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The interaction and mediation role of intrinsic capacity in the association between asthma and all-cause mortality

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Asthma and intrinsic capacity (IC) decline were individually examined with mortality, yet the complex interplay between them remains largely unknown. This study aimed to examine the potential roles of IC decline in the association between asthma and all-cause mortality. We conducted a prospective cohort study using data from UK Biobank, where IC decline was defined as a decline in any domain of psychological, sensory, vitality, and locomotion. Cox proportional hazard models were used to examine the associations between asthma, IC decline, and all-cause mortality. The relative excess risk due to additive interaction (RERI) was calculated. Mediation analysis was performed to explore the mediating effect of IC decline. And a four-way decomposition method was utilized to quantify both the interaction and mediation role of IC decline. Among 439,973 participants, 51,558 (11.7%) had asthma, 290,964 (66.1%) experienced IC decline, and 37,204 deaths occurred during 5.92 million person-years follow-up. Significant multiplicative and additive interactions were observed between asthma and any IC domain decline on all-cause mortality (Multiplicative: HR = 1.14, 95% CI: 1.06–1.24; Additive: RERI = 0.20, 95% CI: 0.11–0.29). The proportion of the association between asthma and all-cause mortality mediated by decline in all four domains was 28.14% (95% CI: 23.84–34.92%). The results of four-way decomposition were similar. Asthma was associated with increased all-cause mortality, and this association may be partially accounted for by both the interaction and mediation effects of IC decline. These findings underscore the importance of comprehensive interventions that address both asthma management and preservation of IC function to enhance health outcomes in middle-late life.

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INTRODUCTION

Asthma, a common chronic inflammation airway disease, has been highlighted for its high prevalence and considerable treatment costs[1]. According to Global Burden of Disease estimates, the incidence and prevalence of asthma has increased over the past thirty years, and asthma was responsible for approximately 0.5 million deaths in 2019 worldwide[2]. Previous studies have demonstrated that asthma is associated with poor quality of life, activity limitation, adverse behavioral and psychosocial outcomes, and mortality[3–6]. Intrinsic capacity (IC, the composite of all the mental and physical capacities of an individual), an essential component of functional ability, has been proposed as an effective marker of healthy ageing by the World Health Organization[7]. IC usually structured into five domains: psychological, sensory, vitality, locomotion, and cognition, and it emphasizes the inherent positive health aspects in older adults[8]. Growing evidence has suggested that IC decline is linked to an elevated risk of adverse health outcomes such as disability, functional decline, and mortality[9,10].

Both asthma and IC have been individually associated with all-cause mortality in previous studies[6,9,11]. However, the interplay between asthma and IC decline remains largely unexplored. Chronic systemic inflammation, indicated by higher levels of inflammatory biomarkers, is commonly observed in individuals with asthma[12,13]. Similarly, elevated inflammatory markers, a mechanism of aging, have been shown to predict future decline in IC[14]. Considering the shared inflammatory mechanisms between asthma and IC decline, it is essential to understand whether their combination leads to a synergistic, additive, or antagonistic effect on mortality. Additionally, although no study has examined the association between asthma and IC decline, evidence have shown that asthma was associated with impairment of some functions, such as psychological[15,16], cognition[17,18], and vitality[19]. A large-scale genome-wide cross-trait analysis also identified potential causal links between asthma and mental health disorders, such as anxiety and depression[16]. A clinical cohort study suggested patients with moderate to severe asthma is prevalent with low muscle strength[19]. Therefore, an important question is whether IC decline plays a mediating role in the association of asthma with all-cause mortality. Also, understanding which modifiable IC domain plays the most crucial role could provide valuable insights for developing preventive strategies and intervention targets against mortality risk in patients with asthma.

In the current study, we conducted comprehensive analyses to examine the combined association of asthma and IC decline with all-cause mortality, and to quantify to what extent IC decline may mediate the association between asthma and all-cause mortality.

METHODS

Study design and participants

UK biobank is a large population-based cohort study that recruited more than 500,000 individuals between 2006 and 2010. At enrollment, sociodemographic, lifestyle, medical history, and other health-related information were collected by touchscreen questionnaires, laboratory tests, and physical measurements. Diseases were diagnosed by ongoing follow-up through linkage to datasets including primary care systems, national hospital

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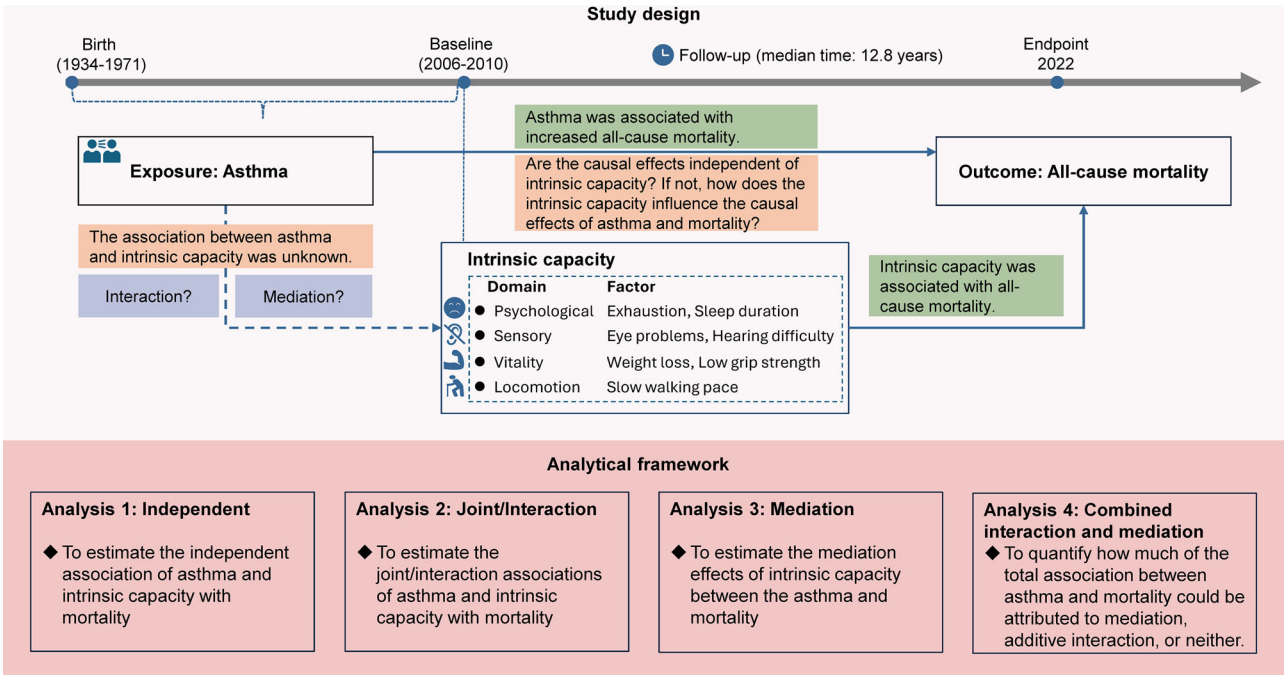

Fig. 1 Study design and analytical framework.

inpatient and outpatient records, and death registrations. The details of the UK biobank are available elsewhere (https://www.ukbiobank.ac.uk/).

