

**Supplementary Table SI.** Variables in the 49-item frailty index and their respective scorings

Variable	Scoring
<b>Cognition</b>	
1. Experience confusion/memory problems	Yes = 1, No = 0
<b>Dependence</b>	
2. Managing money	Difficulty = 1, No difficulty = 0
3. Stooping, crouching, kneeling	Difficulty = 1, No difficulty = 0
4. Lifting or carrying	Difficulty = 1, No difficulty = 0
5. House chores	Difficulty = 1, No difficulty = 0
6. Preparing meals	Difficulty = 1, No difficulty = 0
7. Standing up from armless chair	Difficulty = 1, No difficulty = 0
8. Getting in and out of bed	Difficulty = 1, No difficulty = 0
9. Using fork, knife, drinking from cup	Difficulty = 1, No difficulty = 0
10. Dressing yourself	Difficulty = 1, No difficulty = 0
11. Standing for long periods	Difficulty = 1, No difficulty = 0
12. Grasping/holding small objects	Difficulty = 1, No difficulty = 0
13. Attending social events	Difficulty = 1, No difficulty = 0
14. Pushing or pulling large objects	Difficulty = 1, No difficulty = 0
15. Walking for a quarter mile	Difficulty = 1, No difficulty = 0
16. Walking up 10 steps	Difficulty = 1, No difficulty = 0
<b>Depressive symptoms</b>	
17. Have little interest in doing things	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0
18. Feeling down, depressed, or hopeless	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0
19. Trouble sleeping or sleeping too much	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0
20. Feeling tired or having little energy	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0
21. Poor appetite or overeating	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0
22. Feeling bad about yourself	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0
23. Trouble concentrating on things	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all = 0
<b>Comorbidities</b>	
24. Arthritis	Yes = 1, Suspect = 0.5, No = 0
25. Thyroid problems	Yes = 1, Suspect = 0.5, No = 0
26. Chronic bronchitis	Yes = 1, Suspect = 0.5, No = 0
27. Cancer	Yes = 1, Suspect = 0.5, No = 0

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28. Congestive heart failure	Yes = 1, Suspect = 0.5, No = 0
29. Coronary heart disease	Yes = 1, Suspect = 0.5, No = 0
30. Angina	Yes = 1, Suspect = 0.5, No = 0
31. Heart attack	Yes = 1, Suspect = 0.5, No = 0
32. Stroke	Yes = 1, Suspect = 0.5, No = 0
33. Blood pressure	Yes = 1, Suspect = 0.5, No = 0
34. Diabetes	Yes = 1, Suspect = 0.5, No = 0
35. Weak/failing kidneys	Yes = 1, Suspect = 0.5, No = 0
36. Urinary Leakage	Yes = 1, Suspect = 0.5, No = 0
Hospital utilization and access to care	
37. Self-rated health	Fair, poor = 1, Excellent, very good, good = 0
38. Health now compared with 1 year ago	Worse = 1, About the same, better = 0
39. Overnight hospital patient in past year	Yes = 1, No = 0
40. Frequency of health care use during past year	None = 0, 1- 5 = 0.5, More than 5 = 1
41. Number of prescribed medications	None = 0, 1- 4 = 0.5, 5 and more = 1
Physical performance and anthropometry	
42. Body mass index	<18.5 or $\geq 30 = 1$ , 25-30 = 0.5, 18.5-25 = 0
43. Handgrip strength	Male: For BMI $\leq 24$ , GS $\leq 29$ ; BMI 24.1-28, GS $\leq 30$ ; BMI >28, GS $\leq 32 = 1$
Laboratory values	
44. Glycohemoglobin (%)	0%-5.7% = 0, >5.7% = 1
45. Red blood cell count (million cells/ml)	Male: 4.7-6.1 = 0, Other = 1
46. Hemoglobin (g/dl)	Male: 13.5-18 = 0, Other = 1
47. Red cell distribution width (%)	11.6-14.6 = 0, Other = 1
48. Lymphocyte percent (%)	20-40 = 0, Other = 1
49. Segmented neutrophil percent (%)	40- 80 = 0, Other = 1

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BMI – body mass index, GS – grip strength.

