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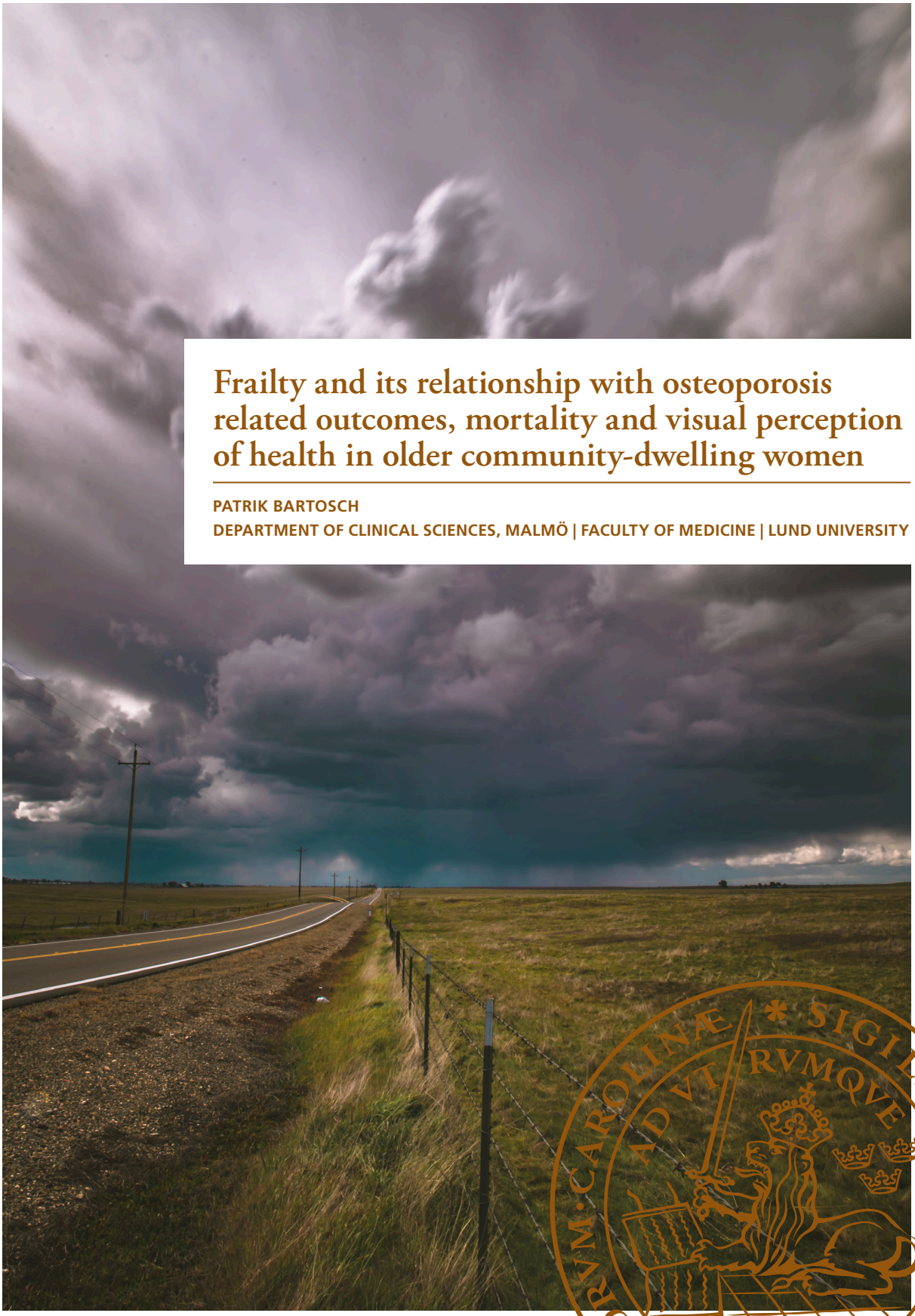

Frailty and its relationship with osteoporosis related outcomes, mortality and visual perception of health in older community-dwelling women

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Patrik Bartosch

LUND
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DOCTORAL DISSERTATION

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All studies were performed in the Malmö Osteoporosis Prospective Risk Assessment (OPRA); 1044 community-dwelling women, all aged 75 at inclusion with re-evaluation at age 80 and 85. Detailed information from physical examinations and questionnaires was collected at all visits. Fractures and mortality were followed for ~15-years. Falls were self-reported for the previous 1-year. At baseline a subjective visual evaluation of general health (VPH) was performed. A frailty index (FI) was created using variables available at all three evaluations.

At age 75, almost half the women (48%) were in good health (FI 0.0–0.1), dropping to 25% at 80y and 14% by 85y. Frailty progression was ~7% annually. A higher frailty index (i.e. higher biological age) was equivalent to being chronologically 5-10-years older and was associated with up to three-fold higher mortality.

Frailty was associated with bone density (overall p_{adj}=0.006) and was a predictor, not just of falls, but frequent falls for more or less the remaining lifetime (10-yrs: OR 3.04). Among women who had not yet acquired a history of falling, frailty was a stronger predictor of falling in future (5-yrs: OR 3.06).

Frailty was associated with a higher risk of fractures, and risk was imminent; within 24 months. Frail women had a 2-4 times higher risk of hip fracture, within 1-yr. Within 2-yrs the risk of a major osteoporotic or any fracture was also doubled, independent of BMD.

A subjective visual perception of health correlated with frailty but was strongest in those looking unhealthy (r=0.42, p<0.001). One consequence of discordance between methods is that pre-frail women appearing healthy had higher mortality than those who looked well and were non-frail (log rank test; p=0.015).

In conclusion, an older woman who is frail risks low bone density, falls and fractures, beyond that expected based on chronological age alone. Since osteoporosis and fragility fractures are primarily age-related diseases, addressing them in the context of frailty could improve strategies to facilitate “healthy ageing”.

Key words

Frailty, fracture, falls, osteoporosis, mortality, elderly women, community-dwelling

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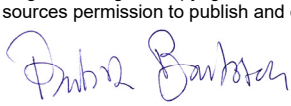
Signature  Date 2023-01-29

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To my kids, Boje and Herman

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1. Progression of frailty and prevalence of osteoporosis in a community cohort of older women
   Bartosch P, Buchebner D, Malmgren L, McGuigan FE, Åkesson KE
   Osteoporosis International. 2018;29(10):2191-2199.
   doi: 10.1007/s00198-019-04876-0

2. Frailty and prediction of recurrent falls over 10 years in a community cohort of 75-year old women
   Bartosch P, Kristensson J, McGuigan FE, Åkesson KE
   Aging Clinical and Experimental Research. 2020; 32(11):2241-2250.
   doi: 10.1007/s40520-019-01467-1

3. In community-dwelling women frailty is associated with imminent risk of osteoporotic fractures
   Bartosch P, Malmgren L, Kristensson J, McGuigan FE, Åkesson KE
   Osteoporosis International. 2021;32(9):1735-1744.
   doi:10.1007/s00198-021-05886-7.

4. A‘snap-shot’ visual estimation of health is associated with frailty in older women
   Bartosch P, Malmgren L, Gerdhem P, Kristensson J, McGuigan FE, Åkesson KE
   Aging Clinical and Experimental Research. 2022; 34:1663–167.
   doi.org/10.1007/s40520-022-02106-y

Other publications not included in this thesis

1. Musculoskeletal health and frailty
   McGuigan FE, **Bartosch P**, Åkesson KE
   Best Pract Res Clin Rheumatol. 2017; 31(2):145-159.
   doi: 10.1016/j.berh.2017.11.002

2. The association between vitamin D, frailty and progression of frailty in community-dwelling older women
   Buchebner D, **Bartosch P**, Malmgren L, McGuigan FE, Gerdhem P, Akesson KE.
   J Clin Endocrinol Metab. 2019;104(12):6139-6147.
   doi: 10.1210/jc.2019-00573

3. Can Frailty in Conjunction with FRAX Identify Additional Women at Risk of Fracture - a Longitudinal Cohort Study of Community Dwelling Older Women?
   Bartosch P, Malmgren L
   BMC Geriatrics 2022; 22(1):951.
   doi: 10.1186/s12877-022-03639-7.

4. Pro-inflammatory protein biomarkers associated with frailty – a longitudinal study in community dwelling women
   Mitchell A, Malmgren L, **Bartosch P**, McGuigan F E, Åkesson K E
   (*submitted, in revision*)

Conference abstracts

1. Frailty Status Predicts Falls in Older Women: A study in the Osteoporosis Prospective Risk Assessment (OPRA) cohort
   P Bartosch, L Malmgren, D Buchebner, F McGuigan, K Åkesson
   6th Fragility Fracture Network Global Congress 2017 (Oral Presentation)
   (http://fragilityfracturenetwork.org/files/ffn2017_final_programme.pdf)

2. A Quantitative Frailty Index Predicts Falls and Fractures in 75y Old Community-Dwelling Women – A 10 Year Longitudinal Study
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   American Society for Bone and Mineral Research Annual Congress 2017.
   J Bone Miner Res 2017, 32 (Suppl 1).

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   Buchebner D, **Bartosch P**, McGuigan F, Akesson KE.
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   J Bone Miner Res 2017, 32 (Suppl 1).

4. Frailty, falls and fractures- A 10 year longitudinal study in 75 year old community-dwelling women.
   K Åkesson**, P Bartosch**, L Malmgren, D Buchebner, F McGuigan
   European Calcified Tissue Society Annual Congress, 2017. Calcif Tissue Int, 2017, Vol 100, Issue 1 (Suppl).

5. Frailty as a risk factor for predicting falls and fractures in community-dwelling older women.
   P Bartosch, L Malmgren, D Buchebner, F McGuigan, K Åkesson
   International Osteoporosis Foundation Annual Congress, 2018

6. A Longitudinal Study of Sarcopenia in Older Community Dwelling Women.
   H Ekstubbe, **P Bartosch**, F McGuigan, K Åkesson
   American Society for Bone and Mineral Research Annual Congress, 2020

7. A 'snap-shot' visual estimation of health is associated with frailty in older women
   P Bartosch, L Malmgren, J Kristensson, F McGuigan, K Åkesson
   International Conference on Frailty and Sarcopenia Research, 2021

8. A 'snap-shot' visual estimation of health is associated with frailty in older women
   P Bartosch, L Malmgren, J Kristensson, F McGuigan, K Åkesson
   American Society for Bone and Mineral Research Annual Congress, 2021

Contributed data to

1. Progression of frailty as measured by cumulative deficit index: A systematic review. (PROSPERO registration number: CRD42020218187).
   Daliya Kaskirbayeva, Hussain Jaafari, Robert West, Silviya Nikolova, Natalie King, Farag Shuweihdi, Andy Clegg. Leeds University, UK.

