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ORIGINAL ARTICLE

Frailty alone and interactively with obesity predicts heart failure: Kuopio Ischaemic Heart Disease Risk Factor Study

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Abstract

Aims We aim to evaluate the association of frailty and high body mass index with risk of incident heart failure.

Methods and results From the Kuopio Ischaemic Heart Disease Risk Factor Study, 408 women and 369 men, aged 61–74 years were included in this study. Frailty was ascertained with the presence of 3–5 and prefrailty 1–2 of the following criteria: weight loss (highest 20% over 7 years), self-reported tiredness, weakness (measured by handgrip strength), slow walking speed (walking pace), and low physical activity (lowest 20%). At the baseline, participants were allocated to frail (n = 36), prefrail (n = 340), and robust (n = 441). HF incidents were obtained by record linkages from the national hospitalization registry in Finland up to 31 December 2019. Multivariate Cox proportional hazards regression estimated the hazard ratio (HR) of incident events, adjusted for potential confounders. Two hundred one HF events were recorded (111 in women and 90 in men) during the 14.2 years follow-up. After adjustment for the age and sex, the risk of HF events was higher among prefrail (HR 1.42, 95% CI 1.08 to 1.79, P = 0.02) and frail (HR 3.39, 95% CI 1.89 to 4.79, $P \leq 0.001$) compared with the robust group. After adjusting for multiple confounders result remained significant for HF indecent in prefrail [1.46 (HR 1.46, 95% CI 1.09 to 1.95, P = 0.01] and frail (HR 3.33, 95% CI 1.86 to 5.70, $P \leq 0.001$). In the sensitivity analysis, significant interaction between high BMI ($\geq$25 kg/m^2) and frailty was observed (P for interaction = 0.02). The association of frailty [multivariate-adjusted HR: 2.88 (1.56 to 5.33), $P \leq 0.001$)] and prefrailty [multivariate-adjusted HR: 1.40 (1.08 to 1.91), P = 0.03)] with risk of HF indecent was more pronounced in those with high BMI.

Conclusions Frailty is highly common in older age, and our results indicated the high risk of HF incident in frail and prefrail groups. While frailty is clinically recognized by weight loss phenotype, our finding showed that frailly and high BMI can coexist and worsen the risk of HF incidence. Further research is warranted to substantiate these results in large studies and clinical settings.

Keywords Frailty; Heart failure; Obesity; Body mass index; Population study

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Introduction

Frailty is the result of cumulative declines in the body's functional and physiologic systems, associated with a decreased reserve and increased susceptibility to stressors.[1] Frail individuals are at significantly higher risk of experiencing adverse outcomes, including cardiovascular events.[2,3] Fried frailty phenotype assessment tool was developed for the Cardiovascular Health Study and has been frequently used in both research and clinical care.[4] This tool is designed utilizing five domains (i) weakness: hand grip strength in the lowest 25%; (ii) slowness based on time to walk 10 m; (iii) weight

loss of more than 5 kg in the past year; (iv) inactivity; and (v) exhaustion, assessed by the depression scale.[4] Recognition of functional decline and frailty in patients of older age and long-term conditions is paramount. Heart failure (HF) afflicts 23 million persons worldwide,[5] and it is a syndrome with symptoms and signs caused by cardiac dysfunction, resulting in reduced longevity. The European Society of Cardiology (ESC) guidelines on HF suggest monitoring frailty as well as causes of frailty in elderly people.[6]

Less is known about the predictive value of frailty for incident HF. The prevalence of frailty in people with HF can be also independent of age, as frailty can also be experienced by younger (<60 years) people with HF.[7] The mechanisms underlying frailty and HF are complex and mostly unknown, but frailty and HF share several physiological pathways, especially with the proinflammatory phenotype.[8] One meta-analysis estimated the overall prevalence as approximately 45%, but the prevalence in the individual studies ranged from 19% to 77%.[9] A meta-analysis for a total of 26 studies involving 6896 patients with HF showed that about half of patients with HF were frail, despite the considerable differences across studies especially for frailty definition and stage of HF.[9] Previously, cross-sectional associations indicated an association between physical frailty and HF.[10]

