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The frailty phenotype as a predictor of all-cause mortality in community-living individuals aged 65 years and older: The Tromsø Study 2001-2015.

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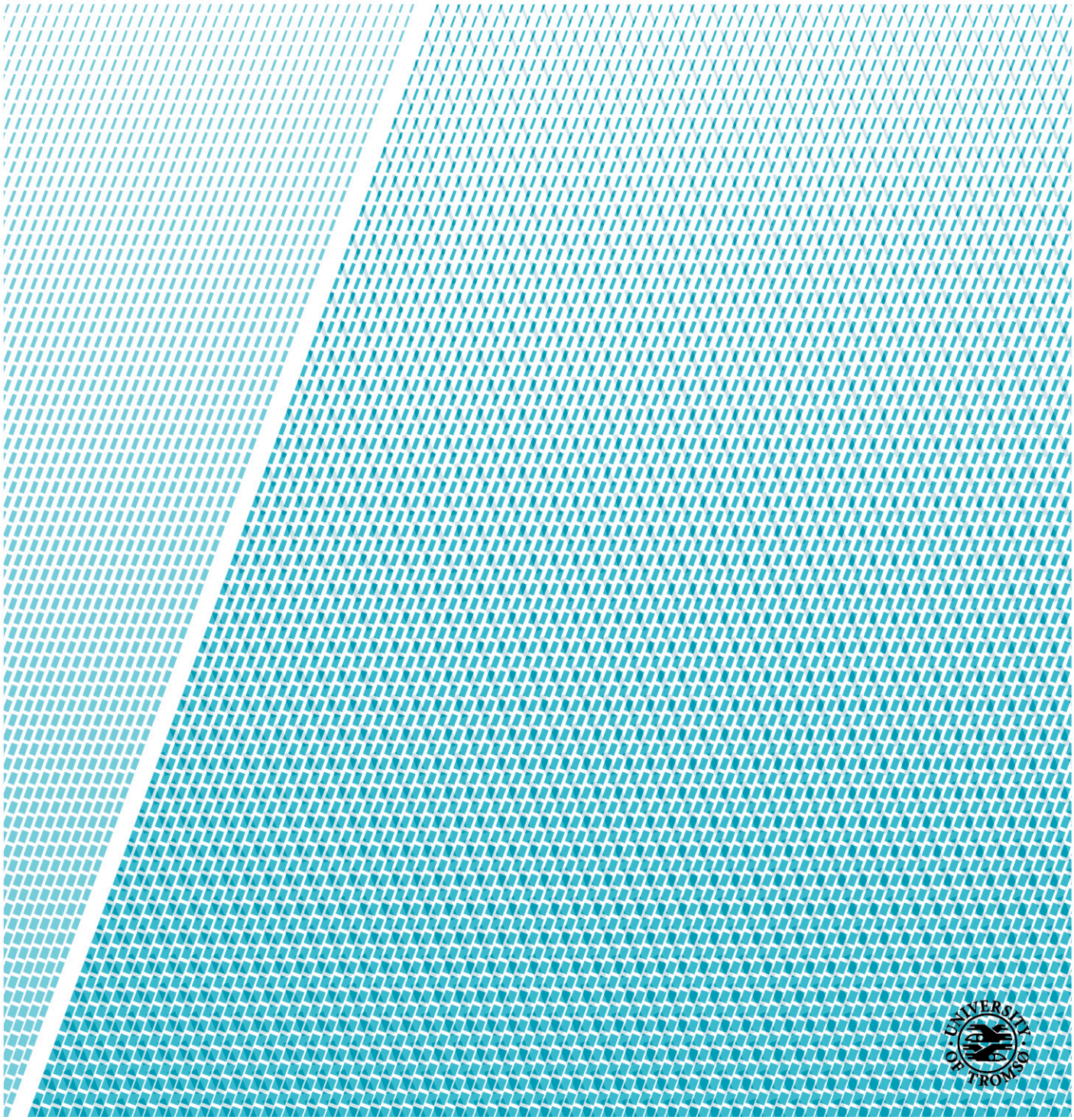

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Abstract

Background: In the light of an aging population, risk factors for adverse outcomes in the elderly constitute an important field of research. Frailty is an age-related syndrome of increased vulnerability to stressors due to declines in several physiologic systems. The aim of this study was to assess the prevalence of frailty and to investigate its ability to predict all-cause mortality in a Norwegian population.

Methods: This prospective cohort study used baseline data from 736 men and women aged 65 years and older in the fifth Tromsø Study (2001-02) to assess the prevalence of frailty, which was defined by a modified version of the frailty phenotype proposed by Fried and colleagues. Participants were followed for all-cause mortality until 31st December 2015. Cox regression models, stratified by sex, were used to analyse the association between frailty and mortality with adjustment for several potential confounders.

Results: The prevalence of frailty and pre-frailty was 3.7% (n=27) and 37.6% (n=277), respectively. With increasing frailty level, individuals displayed a higher prevalence of diseases and disability and were more likely to be older, female and less educated. Multivariate-adjusted hazard ratios indicated an increased risk of mortality in frail men (HR 7.10 (95% CI 3.04,16.61)) and frail women (HR 2.95 (95% CI 1.39,6.26)) compared to non-frail elderly. Pre-frailty showed an overall weaker association with mortality, which was only statistically significant in men.

Conclusion: The frailty prevalence in this Norwegian study sample was lower than previously reported for other countries. Frailty was highly associated with mortality and the findings suggest that the risk might be higher for frail men than frail women.

Abbreviations

ADL	Activities of Daily Living
CCI	Charlson Comorbidity Index
CHD	Coronary Heart Disease
CHS	The Cardiovascular Health Study
FOD-CC	Frailty Operative Definition Consensus Conference
HSCL-10	Hopkins Symptom Checklist - 10
MCAR	Missing completely at random
SHARE	Survey of Health, Aging and Retirement in Europe
SMC	Subjective Memory Complaint
TUG	Timed Up-and-Go (test)
WHO	World Health Organization

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1 Introduction and Framework

1.1 The Aging Society

The constant improvement of health systems, health care, disease prevention and living conditions has led to improved health and well-being as well as significantly longer lives all over the world. The population of people older than 65 in the world is estimated to rise from 461 million in 2004 to 2 billion in 2050 (1).

In Norway, the life expectancy at birth increased from 78.2 for women and 72.0 for men in 1976 to 84.2 and 80.6 in 2016. The gender gap has been decreasing for the last 30 years, but women still live significantly longer than men (2). It is estimated that within the next 30 years the number of people aged 70 years and older will double and in 2060 approximately one in five persons in Norway will belong to that age group. The Norwegian population of people aged 80 years and older is expected to double within the next 20 years (3).

This development of an aging society has considerable impact on the roles of public health and future planning and implementation of health care (1, 4). Measures to improve the quality of life in high ages are becoming more and more important beside the prolongation of life in general (5). Nowadays, many elderly people live in good health until an old age, but uncertainties about future trends remain (4, 6, 7). Increasing lifetime paired with better treatment and chances of survival for conditions like cancer, type 2 diabetes and cardiovascular diseases will likely lead to more people living with chronic illnesses and comorbidities for many years in their later stages of life (7). Thus, preventing or delaying chronic illness and disability through life course approaches as well as assuring access to

adequate health and social care for the elderly is a major public health goal in order to strengthen the ability of older people to actively participate in and contribute to society with good functional status and quality of life (4, 6, 8). Besides the burden of age-related illness and disability for the affected people and their families, the aging society could also represent a challenge for the financial sustainability of the health care and social care systems (9).

Overall, it is therefore important to study and understand the pathways to healthy aging, risk factors for medical conditions specific to advanced age and their associations with adverse health outcomes.

1.2 Frailty

1.2.1 Definition

One important and challenging manifestation of the aging population is the clinical condition of frailty (1). It is one of several complex health states (including urinary incontinence, falls and delirium) that are mostly specific to older age and that cannot be classified as discrete diseases (8). In fact, the term frailty is sometimes used as a loose umbrella term for these geriatric conditions (4) or implies aspects like increased vulnerability, risk of dependence and accelerated aging (5).

