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Public Health

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.
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Frailty and pre-frailty in middle-aged and older adults and its association with
multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank
participants. *Lancet Public Health* 2018; published online June 13. [http://dx.doi.org/10.1016/S2468-2667\(18\)30091-4](http://dx.doi.org/10.1016/S2468-2667(18)30091-4).

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Descriptive cross sectional analysis of baseline variables

Characteristic	Not frail (n=291,839)		Pre-frail (n=185,360)		Frail (n=16,538)		
	Count	%	Count	%	Count	%	p-value
Sex							
Male	138,270	47.4	80,136	43.2	6,587	39.8	<0.001
Female	153,569	52.6	105,224	56.8	9,951	60.2	
Age							
37-45 years	38,533	13.2	23,261	12.5	1,417	8.6	<0.001
45-55 years	86,824	29.8	52,856	28.5	4,370	26.4	
55-65 years	126,499	43.3	79,811	43.1	7,688	46.5	
65-73 years	39,983	13.7	29,432	15.9	3,063	18.5	
Median (IQR)	58 (50-63)		58 (50-63)		59 (52-64)		
Ethnicity							
White	280,563	96.4	170,982	92.6	14,448	87.9	<0.001
Other	10,400	3.6	13,634	7.4	1,995	12.1	
Missing	876		744		95		
Socioeconomic deprivation quintile							
1 (least deprived)	65,753	22.6	32,221	17.4	1,545	9.4	<0.001
2	63,229	21.7	33,673	18.2	1,915	11.6	
3	60,275	20.7	36,046	19.5	2,455	14.9	
4	56,311	19.3	38,740	20.9	3,642	22.1	
5 (most deprived)	45,971	15.8	44,396	24.0	6,952	42.1	
Missing	300		284		29		
Household income							
< £18,000	45,146	17.8	43,616	28.0	7,013	55.7	<0.001
£18,000 – 30,999	63,015	24.8	41,667	26.7	2,925	23.2	
£31,000 – 51,999	70,527	27.8	38,118	24.5	1,730	13.7	
£52,000 – 100,000	58,964	23.2	26,246	16.8	798	6.3	
> £100,000	16,496	6.5	6,237	4.0	130	1.0	
Missing	37,691		29,476		3,942		
University degree							
No	183,944	63.5	130,752	71.5	13,600	84.0	<0.001
Yes	105,589	34.5	52,176	28.5	2,589	16.0	
Missing	2,306		2,432		349		
Smoking status							
Current	25,888	8.9	22,513	12.2	3,312	20.2	<0.001
Previous	100,301	34.5	64,646	35.0	5,653	34.5	
Never	164,772	56.6	97,373	52.8	7,436	45.3	
Missing	878		828		137		
Alcohol frequency							
Daily	66,494	22.8	32,293	17.4	1,739	10.5	<0.001
1-4 times/week	152,120	52.2	84,291	45.5	5,181	31.4	
1-3 times/month	30,315	10.4	22,957	12.3	1,957	11.9	
Occasional/Never	42,766	14.7	45,699	24.7	7,610	46.2	
Missing	144		263		51		
BMI							
<18.5	1,371	0.5	1,034	0.6	150	0.9	<0.001
18.5-24.9	106,856	36.7	46,388	25.3	2,449	15.4	
25.0-29.9	129,710	44.6	77,153	42.0	4,984	31.4	
>30	53,218	18.3	58,919	32.1	8,279	52.2	
Missing	684		1,866		676		
Multimorbidity							
0 LTCs	117,531	40.4	50,187	27.2	1,397	8.5	<0.001
1 LTC	99,227	34.1	59,082	32.0	3,123	19.1	
2 LTCs	40,726	16.9	40,726	22.1	3,987	24.3	
3 LTCs	17,997	6.2	20,941	11.3	3,443	21.0	

≥4 LTCs	7,299	2.5	13,604	7.4	4,435	27.1	<0.001
Missing	641		820		153		
Median (IQR)	1 (0-2)		1 (0-2)		2 (1-4)		<0.001

Multinomial model using age as a continuous variable

Pre-frail vs. Not Frail			Frail vs. Not Frail		
Predictor	Odds ratio	95% CI	Predictor	Odds ratio	95% CI
Sex			Sex		
Male	(ref)	(ref)	Male	(ref)	(ref)
Female	1.18	1.17 – 1.20	Female	1.21	1.17 – 1.26
Age			Age		
OR per 1 year increase	0.999	0.998-0.999	OR per 1 year increase	1.002	1.000-1.004
Socioeconomic deprivation quintile			Socioeconomic deprivation quintile		
1 (least deprived)	(ref)	(ref)	1 (least deprived)	(ref)	(ref)
2	1.05	1.03 – 1.07	2	1.19	1.11 – 1.27
3	1.15	1.13 – 1.17	3	1.48	1.38 – 1.58
4	1.27	1.25 – 1.30	4	2.07	1.94 – 2.21
5 (most deprived)	1.62	1.59 – 1.65	5 (most deprived)	3.71	3.50 – 3.94
Smoking status			Smoking status		
Never	(ref)	(ref)	Never	(ref)	(ref)
Previous	1.05	1.03 – 1.06	Previous	1.07	1.03 – 1.12
Current	1.42	1.39 – 1.45	Current	2.46	2.34 – 2.58
Alcohol frequency			Alcohol frequency		
Daily	0.88	0.87 – 0.90	Daily	0.75	0.71 – 0.80
1-4 times/week	(ref)	(ref)	1-4 times/week	(ref)	(ref)
1-3 times/month	1.23	1.20 – 1.25	1-3 times/month	1.48	1.40 – 1.57
Occasional/Never	1.58	1.56 – 1.61	Occasional/Never	3.05	2.92 – 3.18
BMI			BMI		
<18.5	1.48	1.36 – 1.61	<18.5	2.92	2.42 – 3.55
18.5-24.9	(ref)	(ref)	18.5-24.9	(ref)	(ref)
25.0-29.9	1.35	1.33 – 1.37	25.0-29.9	1.50	1.43 – 1.58
>30	2.18	2.14 – 2.22	>30	4.03	3.84 – 4.24
Multimorbidity			Multimorbidity		
0 LTCs	(ref)	(ref)	0 LTCs	(ref)	(ref)
1 LTC	1.32	1.30 – 1.34	1 LTC	2.27	2.12 – 2.42
2 LTCs	1.72	1.69 – 1.75	2 LTCs	5.14	4.82 – 5.49
3 LTCs	2.26	2.20 – 2.31	3 LTCs	10.41	9.73 – 11.15
≥4 LTCs	3.32	3.22 – 3.43	≥4 LTCs	27.29	25.45 – 29.26