Frailty captures the physical and psychological domain, but it does not entail overweight and obesity as highly prevalent and a significant risk factor for both HF[11] and frailty.[12] Obesity is associated with an increased risk of developing cardiovascular disease (CVD), particularly HF and CHD. Surprisingly, some studies reported a favourable link between overweight status and obesity prognosis of CVD and atrial fibrillation and chronic diseases.[13–15] While the Fried et al.[4] frailty score considers unintentional weight loss, the role of overweight and obesity has not been established, especially with the 'obesity paradox' and HF, whereby less frailty and cachexia remain unanswered.[15,16] This study evaluated the frailty independently and with the interaction of high BMI to predict incident HF.

Methods

Study population

The KIHD is a population-based study designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in men from eastern Finland. A total of 2682 men (82.9% of those eligible) who were 42, 48, 54, or 60 years old and living in the city of Kuopio or its surrounding areas were recruited for the baseline examinations in 1984–1989. These participants underwent re-examinations at 4, 11, and 20 years after baseline. During the 11-year follow-up examination, women were also invited to join the study. The current analysis is based on 11 years of follow-up and initially comprised 2358 participants (1007 men and 1351 women). Of those, 2072 participants were found to be potentially eligible: 193 did not agree to participate, 66 did not respond to the invitation, and 39 declined to provide informed consent, which left 1774 participants (aged 53–74 years) who had baseline assessments carried out between March 1998 and February 2001.[17] Subjects with a history of HF at baseline (n = 153) were excluded from the analyses. The final analytical data were n = 777, women (n = 408) and men (n = 369), with available frailty and HF variables.

The KIHD protocol was approved by the Research Ethics Committee of the University of Kuopio and complies with the Declaration of Helsinki (ClinicalTrials.gov Identifier: NCT03221127). All the subjects signed written informed consent. Study participants were not involved in the design, conduct, reporting, or dissemination plans of the current study.

Frailty ascertainment

We have defined the frailty at 11 years of follow-up using criteria developed originally by Fried and colleagues.[4] To define frailty, we used variables in five domains according to the frailty phenotype definition (handgrip strength, walking speed, physical activity, weight loss, and exhaustion).[4] All assessments were performed by trained nurses for the KIHD study.

Handgrip strength was measured by a hand dynamometer (Martin-Balloon-Vigorimeter; Gebrüder Martin, Tuttlingen, Germany). Measurements were taken with the subjects standing in an upright position and their arms parallel to their body. Two measurements were taken for the dominant hand, and the mean of both values was used for analysis. A 1-min resting gap was given between both handgrip measurements.[18] Study subjects belonging to the lowest quintile, separately for men and women, were considered as frailty and scored 1 for the analyses. We also applied the frailty phenotype cut-offs of <27 kg/m^2 for men and <16 kg/m^2 for women, but they resulted in lower n compared to the corresponding lowest quintiles.

Walking speed was captured by assessing the walking speed as a means of two attempts to walk a 10 m constant distance. Low walking speed was defined as belonging to the lowest 20%. Those belonging to low walking speed received 1 score and otherwise 0.

For the physical activity, the method of assessment and the intra-person variability of various physical activities in the KIHD was described in detail by Lakka and Salonen.[19] Briefly, data on the total leisure-time physical activity were available for the 12-month activity history with a questionnaire modified from the Minnesota leisure-time activity questionnaire (Taylor Questionnaire). All KIHD subjects were

asked to fill in the frequency, duration, and intensity of each activity performed during the previous 12 months. For this study, low physical activity was defined as belonging to the lowest 20%, and those belonging to low physical activity levels received 1 score and otherwise 0.

