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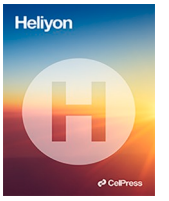

Research article

Lifestyle, air pollution, and risk of multimorbidity in a prospective analysis of the UK Biobank cohort

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ABSTRACT

Background: Although associations between chronic obstructive pulmonary disease (COPD) or ischaemic heart disease (IHD) and lifestyle factors or air pollution factors (referred as LAFs below) are well-established, it is unclear the influences of LAFs on the trajectory of IHD and COPD multimorbidity (referred as ICM below). Therefore, this study investigated the influences of LAFs on the trajectory of ICM from healthy to IHD or COPD, to ICM, and to all-cause death.

Methods: A cohort of 339,213 participants from the UK Biobank aged 37–73 who were free of IHD and COPD were included. A multi-state model was used to analyse the influences of high-risk factors including current smoking or quitting due to illness or physician's advice, current excessive alcohol drinking, physical inactivity, unhealthy body shape, and excessive air pollution with particulates matter with an aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$) on ICM trajectory.

Results: During a median follow-up of 13.74 years, 46,398 participants developed IHD or COPD (referred as IOC below), 3949 developed ICM, and 35,691 died from any cause. All five high-risk factors played crucial but different roles in these transitions. The hazard ratios (95 % confidence intervals) per one-factor increase were 1.29 (1.27–1.3), 1.38 (1.33–1.44), and 1.69 (1.56–1.84) for transitions from baseline to IOC, from IOC to ICM, and from baseline to ICM and 1.19 (1.17–1.21), 1.18 (1.15–1.21), and 1.12 (1.05–1.19) for mortality risk from baseline to all-cause death, from IOC to all-cause death, and from ICM to all-cause death, respectively.

Conclusions: Our study revealed that LAFs have a stronger impact on morbidity outcomes than on morbidity outcomes. These findings provide evidence to develop strategies for managing the trajectory of ICM.

1. Introduction

Medical advancements have significantly lengthened our lifespans while also elevating the likelihood of developing multiple chronic diseases, a condition known as multimorbidity [1]. Among these, ischaemic heart disease (IHD) is a leading cause of death worldwide [2], with 197.2 million people affected in 2019 [3]. Concurrently, chronic obstructive pulmonary disease (COPD) is ranked the third global cause of death by the World Health Organization in 2016 [4], with 212.3 million prevalent cases reported in 2019 [5]. The co-occurrence of IHD and COPD, referred to as IHD and COPD multimorbidity (ICM), significantly exacerbates healthcare challenges by diminishing the quality of life [6], increasing healthcare resource utilization [7,8], contributing to increased mortality rates

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[9], and underscoring the necessity for effective management of risk factors for multimorbidity prevention.

The effect of lifestyle factors or air pollution factors (referred as LAFs below) on COPD or IHD were well-established [10–13]. Moreover, both indoor and outdoor air pollution significantly impact health [14–18]. A study conducted across three prospective cohort revealed that a favourable lifestyle (defined as at least three of the four healthy lifestyle factors) was associated with a substantially lower risk of coronary events than an unfavourable lifestyle (defined as no or only one healthy lifestyle factor) [10]. Another health professional follow-up study on 42,847 men showed that 62 % of coronary events could have been prevented by a low-risk lifestyle [11]. Additionally, a study on 452,762 participants in the UK Biobank showed that each interquartile range increase in particulates matter with an aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$) was associated with 1.17 times the risk of COPD [12]. What's more, a study revealed that the combined of a favourable lifestyle and lower air pollution was associated with a lower risk of cardiovascular disease compared to the combined of an unfavourable lifestyle and higher air pollution [19]. Previous studies have only focused on the effect of LAFs on IHD or COPD (referred as IOC below), which underestimates the disease burden attributable to LAFs and challenges the comparison of the influences of LAFs on different transition stages. To the best of our knowledge, no previous studies have evaluated the influence of LAFs on the trajectory of ICM.

Therefore, we aimed to examine the effect on single and combined LAFs on the trajectory of ICM in UK Biobank population. Importantly, we used a multistate model to investigate the potentially different effects of LAFs on the trajectory of ICM from a state free IHD and COPD to IOC, subsequently to ICM, and finally, to all-cause death. These insights are crucial for developing strategies to manage the trajectory of ICM.

2. Methods

2.1. Study design

The UK Biobank study was a prospective population-based cohort study that recruited over 500,000 volunteers aged 37–73 years from 2006 to 2010. Participants attended one of 22 assessment centres across England, Scotland, and Wales. Participants underwent anthropometric measurements, and biospecimen collection and completed questionnaires on demographics, health behaviours, and medical history. Each participant provided written informed consent for the use of their data for research purposes. The UK Biobank study was approved by the UK Northwest Multicentre Research Ethics Committee (approval no. 11/NW/0382). Our research project was conducted under the specific application number 98577 and to explore the effects of single and combined LAFs on the trajectory of ICM.

Participants meeting any of the following criteria at baseline were excluded: already having (1) ICM (n = 1968), (2) IHD (n = 25,694), or (3) COPD (n = 8237). Consequently, we included a cohort of 466,467 participants to descriptive analysis.