Although there is still no universal definition, frailty is now with growing consensus considered a “syndrome of decreased reserve and resistance to stressors” (10) 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, 10-13). For frail individuals this implicates that small changes like a new

medication or a minor illness can lead to a drastic decline in the health status (1). That is why frailty is sometimes considered the starting point of a “vicious circle” (12, 14) or “domino effect” (15).

The exact pathophysiology of frailty is still uncertain, but is thought to be a multifactorial interaction of physiology, lifestyle, environment, genes and disease (16). Increased inflammatory processes, hormonal changes, several cellular and molecular mechanisms related to loss of muscle strength and tissue (sarcopenia) and nutritional changes in the elderly have been discussed as likely components in the development of frailty (5, 14, 17).

1.2.2 Potential for Prevention and Treatment of Frailty

Especially meaningful for the public health sector and clinical practice are the signs that frailty is not an inevitable part of aging, but can be prevented and even reversed, especially in the early stages (4, 12). Due to the understanding that the causes for frailty are multifactorial, an intervention with multidisciplinary approaches could be most promising (9). Pharmacological interventions including hormone therapies as well as nutritional interventions are investigated regarding their potential efficacy in preventing or treating frailty, but no sufficient evidence is available yet (5, 14). Furthermore, the importance of social activities and engagement of older adults for the prevention of functional decline and mortality is also scientifically investigated and discussed (18, 19). So far, the clearest evidence is available for the positive effect of physical activity. Namely, consistent activity throughout life was shown to have the potential to prevent frailty (5). Exercise training or physical therapy may also be effective in secondary prevention, aimed at stopping or delaying further functional decline in already frail individuals. However, preventive action

should be taken as early as possible, before frailty develops into an irreversible state of disability (14, 20).

1.2.3 The Frailty Phenotype

Connected to the scientific discourse on the potential causes and prevention of frailty is the fundamental question of how frailty can be adequately measured in clinical practice and research. The "Frailty Operative Definition Consensus Conference" (FOD-CC) aimed at finding consensus in 2011, but no agreement about the specific clinical and laboratory biomarkers needed for the identification of frailty could be reached (13). So far, there is no gold standard for an operational definition.

However, two approaches have been validated and utilized most frequently: a frailty index and a frailty phenotype (5). The two approaches identify only partially overlapping frail populations and differ in their predictive ability with regard to various adverse health outcomes (9, 21). Among others, Rockwood and colleagues proposed the frailty index, which measures the number of prevalent deficits in an individual, including diseases and their severity, ability in daily activities as well as physical and neurological features from clinical examinations as a proportion of all considered variables (22). The frailty index was shown to have a high ability to predict adverse outcomes (14, 22).

For the present study, the focus will be on the second frequently used assessment tool: the frailty phenotype suggested by Linda Fried and colleagues in 2001 (10). Fried et al. used data of men and women aged 65 years and older from the prospective Cardiovascular Health Study (CHS) in 1989-90 in the USA. Based on the scientific understanding, that frailty is characterized by the co-occurrence of several factors like decline in lean body mass,

strength, endurance, activity and gait performance, the researchers defined frailty as the presence of three or more of the following characteristics: shrinking (unintentional weight loss), weakness (low grip strength), poor endurance/energy (exhaustion), slowness (low walking speed) and low physical activity (for details of the assessment see Table 1.). The presence of one or two characteristics was considered a hypothetically intermediate or pre-frail state and those individuals with no present characteristic were classified as robust. In their study, this phenotype was predictive of falls, functional decline, hospitalization and death (10).

Since then, the frailty phenotype has been used and tested in numerous studies with different degrees of modification (e.g. 23, 24, 25). Theou et al. conducted a systematic review of 264 studies that used the Fried criteria and found that modification of the frailty phenotype had a considerable effect on frailty identification and predictive abilities among other things. Thus, they stressed the importance of transparency in future studies with regard to how the frailty criteria are measured (26).

One of the repeated criticisms of the frailty phenotype is the omission of any cognitive or psychological measure (e.g. 27, 28). The statement that “mental health assessment and cognitive status evaluation are highly recommended as part of the assessment of frailty” found strong agreement at the FOD-CC in 2011 (13). On the other hand, the frailty phenotype has been considered more practical in clinical settings compared to other assessment tools, due to the relatively small number of components (12). Furthermore, it might be better at capturing the “nature of frailty” with an own discrete pathophysiology (14). This impression could be due to the fact that one important aspect of the frailty phenotype is the differentiation between frailty, disability and comorbidity.

While models like the frailty index include disability and comorbidity in their frailty measures, Fried et al. highlighted that these three conditions are distinct from one another, but often coincide (29). Disability is commonly defined as having difficulty or restriction in the performance of activities of daily living or the need for assistance in these activities (5, 17, 29). In advanced age, disability is mostly a consequence of diseases and age-related physiologic changes influenced by social and behavioural factors. It develops either progressively in connection with the severity of present diseases and comorbidities or suddenly as the result of a single event like a stroke (29, 30). Two components differentiate disability from frailty: the concept of frailty always assumes the accumulation of impairments in *multiple* systems, while disability can be caused by dysfunction in only one system (or more). Secondly, disability does not necessarily imply general vulnerability and instability compared to frailty (5, 29).

According to Fried et al. the difference between comorbidity and frailty is that comorbidity is defined as the coexistence or aggregation of two or more *diagnosed* diseases, whereas frailty is rather understood as the aggregation of several *subclinical* impairments (29). In the CHS, they found that frailty was more strongly associated with comorbidity than with any single disease (10).

Fried and colleagues showed that there is considerable overlap between the three concepts due to many possible causal relationships between them. Frailty could be caused by a disease or comorbidity or could be a promoting factor in the development of chronic diseases. Disability may be a consequence of or a risk factor for frailty and comorbidity. However, all these conditions can seemingly be present individually without the others (13,

29). Inevitably, the relationship of frailty, comorbidity and disability remains unclear, until there is a better understanding of the pathogenesis of frailty (14).

1.2.4 Prevalence of Frailty

The estimation of prevalence is highly tentative, as the identification of frailty is strongly influenced by varying definitions and operationalizations (9, 29, 31). A systematic review of 21 studies of frailty prevalence in community-dwelling persons aged 65 years and older found that the reported prevalence of frailty ranged from 4.0% up to 59.1%. In studies using the frailty phenotype, prevalence was consistently lower, but still varied from 4.0% to 17.0%. Here, the weighted average (by study size) was 9.9% for frailty and 44.2% for pre-frailty (31). In the initial study by Fried et al., 6.9% of the participants were identified as frail and 46.6% were pre-frail. Usually, frailty is more prevalent in women, which could be explained by the longer life expectancy and a lower average lean body mass (10, 31). Furthermore, women are more often affected by chronic diseases that influence physical functioning, whereas men are often struck by immediately fatal diseases (32).

With increasing frailty status (i.e. non-frail, pre-frail, frail), people are more likely to be older, less educated and poorer. In studies which assessed ethnicity, the group of African-Americans often showed the highest frailty prevalence (10, 33, 34). Moreover, chronic diseases, comorbidity and disability are more prevalent in the frail (10, 24). A study by Santos-Eggimann et al. from 2009 used data from the Survey of Health, Aging and Retirement in Europe (SHARE) and found that frailty (using the phenotype criteria) was more prevalent in southern than in northern European countries (35).

1.2.5 Frailty and Mortality

Beside other established adverse outcomes for frailty like disability, falls, institutionalization and hospitalization (10, 23, 36, 37), mortality among frail elderly persons has been investigated in several studies (e.g. 22, 28, 38). A systematic literature review found that in studies using the frailty phenotype, frailty was on average associated with a 50% increased risk of mortality (33). In the study by Fried and colleagues, frailty at baseline was an independent predictor of mortality with 7-year covariate-adjusted hazard ratios (95% confidence interval) of 1.63 (1.27,2.08) for the frail and 1.32 (1.13,1.55) for the pre-frail group compared to those who were non-frail at baseline (10).

When it comes to sex differences, the findings are discordant. Some studies show a higher risk of mortality for women (28, 39). On the other hand, a study on seven different types of frailty scales found that - independent of which scale was used for the assessment of frailty - women showed better survival than men, even though they had higher frailty scores (40).