   Published in: Ageing Res Rev. 2023; 84:101789.
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2. Update of the fracture risk prediction tool FRAX: a systematic review of potential cohorts and analysis plan
   L Vandenput, H Johansson, E McCloskey, E Liu, **KE Åkesson**, F Anderson, R Azagra , C Bager, C Beaudart, H Bischoff-Ferrari, E Biver, O Bruyère, J Cauley, J Center , R Chapurlat, C Christiansen, C Cooper , C Crandall, S Cummings, J da Silva, B Dawson-Hughes, A Diez-Perez, A Dufour, J Eisman , P Elders, S Ferrari, Y Fujita, S Fujiwara, C-C Glüer, I Goldshtein, D Goltzman, V Gudnason, J Hall, D Hans, M Hoff, R Hollick, M Huisman, M Iki, S Ish-Shalom, G Jones, M Karlsson, S Khosla, D Kiel, W-P Koh, F Koromani, M Kotowicz , H Kröger, T Kwok, O Lamy, A Langhammer, B Larijani, K Lippuner, D Mellström, T Merlijn, A Nordström, P Nordström, T O'Neill, B Obermayer-Pietsch, C Ohlsson, E Orwoll, J Pasco, F Rivadeneira, B Schei, A-M Schott, E Shiroma, K Siggeirsdottir, E Simonsick, E Sornay-Rendu, R Sund, K Swart, P Szulc, J Tamaki, D Torgerson, N van Schoor, T van Staa, J Vila, N Wareham, N C Wright, N Yoshimura, M Zillikens, M Zwart , N Harvey, M Lorentzon , W D Leslie, J Kanis
   Osteoporos Int. 2022 Oct;33(10):2103-2136.
   doi: 10.1007/s00198-022-06435-6.

Abbreviations

ADL	Activities of daily life
ANOVA	Analysis of variance
BMD	Bone mineral density
BMI	Body mass index
CFS	Clinical frailty scale
CHSF	Cardiovascular health study frailty
CI	Confidence interval
CIF	Cumulative incidence function
CSHA	Canadian Study of health and aging
DXA	Dual-energy X-ray absorptiometry
FI	Frailty index
FP	Frailty phenotype
FRAX	Fracture risk assessment tool
HR	Hazard ratio
IOF	International Osteoporosis Foundation
IQR	Interquartile range
IRR	Incidence rate ratio
OPRA	Osteoporosis Prospective Risk Assessment cohort
SD	Standard deviation
SHR	Sub-distribution hazard ratios
VPH	Visual perception of health
P-CRP	Plasma C-reactive protein
P-Cr	Plasma creatinine
WHO	World Health Organisation

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Frailty captures typical age-associated health declines in multiple physiological systems which lead to increased vulnerability and ultimately, adverse outcomes. Declines in the musculoskeletal system both contribute to and are a consequence of frailty. We hypothesised that a cohort with single-age older women and long follow-up, would provide unique data on biological vs chronological age in relation to frailty and its progression, and also regarding osteoporosis and fragility fracture.

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Preface

My first real encounter with academic research was in the 10th semester of medical school. During this period the emphasis was on writing and defending a master's thesis, and I had no clue in what area of research I wanted to start. At that time, I had no specific interest in a particular field of medicine but rather had the feeling that whatever I did last was the most interesting. After asking for advice from a study counsellor I was introduced to Professor Kristina Åkesson who was the head of the department of Clinical Sciences in Malmö, specializing in clinical and molecular osteoporosis research. She introduced me to the concept of frailty and suggested that I should write something on this in connection with bone health. Frailty to me was vague and, in all honesty, didn't sound overly exciting, but Kristina had an infectious enthusiasm that impressed me, and I thought the task would fit in well with my life with small kids, so I went along. But, as with everything you throw yourself into really deep, frailty research embraced me and turned out to be a truly interesting and unexplored field. Being a young research field there are still many question marks to be straightened out and some are quite fundamental. For instance: what is it? It is defined as a state of increased vulnerability but vulnerability itself is less clear. One is clearly vulnerable being without social contacts and no money, but does that make you frail? Disability and comorbidities could make you vulnerable, but do they also make you frail? The debate on what should go into frailty and how it should be measured is certainly bustling and probably will be for many years.

From initially measuring frailty by just eye-balling to today's -omics analyses it's a long step and the field is moving in giant strides, but there is still much to be done before a "gold standard" is established. With the current trends in geriatrics that go from treating a single organ dysfunction to look at the combined effects in the body as a whole, frailty research is a hot topic. Even if I'm certain of its clinical value there are two questions that keep lingering in my mind and pop up while I'm woodturning in solitude behind my lathe. Why do people age differently? Can we find those at risk and stop the progress?

Context of this thesis

This thesis was carried out within the clinical and molecular osteoporosis research group. The research focus is on investigating clinical and genetic risk and protective factors that are associated with fracture. This includes the acquisition of maximum 'peak' bone mass in young adulthood, to changes in bone mineral density (BMD) and the effects of ageing on musculoskeletal health.

Fractures in the older population are common, and women are more affected than men, the reason that they are the primary focus of the research group. Fractures have serious consequences both in terms of health costs and also at a personal level. Most importantly, suffering a fracture is often a life changing event and leads to more fractures.

Low bone mineral density (BMD) is one of the most important factors contributing to fracture, and used to diagnose fracture risk. But there are still problems: not all women that fracture have low BMD and not all women with low BMD will fracture.

Since the current strategies for predicting and preventing fractures are insufficient other avenues must be explored, and in the group, research has also included physiological areas associated with ageing, like renal function, the endocrine and immune systems and neuromuscular function, and how they can affect fracture risk.

Non-skeletal risk factors also exist for fracture; one such is propensity to fall, which as we grow older becomes even more important than BMD. And this is where frailty research becomes relevant. Frailty is holistic in its concept and captures age-related changes in a multitude of physiological systems. It is therefore a compelling possibility that the syndrome will capture a number of risk factors, which by themselves do not significantly contribute to risk.

This assumption was also the initial reason underlying my thesis. While frailty and fracture in geriatric settings has been quite well studied, there is still a substantial gap in knowledge at the population level. How frailty associates with musculoskeletal adverse outcomes, and ultimately whether measuring frailty could be useful in managing and preventing fracture.

With more knowledge comes new methods and new questions and with the aid of my supervisors we've tackled the many crossroads and dropped more than a few ideas.

Introduction

" I hope I die before I get old, Talkin' 'bout my geeeeneration". (P. Townsend)

For most of us, frailty is well recognized and something we've encountered in older relatives or the older population in general. The typical presentation of a thin old lady with a hunched back slowly walking the pavement we all know, and we instinctively know that these individuals are fragile. However, while the clinical presentation of frailty has long been recognized in the geriatric field (Figure 1), it has been surprisingly difficult when it comes to clearly define what it really is.

Over time the concept of frailty has evolved from the elusiveness of "human frailties" into a holistic model aiming to quantifiably capture the full spectrum of age-related changes in the body. With age comes frailty but people age differently and some become old in a faster pace than others (1), a fact well-known for anyone that ever attended a class-reunion. This heterogeneity in ageing (biological versus chronological age) also increases as we age; often a striking difference can be seen when comparing the physical health of two 80-year-old individuals. Why some people experience an accelerated physical and cognitive decline is not yet fully known but is certainly a research field of great importance, considering the protracted time in dependence and poor quality of life that often ensues.

With advancements in health care and increased social and economic prosperity in the Western world comes an expected change in the demographics towards a higher proportion of old and very old; more than one third of the population in Europe is expected to be over 60 years old by 2050 (2). In a perfect world we could all enjoy what is referred to as "successful aging"(3, 4) with a long healthy life and only a short period of decline before our demise (5), but increased longevity does not automatically lead to prolonged years in good health and some will have to suffer the discomforts of protracted health problems and disability. In the context of these forthcoming challenges for society, research into frailty is a vital part of preserving health and an active life, as long as possible.

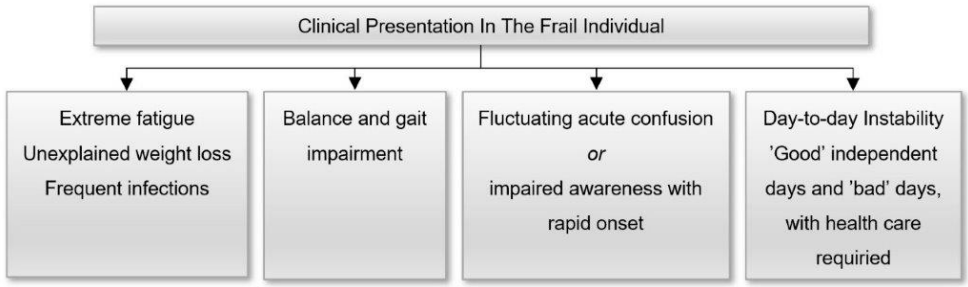


Figure 1. Common clinical presentations of fralty (adapted from Clegg et al. 2013. The Lancet (6))

Frailty – overview

Frailty describes a subset of fragile individuals with a higher biological age than expected. Today the concept has evolved into a dynamic model trying to capture a multitude of factors that signifies aging, or most importantly premature aging (7).

Although there is not yet a consensus on operationalization of the syndrome, frailty is often defined as a clinically recognizable state with increased vulnerability, involving multiple physiological systems and leading to a higher risk of multiple adverse outcomes. It is associated with accelerated decline, both physical and cognitive. The progress into frailty is thought to start early in life but early signs could be difficult to detect and not clinically overt.

In a healthy body most organs and metabolic systems have a reserve capacity to respond to situations demanding higher load (8, 9), such as infections or even walking up stairs. However, the capacities of these biological systems dwindle with age and in the frail individual the physiological reserve capacity is lowered, and therefore the response to situations with higher demands is compromised.

As a consequence, frail individuals experience a disproportional impact from even a minor stressor like a urinary tract infection or change in medications, and often experience a higher impact and a longer time to return to previous state of health (Figure 2). Stressors are not only internal, external factors like social or mental stress could lead to vast changes in health (6).

When reserve capacity is depleted, it is no longer possible to regain homeostasis, and often this is the beginning of the important transition from independent to dependent living and reflects the change from being in robust good health, to frail, often via an intermediate or pre-frail state.

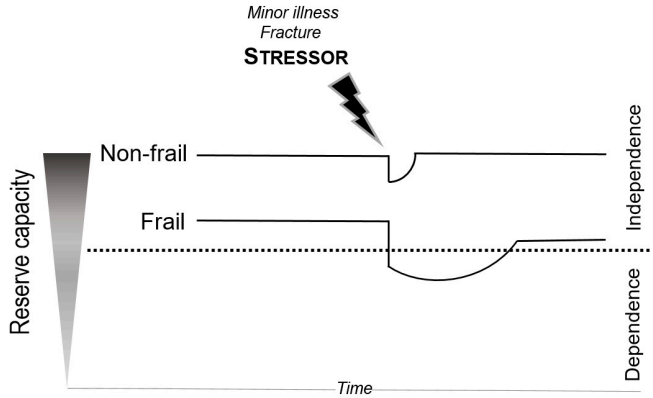


Figure 2. Increased risk of dependency for frail individuals (adapted from Clegg et al. 2013. The Lancet)
Frail individuals have a greater deterioration in health in responce to minor stressors and compared to the non-frail. They also take a longer time to recover their previous state and often a complete return to health is impossible, potentially leading to a loss of independence.

Prevalence

The true prevalence of frailty is uncertain. The wide variation in reported prevalence partly reflects different inclusion or exclusion criteria, but also the lack of consensus definition of the syndrome.