A total of 502,364 participants attended the baseline assessment. We excluded participants who were lost to follow-up (n = 1297), those with conflicting information on asthma diagnoses (n = 19), and those with missing data for the IC factor (n = 61,075), resulting in an analytic cohort of 439,973 participants. Figure 1 provides a general study design. This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies[20], with the corresponding checklist provided in supplementary material.

Temporal sequence of key variables

The assessment timing of exposure, mediator, and outcome in this study is summarized in Fig. 1. Both asthma history (the exposure) and IC decline (the potential mediator) were assessed concurrently at the baseline. All-cause mortality (the outcome) was then prospectively ascertained during follow-up until 2022. While this established temporal order from baseline to outcome, the concurrent measurement of asthma and IC at baseline shaped the interpretation of our mediation analysis. Specifically, we evaluated the role of IC at study entry in explaining future mortality risk associated with asthma, not a causal pathway where asthma led to a subsequent IC decline and then to death.

Assessment of asthma

The information on asthma (J45) based on the International Classification of Diseases codes (ICD-10) was derived from the first occurrence fields, which were generated from the primary care data, inpatient hospital records, death register records, and self-reported medical conditions that were recorded before enrolment and during follow-up. Asthma history was defined as asthma diagnosed before the baseline assessment date.

Assessment of intrinsic capacity

IC was constructed using seven indicators from four of the five domains proposed by Beard and colleagues[7,21,22]. The cognitive capacity was not included due to lack of assessments in the UK Biobank. The four domains assessed were: 1) Psychological: self-reported exhaustion and sleep duration. 2) Sensory: self-reported vision problems and hearing impairment. 3) Vitality: grip strength and self-reported weight loss. Grip strength was measured by assessing the mean values of the right and left hand and comparing them to sex and BMI adjusted cut-off values[23]. 4) Locomotion: self-reported walking pace. Detailed definition of the IC is provided in supplementary Table S1. If any factor within a domain shows decline, this domain is considered to have declined. Similarly, if any domain shows decline, the individual is classified as having an IC decline. We also calculated the IC domain decline number (0 to 4) and pattern (mutually exclusive 16 categories).

Mortality ascertainment

The primary outcome was all-cause mortality, which was defined as any cause of death occurred from baseline. The date and underlying cause of death were obtained by linkage to the national death register records. The follow-up time ascertained from baseline and ended at the date of death or the end of follow-up (December 19, 2022), whichever came first. We additionally considered the cause-specific mortality, including cardiovascular diseases (CVD) (ICD-10: I00-I99) and respiratory (ICD-10: J09-J99).

Covariates

The selection of covariates was informed by similar previous studies and included demographics, lifestyle factors, early-life factors, and medical history[6,24,25]. These included age (continuous, at recruitment), sex (female/male), recruitment center (England/Scotland/Wales), ethnicity (White/non-White), educational level (under college/college or above), Townsend deprivation index (TDI, tertile), body mass index (BMI, underweight/normal weight/overweight/obese), smoking status (current/never or former), moderate alcohol intake (male: 0–28 g/day; female: 0–14 g/

day)[26], healthy physical activity, maternal smoking around birth (yes/no), breastfed as a baby (yes/no), history of hypertension, diabetes, CVD, cancer, and atopy (yes/no). Healthy physical activity was defined as moderate activity at least 150 min per week or vigorous activity 75 min per week (or an equivalent combination) or engaging in moderate activity at least 5 days a week or vigorous activity at least 3 days a week[27]. For those covariates with missing values were classified into "unknown" group.

Statistical analysis

The baseline characteristics were presented as median (interquartile range, IQR) for continuous variables with non-normal distribution and number (percentage) for categorical variables. Differences between groups were compared using Kruskal-Wallis test and Chi-Squared test.

Kaplan-Meier curves and stratified log-rank tests were used to compare all-cause mortality across dementia and IC decline groups. Cox proportional hazard models examined the independent associations of asthma and IC decline (any IC domain, individual IC domains, number/pattern of IC domains, and individual IC factor) with all-cause mortality. The proportional hazards assumption was tested using Schoenfeld residuals, and in case of violations, hazard ratio (HR) were interpreted as weighted averages of the time-varying HR over the entire follow-up period[28]. Model 1 adjusted for age, sex, and recruitment center. Model 2 added ethnicity, educational level, TDI, BMI, smoking status, moderate alcohol intake, healthy physical activity, maternal smoking around birth, and breastfed as a baby. Model 3 (main model) further adjusted for history of hypertension, diabetes, CVD, cancer, and atopy. Model 4 mutually adjusted for asthma and IC decline.

We estimated the multiplicative interaction by including the interaction term between asthma and IC decline to the main model and also calculated the additive interaction using relative excess risk due to interaction (RERI)[29]. Separate models were run for any IC decline and each individual IC domain. We also calculated the joint association of asthma and number/pattern of IC domain with all-cause mortality. The mediating effects of declines in any IC domain and each individual IC domain were separately analyzed. We also included all IC domains in one mediation model to calculate the combined mediating effect. Finally, a four-way decomposition analysis was fitted to assess how much of the total association between asthma and mortality could be attributed to mediation, additive interaction, or neither[30].

We additionally examined the interaction and mediation associations of asthma and IC decline with CVD and respiratory mortality. To test the robustness of our findings, we conducted several sensitivity analyses: 1) excluding deaths within the first two years of follow-up; 2) excluding participants with missing covariates, 3) using multiple imputation for missing covariates; 4) excluding participants with prevalent diseases at baseline; 5) restricting to participants aged 60 years or older at baseline; and 6) dividing the follow-up period into three mutually exclusive intervals (the first two years [period 1], from two years after baseline to March 11, 2020 [period 2], and after March 11, 2020 to end of follow-up [period 3]) to evaluate potential COVID-19 pandemic-related effects. We also examined effect variations by repeating all analyses stratified by sex, age, ethnicity, educational level, and TDI.

All statistical analyses were conducted by using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.3.0 (RStudio, Boston, MA). A two-sided P value < 0.05 was considered statistically significant.

Ethical approval and informed consent

This research was conducted according to the principles expressed in the Declaration of Helsinki. The UK Biobank has ethical approval from the North-West Multicenter Research Ethics Committee (REC reference: 21/NW/0157). All participants provided informed consent.

RESULTS

Population characteristics

The baseline characteristics of participants by asthma and IC decline were shown in Table 1. Among 439,973 participants (mean age 56.5 years, 46.0% male), 51,558 (11.7%) had asthma and 290,964 (66.1%) had any IC decline. Participants with asthma or IC decline were more likely to be non-White, higher level of TDI, higher educational level, obese, moderate alcohol consumption, unhealthy physical activity, and comorbidities.