Functioning in general has received increasing attention as a predictor of adverse outcomes. Lordos et al. showed that the assessment of functional independence was more predictive of survival of 1951 hospitalized patients than the number of diseases they had (41). Furthermore, not just frailty as a phenotype or an accumulation of deficits (index), but also single components of frailty like grip strength and gait speed have been investigated and shown to be predictive of mortality (e.g. 42, 43). Rothman et al. investigated the predictive ability of potential markers for frailty and found that among the Fried criteria slow gait speed, low physical activity and weight loss were independent predictors of death (27).

1.3 Aim of the Study

Rationale

In the light of an aging population, the focus on age-related health problems and risk factors for adverse outcomes in the elderly is an important field in public health policy and research. Frailty is one of these age-related conditions, which leads to serious health consequences for the individual as well as societal costs. Therefore, the analysis of frailty prevalence and the association between frailty and adverse outcomes like mortality is important. Although the association between frailty status and mortality is scientifically well established, there is a lack of data on frailty prevalence and studies of the association between frailty and mortality in a general Norwegian population.

Objectives

The aim of the present study is to (1.) assess the prevalence of frailty following the operative definition of the frailty phenotype by Fried and colleagues and to (2.) investigate the ability of the frailty phenotype and its single markers to predict all-cause mortality among community-dwelling individuals aged 65 years and older in a general Norwegian population using a prospective cohort design.

2 Material and Methods

2.1 Study Design and Population

The Tromsø Study is an epidemiological population-based study in Tromsø, a municipality in Northern Norway with close to 75 000 inhabitants. The first Tromsø Study was initiated in 1974 (Tromsø 1) with a special focus on cardiovascular disease and risk factors in men due to high cardiovascular mortality. Since then, the study has been gradually expanded to include a broader range of diseases and was repeated with new and former participants in 1979, 1986-87, 1994-95, 2001-02, 2007-08 and 2015-16 (Tromsø 2-7). The study involves extensive questionnaires as well as physical examinations and blood samples. In the last four surveys a predefined group of participants was asked to join a second, more extensive examination, when attending the first examination (44, 45).

The present analysis uses a prospective design with baseline data from the fifth survey from 2001-02 (Tromsø 5). Men and women living in Tromsø, who had participated in the second examination of the fourth survey and random samples in the age groups 30, 40, 45, 60 and 75 in the year 2001, were eligible to participate in the fifth Tromsø Study. A total of 10 353 people were invited and 8130 (79%) attended (44).

This study includes all participants from Tromsø 5 aged 65 years and older at baseline (in accordance with the age threshold used in the initial study by Fried et al. 2001), who had available data on the frailty criteria described in the following (n = 736). The flow diagram (Figure 1) shows the inclusion and exclusion process for this study sample.

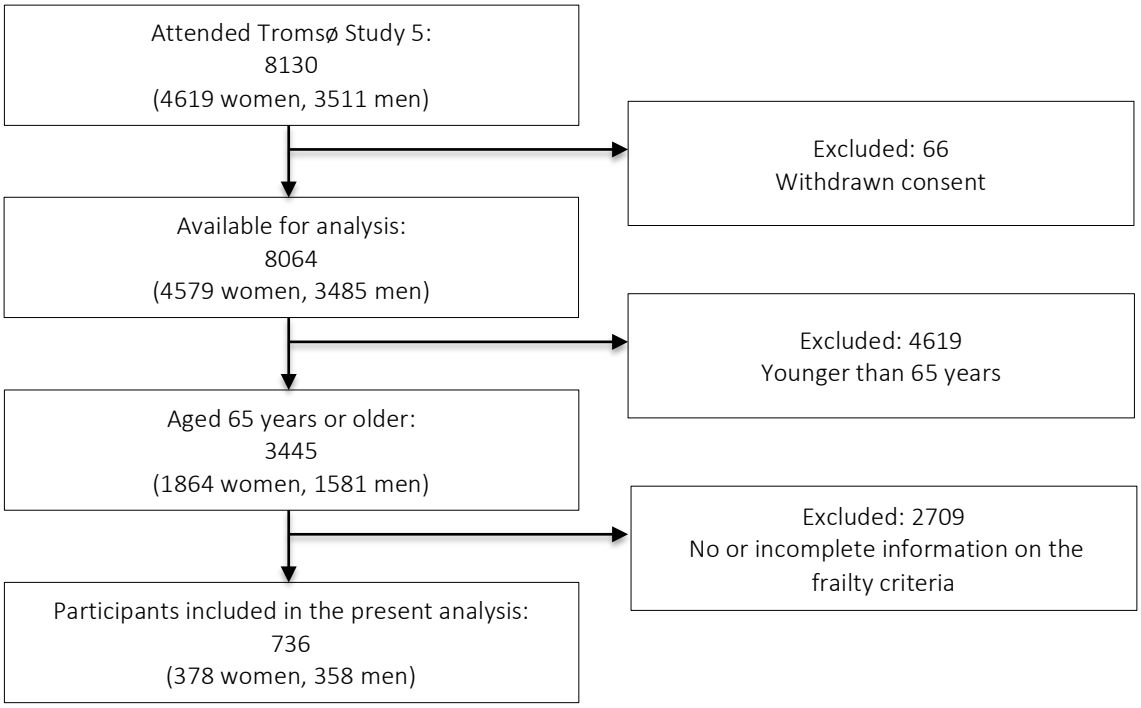

Figure 1. Flow diagram demonstrating inclusion and exclusion of participants for the analysis.

2.2 Measurement of Frailty in the Study

In this study, frailty was defined according to the frailty phenotype by Fried and colleagues (10). The physical activity level and exhaustion was assessed through self-report (questionnaire), while walking speed and grip strength was measured through physical function tests. Information about unintentional weight loss was not available in Tromsø 5. The questionnaire was part of the first examination (total sample of Tromsø 5), while the physical function tests were part of the second examination of a subsample. Table 1 presents the details of the modifications of the frailty phenotype made in the present study compared to the original criteria by Fried and colleagues. In the following, each of the frailty score items and their contribution to the score (0 or 1) is presented. Participants with no present characteristic (0 in total) were considered non-frail, those with one or two as intermediate/pre-frail and those with three or more present characteristics were considered frail.

Table 1. Modification of the frailty phenotype in the Tromsø Study 2001-15.

	Criteria for frailty by Fried et al. 2001	**Criteria for frailty in the Tromsø Study 2001-02**
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 = not frail 1-2 = intermediate/pre-frail 3 or more = frail

2.2.1 Self-report: Exhaustion and Physical Activity

Exhaustion and physical activity level were assessed through questionnaire data. The Tromsø 5 questionnaire Q1 was slightly different for participants under 70 years and participants 70 years and older. However, questions about exhaustion and physical activity levels were identical in both questionnaires.

Exhaustion was assessed through one item in the Hopkins Symptom Checklist 10 (HSCL-10) included in the Q1 questionnaire. The HSCL is a commonly used scale to measure psychological distress like anxiety and depression in population surveys (46) and the 10-item version has been shown to measure mental health problems almost as well as more complex versions (47). Among different questions on emotional states, it contains the following item regarding exhaustion: "Have you experienced any of this the last week: […] That everything is a struggle?". The four response categories are "No complaint", "Little complaint", "Pretty much" and "Very much". For this study, participants who answered "Pretty much" or "Very much" were considered frail by this criterion, contributing with 1 point to the frailty score.

Questions regarding physical activity levels ("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.") were divided into two sections: "Light activity (not sweating/out of breath)" and "Hard physical activity (sweating/out of breath)" with four response categories each ("None", "Less than 1 hour per week", "1-2 hours per week", "3 or more hours per week"). For this study, participants who answered "None" in both questions were considered frail by this criterion, contributing with 1 point to the frailty score.

2.2.2 Timed Up and Go Test

Walking speed was assessed by the Timed Up and Go (TUG) test, which is a test of mobility and balance. The time for the test person to rise from a chair, walk three meters, turn around, walk back to the chair and sit down is recorded (48, 49). In Tromsø 5, the participants were instructed to perform the test with footwear and could use the chair's armrests as support, if needed. TUG test cut-offs for normal mobility vary from <20 seconds (50) to <16, <15, <12 and <10 seconds (51). For this study, the cut-off was set to 15 seconds, which is the middle ground of the various cut-points and has previously been shown to be the preferred threshold for prediction of falls (49, 52). Participants who performed the TUG test and needed 15 seconds or more were considered frail by this criterion, contributing with 1 point to the frailty score. No adjustments for age or sex were made.

