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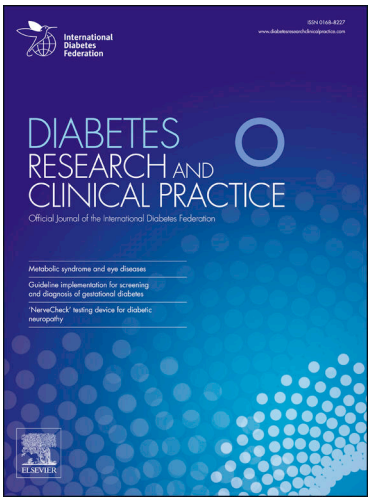

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Individual frailty phenotype components and mortality in adults with type 2 diabetes: A UK Biobank study

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Abstract

Aims: This study aimed to explore associations between frailty components and mortality and rank prognostic relevance of each frailty component in predicting mortality in adults with and without type 2 diabetes (T2D).

Methods: We used data from the UK Biobank. Associations and prognostic discrimination of individual Fried's frailty components and the overall frailty status with all-cause and cardiovascular (CVD) mortality were investigated using Cox proportional-hazard models and C-index in adults with and without T2D.

Results: In both populations the strongest association with all-cause mortality across all frailty components and overall frailty status was observed for slow walking pace (without T2D Hazard Ratio [HR] 2.25, 95%CI: 2.12-2.38 and with T2D HR 1.95, 95%CI: 1.67-2.28). Similarly, slow walking pace was associated with a greater risk of CVD mortality. The combination of T2D and slow walking pace had the strongest association with all-cause and CVD mortality, compared to the combination of T2D and other frailty components or overall frailty status. Slow walking pace also provided the greatest prognostic discrimination.

Conclusion: Slow walking pace has a stronger predictive factor for all-cause and CVD mortality compared to other frailty components and overall frailty status, especially when simultaneously present with T2D.

Keywords: walking-pace, physical function, prognostic relevance

Introduction

Type 2 diabetes (T2D) is a complex metabolic disorder frequently accompanied by accelerated biological aging placing people at higher risk of age-related comorbidities, including frailty

[1]. Frailty is characterised as a state of increased vulnerability to stressors, resulting from the decline in physiological reserves [2]. People with diabetes have consistently been shown to have higher rates of frailty, ranging from 13% [3, 4] to 48% [5, 6] which is significantly higher than 5% to 10% seen in people without diabetes. While the relationship between T2D and frailty is yet to be fully understood, it is increasingly acknowledged that frailty plays a critical role in diabetes outcomes [7], associated with higher risk of microvascular and microvascular complications [4], disability [5], hospitalization and mortality [8]. As a consequence, frailty leads to significantly higher healthcare utilization in people with T2D [9]. Whilst association between frailty and T2D has been established, it is unclear how T2D and frailty interact for health outcomes.

While there is no universally agreed definition of frailty, physical frailty phenotype developed by Fried et al. [2] is one of the most widely used frailty concepts compromising of five physical components: slow walking pace, low activity levels, low handgrip, weight loss and exhaustion. This phenotype has been validated against various outcomes from a range of populations [10-12]. Furthermore, frailty phenotype is the most commonly used measure of frailty in people with diabetes. Hanlon et al. [4] systematic review and meta-analysis reported that 58% of studies investigating frailty prevalence, incidence and clinical outcomes in people with diabetes used frailty phenotype.

Measurement of frailty phenotype involves data collection of all five components and it is assumed that greater number of components is associated with higher risk of a given outcome [2]. While the components of frailty phenotype are thought to contribute equally to the frailty score, each component have different and specific effects on adverse outcomes [13, 14]. Additionally, it possible that these components are redundant. To date, the independent contribution of the five frailty phenotype components have not been well evaluated and it remains unclear if all components are associated with the risk of mortality in people with T2D.

Exploration of these components in people with T2D may be of interest for the more pragmatic frailty screening and intervention development in routine clinical practice.

The aim of this analysis was to investigate the association and prognostic relevance of individual frailty components and overall frailty status with risk of all-cause and cardiovascular (CVD) mortality in adults with and without T2D and to investigate the relative risk of diabetes, frailty and their combination.

