Frailty, sarcopenia, cachexia and malnutrition as comorbid conditions and their associations with mortality: A prospective study from UK Biobank

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Abstract

Background: Frailty, sarcopenia, cachexia and malnutrition are clinical conditions that share similar diagnostic criteria. This study aimed to investigate the clustering and mortality risk among these clinical conditions in middle- and older-aged adults.

Methods: 111,983 participants from UK Biobank were included. Sarcopenia was defined according to the EWGSOP 2019 while frailty using a modified version of the Fried criteria. Cachexia was defined using the Evans et al. classification and malnutrition using the GLIM. The exposure variable was categorised as: no conditions; frailty only (one condition); frailty with sarcopenia (two conditions); frailty with ≥2 other conditions (three or four conditions). Its association with all-cause mortality was investigated using Cox-proportional hazard analysis.

Results: Frailty had the highest prevalence (45%) and was present in 92.1% of people with malnutrition and everyone with sarcopenia or cachexia. Compared with people no clinical conditions, those with frailty only and frailty with sarcopenia had higher risk of all-cause mortality. Individuals with frailty plus ≥2 other had even higher risk (HR: 4.96 [95% CI: 2.73 to 9.01]).

Conclusions: The four clinical conditions investigated overlapped considerably, being frailty the most common. The risk of all-cause mortality increased with the increasing number of conditions in addition to frailty.

Keywords: Frailty; Sarcopenia; Malnutrition; Cachexia; Mortality.

Introduction

Frailty, sarcopenia, cachexia and malnutrition are common clinical conditions that can herald early stages of disability (1). These conditions are widely recognised as predisposing to falls, fractures, hospitalisations, morbidity and mortality in middle-aged and older adults (2-5). However, they also share similar diagnostic criteria and aetiologies (1).

Frailty is a multisystem dysregulation characterised by weakness, slowness, low levels of physical activity, exhaustion and weight loss (6, 7). Sarcopenia – defined as the age-associated loss of muscle mass and function – was classified as a disease in the International Classification of Diseases in 2016 (8) and contributes to frailty as a result of weakness and slowness (9). Malnutrition, on the other hand, is a chronic energy deficiency due to inadequate food consumption, poor assimilation of nutrients, or disease-associated inflammatory mechanisms (10). Malnutrition also contributes to loss of muscle mass and strength, which are part of the pathogenesis of both sarcopenia and frailty (11). Finally, cachexia is a multifactorial syndrome characterised by progressive weight loss, reduction of muscle quantity and quality, anorexia, fatigue and increased inflammatory response (12); features also present in frailty, sarcopenia and malnutrition (Supplementary Figure 1).

Due to their similarities, it is likely that a significant proportion of people have multiple or even all these conditions. Moreover, since each of these clinical conditions is individually associated with worse health-related outcomes (4, 5, 13, 14), having more than one may have a cumulative impact on mortality. To our knowledge, only one article has investigated the prevalence and overlap among these conditions in older inpatients (15). However, it is recognised that these conditions start earlier in life. Therefore, this study aimed to investigate the clustering and mortality risk among these clinical conditions in the middle- and older-aged adults from the UK Biobank study.

Methods

UK Biobank (www.ukbiobank.co.uk) is a large, general population cohort study. Between 2006 and 2010, UK Biobank recruited over 500,000 participants (5.5% response rate), aged 37-73 years (16). Participants attended one of 22 assessment centres across England, Wales and Scotland (17, 18) where they completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples, as is described in detail elsewhere (17, 18).

Sarcopenia definition

The European Working Group on Sarcopenia in Older People 2019 (EWGSOP2) statement was used to define sarcopenia (9). Suspected sarcopenia or pre-sarcopenia was defined as low grip strength (9). Sarcopenia was defined as the combination of low grip strength plus low muscle mass, and severe sarcopenia was defined as sarcopenia with the addition of slow gait speed (9). Due to the low number of UK Biobank participants with severe sarcopenia (n=469), these two groups were pooled (hereafter called 'sarcopenia') (see supplementary methods).

Frailty definition

An adapted version of the frailty classification derived by Fried et al. was used in this study. The Fried classification uses the following five criteria: weight loss, exhaustion, physical activity, walking speed and grip strength (7). However, some of these items had to be adapted to fit the data available within UK Biobank. Weight loss, tiredness/exhaustion, gait speed and grip strength were derived following a similar approach previously published by Hanlon et al (19). Physical activity, in turn, was based on self-report, collected using the International Physical Activity Questionnaire (IPAQ) short form (20). Participants were classified as frail if they fulfilled three or more criteria, prefrail if they fulfilled one or two criteria and robust (normal) if they did not fulfil any criteria (see supplementary methods).