2.2.3 Grip Strength

Grip strength in Tromsø 5 was measured using a Martin vigorimeter. This is a dynamometer with an air-filled rubber bulb, which has to be squeezed by the test person. The pressure is registered by a pointer on the dial of a manometer, measured in bar. A comparison study of the Martin vigorimeter and the Jamar dynamometer showed high correlation (53). In Tromsø 5, the participants were instructed to use their non-dominant hand, not support their arm against anything (neither their body) and squeeze as hard as they could. The test was repeated once after the first. The test results were converted to kPa (to be comparable with Jamar dynamometer; conversion factor: 100) before the results were divided into 5 centiles adjusted for sex and BMI-group (≤24, 24.1-26, 26.1-28 and >28). Participants in the lowest centile (the weakest 20%) were considered frail by this criterion, contributing with 1 point to the frailty score. This lowest-quintile approach follows the identification of low grip

strength in the initial study by Fried and colleagues (10) and has previously been shown to have high agreement with population-independent cut points for the Fried criteria (54).

2.3 Covariates

In this analysis, age is included as a likely confounder, because both frailty and mortality increase with age. Due to previous findings that show different strengths of association between frailty and mortality for men and women (40), sex is expected to be an effect modifier.

Both comorbidity and disability are associated with frailty and mortality and are therefore considered potential confounders in the study. They are especially relevant covariates as a result of the conceptual framework by Fried and colleagues, which aims at identifying and analysing frailty as a syndrome independent of these conditions (29). Comorbidity was defined as the presence of two or more of the following diseases at baseline (reported in two questionnaires with identical questions for participants younger than 70 years and 70 years or older): pulmonary disease (asthma/chronic bronchitis/emphysema), cancer, diabetes, stroke, coronary heart disease (angina pectoris and/or heart attack) and peptic ulcer. This definition of comorbidity was based on the diseases used in the Charlson Comorbidity Index (CCI) (55) without weighting of diseases. Chaudhry et al. found that a self-reported comorbidity index can compare to CCIs derived from administrative data and suggested that it can be useful for comorbidity risk adjustment when objective data is not available (56). The comorbidity measure in the present analysis is slightly compromised by the fact that the questions in the questionnaire also included previous disease ("Do you or did you have…"). Disability was defined by having difficulties performing everyday activities

(reported in the first questionnaire for participants 70 years or older - hence, there is no information on disability for the 65 to 69-year-olds in the sample). The wording of the questions were “Due to chronic health problems, do you have difficulties with”; 1) “Mobility inside your own home?”, 2) “To move out of your own home without assistance?”, 3) “Participation in leisure-time activities?”, 4) “Using public transport?” or 5) “Performing necessary daily errands?” with three response categories (“No difficulties”, “Some difficulties”, “Great difficulties”). For this study, participants reporting “Some difficulties” or “Great difficulties” in one or more daily activities were considered disabled.

Furthermore, smoking status (current daily smoker or non-smoker at baseline) was included as a potential confounder. The strong association between smoking and mortality is well-established, but smoking has also been shown to be predictive of frailty (4, 57). Education was included as a covariate, because higher education is generally associated with better health and longer life expectancy (4, 7). As previously done for the age group 65 years and older in the Tromsø Study (42), years of education were grouped into primary school (7 years), high school (8-12 years) and university college/university (13+ years) in accordance with the Norwegian school system before 1969 (58). Alcohol was considered as a covariate, but the available variables on alcohol consumption did not capture abuse very well, which would have been most relevant as a confounder for the present study. Moreover, Fried and colleagues as well as other studies on frailty and mortality did not adjust for alcohol consumption (10, 22, 28). Subjective memory complaints (SMC), which are associated with an increased risk for cognitive decline (59, 60), were assessed in the Tromsø Study. However, SMC were not included in the present analysis, because they are not considered a confounder, but rather a component of the frailty phenotype (27, 61), which is disregarded

by the Fried criteria. Nevertheless, potential differences in prevalence of SMC between frail and non-frail participants were examined on the basis of one broad item ("If memory problems, is it a problem in your daily life?").

2.4 Endpoint and Follow-up

The data from the Tromsø Study was linked to the Norwegian Cause of Death Registry with available death certificate data for each participant. The study participants were followed for all-cause mortality from study entrance (examination date in the survey) until 31st of December 2015, death or emigration, whichever came first. None of the included participants emigrated from Norway during follow-up.

2.5 Statistical Analysis

Descriptive statistics were used to assess the prevalence of frailty and to compare selected characteristics between non-frail, intermediate and frail participants. Whether these differences were significant was evaluated by chi-square tests for categorical variables and univariate linear regression for continuous variables.

Cox regression was used to calculate hazard ratios with 95% confidence intervals for analysis of the association between frailty at baseline and all-cause mortality. The number of days from the date of examination up until the day of death or end of study - whichever came first - was used as the time-scale. Age was taken into consideration as a time-scale, but due to the lack of information on the exact age of participants at study entry (only given in total years in the available data set), time in study was chosen as the time-scale to avoid loss of information.

Possible effect modification was investigated through the use of interaction terms in the regression analysis. A significant interaction term between sex and the “frail” level of the frailty score (with non-frail as reference) confirmed that sex is an effect modifier in this study. Accordingly, separate analyses were performed for men and women.

In addition to the ordinal frailty score, a binary frailty variable as an alternative predictor was created by combining the intermediate and frail level of the score. This binary variable was initially created due to the small number of frail people in the study sample, but offered the opportunity to additionally investigate the abilities of a predictor with a lower threshold for frailty identification. So in this dichotomized variable, every participant with one or more present characteristics was considered frail. In a third step, the four frailty characteristics (i.e. exhaustion, physical activity, grip strength and walking speed) were used as four independent variables to investigate each single item’s ability to predict mortality. All analyses were run in three regression models, and were split by sex. The first model adjusted for age, the second for age, disability and comorbidity and the last model also included smoking and education as covariates.

Lastly, the joint effect of frailty and disability as well as frailty and comorbidity on mortality was investigated using a combined score of the binary frailty variable with disability and comorbidity respectively. The participants were grouped into the following categories: 1) frail and disabled/comorbid, 2) frail, but not disabled/comorbid, 3) not frail, but disabled/comorbid and 4) not frail and not disabled/comorbid, which was used as the reference group.

The log−log plot was examined for the total sample as well as men and women separately to check the proportional hazards assumption. No violation of this assumption was detected. All statistical analyses were performed using IBM SPSS Statistics (Version 24).

2.6 Ethics

The Tromsø Study has been approved by The Regional Committee of Medical and Health Research Ethics (REC North) and the Norwegian Data Protection Authority and performed in accordance with the 1964 Helsinki declaration and its later amendments. The participants of Tromsø 5 have given written informed consent.

3 Results

3.1 Baseline Characteristics

Out of the 736 participants, 378 were female and 358 were male. The mean age was 77 (SD ± 3) years ranging from 65 to 87 years. The majority of participants were 74 to 81 years old (n = 686). According to the modified frailty phenotype, 3.7% of study participants were frail (n=27), 37.6% were pre-frail and 58.7% were non-frail (Table 2). The prevalence of frailty was highest in the age group 80-84 years (8.4%), followed by ages 75-79 (2.7%) and 70-74 years (2.0%). The number of participants in the lowest and especially in the highest age group was very low and none of them were classified as frail. Frailty as well as intermediate frailty was more prevalent in women than in men. A proportion of 4.2% of women and 3.1% of men were frail, while 45.8% of women and 29.1% of men were pre-frail.

Table 2. Prevalence of frailty by age groups. The Tromsø Study 2001-15.

	65-69 (n=24)	70-74 (n=49)	75-79 (n=517)	80-84 (n=143)	85-89 (n=3)	Total (n=736)
Not Frail	18 (75.0)	35 (71.4)	304 (58.8)	74 (51.7)	1 (33.3)	432 (58.7)
Intermediate	6 (25.0)	13 (26.5)	199 (38.5)	57 (39.9)	2 (66.7)	277 (37.6)
Frail	0	1 (2.0)	14 (2.7)	12 (8.4)	0	27 (3.7)

Among the single frailty markers (Table 3), low walking speed was most prevalent (19.3%) followed by low grip strength (18.3%) and low physical activity level (13.2%). Only 6.7% of the participants reported exhaustion. In accordance with the higher overall frailty prevalence in women, all single frailty markers occurred more often in women than in men.

