5}$ exposure was associated with a higher risk of incident HF. The HR per IQR increment in $PM_{2.5}$ was 1.11 (95% CI: 1.08, 1.14). Compared with participants exposed to low $PM_{2.5}$, the HR for those with high $PM_{2.5}$ exposure after fully adjusting for covariates, including PA, was 1.16 (95% CI: 1.11, 1.21). Furthermore, results of stratified analyses showed that there was a reduced risk of developing HF in every $PM_{2.5}$ stratum associated with PA, whereas exposure to high levels of $PM_{2.5}$ increased the risk of developing HF in each PA stratum (Table 3).

3.3 Joint association of PA and $PM_{2.5}$ with incident HF

Table 4 displays the results on the combined effects of PA and $PM_{2.5}$ exposure on HF.

Participants with high $PM_{2.5}$ exposure and low PA had the highest risk of developing HF. Conversely, the reference subgroup consisted of those with low $PM_{2.5}$ exposure and high PA had the lowest risk of incident HF. The HR for those with low PA and high $PM_{2.5}$ exposure was 1.90 (95% CI: 1.76, 2.06). A significant positive RERI was observed, indicating the existence of positive additive interactions. Specifically, for low PA with high $PM_{2.5}$ exposure, the RERI was 0.24 (95% CI: 0.07, 0.40), which suggested there would be 0.24 relative excess risk because of the synergistic additive interaction.

3.4 Sensitivity analyses

In the sensitivity analyses, the results were robust after accounting for the residential noise exposure (Table S1). After excluding incident cases of HF within the first two years of follow-up, the effect estimates did not materially change (Table S2). Excluding participants who had pre-existing coronary heart disease or atrial fibrillation at baseline did not significantly change our results (Table S3). Restriction of the analysis to individuals who had a fixed home address throughout the follow-up period yielded similar results (Table S4). Moreover, the observed associations of PA and $PM_{2.5}$ exposure with HF did not change significantly after we restricted incident HF cases to the source of hospital admission data (Table S5).

4. Discussion

In this large prospective study, we found that PA was related to a reduced risk of

incident HF, whereas long-term exposure to $PM_{2.5}$ was associated with a higher risk of incident HF. The beneficial effects of PA on HF were robust in participants with different levels of $PM_{2.5}$ exposure. The positive association of long-term exposure to $PM_{2.5}$ and HF was also observed in participants with various levels of PA. Additionally, there was a synergistic additive interaction between low PA and high $PM_{2.5}$ exposure on HF, suggesting individuals with low PA may pay more attention to air pollution.

The inverse association between PA and HF, observed in our study, was consistent with previous research (Andersen et al., 2014; Bell et al., 2013; Wang et al., 2010). Substantial evidence has indicated that PA is an important protective factor against HF (Aune et al., 2021; Pandey et al., 2015). Several potential mechanisms have been proposed for the direct benefits of PA on development of HF, including the enhancement of myocardial oxygen supply, increase of capillary density, and reduction of interstitial fibrosis, which can effectively prevent the impairment of cardiac function (Emter et al., 2011; Miyachi et al., 2009). Furthermore, PA could decrease the risk of HF by lowering the chance of developing cardiovascular diseases such as hypertension and coronary heart disease, which are related to the development of HF (Aune et al., 2015; Hollingworth et al., 2015; Sofi et al., 2008).

The deleterious effect of $PM_{2.5}$ on HF has been well-established (Bai et al., 2019b; Carey et al., 2016; Stockfelt et al., 2017). Similarly, we observed that $PM_{2.5}$ was associated with an increased risk of HF. Emerging evidence indicates that $PM_{2.5}$ exposure can contribute to oxidative stress, autonomic imbalance, and systemic

inflammation, which then diminishes cardiac output and increases blood pressure (Bai et al., 2019a; Rajagopalan et al., 2018). Overstimulation of these pathways might further cause endothelial dysfunction, left ventricular hypertrophy, and myocardial fibrosis (Brook et al., 2010; Wold et al., 2012), thus, increasing the risk of HF. Of note, our results indicate that $PM_{2.5}$ exposure, even at a relatively low level (a median of 9.9 $\mu g/m^3$ in the present study), might still increase the risk of incident HF, suggesting the need to formulate more rigorous environmental health policies to reduce air pollution for HF prevention.

To the best of our knowledge, this is the first prospective study to explore the joint association of $PM_{2.5}$ exposure and PA with incident HF. We observed the beneficial effects of PA on HF remained regardless of levels of $PM_{2.5}$ exposure, highlighting the important role of PA in the prevention of HF. Our finding is similar with previous studies which suggested that the benefits of PA counterbalanced the deleterious effects of air pollution for health outcomes such as blood pressure(Avila-Palencia et al., 2019), respiratory diseases (Fisher et al., 2016), myocardial infarction (Kubesch et al., 2018), and mortality (Andersen et al., 2015). However, some studies also reported that air pollution could counteract the benefits of PA (Endes et al., 2017; Guo et al., 2020). For example, a longitudinal cohort study that included 278,065 Taiwan residents found that the increased intake of $PM_{2.5}$ due to PA may attenuate the benefits of habitual PA on lung function (Guo et al., 2020). A randomized crossover study among 135 participants aged 60 years and older showed that acute exposure to traffic pollution diminished the beneficial cardiopulmonary effects of walking (Sinharay et

al., 2018). There were augmented harmful effects of air pollution because outdoor PA might induce the amplified inhalation and deposition of air pollutants attributable to high frequency breathing (Giles and Koehle, 2014). Since a number of factors (e.g., study design, study population, health outcome and PA measurement) varied, it is difficult to directly compare our results with the previous studies. Further studies are warranted to disentangle risk–benefit relationship between air pollution and PA.