Cachexia definition and measures

Cachexia was defined according to Evans et al. as a body mass index (BMI) <20 kg/m^2 and the presence of three out of five of the following weakness/fatigue components: low grip strength, low muscle mass, fatigue, anorexia and abnormal biochemistry (12).

After excluding people with missing data for some of the components (see supplementary methods), 454,292 participants met the criteria for cachexia in UK Biobank.

Malnutrition definition and measures

In accordance with the last guideline of the Global Leadership Initiative on Malnutrition (GLIM) – from the European Society for Clinical Nutrition and Metabolism (ESPEN)(10) – malnutrition was defined as the presence of at least one phenotypic (low muscle mass or low BMI) and one etiologic (anorexia or inflammation) criteria (10).

After excluding people with missing data for some of the components (see supplementary methods), 142,880 were finally included as fulfilling the criteria for non-malnutrition (normal

phenotypic and etiologic criteria) and malnutrition (at least one phenotypic and one etiologic criterion).

More information about the measures of sarcopenia, frailty, cachexia and malnutrition is available in supplementary methods and supplementary Tables 1 and 2.

All-cause mortality

The outcome in the current study was all-cause mortality. Date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Details of the linkage procedure can be found at http://www.ic.nhs.uk/services/medical-research-information-service. Mortality data were available until June 2020. Therefore, mortality follow-up was censored on this data or the date of death if this occurred earlier.

Covariates

Age was calculated from dates of birth and baseline assessment. Ethnicity was self-reported and categorised into: White, South Asian, Black, Chinese, and mixed ethnic background. Area-based socioeconomic status (deprivation) was derived from the postcode of residence, using the Townsend score (21) which is based on four Census variables; unemployment, non-car ownership, non-house ownership and household overcrowding. Self-reported smoking status was categorised as never, former or current smoker. Total time spent in sedentary behaviours was derived from the sum of self-reported time spent driving, using a computer and watching television. Waist circumference (WC) was used to derive central obesity, defined as ≥88 cm for women and ≥102 cm for men (22). Hours of sleep were self-reported. Frequency of alcohol intake was self-reported at baseline via touch-screen questionnaire and categorised as daily/almost daily, 3-4 times a week, once/twice a week, 1-3 times a month, special occasions only and never. Red and processed meat were also collected through the touch-screen questionnaire at baseline. Prevalent morbidity was ascertained during a nurse-led interview at baseline. We calculated morbidity count based on 43 long-term conditions (LTCs) and coded as ordinal 1, 2, 3, 4 and ≥5. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Statistical analyses

The prevalence and overlap of each clinical condition were determined both for the whole study population and stratified by sex. In addition, four categories were created according to the number of conditions that each participant had, structured around frailty as was the most prevalent condition: i) no conditions; ii) frailty only (one condition); iii) frailty with sarcopenia (two conditions); iv) frailty with ≥2 other conditions (individuals with three or four conditions).

Descriptive characteristics, broken down by the combination of these four conditions were derived using means with standard deviations (SD) for quantitative variables and percentages for categorical variables. Associations between the combinations of these four clinical conditions with all-cause mortality were investigated using Cox-proportional hazard models. Individuals with none of the aforementioned clinical conditions were used as the reference group. The results are reported as hazard ratios (HR) and their 95% confidence intervals (95% CI). The proportional hazard assumption was checked based on Schoenfeld residuals. Because poor health may be manifested as frailty, sarcopenia, malnutrition, and cachexia and eventually causing death, such reverse causation was minimised using a 2-year landmark analysis (n=109). The cumulative crude hazard rate mortality was estimated using the Nelson-Aalen estimator.

The Cox proportional analyses were adjusted for confounding factors, including sociodemographic covariates (age, sex, ethnicity and deprivation), comorbidities, lifestyle factors (smoking, sleep duration, total discretionary sedentary time, alcohol, red meat and processed meat intake) and WC at baseline. These factors were chosen because of their potential influence on both the exposures and the outcome.

Only individuals with full data available for the four clinical conditions and covariates investigated in this study were included. Finally, STATA 16 statistical software (StataCorp LP) was used to perform the analyses.