2.2. Assessment of lifestyle factors and air pollution

Using baseline questionnaires and physical measurements, we assessed the following five LAFs of interest: tobacco smoking, alcohol consumption, body shape, physical activity [20], and ambient air pollution. Regarding smoking, we assigned current and former smokers who quitted because of illness or physician's advice to the high-risk group. Regarding alcohol consumption, we assigned males and females with weekly alcohol consumption $\geq$14 units to the high-risk group [21,22]. Regarding body shape, body mass index (BMI) and waist circumference (WC) were considered indicators for energy balance [23]. Participants having BMI <18.5 or $\geq$30.0 kg/m^2 or WC $\geq$ 102 cm (males)/88 cm (females) were assigned to the high-risk group [24], which emphasised avoidance of extremely high or low weight and abdominal obesity. Regarding physical activity, participants who met the 2017 UK physical activity guidelines of 150 min of walking or moderate activity or 75 min of vigorous activity per week (data-filed 22036) were assigned to the low-risk group [25]. $PM_{2.5}$ was considered the most dangerous pollutant owing to its ability to penetrate the lung barrier and enter the blood system, resulting in cardiovascular and respiratory diseases and cancers. Long-term exposure to $PM_{2.5}$ was measured using a land use regression model developed for the European Study of Cohort for Air Pollution Effects (ESCAPE) [26]. The distribution of $PM_{2.5}$ was shown in Fig. S1. Regarding air pollution, we assigned participants residing in environments with >10 $\mu g/m^3$ of $PM_{2.5}$ to the high-risk group, according to the WHO guideline [27]. Additional details on the assessment of each factor are presented in Table S1. Participants belonging to the high-risk group were assigned code 1; otherwise, they were assigned code 0. The number of high-risk LAFs ranged 0–5.

2.3. Covariates

Using a baseline questionnaire, we assessed the following covariates: sociodemographic characteristics, ethnicity, education level, socioeconomic status, family history of bronchitis/emphysema, and family history of heart disease. Ethnicity was categorised as White, Asian or Asian British, Black or Black British, or other. Education level was categorised as high (college or university degree), intermediate (A/AS levels or equivalent, O levels/General Certificate of Secondary Education or equivalent), or low (none of the aforementioned) [28]. Socioeconomic status was measured using the Townsend Deprivation Index, a composite score based on the participants' residential postcode at recruitment and categorised based on quartiles [29]. Lower Townsend Deprivation Index values indicate higher socioeconomic levels. A family history of heart disease or bronchitis/emphysema was defined using self-reported. Additional details of covariates are presented in Table S2. We did not consider clinical factors such as total cholesterol level, blood

pressure, forced expiratory volume, and forced vital capacity because they are potential mediators between LAFs and ICM [30]. The missing data for alcohol consumption, tobacco smoking, physical activity, ambient air pollution, ethnicity, and education level were 1, 503, 1,608, 89,869, 30,964, 1,039, and 2,272, respectively. We excluded the participants with missing variables and 339,213 participants were included in the multistate analyses (Fig. S2).

2.4. Follow-up for COPD, IHD, and all-cause death

The incidence of COPD in the UK Biobank is based on medical history and linkage to hospital admission data. We used the diagnosed of COPD provided by UK Biobank, which was defined by the International Classification of Diseases (ICD, 10th Revision) as J43–J44 (J43: emphysema; J44: other chronic obstructive pulmonary disease). Similarly, IHD was defined with the ICD 10 codes I20–I25. ICM was defined as having COPD and IHD during follow-up. The causes of death were mainly ascertained by the National Health Service (NHS) Information Centre in England and Wales and the NHS Central Register for Scotland. The period of followed up of participants from enrolment until death, loss to follow-up, the outcomes (i.e. COPD, IHD, ICM), or May 31, 2023, whichever came first. Moreover, we calculated the mean survival time of the participants from baseline to the occurrence of COPD, IHD, ICM, and all-cause death.

2.5. Statistical analysis

We used the Cox proportional hazards model to estimate the hazard ratios (HRs) and 95 % CIs of IOC, ICM, and all-cause mortality for high-risk LAFs (individual or combined). The model was adjusted for age, sex, ethnicity, education level, Townsend Deprivation Index score, family history of bronchitis/emphysema, and family history of heart disease in the subsequent analyses. The model simultaneously included five LAFs in the analyses of individual LAFs. The number of high-risk LAFs was entered into the model as a categorical variable, with 0–1 high-risk LAF as the reference group because 0 and 1 high-risk LAF had no significant difference in the transitions. High-risk LAFs were also entered into a separate model as an ordinal variable to assess the HR of events of interest per factor increase in the number of LAFs.