The weight change criteria according to the frailty phenotype refer to a loss of ≥5% of body weight over 12 months. We used a surrogate indicating a longer-term weight change for 7 years before the frailty ascertainment, which may affect the proportion of prefrailty and frailty. Those belonging to the highest 20%, that is, highest weight loss over the past 7 years corresponded to approximately ≥16% loss in weight. Subjects in the highest 20% of weight loss received 1 score and otherwise 0.

Self-reported exhaustion was defined by Fried and colleagues[4] using two questions from the Center for Epidemiologic Studies Depression Scale (CESD) ('I felt that anything I did was a big effort' and 'I felt that I could not keep on doing things'). In the KIHD data, the assessment of tiredness (exhaustion) was conducted by merging two measurements for feeling tired over the past 12 months and feeling for lack of energy over the past 12 months before the frailty ascertainment at 11 years follow-up. If the response to both questions was yes, daily, the subject received 1 score and otherwise 0.

According to the frailty phenotype,[4] the final frailty score was computed by adding the results from these five categories. Frailty was present for the score of 3 or more, prefrailty for the score of 1–2, and robust for the score of 0.

Assessment of heart failure

All HF events that occurred from the 11-year follow-up through to 31 December 2019 were included. Data on events were obtained by record linkages from the national computerized hospitalization registry, which covers every hospitalization and visit in outpatient specialized health care in Finland (Permission THL/93/5.05.00/2013). Data on vital status were obtained from Statistics Finland (Permission TK/782/07.03.00/2021). The diagnostic classification of HF cases was coded according to the International Classification of Diseases, Tenth Revision (ICD-10), and codes I50.0–I50.9 and I11.0 were considered as HF, and the accuracy was verified by a physician. The aetiology for HF was derived from the KIHD classification, I25.5 (ischaemic cardiomyopathy) belongs to chronic ischaemic heart disease, and it is dealt with as a separate outcome compared to heart failure. Correspondingly, I42 refers to cardiomyopathy, and in the KIHD cohort, it is distinguished from heart failure. The KIHD study, consequently, applies a strict definition of heart failure. In KIHD, the ejection fraction rate data were available for 209 men at 11-year follow-up and for 58 men at 20-year follow-up, with little information available for women.

Other measurements

A comprehensive description of the socio-demographic and lifestyle characteristics, prevalent medical conditions, and use of medication consumption have been reported previously.[17] Education and annual income were assessed by using self-administered questionnaires. Dietary intakes were assessed by using a 4-day food recording at the time of blood sampling.[20] Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in meters. Subjects were grouped according to BMI < 25 versus ≥ 25 kg/m^2.

Statistical analysis

The univariate associations of the frailty scores with demographic, lifestyle, and clinical characteristics at baseline were assessed by linear regression for continuous variables and χ^2 test for categorical variables. Kaplan–Meier survival curve was derived to evaluate survival rates in different frailty status. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) of incident events. The validity of the proportional hazard assumption was evaluated by using Schoenfeld residuals, and the assumptions were met. The analyses were controlled for possible confounders, which were selected based on established risk factors for HF,[21] or on associations with exposures or outcomes in the present analysis (*Table* S1).

Two different models were used to control for confounding factors. Model 1 was adjusted for age (years), gender, and examination year. The multivariable model 2 included model 1 and smoking (pack/years), years of education, intake of alcohol (grams/week), systolic and diastolic blood pressure (mm Hg), resting heart rate, and use of beta-blockers, anti-hypercholesterolaemia or other antihypertensive medications at baseline or during follow-up (yes or no). Further adjustment for potential confounders, such as concentrations of serum fasting blood glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride, heart rate, history of chronic obstructive pulmonary disease (COPD), and total cancer did not materially change the associations (<5% change in estimates). Statistical significance of the interactions on a multiplicative scale was assessed by stratified analysis according to overweight and obesity and likelihood ratio tests with a cross-product term. All *P*-values were two-sided ($\alpha = 0.05$). Data were analysed using the SPSS software version 27 for windows (Armonk, NY: IBM Corp.). For the competing risk analyses, we applied the R version 4.2.1 and R packages 'survival' and 'cmprsk'.