Table 3. Prevalence of the single frailty criteria at baseline. The Tromsø Study 2001-15.

	Women and Men (n = 736)	Women (n = 378)	Men (n = 358)
Exhaustion, n (%)	49 (6.7)	38 (10.1)	11 (3.1)
Low physical activity, n (%)	97 (13.2)	65 (17.2)	32 (8.9)
Low grip strength, n (%)	135 (18.3)	75 (19.8)	60 (16.8)
Low walking speed, n (%)	142 (19.3)	91 (24.1)	51 (14.2)

At baseline, frail participants differed from pre-frail and non-frail participants with regard to various characteristics (Table 4). With increasing frailty status participants were more likely to be older and less educated. Frail participants also had a higher mean BMI (27.6 ± 6.2) than pre-frail (26.9 ± 4.3) or non-frail (26.5 ± 3.7) participants, although the standard deviation indicates that there was also the strongest variation in BMI among those who were classified as frail. A quarter of the frail cohort reported to be current daily smokers compared to 18.4% and 14.2% of the pre-frail and non-frail group, respectively. However, the association between smoking status and frailty status was not statistically significant. Furthermore, those who were classified as frail were more likely to report that memory problems affect their daily life (SMC).

There was also a stepwise increase in comorbidity and disability with increasing frailty status. Almost all frail individuals reported disability (91.7%), compared to 46.8% of the pre-frail and 17.2% of the frail. A proportion of 15.5% of the non-frail, 28.5% of the pre-frail and 61.9% of the frail participants reported comorbidity. Both disability and comorbidity were more prevalent in women (92.3% vs. 90.9% disability among frail women and men; 64.3% vs. 57.1% comorbidity among frail women and men, respectively). All included diseases except for cancer were most prevalent among the frail.

Table 4. Baseline characteristics by frailty status. The Tromsø Study 2001-15.

Factor	Total (n = 736)	Not Frail (n = 432)	Intermediate (n = 277)	Frail (n = 27)	p-value
Age, mean ± SD	77.0 ± 3.0	76.7 ± 3.1	77.4 ± 2.7	78.1 ± 2.7	< 0.001
Sex, n (%)					
Female	378 (51.4)	189 (43.8)	173 (62.5)	16 (59.3)	< 0.001
Male	358 (48.6)	243 (56.3)	104 (37.5)	11 (40.7)	
Education, n (%)					
≤ 7	332 (47.0)	164 (39.7)	150 (56.4)	18 (66.7)	< 0.001
8-12	300 (42.5)	193 (46.7)	99 (37.2)	8 (29.6)	
>12	74 (10.5)	56 (13.6)	17 (6.4)	1 (3.7)	
BMI, mean ± SD	26.7 ± 4.1	26.5 ± 3.7	26.9 ± 4.3	27.6 ± 6.2	0.055
Daily Smoking, n (%)					
Current	119 (16.2)	61 (14.2)	51 (18.4)	7 (25.9)	0.097
Former	349 (47.5)	221 (51.4)	118 (42.6)	10 (37.0)	
Never	266 (36.2)	148 (34.4)	108 (39.0)	10 (37.0)	
Disability, n (%)	195 (31.2)	63 (17.2)	110 (46.8)	22 (91.7)	< 0.001
Disease, n (%)					
Pulmonary Disease*	112 (15.5)	57 (13.5)	48 (17.5)	7 (25.9)	0.110
Cancer (ever)	85 (13.7)	55 (14.7)	28 (12.1)	2 (11.8)	0.650
Diabetes	56 (7.7)	25 (5.9)	23 (8.4)	8 (29.6)	< 0.001
Stroke	56 (7.8)	18 (4.3)	27 (9.9)	11 (40.7)	< 0.001
CHD**	181 (24.9)	83 (19.4)	85 (31.3)	13 (48.1)	< 0.001
Peptic Ulcer	76 (13.4)	39 (11.3)	34 (16.4)	3 (20.0)	0.169
Comorbidity, n (%)	127 (22.0)	53 (15.5)	61 (28.5)	13 (61.9)	< 0.001
Subjective Memory Complaint, n (%)	105 (18.4)	51 (15.1)	48 (22.2)	6 (35.3)	0.020

*Asthma/ Chronic Bronchitis/ Emphysema
** Coronary heart disease: angina pectoris and/or heart attack
p-value: Chi-square test for dichotomous or ordinal variables, linear regression for continuous variables.

Frailty as a dichotomized variable (combined intermediate and frail level) yielded a prevalence of 41.3% (50% for women, 32.1% for men). Figure 1 shows the overlap of this frailty variable with disability and comorbidity among those participants who had at least one of the three conditions (n = 292). A proportion of 22.4% of those who were frail reported both disability and comorbidity. Further, 27.8% were disabled and frail, 8.8% were comorbid and frail and 41% were only classified as frail.

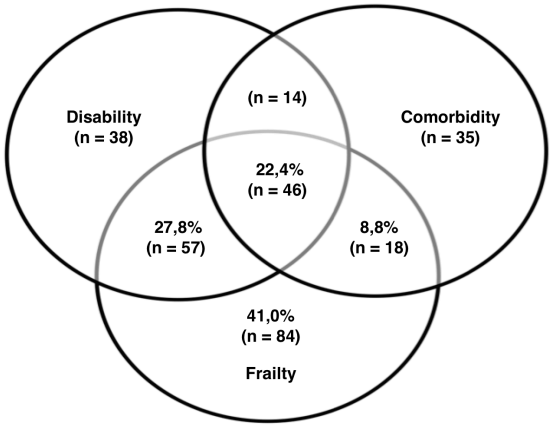

Figure 2. Venn diagram of the overlap between frailty (including pre-frailty), comorbidity and disability in the sample (following the example of Fried et al. 2001). The Tromsø Study 2001-15.

3.2 Survival

Out of the 736 participants, 508 died during follow-up (69%); 230 women (60.8%) and 278 men (77.7%). Women had a median survival of 4606 days, whereas half of the men had died after 3609 days (Table 5). Among the frail, the median survival time was 2151 and 1028 days for women and men, respectively. For both sexes, the percentage of individuals alive at study end, as well as the median survival time, decreased with increasing frailty status. The mortality in men was considerably higher compared to women irrespective of the frailty status.

Table 5. Survival status at follow-up and median survival by sex and frailty status. The Tromsø Study 2001-15.

	Women			Men		
	Alive	Dead	Median survival (days)	Alive	Dead	Median survival (days)
Not Frail	89 (47.1)	100 (52.9)	5033	70 (28.8)	173 (71.2)	4218
Intermediate	58 (33.5)	115 (66.5)	4422	10 (9.6)	94 (90.4)	2751
Frail	1 (6.3)	15 (93.8)	2151	0	11 (100)	1028
Total	148 (39.2)	230 (60.8)	4606	80 (22.3)	278 (77.7)	3609

3.2.1 Frailty Status and Mortality

In three Cox regression models, the association between frailty and mortality was assessed for women and men. The sample size varied between the models due to missing data on the covariates. Hazard ratios with 95% confidence intervals for all-cause mortality are displayed in Table 6, firstly for participants classified as pre-frail/intermediate and frail relative to those who were not frail and secondly for the combined frailty group (intermediate and frail together) compared to those who were not frail.

Table 6. Hazard Ratios (95% CI) for all-cause mortality by two types of frailty measures for women and men. The Tromsø Study 2001-15.