Furthermore, we used multistate model to assess the role of individual and combined LAFs in disease progression from baseline to IOC, ICM, and all-cause death [31]. The multistate model is an extension of the competing risk model and is useful for exploring how certain factors influence different phases of a process [32]. In line with previous studies [20,33], six transition stages were constructed based on the ICM trajectory (Fig. 1): (i) baseline to IOC, (ii) IOC to ICM, (iii) baseline to ICM, (iv) ICM to all-cause death, (v) IOC to death from any cause, and (vi) baseline to death from a disease other than IOC. What's more, we divided the IOC into two individual diseases, COPD and IHD, resulting in nine transitions. Regarding participants who entered different states on the same date (i.e., IHD and all-cause death), we calculated the entering date of the theoretically prior state as the entering date of the later state minus 0.5 days. For example, the date of IHD occurrence was equal to the date of death minus 0.5 days in participants who died from IHD.

Several sensitivity analyses for the multistate analyses were conducted: (i) to test whether the baseline disease status affects the trajectory of ICM, we additionally adjusted for diabetes, hypertension, asthma, and cancer at baseline; (ii) to exclude the possible influence of delayed diagnosis of IOC, we excluded IOC events occurring in the first two years of follow-up; (iii) considering that participants who developed ICM on the same date might have done so due to delayed diagnosis, we excluded those participants to avoid bias; (iv) to account for the potential impact of baseline cancer status on the development of IHD, we excluded participants with cancer at baseline. (v) to validate whether there were differences in the impact of $PM_{2.5}$ on the trajectory of ICM when treated as a categorical variable versus a continuous variable, we explored its effects by treating $PM_{2.5}$ as a continuous variable. To explore the effects of the category of sex, age, and Townsend Deprivation Index on the trajectory of ICM, we used a multistate model to explore the effect according to these variables. All the analyses were performed using the R software (version 4.2.0). The multistate model was performed using the 'mstate' package of R. All statistical tests were two-tailed, and statistical significance was set at $P < 0.05$.

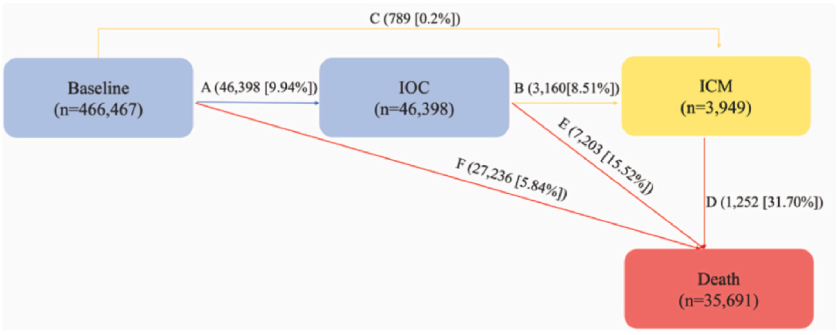

Fig. 1. Number (percentages) of participants for Pattern A from baseline to IOC, ICM, and death. IOC presents ischaemic heart disease or chronic obstructive pulmonary disease. ICM presents ischaemic heart disease and chronic obstructive pulmonary disease multimorbidity.

3. Results

3.1. Descriptive analysis

The mean age of 466,467 participants was 56.16 years (standard deviation [SD], 8.09 years) at baseline. Of them, 44.22 % were males, and 94.67 % were White. During a median follow-up of 13.74 years (IQR 13.01–14.46 years; total person-years (PYs) 6,277,018), 46,398 participants experienced IOC, with a crude incidence rate of 7.77 per 1000 PYs (transition A, Fig. 1). A total of 3160 participants (12.73/1000 PYs) developed ICM from the IOC (transition B), whereas 789 (122.75/1000 PYs) developed ICM from the baseline (transition C). Subsequently, 1252 participants (86.36/1000 PYs) died from any cause from ICM (transition D), 7203 (27.50/1000 PYs) died from IOC (transition E), and 27,236 (117.80/1000 PYs) died from the baseline (transition F). The primary cause of death from baseline was cancer (ICD-10: C00–C97), accounting for 55.56 % of the deaths. 37.53 % death from IOC and ICM was caused by diseases in the circulatory system (ICD-10: I00–I99) and respiratory system (ICD-10: J00–J99). In the analysis for individual diseases, the mortality rate among participants with ICM was 31.70 %, which was higher than the mortality rate of any single (IHD or COPD) (Fig. S3).

Participants who developed IOC or ICM were more likely to be older, males, and had lower economic levels, lower education levels, higher smoking rates, higher Townsend Deprivation Index, family history of bronchitis/emphysema, and heart disease than those who were free of IHD and COPD during the follow-up (Table S3).

Participants who developed ICM on the same date were more likely to be older, males, and had lower education levels, higher

Table 1
Hazard ratios (95 % confidence intervals) for Pattern A by lifestyle and air pollution factors.