Results

Baseline characteristics

Among the 777 participants aged 68.5 ± 2.9 years, frailty prevalence was 4.6% (n = 36), prefrailty 43.8% (n = 340) and robust 51.6% (n = 441). *Table 1* shows the baseline characteristics of the entire population. Frail participants were older, had lower education and income, had higher BMI, were less physically active, had higher serum fasting blood glucose and triglyceride concentration, higher mean resting heart rate, lower hand grip strength, and were more often users of anti-hypertensive medication, as compared with prefrail and robust counterparts.

Associations between frailty status and heart failure

During a mean follow-up of 14.2 years, 201 HF cases (111 cases in women and 90 cases in men) occurred. After adjustment for age and sex, prefrailty and frailty were associated with higher hazards of HF (HR 1.42, 95% CI 1.08 to 1.79, P = 0.02) and (HR 3.39, 95% CI 1.89 to 4.79, $P \leq 0.001$), respectively (Model 1, *Table 2*). Further adjustments for the potential confounders did not materially change the association (HR 1.46, 95% CI 1.09 to 1.95, P = 0.01 for prefrail and HR 3.33, 95% CI 1.86 to 5.70, $P \leq 0.001$ for frail) (Model 2, *Table 2*). Kaplan–Meier survival curve has shown lower survival of frail than non-frail patients ($P < 0.001$) (*Figure* S1). Given the population age at the baseline, we account for the number of deaths as competing risk factors, therefore we have conducted additional analysis (*Table* S2), and frailty remained a significant predictor of HF, censored for death.

The correlations between the frailty score and high BMI were weak (r = 0.16, $P < 0.001$); however, we found statistically significant interactions between the obesity status for frailty score (P for interaction = 0.02). Further, we evaluated the associations based on the obesity status, and the direct associations between frailty status and risk of HF were mainly observed among high BMI participants, [(multivariate-adjusted HRs for HF were 1.40 (1.08 to 1.91), P = 0.03) among prefrail participants and 2.88 (1.56 to 5.33), $P \leq 0.001$) among frail participants] (*Table 3*).

Table 1 Baseline characteristics according to frailty score

Variables	Frailty score			
	Robust (n = 401)	Prefrail (n = 340)	Frail (n = 36)	P-trend
Age (years)	68.2 (2.9)	68.7 (2.9)	69.7 (2.7)	<0.001
Education (years)	8.9 (3.6)	8.5 (3.2)	7.9 (3.1)	<0.001
Income (euro/year)	13 221 (8120)	13 011 (7551)	12 702 (6841)	0.02
Body mass index (kg/m^2)	27.2 (3.7)	28.4 (4.6)	28.9 (4.2)	<0.001
Smoking (%)	36.7%	36.5%	36.1%	0.45
Physical activity (kcal/day)	216.6 (204.5)	149.2 (147.6)	69.3 (71.8)	0.04
Alcohol intake (g/week)	38.4 (67.8)	34.5 (66.7)	39.2 (65.9)	0.12
Low-density lipoprotein, mmol/L	3.59 (0.85)	3.61 (0.95)	3.41 (1.07)	0.44
High-density lipoprotein, mmol/L	1.26 (0.32)	1.23 (0.31)	1.32 (0.33)	0.51
Triglycerides, mmol/L	1.23 (0.59)	1.29 (0.61)	1.36 (0.68)	0.01
Fasting blood glucose, mmol/L	5.08 (1.09)	5.20 (1.35)	5.33 (1.20)	0.02
Mean resting heart rate (b.p.m.)	62 (9)	64 (10)	65 (11)	0.005
Anti-hypercholesterolemia medication (%)	6.8%	5.3%	7.4%	0.27
Anti-hypertensive medication (%)	44.9%	54.4%	72.2%	0.03
Use of beta-blockers (%)	41.3%	49.7%	66.1%	0.04
Systolic blood pressure (mmHg)	139.1 (18.4)	138.9 (17.2)	136.8 (20.1)	0.65
Diastolic blood pressure (mmHg)	80.1 (8.8)	79.7 (8.6)	79.4 (9.3)	0.03
Hand grip strength (kPA)	82.4 (22.6)	71.6 (16.4)	56.1 (19.3)	<0.001
Diabetes (%)	12.5%	13.8%	25.0%	0.10

Values are means (SD) or percentages.