	Model A (n=736)		Model B (n=497)		Model C (n=481)	
	Women (n = 378)	Men (n = 358)	Women (n = 245)	Men (n = 252)	Women (n = 235)	Men (n = 246)
Not Frail (reference)	1.0	1.0	1.0	1.0	1.0	1.0
Intermediate	1.37 (1.04, 1.79)	1.80 (1.40, 2.33)	1.24 (0.87, 1.77)	1.68 (1.23, 2.28)	1.15 (0.78, 1.70)	1.65 (1.21, 2.25)
Frail	3.42 (1.97, 5.95)	8.11 (4.27, 15.42)	3.38 (1.61, 7.09)	6.73 (2.94, 15.44)	2.95 (1.39, 6.26)	7.10 (3.04, 16.61)
Frail*	1.46 (1.12, 1.90)	1.94 (1.51, 2.48)	1.29 (0.90, 1.83)	1.76 (1.30, 2.38)	1.20 (0.82, 1.77)	1.74 (1.28, 2.35)

*Binary variable: Individuals were defined as frail, if one or more of the assessed frailty characteristics were present at baseline.
Model A = adjusted for age
Model B = adjusted for age, comorbidity and disability
Model C = adjusted for age, comorbidity, disability, smoking and education

In the age-adjusted model, frail women had a 3.42 higher risk of death compared to those who were not frail (CI 1.97,5.95). After adjusting for comorbidity and disability in the second model and for smoking and education additionally in the third model, the risk of death decreased but remained statistically significant (HR 3.38 (CI 1.61,7.09) and HR 2.95 (CI 1.39,6.26), respectively). For frail men, the risk of death was 8.11 times higher compared to those who were not frail when adjusted for age (CI 4.27,15.42), 6.73 times higher when adjusted for age, disability and comorbidity (CI 2.94,15.44) and 7.10 times higher in the fully

adjusted model including education and smoking (CI 3.04,16.61). Intermediate frailty also significantly predicted death for women (HR 1.37 (CI 1.04,1.79)) and men (HR 1.80 (CI 1.40,2.33)) relative to the non-frail after adjustment for age, although the hazard ratios were consistently lower than those of the frail group. In the further adjusted models, pre-frailty remained a statistically significant predictor of death for men, but not for women. Figure 3 displays the fully adjusted survival curves for the non-frail, intermediate and frail group stratified by sex.

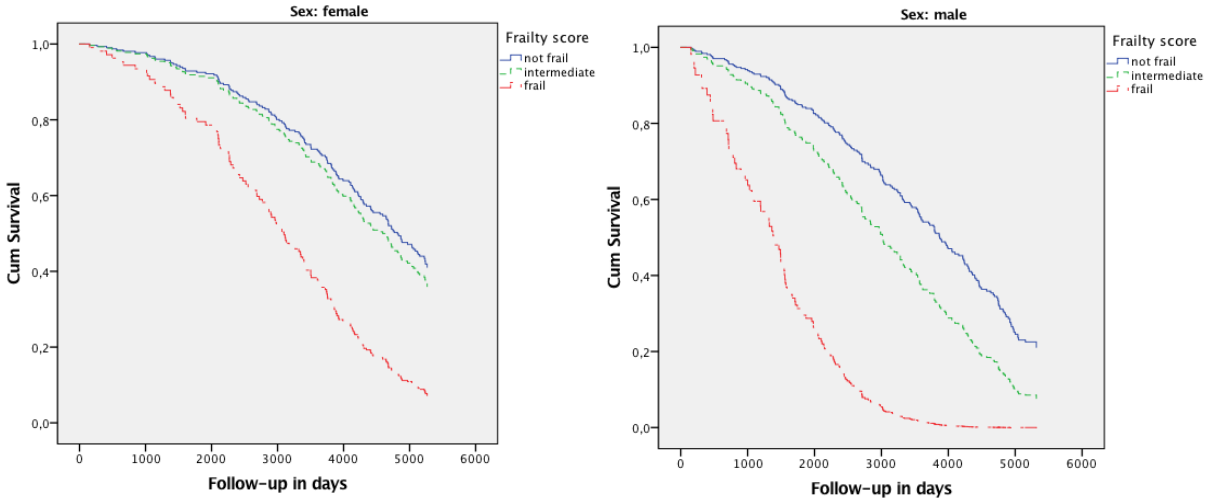

Figure 3. Survival curves according to frailty score for women and men adjusted for age, comorbidity, disability, smoking and education. The Tromsø Study 2001-15.

The dichotomized frailty variable was a significant predictor of mortality for men in all models with hazard ratios from 1.94 (CI 1.51,2.48) adjusted for age to 1.74 (CI 1.28,2.35) in the fully adjusted model. For women, this variable was only able to significantly predict mortality in the age-adjusted model with a hazard ratio of 1.46 (CI 1.12,1.90).

3.2.2 Frailty Markers and Mortality

The same regression models were used to assess the ability of each single frailty marker to independently predict all-cause mortality. Table 7 shows hazard ratios with 95% confidence interval for exhaustion, low physical activity, low grip strength and low walking speed (adjusted for each other). Men had consistently higher hazard ratios for all criteria compared to women. In the age-adjusted model, exhaustion, physical activity and low walking speed predicted mortality significantly for women with approximately 50% increased risk. After adjustment, only low physical activity remained a statistically significant predictor for mortality in women with a hazard ratio of 1.80 (CI 1.19,2.73). For men, all four frailty markers predicted mortality significantly after age-adjustment. In the fully adjusted model, low physical activity (HR 2.50 (CI 1.47,4.23)) and low grip strength (HR 1.47 (CI 1.00,2.17)) remained statistically significant predictors.

Table 7. Hazard Ratios (95% CI) for all-cause mortality by single frailty criteria for women and men. The Tromsø Study 2001-15.

	Model A (n=736)		Model B (n=497)		Model C (n=481)	
	Women	Men	Women	Men	Women	Men
Exhaustion	1.50 (1.00, 2.23)	3.21 (1.73, 5.96)	1.23 (0.71, 2.13)	1.99 (0.83, 4.81)	1.21 (0.70, 2.12)	2.00 (0.81, 4.93)
Low physical activity	1.54 (1.12, 2.13)	2.26 (1.52, 3.35)	2.05 (1.38, 3.04)	2.20 (1.35, 3.60)	1.80 (1.19, 2.73)	2.50 (1.47, 4.23)
Low grip strength	1.25 (0.91, 1.72)	1.50 (1.09, 2.07)	1.18 (0.78, 1.78)	1.52 (1.03, 2.23)	1.16 (0.76, 1.77)	1.47 (1.00, 2.17)
Low walking speed	1.46 (1.09, 1.96)	1.57 (1.12, 2.19)	1.10 (0.75, 1.62)	1.44 (0.96, 2.17)	1.21 (0.81, 1.81)	1.37 (0.91, 2.08)

Model A = adjusted for age
Model B = adjusted for age, comorbidity and disability
Model C = adjusted for age, comorbidity, disability, smoking and education
Note: All single frailty characteristics are adjusted for each other.

3.2.3 Combined Analyses

The joint effect of frailty and disability as well as frailty and comorbidity on mortality was examined for women and men, together and separately, in a Cox regression model adjusted for age, smoking, education and comorbidity or disability, respectively (Tables 8 and 9). The dichotomized frailty variable was used for these combined scores, and the group of participants with neither frailty nor disability and neither frailty nor comorbidity, respectively, were used as the reference group.

A linear trend was observed for the joint effect of frailty and disability on mortality. Individuals who were both frail and disabled had a 2.13 (CI 1.58,2.87) times higher mortality risk than those who were neither frail nor disabled. When stratified by sex, women had no statistically significant increased risk compared to the reference group. In men, frailty and disability was highly associated with mortality (HR 2.75 (CI 1.83,4.12)), as well as frailty and non-disability (HR 1.63 (CI 1.11,2.38)).

Table 8. Hazard Ratios (95% CI) for all-cause mortality by joint effect of frailty* and disability. The Tromsø Study 2001-15.

	Women and men (n = 481)	Women (n = 235)	Men (n = 246)
Not frail & not disabled	1.0	1.0	1.0
Not frail & disabled	1.25 (0.86, 1.80)	1.00 (0.51, 1.95)	1.39 (0.89, 2.19)
Frail, & not disabled	1.47 (1.10, 1.97)	1.10 (0.70, 1.74)	1.63 (1.11, 2.38)
Frail & disabled	2.13 (1.58, 2.87)	1.47 (0.93, 2.33)	2.75 (1.83, 4.12)

Note: adjusted for age, comorbidity, smoking and education.
*Binary variable: Individuals were defined as frail, if one or more of the assessed frailty characteristics were present at baseline.

The combined analysis of frailty and comorbidity displayed a higher risk of death for those who are comorbid but not frail (HR 1.74 (CI 1.21,2.51)), than those who are frail but not comorbid (HR 1.62 (CI 1.24,2.11)). However, the strongest association with mortality was shown by the joint effect of both frailty and comorbidity in women and men together (HR 2.35 (CI 1.66,3.32)) as well as separately (women: HR 1.87 (CI 1.08,3.25); men: HR 2.49 (CI 1.55,3.99)). Overall the association was stronger and more statistically significant in men.