Transitions	No. of events	HRs (95%CIs)	*P*
Tobacco smoking			
Baseline → IOC	8082	**2.34 (2.28–2.41)**	**<0.001**
IOC → ICM	966	**2.66 (2.44–2.91)**	**<0.001**
Baseline → ICM	244	**5.42 (4.55–6.45)**	**<0.001**
Baseline → Death	3202	**1.64 (1.57–1.70)**	**<0.001**
IOC → Death	1649	**1.87 (1.76–1.99)**	**<0.001**
ICM → Death	424	**1.41 (1.22–1.62)**	**<0.001**
Excessive alcohol drinking			
Baseline → IOC	22,433	**1.03 (1.00–1.05)**	**0.034**
IOC → ICM	1520	1.08 (0.98–1.19)	0.101
Baseline → ICM	393	1.16 (0.96–1.40)	0.129
Baseline → Death	12,466	**1.05 (1.02–1.08)**	**0.002**
IOC → Death	3359	1.02 (0.96–1.08)	0.59
ICM → Death	601	1.04 (0.89–1.22)	0.603
Unhealthy body shape			
Baseline → IOC	14,851	**1.40 (1.37–1.43)**	**<0.001**
IOC → ICM	1116	**1.24 (1.14–1.35)**	**<0.001**
Baseline → ICM	274	**1.58 (1.34–1.88)**	**<0.001**
Baseline → Death	7762	**1.26 (1.22–1.30)**	**<0.001**
IOC → Death	2321	**1.08 (1.02–1.14)**	**0.007**
ICM → Death	428	0.98 (0.85–1.12)	0.724
Low physical activity			
Baseline → IOC	6484	**1.11 (1.08–1.14)**	**<0.001**
IOC → ICM	506	**1.24 (1.12–1.37)**	**<0.001**
Baseline → ICM	108	1.11 (0.90–1.37)	0.339
Baseline → Death	3728	**1.2 (1.16–1.25)**	**<0.001**
IOC → Death	1094	**1.23 (1.15–1.31)**	**<0.001**
ICM → Death	206	1.17 (1.00–1.38)	0.051
Excessive air pollution			
Baseline → IOC	15,896	**1.04 (1.02–1.07)**	**<0.001**
IOC → ICM	1180	**1.12 (1.03–1.23)**	**0.010**
Baseline → ICM	303	**1.22 (1.02–1.45)**	**0.029**
Baseline → Death	8709	**1.06 (1.03–1.10)**	**<0.001**
IOC → Death	2390	0.98 (0.93–1.04)	0.58
ICM → Death	473	1.08 (0.94–1.25)	0.274

No. refers to the number of events in each transition with the corresponding exposure. HR, hazard ratio; CI, confidence interval. IOC, ischaemic heart disease or chronic obstructive pulmonary disease; ICM, chronic obstructive pulmonary disease and ischaemic heart disease multimorbidity. The multivariate models were adjusted for age, sex, ethnicity, educational level, Townsend Deprivation Index, family history of bronchitis/emphysema, and family history of heart disease. The five factors were mutually adjusted in the analyses of dichotomous lifestyle and air pollution factors. Values in bold indicate statistical significance ($P < 0.05$). High-risk lifestyle and air pollution factors were defined as follows: current smoking or quitted owing to illness or physician's advice; weekly drinking ≥14 units; low physical activity with less than 150 min of walking or moderate activity or 75 min of vigorous activity per week; having body mass index <18.5 or ≥30.0 kg/m^2 or waist circumference ≥102 cm (males)/88 cm (females); having PM2.5 ≥ 10 $\mu g/m^3$.

smoking rates, higher Townsend Deprivation Index, and a family history of bronchitis/emphysema compared with the overall cohort (Table S4). Furthermore, females were more likely to have high-risk LAFs than males, with 28.97 % of females and 23.39 % of males having three or more high-risk LAFs.

3.2. The effect of high-risk LAFs on IOC, ICM, and all-cause death using conventional method

All five high-risk LAFs were associated with an increased risk of IOC, ICM, and all-cause mortality using conventional analysis of