Table 2 Hazard ratios and 95% confidence intervals for the association between frailty and incident heart failure

Frailty status	Events/Total 201/777	Model 1		Model 2	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Robust	88/401	Reference	–	Reference	–
Prefrail	97/340	1.42 (1.08–1.79)	0.02	1.46 (1.09–1.95)	0.01
Frail	16/36	3.39 (1.89–4.79)	<0.001	3.33 (1.86–5.70)	<0.001

Model 1: Age and sex. Model 2: Model 1 plus smoking status, body mass index, alcohol intake, leisure-time physical activity, education, history of type 2 diabetes, and use of beta-blockers, anti-hypertensive and lipid medications.
CI, confidence interval; HR, hazard ratio.

Table 3 Multivariate-adjusted hazard ratios and 95% confidence intervals for the association between frailty and incident heart failure according to body mass index status

Frailty status	Events/Total 42/205	BMI <25 kg/m^2 HR (95% CI)	*P*-value	Events/Total 159/572	BMI ≥25 kg/m^2 HR (95% CI)	*P*-value
Robust	19/114	Reference	–	69/287	Reference	–
Prefrail	20/84	1.19 (0.69–2.29)	0.49	77/256	1.40 (1.08–1.91)	0.03
Frail	3/7	3.01 (0.74–5.66)	0.32	13/29	2.88 (1.56–5.33)	<0.001

Age and sex, smoking status, alcohol intake, leisure-time physical activity, education, history of type 2 diabetes, and use of beta-blockers, anti-hypertensive, and lipid medications.
BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Discussion

In this study, we studied the participants in KIHD and showed frailty and prefrailty defined according to frailty phenotype were predictors of incident HF, after adjusting for potential confounders. Notable, we identified significant interactions between high BMI with frailty and prefrailty in terms of predicting incident HF. To our knowledge, this is the first prospective study that has analysed frailty as well as prefrailty and their interaction with obesity to predict the incidence of HF in middle-aged adults.

Clinical implications of frailty and obesity are indeed paramount predictions of mortality, disability diminished quality of life, functional decile, and many other adverse outcomes.[22–26] Although there are numerous studies evaluating the prevalence of physical frailty in patients with HF, there are limited data available for the estimates of the association between frailty and HF as shown in the systemic review by Marengoni et al.,[25] particularly from prospective studies. Our results are in agreement with the Women's Health Initiative Observational Study[27] on the longitudinal association between frailty and HF, showing a significant increase in the risk of developing HF during a median follow-up of 11.4 years in women affected by frailty at baseline.[27] In the study by Damluji et al.[28] from National Health and Aging Trends Study, during a 6-year follow-up, the incidences of death and each cardiovascular outcomes were significantly higher in the frail than in the non-frail patients including major adverse cardiovascular events, although the evidence on HF was not reported. Our observational evidence suggests that frailty and prefrailty can be utilized to predict HF in both middle aged and older adults. Recent studies have also shown the prognostic value of the Rockwood Clinical Frailty Score in HF.