Overall, higher frailty is associated with higher chronological age - women are generally more frail then men, and African Americans more than Caucasian populations. In a systematic literature review (21 studies, n=61500, age 65+,) the reported prevalence ranged from 4.0% to 59% depending on the instruments used (10), although the studies that used the Fried Frailty Phenotype had a narrower range of 4.0% to 17%. The weighted average prevalence showed that approximately one in ten over 65 years were frail (10.7%). For the intermediate state, pre-frailty, this was four times higher (41.6%). In a white paper from the American Medical Association the prevalence of frailty in those aged 80 and over was estimated to be 40% (11). Studies in disease-specific cohorts generally showed a higher prevalence, illustrating the connection between frailty and disease (12-16).

Frailty, disease and mortality

Frailty is strongly associated with mortality, both in a direct pathway but also indirectly. Death is the ultimate outcome of advancing frailty, and all available indices predict mortality better than chronological age (17). However, frailty is also a predictor of many adverse outcomes and diseases that themselves are associated with mortality (18, 19). The Geroscience hypothesis suggests that aging is a common risk factor of most chronical diseases, such as CVD, heart failure, dementia, osteoporosis and fragility fracture, and cancer among others (Figure 3) (20). Supporting this is the fact that multi-morbidity is more common in the older

adult than a single disease. Therefore, if there are ways of manipulating fundamental ageing mechanisms, this could possibly delay the onset of multiple chronical diseases (20).

Current findings suggest that the gain of treating chronic diseases one at a time is surprisingly low (21) and there are indications that interventions aiming to slow the very mechanisms of ageing could be more effective (22, 23). The geroscience hypothesis is in many ways closely connected to the aetiology of frailty and studies have shown that, with the holistic objective of frailty, the number of systems with abnormal measurements is more predictive of frailty then the individual abnormal system alone. This suggests that failing in multiple systems is an important cause of frailty, and that it might not be enough to focus on an isolated organ failure to prevent frailty (22).

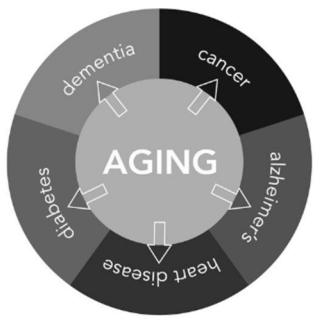


Figure 3. The Geroscience hypothesis (reproduced from the American Federation for Aging Research website) Aging is common risk factor for chronic disease. Hypothetically, therapeutically addressing the physiology of aging could delay disease appearance or severity.

Frailty – aetiology

The pathophysiology of frailty is closely related that of aging, even though the definitive aetiology is still a subject for debate. The pace of progression into frailty is individual - not all individuals become frail - but for some older inividuals this path is accelerated with premature frailty as a result (1). Seeing that frailty is overlapping aging but different in terms of progression implies that there is potential for interventions that slow the pace of aging (24-27).

During the entire life cellular and molecular damage accumulates. The reasons for this are not entirely known and it has been suggested that genetic and epigenetic factors combined with external factors such as environmental, nutrition and general life-style factors contribute (1, 28) (Figure 4). With time, regulatory pathways and cellular maintenance are affected and the cellular damage accumulates enough to

impact the function of an organ and ultimately these converge into a failing organ system. These changes appear globally and affect neuronal, endocrine, muscle and other systems (6). Eventually a critical limit is reached where the system is no longer able to counteract temporary changes in health. At this stage frailty becomes overt, with visible, measurable signs and symptoms typical for the frail individual, such as slow gait, low energy and exhaustion (29, 30).

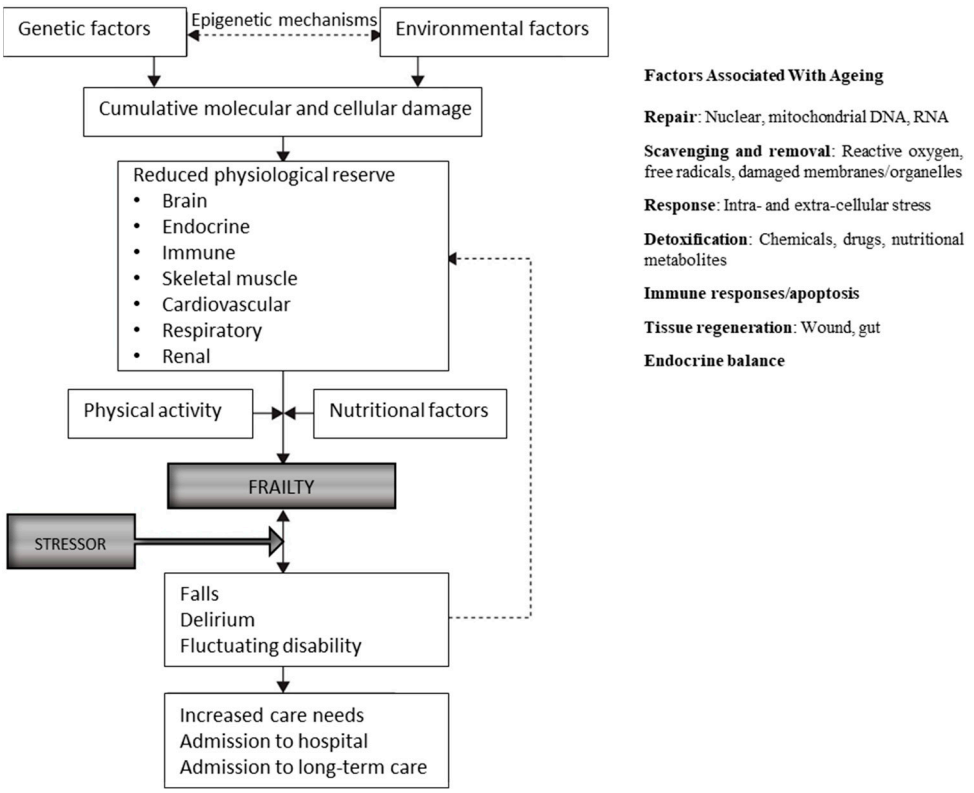


Figure 4. The pathophysiology of frailty (adapted from Clegg et al The Lancet, 2013, with permission)
Genetic and environmental factors contibute to cellular damage, which accumulates and leads to reduced capacity in higher level systems, which, in conjunction with physical activity and nutritional factors, leads into frailty.

Frailty and sarcopenia

Related to frailty, sarcopenia is the involuntary loss of skeletal muscle tissue and strength that is associated with age. Showing similarities to frailty in the pathophysiology there is an overlap between the two syndromes, and sarcopenia is an important cause of frailty. However, a sarcopenic patient is not automatically frail and vice versa. Furthermore, frailty encompasses a considerably wider spectrum of deficits (31). Sarcopenia involves losses to both muscle mass and muscle strength and the processes leading to this muscle wasting is thought to start

between 30 and 40 years old. With a suggested linear decline it has been found that almost half of the mass could be lost by age 80 (32). The changes in skeletal muscle are characterized by a decline in number and size of muscle fibres. Additionally there is a change in the quality, with infiltration of fibrous and adipose tissue (33). The aetiology of sarcopenia is multifactorial, and at a cellular level by of activation of inflammatory pathways, neuromuscular and hormonal changes (34, 35).

Measuring frailty

While many researchers agree on the multimodality of frailty and that it leads to a state of lost resilience, there is currently no uniform operational or conceptual definition of it (36-39). Analogous to this there is still no definite answers to which physical aspects of the body or "domains" should be included, or the number of variables necessary to capture frailty. Although it is clear that musculoskeletal competence is an important inclusion.

A systematic review by de Vries et al. (40) lists eight frailty risk factors, based on arguments by earlier research and "ample discussions", judged to be of great importance:

- Mobility, energy
- Nutritional status
- Physical activity
- Strength
- Cognition
- Mood
- Social relations/support

Investigating eight commonly used scales one study found that the majority of these included deficits in mobility, energy, nutrition, mood, cognition, activities of daily life (ADL) and self-rated health (41). In another more specific review, including twenty frailty instruments, 85% included mobility, 70% nutritional status, 42% physical activity, 40% strength, 40% cognition, 35% mood, 30% energy level, 30% social relations/support and concludes that the physical domain is represented in all instruments (40).

Many conceptual models are strongly connected to medical science, emphasising the estimation of physical losses. Recently there has however been arguments against this perception of a "human machine" that can be evaluated solely through physical measures, and an integral approach has been proposed (42). This model looks at an individual in her context as a whole and stresses the importance that also psychological and social aspects of life should be included (43). In the other end of the spectrum of frailty instruments is the more recent development of using only

circulating biomarkers (44). Whether a wide coverage of domains is better than a lesser is still an open question and an area for further research.

The variety of data used to conceptualise frailty makes it challenging to compare results from different studies and hampers the interpretation and generalization of findings. To ameliorate this, recent attempts to reach consensus has proposed a core set of frailty data and outcomes to be used in all frailty studies (45).

Frailty instruments

It has been estimated that there are currently more than 50 indices to measure frailty. The majority of frailty instruments were created by research groups in USA and Canada (46). These indices are different in many ways and designed in a variety of settings and specific diseases. They differ in how many domains that are covered but also the number of variables used, range from only one to 92 variables (17, 47).

For a majority of the highly cited frailty instruments the most common context for measuring frailty is as a risk factor for adverse outcomes or identifying risk factors for frailty (48). In such epidemiologic settings it is feasible to use large multi-variable data, often from questionnaires or medical journals, to assess frailty, therefore the deficit accumulation index is widely used (6). In other situations, e.g. clinical decision making or screening, it is more important to do quick assessments and therefore use fewer variables. For this purpose the FRAIL scale (49), the Cardiovascular Health Study Frailty Screening Measure (CHSF) (30) and the Clinical Frailty Scale (CFS) (50), have been widely used. The latter especially was actualized as a tool of triage during the COVID pandemic.

Despite the abundance of instruments there are two principal models that have been extensively validated and gained the most usage (51). The frailty phenotype model (FP) and the deficit accumulation model (FI) are distinctly different in describing the physiological underpinnings and also the way to operationalise frailty.

Frailty phenotype

The Frailty phenotype model was first described by Fried et al. in the Cardiovascular Health Study, in the United States (n = 5210, mixed, 65+) (30). This model assumes the existence of a typical frail phenotype, with traits similar to those generally observed in clinic.

Fried et al. suggest that frailty has a distinct biological aetiology and offers a unified theory - “the cycle of frailty”. As a result of dysregulation or decrements in multiple physical domains, a chain reaction takes place where typical traits of frailty effect each other, spiralling downwards in declining energetics and reserve - eventually manifested in the typical frailty phenotype (Figure 5).