All covariates highlighted in bold are statistically significant (p<0.001)
 *p = 0.0012, **p = 0.08
 Results based on n=488,087 participants with complete data for all covariates (5650 (1.1%) missing data)

Weight loss – univariate analysis – Cox PH model

Age	Females		Males	
	HR	95% CI	HR	95% CI
37-45	1.14	0.8-1.62	1.38	1.01-1.88
45-55	1.43	1.22-1.68	1.58	1.37-1.81
55-65	1.46	1.33-1.6	1.28	1.18-1.39
65-73	1.48	1.31-1.68	1.28	1.16-1.41

Low grip strength – univariate analysis – Cox PH model

Age	Females		Males	
	HR	95% CI	HR	95% CI
37-45	1.53	0.92-2.55	2.10	1.43-3.10
45-55	1.66	1.38-2.0	2.14	1.83-2.51
55-65	1.22	1.11-1.35	1.73	1.60-1.87
65-73	1.37	1.22-1.53	1.45	1.34-1.58

Low physical activity – univariate analysis – Cox PH model

Age	Females		Males	
	HR	95% CI	HR	95% CI
37-45	1.31	0.88-1.97	2.43	1.77-3.34
45-55	1.66	1.43-1.92	2.59	2.26-2.98
55-65	1.86	1.69-2.05	2.56	2.37-2.76
65-73	1.82	1.61-2.06	2.09	1.90-2.31

Self-reported exhaustion – univariate analysis – Cox PH model

Age	Females		Males	
	HR	95% CI	HR	95% CI
37-45	1.49	1.08-2.06	1.93	1.43-2.61
45-55	1.66	1.43-1.92	2.05	1.78-2.35
55-65	1.63	1.48-1.80	1.90	1.75-2.06
65-73	1.67	1.45-1.92	1.95	1.75-2.17

Self-reported slow walking speed – univariate analysis – Cox PH model

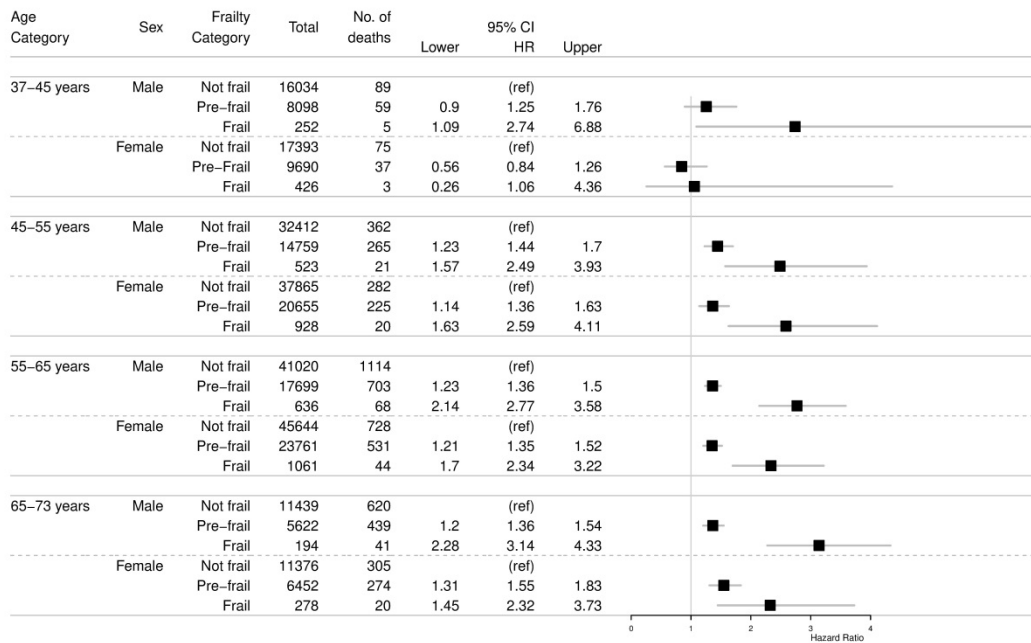
Age	Females		Males	
	HR	95% CI	HR	95% CI
37-45	3.18	2.13-4.74	3.57	2.46-5.18
45-55	3.12	2.63-3.67	4.00	3.46-4.63
55-65	2.61	2.38-2.87	3.35	3.12-3.59
65-73	2.43	2.16-2.73	2.60	2.39-2.83

Cox PH model. Mortality risk associated with increasing number of frailty indicators.