Independent association of asthma and IC with all-cause mortality

A total of 37,204 deaths occurred during 5.92 million person-years follow-up (medium 12.8 years). Participants with asthma or with any IC decline had a significantly higher probability of survival than those without asthma or full capacity (asthma: log-rank $p < 0.001$; declines in IC: log-rank $p < 0.001$; supplementary Figure S1). After adjusting for covariates and each other (Model 4, Table 2), asthma (HR = 1.18, 95% CI: 1.15–1.22) and any IC decline (HR = 1.24, 95% CI: 1.21–1.27) was significantly associated with all-cause mortality. Each individual IC domain decline was associated with a higher risk of all-cause mortality, and the HRs ranged from 1.02 to 1.79. Each additional IC domain decline was associated with 19% higher risks of all-cause mortality (Table 2). Compared with participants with full capacity, those with declines in all four IC domain had the highest risk of all-cause mortality (HR = 2.30, 95% CI: 2.16–2.44, Supplementary Table S2).

Joint and interaction associations of asthma and IC with all-cause mortality

Both significant multiplicative and additive interactions were observed between asthma and any IC decline on all-cause mortality (Multiplicative: HR = 1.14, 95% CI: 1.06–1.24; Additive: RERI = 0.20, 95% CI: 0.11–0.29), the additive interactions were also significant in each individual domain (Fig. 2). Individuals with both asthma and all four IC domain decline experienced 2.35 times (95% CI: 2.10–2.63) the risk of all-cause mortality compared with those without asthma and full capacity (Fig. 2). Considering the joint association of asthma and pattern of IC domain decline on the all-cause mortality, the HRs for individuals with asthma and declines in psychological, vitality, and locomotion domain compared with those without asthma and full capacity were 2.68 (95% CI: 2.40–3.00, Supplementary Figure S2).

Mediation roles of IC on associations of asthma and mortality

Asthma was associated with an increased risk of declines in any IC domain, as well as in each individual IC domain, number of IC domain, and pattern of IC domain decline (Table 3). In all mediation analyses, the natural direct effect of asthma on all-cause mortality remained statistically significant. The proportion of the association between asthma and all-cause mortality mediated by decline in any IC domain was 4.79% (95% CI: 3.88–6.03%). When all four IC domains were included in one mediation model, the overall mediating effect was significant, with an intermediate ratio of 28.14% (95% CI: 23.84–34.92%) (Table 4).

Combined interaction and mediation effects

Figure 3 summarizes the overall contribution of declines in any IC domain, each individual IC domain, and all IC domain as a whole through interaction and mediation, to the association between asthma and all-cause mortality. All mediations and interactions

Table 1. Baseline characteristics of the study participants.

Characteristics	Total (N = 439,973)	Asthma		*P*-value	Declines in any IC domain		*P*-value
		No (N = 388,415)	Yes (N = 51,558)		No (N = 149,009)	Yes (N = 290,964)	
Age, median (IQR)	58 (50, 63)	58 (50, 63)	57 (49, 63)	<0.001	56 (48, 62)	59 (51, 64)	<0.001
Sex, n (%)				<0.001			<0.001
Female	237,773 (54.0)	208,461 (53.7)	29,312 (56.9)		82,190 (55.2)	155,583 (53.5)	
Male	202,200 (46.0)	179,954 (46.3)	22,246 (43.1)		66,819 (44.8)	135,381 (46.5)	
Recruitment center, n (%)				<0.001			<0.001
England	389,158 (88.5)	343,621 (88.5)	45,537 (88.3)		129,911 (87.2)	259,247 (89.1)	
Scotland	32,304 (7.3)	28,908 (7.4)	3396 (6.6)		12,943 (8.7)	19,361 (6.7)	
Wales	18,511 (4.2)	15,886 (4.1)	2625 (5.1)		6155 (4.1)	12,356 (4.2)	
Ethnicity, n (%)				<0.001			<0.001
White	417,582 (94.9)	368,732 (94.9)	48,850 (94.7)		143,757 (96.5)	273,825 (94.1)	
Non-White	21,094 (4.8)	18,553 (4.8)	2541 (4.9)		4891 (3.3)	16,203 (5.6)	
Unknown	1297 (0.3)	1,130 (0.3)	167 (0.3)		361 (0.2)	936 (0.3)	
Educational level, n (%)				<0.001			<0.001
Under college	238,296 (54.2)	210,873 (54.3)	27,423 (53.2)		75,067 (50.4)	163,229 (56.1)	
College or above	197,909 (45.0)	174,214 (44.9)	23,695 (46.0)		73,039 (49.0)	124,870 (42.9)	
Unknown	3768 (0.9)	3,328 (0.9)	440 (0.9)		903 (0.6)	2865 (1.0)	
TDI, n (%)				<0.001			<0.001
First tertile	151,246 (34.4)	134,343 (34.6)	16,903 (32.8)		57,259 (38.4)	93,987 (32.3)	
Second tertile	147,021 (33.4)	130,421 (33.6)	16,600 (32.2)		51,071 (34.3)	95,950 (33.0)	
Third tertile	141,163 (32.1)	123,179 (31.7)	17,984 (34.9)		40,516 (27.2)	100,647 (34.6)	
Unknown	543 (0.1)	472 (0.1)	71 (0.1)		163 (0.1)	380 (0.1)	
Body mass index, n (%)				<0.001			<0.001
Underweight	2183 (0.5)	1943 (0.5)	240 (0.5)		706 (0.5)	1477 (0.5)	
Normal	144,357 (32.8)	129,278 (33.3)	15,079 (29.2)		59,967 (40.2)	84,390 (29.0)	
Overweight	187,720 (42.7)	166,572 (42.9)	21,148 (41.0)		64,238 (43.1)	123,482 (42.4)	
Obese	105,531 (24.0)	90,464 (23.3)	15,067 (29.2)		24,081 (16.2)	81,450 (28.0)	
Unknown	182 (0.0)	158 (0.0)	24 (0.0)		17 (0.0)	165 (0.1)	
Smoking status, n (%)				<0.001			<0.001
Current	45,244 (10.3)	40,332 (10.4)	4912 (9.5)		13,385 (9.0)	31,859 (10.9)	
Never/former	393,446 (89.4)	346,977 (89.3)	46,469 (90.1)		135,331 (90.8)	258,115 (88.7)	
Unknown	1283 (0.3)	1,106 (0.3)	177 (0.3)		293 (0.2)	990 (0.3)	
Moderate alcohol intake, n (%)				<0.001			<0.001
No	306,274 (69.6)	271,896 (70.0)	34,378 (66.7)		112,011 (75.2)	194,263 (66.8)	
Yes	96,551 (21.9)	83,941 (21.6)	12,610 (24.5)		25,013 (16.8)	71,538 (24.6)	
Unknown	37,148 (8.4)	32,578 (8.4)	4570 (8.9)		11,985 (8.0)	25,163 (8.6)	
Healthy physical activity, n (%)				<0.001			<0.001
No	151,628 (34.5)	133,095 (34.3)	18,533 (35.9)		49,382 (33.1)	102,246 (35.1)	
Yes	267,802 (60.9)	237,448 (61.1)	30,354 (58.9)		94,942 (63.7)	172,860 (59.4)	
Unknown	20,543 (4.7)	17,872 (4.6)	2671 (5.2)		4685 (3.1)	15,858 (5.5)	
Maternal smoking around birth, n (%)				<0.001			<0.001
No	270,033 (61.4)	239,439 (61.6)	30,594 (59.3)		95,507 (64.1)	174,526 (60.0)	
Yes	113,001 (25.7)	98,606 (25.4)	14,395 (27.9)		35,577 (23.9)	77,424 (26.6)	
Unknown	56,939 (12.9)	50,370 (13.0)	6569 (12.7)		17,925 (12.0)	39,014 (13.4)	
Breastfed as a baby, n (%)				<0.001			<0.001
No	94,557 (21.5)	82,473 (21.2)	12,084 (23.4)		33,571 (22.5)	60,986 (21.0)	
Yes	246,274 (56.0)	218,002 (56.1)	28,272 (54.8)		86,017 (57.7)	160,257 (55.1)	
Unknown	99,142 (22.5)	87,940 (22.6)	11,202 (21.7)		29,421 (19.7)	69,721 (24.0)	
Hypertension, n (%)	118,606 (27.0)	103,568 (26.7)	15,038 (29.2)	<0.001	30,329 (20.4)	88,277 (30.3)	<0.001
Diabetes, n (%)	22,262 (5.1)	19,159 (4.9)	3103 (6.0)	<0.001	3633 (2.4)	18,629 (6.4)	<0.001
CVD, n (%)	24,875 (5.7)	21,387 (5.5)	3488 (6.8)	<0.001	4765 (3.2)	20,110 (6.9)	<0.001
Cancer, n (%)	38,438 (8.7)	33,776 (8.7)	4662 (9.0)	0.009	11,436 (7.7)	27,002 (9.3)	<0.001
Atopy, n (%)	107,512 (24.4)	82,971 (21.4)	24,541 (47.6)	<0.001	36,082 (24.2)	71,430 (24.5)	<0.001