Furthermore, we found a synergistic additive interaction between low PA and high $PM_{2.5}$ exposure on HF. Previous studies indicated that the joint effects of two factors appear to follow an additive pattern under certain simple biologic models (Li and Chambless, 2007). The relative excess risk due to interaction (RERI) is often considered the standard measure for interaction on the additive scale, which better reflects biologic interaction compared with interaction on a multiplicative scale (de Mutsert et al., 2011). Additionally, measuring interaction on the additive scale can be used to assess whether there is synergism between the two risk factors (i.e., whether the combined excess risk is greater than the sum of their individual excess risks) and is more appropriate for assessing the public health importance of interactions (Knol and VanderWeele, 2012). In this study, the significant RERI indicated low PA and high $PM_{2.5}$ exposure synergistically increased the risk of HF, suggesting that the interactive effect of low PA and high $PM_{2.5}$ exposure was greater than the sum of the individual effects of the two factors. Given these results, it could be speculated that air pollution could modify the impact of PA on HF, which indicated that people with low PA might pay more attention to the air pollution. Further studies are needed to confirm

312 our findings.

313 Although the underlying mechanisms for the joint effects of PA and $PM_{2.5}$ exposure
314 on the incident HF remain unclear, several hypotheses have been proposed. A prior
315 study indicated that the additional inhaled air pollutants due to PA only account for a
316 small fraction of the total inhaled air pollutants (Rojas-Rueda et al., 2011). This might
317 partly explain the general protective effects of PA on HF regardless of levels of $PM_{2.5}$
318 exposure. Additionally, the long-term benefits of PA might reverse the acute adverse
319 health effects associated with the additional intake of air pollutants during PA
320 (Andersen et al., 2015). Previous studies also showed that PA was negatively related
321 to markers of systemic inflammation and could block the oxidative stress response
322 caused by air pollution exposure (Hou et al., 2020; Zhang et al., 2018). Thus, people
323 with low level of PA might be more susceptible to impairment of cardiac function
324 given high level of $PM_{2.5}$ exposure. It is also possible that individuals with low PA are
325 prone to overweight and obesity with changes in respiratory physiology, which may
326 enhance susceptibility to air pollution (Li et al., 2021; Xing et al., 2020).

327 Our study possessed several strengths such as a large sample size, uniform data
328 collection protocols, and long-time follow up. Moreover, we assessed the combined
329 effects of long-term $PM_{2.5}$ exposure and PA with incident HF for the first time, which
330 provided new insight on HF. However, we acknowledge that our study also has some
331 limitations. First, $PM_{2.5}$ exposure was estimated based on participants' residential
332 address at baseline without considering possible changes in $PM_{2.5}$ exposure
333 throughout the follow-up period since only the baseline assessment was available in

the UK Biobank. Fortunately, $PM_{2.5}$ levels in the UK have appeared relatively stable (https://www.gov.uk/government/statistics/emissions-of-air-pollutants) and it is reasonable to estimate that $PM_{2.5}$ pollution could remain largely unchanged. Further cohort studies with prolonged measurement of air pollution are needed to investigate the association of air pollution changes with HF. Second, PA was assessed by questionnaire and was only reported at baseline, which might introduce some bias and influence the effect estimates of PA. Furthermore, we did not distinguish whether participants performed PA indoors and outdoors because the relevant information was unavailable. Further studies with detailed information on place and environment of PA are warranted to explore the joint associations of outdoor PA and ambient $PM_{2.5}$ exposure with HF. Third, the definition of HF was based on self-reported information and medical records, which may result in potential misclassification. Future studies using more comprehensive methods, including the integration of clinical, laboratory and imaging data are needed to provide a more accurate assessment of HF. Fourth, although we considered major potential confounding factors in our analysis, some residual or unmeasured factors might still exist. For example, we cannot take into account the non-residential sources of exposure (e.g., workplace exposure) and individual activity pattern, which might produce confounding bias. Fifth, our study was observational, which limited our ability to confirm the presumed causality of results. In addition, since the majority of participants were of European ancestry, it should be cautious when generalizing our results to other populations. Finally, our study was conducted in an area with relatively low air pollution. Further studies

should consider areas experiencing higher air pollution to corroborate our findings.

5. Conclusions

In conclusion, higher PA and lower $PM_{2.5}$ were associated with a decreased risk of incident HF. The benefits of PA on HF were stable regardless of the levels of $PM_{2.5}$ exposure, indicating that high PA might still be appropriate for those residing in relatively polluted areas to prevent HF. Additionally, people with low PA might pay more attention to air pollution.

Contributors

HZ and HL conceived and designed the study, interpreted the data, and drafted and critically revised the manuscript. HZ and MC performed the statistical analysis. All authors contributed to the interpretation of the results and critical revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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