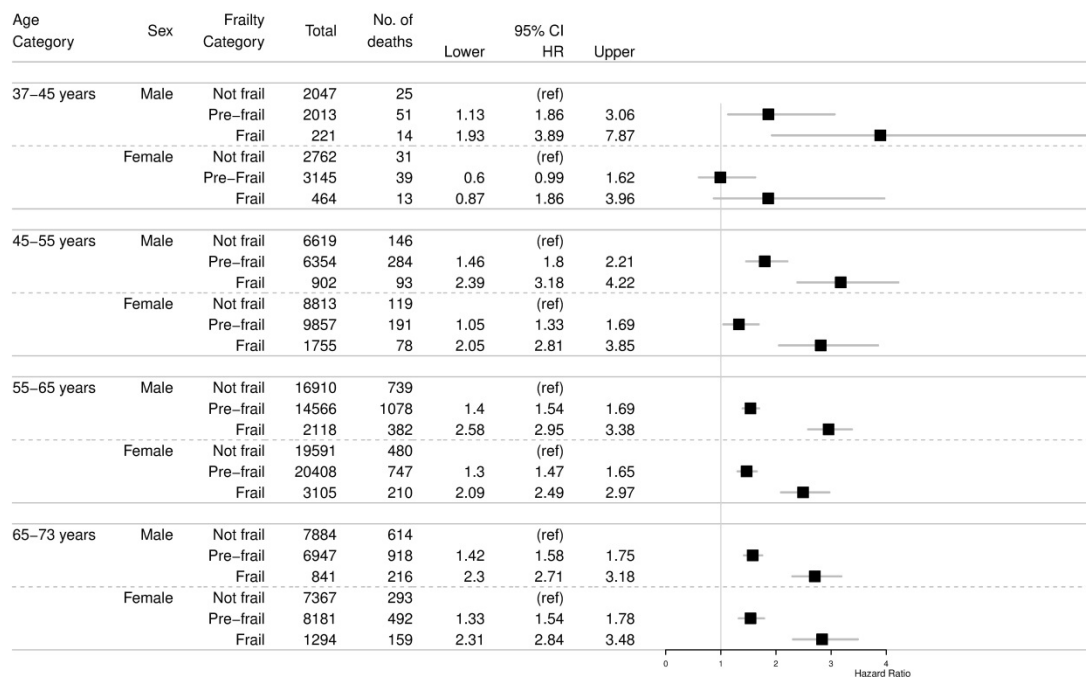
Number of frailty indicators	Hazard Ratios (95% confidence intervals)								
	All participants (age/sex adjusted) (n = 493,737)	Females				Males			
		37-45 years (n=34,218)	45-55 years (n=81,144)	55-65 years (n=116,759)	65-73 years (n=36,623)	37-45 years (n=28,993)	45-55 years (n=62,906)	55-65 years (n=97,239)	65-73 years (n=35,855)
0 indicators	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
1 indicator	1.44 (1.39 - 1.50)	0.96 (0.69 - 1.34)	1.36 (1.17 - 1.59)	1.40 (1.29 - 1.53)	1.46 (1.30 - 1.65)	1.49 (1.12 - 1.99)	1.62 (1.42 - 1.86)	1.44 (1.34 - 1.55)	1.47 (1.35 - 1.60)
2 indicators	2.48 (2.36 - 2.60)	1.91 (1.25 - 2.92)	2.33 (1.92 - 2.82)	2.13 (1.91 - 2.38)	2.15 (1.86 - 2.48)	2.78 (1.89 - 4.09)	3.58 (3.04 - 4.22)	2.77 (2.53 - 3.03)	2.44 (2.19 - 2.71)
3 indicators	3.71 (3.46 - 3.96)	3.24 (1.78 - 5.89)	3.90 (3.03 - 5.02)	3.06 (2.62 - 3.56)	3.26 (2.70 - 3.94)	6.10 (3.56 - 10.45)	5.15 (4.04 - 6.55)	4.55 (4.04 - 5.12)	3.07 (2.63 - 3.60)
4 indicators	5.37 (4.82 - 5.97)	4.10 (1.51 - 11.13)	5.64 (3.79 - 8.38)	3.77 (2.89 - 4.91)	4.03 (2.97 - 5.47)	9.62 (3.93 - 23.56)	8.47 (5.96 - 12.05)	6.08 (5.04 - 7.34)	6.15 (4.86 - 7.79)
5 indicators	6.13 (4.59 - 8.19)	-	4.03 (1.01 - 16.17)	5.79 (3.12 - 10.79)	3.65 (1.37 - 9.75)	-	15.45 (7.33 - 32.58)	6.69 (4.02 - 11.12)	5.58 (2.79 - 11.19)

Multimorbidity – subgroup analyses – ‘0-1 comorbidities’ versus ‘2 or more’

MMcount 0 or 1 – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for socioeconomic status, BMI, smoking and alcohol frequency

