The frailty phenotype and its association with all-cause mortality in community-living Norwegian women and men aged 70 years and older: The Tromsø Study 2001-2016.

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Running title

Frailty and mortality in a Norwegian cohort

Abstract

Aim: There is a lack of studies on frailty prevalence and the association between frailty and mortality in a Norwegian general population. Findings regarding sex differences in the association between frailty and mortality have been inconsistent. The aim of this study was to investigate the association between the frailty phenotype and all-cause mortality in men and women in a Norwegian cohort study.

Methods: We followed 712 participants (52% women) aged 70 years and older participating in the population-based Tromsø 5 Study in 2001-02 for all-cause mortality up to 2016. The frailty status at baseline was defined by a modified version of Fried's frailty criteria. Cox regression models were used to analyze the association between frailty and mortality with adjustment for age, sex, disability, comorbidity, smoking status and years of education.

Results: In total, 3.8% (n=27) of participants were frail (women: 4.4%, men: 3.2%) and 38.1% (n=271) were pre-frail (women: 45.8%, men: 29.9%). During follow-up (mean 10.1 years), 501 (70%) participants died. We found an increased risk of mortality for frail elderly (multivariate-adjusted HR 4.16 (95% CI 2.40, 7.22)) compared to non-frail elderly. In sex-stratified analysis the adjusted HR was 7.09 (95% CI 3.03, 16.58) for frail men and 2.93 (95% CI 1.38, 6.22) for frail women. Results for pre-frailty showed an overall weaker association with mortality.

Conclusions: While frailty was more prevalent in women than in men, the findings suggest that the association between frailty and mortality is stronger in men than in women.

Keywords: Cohort Studies, Epidemiology, Frail Elderly, Mortality, Norway

Introduction

A challenging manifestation of the aging population is the clinical condition of frailty[1]. Although there is no universal definition, frailty is, with growing consensus, considered a *"syndrome of decreased reserve and resistance to stressors"*[2] following an age-related accumulative degeneration of several physiologic systems and leading to a state of increased risk of adverse health outcomes like falls, disability, institutionalization and mortality[1-4]. For frail individuals this implies that stressors like changes in medication use or minor illnesses can lead to a drastic decline in health[1]. The exact pathophysiology of frailty is still uncertain but is thought to be a multifactorial interaction of physiology, lifestyle, environment, genes and disease[5]. Even though there is no gold standard for an operational definition, one of the most frequently used approaches is the frailty phenotype suggested by Fried and colleagues in 2001, which defines frailty as the presence of three or more of the following characteristics: unintentional weight loss, low grip strength, exhaustion, low walking speed and low physical activity[2]. The association between the presence of frailty and an increased risk of mortality has been described before[2, 6-8], but there is a lack of studies on frailty prevalence and the association between frailty and mortality in a Norwegian general population. Further, previous studies showed inconsistent results regarding sex differences in this association[8-11]. The aim of this study is to investigate the association between the frailty phenotype and all-cause mortality among community-dwelling men and women aged 70 years and older in a Norwegian population-based study.

Methods

Sample

The Tromsø Study is a population-based study in the Tromsø municipality consisting of seven surveys conducted between 1974 and 2016 (Tromsø 1-7), to which total birth cohorts and random samples of the population were invited (participation rates 65-79%). A total of 40,051

women and men participated in one or more surveys. Data collection consisted of questionnaires, biological sampling and clinical examinations. In Tromsø 4-7 a predefined group was invited to a second, more extensive clinical examination after attending the first visit[12, 13].

Participants in the second examination of Tromsø 4 and additional samples in the age groups 30, 40, 45, 60 and 75 were eligible for invitation to Tromsø 5 (2001-02). A total of 10,353 women and men were invited and 8130 (79%) attended[12]. Questionnaires for participants 70 years and older included all covariates of interest for the present analysis. Therefore, our sample included participants from Tromsø 5 aged 70 years or older (n=2,131, participation rate 83%). We excluded subjects with incomplete data for frailty definition (n=1419), leaving 712 participants (52% women) aged 70-87 years for analysis (Figure 1).

Norway has a unique personal identification system that allows exact matching of population register data. The Tromsø Study participant list was linked to the Norwegian Cause of Death Registry and the participants were followed until 1st of January 2016, death or emigration, whichever came first. None of the included participants emigrated from Norway during follow-up, i.e. mortality follow-up was complete.

The Regional Committee of Medical and Health Research Ethics and the Norwegian Data Protection Authority have approved the Tromsø Study, and all procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments. The participants gave written informed consent.

Frailty Measurement

A modified version of the frailty phenotype by Fried et al.[2] was used to identify frailty based on exhaustion, grip strength, walking speed and physical activity level. Information about unintentional weight loss was unavailable. All single frailty markers were dichotomized. Participants with score 0 on all frailty markers were considered non-frail, those with 1 or 2 as

pre-frail and those with 3 or more present frailty markers were considered frail.