**Supplementary Table SII.** Population characteristics by categories of asthma status in original cohort

<b>Variables</b>	<b>Total</b>	<b>Without asthma</b>	<b>Asthma</b>	<b>P-value</b>
Participants ( <i>n</i> )	29589	25292	4297	
Age [years], mean $\pm$ SD	49.5 $\pm$ 17.6	49.9 $\pm$ 17.6	47.3 $\pm$ 17.5	< 0.001
Sex, <i>n</i> (%)				< 0.001
Male	14814 (50.1)	12373 (48.9)	2441 (56.8)	
Female	14775 (49.9)	12919 (51.1)	1856 (43.2)	
Race/ethnicity, <i>n</i> (%)				< 0.001
Non-Hispanic White	13119 (44.3)	11054 (43.7)	2065 (48.1)	
Non-Hispanic Black	6285 (21.2)	5231 (20.7)	1054 (24.5)	
Mexican American	4428 (15.0)	4046 (16)	382 (8.9)	
Others	5757 (19.5)	4961 (19.6)	796 (18.5)	
Marital status, <i>n</i> (%)				< 0.001
Married or living with a partner	17666 (59.7)	15382 (60.8)	2284 (53.2)	
Living alone	11923 (40.3)	9910 (39.2)	2013 (46.8)	
Family income, <i>n</i> (%)				< 0.001
Low	9156 (30.9)	7588 (30)	1568 (36.5)	
Medium	11196 (37.8)	9707 (38.4)	1489 (34.7)	
High	9237 (31.2)	7997 (31.6)	1240 (28.9)	
Education level [year], <i>n</i> (%)				< 0.001
< 9	2836 (9.6)	2518 (10)	318 (7.4)	
9–12	10891 (36.8)	9340 (36.9)	1551 (36.1)	
> 12	15862 (53.6)	13434 (53.1)	2428 (56.5)	
Smoking status, <i>n</i> (%)				< 0.001
Never	16149 (54.6)	14020 (55.4)	2129 (49.5)	
Former	7240 (24.5)	6164 (24.4)	1076 (25)	
Current	6200 (21.0)	5108 (20.2)	1092 (25.4)	
Alcohol status, <i>n</i> (%)				< 0.001
Never	4102 (13.9)	3601 (14.2)	501 (11.7)	
Former	4848 (16.4)	4115 (16.3)	733 (17.1)	
Current	20639 (69.8)	17576 (69.5)	3063 (71.3)	
BMI, mean $\pm$ SD	29.2 $\pm$ 7.0	29.0 $\pm$ 6.8	30.8 $\pm$ 8.2	< 0.001
Type 2 diabetes, <i>n</i> (%)				< 0.001
No	24120 (81.5)	20742 (82)	3378 (78.6)	
Yes	5469 (18.5)	4550 (18)	919 (21.4)	
Hypertension, <i>n</i> (%)				< 0.001

No	16970 (57.4)	14674 (58)	2296 (53.4)	
Yes	12619 (42.6)	10618 (42)	2001 (46.6)	
Stroke, <i>n</i> (%)				< 0.001
No	28433 (96.1)	24375 (96.4)	4058 (94.4)	
Yes	1156 (3.9)	917 (3.6)	239 (5.6)	
CHD (%)				0.025
No	28390 (95.9)	24294 (96.1)	4096 (95.3)	
Yes	1199 (4.1)	998 (3.9)	201 (4.7)	
Frailty status, <i>n</i> (%)				< 0.001
No	23086 (78.0)	20282 (80.2)	2804 (65.3)	
Yes	6503 (22.0)	5010 (19.8)	1493 (34.7)	

BMI – body mass index, CHD – coronary heart disease.