Methods

Study design

This research was conducted using the UK Biobank under Application Number 52553 and reported following STROBE guidelines (Checklist C1). The UK Biobank is a large population-based prospective study designed to investigate non-genetic and genetic determinants of health and diseases in middle age and older people in UK [15]. A total of 502,536 participants were recruited between 2006 and 2010 and attended 22 assessments centres across England, Scotland and Wales. Participants were asked to complete a touchscreen questionnaire, nurse-led interview and physical measurements. Data have been linked to hospital and mortality records. All participants gave written informed consent for data collection, analysis and linkage. Ethical approval was obtained by the North-West Research Ethics Committee (16/NW/0274).

Assessment of baseline characteristics

T2D status was based on a validated algorithm which consist of self-reported disease, medication and T2D noted in the medical history [16]. A previous medical history of cancer or

CVD (defined as peripheral vascular disease, angina, heart attack/myocardial infarction, heart failure/ pulmonary oedema, stroke and transient ischaemic attack was self-reported during the baseline visit. Systolic and diastolic blood pressure was recorded using an automated machine. Lipid-lowering medication and antihypertensive drugs were self-reported. Low-density lipoprotein (LDL) cholesterol was measured by biochemical assays collected at baseline, using Beckman Coulter AU5800 Platform.

Age was calculated from the date of birth and baseline assessment date. Body mass index (BMI) was calculated as (weight/heigh^2) measured at the baseline. Self-reported smoking status was divided into three categories: current, non-smokers and previous smokers. Ethnicity was categorised into white and non-white as majority of the sample is white (94%). Employment was categorised into employed, unemployed, retired and other. Alcohol intake was categorised into never/special occasion, 1-3 drinks per month, 1-4 drinks per week, daily or almost daily. Socioeconomic deprivation was based on the Townsend deprivation score which is a measure based on unemployment, household overcrowding, non-home ownership and non-car ownership with higher values indicating higher levels of deprivation [17].

Frailty phenotype

Frailty status was assessed by Fried frailty phenotype which consists of five components related to frailty: weight loss, exhaustion, low physical activity, slow walking pace and low hangdrip. Each frailty deficits are adapted to available Biobank data (Table S1) [3]. Handgrip strength was assessed with Jamar J00105 hydraulic hand dynamometer. Variables related to frailty such as weight loss, exhaustion, walking pace and physical activity were self-reported using questionnaires. Physical activity (MET-hours/week) was calculated by multiplying the number of hours/week of each reported physical activity by the metabolic equivalent (MET) of that activity, summing across all activities, and categorizing the total by quintiles. Individuals with

none of the indicators were characterised as robust. Those with one or two indicators were considered to represent pre-frail group and those with three or more indicators were categorised into frail group [2]. Only UK Biobank participants with information available for all covariates and frailty components were included.

Assessment of Outcomes

Date of death was obtained from the National Health Service (NHS) Information Centre in England and Wales; and the NHS Central Register Scotland. End of follow-up for each participant was recorded as the date of death or censoring dates (30 September, 2021 for England and Wales and 31 October, 2021 for Scotland), whichever came first. Cause of death was classified using the International Classification of Diseases (ICD-10) code assigned to the underlying (primary) cause of death. We defined cardiovascular mortality using the ICD-10 codes I00–I79.

Statistical analysis

Summary measures were described using mean (standard deviation) or median (interquartile range) for continuous variables, categorical data were given as a count (percentage).The association of individual frailty components and frailty status with all-cause and CVD mortality was assessed with Cox proportional hazard models, separately in subjects with and without T2D. The proportional hazards assumption was tested visually with log(-log) plots. To minimise potential risk of reverse causation bias, participants who died within two years of follow-up were excluded. Results were reported as hazard ratios (HR) together with 95% confidence intervals (95% CI). There were two models used in this analysis: Model 1, adjusted for age and sex (base model), and model 2, adjusted for deprivation (Townsend score), ethnicity, lipid-lowering medication, antihypertensive medication, LDL cholesterol, prevalent CVD, prevalent cancer, BMI, systolic blood pressure, smoking and alcohol (maximally