Exhaustion was defined through one item from the Hopkins Symptom Checklist 10 (HSCL-10): "During the last week, have you experienced that everything is a struggle?". Participants reporting one of the highest two ("pretty much" or "very much") of four categories were considered exhausted. Physical activity level was defined by self-reported weekly average of light (not sweating/out of breath) and hard (sweating/out of breath) leisure time physical activity, where 0 weekly hours in light and hard physical activity were considered low physical activity. Walking speed was assessed by the Timed Up and Go (TUG) test (time for the participant to rise from a chair, walk three meters, turn around, walk back to the chair and sit down[14, 15]). The participants were instructed to perform the test with footwear and could use the chair's armrests as support, if needed. The cut-off for low walking speed was set to 15 seconds, which is the middle ground of various suggested cut-points[16, 17] and has previously been shown to be the preferred threshold for prediction of falls[15]. Grip strength was measured using a Martin vigorimeter (bar). The participants were given two attempts and were instructed not to support their arm against anything and to use their non-dominant hand. The results were divided into 5 centiles adjusted for sex and BMI-group (≤24, 24.1-26, 26.1-28 and >28). The lowest centile (the weakest 20%) was considered low grip strength in accordance with the suggestion from Fried and colleagues[2] and has previously been shown to have high agreement with population-independent cut points for the Fried criteria[18]. A comparison of the frailty definition in the present study and the original Fried criteria is presented in the supporting information (Table S1).

Covariates

Age was included as a continuous variable. Self-reported smoking status was dichotomized into current daily smoking or non-smoking at baseline. Years of education were grouped into primary school (7 years), high school (8-12 years) and college/university (13+

years). Comorbidity was defined through self-report (previous and/or current disease) of two or more of the following diseases at baseline: pulmonary disease (asthma/chronic bronchitis/emphysema), cancer, diabetes, stroke, coronary heart disease (angina pectoris and/or heart attack) and peptic ulcer, based on the Charlson Comorbidity Index (CCI)[19] without weighting of diseases. Disability was defined as difficulties in performing everyday activities due to chronic health problems (mobility inside own home, moving out of home without assistance, participation in leisure-time activities, using public transport or performing necessary daily errands). Participants reporting some or great difficulties in one or more daily activities were classified as disabled.

Statistics

Baseline characteristics are presented as frequencies and mean values stratified by frailty status (Table 1), sex (Table S2) and completeness of frailty data (Table S3). Statistical differences were tested with χ^2-tests and t-test or linear regression for categorical and continuous variables, respectively. Frequencies of single frailty markers stratified by sex at baseline are presented in Table 2. Cox regression was used to calculate hazard ratios (HR) with 95% confidence intervals (CI) for analysis of the association between frailty status at baseline and all-cause mortality (Table 3, Figure 2). In accordance with Fried et al.[2], the time from study entry up until the day of death or end of study - whichever came first - was used as the time-scale. The log−log plot and Schoenfeld residuals were examined for the total sample and for men and women separately. No violation of the proportional hazards assumption was detected. Three regression models were run for women and men combined and separately. The first model included the whole sample, the second a reduced sample with complete data for all covariates and both models adjusted for age (and sex when women and men combined). The third model additionally adjusted for disability, comorbidity, smoking and education. As a sensitivity analysis, the third model was run again in a sample with multiply imputed missing

data among the covariates (Table S4). Possible interaction between sex and frailty status was investigated by adding interaction terms in the regression analysis. All analyses were performed using STATA 14.2 (StataCorp LLP, College Station, TX). A p-value of <0.05 was regarded as statistically significant.

Results

Mean age was 77.4 (SD ± 2.4, range = 70-87 years) with a majority of participants being 74-81 years old (n=686). In total, 3.8% (n=27) were defined as frail and 38.1% (n=271) as pre-frail. Among women, 4.4% were frail and 45.8% were pre-frail. Among men, 3.2% were frail and 29.9% were pre-frail. Frail participants differed from pre-frail and non-frail participants (Table 1); with increasing frailty status participants were more likely to be older, female and to have shorter length of education. There was a stepwise increase in comorbidity and disability with increasing frailty status. Among the frail individuals, 91.7% reported disability (92.3% of women, 90.9% of men) and 61.9% reported comorbidity (64.3% of women, 57.1% of men). Table 2 displays the prevalence of each frailty marker.

Out of the 712 participants, 501 (70.4%) died during follow-up (226 women (61.6%) and 275 men (79.7%)). Women had a median survival of 12.5 years, whereas half of the men had died after 9.7 years. Among the frail, the median survival time was 5.9 and 2.8 years for women and men, respectively. Figure 2 displays the age-adjusted survival curves based on the Cox model for women and men according to their frailty status at baseline.