Results

From the total UK Biobank population, 111,983 (53.5% women) had available data for all four clinical conditions and were, therefore, included in the final analyses (Supplementary Figure 2). Of them, 50,438 (45.0%) had frailty (including pre-frail) 6,446 (5.8%) had sarcopenia (including pre-sarcopenia), 63 (0.06%) malnutrition and 43 (0.04%) had cachexia (Table 1).

All conditions overlapped considerably. For instance, 12.8% of the individuals with frailty also had sarcopenia, and 0.1% also had either cachexia or malnutrition. All sarcopenic people had frailty, 68.2% of people with malnutrition had cachexia, 90.5% sarcopenia and 92.1% frailty, and all participants with cachexia also had sarcopenia, frailty and malnutrition (Table 2). The prevalence data and overlap by sex are shown in Table 2.

The cohort's characteristics by the number of clinical conditions are presented in Table 3. In summary, the prevalence of frailty only (39.25%) was higher than the prevalence of frailty with sarcopenia (5.7%), which in turn was higher than the combination of frailty with ≥2 other conditions (0.05%). In comparison to those with no conditions, participants with one or more clinical conditions were older, more deprived, more likely to be female, from a non-white background, and current smokers. They had lower grip strength values, body weight, height and WC. They also had a higher prevalence of comorbidities compared with those with no clinical conditions (Table 3).

The median follow-up period was 9.3 years (interquartile range: 8.6–10.0) after the 2 years-landmark period for all-cause mortality. Over the follow-up, 3,547 (3.2%) participants died. As is shown in Figure 1, the risk of all-cause mortality increased with the numbers of clinical conditions. After adjustment for confounding factors, and compared with people without no clinical conditions, people with frailty only had 13% higher risk of all-cause mortality while those with frailty and sarcopenia had 27% higher risk. However, the risk was almost 5-fold in those with frailty and ≥2 conditions (i.e., three or four clinical conditions) in comparison to those without (HR: 4.96 [95% CI: 2.73 to 9.01]). The individual associations of each condition with all-cause mortality are shown in appendices (Supplementary Figure 3).

Similar results were found when the crude cumulative mortality curves by age were investigated (Figure 2). Individuals with a higher number of clinical conditions had a sharper gradient compared with those without any condition. In particular, individuals with frailty with ≥2 other clinical conditions had the highest mortality rate across age (Figure 2).

Discussion

Main findings of this study

Sarcopenia, frailty, malnutrition and cachexia are phenotypically similar (1). As these conditions share underlying mechanisms for their operational definition, differentiation of participants is complicated (1). In this study, we demonstrated significant clustering of these

clinical conditions. However, frailty was the most common condition being present in 45% of the whole population studied, 92.1% of people with malnutrition and everyone diagnosed with sarcopenia or cachexia. Furthermore, we demonstrated that the risk of all-cause mortality increased with the numbers of clinical conditions present. In fact, people with three or four conditions (frailty plus at least two other conditions) had almost five-fold risk of dying. Considering the ageing population, clinical conditions are likely to become more prevalent. Nevertheless, despite the fact that these conditions are more frequent in older stages, their development could begin earlier in life as it was demonstrated with our findings. In consequence, studying these conditions sooner in life might be a good strategy to prevent further complications later.

What is already known on this topic?

The overlap between sarcopenia and frailty (2, 23), between sarcopenia, cachexia and malnutrition (24), and among other clinical conditions have been previously reported (25). For example, Bulut et al. investigated the frequency and overlap among different conditions – including frailty, sarcopenia and malnutrition– in a cohort of 2,816 geriatric outpatients. They identified that 53% of the frail participants were also sarcopenic and that 48% of the population older than 80 years of age had more than four conditions (25). However, to our knowledge, only one study has investigated the overlap and prevalence of the four clinical conditions included in this study (15). Gingrich et al. demonstrated that sarcopenia was the most prevalent syndrome among 100 German inpatients (42%), followed by frailty (33%), cachexia (32%) and malnutrition (15%) (15). They also highlighted that 63% of the participants studied had at least one condition. In our study, in turn, frailty was the most common condition, and 39.25% of the individuals included had at least one clinical condition. However, the population of Gringrich et al. and the population included in this study are different. In the former, participants were older, hospitalised and had medical complications (15). In our study, participants were recruited from the general adult population and were middle-aged as well as older.

What this study adds?