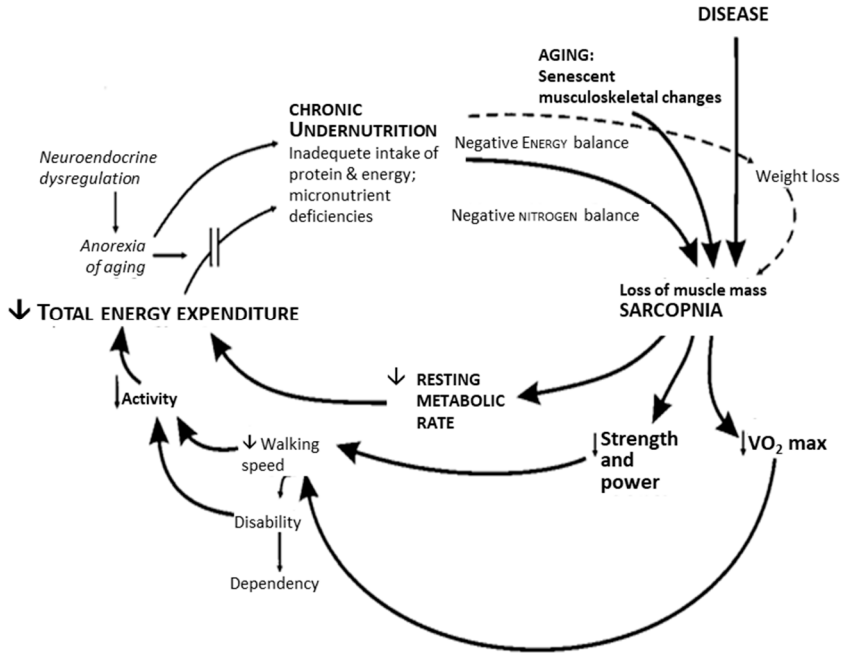


Figure 5. Cycle of frailty (reproduced with permission from Fried et al, J Gerontol A Biol Sci Med Sci, 2001) (30)
The vicious cycle of frailty results from dysregulated energetics and altered physiologic functioning in the five suggested phenotypic manifestations.

In the frailty phenotype model, disability and comorbidities are related to frailty but distinct entities; not all frail patients have disabilities and not all disabled are frail. Furthermore, a single disease or disability does not necessarily make a patient frail. Fried proposes that this distinction would improve the understanding of the aging process and also promote development of differentiated treatment strategies (52). To operationalize frailty typical traits associated with aging and frailty were used, five criteria in all (30):

- Shrinking (unintended weight loss prior year)
- Weakness (grip strength)
- Poor endurance/exhaustion (self-reported)
- Slowness (gait speed)
- Low physical activity (Kcals/week)

Based on these, individuals can be categorised into three groups. With deficits in three or more of the components, frailty was present. 1-2 deficits or alternatively, no deficits signified pre-fail and robust stages, respectively (30, 53). Currently the frailty phenotype is the most used instrument for assessing frailty (48).

The deficit accumulation index

The deficit accumulation index or frailty index was originally developed in the Canadian Study of Health and Aging (CSHA) by researchers Rockwood and Mitnitski (17, 54). The frailty index, contrary to the FP, does not give a clear biological explanation for frailty but rather sees it as the cumulative effect of deficits in health leading up to a frail state. Behind the index is the seemingly simple postulate "*The more individuals have wrong with them, the higher the likelihood that they will be frail*" (55). Equally simple is the calculation of and index, where acquired deficits are counted and then divided by the total numbers of variables in the index. The resulting score ranges from 0.0 to 1.0 with higher score indicating higher frailty. Different from the FP the frailty index is continuous and does not use specific cut-offs for defining frailty categories. The FI model does not distinguish disability and comorbidities, and a vast array of signs, symptoms, diseases, biomarkers can be used, as they fulfil five specific criteria for a variable (56).

- The variable must be associated with health status
- Prevalence of the variable must increase with age
- It must not saturate too early (e.g., presbyopia is unsuitable)
- The deficits must cover a range of systems
- For a frailty index to be followed longitudinally, identical variables must be used at all time points

Furthermore, it has been demonstrated that, as long as these criteria are adhered to, studies using different FIs show consistent results, even if different deficits and different number of deficits are used (56). Typically, the FIs show an increase in frailty of 3% per year, and a sub-maximum limit of 0.67 where more accumulation of deficits seems incompatible with life. Moreover, the distribution of frailty shows a typically skewed gamma distribution in tested populations.

There are advantages and disadvantages to both models. The frailty index provides a simple concept and appears insensitive to the precise composition of the index. This high flexibility makes it possible to use primary data from diverse cohorts, even those not originally designed to measure frailty.

The FP has the advantage of being the most used index and therefore is preferable when comparison to other findings is imperative. It is also simpler to use, but because of its categorical nature likely less sensible in detecting minor impairments. This could be an negative aspect in intervention studies, where the progression of frailty must be followed (57).

Frailty and musculoskeletal health

Rationale

There is a close connection between frailty and musculoskeletal health. As mentioned earlier, musculoskeletal function is one of the most common variables to be included in the attempts to quantify frailty, and with lost musculoskeletal competence independence is lost. There are many reasons to study frailty in this context:

Firstly, frailty and fracture are intricately linked – being frail leads to fracture and having a fracture leads to being frail. And after even a simple fracture, functional recovery is poorer in the frail patient (58).

Secondly, there is an urgent need to prevent the occurrence of osteoporosis related fragility fracture, exemplified by the fact that every day almost 12,000 individuals in the EU suffer one (almost 500 per hour), often with devastating consequences on their quality of life (59). Preventing the very first fracture is the ideal, but difficult to do. Preventing subsequent fractures is more realistic and because of this, it is the main ambition of the International Osteoporosis Foundation (IOF) (60).

Thirdly, the current strategies using dual-energy x-ray absorptiometry (DXA) measuring bone density, or the Fracture Risk Assessment Tool (FRAX ®) are not sufficient to correctly identify all those at risk.

Fourthly, frailty captures age-related deficits in multiple physiological systems which feed into and are associated with musculoskeletal health *directly* or *indirectly* - bone mineral density (BMD), bone strength, sarcopenia, falls propensity and ultimately fracture. Apart from these known risk factors it is also possible that frailty captures novel risk factors not yet considered (Figure 6).

Fifth, frailty status has implications to treatment strategies for both primary and secondary fracture prevention, e.g. by directing decisions of pharmacological or non-pharmacological treatment, or immediate or longer acting medications.

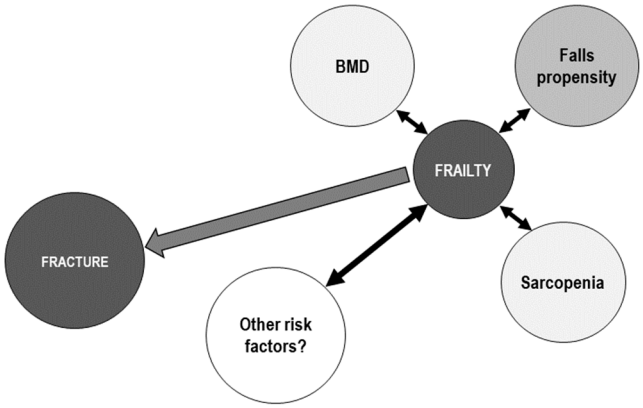
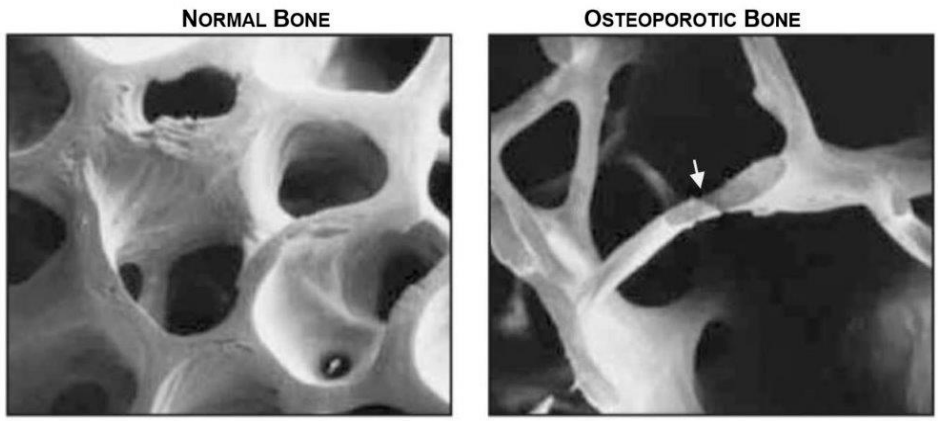


Figure 6. Frailty and the relationship to risk factors for fracture
The combined effect of sub-clincal risk factors poses increased risk for impaired muskuloskeletal health.

Osteoporosis

Definition and epidemiology

Osteoporosis is the most common bone disease (61). Structurally it is characterized by low bone mass and a disrupted microarchitecture leading to a more fragile tissue and consequently a higher risk of fracture (Picture 1).



Picture 1. Scanning electron micrographs from bone biopsies
Osteoporotic bone has low mineral mass, a lower number of trabeculae and decreased cortical thickness. The increased porosity makes the bone fragile and susceptibility to fracture. The arrow indicates disconnected bone (Reproduced from Lindsay R et al. JBMR 1986 with permission (62)).

In 2019 it was estimated that 25.5 million women and 6.5 million men in the European Union (including Switzerland and the UK) were suffering from osteoporosis (59). Worldwide this number is estimated to be over 200 million (61). Within the EU the estimated prevalence for women aged 50 years or older is 22% (for men 6.6%) (63). While osteoporosis normally is a "silent" disease the clinical relevance lies in its outcome – fracture.

Aetiology

The pathophysiological underpinnings of osteoporosis are complex and multifactorial, with a strong genetic influence (64). Osteoporosis may be primary or secondary. Primary osteoporosis is typically due to the bone loss associated with aging or menopausal estrogen depletion; explaining the higher prevalence seen in women. The causes for secondary osteoporosis are many e.g. disorders in the endocrine system, hyperparathyroidism or induced by glucocorticoid treatment. Factors not directly associated with bone metabolism such as celiac disease, eating disorders (affecting the gastrointestinal tract) and rheumatoid arthritis (autoimmune disorders) or cancer therapies or changes in the gut microbiome can also induce osteoporosis (65-67). External factors including smoking, alcohol, nutrition, lifestyle and environmental factors are important (68, 69) (Table 1).

Table 1. Risk factors for osteoporosis and fragilty fracture

Risk factors for osteoporosis	Risk factors for fragility fracture
Old age	
Female sex	
Genetic	
Premature menopause (gonadal insufficiency)	
Low body weight / BMI	Low bone density
Physical inactivity	Falls propensity
Smoking	Previous fracture
Alcohol	
Dietary (Calcium, vitamin D, etc)	
Chronic diseases (e.g. hyperparathyroidism)	
Medications (e.g. corticosteroids)	

Diagnosis of osteoporosis

Osteoporosis is diagnosed using dual-energy X-ray absorptiometry (DXA) to measure bone mineral density (BMD) and calculate the bone mass per unit area (g/cm2) at the lumbar spine and femoral neck. The result is expressed as T-score, which describes, in standard deviations (SD), how the BMD compares to a typical young healthy, same sex population at the peak of their bone mass. A T-score of -2.5 SD or below at the femoral neck is defined as osteoporosis (Table 2). The addition of fractures indicates established or severe osteoporosis.

Table 2. WHO definitions of osteoporosis based on bone mineral density (BMD) measured at femoral neck

Definition	Criteria for classification	T-score
Normal	BMD within 1 SD of the young adult reference population	> -1.0
Osteopenia (low BMD)	BMD between 1 and 2.5 SD below the young adult reference population	-1.0 to -2.5
Osteoporosis	BMD more than 2.5 SD below the young adult reference population	≤ -2.5
Established osteoporosis	BMD more than 2.5 SD below the young adult reference population *plus* one or multiple fractures	≤ -2.5

Despite being the gold standard for diagnosing osteoporosis and fracture risk, DXA has limitations. A low BMD does indeed increase the risk of fracture, but other factors, such as estimations of bone quality and strength, cannot be captured. Therefore, a person with osteoporosis may not necessarily fracture and contrary, many that fracture do not have BMD that is low enough to indicate osteoporosis. Other weaknesses of DXA are that individuals with degenerative changes (common at the spine in the elderly), often have a misleadingly high BMD (70) while osteomalacia, resulting from malnutrition in the elderly, cannot be differentiated.