Adjusted for age and sex (model 2), frail participants had a 5.96 times higher risk of death (CI 3.58, 9.93) compared to non-frail elderly (Table 3). After further adjustment for disability, comorbidity, smoking and education the hazard ratio dropped to 4.16 (CI 2.40, 7.22). When the analysis was stratified by sex, frail women had a 4.53 higher risk of death compared to those who were not frail (CI 2.34, 8.78) in the age-adjusted model. After further covariate adjustment, the risk of death was attenuated, but remained statistically significant (HR 2.93 (CI 1.38, 6.22)).

For frail men, the risk of death was 8.55 times higher compared to those who were not frail when adjusted for age (CI 3.84, 19.03) and 7.09 times higher in the multivariate-adjusted model (CI 3.03, 16.58). Pre-frailty was also associated with all-cause mortality (HR 1.50 (CI 1.18, 1.91) relative to non-frailty after multivariate-adjustment. In sex-stratified analysis, pre-frailty was significantly associated with mortality in men, but not in women. In the multivariate-adjusted model, there was a significant interaction (p = 0.046) between sex and frailty. Using multiple imputation attenuated the results slightly, but the conclusions remained unaltered (Table S4).

Discussion

In this prospective cohort study of 712 community-dwelling women and men aged 70 years and older we found that frailty was significantly associated with increased all-cause mortality. This association was stronger in men than in women.

Frailty prevalence

In accordance with our findings, several previous studies showed higher frailty prevalence among women compared to men[2, 6, 7, 20], an increase in frailty with increasing age[2, 6, 9, 20, 21] as well as the general tendency of a higher prevalence of diseases and adverse socioeconomic and lifestyle-related factors among the frail[2, 20, 21].

Frailty, comorbidity and disability

The overlap of frailty with comorbidity in the present study (62%) is similar to that in the study by Fried and colleagues (68%)[2]. In the present study, a vast majority of those who were classified as frail also reported disability (92%). In Fried et al., only 27% of the frail participants also reported difficulty in activities of daily living (ADL)[2]. However, the findings in the present study are in accordance with studies challenging the assumption that disability

and frailty only overlap modestly. Theou et al. examined the overlap of the frailty phenotype with disability in the Canadian Study of Health and Aging and found that 84% of frail people also reported disability[22]. In an analysis from the National Health and Nutrition Examination Survey (NHANES) as many as 98% of frail people aged 50 years or older had ADL disability, suggesting that frailty might not be a pre-disability state[23]. These studies all vary in the way in which the criteria for the frailty phenotype were modified and how disability was measured, which can strongly influence the amount of overlap between the concepts. Nevertheless, the overlap in the present study also suggest that the frailty phenotype does not only identify participants at high risk of disability, but more specifically those being in an especially vulnerable state of disability.

Frailty and all-cause mortality

We found a strong association between frailty status and all-cause mortality. Further, the effect sizes and interaction analysis suggest that the association is stronger for men. This is in accordance with results from a systematic review using the frailty phenotype, which found a 2.66 times increased mortality risk for frail men (95% CI 2.02, 3.50) and 1.88 for frail women (95% CI 1.64, 2.15) compared to non-frail individuals[10]. Equally, a study of Mexican Americans aged ≥ 65 found a 3.04 times higher mortality risk for frail men (95% CI 2.16, 4.28) and 1.92 higher risk for frail women (95% CI 1.39, 2.65) compared to those who were non-frail[11]. Theou et al. found an association between frailty and mortality that was statistically significant for both genders, but stronger for men on seven different frailty scales[24]. Conversely, two US studies using different frailty measures[7, 9] and a Finnish study using the phenotype found a stronger association of frailty and mortality among women[8].

The finding of a higher frailty prevalence in women, but higher frailty-associated mortality in men is in line with the Male-Female Health-Survival Paradox, which refers to the phenomenon that women have a higher rate of disability, diseases and worse self-reported

health, but also greater longevity compared to men[25]. Women seem to be able to live longer with frailty, whereas men tend to die more suddenly[7, 8]. Women are also more likely to have a stronger social support system and to actively seek help when needed compared to men[10, 11], which could compensate for some of the risk associated with frailty.

Limitations

Volunteer bias and missingness of frailty measures affect the estimation of the true prevalence of the frailty phenotype and its association with mortality. Study participants tend to be healthier than non-attendees[26]. Non-attendance by the most ill individuals may have led to an underestimation of frailty prevalence and its association with mortality in this study.

Participants excluded due to missing data on frailty criteria were younger and comprised more women and current smokers compared to those with complete frailty data, but there were no significant differences in disease prevalence (Table S3).