IC intrinsic capacity, *IQR* interquartile range, *TDI* townsend deprivation index, *CVD* cardiovascular diseases.

Table 2. Independent associations of asthma and intrinsic capacity with all-cause mortality.

Exposures	Cases/person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Asthma					
No	32,320/5,227,034	Reference	Reference	Reference	Reference
Yes	4884/691,853	**1.24 (1.20–1.28)**	**1.21 (1.18–1.25)**	**1.19 (1.16–1.23)**	**1.18 (1.15–1.22)**
Declines in IC					
Any IC domain					
No	8745/2,033,855	Reference	Reference	Reference	
Yes	28,459/3,885,031	**1.45 (1.42–1.49)**	**1.30 (1.27–1.33)**	**1.24 (1.21–1.27)**	**1.24 (1.21–1.27)**
Each individual IC domain					
Psychological	14,184/1,953,058	**1.38 (1.35–1.41)**	**1.24 (1.21–1.26)**	**1.19 (1.16–1.21)**	**1.19 (1.16–1.21)**
Sensory	13,426/1,659,843	**1.07 (1.05–1.09)**	**1.05 (1.02–1.07)**	**1.03 (1.00–1.05)**	**1.02 (1.00–1.05)**
Vitality	15,569/1,836,559	**1.46 (1.43–1.49)**	**1.33 (1.30–1.35)**	**1.25 (1.23–1.28)**	**1.25 (1.22–1.28)**
Locomotion	7041/420,605	**2.61 (2.54–2.68)**	**2.06 (2.00–2.12)**	**1.81 (1.76–1.86)**	**1.79 (1.74–1.85)**
Number of IC domain					
0	8745/2,033,855	Reference	Reference	Reference	Reference
1	13,487/2,340,249	**1.19 (1.16–1.22)**	**1.13 (1.10–1.16)**	**1.12 (1.09–1.15)**	**1.11 (1.08–1.14)**
2	9438/1,161,251	**1.56 (1.51–1.60)**	**1.39 (1.35–1.43)**	**1.32 (1.28–1.36)**	**1.31 (1.28–1.35)**
3	4279/326,813	**2.40 (2.31–2.49)**	**1.92 (1.85–2.00)**	**1.70 (1.64–1.77)**	**1.69 (1.63–1.76)**
4	1255/56,719	**3.84 (3.62–4.07)**	**2.66 (2.50–2.83)**	**2.15 (2.02–2.29)**	**2.11 (1.99–2.25)**
Each additional IC domain		**1.35 (1.33–1.36)**	**1.25 (1.23–1.26)**	**1.19 (1.18–1.21)**	**1.19 (1.18–1.20)**

Model 1: adjusted for age, sex, and recruitment center.
Model 2: model 1 additionally adjusted for ethnicity, educational level, Townsend deprivation index, body mass index, smoking status, moderate alcohol intake, healthy physical activity, maternal smoking around birth, and breastfed as a baby.
Model 3: model 2 additionally adjusted for hypertension, diabetes, cardiovascular diseases, cancer, and atopy.
Model 4: for asthma and all-cause mortality, model 3 additionally adjusted for declines in any IC domain; for declines in IC and all-cause mortality, model 4 additionally adjusted for asthma.
IC intrinsic capacity, *HR* hazard ratio, *CI* confidence interval.
Bold values indicate statistically significant hazard ratios ($P < 0.05$).

were statistically significant ($P < 0.05$). Overall, the results of four-way decomposition analysis found that 76.48% of the association could be explained by any IC domain, 7.26% was mediated via any IC domain and 69.22% was attributed to the interaction with any IC domain (Supplementary Table S3). When considered each individual IC domain, the locomotion domain contributed the greatest in relation to all-cause mortality, with 43.26% of the association explained by locomotion decline (Mediation: 24.85%, Interaction: 18.41%, Supplementary Table S4).

Additional analysis

Significant additive interaction was also observed between asthma and IC decline for respiratory mortality (Additive: RERI = 1.46, 95% CI: 0.76–2.10). The proportion of the association between asthma and mortality mediated by IC decline was 5.38% for cardiovascular mortality and 3.35% for respiratory mortality (Supplementary Table S5).

Overall, a series of sensitivity analyses confirmed the robustness of the main findings. Specifically, when excluding deaths within the first two years of follow-up, excluding participants with missing covariates, applying multiple imputation for missing covariates, excluding participants with prevalent diseases at baseline, or restricting to participants aged 60 years or older at baseline, the interaction and mediation effects of IC decline in the association between asthma and all-cause mortality remained consistent (additive interaction: RERI = 0.19–0.28; mediation proportion = 4.38–5.29%, Supplementary Tables S6-S7). Additionally, when dividing the follow-up period into three mutually exclusive intervals, the additive interaction of asthma and IC decline with all-cause mortality remained persistent in period 2 and 3, while the additive effect in period 1 became marginally non-significant (RERI = 0.38, 95% CI: -0.04–0.73). A similar pattern was observed for the mediation effect of IC decline, which was evident in periods 2 and 3 (mediation: period 2 :7.76%; period 3: 5.10%) but not in period 1 (Supplementary Table S8).