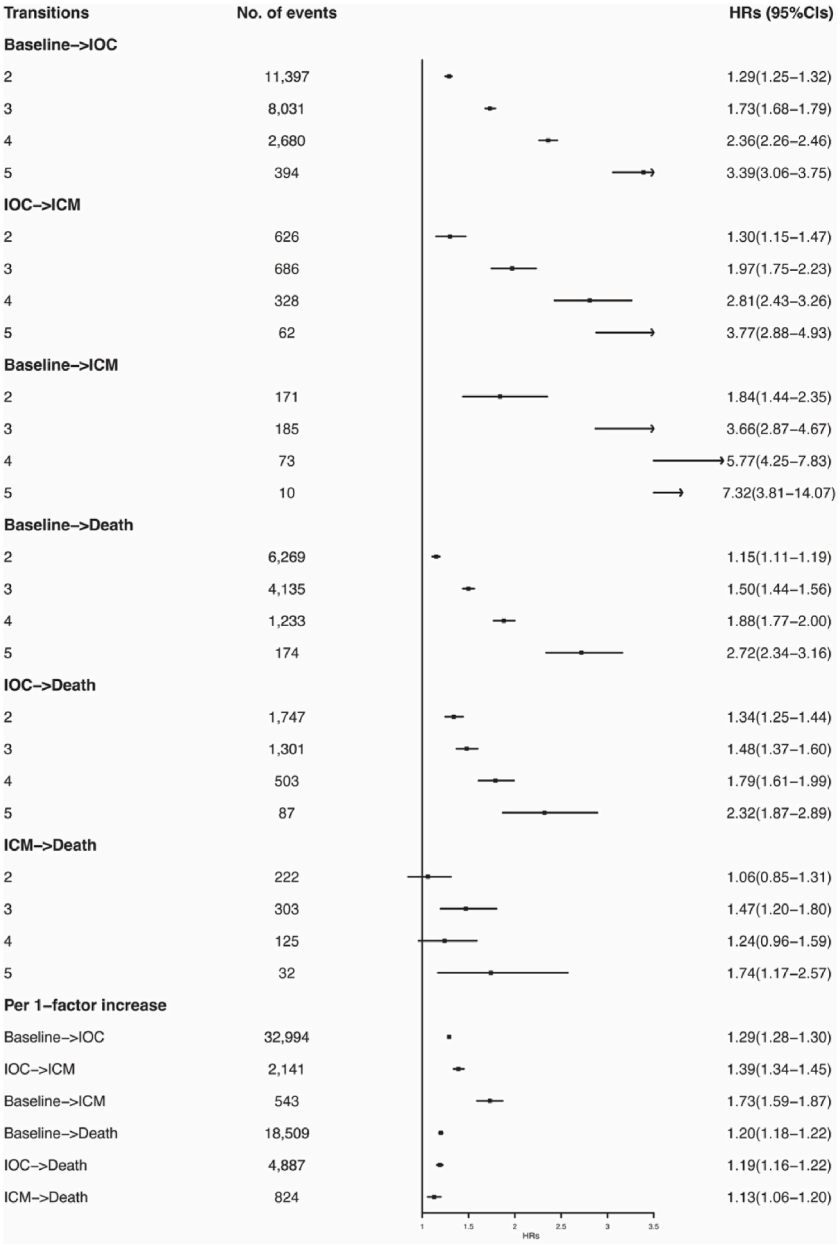

Fig. 2. Hazard ratios (95%CIs) for Pattern A by number of high-risk lifestyle and air pollution factors among 339,213 participants. No. of events refers to the number of events in each transition with the corresponding exposure; HR, hazard ratio; CI, confidence interval; IOC, ischaemic heart disease or chronic obstructive pulmonary disease; ICM, ischaemic heart disease and chronic obstructive pulmonary disease multimorbidity. Multivariable models were adjusted for age, sex, ethnicity, education level, Townsend Deprivation Index, family history of bronchitis/emphysema, and family history of heart disease. The reference group was those having 0–1 lifestyle and air pollution factors. High-risk lifestyle and air pollution factors were defined as follows: current smoking or having quit due to illness or physician's advice; weekly drinking $\geq$14 units; low physical activity with <150 min of walking or moderate activity per week or 75 min of vigorous activity; having BMI <18.5 or $\geq$30.0 kg/m^2 or having waist circumference $\geq$102 cm (men)/88 cm (women); having $PM_{2.5} \geq 10\ \mu g/m^3$.

Cox proportional hazards model (Table S5). Tobacco smoking showed the strongest association with IOC, ICM, and all-cause mortality (HRs (95 % CIs): 2.34 (2.28–2.41), 5.18 (4.78–5.6), and 1.99 (1.92–2.04), respectively). The hazard ratio of IOC, ICM, and all-cause death with an increasing number of high-risk were 1.29 (1.28–1.3), 1.74 (1.68–1.81), and 1.25(1.24–1.27), respectively.

We used the conventional analysis strategy to explore the effect of risk factors for multimorbidity and observed a slightly stronger association between LAFs and ICM than between LAFs and IOC. This strategy uses participants free of IHD and COPD at baseline to directly analyse the association between LAFs and the ICM. Those who developed only COPD or IHD and survived or died during the follow-up period were simply regarded as censored. We found it difficult to distinguish whether LAFs has a different impact on the trajectory of ICM.

3.3. The effect of high-risk LAFs on the trajectory of ICM using multi-state model

Multistate analyses showed the same results for the transition from baseline to IOC as the Cox regression analyses but further distinguished the roles of high-risk LAFs in the trajectories of ICM (Table 1). Smoking was the most dangerous risk factor among the five LAFs in the trajectories of ICM. The influence of an unhealthy body shape on the transition to IOC was stronger than that on the transition to subsequent ICM. Moreover, the effect of the association of smoking, unhealthy body shape, and excessive air pollution with mortality outcomes (either from IOC or ICM to mortality) was less than that with morbidity outcomes. We observed that LAFs influenced each transition but to different extents. We found that high-risk LAFs had a greater risk on morbidity outcomes than on mortality outcomes, suggesting that the interventions for LAFs can exert a more pronounced impact on preventing or addressing the early stages of the disease, and their efficacy diminishes in the later stages.

Gradients in the associations were observed between the number of high-risk LAFs and all six transitions when LAFs were combined (Fig. 2). We also observed a stronger association of the number of LAFs with morbidity outcomes (from baseline to IOC or ICM) than with mortality outcomes (from baseline, IOC, or ICM to death). The adjusted HRs (95 % CIs) per one-factor increase were 1.29 (1.28–1.30) from baseline to IOC, 1.39 (1.34–1.45) from IOC to ICM, 1.73 (1.59–1.87) from baseline to ICM, 1.2 (1.18–1.22) from baseline to death, 1.19 (1.16–1.22) from IOC to all-cause death, and 1.13 (1.06–1.20) from ICM to all-cause death, respectively.