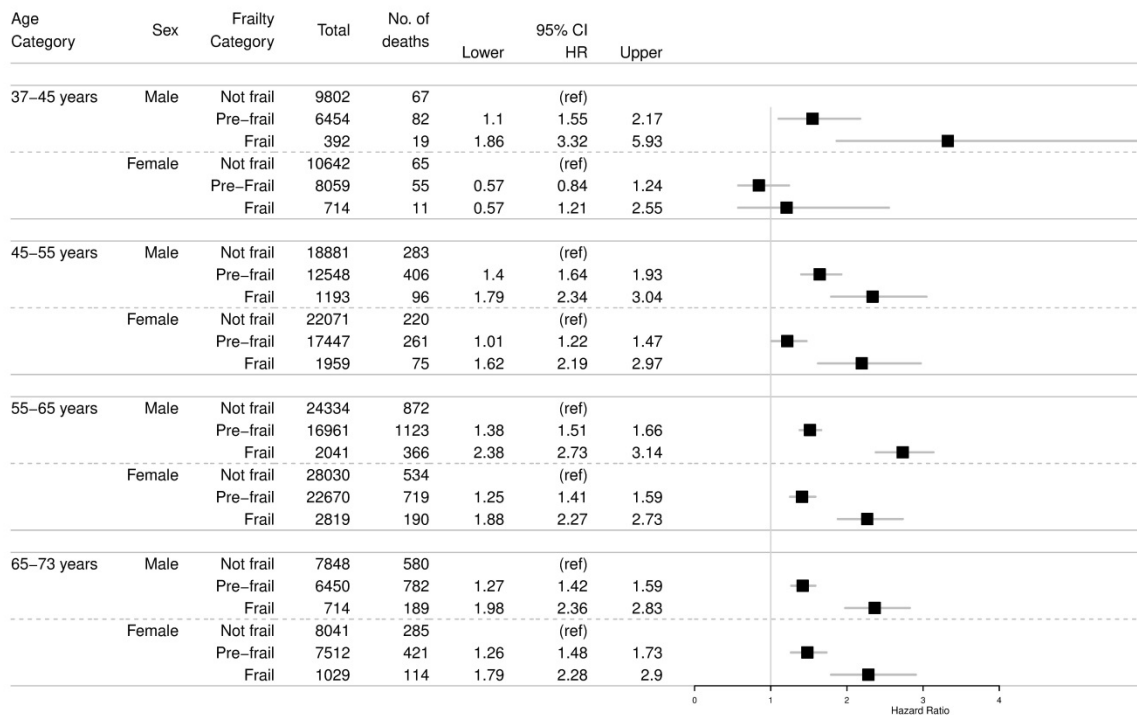


MMcount 2 or more – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for socioeconomic status, BMI, smoking and alcohol frequency

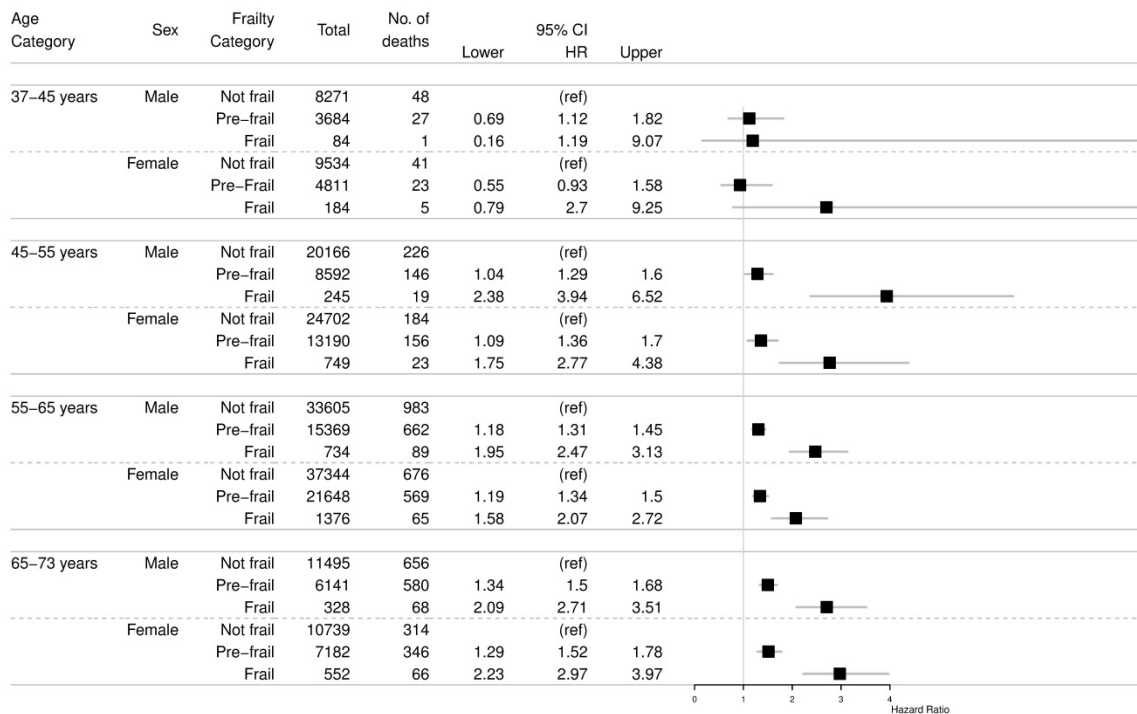


Socioeconomic status – most deprived 50% versus least deprived 50%

Most deprived 50% – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for multimorbidity count, BMI, alcohol frequency and smoking

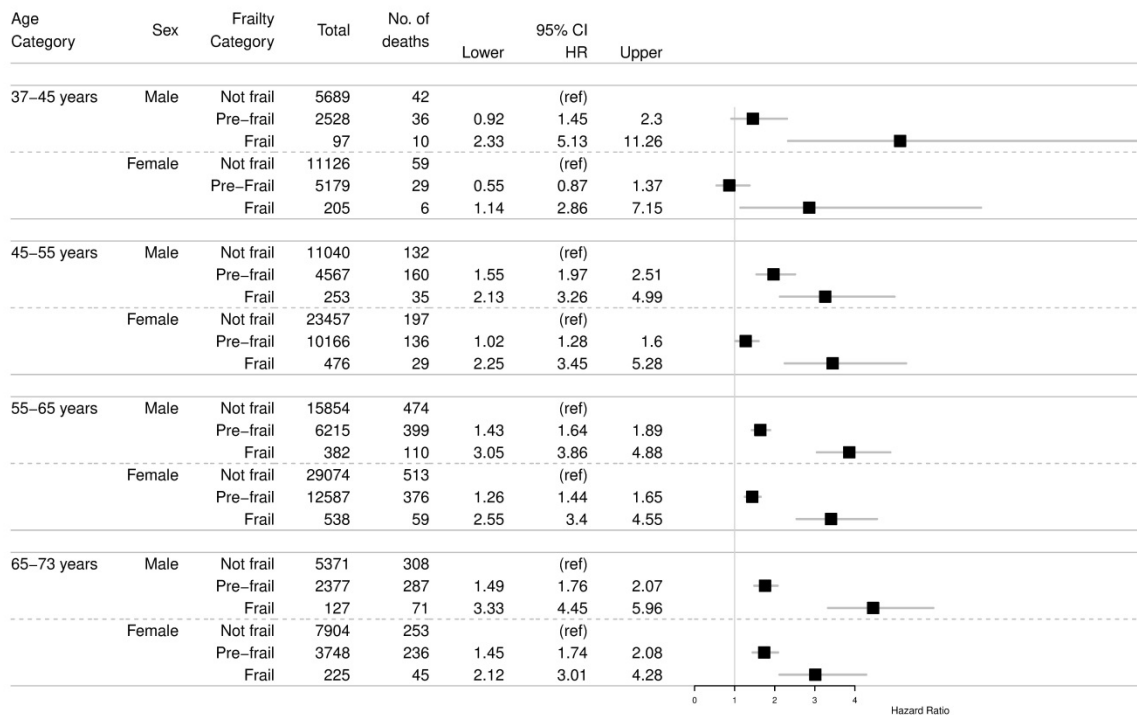


Most affluent 50% – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for multimorbidity count, BMI, alcohol frequency and smoking