Previous studies have focused on investigating the independent associations with mortality of frailty (13), sarcopenia (14), cachexia (26) and malnutrition (4). Other studies have also shown that people with two conditions, such as sarcopenia and malnutrition had 4.7 [95% CI: 2.09 to 10.97]) times risk of dying compared to those without sarcopenia or malnutrition (27).

However, to our knowledge, this is the first study to explore the cumulative risk across four levels of increasing numbers of conditions in middle and older age people.

Finally, although consensus definitions have been developed for the four clinical conditions included (7, 9, 10, 12), the lack of universal and standardised definitions for all of them still remains as one of the main challenges and priorities. In this context, there is a need for a more comprehensive approach to a better understanding of all these conditions, how to identify them in early stages and a more in-depth study of the age-related changes in physical capability, body composition and health associated beyond the ageing progress. Furthermore, considering that these conditions share many of the parameters used for their definitions and, therefore, the overlap is highly probably among them, the creation of a unique and global definition could have a high impact in clinical practise as well as in a better diagnostic.

Limitations of this study

Using the UK Biobank study provided the opportunity to test our research question in a large general population cohort as well as the opportunity to work with information collected using validated and standardised methods. However, UK Biobank is not representative of the UK population in terms of lifestyle, ethnicity and prevalent disease (28). Therefore, whilst estimates of effect sizes could be generalised, summary statistics should not be (29). In terms of the clinical conditions studied, there were different limitations for each one. For instance, the frailty phenotype was created using similar, but not identical variables to those suggested by Fried et al. (7). Sarcopenia was estimated using BIA instead of dual-energy X-ray absorptiometry (DXA). DXA is the most commonly used method for deriving muscle mass, but, in UK Biobank, only 5,000 participants had data available from DXA. Weight loss was not used for the definition of malnutrition nor cachexia as it was not clear if this weight loss was intentional or not. However, as both definitions recommend the use of BMI when weight loss is not documented, both syndromes were correctly derived. Furthermore, the four clinical conditions are dynamic states and are likely to have changed over time. In this context, it is likely that a proportion of those identified as without clinical conditions at baseline might have become sarcopenic, frailty, with malnutrition or cachexia during the follow-up period. Finally, although frailty, sarcopenia, cachexia and malnutrition could occur early in life, they are more characteristics of an elderly population. As the mean age of the participants in this study ranged from 55 to 61 years, the prevalence was lower than studies conducted on older populations. Therefore, the analyses should be repeated in an older study population.

Conclusion

Frailty was the most prevalent clinical condition in this study and was also present in almost all people with sarcopenia, cachexia and malnutrition. In addition, the cumulative risk of all-cause mortality increased with increasing numbers of clinical conditions and was particularly high among people with three or four conditions, who had an almost 5-fold risk of dying. Considering that our study population included middle-aged as well as elderly participants, our results may be a conservative estimate of the level of risk in the elderly. However, our results highlight the high prevalence of these clinical conditions before ageing, emphasising the relevance of early detection in middle-age adults for their high association with mortality.

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Authorship Statement

F.P-R, F.K.H, J.P.P and C.C-M contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. F.P-R performed the literature search. F.P-R performed the analyses with support from F.K.H, J. P.P and C.C-M. All authors critically reviewed this and previous drafts. All authors approved the final draft for submission. J.P.P, C.C-M and F.K.H contributed equally to this work and are joint senior authors. F.K.H is the guarantor.

Data statement

All UK Biobank information is available online on the webpage www.ukbiobank. Data access are available through applications. This research was conducted using the application number 7155.

Conflict of interest

None to declare

Words

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Table 1. Numbers of participants by each clinical condition

	Sarcopenia			Frailty			Cachexia			Malnutrition		
	Women	**Men**	**Total**	**Women**	**Men**	**Total**	**Women**	**Men**	**Total**	**Women**	**Men**	**Total**
Normal, n (%)	55,994 (93.4)	49,543 (95.2)	105,537 (94.2)	31,983 (53.4)	29,562 (56.8)	61,545 (55.0)	59,904 (99.9)	52,036 (99.9)	111,940 (99.9)	59,889 (99.9)	52,031 (99.9)	111,920 (99.9)
Pre-condition, n (%)	3,903 (6.5)	2,498 (4.7)	6,401 (5.7)	27,149 (45.3)	22,028 (42.3)	49,177 (43.9)	-	-	-	-	-	-
Condition, n (%)	36 (0.1)	9 (0.1)	45 (0.1)	801 (1.3)	460 (0.9)	1,261 (1.1)	29 (0.1)	14 (0.1)	43 (0.1)	44 (0.1)	19 (0.1)	63 (0.1)
Total	**59,933**	**52,050**	**111,983**	**59,933**	**52,050**	**111,983**	**59,933**	**52,050**	**111,983**	**59,933**	**52,050**	**111,983**

Data presents as absolute numbers and prevalence (%) for each clinical condition (total and by sex).