Frailty and osteoporosis

To date research on the association between frailty and BMD is sparse, and the results inconsistent. In part this is related to differences in age, sex and ethnicity of the examined cohorts, relatively small sample sizes and the use of different definitions of frailty (71-77). One study in men (age 40-79) which assessed calcaneal QUS (which reflects bone density and possibly bone quality) demonstrated a significant association between increasing frailty (across the three Fried categories) and lower bone strength (78), even with after adjusting for age.

How frailty and bone are linked is not entirely clear although a number of underlying mechanisms are indicated. With frailty comes less mobility and low physical activity; this reduced mechanical load leading to reduced bone strength.

Typically for frailty defined by the Frailty Phenotype is a reduced BMI, possibly reflecting sarcopenia and loss of body fat, leading to altered crosstalk between bone-adipose and bone-muscle tissue (79, 80). Low-grade inflammation (inflamm-aging) has often been associated with aging, age-related diseases (including osteoporosis), hormonal and nutritional insufficiency (6, 81).

Bone development

From birth into puberty and age 20-30 bone growth is rapid and bone mass continues to increase up to when a maximum or “peak bone mass” is attained. From this point there is a plateau of relative equilibrium followed by a gradual decline into old age. For women this decline is accelerated around menopause when estrogen production declines, while for men the loss in bone mass is less pronounced (Figure 7).

Through the course of life, the skeleton is an active metabolic tissue in a continual state of remodeling, with bone formation and resorption. This is performed by osteoblasts (bone-forming), osteocytes and bone-resorbing osteoclasts, the main cell types involved in bone remodeling process. During growth remodeling shapes the bones. In adulthood damage to the bone from daily stress or major injury is repaired. In an adult, almost 10% of the skeletal mass is remodeled each year leading to a complete regeneration every 10 years (82).

There are two distinct types of bone. Cortical bone is the outer shell of most bones and covers the bone marrow. It is a high-density, rigid tissue with slow turnover and 80% of the skeleton is made of this, typically the shaft (diaphysis) of long bones. Covered by this, especially on the end of long bones (epiphysis) and the vertebrae, is trabecular or cancellous bone. This is less dense, has a spongy inner network of trabeculae (pates and bars), is highly vascular and more metabolically active than cortical bone.

The skeleton has multiple functions; not only does it provide structural support and mobility, but also produces red and white blood cells, and regulates mineral homeostasis. Bone also functions as an endocrine organ with complex crosstalk with other tissues (muscle, fat, liver, among others) and is involved in modulation of testosterone production and glucose tolerance (83).

The skeleton is not exempt from the physiological changes that comes with ageing and with cellular changes and the accumulation of senescent cells, the balance of bone formation and resorption is altered, ultimately leading to a low bone turnover and reduced bone strength (84).

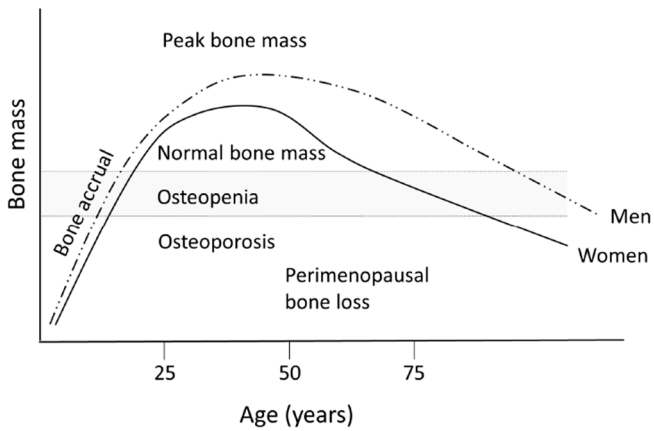


Figure 7. Bone mass throughout the life cycle (with permission from Linnea Malmgren)
During childhood and adolescense there is a positive bone turnover associated with growth and between the ages of 20-30 peak bone mass is reached. In the years following this bone formation-resorption are in balance but then follows a gradual loss of bone ranging from 0.5-1% a year, but with a distinct acceleration of loss for women in the perimenopausal and postmenopausal period.

Several factors, both external and internal, can affect bone turnover in a negative or positive way, promoting or inhibiting the activity of bone remodeling cells. In homeostasis this turnover is balanced, but in diseases like osteoporosis, resorption exceeds the formation resulting in fragile bone and a higher risk of fractures.

Fragility fracture

Fragile bone due to low bone mass and poor quality, is less able to withstand impact, and osteoporotic fractures most often result from low energy trauma, typically a fall on the same level. Fragility fractures are the clinical outcome of osteoporosis and estimated at 3.5 million fractures per year in Europe alone (63). In Sweden almost every second woman will suffer a fragility fracture by the age of 80 (85). This means that over the age of 50, a woman has a fifty percent risk over her lifetime of suffering a fracture. In a Swedish setting there are about 85-90000 osteoporosis related fractures every year (86).

The most common fracture sites include the distal radius, proximal humerus, hip, pelvis and vertebra. Of these hip fracture is the most devastating in terms of morbidity, disability mortality, and the high societal cost (87, 88). Hip fractures are painful and surgical intervention and hospitalization are necessary in the majority of cases. One in five patients die with the following year, often because of underlying medical conditions and high frailty (89). For survivors there are serious consequences on quality of life.

These detrimental effects and the importance of age at fracture are demonstrated in figure 8. A hip fracture sustained between ages 75-80 leads to the highest loss of life-years of all fractures (90) and, in terms of life quality, the longest extended period of disabled life (91). This emphasizes why the hip must be a priority for prevention.

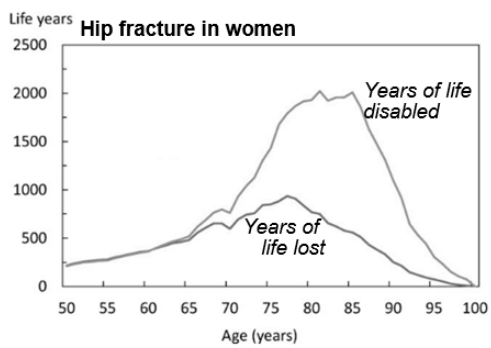


Figure 8. Years of life lost and years lost due to disability by age for hip fractures in women (reprinted from Borgström (91))

Figure reflecting that most hip fractures occur around age 77, and “years of life lost” peaked at the same age, while ”years lived with disability” peaked at age 81.

Fracture sites during aging

In the context of aging and increasing frailty, figure 9 illustrates how the incidence of specific fracture types varies across the age-spectrum, from age 50 and above.

The wrist or distal forearm is the most common site of fracture in perimenopausal women and typically the first clinical fracture, usually 10-15 years before other sites (92), and consequently considered an 'indicator fracture'. In Caucasian women the incidence increases rapidly between ages 45 and 60, most likely because of rapid postmenopausal bone loss. In most cases wrist fractures are caused by a fall, forwards and backwards (93, 94). Because these more often occur in a younger and relative healthy population it has been difficult to identify strong risk factors (95, 96).

Hip fractures typically occur in frailer individuals and incidence increases with age; with a steeper rise seen after age 75. In Swedish women the mean age for a hip fracture is 80 years old. In addition to low BMD, reflecting the higher age, risk factors are typically impaired balance, postural instability, medications and lower muscle function (97, 98), factors all common with increasing frailty. This helps explain the pattern of wrist and hip fractures. Age-related declines influence the speed and strength of the protective extension of the arm during a fall, and then the energy is directed to other parts of the body e.g. the hip (99). The variation in hip fracture incidence between populations is however high and in Scandinavian and North Americans the rates are nearly seven times higher than in southern Europe (100).

The incidence of radiographically identified vertebral fractures is higher than that of other osteoporotic fractures, however these are greatly under diagnosed in clinic and only a third come to specialist attention (101, 102). Vertebral fractures can occur without trauma, often resulting from daily routine activities. European estimates suggest that one in eight over age 50 has sustained a vertebral deformity (103). The incidence increases with age and in the oldest old more than 60% are affected (104) While difficult to diagnose and sometimes asymptomatic, in cases that are identified, there is substantial disability from pain and hugely reduced quality of life.

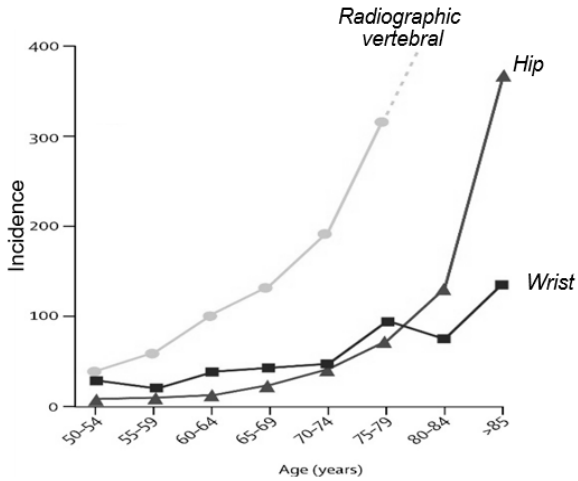


Figure 9. Age-specific and sex-specific incidence of radiographic vertebral, hip, and distal forearm fractures (reproduced with permission from from Sambrook et al. 2006. Lancet (101))

Fracture risk

The incidences of fractures have different peaks, one in adolescence and the other late in life. In young men the fracture incidence is almost double that of women and fractures typically result from high energy trauma (sports activities, traffic accidents or falls from hights). The second peak starts around age 50 for women, largely related to the development of osteoporosis, but almost 20 years later for men (105).

Preventing the occurrence of a first fracture has profound implications for healthy ageing, as we know that this leads to higher frailty, but most importantly it doubles the risk of a second fracture (106, 107). Having a vertebral fractures increases the risk ten-fold for having another fracture at *the same* site (this is also the case for hip and wrist fractures) (108). The risk for a subsequent fracture at *another* site is also higher - a vertebral fracture gives a three times higher risk for having a hip fracture and an up to four times higher risk of a wrist fracture (109).

However, primary fracture prevention is notoriously difficult and secondary prevention, beginning with an initial fracture, is currently the most effective strategy (110, 111).

Estimating fracture risk using FRAX

The commonly used Fracture Risk Assessment Tool (FRAX®) developed by the University of Sheffield is used for calculating the probability for a major osteoporotic or hip fracture. The algorithm uses multiple known risk factors such as age, BMD, use of corticosteroids and smoking to calculate the absolute 10-year risk for a fracture (112). FRAX was developed and validated in independent cohorts and

has many advantages; it is country specific, inexpensive, easily available and can be used without BMD, which is important in countries where DXA equipment is sparse.

There are disadvantages, however. It has been demonstrated that previous falls is associated with incident fracture independently of FRAX (113), and it has been argued that the current algorithm may underestimate the fracture risk in individuals with higher falls propensity (114). In an aging population the risk factors for fracture change over time and the initially important BMD becomes less predictive and falls propensity a more prominent risk factor. Thus, there is a risk that FRAX is also less efficient in this setting. This shortcoming has however recently been acknowledged and an updated FRAX tool is currently being developed (115). Considering the shortened life expectancy that comes with age, it also becomes less relevant to make long-time (i.e. 10 year) predictions.