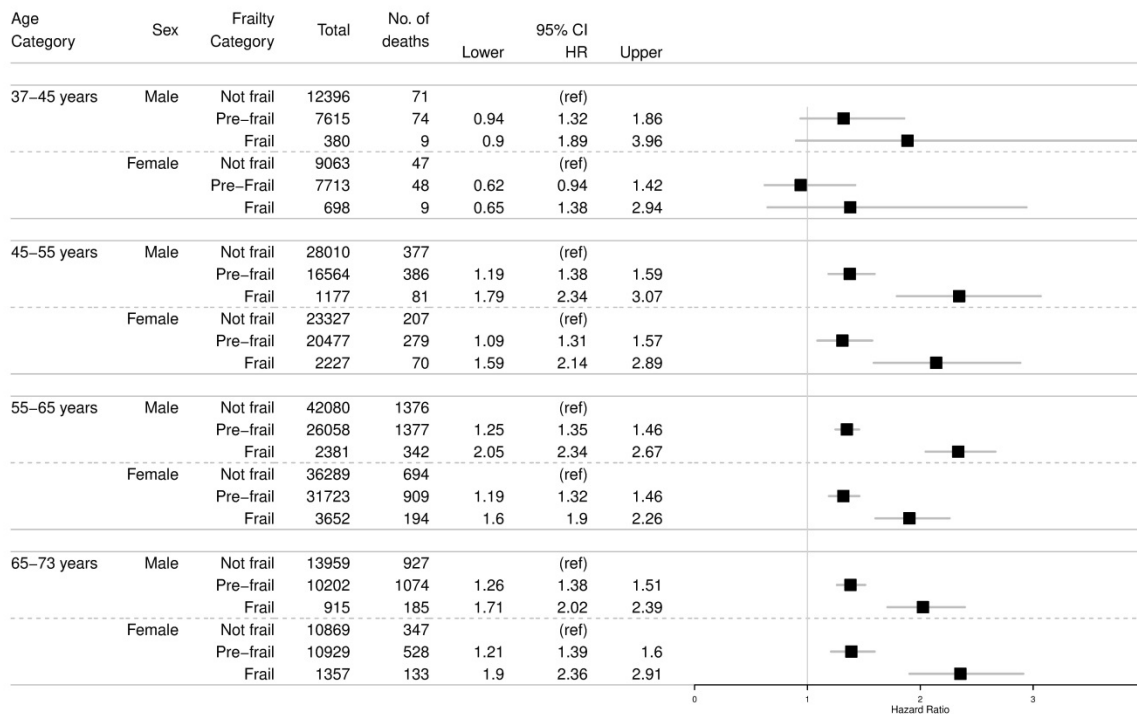


Body Mass Index – <25 versus >25

BMI <25 – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for multimorbidity count, socioeconomic status, alcohol frequency and smoking

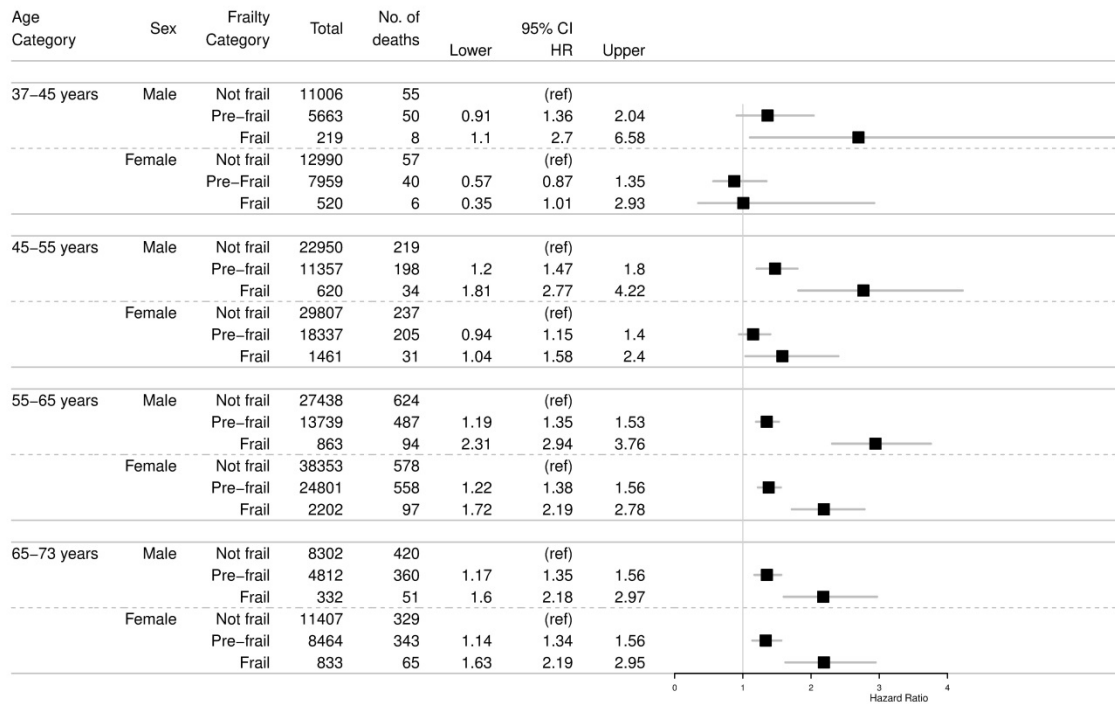


BMI >25 – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for multimorbidity count, socioeconomic status, alcohol frequency and smoking