Table 2. Prevalence of comorbid clinical conditions by sex.

	Total				**Women**				**Men**			
	S	**F**	**C**	**M**	**S**	**F**	**C**	**M**	**S**	**F**	**C**	**M**
Sarcopenia, n (%)	-	6,446 (100)	43 (0.7)	57 (0.9)	-	3,939 (100)	29 (0.7)	41 (1.0)	-	2,507 (100)	14 (0.6)	16 (0.6)
Frailty, n (%)	6,446 (12.8)	-	43 (0.1)	58 (0.1)	3,939 (14.1)	-	29 (0.1)	42 (0.1)	2,507 (11.2)	-	14 (0.1)	16 (0.1)
Cachexia, n (%)	43 (100)	43 (100)	-	43 (100)	29 (100)	29 (100)	-	29 (100)	14 (100)	14 (100)	-	14 (100)
Malnutrition, n (%)	57 (90.5)	58 (92.1)	43 (68.2)	-	41 (93.2)	42 (95.4)	29 (65.9)	-	16 (84.2)	16 (84.2)	14 (73.7)	-

Data and overlap present as absolute numbers and prevalence (%) for each clinical condition (total and by sex). Data for sarcopenia and frailty include pre-condition.

S: sarcopenia; F: frailty; C: cachexia; M: malnutrition.

Table 3. Cohort's characteristic by numbers of clinical conditions

	No conditions	Frailty only	Frailty with sarcopenia	Frailty with ≥ 2 conditions
Socio-demographics				
Total, n (%)	61,540 (55.0)	43,996 (39.25)	6,390 (5.7)	57 (0.05)
Age (years), mean (SD)	55.7 (8.0)	55.6 (8.0)	59.4 (7.1)	61.4 (7.0)
Sex (females), n (%)	31,981 (52.0)	24,012 (54.6)	3,899 (61.0)	41 (71.9)
Ethnicity, n (%)				
White	59,825 (97.2)	42,369 (96.3)	6,021 (94.2)	54 (94.7)
Mixed	638 (1.0)	561 (1.3)	106 (1.7)	0
South Asian	471 (0.8)	497 (1.1)	191 (3.0)	3 (5.3)
Black	470 (0.8)	453 (1.0)	45 (0.7)	0
Chinese	136 (0.2)	116 (0.3)	27 (0.4)	0
Deprivation, n (%)				
Lower	23,399 (38.0)	15,885 (36.1)	2,072 (32.4)	13 (22.8)
Middle	21,460 (34.9)	15,208 (34.6)	2,202 (34.5)	17 (29.8)
Higher	16,681 (27.1)	12,903 (29.3)	2,116 (33.1)	27 (47.4)
Obesity-related markers				
Body weight (kg), mean (SD)	74.3 (12.8)	76.1 (13.4)	71.8 (12.4)	52.6 (6.9)
Height (m), mean (SD)	1.70 (0.09)	1.69 (0.09)	1.65 (0.09)	1.64 (0.08)
Waist Circumference (cm)	85.8 (11.2)	88.1 (11.6)	87.0 (11.5)	74.9 (9.0)
Central obesity, n (%)	10,259 (16.7)	11,323 (25.7)	1,630 (25.5)	4 (7.0)
Lifestyle and health status				
Handgrip (kg), mean (SD)	33.7 (9.9)	31.1 (10.2)	16.7 (5.8)	13.4 (6.0)
Total Sedentary behaviour ($h.day^{-1}$), mean (SD)	4.7 (2.0)	5.0 (2.1)	4.9 (2.0)	4.9 (2.8)
Smoking status, n (%)				
Never	35,696 (58.0)	25,156 (57.2)	3,749 (58.7)	24 (42.1)
Previous	21,810 (35.4)	15,566 (35.4)	2,254 (35.3)	18 (31.6)
Current	4,034 (6.6)	3,274 (7.4)	387 (6.0)	15 (26.3)
Alcohol frequency intake, n (%)				
Daily or almost daily	16,419 (26.7)	40,341 (23.5)	1,460 (22.8)	14 (24.6)
3-4 times a week	17,639 (28.7)	11,457 (26.0)	1,506 (23.6)	8 (14.0)
Once or twice a week	14,902 (24.2)	11,024 (25.1)	1,555 (24.3)	8 (14.0)
1-3 times a month	5,742 (9.3)	4,808 (10.9)	644 (10.1)	5 (8.8)
Special occasions only	4,193 (6.8)	3,972 (9.0)	702 (11.0)	10 (17.5)
Never	2,645 (4.3)	2,394 (5.)	523 (8.2)	12 (21.1)
Red meat (portion.week-1), mean (SD)	2.0 (1.4)	2.0 (1.4)	2.0 (1.4)	1.9 (1.3)
Processed meat intake (portion.week-1), mean (SD)	1.8 (1.1)	1.8 (1.1)	1.8 (1.1)	1.9 (1.2)
Sleep time (hours), mean (SD)	7.2 (0.9)	7.1 (1.0)	7.1 (1.1)	7.1 (1.6)
Multimorbidity, n (%)				
0	27,654 (44.9)	16,515 (37.5)	1,933 (30.3)	5 (8.7)