Frailty and fracture

How frailty is related to fractures is still relatively unexplored in healthy population-based settings. The current available studies are hampered by the heterogeneity in frailty criteria and fracture outcomes, therefore, it is difficult to draw definite conclusions on the importance of frailty from these. In a recent systematic review and meta-analysis including community-dwelling older men and women (n=96,564, mean age 75-76) frailty showed a 70% increased odds risk for having a future fracture of any type. For pre-frail individuals a 30% increase in odds were reported. (116). Another large-scale systematic review using five studies and included subjects aged 55 or older (men and women, n= 103,783) showed similar results with higher risk than for those who were robust (HR_{Frail} 1.67; 95% CI (1.46-1.91) and ($HR_{Pre\text{-}frail}$ 1.28; 95% CI (1.16-1.40)) (117).

Once a major osteoporotic fracture is sustained there follows an accelerated development of frailty characteristics (118), and for both sexes mortality is higher than in general population, and continues to be higher for over 10 years (88). This is even more pronounced in men that have had a hip fracture. Men typically have hip fractures at younger ages than women, but even so the early mortality is higher and their overall health worse, with more comorbidities (119-121). In this context, there is an arguments that elderly with osteoporosis-related fracture should not be considered as “average elderly” but rather, as already frail individuals (106).

Timeframes for fracture risk

Knowing that a first fracture leads to another, when this first fracture occurs has implications for management and treatment. If a woman sustains a fracture at age 50 her next fracture could well be many years away. If this fracture instead occurred at age 70 the probability is that the next fracture will occur within the next few years. Since in older populations making long-term (10 year) predictions is less meaningful, if the older woman also happens to be frail it is likely that her timeframe

to next fracture will be even shorter (i.e. imminent) and therefore fracture management needs to be adapted not only to age but also frailty status.

Pharmacological treatment to increase BMD or slow bone loss can reduce the fracture risk in the 70-year-old woman, but this requires time to achieve full effect therefore other strategies such as balance or muscular training are likely to be more effective with more immediate effect.

Falls

Frailty overarches the link between osteoporosis, falls and fracture. In community-dwelling populations 65 and over, every third person experiences at least one fall annually and fifteen percent of these falls lead to significant injury (122-124). Globally, WHO estimates that 37.3 million falls need some form of medical attention (125). The consequences of falls lead to extensive personal and economic costs from fractures and disability (126). Aside from this, falls impact on health and wellbeing through psychosocial consequences, with fallers losing confidence and acquiring a fear of falling (a risk factor in itself for more falls) leading to less physical activity and social opportunities, and ultimately isolation and loss of independence (127)

Frailty becomes particularly relevant when you consider that falls from standing height are the main cause for fractures in the elderly, and a simple fall is the reason behind 98% of all hip fractures (128). Hence, preventing falls is critically important in terms of fracture prevention and frailty prevention.

Why older people start falling is however complex and a combination of environmental circumstances (e.g. tripping on rugs or slipping on wet floors), general health status, and pure chance makes it difficult to predict (129). To identify individuals at risk a number of fall scales have been developed, but so far these have limited usage and predictability (130, 131).

Since many frailty indices include variables of muscle strength, balance and gait, it is not surprising that frailty has been associated with falls in several systematic reviews (123, 132-134). However, the associations vary considerable depending on study populations, settings and age ranges (123), and the findings are still unclear when looking at pre-frailty.

The relationship between frailty, falls and fracture is highly complex and difficult to untangle. Higher frailty leads to falls and falls are often a prerequisite for sustaining a fracture. On the other hand a previous fall or a fracture are both, by themselves strong risk factors for future falls and fractures (135). Additionally, a fall or a fracture leads to higher frailty, which gives more falls – leading into a

vicious cycle of worsening health, which could be entered through any of these events (Figure 10).

This cycle can be seen as a point-of-no-return and once in it the chances for successful intervention, in terms of frailty or fracture, are low. Therefore, in terms of "successful ageing" it is imperative to not enter the cycle, which means recognising those at risk and applying timely interventions before an individual can enter.

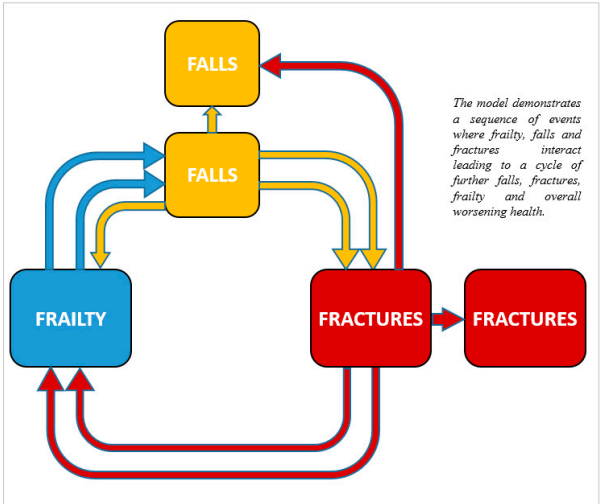


Figure 10. The vicious cycle of frailty-falls-fracture

Visual perception of health

In a clinical situation the visual estimation of general health is often the overall assessment that guides further investigations (136), but little is known how this relates to quantitively measured frailty. If a mere brief visual estimation of a clinically trained health worker would suffice, why go through the often cumbersome physical assessment of frailty?

The progression of physiological and cellular level changes eventually lead to overt manifestations of frailty, apparent to the clinician. If these changes have not accumulated enough to give visual cues the intermediate, pre-frail stage may not be recognized, and an opportunity to prevent the trajectory into overt frailty may be missed (137, 138).

The impression of an individual's overall health is guided by a number of cues, both visual and contextual, referring to the experience of the observer. Musculoskeletal fitness is often a distinct sign of frailty, but many other signs could influence. In a

study by Lauck et al health care professionals (HCPs) rated photographs of transcatheter aortic valve implantation (TAVI) patients and were then interviewed on how they formed their impression of frailty. From the emerging theme "looking at the outside" HCPs referred to posture, stance, body language and body habitus as important factors. From another theme "Thinking about the inside" inferences about frailty were based on e.g. facial expressions and grooming (Figure 11) (139). When general health is assessed in a person-to-person situation it is also likely that subtle cues like smell and tonal quality of the voice could affect the impression.

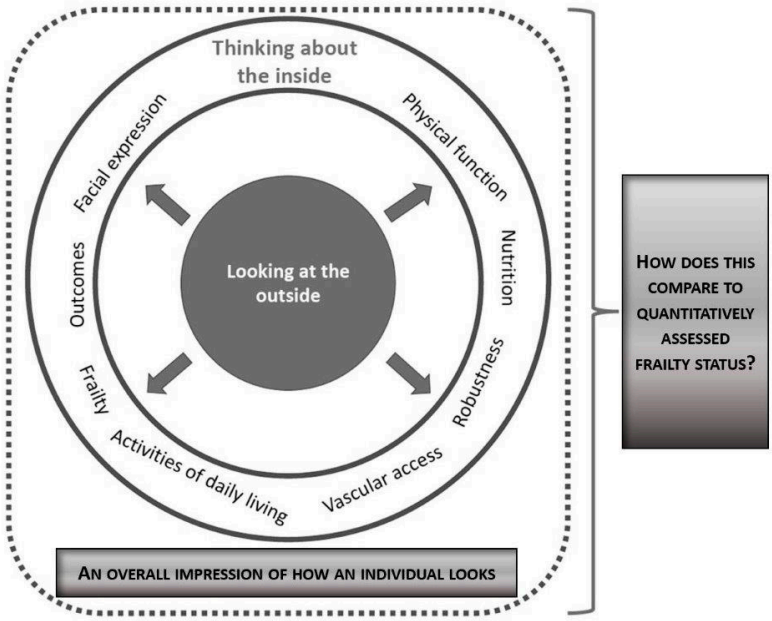


Figure 11. Conceptualisation of the content analysis themes from the interviews with healthcare professionals to ascertain how they form impressions of frailty (adapted from Lauck et al 2021, with permission).

Frailty is important to identify as part of healthy ageing, but little is studied of the reliability of a visual estimation, and only a handful of studies on the subject exists (136, 139-142). Predominantly performed in specific patient groups, with a large difference in settings and study design, these results are diverse and sometimes inconsistent. In community-dwelling populations there are to our knowledge few or no existing studies. In the OPRA cohort a visual perception of health (VPH) has previously shown to be associated with mortality over 10 years (143) and also to an early fall risk (144).

Rationale for this thesis

When the first plans were made for this thesis in 2017 frailty research was still a primary interest in the field of geriatrics, but in musculoskeletal research little was done. Beyond the well-established risk factors for osteoporosis and fragility fractures there was a notion that there was still a multitude of risk factors that couldn't easily be accounted for.

The concept of frailty captures accumulated age-related changes in every physiological system in the body. Research in other areas has shown deficiencies in a variety of different systems may be a stronger risk factor for adverse outcomes than just one individual factor, which goes against the established way of thinking. Since osteoporosis and fragility fractures are primarily an age-related disease, we hypothesised that studying it in the context of frailty made sense.

The first and most obvious gap/obstacle was: How do you address frailty in an established cohort that was designed specifically to investigate osteoporosis and fracture?

We also believed that the OPRA cohort with its single age participants and long follow-up time would provide unique information on biological vs chronological age in relation to frailty and its progression, and also in relation to fracture.

The obvious gap in knowledge was the lack of consistent evidence for the relationship between frailty, osteoporosis and fragility fracture, a confirmation that is especially needed to inform clinical management (both prevention and treatment).

Fractures and especially hip fractures have a huge impact on wellbeing in the 'young elderly'. These are still active and generally healthy, but the mid-seventies are a critical junction for future health trajectories and avoiding fracture at this age is pivotal for maintaining health and successful ageing. So there is absolute need for data to fill the gap in knowledge on how fracture influences frailty and its progression and how frailty influences the risk of sustaining a fracture.

Since the OPRA cohort had already sought to explore the concept of frailty with a visual estimation of general health the next obvious step was see this actually related to quantified frailty. To put this in context: when the clinicians measure a patient's health by just looking, are they making the right judgements? And, what might happen if these judgements turns out to be wrong? This was a one-of-a-kind study, since there is nothing in the literature assessing these questions in population-based studies.