Estimates of frailty prevalence are tentative as the identification of frailty is substantially influenced by varying definitions and modifications[27, 28]. In this analysis we used four of the five Fried criteria to detect frailty. If unintentional weight loss had been available for assessment, there might have been more individuals classified as frail or pre-frail, as suggested in a systematic review on modifications of the frailty phenotype where 4-item phenotype scales estimated lower prevalence than 5-item phenotypes[28].

The two self-reported frailty markers, exhaustion and physical activity level, might have been affected by information bias. A previous analysis from the Tromsø Study found that self-reported leisure time activity is over-reported in both men and women, but the degree of overestimation is greater among men[29]. A qualitative study from Spain on gender differences in the perception of health and vulnerability found that women tend to emphasize their exhaustion and report worse self-perceived health than men, while men tend to downplay their health problems[30]. Consequently, if men did report exhaustion and inactivity in this study, it

might have signaled a higher severity than in women, meaning that the same frailty score for men and women would have been be more lethal for men.

Most covariates were dichotomized in this analysis, which leads to loss of information and potential for unaccounted confounding. Comorbidity was assessed through self-report of current as well as previous diseases and did not include weighing for the severity of the disease. Furthermore, confounding of the association between frailty and mortality by the effect of single diseases is possible and might have led to an overestimation of the strength of association, given the higher disease prevalence among the frail.

The HRs for frail participants in the present study are considerably larger than in most previous findings. These results have to be interpreted with caution due to the low number of frail people in the sample, which led to low precision of the effect estimates.

The vast majority of participants were aged 74 to 81 years, so the findings are most valid for this age group. Further, the results should not be generalized to the population of older people living in nursing homes and the like, where the prevalence and severity of frailty is expected to be considerably higher than among community-dwelling individuals[2, 27].

Major strengths of the study are the high participation rate and the ascertainment of mortality status for every participant, resulting in complete follow-up.

In this population-based study of 712 community-dwelling Norwegian women and men aged 70 years and older we found a significant association between frailty and mortality. Although frailty was more prevalent in women, the results suggest that the risk of death might be higher for frail men than for frail women. Continued efforts should be made to agree on universal definitions and measurements of frailty, in order to enable comparable research and to provide a firm basis for potential prevention and intervention strategies.

Disclosure statement

The authors declare no conflict of interest.

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Table 1. Baseline characteristics by frailty status. The Tromsø Study 2001-02.

	Total (n = 712)	Non-Frail (n = 414)	Pre-Frail (n = 271)	Frail (n = 27)	p§
Age, mean ± SD	77.4 ± 2.4	77.2 ± 2.4	77.7 ± 2.3	78.3 ± 2.6	0.001
Sex, n (%)					
Female	367 (51.5)	183 (44.2)	168 (62.0)	16 (59.3)	< 0.001
Male	345 (48.5)	231 (55.8)	103 (38.0)	11 (40.7)	
Education, n (%)					
≤ 7 years	322 (47.1)	156 (39.4)	148 (56.9)	18 (66.7)	< 0.001
8-12 years	289 (42.3)	186 (47.0)	95 (36.5)	8 (29.6)	
>12 years	72 (10.5)	54 (13.6)	17 (6.5)	1 (3.7)	
BMI, mean ± SD	26.6 ± 4.1	26.4 ± 3.7	26.9 ± 4.3	27.6 ± 6.2	0.039
Daily Smoking, n (%)					
Current Smoker	113 (15.9)	55 (13.4)	51 (18.8)	7 (25.9)	0.056
Non-Smoker	597 (84.1)	357 (86.7)	220 (81.2)	20 (74.1)	
Disability, n (%)	195 (31.2)	63 (17.2)	110 (46.8)	22 (91.7)	< 0.001
Comorbidity, n (%)	126 (22.7)	53 (16.4)	60 (28.6)	13 (61.9)	< 0.001
Disease, n (%)					
Pulmonary Disease †	110 (15.7)	55 (13.6)	48 (17.9)	7 (25.9)	0.106
Cancer	85 (14.2)	55 (15.5)	28 (12.3)	2 (11.8)	0.552
Diabetes	55 (7.8)	25 (6.1)	22 (8.2)	8 (29.6)	< 0.001
Stroke	56 (8.0)	18 (4.4)	27 (10.2)	11 (40.7)	< 0.001
CHD ‡	177 (25.2)	80 (19.6)	84 (31.6)	13 (48.2)	< 0.001
Peptic Ulcer	75 (13.7)	38 (11.6)	34 (16.8)	3 (20.0)	0.189
SMC, n (%)	102 (18.5)	48 (14.9)	48 (22.5)	6 (35.3)	0.016

†Including asthma, chronic bronchitis and/or emphysema. ‡Including angina pectoris and/or heart attack.