1	20,899 (34.0)	15,071 (34.3)	2,110 (33.0)	14 (24.6)
2	9,145 (14.9)	7,992 (18.2)	1,411 (22.1)	18 (31.6)
3	2,912 (4.7)	3,085 (7.0)	629 (9.8)	14 (24.6)
4	725 (1.2)	946 (2.1)	204 (3.2)	5 (8.7)
≥5	205 (0.3)	387 (0.9)	103 (1.6)	1 (1.8)

Frailty only represents 43991 people with frailty (pre-frail or frail) and five people with only malnutrition. Frailty with sarcopenia represents 6,390 people with frailty (pre-frail or frail) and sarcopenia (pre-sarcopenia, sarcopenia or severe sarcopenia). Frailty with ≥2 conditions represents the combination of frailty, sarcopenia and cachexia or malnutrition.
BMI: body mass index; SD: standard deviation.

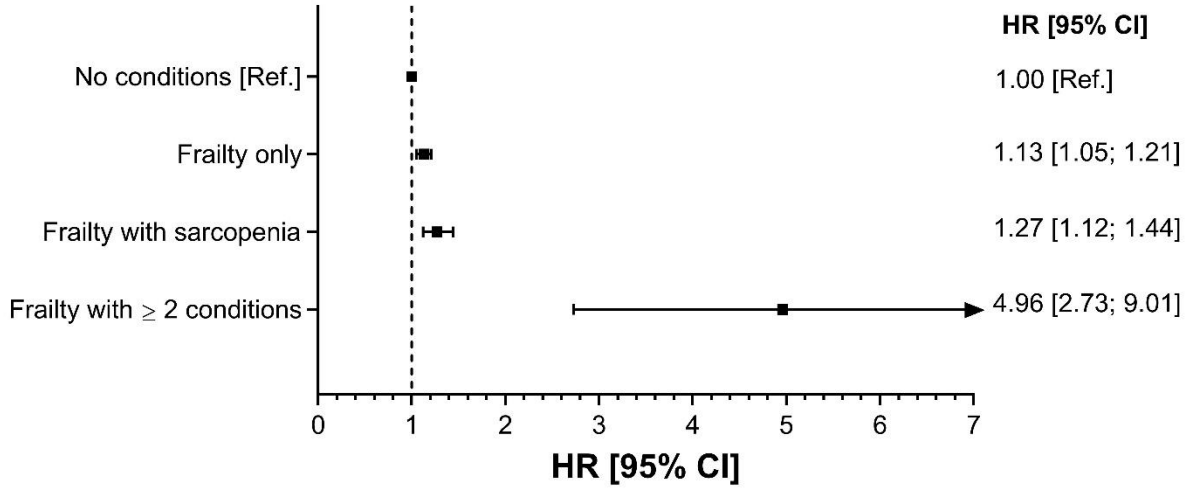

Figure 1. Association between numbers of clinical conditions and all-cause mortality

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by cumulative clinical conditions. People with no conditions were used as the reference group (normal).