adjusted model). To assess whether T2D modified the association frailty components and frailty overall status with mortality outcomes, likelihood ratio tests were conducted. For descriptive purposes, we also explored joint risk association of diabetes and frailty components with the mortality outcomes, adjusted for the same two models. We used non-T2D and absence of each frailty component as the reference group. In order to further help quantify the comparative relevance of each frailty component, we used the fully adjusted HRs to calculate the population-attributable risks (PAR) expressed as a percentage. Values were calculated using Miettinen's equation recommended for adjusted estimates, expressed as PAR= p*100 (1 – $1/HR_{adj})_2$, where p=prevalence within cases, and HR_{adj} = the adjusted HR [18, 19]. To quantify model predictive discrimination, this analysis used the concordance index (Harrell's C-index) for risk of all-cause and CVD mortality. Each frailty component was added individually to a base model containing age and sex and to maximally adjusted model to allow for comparison between each component. The added prognostic value of each investigated factor was quantified as the difference in C-index compared to the base model and maximally adjusted model. $P < 0.05$ or 95% CI not crossing the null were taken as significant. All analysis were conducted using Stata (Statistical Software IC16.0 StataCorp LLC, College Station, TX, USA).

Results

Out of 502,536 UK Biobank participants, 395,508 had complete outcome, frailty and covariate data and were included in this study (data selection flow shown in Supplementary Figure S1). In this study, 17,252 (4.3%) were classified as having T2D. Baseline characteristics are summarised in Table S2. Compared to those without T2D, adults with T2D were more likely to be men (45.4% vs 63.2%), from a non-white ethnic minority (5.0% vs 13.4%) and were older (median 57 years vs 62 years), more likely to live within most deprived quintile (28.2% vs 18%), and be unemployed (6.9% vs 2.3%). In those without T2D, 19,624 (5.2%) died from all

causes and 3,441 (0.9%) from CVD over a median (IQR) follow-up of 12.5 (11.8-13.2) years. In those with T2D, 2,418 (14.0%) died from all-causes and 664 (3.8%) from CVD.

Frailty prevalence was higher in T2D compared to adults without T2D (12.4% vs 2.7%; OR 5.23, 95% confidence interval [CI]: 4.98-5.07). Prevalence of all frailty components prevalence were also higher in adults with T2D, with the highest OR observed for walking pace (OR 3.76, 95%CI: 3.61-3.91) after adjusting for age and sex (Table 1).

Results for all-cause mortality with individual frailty components and overall frailty status in people with and without T2D are shown in Table 2. All five components were significantly associated with all-cause mortality. In both populations the strongest association amongst all frailty components was observed for slow walking pace (without T2D HR 2.25, 95%CI: 2.12-2.38 and with T2D HR 1.95, 95%CI: 1.67-2.28) maximally adjusted models. Overall frailty status provided a risk profile similar of that for slow walking pace (without T2D HR 2.14, 95%CI: 1.99-2.29: and with T2D HR 1.80, 95%CI: 1.54-2.10). The strength of association between frailty component and all-cause mortality was similar across those with and without T2D in the fully adjusted model, apart from frailty status where associations were stronger in those without T2D.

Results for CVD mortality are presented in Table 3, also found that slow walking pace (without T2D HR 2.36, 95%CI: 2.08-2.69: with T2D HR 3.03; 95%CI: 2.21-4.16) was associated with a greater risk than other frailty components or overall frailty status (without T2D HR 1.94, 95%CI: 1.65-2.29: with T2D HR 2.04, 95%CI: 1.51-2.75). The strength of association between frailty components and status with CVD mortality was similar across individuals with and without T2D.

The results of frailty components and frailty status in combination with T2D status with risk of all-cause mortality are shown in Figure 1 (data used to create figure can be found in Table S3).

The combination of both T2D and presence of frailty or a frailty component was associated with greater risk of all-cause mortality compared to the reference category of no-T2D and absence of frailty. The highest risk for mortality was observed in people having both T2D and slow walking pace, which was more than three times higher (HR 3.19, 95%CI: 2.91-3.50) in the maximally adjusted model. The risk of mortality was less pronounced in those with T2D and other frailty components, including overall frailty status (HR 2.69, 95%CI: 2.41-3.00). Slow walking pace and presence of T2D also had strongest association with CVD-mortality (HR 4.17; 95% CI 3.49-4.99) compared to T2D and overall frailty status (HR 2.95; 95%CI 2.38-3.66) or other frailty indicators (Figure 2 and Table S4).

Frailty components and status were associated with PAR values higher in T2D than in those without (Figure S2). Slow walking pace had the highest PAR values (A) 16.4% for all-cause, and 27.1% for CVD mortality (B) than other frailty components or frailty in T2D. Pre-frailty status had the highest PAR values in those without T2D (Figure S2).