§p-value: Chi-square test for dichotomous or ordinal variables, linear regression for continuous variables.

BMI, Body Mass Index; CHD, Coronary Heart Disease; SMC, Subjective Memory Complaint.

Table 2. Prevalence of the single frailty markers at baseline. The Tromsø Study 2001-02.

	All (n = 712)	Women (n = 367)	Men (n = 345)
Exhaustion, n (%)	48 (6.8)	37 (10.1)	11 (3.2)
Low physical activity, n (%)	97 (13.6)	65 (17.7)	32 (9.3)
Low grip strength, n (%)	130 (18.3)	71 (19.4)	59 (17.1)
Low walking speed, n (%)	141 (19.8)	90 (24.5)	51 (14.8)

Table 3. Hazard Ratios (95% Confidence Intervals) for all-cause mortality by frailty status at baseline. The Tromsø Study 2001-02.

	Model 1†				Model 2†				Model 3†			
	All‡ (n=712)	Women (n=367)	Men (n=345)	Interaction§	All‡ (n=481)	Women (n=235)	Men (n=246)	Interaction§	All‡ (n=481)	Women (n=235)	Men (n=246)	Interaction§
Non-frail (ref.)	1.0	1.0	1.0		1.0	1.0	1.0		1.0	1.0	1.0	
Pre-frail	1.57 (1.30, 1.90)	1.35 (1.03, 1.78)	1.76 (1.36, 2.27)	0.200	1.65 (1.32, 2.08)	1.37 (0.97, 1.92)	1.88 (1.39, 2.54)	0.173	1.50 (1.18, 1.91)	1.15 (0.78, 1.70)	1.65 (1.21, 2.25)	0.158
Frail	4.82 (3.17, 7.32)	3.41 (1.96, 5.92)	8.01 (4.21, 15.24)	0.050	5.96 (3.58, 9.93)	4.53 (2.34, 8.78)	8.55 (3.84, 19.03)	0.188	4.16 (2.40, 7.22)	2.93 (1.38, 6.22)	7.09 (3.03, 16.58)	0.046

†Model 1 = full sample, adjusted for age. Model 2 = sample with complete data for all covariates, adjusted for age. Model 3 = sample with complete data for all covariates, adjusted for age, comorbidity, disability, smoking and education.

‡Additional adjustment for sex.

§P-value for interaction term between frailty status and sex.