Additive interactions remained significant in subgroup among participants who were female or male, older, White, less educated, and at a higher TDI level (Supplementary Table S9). The mediating effects of any IC decline in subgroups were similar, except in the non-white group (Supplementary Table S10).

DISCUSSION

In this large prospective cohort study conducted in the UK, both asthma and IC decline were associated with an increased risk of all-cause mortality. We found both mediation and interaction between asthma and IC decline. Specifically, significant additive interactions were observed between asthma and each individual IC domain decline on mortality risk. Additionally, the association between asthma and mortality was partially mediated through IC decline, with the locomotion domain showing the highest mediation proportion.

Comparisons and interpretations

Our study investigated the interaction effect of asthma and IC decline on all-cause mortality. Both asthma and IC decline have been independently linked to increased mortality risk, as reported in previous research[6,9,31]. However, the interaction between

Asthma and IC decline	Cases/person−years	HR (95% CI)	Estimates (95% CI)
Asthma and any IC domain			
No asthma, no any IC decline	7,936/1,831,110		Reference
Only asthma	809/202,745		1.06 (0.99−1.14)
Only any IC decline	24,384/3,395,924		1.22 (1.19−1.25)
Asthma & any IC decline	4,075/489,108		1.48 (1.43−1.54)
HR for the interaction term (multiplicative scale)			1.14 [1.06, 1.24]
RERI (additive scale)			0.20 [0.11, 0.29]
Asthma and each individual IC domain			
Psychological			
No asthma, no psychological decline	20,362/3,536,883		Reference
Only asthma	2,658/428,946		1.16 (1.12−1.21)
Only psychological decline	11,958/1,690,151		1.18 (1.15−1.20)
Asthma & psychological decline	2,226/262,907		1.43 (1.36−1.49)
HR for the interaction term (multiplicative scale)			1.04 [0.98, 1.10]
RERI (additive scale)			0.08 [0.01, 0.16]
Sensory			
No asthma, no sensory decline	20,879/3,779,684		Reference
Only asthma	2,899/479,359		1.17 (1.12−1.22)
Only sensory decline	11,441/1,447,349		1.01 (0.99−1.04)
Asthma & sensory decline	1,985/212,494		1.25 (1.19−1.31)
HR for the interaction term (multiplicative scale)			1.06 [0.99, 1.12]
RERI (additive scale)			0.07 [0.00, 0.14]
Vitality			
No asthma, no vitality decline	19,209/3,637,577		Reference
Only asthma	2,426/444,751		1.15 (1.10−1.20)
Only vitality decline	13,111/1,589,456		1.24 (1.21−1.27)
Asthma & vitality decline	2,458/247,102		1.51 (1.45−1.58)
HR for the interaction term (multiplicative scale)			1.06 [1.00, 1.13]
RERI (additive scale)			0.12 [0.04, 0.20]
Locomotion			
No asthma, no locomotion decline	26,752/4,883,702		Reference
Only asthma	3,411/614,580		1.13 (1.09−1.17)
Only locomotion decline	5,568/343,332		1.78 (1.72−1.83)
Asthma & locomotion decline	1,473/77,273		2.12 (2.01−2.24)
HR for the interaction term (multiplicative scale)			1.06 [0.99, 1.13]
RERI (additive scale)			0.22 [0.09, 0.34]
Asthma and number of IC domain			
Without asthma			
0 IC domain decline	7,936/1,831,110		Reference
1 IC domain decline	11,987/2,077,135		1.11 (1.08−1.14)
2 IC domain decline	8,030/1,006,435		1.29 (1.25−1.33)
3 IC domain decline	3,437/269,129		1.66 (1.60−1.74)
4 IC domain decline	930/43,224		2.12 (1.98−2.27)
With asthma			
0 IC domain decline	809/202,745		1.06 (0.99−1.14)
1 IC domain decline	1,500/263,113		1.24 (1.18−1.31)
2 IC domain decline	1,408/154,816		1.58 (1.49−1.68)
3 IC domain decline	842/57,684		1.99 (1.85−2.14)
4 IC domain decline	325/13,495		2.35 (2.10−2.63)

Fig. 2 Joint and interaction associations of asthma and declines in intrinsic capacity with all-cause mortality. All analyses were adjusted for age, sex, recruitment center, ethnicity, educational level, Townsend deprivation index, body mass index, smoking status, moderate alcohol intake, healthy physical activity, maternal smoking around birth, breastfed as a baby, history of hypertension, diabetes, cardiovascular diseases, cancer, and atopy. Additive interaction was estimated by RERI ($HR_{asthma\ \&\ IC\ decline} - HR_{only\ asthma} - HR_{only\ IC\ decline} + 1$; null value = 0). IC intrinsic capacity, HR hazard ratio, CI confidence interval, RERI relative excess risk due to interaction.

Table 3. Associations between asthma and intrinsic capacity.

Outcomes	OR (95% CI)
Declines in any IC domain	
No	Reference
Yes	**1.25 (1.22–1.27)**
Declines in each IC domain	
Psychological	**1.20 (1.18–1.23)**
Sensory	**1.15 (1.13–1.18)**
Vitality	**1.20 (1.18–1.22)**
Locomotion	**1.65 (1.59–1.70)**
Number of IC domain decline	
0	Reference
1	**1.13 (1.11–1.16)**
2	**1.34 (1.30–1.38)**
3	**1.76 (1.69–1.83)**
4	**2.33 (2.16–2.51)**
Pattern of IC domain decline	
None	Reference
Only psychological	**1.14 (1.10–1.17)**
Only sensory	**1.11 (1.07–1.15)**
Only vitality	**1.12 (1.09–1.16)**
Only locomotion	**1.45 (1.33–1.58)**
Psychological + sensory	**1.25 (1.19–1.30)**
Psychological + vitality	**1.33 (1.28–1.39)**
Psychological + locomotion	**1.76 (1.62–1.91)**
Sensory + vitality	**1.29 (1.24–1.35)**
Sensory + locomotion	**1.64 (1.46–1.84)**
Vitality + locomotion	**1.69 (1.56–1.83)**
Psychological + sensory + vitality	**1.53 (1.45–1.61)**
Psychological + sensory + locomotion	**2.05 (1.86–2.26)**
Psychological + vitality + locomotion	**2.14 (2.00–2.28)**
Sensory + vitality + locomotion	**2.00 (1.82–2.21)**
Psychological + sensory + vitality + locomotion	**2.43 (2.26–2.62)**
Individual IC factor decline	
Exhaustion	**1.32 (1.29–1.36)**
Sleep duration	**1.15 (1.13–1.18)**
Eye problems	**1.14 (1.09–1.19)**
Hearing difficulty	**1.15 (1.12–1.17)**
Weight loss	**1.16 (1.13–1.19)**
Low grip strength	**1.19 (1.16–1.22)**
Slow walking pace	**1.65 (1.59–1.70)**

All analyses were adjusted for age, sex, recruitment center, ethnicity, educational level, Townsend deprivation index, body mass index, smoking status, moderate alcohol intake, healthy physical activity, maternal smoking around birth, breastfed as a baby, history of hypertension, diabetes, cardiovascular diseases, cancer, and atopy.
IC intrinsic capacity, *OR* odds ratio, *CI* confidence interval.
Bold values indicate statistically significant hazard ratios ($P < 0.05$).

asthma and IC decline has been underexplored. Consistent with our hypothesis, the findings indicated a significant synergy association, which means combined effect is greater than the sum of their individual effects. Only one study has revealed the joint effect of asthma and certain IC components, such as sleep duration, on moratlity[32]. Several mechanisms may explain this synergistic effect, including chronic inflammation and decreased physical function. Recent studies have found that asthma and IC decline are associated with chronic inflammation and increase vulnerability to cardiovascular events, which both result in elevated death risk[21,33–35]. Also, asthma may lead to respiratory dysfunction, which exacerbates exercise intolerance and activity limitation[36,37]. IC decline, in turn, can cause functional limitation and disability, further amplifying the negative impact of asthma on health outcomes[9,10].