Frailty components and status also had higher C-index values in participants with T2D (Tables S5- S8). For all-cause mortality, the addition of walking pace provided the greatest improvement in prognostic discrimination compared to other frailty components or overall risk status. In maximally adjusted models, C-index change for walking pace was +0.006 (95%CI, 0.005 to 0.008) for adults without T2D and C-index change +0.013 (95%CI, 0.007 to 0.018) in adults with T2D. Walking pace also provided an improvement in prognostic discrimination for CVD-mortality with C-index change of +0.008 (95%CI 0.005 to 0.010) in adults without T2D and 0.020 (95%CI 0.007 to 0.033) in adults with T2D.

Discussion

T2D and frailty is a severe phenotype with a three-fold increased risk of mortality compared to those without it. This study suggests that not all five components of frailty contribute equally to the risk of mortality, with slow walking pace having the strongest association with all-cause and CVD mortality in both individuals with and without T2D. Over 1 in 5 (20.5%) of people with T2D reported a slow walking pace, with an odds of being a slower walker 3.8 times greater than those without diabetes. Walking pace had a higher PAR in T2D than frailty status, with potentially 27.1% of CVD mortality cases being attributable to poor physical function as measured by a slow walking pace. Walking pace also provided greater prognostic discrimination than that associated with frailty status. When combined, subjects with a slow walking pace and T2D had 3 times the risk of all-cause mortality and 4 times the risk of CVD mortality compared to those with brisk walking pace without diabetes.

Whilst the higher risk of frailty in T2D and higher risk of death have been well-established [4, 8], to our knowledge this is the first study to explore individual components of frailty and T2D with all-cause and CVD mortality. The results of this analysis suggest that self-reported slow walking pace was the most informative frailty component which also acted as a stronger prognostic marker than overall frailty. The findings for mortality outcomes are consistent with another study in older adults which found that walking pace was the strongest predictor of chronic disability, long term nursing-home stay and injurious fall compared to other frailty components [20]. Studies focusing on slow walking pace have also repeatedly shown a higher risk of mortality and adverse outcomes with strongest prognostic discrimination than other lifestyle behaviours or factors [21-23].

Identifying a slow walking pace as having the strongest association with mortality in T2D has implications for assessment and management of people with T2D. It has been shown that increase in usual gait speed over 1-year period decreased risk of mortality after adjusting for multiple risk factors whereas improvement in self-reported physical function questionnaires

and activities of daily living (ADL) was not associated with survival [24]. Similar results were seen in elderly veterans where improved gait speed improved health status and physical function, which resulted in fewer disabilities and healthcare utilisation [25]. Walking pace is thought to be a subclinical indicator of physiological reserve and function and is linked to physical resilience, defined as the ability to recover from "stressors"[26]. As such, walking pace tests form the basis for assessing the effectiveness of pulmonary programmes at improving physical function [27]. While there is an increase in studies analysing the effect of interventions targeting frailty [28], very few have evaluated the effect of interventions on components of frailty [29]. Further research could potentially focus on more modifiable components, such as walking pace [30], and help customise interventions for diabetes management, for example, by identifying those with a slow walking pace and referring to rehabilitation type interventions to improve physical function.

The strengths of this study includes large sample size, with data related to lifestyle, conditions and mortality. However, there are several limitations in the study. First, this study used baseline data thus we were not able to assess the impact of diabetes on frailty status over time. T2D was identified using algorithm developed by Eastwood et al [30] based on self-report physician-diagnosed T2D, which may be subject to errors as some participants may not recall their diagnosis accurately or do not want to report it [31, 32]. While authors have found that it was pragmatic and valid approach, the overall prevalence was slightly lower than the general population. Nevertheless, self-reporting have been shown to be a valid method in distinguishing diabetes [33]. Other than handgrip strength which was assessed by trained staff according to standard operating procedures, this study used self-report measures which are subject to bias. Further, UK Biobank did not aim to assess frailty specifically. However, it has been shown that self-reported indicators of frailty produce similar prevalence estimated to test based measures [34]. It is important to note that this study may not be applicable to older adults

aged 70 and older as Biobank participant age range is 37-73 years and those from ethnic minority background. Finally, as this is an observational study, causality between frailty components and mortality cannot be confirmed. Nevertheless, this study gives novel insight into frailty and T2D in middle-aged adults.