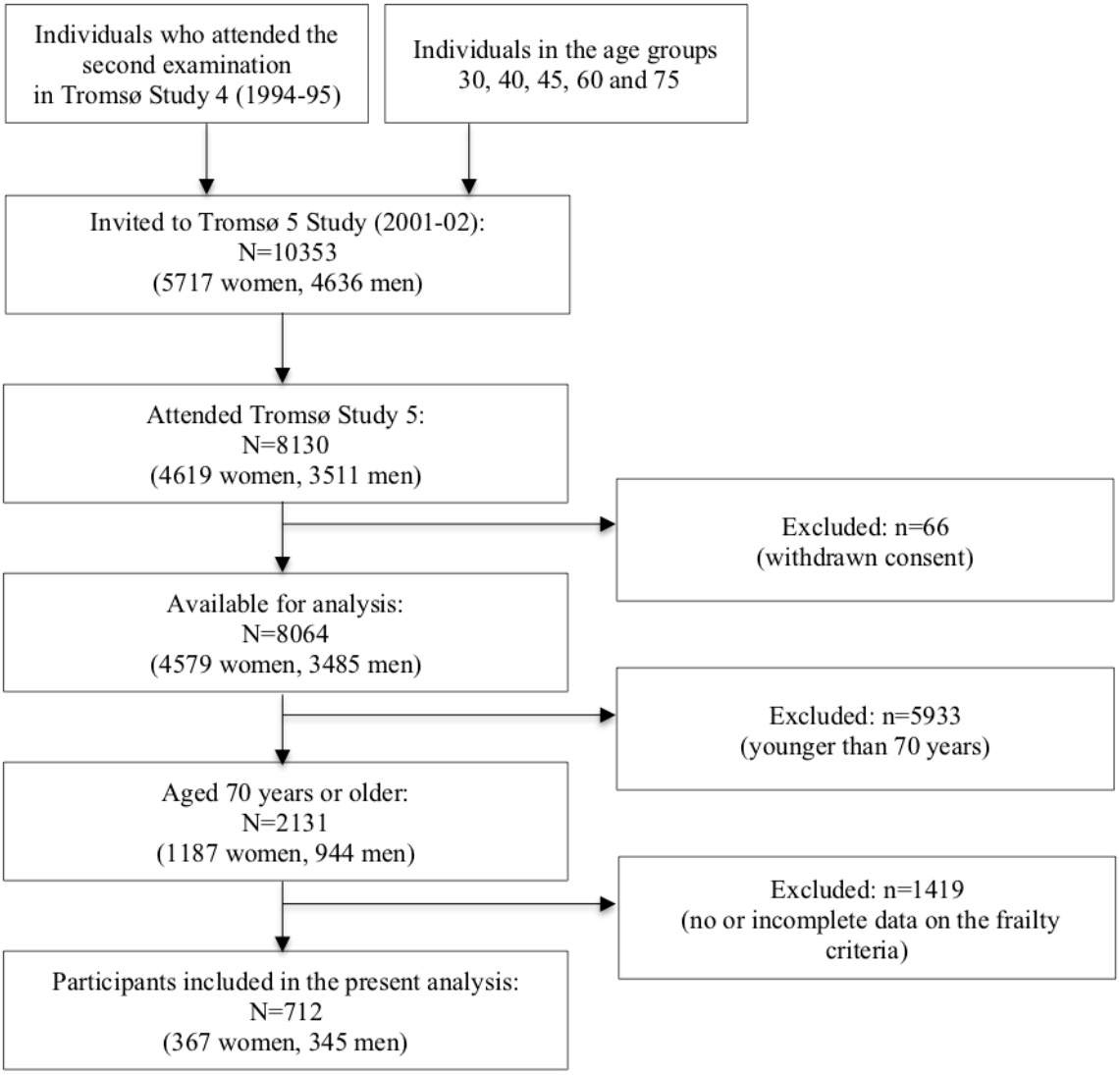

Figure 1. Flow diagram demonstrating inclusion and exclusion of participants for the analysis.