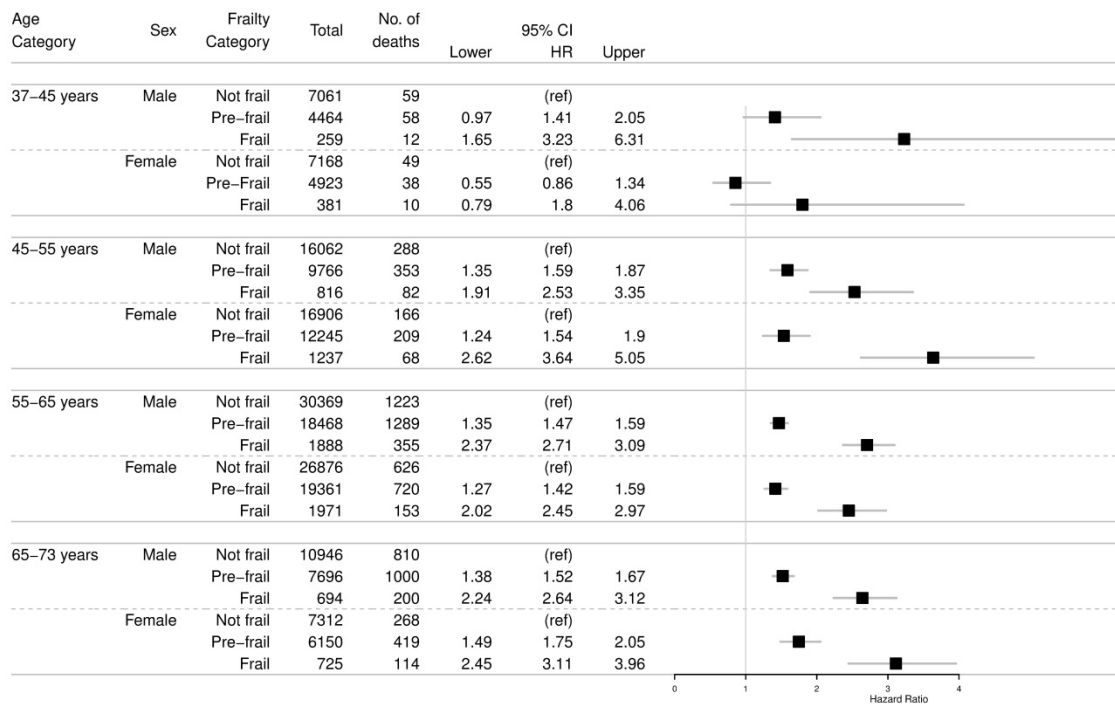


Smoking – Never versus Current or Previous

Never smokers – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for multimorbidity count, socioeconomic status, BMI, alcohol frequency

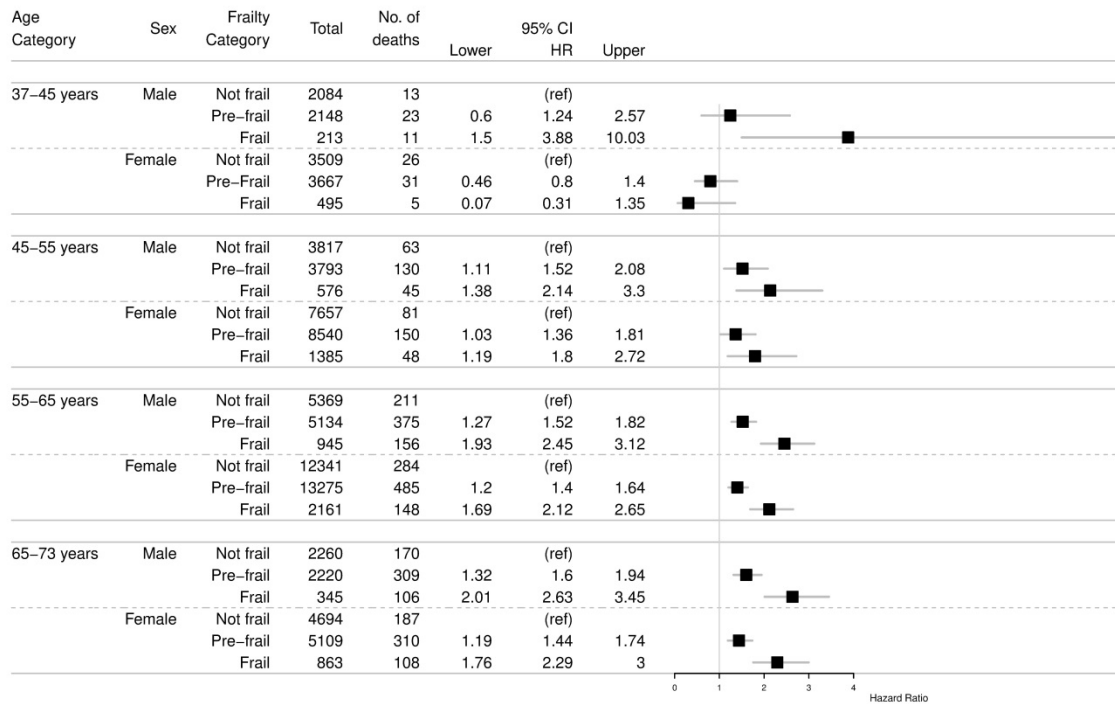


Current or previous smokers – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for multimorbidity count, socioeconomic status, BMI, alcohol frequency