**Supplementary Table SIII.** Mendelian randomization analysis of the effects of asthma on frailty risk (Exposure:

Asthma || finn-b-J10\_ASTHMA; Outcome: Frailty index || ebi-a-GCST90020053)

SNP	EAE	OAE	EAO	OAO	Exposure			Outcome			F
					se	beta	P-value	se	beta	P-value	
rs11667612	T	G	T	G	0.0259	0.1471	1.43E-08	0.01	8.00E-04	0.9344	32.2571 4
rs118013485	A	G	A	G	0.0197	-0.1108	1.92E-08	0.0068	-0.0083	0.2205	31.6334 9
rs12761415	G	A	G	A	0.0155	0.0857	3.17E-08	0.0043	0.0134	0.00170098	30.5702
rs17293632	T	C	T	C	0.0131	0.099	4.66E-14	0.0039	0.0088	0.02329	57.1120 6
rs1837253	C	T	C	T	0.0137	0.1345	1.23E-22	0.0037	0.0065	0.0846408	96.3836 6
rs186856025	T	C	T	C	0.0248	-0.1571	2.32E-10	0.0053	-0.0112	0.0366303	40.1281 4
rs2325259	C	T	C	T	0.0134	-0.0758	1.69E-08	0.0035	-0.005	0.151	31.9984 4
rs35656734	T	C	T	C	0.0131	-0.1122	1.00E-17	0.0038	-0.0193	2.94E-07	73.3572 6
rs60227565	A	G	A	G	0.0161	-0.1189	1.74E-13	0.0049	-0.0189	0.000124	54.5396
rs62192043	A	G	A	G	0.014	-0.1015	3.51E-13	0.0038	-0.0175	3.97E-06	52.5625
rs6894249	G	A	G	A	0.0116	0.0932	9.29E-16	0.0034	0.006	0.0747894	64.5529 1
rs7035413	G	A	G	A	0.0148	0.1302	1.69E-18	0.0039	0.0053	0.175	77.3924 4
rs7126418	T	A	T	A	0.0118	0.0655	2.60E-08	0.0033	0.0072	0.0313798	30.8119 1
rs74630264	A	G	A	G	0.0214	-0.1501	2.49E-12	0.0202	0.0013	0.95	49.1964 6
rs8074437	G	T	G	T	0.0117	0.0981	4.17E-17	0.0033	0.0049	0.141	70.3017 8

SNP – single nucleotide polymorphism, EAE – effect allele exposure, OAE – other allele exposure, EAO – effect allele outcome, OAO – other allele outcome, SE – standard error, F – F value.

**Supplementary Table SIV.** Mendelian randomization analysis of the effects of frailty on asthma risk (Exposure: Frailty index || ebi-a-GCST90020053; Outcome: asthma || finn-b-J10\_ASTHMA)