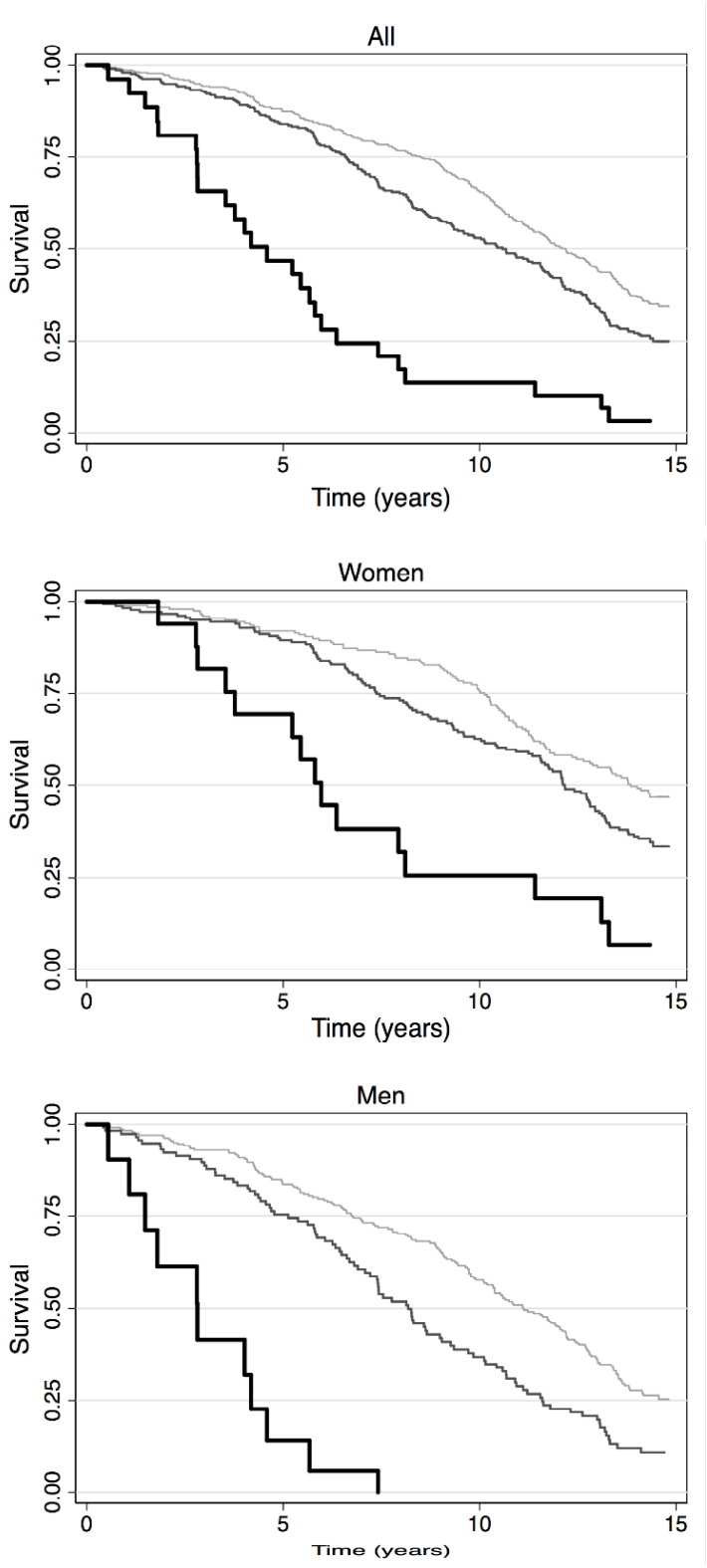

Figure 2. Age-adjusted survival curves based on the Cox model by frailty status; non-frail (thin line), pre-frail (medium line) and frail (thick line), for all (n=712), and women (n=367) and men (n=345) separately. The Tromsø Study 2001-02.

Table S1. Modification of the frailty phenotype in the Tromsø Study 2001-02.

	Criteria for frailty by Fried et al. 2001	**Criteria for frailty in the Tromsø Study**
Exhaustion	Two questions from the Center for Epidemiologic Studies Depression Scale: (a) I felt that everything I did was an effort (b) I could not get going How often in the last week did you feel this way? 0 = rarely or none of the time (<1 day) 1 = some or a little of the time (1–2 days) 2 = a moderate amount of the time (3-4 days) 3 = most of the time Answer 2 or 3 led to categorization as frail by the exhaustion criterion.	One question from the Hopkins Symptom Checklist (HSCL-10): Have you experienced any of this the last week: That everything is a struggle? 1 = No complaint 2 = Little complaint 3 = Pretty much 4 = Very much Answer 3 or 4 leads to categorization as frail by the exhaustion criterion.
Physical Activity	Minnesota Leisure Time Activity Questionnaire asking about walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, swimming. Kilocalories per week expended were calculated using a standardized algorithm. The lowest 20% were identified, resulting in the following cut-off for the physical activity criterion for frailty: Men: Those with <383 kilocalories of physical activity per week were considered frail by this criterion. Women: Those with <270 kilocalories per week were considered frail by this criterion.	Self-report: How has your physical activity in leisure time been during this last year? Think of your weekly average for the year. Time spent going to work counts as leisure time. Light activity (not sweating/out of breath): 1 = None 2 = Less than 1 hour per week 3 = 1-2 hours per week 4 = 3 or more hours per week Hard physical activity (sweating/out of breath): 1 = None 2 = Less than 1 hour per week 3 = 1-2 hours per week 4 = 3 or more hours per week Answer 1 in both questions leads to categorization as frail by this criterion.
Weight Loss	In the last year, have you lost more than 10 pounds unintentionally (not due to dieting or exercise)? The answer yes led to categorization as frail for the weight loss criterion.	Not available
Grip Strength	Measured by Jamar dynamometer (kg) Stratified by sex and BMI quartiles. Lowest 20% were identified, resulting in the following cut-off for the grip strength criterion for frailty: Men: BMI ≤ 24 and grip strength ≤ 29 kg BMI 24.1–26 and grip strength ≤ 30 kg BMI 26.1–28 and grip strength ≤ 30 kg BMI > 28 and grip strength ≤ 32 kg Women: BMI ≤ 23 and grip strength ≤ 17 kg BMI 23.1–26 and grip strength ≤ 17.3 kg BMI 26.1–29 and grip strength ≤ 18 kg BMI > 29 and grip strength ≤ 21 kg	Measured by Martin vigorimeter (bar) Stratified by sex and BMI (≤24, 24.1-26, 26.1-28 or >28). Participants are categorized as frail if they are part of the lowest quintile for grip strength adjusted for sex and BMI.
Walking Speed	Time to walk 15 feet stratified by sex and height (gender-specific cut-off at medium height): Lowest 20% were identified, resulting in the following cut-off for the walking speed criterion for frailty: Men Height ≤ 173 cm and ≥ 7 seconds Height > 173 cm and ≥ 6 seconds Women Height ≤ 159 cm and ≥ 7 seconds Height > 159 cm and ≥ 6 seconds	Measured by Timed-Up-and-Go (TUG) test: Cut-off for TUG ≥15 seconds (not adjusted for height or sex) Participants are categorized as frail, if they needed more than 15 seconds to stand up from a chair, walk a distance of 3 meters, turn, return and sit down again.
Frailty Score	Categorization by sum of present characteristics: 0 = not frail/robust 1-2 = intermediate/pre-frail 3 or more = frail	Categorization by sum of present characteristics: 0 = non-frail 1-2 = pre-frail 3 or more = frail

Table S2. Baseline characteristics by sex. The Tromsø Study 2001-02.