Smoking was significantly associated with all transitions after dividing the IOC into COPD and IHD (Table 2). The hazard ratios for an unhealthy body shape from the transition baseline to IHD were greater than that from the transition baseline to COPD. In contrast, excessive air pollution was associated with the transition from baseline to COPD but not with IHD. We also observed gradients in the associations of combined LAFs with all transitions (Table 3). LAFs had a greater impact on from baseline to COPD than that from baseline to IHD; contrast results were observed on the transition from COPD to ICM than that from IHD to ICM. LAFs had the greatest impact on the transition from baseline to ICM.

Table 2
Hazard ratios (95 % confidence intervals) for each transition in Pattern B by lifestyle and air pollution factors.

	No. of events	Tobacco smoking	Excessive alcohol drinking	Unhealthy body shape	Low physical activity	Excessive air pollution
Baseline → IOC						
Baseline → COPD	9473	**6.21 (5.96–6.48)**	**1.10 (1.05–1.15)**	**1.29 (1.24–1.35)**	**1.22 (1.16–1.28)**	**1.08 (1.04–1.13)**
Baseline → IHD	23,521	**1.35 (1.30–1.39)**	1.00 (0.97–1.03)	**1.45 (1.41–1.49)**	**1.06 (1.03–1.10)**	1.03 (1.00–1.05)
IOC → ICM						
COPD → ICM	964	**1.20 (1.05–1.37)**	0.98 (0.85–1.13)	**1.26 (1.11–1.43)**	**1.22 (1.06–1.41)**	1.06 (0.93–1.22)
IHD → ICM	1177	**3.85 (3.41–4.34)**	1.12 (0.99–1.28)	**1.19 (1.06–1.34)**	**1.20 (1.04–1.38)**	**1.16 (1.03–1.31)**
Baseline → ICM	543	**5.42 (4.55–6.45)**	1.16 (0.96–1.40)	**1.58 (1.34–1.88)**	1.11 (0.90–1.37)	**1.22 (1.02–1.45)**
Baseline → Death	18,509	**1.64 (1.57–1.70)**	**1.05 (1.02–1.08)**	**1.26 (1.22–1.30)**	**1.20 (1.16–1.25)**	**1.06 (1.03–1.10)**
IOC → Death						
COPD → Death	2016	**1.56 (1.42–1.71)**	1.01 (0.92–1.12)	0.96 (0.88–1.05)	1.08 (0.97–1.20)	0.89 (0.81–0.98)
IHD → Death	2871	**1.44 (1.31–1.59)**	1.00 (0.92–1.08)	**1.19 (1.10–1.28)**	**1.28 (1.18–1.40)**	1.03 (0.95–1.11)
ICM → Death	824	**1.41 (1.22–1.62)**	1.04 (0.89–1.22)	0.98 (0.85–1.12)	1.17 (1.00–1.38)	1.08 (0.94–1.25)

No. where denotes the number of transitions. COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; IOC, ischaemic heart disease or chronic obstructive pulmonary disease; ICM, ischaemic heart disease and chronic obstructive pulmonary disease. The multivariate models were adjusted for age, sex, ethnicity, educational level, Townsend Deprivation Index, family history of bronchitis/emphysema, and family history of heart disease. The five factors were mutually adjusted in the analyses of dichotomous lifestyle and air pollution factors. Values in bold indicate statistical significance ($P<0.05$).

High-risk lifestyle factors and air pollution factors were defined as follows: current smoking or quitted owing to illness or doctor's advice; weekly drinking ≥14 units; low physical activity with less than 150 min of walking or moderate activity or 75 min of vigorous activity per week; having body mass index <18.5 or ≥30.0 kg/m^2 or having waist circumference ≥102 cm (males)/88 cm (females); having $PM_{2.5} \geq 10\ \mu g/m^3$.

Table 3
Hazard ratios (95 % confidence intervals) for each transition in Pattern B by number of high-risk factors.

	No. of events	0–1	2	3	4	5	Ordinal scale
Baseline → IOC							
Baseline → COPD	9473	Reference	**1.66 (1.57–1.76)**	**2.94 (2.78–3.12)**	**4.96 (4.61–5.33)**	**8.13 (7.04–9.38)**	**1.65 (1.62–1.68)**
Baseline → IHD	23,521	Reference	**1.19 (1.16–1.23)**	**1.42 (1.37–1.47)**	**1.66 (1.57–1.76)**	**2.08 (1.79–2.40)**	**1.16 (1.15–1.18)**
IOC → ICM							
COPD → ICM	964	Reference	0.95 (0.78–1.14)	**1.21 (1.00–1.45)**	**1.45 (1.17–1.80)**	**1.79 (1.25–2.56)**	**1.15 (1.08–1.21)**
IHD→ ICM	1177	Reference	**1.43 (1.21–1.67)**	**2.22 (1.89–2.62)**	**3.45 (2.83–4.22)**	**4.91 (3.25–7.44)**	**1.47 (1.40–1.56)**
Baseline → ICM	543	Reference	**1.84 (1.44–2.35)**	**3.66 (2.87–4.67)**	**5.77 (4.25–7.83)**	**7.32 (3.81–14.07)**	**1.73 (1.59–1.87)**
Baseline → Death	18,509	Reference	**1.15 (1.11–1.19)**	**1.50 (1.44–1.56)**	**1.88 (1.77–2.00)**	**2.72 (2.34–3.16)**	**1.20 (1.18–1.22)**
IOC → Death							
COPD → Death	2016	Reference	**1.27 (1.16–1.39)**	**1.34 (1.21–1.49)**	**1.64 (1.41–1.9)**	**2.65 (1.89–3.72)**	**1.16 (1.12–1.20)**
IHD → Death	2871	Reference	**1.28 (1.13–1.46)**	**1.29 (1.13–1.47)**	**1.35 (1.15–1.59)**	**1.40 (1.04–1.88)**	**1.08 (1.04–1.13)**
ICM → Death	824	Reference	1.06 (0.85–1.31)	**1.47 (1.20–1.80)**	1.24 (0.96–1.59)	**1.74 (1.17–2.57)**	**1.13 (1.06–1.20)**