Frailty only represents 43991 people with frailty (pre-frail or frail) and five people with only malnutrition. Frailty with sarcopenia represents 6,390 people with frailty (pre-frail or frail) and sarcopenia (pre-sarcopenia, sarcopenia or severe sarcopenia). Frailty with ≥2 conditions represents the combination of frailty, sarcopenia and cachexia or malnutrition.

All analyses were conducted using a 2-years landmark analysis and adjusted for age, sex, deprivation, smoking status, ethnicity, discretionary sedentary time, waist circumference, dietary intake (alcohol, red meat and processed meat intake), and multimorbidity at baseline.

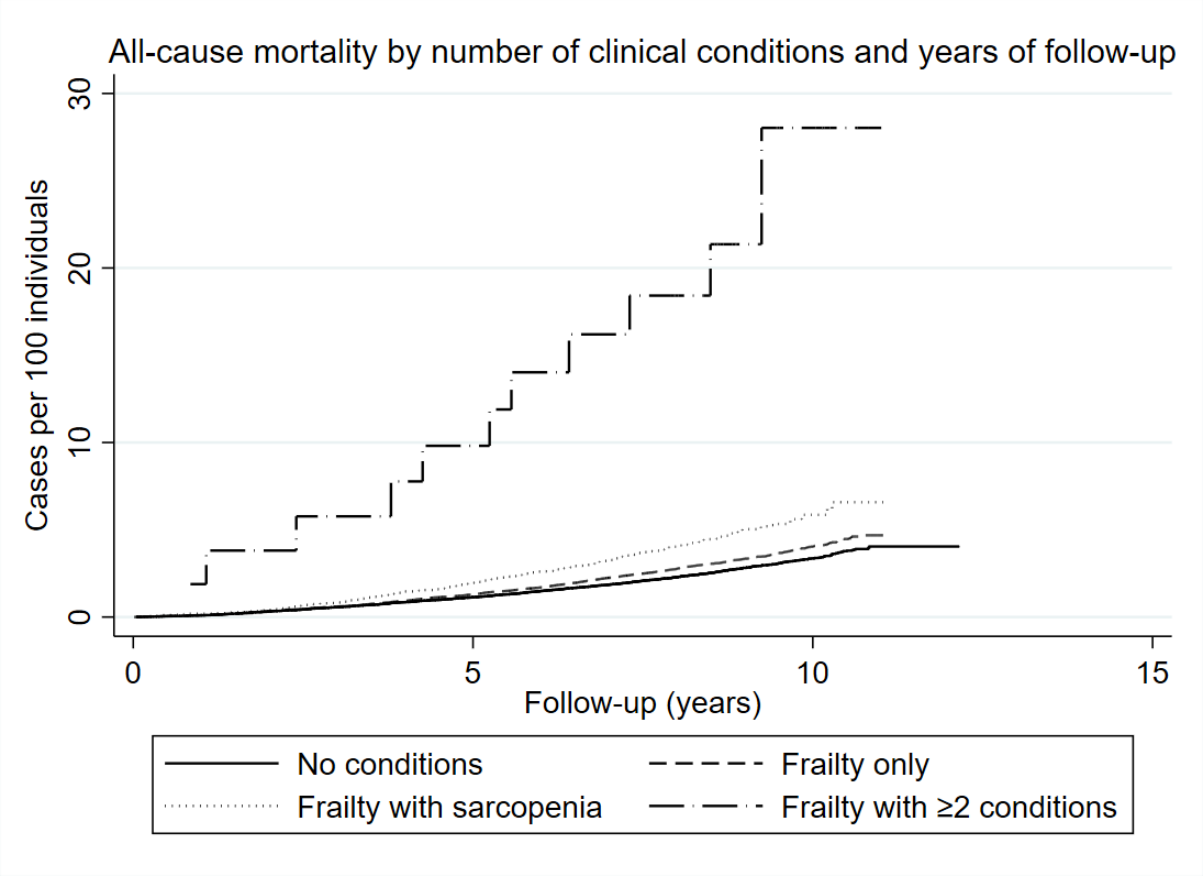

Figure 2. Crude cumulative hazard plot of All-cause mortality by numbers of clinical conditions by follow-up

Frailty only represents 43991 people with frailty (pre-frail or frail) and five people with only malnutrition. Frailty with sarcopenia represents 6,390 people with frailty (pre-frail or frail) and sarcopenia (pre-sarcopenia, sarcopenia or severe sarcopenia). Frailty with ≥2 conditions represents the combination of frailty, sarcopenia and cachexia or malnutrition.