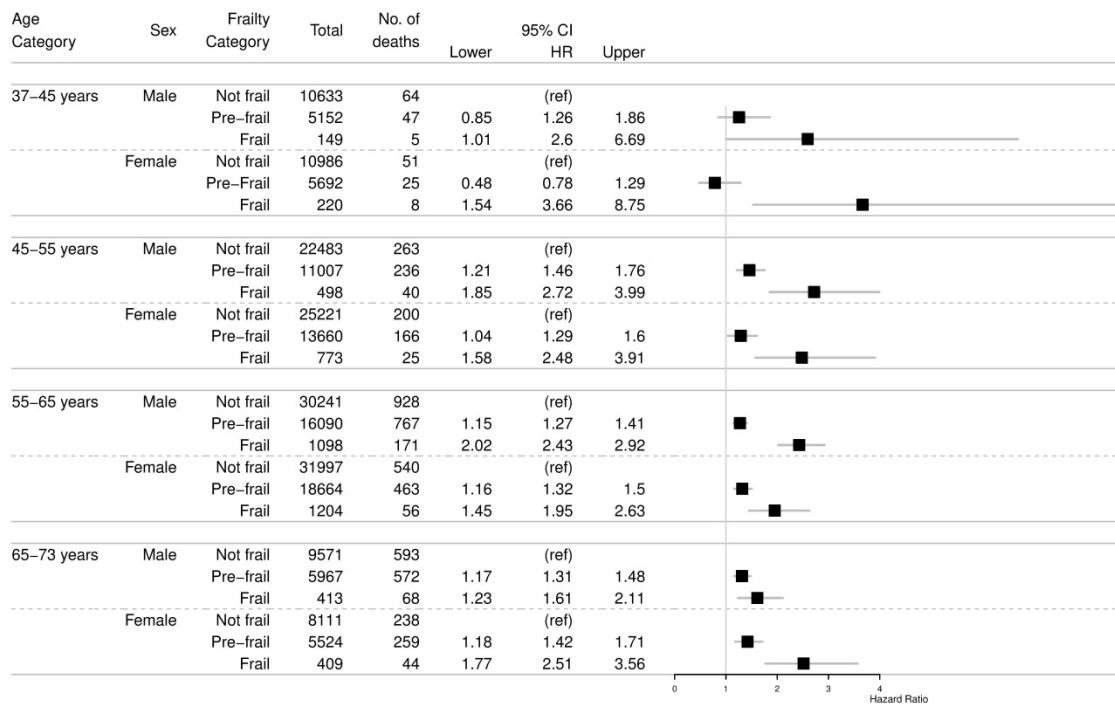


Alcohol frequency – never/occasional versus 1-4 per week versus daily

Never or special occasions only – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for multimorbidity count, socioeconomic status, BMI and smoking



1–4 times per week – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for multimorbidity count, socioeconomic status, BMI and smoking

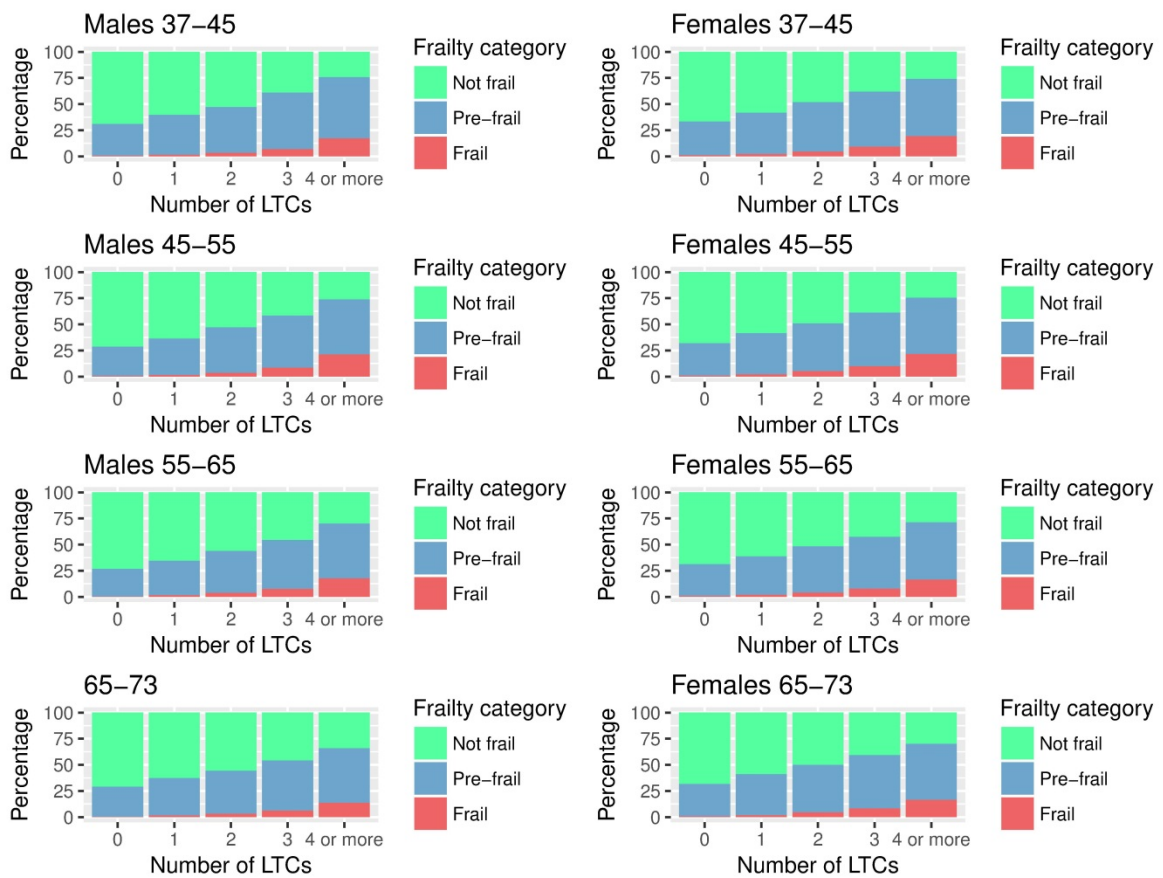


Daily or almost daily – Hazard ratios of all-cause mortality for frailty status stratified by age and sex, adjusted for multimorbidity count, socioeconomic status, BMI and smoking