Results from the four-way decomposition also indicated a higher interaction proportion attributable to vitality domain than the others. A clinical cohort study reported that low muscle mass is prevalent among patients with moderate to severe asthma[19]. However, the mechanisms behind the interaction of asthma and different IC domains remain unclear. Future research should focus on better understanding the specific pathways and mechanisms behind the distinct interactions between asthma and different IC domains to inform tailored interventions aimed at improving health outcomes in individuals with asthma.

Our findings indicate that IC decline may play a partial mediating role in the relationship between asthma and increased mortality risk. While the association between asthma and certain functional impairments has been well-established[35,37,38], the association of asthma with IC as a composite measure of healthy ageing has remained largely unexplored. Our study is the first to examine the association between asthma and IC decline and to assess the potential mediating role of IC in asthma-related death risk. We observed that asthmatics have a higher risk of experiencing IC decline, which in turn may increase the mortality risk. These results support the hypothesis that asthma may contribute to the acceleration of IC decline, ultimately increasing the risk of mortality.

Furthermore, we identified significant mediated proportions of decline in specific IC domains, including psychological, vitality, and locomotion. These findings underscore the importance of considering these specific IC domains when understanding how asthma influences mortality risk. For instance, a retrospective cohort study revealed a potential psychological mechanism (8.13% mediated by depressive symptoms) underlying the relationship between asthma-COPD overlap and all-cause mortality[11]. In particular, the locomotion domain is marked by slow walking pace, which is a known marker of overall muscle fitness[39], and it exhibited a notable mediation effect. While no prior research has detected the mediating role of locomotion in the asthma-death relationship, a study conducted in Spain found that asthma patients reported lower levels of physical activity[40]. Also, there is a clear association between asthma and activity limitation, such as lung function changes, alterations in energy expenditure, performance during cardiopulmonary exercise test, or walking tests[37].

Although there was no conclusive evidence of the causal relationship, several factors may explain these association. For instance, asthma may contribute to chronic inflammation and respiratory dysfunction, which may lead to a gradual decline in physical function and muscle strength, all of which are crucial components of IC[14,37,41].

While the statistical significance of these findings is clear, it is important to note that some of the observed effects, such as the RERI of 0.20, may be small in clinical magnitude. Therefore, it is important to contextualize these findings within the general scope of clinical and public health relevance. Specifically, future studies should examine the absolute risk associated with asthma-induced IC decline, considering how these modest effects might accumulate over time, particularly in populations with long-term asthma. Moreover, while asthma is clearly associated with IC decline and mortality, the magnitude of this association may vary across individuals. Interventions targeting asthma management, early IC assessments, and measures to preserve IC function could provide meaningful benefits, even for those with modest declines in IC.

Table 4. Mediation analyses of intrinsic capacity in the association between asthma and all-cause mortality.

Mediator Declines in IC	Natural direct effect HR (95% CI)	Natural indirect effect HR (95% CI)	Proportion mediated (95% CI)	P-value for mediation
Any IC domain	1.18 (1.15, 1.22)	1.01 (1.01, 1.01)	4.79 (3.88, 6.03)	<0.001
Each individual IC domain				
Psychological	1.18 (1.15, 1.22)	1.01 (1.01, 1.01)	4.48 (3.49, 5.71)	<0.001
Sensory	1.19 (1.16, 1.23)	1.00 (1.00, 1.00)	0.41 (-0.02, 0.87)	0.056
Vitality	1.18 (1.15, 1.22)	1.01 (1.01, 1.01)	5.62 (4.30, 7.19)	<0.001
Locomotion	1.14 (1.11, 1.18)	1.04 (1.03, 1.04)	22.61 (18.94, 27.69)	<0.001
All IC domain	1.13 (1.10, 1.17)	1.05 (1.04, 1.05)	28.14 (23.84, 34.92)	<0.001

All analyses were adjusted for age, sex, recruitment center, ethnicity, educational level, Townsend deprivation index, body mass index, smoking status, moderate alcohol intake, healthy physical activity, maternal smoking around birth, breastfed as a baby, history of hypertension, diabetes, cardiovascular diseases, cancer, and atopy.
IC intrinsic capacity, *HR* hazard ratio, *CI* confidence interval.