Table 9. Hazard Ratios (95% CI) for all-cause mortality by the joint effect of frailty* and comorbidity. The Tromsø Study 2001-15.

	Women and men (n = 481)	Women (n = 235)	Men (n = 246)
Not frail & not comorbid	1.0	1.0	1.0
Not frail & comorbid	1.74 (1.21, 2.51)	1.38 (0.66, 2.85)	1.94 (1.26, 2.99)
Frail & not comorbid	1.62 (1.24, 2.11)	1.16 (0.76, 1.78)	1.94 (1.37, 2.75)
Frail & comorbid	2.35 (1.66, 3.32)	1.87 (1.08, 3.25)	2.49 (1.55, 3.99)

Note: adjusted for age, disability, smoking and education.
*Binary variable: Individuals were defined as frail, if one or more of the assessed frailty characteristics were present at baseline.

4 Discussion

4.1 Findings

This prospective cohort study assessed the prevalence of frailty and investigated its ability to predict mortality among 736 community-dwelling men and women aged 65 years and older in the municipality of Tromsø.

A proportion of 3.7% of the participants included in the present analysis were classified as frail by the frailty phenotype. This prevalence is quite low compared to findings in other studies of community-dwelling individuals aged 65 years and older using the frailty phenotype. Fried et al. reported a prevalence of 6.9% in the original study of the CHS population in the USA (10). A study in the Netherlands found a frailty prevalence of 8.7% (24). In SHARE, the weighted European average was 17% (95% CI 15.3,18.7). Out of the ten examined countries, Switzerland and Sweden were on the lower end of the spectrum with a frailty prevalence of 5.8% (CI 3.5,8.1) and 8.6% (CI 6.5,10.8), respectively. The highest prevalence was reported for Italy (23.0% (CI 18.0,28.0)) and Spain (27.3% (23.5,31.0)) (35). It is thinkable that the prevalence of frailty in Norway is indeed on the lower end of the spectrum, which would be in line with the findings of SHARE that frailty is less prevalent in northern Europe (ibid.).

The vast majority of the Tromsø Study participants are Caucasian (44), so differences in frailty prevalence between ethnicities, which have been reported in previous studies (10, 33, 34), could not be examined in this study. The finding of numerous studies, that frailty is more prevalent in women (10, 22, 24, 28) and increases with age (10, 22, 24, 62, 63)

irrespective of the type of frailty scale, was confirmed in the present study. The general tendency of a higher prevalence of diseases as well as adverse socioeconomic and lifestyle-related factors among the frail (10, 62) holds true for this study sample as well. In addition, the overlap of frailty with comorbidity in this analysis is similar to that in the study by Fried and colleagues (61.7% vs. 67.7% in Fried et al. 2001). In the present study, a vast majority of those who were classified as frail also reported disability (91.7%). This is very different from the study by Fried et al., in which only 27% of the frail participants also reported difficulty in ADL (10). However, the findings of the present study are in accordance with some studies that have challenged the view of Fried et al. 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 83,9% of frail people also reported disability (64). In a study using data from the US National Health and Nutrition Examination Survey as many as 97.8% of frail people aged 50 years or older had ADL disability, which led the authors to suggest that frailty might not be a pre-disability state after all (21). These studies all vary in the way that 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 present analysis also suggests that the frailty phenotype did not simply identify people who were at high risk of disability, but perhaps rather those who were in an especially vulnerable state of disability. This still does not imply that frailty and disability are the same. The majority of those who were classified as disabled in the present study did not meet three or more of the frailty criteria (88.7%).

This analysis found a strong association between frailty status and all-cause mortality in both men and women. Sex was found to be an effect modifier instead of a confounder, which is

why all analyses were stratified by sex. The same was also reported in other studies that investigated interaction between frailty and sex (28, 39). Overall, the analyses showed a dose-response relationship between the level of frailty and mortality risk. Further, the effect was consistently larger for men. These results correspond with the findings of a systematic review of studies on frailty and mortality in community-living adults aged 65 years and older that used the frailty phenotype as the definition of frailty. In this review both frail men and women had an increased risk of mortality compared to non-frail individuals with 2.66 times increased risk for men and 1.88 for women (65). Equally, a study on frail Mexican Americans (aged ≥ 65) reported higher frailty prevalence in women, but with regard to mortality 3.04 times higher risk (95% CI 2.16,4.28) for frail men and 1.92 higher risk (95% CI 1.39,2.65) for frail women compared to non-frail individuals (66). 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 (phenotype: HR 2.03 (CI 1.82,2.25) for men) (40). Conversely, a US study using the frailty index and a Finnish study using the phenotype found a stronger association of frailty and mortality among women (39, 63).

The hazard ratios 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 very low number of frail people in the sample, which led to low precision of the effect estimates (visible as wide confidence intervals). Nevertheless, the association between frailty and mortality is statistically significant for men and women even after adjustment for several potential confounders.

Like the full frailty score, the intermediate frailty status (i.e. one or two present frailty criteria) as well as exhaustion, low physical activity, low grip strength and low walking speed

as single frailty markers were all more prevalent in women than in men in the present analysis. These measures show an overall weaker association with mortality compared to the full frailty score, but for men the effect is still statistically significant and larger than for women. Findings in previous studies are inconclusive. Fried et al. reported a significantly increased risk of mortality for pre-frail individuals without analysing sex differences (10). The systematic review of Chang et al. found increased risk of mortality in pre-frail men and women with just a slightly higher risk for men compared to women. In contrast, a study that investigated sex differences in nine different potential frailty markers (body weight, peak expiratory flow, cognition, vision and hearing problems, incontinence, sense of mastery, depressive symptoms and physical activity), the association of each marker with mortality, independent of disability and comorbidity, was generally stronger for women than for men (28). In the present analysis, low physical activity level predicted mortality in both men and women stronger than any of the other frailty markers. This is in accordance with various studies showing the association of physical activity level and mortality (67-69). The results of the present study did not confirm walking speed and grip strength as significant predictors of mortality for both sexes, like previously suggested by studies using Tromsø Study data (42, 43). Only in men, grip strength showed a significant association with mortality. However, the present study only used dichotomized variables, which could have limited the ability of these measures as single predictors. In correspondence with the results of pre-frailty and the single frailty items, the binary frailty variable with combined pre-frail and frail status was able to significantly predict mortality in men, but not in women.

Overall, these findings suggest that functional decline in *single* systems or intermediate frailty has more adverse implications for men, who could particularly benefit from early interventions before frailty manifests itself as a complex syndrome.

The joint analyses in the present study showed that the risk of mortality increases when frailty co-occurs with disability or comorbidity. Frailty alone had a stronger association with mortality than disability alone, but weaker than comorbidity alone. Nevertheless, for disability as well as comorbidity the effect was stronger when frailty was present too. Once again, this could indicate that the frailty phenotype might be able to detect the particularly vulnerable individuals among those with present disability and comorbidities.

In general, the finding of higher frailty prevalence in women, but higher frailty-associated mortality in men is in line with the extensively discussed Male-Female Health-Survival Paradox, which describes the phenomenon, that women have a higher rate of disability, diseases and worse self-reported health, but also greater longevity than men. This observation is made all over the world and is thought to have biological as well as environmental (behavioural, cultural, social) causes (70). Women seem to be able to live longer with frailty and show a rather steady decline, whereas men tend to die more suddenly (28, 39). Women are also more likely to have a strong social support system and to actively seek help when needed (62), which could compensate for some of the risk associated with frailty.