Age Category	Sex	Frailty Category	Total	No. of deaths	95% CI			
					Lower	HR	Upper	
37–45 years	Male	Not frail	3285	21		(ref)		
		Pre-frail	1431	25	1.16	2.12	3.87	■
		Frail	58	3	0.56	2.15	8.22	■
	Female	Not frail	2569	13		(ref)		
		Pre-Frail	1353	5	0.25	0.71	2.05	■
		Frail	51	2	1.12	6.12	33.47	■
45–55 years	Male	Not frail	9352	138		(ref)		
		Pre-frail	4003	129	1.25	1.61	2.07	■
		Frail	181	19	1.35	2.35	4.11	■
	Female	Not frail	7958	73		(ref)		
		Pre-frail	3834	45	0.71	1.04	1.54	■
		Frail	164	12	2.38	4.74	9.45	■
55–65 years	Male	Not frail	18206	572		(ref)		
		Pre-frail	8183	480	1.36	1.55	1.76	■
		Frail	443	99	2.8	3.54	4.48	■
	Female	Not frail	13550	244		(ref)		
		Pre-frail	6489	189	1.13	1.38	1.69	■
		Frail	298	31	2.35	3.53	5.32	■
65–73 years	Male	Not frail	6162	392		(ref)		
		Pre-frail	3367	368	1.29	1.49	1.73	■
		Frail	184	55	2.31	3.12	4.21	■
	Female	Not frail	3852	107		(ref)		
		Pre-frail	2267	125	1.38	1.8	2.36	■
		Frail	123	16	1.78	3.15	5.57	■



Relationship between frailty prevalence and number of LTCs: Analysis stratified by age and sex



Categorisation of Long-Term Conditions

Morbidity grouping*	Conditions included
Hypertension	Hypertension Essential hypertension
Coronary heart disease	Heart attack/MI Angina
Diabetes	Diabetic nephropathy Diabetic neuropathy/ulcers Diabetes Type 1 diabetes Type 2 diabetes Diabetic eye disease
Stroke/TIA	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke
Atrial fibrillation	Atrial fibrillation
Heart failure	Cardiomyopathy Hypertrophic cardiomyopathy Heart failure/pulmonary oedema
Peripheral vascular disease	Peripheral vascular disease Leg claudication/intermittent claudication
COPD	COPD/Chronic obstructive pulmonary disease Emphysema/Chronic bronchitis Emphysema
Asthma	Asthma
Bronchiectasis	Bronchiectasis
Cancer	“yes”/“no” to “have you ever had cancer?”
Dyspepsia	Gastro-oesophageal reflux (GORD) Oesophagitis/Barrett’s oesophagus Gastric stomach ulcers Gastric erosions/gastritis Duodenal ulcer Dyspepsia/indigestion Hiatus hernia Helicobacter pylori
Diverticular disease	Diverticular disease/diverticulitis
Irritable bowel syndrome	Irritable bowel syndrome
Chronic liver disease	Oesophageal varices Non infective hepatitis Liver failure/cirrhosis Primary biliary cirrhosis
Inflammatory bowel disease	Inflammatory bowel disease Crohn’s disease Ulcerative colitis
Constipation	Constipation
Viral hepatitis	Hepatitis B Hepatitis C Hepatitis D

Depression	Depression Postnatal depression
Anxiety	Anxiety/panic attacks Nervous breakdown Post-traumatic stress disorder Obsessive compulsive disorder Stress Insomnia Psychological/psychiatric problem
Schizophrenia/Bipolar affective disorder Bipolar	Scizophrenia Mania Bipolar disorder Manic depression
Connective tissue diseases	Myositis/myopathy Systemic lupus erythematosus/SLE Connective tissue disorder Sjogren's syndrome sicca syndrome Dermatopolymyositis Scleroderma/systemic sclerosis Rheumatoid arthritis Psoriatic arthropathy Dermatomyositis Polymyositis Polymyalgia rheumatica
Painful conditions	Back pain Joint pain Headaches (not migraine) Sciatica Plantar fasciitis Carpal tunnel syndrome Fibromyalgia Arthritis Shingles Disc problem Prolapsed disc/slipped disc Spine arthritis/spondylitis Ankylosing spondylitis Back problem Osteoarthritis Gout Cervical spondylosis Trigeminal neuralgia Disc degeneration Trapped nerve/compressed nerve
Osteoporosis	Osteoporosis
Thyroid disorders	Thyroid problem (not cancer) Hyperthyroidism/thyrototoxicosis Hypothyroidism/myxoedema Grave's disease Thyroid goitre Thyroitis

Alcohol problems	Alcohol dependency Alcoholic liver disease/alcoholic cirrhosis
Chronic kidney disease	Polycystic kidney Diabetic nephropathy Renal/kidney failure Renal failure requiring dialysis Renal failure not requiring dialysis Kidney nephropathy Immunoglobulin A (IgA) nephropathy
Prostate disorders	Prostate problem (not cancer) Enlarged prostate Benign prostatic hypertrophy
Glaucoma	Glaucoma
Epilepsy	Epilepsy
Dementia	Dementia/Alzheimer/cognitive impairment
Psoriasis or eczema	Eczema/dermatitis Psoriasis
Migraine	Migraine
Chronic sinusitis	Chronic sinusitis
Anorexia or bulimia	Anorexia, bulimia/other eating disorder
Parkinson's disease	Parkinson's disease
Multiple sclerosis	Multiple sclerosis
Chronic fatigue syndrome	Chronic fatigue syndrome
Endometriosis	Endometriosis
Meniere disease	Meniere disease
Pernicious anaemia	Pernicious anaemia
Polycystic ovaries	Polycystic ovaries
*Self-report lifetime diagnosis by doctor recorded by nurse-led interview (UK Biobank data field 20002), except cancer diagnosis which was reported by touch-screen questionnaire. The list of disease groupings was based on Barnett et al (2012)	