Conclusion

While frailty phenotype is a multicomponent model, assessing all five components may be a barrier for routine clinical practice and may not be necessary within diabetes management as not all provide additional information on frailty state. A pragmatic simple measure of slow walking pace identifies more people whilst being a stronger predictor of mortality outcomes than did overall frailty status. Additionally, this can easily be implemented in routine care. Further research is required to establish whether identifying slow walkers and referring rehabilitation style exercise programmes can improve longer-term outcomes within the management of T2D.

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Conflict of Interest

The authors declare no conflict of interest.

Author's contributions

Monika Mickute contributed to the study conception, design, statistical analysis, data interpretation and drafting of the manuscript.

Francesco Zaccardi advised on statistical analysis and contributed to the critical revision of the manuscript.

Cameron Razieh contributed to the critical revision of the manuscript.

Jack Sargeant contributed to the critical revision of the manuscript.

Alice C. Smith contributed to the critical revision of the manuscript.

Thomas J. Wilkinson contributed to the critical revision of the manuscript.

Hannah M. L. Young

David Webb contributed to the critical revision of the manuscript.

Melanie J Davies contributed to the critical revision of the manuscript.

Kamlesh Khunti contributed to the critical revision of the manuscript.

Thomas Yates contributed to the study conception, design, analysis, data interpretation and critical revision of the manuscript.

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Figure 1: Frailty components and risk of all-cause mortality

Figure 2: Frailty indicators and cardiovascular disease mortality.

Figure legends

Figure 1

Adjusted for Model 2. Age, sex, ethnicity, smoking, BMI, systolic BP, lipid-lowering medication, blood-pressure medications, LDL cholesterol, employment, alcohol, smoking, deprivation, prevalent CVD, prevalent cancer.

Figure 2

Adjusted for Model 2. Age, sex, ethnicity, smoking, BMI, systolic BP, lipid-lowering medication, blood-pressure medications, LDL cholesterol, employment, alcohol, smoking, deprivation, prevalent CVD, prevalent cancer

Table 1: Frailty prevalence

	All participants 397,254	No T2D 378,256	T2D 17,252	OR (95% CI)*
Frailty components				
Slow walking pace	25,702 (6.5)	22,162 (5.9)	3,540 (20.5)	3.76 (3.61, 3.91)
Low physical activity	79,269 (20)	74,498 (19.7)	4,771 (27.7)	1.61 (1.55, 1.67)
Low handgrip	34,706 (8.8)	30,847 (8.2)	3,859 (22.4)	2.93 (2.82, 3.04)
Weight loss	60,989 (15.4)	55,962 (14.8)	5,027 (29.1)	2.52 (2.43, 2.61)
Exhaustion	45,740 (11.6)	42,435 (11.2)	3,305 (19.2)	2.33 (2.36, 2.42)
Frailty status				
Pre-frail	167,833 (42.4)	157,924 (41.8)	9,909 (57.4)	1.96 (1.89, 2.02)
Frail	12,444 (3.2)	10,312 (2.7)	2,132 (12.4)	5.23 (4.98, 5.07)

*Adjusted for age and sex

OR, Odds Ratio; T2D, Type 2 Diabetes

Table 2: All-cause mortality in adults with and without T2D

		Without T2D	With T2D	Interaction p value
Unadjusted	**Frailty indicators**			
	Slow walking pace	3.73 (3.56, 3.89)	2.67 (2.35, 3.03)	**0.001**
	Low physical activity	1.15 (1.10, 1.19)	1.25 (1.12, 1.39)	0.138
	Low handgrip strength	2.18 (2.10, 2.28)	1.96 (1.72, 2.23)	0.106
	Weight loss	1.10 (1.06, 1.14)	0.99 (0.89, 1.09)	0.041
	Exhaustion	1.21 (1.16,1.27)	1.23 (1.10, 1.38)	0.807
	Frail status			
	Pre-frail	1.29 (1.25, 1.33)	1.29 (1.17, 1.42)	0.992
	Frail	2.80 (2.64, 2.97)	2.06 (1.82, 2.32)	0.001
Model 1	**Frailty indicators**			
	Slow walking pace	2.93 (2.80, 3.07)	2.32 (2.32, 3.00)	**0.050**
	Low physical activity	1.27 (1.22, 1.32)	1.34 (1.20, 1.50)	0.308
	Low handgrip strength	1.35 (1.29, 1.40)	1.53 (1.34, 1.75)	0.395