Aims

Overall aim of this thesis

This project aimed to investigate how a quantified measurement of frailty is associated to osteoporosis related adverse outcomes, mortality and a visual estimation of health in a large cohort of elderly community-dwelling women. The specific aims were:

1. To construct a feasible measure of frailty with variables available at baseline and all follow-up examinations (5 and10-year), and with this:
2. Determine the distribution of frailty at different time-points and how this changes over time
    a. Determine the progression rate of frailty
    b. Explore frailty's association with mortality over 5 and 10 years?
    c. Explore frailty's association with osteoporosis?
3. To understand how patterns of frailty and falls propensity interact, particularly in those who have not yet entered the fall-frailty cycle. To explore different timeframes of prediction. Specifically, we wanted to:
    a. Describe the proportion who are frail at age 75, 80 and 85 and the number reporting recent falls
    b. Determine the association between frailty and risk of recurrent falls
    c. Determine if a gradual increase in frailty is associated with the number of future falls
    d. Explore the relationship of frailty to future falls in women with or without previous falls
4. To explore the association between frailty and fracture, addressing whether frailty can independently predict fracture and if so which fracture types and over what time periods. Specifically, we wanted to:
    a. Investigate whether a frail person is at increased *imminent* risk (1 and 2 years) as well as *longer* term (5-10 years)
    b. Explore the association of frailty with different fracture sites

c. Investigate whether early stages of frailty and progression of frailty interact with fracture risk

5. To characterize the relationship between a subjective visual perception of health and objectively measured frailty (previously developed frailty index). Specifically, we wanted to:
    a. Quantify frailty in women who looked health and unhealthy
    b. Determine the correlation between these subjective and objective measures
    c. Determine what proportion of variation in the frailty index is reflected in the visual perception
    d. Explore the implication for mortality when these measures are concordant or discordant.

Material and Methods

Study population

For this thesis all the included studies used data from the Osteoporosis Prospective Risk Assessment (OPRA) cohort of 75-year old community-dwelling women. Women living in Malmö (Sweden) were randomly selected from population registries and invited on their 75th birthday. A total of 1604 women were invited during the years 1995-1999 representing one third of the population of 75-year-old women living in Malmö. This age of participants was decided on because it represents a period where age-related bone loss is already apparent and osteoporotic fractures become more frequent. No exclusion criteria were applied.

A total of 1044 women participated in the baseline investigation, representing a participation rate of 67%. Follow-up investigations were performed at 5 years (age 80, n= 715 attended) and at 10 years (age 85, n= 382 attended). Study design and reasons for non-attendance shown in Figure 12, and also described in detail (145, 146).

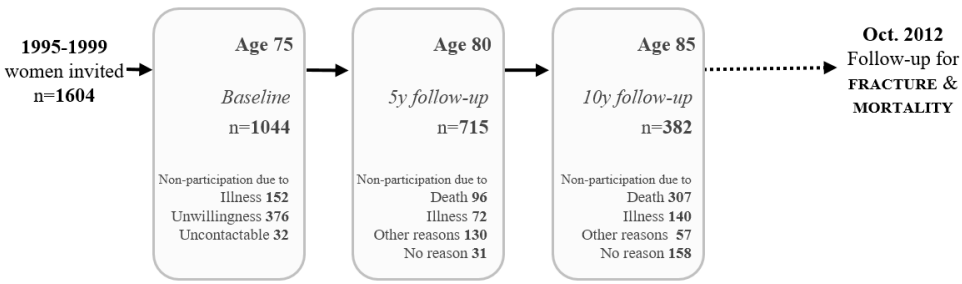


Figure 12. The Osteoporosis Prospective Risk Assessment (OPRA) cohort
Participation at each investigation and reasons for non-attendance

The participants were followed prospectively for fractures and mortality up to October 2012 (a total follow-up of 15 years; range 13.4-17). At each investigation anthropometrics, questionnaires on health, nutrition, medication, smoking/alcohol habits and lifestyle were collected. Additionally, bone mineral density (BMD) and physical assessments were performed, and blood and urine samples were analysed.

All procedures performed were in accordance with the ethical standards of the regional ethical review board in Lund (Dnr: 2014804), adhering to the principles of the Helsinki Declaration. All women provided written informed consent.

Blood biochemistry

Blood samples were collected (non-fasting; morning) and stored at -80°C. All analyses were performed at the accredited laboratory in the Department of Clinical Chemistry, Skåne University Hospital, Sweden.

Plasma creatinine (p-Cr) values were IDMS traceable and analysed according to the current standard in use (147).

C-reactive protein (P-CRP) was measured by routine methods using Roche Diagnostics (Cobas) (148).

Vitamin D (25OHD) was assessed using liquid chromatography mass spectrophotometry (LC-MS) linked to a High-Performance Liquid Chromatography (HPLC) system (149).

Frailty Index construction

For construction of a quantified measurement of frailty that could be followed in the cohort over 10 years, we used principles described by Searle et al. (56). These state that a variety of signs and symptoms can be used to create a frailty index (FI), as long as they fulfil five basic criteria, described earlier.

After identifying the variables to include in the index, for continuous variables we used either clinically relevant cut-points or identified the cut-off values by plotting the variable against an interim FI to score the deficit (as present/non-present). Categorical values were converted to binary values (1=deficit present) and (0=deficit absent); those with more than two categories were scored between 0 and 1 (e.g., high = 1.0; medium = 0.5; low = 0.0).

The Frailty Index was then calculated by dividing the number of deficits present by the total number of deficits examined, giving a score from 0.0–1.0, where a higher score indicates a higher frailty status.

It is recommended that an index consist of 30–40 variables. However, since the availability of suitable data in the OPRA cohort was limited at baseline, our indices were constructed using the following approach (Figure 13):

With data collected at the 5-year follow-up (age 80), a "full" 40-variable index was initially constructed and validated against mortality outcomes. From this index, 10 variables available at time-points (including baseline) were selected and used to construct a 10-variable index that was also validated against mortality (the ultimate manifestation of vulnerability and age-related accumulation of deficits).

To ensure a wider coverage of biological domains essential for a measurement of frailty, additional variables (such as biomarkers) were added as covariates in logistic regression analysis to identify further variables associated with mortality risk.

From the results of this, a 13-variable index was created that could be compared longitudinally at all examinations (age 75 to 85) (table 3).

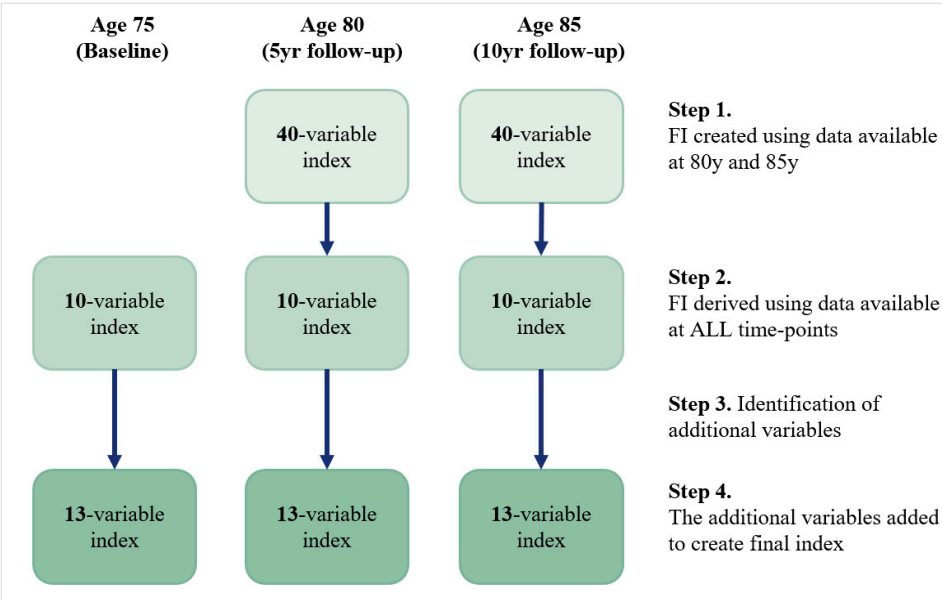


Figure 13. Activity flow for creation of a Frailty Index in OPRA
The final index facilitates comparison longitudinally across 10-years of followup

Table 3. Components included in the 13-variable frailty index constructed at ages 75, 80, and 85

Variable	Measurement Units	Scoring or Cut Point
Daily physical activity	Categories (1=lowest; 6 highest)	Cat 1-3=1; Cat 4=0.5; Cat 5-6=0
Average time outdoors	Hours	< 1h= 1; ≥ 1h =0
Gait (speed, 2 x 15m)	m/s	>1.20 = 1; <1.20 = 0
Gait (steps taken, 2 x 15m)	No. of steps	<54 = 0; >54 = 1
Balance (2 legs, eyes closed)	Seconds	Failed test=1; passed test=0
Muscle strength (knee)*	Nms	>213 = 0; <213 = 1
Diabetes	Yes/No	Yes = 1; No = 0
Cancer	Yes/No	Yes = 1; No = 0
Diseases affecting balance	Yes/No	Yes = 1; No = 0
Polypharmacy (≥5 medications)	Yes/No	Yes = 1; No = 0
Self-estimated fall risk	Categories (1=lowest; 5 highest)	Cat 1-5: 0.0; 0.25; 0.5; 0.75; 1.0
P-CRP	mg/L	>= 4.21 =1; <4.21=0
P-Creatinine	umol/L	>=82.02=1; <82.02

**Voluntary maximal, isometric muscle strength of the right knee (knee extension at 90o) measured using a Biodex computerized dynamometer*

The three indices created (40-, 10- and 13-variable) were tested for correlation. Based on this, and the association with mortality this 13-variable index was used in study 1 to follow the progression of frailty and relationship with BMD and mortality (150).

"Refined" Frailty Index

With the relatively few variables in the original frailty index (150), it was observed that dichotomizing the continuous variables (56) leads to clustering of individuals with identical frailty score; especially among the lower scores (i.e. the less frail). We therefore believed that the FI was not sufficiently discriminative for investigating pre-frailty in the cohort and therefore had the potential to be improved.

On the basis that dichotomization using set thresholds inevitably leads to a loss of information and precision (151) we refined the index, and therefore each applicable variable was reverted to its continuous value and then recalculated to values between 0.0 and 1.0. This refined, non-dichotomous index was used in study/papers 2,3 and 4 (152-154). Six of the original 13 variables were continuous variables and recalculated (Table 4). The remaining seven variables were used with their original stratifications.

Table 4. Components recalculated in the redefined frailty index constructed at ages 75, 80 and 85

No.	Variable	Measurement Units (range)	Scoring* or Cut Point
3	Gait - walking speed (2 x15m)	m/s (0.20-2.22)[a]	1.0-0.0
4	Gait - walking steps (2 x15m)	No. of steps (20-120)[a]	0.0-1.0
5	Balance (2 legs, eyes closed)	Seconds (0-60)[a]	1.0-0.0
6	Muscle strength (knee extension)[b]	Nms. (80-450)[a]	1.0-0.0
12	P-CRP	mg/L (0.6-50)[a]	0.0-1.0
13	P-Creatinine	umol/L (40-200)[a]	0.0-1.0

[a]Range and min/max values in the cohort. [b]Voluntary maximal, isometric muscle strength of the right knee (knee extension at 90°) measured using a Biodex computerized dynamometer.

Recalculation of variables

For each variable, the values signifying the *most frail* state were scored as one (these could be the highest or lowest values depending on the variable in question), and the opposing values (signifying the *most robust*) in the cohort was scored as zero. All other values were recalculated to be continuous between one and zero.

As an example of how a variable was re-calculated we look at "Gait - number of steps taken to walk 2x15 m". Dichotomized, the cut-points were <54 steps=0 (deficit absent) and ≥54 steps=1 (deficit present). Originally, at each visit, number of steps was recorded as a continuous variable, with values in the cohort ranging from 9 to 160. Taking more steps indicates a shorter stride, hence a more frail state and therefore a score closer to one. Fewer steps indicate a longer stride, hence a more robust state and therefore a score closer to zero.