The interaction between frailty and obesity was expected. A large observational cross-sectional study suggested associations between higher body fat, and central adiposity using waist circumference with frailty among 4984 older community-dwelling participants aged ≥60 years old.[29] Multiple studies highlight risks associated with obesity both in causing and aggravating HF.[30,31] Our data are the first published results both evaluating the combined association between frailty status and obesity with HF. In this dataset, baseline obesity showed a significant interaction with both frailty and prefrailty, increasing the risk of incident HF. At baseline, frail individuals were more obese compared to prefrail and robust, assuming that higher BMI in this group represents increased fat mass but not muscle mass. We could not provide further data on body composition, Health ABC Study showed high BMI at baseline and greater losses of lean body mass in older men and women who developed HF and lost weight compared with those without HF.[32] Our results emphasize the importance of the evaluation of frailty and BMI in clinical practice with major cardiovascular outcomes such as HF, especially because the Fried score does not include obesity assessment. Based on current observational data, in frailty and prefrailty, weight loss (and lean mass loss) and overweight are potential exacerbating factors for incident HF. While unintentional weight loss is an integrated part of frailty, obesity is also known as a common condition and a risk factor for higher risk of frailty. Systematic review and meta-analysis in community-dwelling older by Yuan et al. showed that both obesity and being underweight are associated with an increased risk of frailty in community-dwelling older adults.[33] This might be due to the fact that obesity and frailty share common pathophysiological pathways such as inflammation in older people.[34–36]

The biological underpinnings of frailty remain unclear, and the interactions with HF are complex. It is conceptually plausible to consider chronic inflammation as an important underlying factor, which is associated with both frailty and HF. Indeed, frailty is associated with circulating inflammatory cytokines and sarcopenia, features that are both associated with HF.[8,37,38] Despite this, the inflammation that leads to frailty was suggested to be also independent of HF.[8] Other potential mechanisms that may underpin frailty causing HF are DNA damage, impaired autophagy, and mitochondrial dysfunction, which are biological processes that occur in both aging and HF. Loss of muscle mass and strength (secondary sarcopenia) is highly common in patients with heart failure (Sarc-HF) (prevalence is 35–69%).[39–41] Secondary sarcopenia has been implicated as both a cause and consequence of HF. Secondary sarcopenia is one of the important predictors of HF in non-chronic heart disease[42] and has a negative impact on the prognosis of HF in this population. Whereas it remains unclear how biological mechanisms aggravate

sarcopenia in older adults with HF. In patients with HF and sarcopenia, exercise capacity, weight-adjusted peak maximal oxygen consumption, left ventricular function, and hospitalization rates are significantly worse than in those without sarcopenia.[43,44] The underlying mechanisms might be biomarkers of systemic inflammation, nutritional status, oxidative stress, endocrine activity, muscle protein turnover, and neuromuscular function.[45]

The strength of this study is that HF was assessed with careful, adjudicated assessments with clear delineation of disease onset using national hospitalization records. The analysis stands out as being able to define modified frailty and high BMI measures at baseline to predict incident HF. Limitations of this analysis are limited sample size that may have reduced the power of this study. Although the proportion was reliable the number of subjects with frailty was relatively low, also the existence of association with prefrailty, assuming the transition to frailty if followed up for longer, could show how baseline frailty can increase the risk of incident HF. Our study utilized a modified Fried frailty definition, specifically in terms of weight loss originally defined as a 5% change, which could lead to an overestimation of frailty in this population. Frailty has a dynamic nature, and it may improve or deteriorate in people over time, which we could not control in the current study. Longitudinal studies are warranted to further substantiate these findings. Although our study showed a link between frailty and time-to-first HF event, it is important that frailty can lead to recurrent hospitalization which aggravates the prognosis of HF. A low number of HF events were another limitation of this study as well as the relatively low number of those with frailty and BMI. It is important to note that in older age trajectory of frailty is more towards worsening the condition and co-existing risk elevation for prefrail and high BMI may indicate this. Finally, it should be noted that our study population consists predominantly of relatively healthy middle-aged White European descent, limiting the generalizability of our findings to other age groups and ethnicities and to older HF populations in which multimorbidity is endemic.

In conclusion, frailty and prefrailty at baseline are associated with incident HF over time. There was a significant interaction between frailty status and high BMI with incident HF. Further studies are warranted to investigate the interaction of frailty and high BMI in a larger population.

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Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan–Meier survival curves by frailty status.
Table S1. Univariate HRs for all covariates and heart failure.
Table S2. Competing multivariate risk analyses for frailty, HF, and death.

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