	Weight loss	1.25 (1.21, 1.31)	1.15 (1.05, 1.27)	0.239
	Exhaustion	1.72 (1.64, 1.79)	1.59 (1.43, 1.79)	0.321
	Frail status			
	Pre-frail	1.35 (1.31, 1.39)	1.43 (1.30, 1.58)	0.218
	Frail	2.87 (2.71, 3.05)	2.45 (2.16, 2.78)	0.021
Model 2	**Frailty indicators**			
	Slow walking pace	2.25 (2.12, 2.38)	1.95 (1.67, 2.28)	0.105
	Low physical activity	1.21 (1.16, 1.26)	1.21 (1.08, 1.36)	0.936
	Low handgrip strength	1.27 (1.22, 1.32)	1.39 (1.22, 1.61)	0.547
	Weight loss	1.17 (1.12, 1.22)	1.06 (0.96, 1.17)	0.153
	Exhaustion	1.39 (1.33, 1.46)	1.20 (1.06, 1.36)	0.148
	Frail status			
	Pre-frail	1.24 (1.21, 1.28)	1.25 (1.13, 1.38)	0.789
	Frail	2.14 (1.99, 2.29)	1.80 (1.54. 2.10)	**0.042**

Mode 1. Age, sex
Model 2. Age, sex, ethnicity, smoking, BMI, systolic BP, lipid-lowering medication, blood-pressure medications, LDL cholesterol, employment, alcohol, smoking, deprivation, prevalent CVD, prevalent cancer.

Table 3: Cardiovascular disease cause mortality in adults with and without T2D

		Without T2D	With T2D	Interaction p value
Unadjusted	**Frailty indicators**			
	Slow walking pace	5.17 (4.67, 5.74)	4.31 (3.29, 5.64)	0.219
	Low physical activity	1.14 (1.03, 1.25)	1.38 (1.11, 1.71)	0.098
	Low handgrip strength	2.54 (2.32, 2.79)	2.19 (1.70, 2.83)	0.297
	Weight loss	1.12 (1.02, 1.23)	0.91 (0.76, 1.09)	0.056
	Exhaustion	1.13 (1.02, 1.26)	1.18 (0.96, 1.46)	0.709
	Frail status			
	Pre-frail	1.41 (1.32, 1.51)	1.57 (1.29, 1.91)	0.309
	Frail	3.11 (2.71, 3.58)	2.40 (1.89, 3.06)	0.068
Model 1	**Frailty indicators**			
	Slow walking pace	4.01 (3.61, 4.45)	4.41 (3.37, 5.78)	0.675
	Low physical activity	1. 29 (1.17, 1.42)	1.48 (1.19, 1.83)	0.172
	Low handgrip strength	1.54 (1.40, 1.70)	1.74 (1.35, 2.26)	0.895
	Weight loss	1.32 (1.20, 1.45)	1.09 (0.90, 1.31)	0.152
	Exhaustion	1.73 (1.55, 1.92)	1.57 (1.26, 1.94)	0.172

	Frail status			
	Pre-frail	1.51 (1.41, 1.62)	1.78 (1.46, 2.16)	0.793
	Frail	3.37 (2.94, 3.88)	3.03 (2.37, 3.87)	0.576
Model 2	**Frailty indicators**			
	Slow walking pace	2.36 (2.08, 2.69)	3.03 (2.21, 4.16)	0.441
	Low physical activity	1.17 (1.06, 1.29)	1.27 (1.01, 1.59)	0.540
	Low handgrip strength	1.40 (1.27, 1.55)	1.62 (1.23, 2.14)	0.623
	Weight loss	1.19 (1.08, 1.32)	0.99 (0.81, 1.20)	0.160
	Exhaustion	1.23 (1.09, 1.38)	1.06 (0.84, 1.35)	0.552
	Frail status			
	Pre-frail	1.29 (1.20, 1.39)	1.39, (1.14, 1.71)	0.414
	Frail	1.94 (1.65, 2.29)	2.04 (1.51, 2.75)	0.724

Mode 1. Age, sex
Model 2. Age, sex, ethnicity, smoking, BMI, systolic BP, lipid-lowering medication, blood-pressure medications, LDL cholesterol, employment, alcohol, smoking, deprivation, prevalent CVD, prevalent cancer.