No. of events refers to the number of events in each transition: COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; IOC, ischaemic heart disease or chronic obstructive pulmonary disease; ICM, ischaemic heart disease, and chronic obstructive pulmonary disease multimorbidity.
The multivariate models were adjusted for age, sex, ethnicity, educational level, Townsend Deprivation Index, family history of bronchitis/emphysema, and family history of heart disease. Values in bold indicate statistical significance ($P < 0.05$).

High-risk lifestyle factors and air pollution factors were defined as follows: current smoking or quitted owing to illness or doctor's advice; weekly drinking ≥14 units; low physical activity with less than 150 min of walking or moderate activity or 75 min of vigorous activity per week; having body mass index <18.5 or ≥30.0 kg/m^2 or having waist circumference ≥102 cm (males)/88 cm (females); having $PM_{2.5} \geq 10\ \mu g/m^3$.

The reference group was those with 0–1 lifestyle factors and air pollution factors. High-risk lifestyle and air pollution factors were defined as follows: current smoking or quitted because of illness or physician's advice; weekly drinking ≥14 units; low physical activity with less than 150 min of walking or moderate activity or 75 min of vigorous activity per week; having BMI <18.5 or ≥30.0 kg/m^2 or waist circumference ≥102 cm (males)/88 cm (females); having $PM_{2.5} \geq 10\ \mu g/m^3$.

3.4. Sensitivity and stratified analyses

The results were not substantially altered in sensitivity analyses in lifestyle and air pollution or in combined of high-risk lifestyle and air pollution (Tables S6 and S7). Compared to treating $PM_{2.5}$ as a categorical variable, the trend of its impact on the trajectory of ICM is consistent when treated as a continuous variable and the effect size was smaller (Table S8). Taking those with 0–1 high-risk LAFs as the reference, the associations of having 4–5 factors with all transitions were stronger among middle-aged participants when the analysis was stratified by age (<50 years, 50–59 years, ≥60 years). Furthermore, the HRs of almost all transitions increased as the Townsend Deprivation Index increased (Figs. S4 and S5).

4. Discussion

The present prospective study of the UK biobank data demonstrated that the five high-risk LAFs played important roles in all disease transition stages, to different extents. The association of LAFs with morbidity outcomes was stronger than with mortality outcomes. In addition, a stronger impact of LAFs on morbidity outcomes (from baseline to IOC and from IOC to ICM) was observed among middle-aged participants than among older participants. Moreover, we found that single LAFs had different effects on disease-specific transitions when IOC was further divided into IHD and COPD.

Four previous studies have estimated the association of LAFs with IHD or COPD among participants without IHD or COPD at baseline, respectively [10–13]. A study using three prospective cohorts revealed that an unfavourable lifestyle (no or only one healthy lifestyle factor) was associated with a higher risk of coronary events than a favourable lifestyle [10]. Another health professional follow-up study on 42,847 men showed that men in the low-risk group for all five lifestyle practices had a relative risk of 0.37 (95 % CI, 0.26–0.53)] when compared with remaining men in the population [11]. A previous study using 452,762 participants from the UK Biobank showed that each IQR increase in $PM_{2.5}$ was associated with the increased risk of COPD [12]. Additionally, UK Biobank study revealed that ambient air pollution was associated with lower lung function and increased COPD prevalence [13]. Furthermore, while several studies have highlighted significant impacts of both indoor and outdoor air pollution on health [14–18], previous studies have primarily focused on the effect of LAFs on IOC, thereby underestimating the disease burden attributable to LAFs and complicating the comparison of their influences across different transition stages. Our study expands on this by exploring the impact of LAFs on the trajectory of ICM, allowing for a comprehensive comparison of their effect on various transition stages.

In our study, we found that a single LAF had a distinct effect on different transition stages. For example, an unhealthy body shape was associated with an increased risk of all morbidity outcomes but was not associated with mortality risk from ICM to all-cause death. Single LAFs exerted different influences on disease-specific transitions, even within certain transition stages. For example, smoking, and excessive air pollution were more specifically related to COPD risk than IHD risk, whereas unhealthy body shape was more related to IHD risk than to COPD risk. Smoking and excessive air pollution were well-established risk factor for COPD due to its role in causing

chronic inflammation, oxidative stress, and direct damage to the respiratory [34,35], however, unhealthy body shape, involving metabolic syndrome, obesity, is directly linked to the IHD [36]. Furthermore, our analyses showed that tobacco smoking had the highest effect on all transitions, followed by an unhealthy body shape, low physical activity, excessive air pollution, and excessive alcohol consumption.