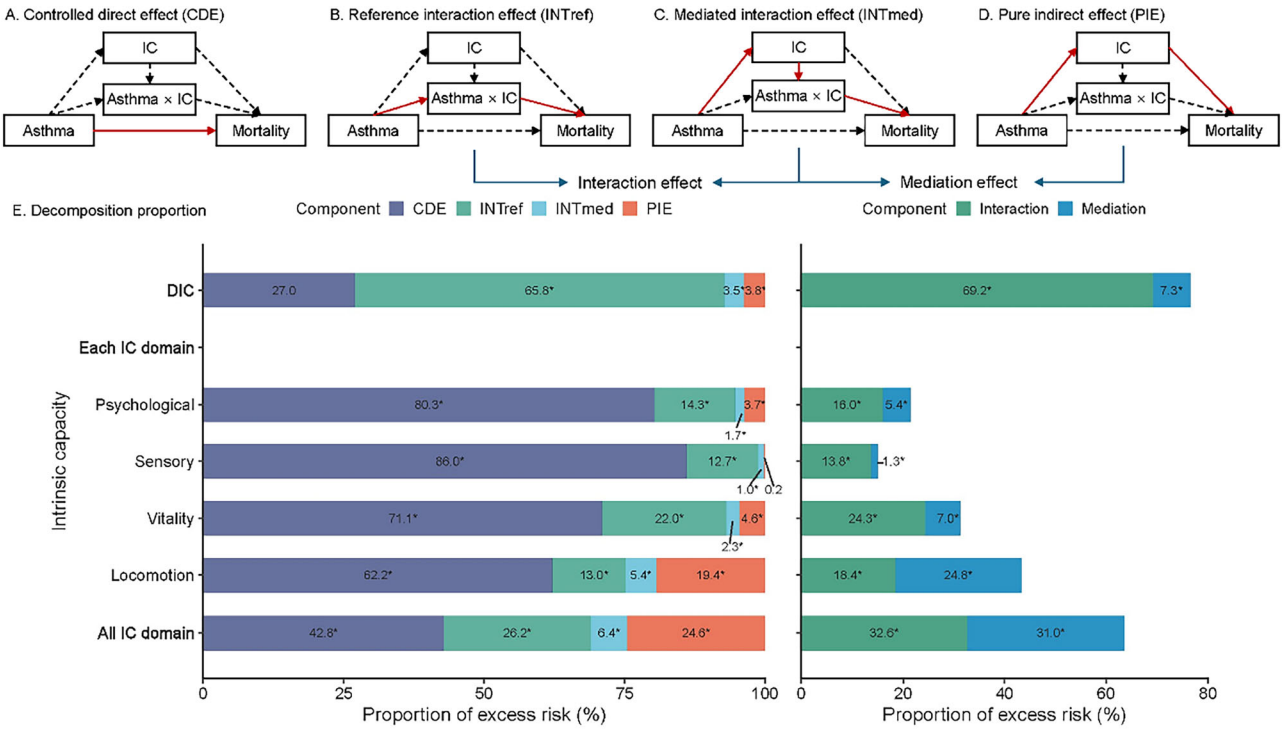

Fig. 3 Four-way decomposition analysis of the association between asthma and all-cause mortality, treating intrinsic capacity as both an interactor and a mediator. Adjusted confounders including age, sex, recruitment center, ethnicity, educational level, Townsend deprivation index, body mass index, smoking status, moderate alcohol intake, healthy physical activity, maternal smoking around birth, breastfed as a baby, history of hypertension, diabetes, cardiovascular diseases, cancer, and atopy. **A** The controlled direct effect (CDE) is due to neither mediation nor interaction. **B** The reference interaction (INTref) is only due to interaction. **C** The mediated interaction (INTmed) is due to both mediation and interaction. **D** The pure indirect effect (PIE) is only due to mediation. **E** The decomposition proportion of the excess risk of asthma on mortality that is explained by intrinsic capacity. IC intrinsic capacity, CDE controlled direct effect, INTref reference interaction, INTmed mediated interaction, PIE pure indirect effect.

Implications

The clinical and public health implications of these findings are significant. From a clinical perspective, healthcare providers should recognize that asthma is not only a respiratory condition but also a potential contributor to IC decline and increased mortality risk. Integrating IC assessments into routine asthma management could help mitigate the long-term impact of asthma on respiratory health. While complete prevention of asthma is challenging, early intervention in key domains of IC could reduce the asthma burden, as these were found to partially mediate the relationship between asthma and mortality. From a public health perspective, our results suggest that public health campaigns should focus on the interaction between asthma and IC decline. Although the absolute magnitude of the effect may appear modest, when considered at the population level, given the high prevalence of both asthma and IC decline in aging populations, even a small relative risk increase translates to a substantial number of preventable deaths. Efforts should focus on raising awareness about the potential long-term impact of asthma on both physical and mental health, and the need for early interventions that promote physical activity and mental health support[42,43]. Policymakers should also prioritize developing

tailored interventions to reduce the burden of asthma-related functional decline, which could improve quality of life and reduce the incidence of premature mortality.

Strengths and limitations

The strengths of this study are, first, the use of prospective cohort data with the large sample size, which allowed us to perform joint and subgroup analyses with sufficient statistical power. Second, we comprehensively evaluated the interplay between asthma and IC decline, including individual IC domain, IC number, and IC pattern. Finally, we investigated the complex role of IC decline in the association between asthma and all-cause mortality, examining whether IC decline modified or mediated these associations.

However, our study also has several limitations. First, IC factors were assessed only at baseline via self-report using indicators that differ from established measures, potentially introducing measurement inaccuracies and limiting comparability with other studies. Similarly, asthma was treated as a binary, static exposure, lacking data on severity, duration, and exacerbation frequency over the follow-up period, which may lead to misclassification and potentially bias the effect estimates. Second, a notable limitation of this study is the lack of cognitive assessments to measure IC decline, which may have led to an underestimation of IC decline and could weaken its observed associations with all-cause mortality. Furthermore, we cannot rule out residual confounding, which may attenuate the detected interaction between asthma and IC decline, or bias the estimation of IC decline's mediating role. Future studies incorporating cognitive assessments are needed to validate the findings of our study. Third, despite adjusting for a wide range of potential confounders, residual confounding from unmeasured factors remains possible. Finally, the observational nature of our study and concurrent measurement of IC decline and asthma history limit our ability to establish causal interpretations or temporal precedence of the observed mediation effects. While these findings highlight important associations, longitudinal studies are needed to better evaluate causality.

CONCLUSIONS

Our findings indicate that asthma is associated with all-cause mortality and with IC decline, with evidence of both mediation and interaction between asthma and IC decline. Notably, asthma and each individual IC domain decline were jointly associated with higher mortality. In addition, the mediation analysis suggests that the association between asthma and all-cause mortality may be linked to higher likelihood of IC decline, particularly in the locomotion domain. These findings underscore the potential importance of comprehensive interventions that address both asthma management and preservation of IC function to reduce mortality risk.

DATA AVAILABILITY

The main data used in this study were accessed from the publicly available UK biobank Resource (https://www.ukbiobank.ac.uk) under application number 79095, which cannot be shared with other investigators due to data privacy laws. The UK biobank can be accessed by researchers on the application.