4.2 Methodological Considerations

4.2.1 Bias and Confounding

4.2.1.1 Selection Bias

Population-based studies face a type of selection bias - the participation bias or non-response bias - when randomization of the study sample is not possible and active and voluntary participation is demanded (71). People who attend an epidemiological study tend to be healthier than those who do not attend, which can influence the estimation of disease prevalence (72, 73). In another Norwegian epidemiological study, the third Nord-Trøndelag Health Study, about a fifth of the non-respondents aged 80 years or older reported being too ill to attend the study (74). This reason for non-participation is likely to have affected the Tromsø Study as well. The very frail elderly were probably less likely to attend the study, so the measured prevalence might be a conservative estimate of the true frailty prevalence in the population. Furthermore, mortality has been shown to be higher among non-participants compared to participants. However, studies suggest that this bias does not necessarily affect the association between exposure variables and mortality (74, 75). So in the present study, the measured association between frailty and mortality is not expected to have been influenced by a non-response bias. Both exposed and unexposed participants were drawn from the same population and the outcome of interest (death) had not yet occurred when the frailty status was measured, which is a typical strength of prospective cohort studies compared to case-control studies and makes it less prone to this type of selection bias (71).

One of the biggest challenges of cohort studies is the loss to follow-up bias. This different type of selection bias occurs when participants, who drop out of the study during follow-up,

are systematically different from those who remain in the study (76). In the present analysis, no censoring of cases due to loss to follow-up or emigration was necessary and all-cause mortality could be ascertained for every participant, which constitutes a major strength of the study.

4.2.1.2 Information Bias

Information bias or misclassification can be caused by error in the instruments and approaches used to obtain measures of participant characteristics. Further, self-reported information can be influenced by social desirability or varying abilities of individuals to recall past events, diseases and behaviours (77). Misclassification in studies is especially problematic when it is differential, meaning that the amount of misclassification differs between comparison groups (76). Yet, misclassification of exposure status in prospective cohort studies is commonly considered to be non-differential due to the independence of exposure assessment from the outcome of interest (78). In the following, potential sources of reporting bias and misclassification of frailty in the present study are discussed.

The frailty phenotype used in the present analysis was a modified version of the original model suggested by Fried et al. in the CHS (10). The impact of these modifications on frailty prevalence and predictive ability is difficult to estimate. However, the use of two objective measurements (TUG test and grip strength) can be considered a strength. A limitation and potential explanation of the lower overall prevalence of frailty in this study could be the use of only four of the five Fried criteria to detect frailty. If unintentional weight loss would have been available to assess as well, there might have been some more individuals classified as frail or pre-frail. The systematic review by Theou et al. on modifications of the frailty phenotype found that 4-item phenotype scales generally estimated lower prevalence than

5-item phenotypes (26). Nevertheless, the inclusion of weight loss in this analysis would probably not have made an overly large difference to the amount of detected frailty cases, given that it was the item of the frailty phenotype with the lowest prevalence in previous studies (10, 24, 79).

The difference in frailty prevalence between men and women in the present study sample could be explained by physiological differences, but it is also possible that reporting bias influenced the findings (32). Especially the two self-reported frailty markers, exhaustion and physical activity level, might be affected by information bias. A study comparing self-reported and objectively measured physical activity in 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 (80). Further, 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 (81). Those tendencies might have contributed to the sex differences in prevalence of the self-reported criteria for frailty and disability in the present study as well. Moreover, men had higher hazard ratios than women in all single frailty markers, but the sex difference in mortality risk was considerably bigger in the two self-reported frailty markers compared to the performance-based ones. Beside potential biological explanations, this could indicate that if men did report exhaustion and inactivity, it might have signalled a higher severity than in women.

Another limitation of this study could be the lack of ascertainment of frailty status in the course of the follow-up period. As previously reported, frailty is a dynamic process and not necessarily an irreversible state. One study found that although an increase of frailty over

time is much more common, some people return from frailty to pre-frailty or from pre-frailty to robustness. A transition from frailty to a robust state is very rare (82). Another study reassessed frailty after two years and found that an observed increase in frailty between baseline and reassessment might be a better predictor of future mortality than a single measurement (39). Hence, a follow-up of frailty status could have increased the accuracy of the estimates of association between frailty and mortality in the present study.

Participants who took certain medications or had Parkinson's disease, stroke or cognitive impairment (Mini-Mental scores < 18) were excluded in the original study by Fried and colleagues, because the researchers presumed that these individuals might display frailty markers as a consequence of these single conditions (10). The present study only contained information about history of stroke among the participants, but did not exclude those who previously had been affected by stroke. This may have introduced misclassification, and indeed, the percentage of individuals with a stroke was considerably higher among those who were classified as frail compared to pre-frail and non-frail participants in this study. On the other hand, this study does not provide information on causality, i.e. whether the observed frailty in any participant was the result of an accumulative functional decline or of a single condition, so the exclusion of participants based on certain former or current conditions could have introduced a bias itself.

4.2.1.3 Missing Data

The present analysis was a complete-case analysis, meaning that only participants with non-missing data on the included variables were included, which is a commonly used approach in prospective cohort studies (83). It can, however, introduce bias when participants with complete data differ from those with missing values, indicating that these cases are not

missing completely at random (MCAR). Moreover, complete-case analysis can result in the drastic reduction of sample size and might therefore lead to lower precision of estimates (83-85).

2709 participants of Tromsø 5 aged 65 years and older were not included in the present analysis due to missing data on one or more of the frailty criteria. Up to 255 cases of the selected study sample were excluded from the adjusted Cox regression models due to missing values among the covariates. On average, excluded participants were younger and healthier (less reported diseases and complaints) and comprised more women and current daily smokers. For at least some of the variables the Tromsø Study design itself - instead of omissions by participants - led to missing values. For example, data on grip strength and walking speed is missing for many participants, because these measurements were only conducted in a subsample of Tromsø 5. Disability data is missing on all individuals younger than 70 years due to different questionnaires for this age group in Tromsø 5. However, as the number of participants in the sample younger than 70 years was very low (n=24), this exclusion might not have had a great influence on the effect estimates.

Although there is no clear consensus, some researchers suggest that when the reasons for missing data among the predictors are independent of the outcome, the bias in a complete-case analysis might be negligible even though the data is not MCAR (84, 86, 87). In this case, the outcome mortality occurred after the collection of baseline data so the reasons for missing data on frailty and other covariates were at least not directly related to the outcome. Nevertheless, the exclusion of large numbers of participants did likely contribute to the low precision of estimates of the association between frailty and mortality.

4.2.1.4 Confounding

A confounder is a variable that is associated with the exposure and the outcome and does not lie on the causal pathway between these two (88, 89). Naturally, mortality is influenced by numerous factors, so there might be confounding variables, which were not taken into account in this study. The present analysis adjusted for several potential confounders, namely age, disability, comorbidity, smoking and education. Yet, this adjustment might have been incomprehensive and could have resulted in residual confounding (88). Most covariates were dichotomized in this analysis, which is practical but leads to loss of information and therefore creates potential for unaccounted confounding. Moreover, comorbidity was assessed through self-report of current as well as previous diseases. When two diseases were reported, it did not necessarily mean that they were both prevalent at baseline. Thus, the variable might not have adjusted for prevalent comorbidity appropriately. On the other hand, one could argue that this comorbidity measure took into account the potential long-term consequences of previous diseases. Furthermore, the analysis did not include single diseases as covariates and no information on the severity of the assessed conditions was available in the Tromsø Study. Given the higher disease prevalence among the frail, 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.

4.2.2 Statistical Consideration

As mentioned in the method section, the age of participants instead of the time in study can be used as the time-scale in Cox regression. Some researchers suggest, that age is the reasonable choice when the entry into the study is not connected to a specific event (e.g.

cancer diagnosis) (90) and when the study outcome or predictor of interest is closely associated with age (91), which is both the case for the present analysis. Potentially, age as the time-scale would have controlled the effect of age on the association between frailty and mortality more effectively than as a covariate (91).

4.2.3 External Validity

Due to very low numbers of participants in the lowest and highest age groups of the study sample, no robust conclusions about frailty prevalence and association with mortality in the very old or young elderly can be drawn from the results of the present analysis. The findings are most valid for the 74 to 81 year old individuals in the population. Further, the results should not be generalized to the population of institutionalized elderly, where the prevalence and severity of frailty is expected to be considerably higher (10, 29, 37).

5 Conclusion

The prevalence of frailty among 736 women and men aged 65 years and older from the fifth Tromsø Study was low compared to previous findings in other countries. Those who were frail were often affected by disability and comorbidity as well. However, this study confirms previous findings that frailty is not an inevitable part of aging, disability and illness.

Furthermore, this study adds to the knowledge that frailty is highly associated with mortality. The present findings suggest that although frailty was more prevalent in women, 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.

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