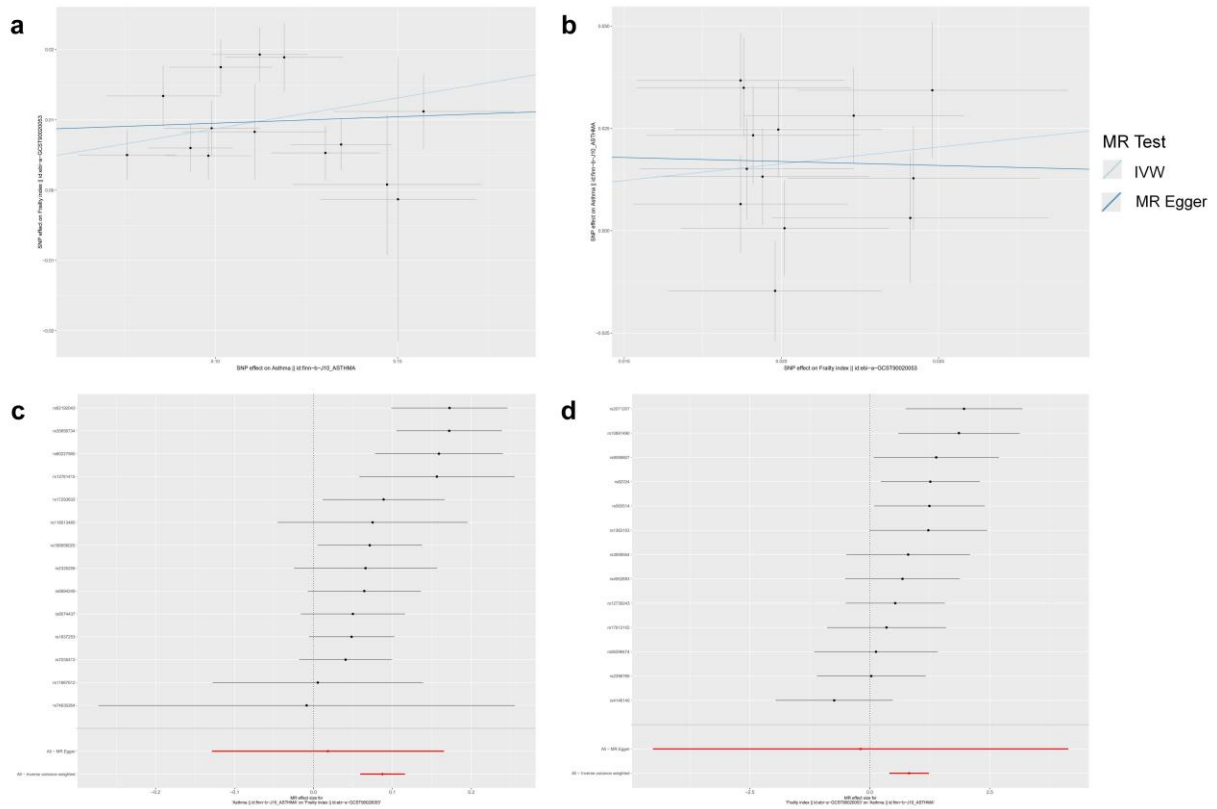
SNP	EAE	OA E	EA O	OA O	Exposure			Outcome			F
					se	beta	P-value	se	beta	P-value	
rs10891490	C	T	C	T	0.0034	-0.0188	2.00E-08	0.0121	-0.0349	0.00399797	30.57439
rs12739243	C	T	C	T	0.004	-0.0242	1.28E-09	0.0127	-0.0128	0.3126	36.6025
rs1363103	C	T	C	T	0.0034	-0.0191	2.23E-08	0.0119	-0.0233	0.0503802	31.55796
rs17612102	C	T	C	T	0.0034	0.0187	2.85E-08	0.0118	0.0065	0.5822	30.25
rs2071207	C	T	C	T	0.0033	-0.0187	1.47E-08	0.0116	-0.0367	0.001562	32.11111
rs2396766	A	G	A	G	0.0033	0.0201	1.22E-09	0.0116	6.00E-04	0.9594	37.09917
rs3959554	G	A	G	A	0.0034	0.0189	1.74E-08	0.0124	0.0151	0.2241	30.90052
rs4146140	T	C	T	C	0.0034	-0.0198	6.83E-09	0.0123	0.0147	0.232	33.91349
rs4952693	T	C	T	C	0.0034	-0.0194	1.47E-08	0.0118	-0.0132	0.2648	32.55709
rs56299474	A	C	A	C	0.0044	0.0241	3.94E-08	0.0158	0.0031	0.846	30.00052
rs583514	C	T	C	T	0.0033	0.0199	1.65E-09	0.0117	0.0247	0.0342397	36.36455
rs8089807	T	C	T	C	0.0043	-0.0248	6.50E-09	0.0165	-0.0343	0.0375803	33.26339
rs82334	C	A	C	A	0.0035	-0.0223	3.13E-10	0.0117	-0.0281	0.0168702	40.5951

SNP – single nucleotide polymorphism, EAE – effect allele exposure, OAE – other allele exposure, EAO – effect allele outcome, OAO – other allele outcome, SE – standard error, F – F value.

**Supplementary Figure S1.** Scatter and forest plots of genetic associations: asthma on frailty and frailty on asthma.

The slopes of each line represent the causal association for each method. The blue line represents the inverse-variance weighted estimate and the dark blue line represents the Mendelian randomization-Egger estimate.

**A** – Asthma on frailty. **B** – Frailty on asthma. Forest plots show the causal effects of single nucleotide polymorphisms associated with **(C)** asthma on frailty and **(D)** frailty on asthma



**Supplementary Figure S2.** Leave-one-out analyses of the association between asthma and frailty. **A** – Leave-one-out analyses of asthma on frailty. **B** – Leave-one-out analyses of frailty on asthma. Funnel plot to assess heterogeneity. The blue line represents the inverse-variance weighted estimate, and the dark blue line represents the Mendelian randomization-Egger estimate. **C** – Asthma on frailty. **D** – Frailty on asthma