In addition to LAFs, several other factors affect the ICM trajectory and may cover up the relative importance of LAFs in determining the risk of developing ICM. The prevalence and mortality rates of IHD and COPD have progressively declined over the last few decades in most Western countries [5,37], partly owing to effective medical intervention [38–41]. Nonetheless, LAFs remain non-negligible contributors to the ICM trajectory. HRs of the five high-risk LAFs from baseline to IOC and then to ICM were more than three times higher than those with 0–1 LAFs, suggesting a considerable potential of LAFs intervention to prevent the progression of ICM. In the era of ageing and multimorbidity, the LAFs intervention is of great significance to reduce the rising medication cost and burden of polypharmacy.

Moreover, our stratified analysis revealed that LAFs had a relatively larger effect on the risk of IOC and subsequent ICM among middle-aged participants than older participants. This may be attributed to the relatively higher baseline hazard for older participants and the survival effect, i.e., participants at high risk of death had already died before enrolment. These findings indicate the importance of strengthening lifestyle interventions and improving air quality among middle-aged participants.

We calculated the survival time associated with each transition and observed a notably short duration from ICM onset to all-cause death, emphasising the importance value of early intervention of LAFs. Furthermore, we noted that the duration from COPD to ICM was relatively short when comparing survival times from IHD to ICM. We gained a more comprehensive understanding of the trajectory of ICM through these analyses, thereby providing valuable insights into its prevention.

Our study demonstrated that COPD and IHD mutually influence each other. However, the mechanism underlying ICM remain unclear. Various biological processes, including hypoxia, systemic inflammation, endothelial dysfunction, heightened platelet reactivity, arterial stiffness, and right ventricle modification, interact in the development of ICM [42], which therefore deserves special attention in early diagnosis and treatment.

The major strengths of the current study include the large sample size of UK biobank participants, which enabled the study of two main causes of death (IHD and COPD) and the trajectory of ICM. Another distinctive feature of our study is the use of a multistate model, which yielded less biased estimates than the conventional Cox regression model and distinguished the impact of LAFs on each transition on the ICM trajectory. This is also one of the largest prospective studies on the association between LAFs and ICM worldwide.

Nevertheless, our study had some limitations. First, behavioural changes before and after baseline examinations might have influenced these events. We attempted to reduce the effects of behavioural changes related to COPD or IHD by excluding all patients with a history of COPD or IHD. Second, we did not adjust for IHD treatment and medication adherence, and compliance may be correlated with adherence to a healthy lifestyle. However, education and Townsend Deprivation Index, which served as surrogates for several health-related behaviours, were adjusted. Third, we did not consider the effect of diet on ICM trajectory; however, an unhealthy body shape was a surrogate for this effect. Fourth, the observational nature of this study precludes causal inferences. However, the causal association between LAFs and IHD or COPD is supported by emerging evidence from prospective cohort studies, Mendelian randomization studies [43,44], and randomized controlled trails [45,46]. Nevertheless, the causal roles of modifiable LAFs in the ICM trajectory require further research.

5. Conclusions

This large-scale prospective cohort study revealed that LAFs differently influenced the trajectory of ICM and had diverse impacts on disease-specific transitions. Our findings further contribute to the body of evidence that emphasizes the importance of integrating comprehensive lifestyle interventions and air pollution control into both health management and the trajectory of ICM management if the observed associations are causal. Further studies are warranted to determine whether genetic susceptibility modifies the effect of LAFs on ICM trajectory and to determine the clinical biomarkers that mediate the effect of LAFs.

Ethical approval and consent to participate

This research has been conducted using data from UK Biobank, a major biomedical database, https://www.ukbiobank.ac.uk/enable-your-research/manage-your-project. The UK Biobank study received ethical approval from the UK Northwest Multicenter Research Ethics Committee (Approval: 11/NW/0382). This study was performed under UK Biobank application number 98577. Participants of UK Biobank gave written informed consent before taking part.

Consent for publication

Not applicable.

Data availability

This research has been conducted using data from UK Biobank, a major biomedical database, https://www.ukbiobank.ac.uk/enable-your-research/manage-your-project.

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CRediT authorship contribution statement

Fei Chen: Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Investigation, Data curation, Conceptualization. **Ying Yang:** Writing – review & editing, Validation, Methodology, Conceptualization. **Liping Yu:** Writing – review & editing, Conceptualization. **Lulu Song:** Writing – review & editing, Conceptualization. **Jinping Zhang:** Writing – review & editing, Conceptualization. **Xin Wang:** Writing – review & editing, Conceptualization. **Xian Jin:** Writing – review & editing, Conceptualization. **Wanlu Ma:** Writing – review & editing, Conceptualization. **Bo Zhang:** Writing – review & editing, Supervision, Resources, Conceptualization.

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 data

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