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REFERENCES

1. Mukherjee, M. et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med.* **14**, 113 (2016).
2. GBD 2019 Chronic Respiratory Diseases Collaborators Global burden of chronic respiratory diseases and risk factors, 1990-2019: an update from the Global Burden of Disease Study 2019. *EClinicalMedicine* **59**, 101936 (2023).
3. Stanescu, S., Kirby, S. E., Thomas, M., Yardley, L. & Ainsworth, B. A systematic review of psychological, physical health factors, and quality of life in adult asthma. *NPJ Prim. Care Respir. Med.* **29**, 37 (2019).
4. Ford, E. S. et al. Self-reported asthma and health-related quality of life: findings from the behavioral risk factor surveillance system. *Chest* **123**, 119–127 (2003).
5. Ampon, R. D., Williamson, M., Correll, P. K. & Marks, G. B. Impact of asthma on self-reported health status and quality of life: a population based study of Australians aged 18-64. *Thorax* **60**, 735–739 (2005).
6. Lemmetyinen, R. E. et al. Higher mortality of adults with asthma: A 15-year follow-up of a population-based cohort. *Allergy* **73**, 1479–1488 (2018).
7. Beard, J. R. et al. The world report on ageing and health: a policy framework for healthy ageing. *Lancet* **387**, 2145–2154 (2016).
8. Cesari, M. et al. Evidence for the domains supporting the construct of intrinsic capacity. *J. Gerontol. A Biol. Sci. Med. Sci.* **73**, 1653–1660 (2018).
9. Sánchez-Sánchez, J. L. et al. Association of intrinsic capacity with functional decline and mortality in older adults: a systematic review and meta-analysis of longitudinal studies. *Lancet Healthy Longev.* **5**, e480–e492 (2024).
10. Stolz, E., Mayerl, H., Freidl, W., Roller-Wirnsberger, R. & Gill, T. M. Intrinsic capacity predicts negative health outcomes in older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* **77**, 101–105 (2022).
11. Zhu, M. & Chen, A. Epidemiological characteristics of asthma-COPD overlap, its association with all-cause mortality, and the mediating role of depressive symptoms: evidence from NHANES 2005-2018. *BMC Public. Health* **24**, 1423 (2024).
12. Macedo, P. et al. Inflammatory biomarkers in airways of patients with severe asthma compared with non-severe asthma. *Clin. Exp. Allergy* **39**, 1668–1676 (2009).
13. Naik, S. P. et al. Evaluation of inflammatory markers interleukin-6 (IL-6) and matrix metalloproteinase-9 (MMP-9) in asthma. *J. Asthma* **54**, 584–593 (2017).
14. Li, X. & Ma, L. From biological aging to functional decline: Insights into chronic inflammation and intrinsic capacity. *Ageing Res. Rev.* **93**, 102175 (2024).
15. Wright, R. J., Rodriguez, M. & Cohen, S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. *Thorax* **53**, 1066–1074 (1998).
16. Zhu, Z. et al. Shared genetics of asthma and mental health disorders: a large-scale genome-wide cross-trait analysis. *Eur. Respir. J.* **54**, 1901507 (2019).
17. Nair, A. K. et al. Impact of asthma on the brain: evidence from diffusion MRI, CSF biomarkers and cognitive decline. *Brain Commun.* **5**, fcad180 (2023).
18. Caldera-Alvarado, G., Khan, D. A., Defina, L. F., Pieper, A. & Brown, E. S. Relationship between asthma and cognition: the cooper center longitudinal study. *Allergy* **68**, 545–548 (2013).
19. Visser, E., de Jong, K., van Zutphen, T., Kerstjens, H. A. M. & Ten Brinke, A. Muscle function in moderate to severe asthma: association with clinical outcomes and inflammatory markers. *J. Allergy Clin. Immunol. Pract.* **11**, 1439–47.e3 (2023).
20. von Elm, E. et al. The strengthening the reporting of observational studies in epidemiology (strobe) statement: guidelines for reporting observational studies. *Lancet* **370**, 1453–1457 (2007).
21. Ramírez-Vélez, R. et al. Association of intrinsic capacity with incidence and mortality of cardiovascular disease: prospective study in UK biobank. *J. Cachexia Sarcopenia Muscle* **14**, 2054–2063 (2023).
22. Beard, J. R., Jotheeswaran, A. T., Cesari, M. & Araujo de Carvalho, I. The structure and predictive value of intrinsic capacity in a longitudinal study of ageing. *BMJ Open.* **9**, e026119 (2019).
23. Fried, L. P. et al. Frailty in older adults: evidence for a phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* **56**, M146–M156 (2001).
24. Jani, B. D. et al. Relationship between multimorbidity, demographic factors and mortality: findings from the UK Biobank cohort. *BMC Med.* **17**, 74 (2019).
25. Caffrey Osvald, E. et al. Asthma and all-cause mortality in children and young adults: a population-based study. *Thorax* **75**, 1040–1046 (2020).
26. Lourida, I. et al. Association of lifestyle and genetic risk with incidence of dementia. *Jama* **322**, 430–437 (2019).
27. Lloyd-Jones, D. M. et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the american heart association's strategic impact goal through 2020 and beyond. *Circulation* **121**, 586–613 (2010).
28. Stensrud, M. J. & Hernán, M. A. Why test for proportional hazards?. *Jama* **323**, 1401–1402 (2020).
29. VanderWeele, T. J. & Knol, M. J. A Tutorial on Interaction. *Epidemiol. Methods* **3**, 33–72 (2014).
30. VanderWeele, T. J. A unification of mediation and interaction: a 4-way decomposition. *Epidemiology* **25**, 749–761 (2014).
31. To, T. et al. Asthma deaths in a large provincial health system. A 10-year population-based study. *Ann. Am. Thorac. Soc.* **11**, 1210–1217 (2014).

32. Zhao, Y., Cheng, X. & Song, C. Joint associations of asthma and sleep duration with cardiovascular disease and all-cause mortality: a prospective cohort study. *Ann. Epidemiol.* **88**, 1–6 (2023).
33. Pollevick, M. E. et al. The relationship between asthma and cardiovascular disease: an examination of the framingham offspring study. *Chest* **159**, 1338–1345 (2021).
34. Lu, W. H. et al. Plasma inflammation-related biomarkers are associated with intrinsic capacity in community-dwelling older adults. *J. Cachexia Sarcopenia Muscle* **14**, 930–939 (2023).
35. Boulet, L. P., Robitaille, C., Deschesnes, F., Villeneuve, H. & Boulay, M. Comparative clinical, physiological, and inflammatory characteristics of elderly subjects with or without asthma and young subjects with asthma. *Chest* **152**, 1203–1213 (2017).
36. Foster, J. M., McDonald, V. M., Guo, M. & Reddel, H. K. "I have lost in every facet of my life": the hidden burden of severe asthma. *Eur. Respir. J.* **50**, 1700765 (2017).
37. Vermeulen, F., Garcia, G., Ninane, V. & Laveneziana, P. Activity limitation and exertional dyspnea in adult asthmatic patients: what do we know?. *Respir. Med.* **117**, 122–130 (2016).
38. Hu, J. et al. Asthma and cognitive dysfunction in older adults: the mediating role of systemic immune-inflammation index. *Sci. Rep.* **14**, 27194 (2024).
39. Yates, T. et al. Association of walking pace and handgrip strength with all-cause, cardiovascular, and cancer mortality: a UK biobank observational study. *Eur. Heart J.* **38**, 3232–3240 (2017).
40. De-Miguel-Diez, J. et al. Association between asthma and lower levels of physical activity: results of a population-based case-control study in Spain. *J. Clin. Med.* **13**, 591 (2024).
41. Tattersall, M. C., Jarjour, N. N. & Busse, P. J. Systemic inflammation in asthma: what are the risks and impacts outside the airway?. *J. Allergy Clin. Immunol. Pract.* **12**, 849–862 (2024).
42. McLoughlin, R. F., Clark, V. L., Urroz, P. D., Gibson, P. G. & McDonald, V. M. Increasing physical activity in severe asthma: a systematic review and meta-analysis. *Eur. Respir. J.* **60**, 2200546 (2022).
43. González-Freire, B., Vázquez, I. & Pértega-Díaz, S. The relationship of psychological factors and asthma control to health-related quality of life. *J. Allergy Clin. Immunol. Pract.* **8**, 197–207 (2020).

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AUTHOR CONTRIBUTIONS

Dr X.X. and C.X. have full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. X.X. conceptualized the study design and supervised the whole project. Y.C. conducted the statistical analyses and drafted the original manuscript. Y.Z. provided support on statistical methods and manuscript revision. J.L. verified the data and statistical analyses. All authors contributed to and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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