	Women (n=367)	Men (n=345)	p-value§
Age, mean ± SD	77.4 ± 2.3	77.3 ± 2.4	0.632
Frailty phenotype, n (%)			
Non-frail	183 (49.9)	231 (67.0)	<0.001
Pre-frail	168 (45.8)	103 (29.9)	
Frail	16 (4.4)	11 (3.2)	
Education, n (%)			
≤ 7 years	198 (56.3)	124 (37.5)	<0.001
8-12 years	126 (35.8)	163 (49.2)	
>12 years	28 (8.0)	44 (13.3)	
BMI, mean ± SD	27.0 ± 4.4	26.3 ± 3.6	0.022
Daily Smoking, n (%)			
Current Smoker	56 (15.3)	57 (16.6)	0.621
Non-Smoker	311 (84.7)	286 (83.4)	
Disability, n (%)	115 (35.5)	80 (26.6)	0.016
Comorbidity, n (%)	62 (22.6)	64 (22.9)	0.930
Disease, n (%)			
Pulmonary Disease†	64 (17.9)	46 (13.5)	0.108
Cancer	38 (12.9)	47 (15.4)	0.375
Diabetes	34 (9.5)	21 (6.1)	0.097
Stroke	24 (6.7)	32 (9.4)	0.188
CHD‡	77 (21.5)	100 (29.1)	0.021
Peptic Ulcer	29 (10.7)	46 (16.7)	0.041
SMC, n (%)	46 (16.9)	56 (20.1)	0.330

†Including asthma, chronic bronchitis and/or emphysema. ‡Including angina pectoris and/or heart attack.
§p-value: Chi-square test for dichotomous or ordinal variables, t-test for continuous variables.
BMI, Body Mass Index; CHD, Coronary Heart Disease; SMC, Subjective Memory Complaint.

Table S3. Baseline characteristics of participants (70+) with complete and missing data on frailty. The Tromsø Study 2001-02.

	Complete frailty data (n = 712)	Incomplete or missing frailty data (n=1419)	p-value§
Age, mean ± SD	77.42 ± 2.36	74.03 ± 3.16	< 0.001
Sex, n (%)			
Female	367 (51.5)	820 (57.8)	0.006
Male	345 (48.5)	599 (42.2)	
Education, n (%)			
≤ 7 years	322 (47.1)	610 (48.6)	0.587
8-12 years	289 (42.3)	531 (42.3)	
>12 years	72 (10.5)	115 (9.2)	
BMI, mean ± SD	26.6 ± 4.1	26.6 ± 4.3	0.949
Daily Smoking, n (%)			
Current Smoker	113 (15.9)	292 (20.9)	0.006
Non-Smoker	597 (84.1)	1107 (79.1)	
Disability, n (%)	195 (31.2)	308 (28.0)	0.153
Comorbidity, n (%)	126 (22.7)	198 (20.2)	0.253
Disease, n (%)			
Pulmonary Disease†	110 (15.7)	210 (15.3)	0.797
Cancer	85 (14.2)	148 (13.3)	0.597
Diabetes	55 (7.8)	80 (5.8)	0.079
Stroke	56 (8.0)	90 (6.6)	0.245
CHD‡	177 (25.2)	319 (23.1)	0.276
Peptic Ulcer	75 (13.7)	135 (13.7)	0.987
SMC, n (%)	102 (18.5)	158 (14.9)	0.061

†Including asthma, chronic bronchitis and/or emphysema. ‡Including angina pectoris and/or heart attack.
§p-value: Chi-square test for dichotomous or ordinal variables, t-test for continuous variables.
BMI, Body Mass Index; CHD, Coronary Heart Disease; SMC, Subjective Memory Complaint.

Table S4. Hazard Ratios† (95% Confidence Intervals) for all-cause mortality by frailty status at baseline using multiple imputation‡. The Tromsø Study 2001-02.

	All§ (n=712)	Women (n=367)	Men (n=345)	Interaction¶
Non-frail (ref.)	1.0	1.0	1.0	
Pre-frail	1.38 (1.13, 1.69)	1.11 (0.82, 1.51)	1.54 (1.18, 2.01)	0.210
Frail	3.37 (2.15, 5.31)	2.16 (1.18, 3.96)	6.41 (3.20, 12.84)	0.017

†adjusted for age, comorbidity, disability, smoking and education
‡Assuming data was missing at random, multiple imputation was performed to address missing values among the covariates comorbidity, disability, smoking and education. Five hundred duplicate datasets were created to reduce sampling variability from the imputation simulation. Missing values were replaced by imputed values based on the observed information. The imputation model included all variables from the final regression model, including the interaction term between sex and frailty. The Nelson-Aalen cumulative hazard estimator was used as a predictor in the imputation models. Estimates from the five hundred imputed datasets were combined with Rubin's rules to obtain HRs and 95% CIs.
§Additional adjustment for sex.
¶P-value for interaction term between frailty status and sex.