To implement this re-scoring: First**,** we examined the range of values across the entire cohort to identify extreme outliers (e.g. number of steps at baseline ranges 21–160). Secondly, the highest (V_{max}) and lowest (V_{min}) values were set to 1 and 0, respectively. Thirdly, each participant's original value (V_{orig}) was reclassified using the formula $(V_{orig}-V_{min})/(V_{max}-V_{min})$, for example, using minimum and maximum values found at baseline, $(V_{28}-V_{21})/(V_{160}-V_{21}) = 0.05$ as shown in the table below.

For other variables e.g. walking speed (values throughout the cohort ranged from 0.20 to 3.16 and at baseline examination from 0.29 to 2.14), in this case, a lower values indicate a more frail state, and higher values indicate a more robust state, therefore an additional step ($1-V_{reclassified}$) was performed as shown in table 5 below.

Table 5. Examples of recalculation of variables for the redefined frailty index

		Original Value	Reclassified Value $(V_{orig}-V_{21})/(V_{160}-V_{21})$	New Inverted value $(1-V_{reclassified})$
Number of steps (2x15 m)	*Longer stride = more robust*	28	0.05	-
		75	0.39	-
		98	0.55	-
	Shorter stride = more frail	110	0.64	-
		155	0.96	-
			Reclassified Value $(V_{orig}-V_{0.29})/(V_{2.14}-V_{0.29})$	
Walking speed (2x15 m)	High speed = *more robust*	2.05	0.95	0.05
		1.88	0.86	0.14
		1.35	0.57	0.43
	Low speed = *more frail*	0.98	0.37	0.63
		0.35	0.03	0.97

Values used in these example calculations refer to minimum and maximum values at baseline examination. For the actual calculations the limits were extracted using values from all examinations.

Validation and testing of the OPRA frailty indices

To be sure that the 'original' and 'refined' indices were similarly effective we compared them to each other and to the 40-variable index using correlation analysis and survival analysis.

We found that the indices had strong statistically significant correlation at both available timepoints. They were also similar in predicting mortality (Table 6 and 7).

Table 6. Correlation between frailty indices at at ages 75, 80 and 85

*Values are *Spearman's rho

		40-Variable Index			13-Variable Index		
		75y	80y	85y	75y	80y	85y
13-Variable Index$_{refined}$	75y	-	-	-	r=0.89	-	-
	80y	-	r=0.81	-	-	r=0.89	-
	85y	-	-	r=0.81	-	-	r=0.91

Table 7. Mortality hazard ratios for frail women compared to non-frail women

	HR	95%CI	p
40-Variable Index	3.5	2.5 – 4.8	<0.001
13-Variable Index	2.9	2.1 – 4.1	<0.001
13-Variable Index$_{refined}$	3.0	2.2 – 4.1	<0.001

Missing values

How to handle missing values when constructing a frailty index is not clearly described in the literature. A limit of 5% maximum missing is often considered, but the variation is extensive with many examples of much higher values. At baseline

the majority of variables had less than 5% missing values while "self-estimated risk of falling" and "diseases affecting balance" had 13.5% and 14.9% missing, respectively. Overall, 80% of cases had valid data for at least 12 out of the 13 variables. At 5-year follow-up this was similar, with only P-CRP (6.3%) and "Maximum repeated work extensions" (21.4%) having more missing.

To determine if there was any significant impact from "missingness" on the performance of the frailty index, the effect of missing variables on the predictive ability was formally assessed. Several indices with different limits on missing value were created (e.g., a 13-variable index where any individual missing two values was excluded). Testing these variations showed little difference in the prediction of mortality; therefore, it was decided to use the indices without excluding limits.

Distribution of frailty

Typical of all frailty indices, the distribution of scores is skewed, approximated by a gamma density function (155). This distribution was also observed in the indices constructed in OPRA. Furthermore, as expected the distribution changed over time towards normality, indicating the expected accumulation of deficits in the cohort with age (Figure 14). Distributions of mean and median of all indices were comparable as illustrated in Figure 15 a and b.

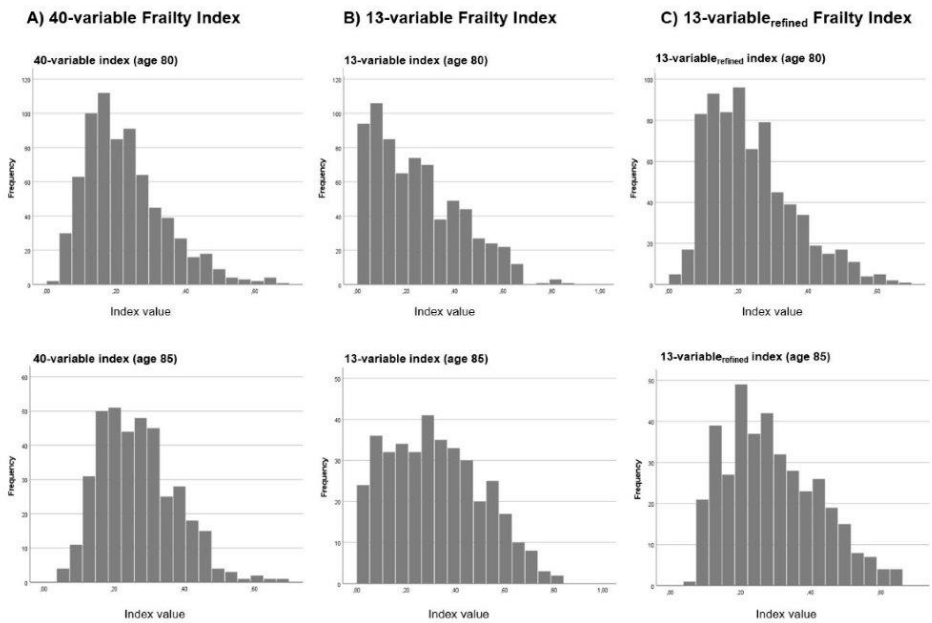


Figure 14. Frailty index distribution at ages 80 and 85. A) 40-variable index, B) 13-variable index, C) 13-variable refined index

All three indices were comparable and display the typically skewed distribution common to all frailty indices.

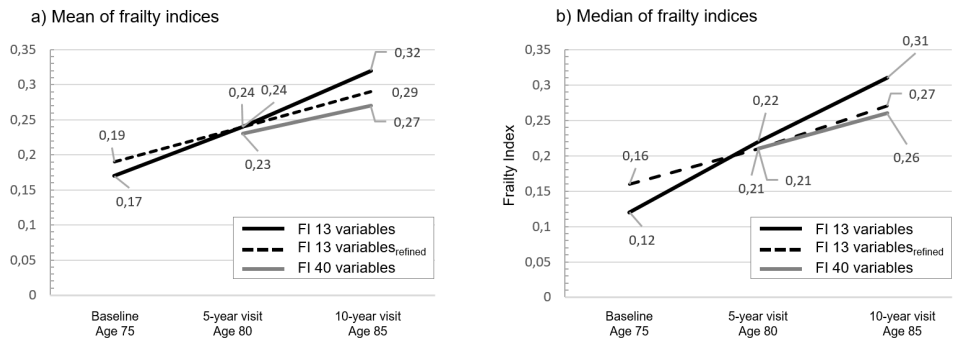


Figure 15 a and b. Distribution, mean and median of the three frailty indices at baseline, 5- and 10-year visit
The three indices were comparable in mean and median values, and increase over time.

Measurement of bone density

Bone mineral density (BMD, g/cm2) measurements were made with a Lunar® DPX-L scan (Lunar Corporation, Madison, Wisc.,USA) at the femoral neck. Osteoporosis was defined as having a T-score below -2.5.

Fracture assessment

Incident fractures were prospectively followed until October 2012 (up to 15 years) through the X-ray files at the Radiology Department, Malmö, Skåne University Hospital. This hospital is the only one treating fractures in the catchment area and therefore loss to follow-up was very low. Fractures were reported as any fracture, major osteoporotic fractures (MOFs) as defined by FRAX (i.e. hip, vertebral, distal radius and proximal humerus) (http://www.shef.ac. uk/FRAX), and hip and vertebral fracture. Fractures resulting from pathology and high energy were excluded. Fractures occurring prior to inclusion (specifically, between ages 50 and 75) were also registered (156).

In the older potentially frail population timeframes for fracture are particularly important for risk assessment and appropriate intervention. Therefore short (1-2 years) and long term (5-10 years) perspectives were examined (Figure 16).

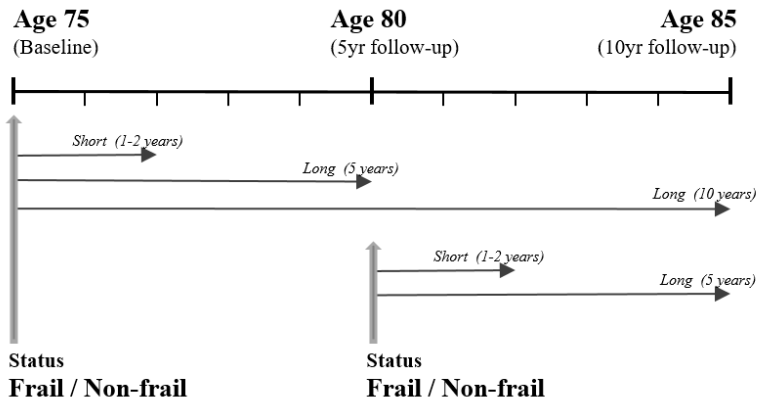


Figure 16. Illustrates the timeframes for fracture risk estimation
Short (1-2 yrs) and long term (5 yrs and 10 yrs) estimates were calculated based on frailty status at age 75 and then on frailty status at age 80.

Falls assessment

At baseline, 5-year and 10-year follow-up visits participants provided information on whether they had fallen in the previous 12 months and if they had fallen, how many times they fell during that period. In the analysis fall outcomes were defined variously: at least one fall, recurrent falls (i.e., 2 or more falls) and number of falls.

Visual perception of health

At baseline 1004 identically aged women (75yrs) were subjected to a visual evaluation of general health within the first 15 seconds of sight, here named visual perception of health (VPH). Women were estimated by two independent healthcare professionals (nurse, physiotherapist) using an arbitrary scale ranging from 1 to 100, where "1" represented a very healthy appearance and "100" a very unhealthy appearance. The correlation between observers was satisfactory ($r = 0.51–0.59$, $p < 0.0001$) (157). The observers had no other information beforehand than the name of the subject. Because of the unique study design i.e. identically aged women, the observers were essentially deciding if each participant looked older or younger than their actual age (biological versus chronological age).

Evaluation and results were not discussed among observers during the study. VPH was analysed as tertiles equating to "good", "intermediate" and "poor" health. (143, 144, 157).

Mortality assessment

Information on date of death was collected from the Swedish national population register. For this thesis mortality was assessed prospectively from age 75 until age 85 or end of study (Study started 1995-97 and ended in October 2012).

Power analyses

The OPRA cohort was initially designed to study fractures and bone density. A priori power analyses were therefore carried out to determine the sample size needed to detect differences in BMD and markers of bone turnover. Based on a supposition of a SD of 0.13 g/cm2 in BMD it was found that 850 individuals gave over 80% power to detect a 0.056 g/cm2 difference between equal groups at a 5% significance level. A baseline sample size of 1000 women was therefore deemed adequate.

For our studies on frailty and fracture, no *a priori* calculations were performed. While the incidence of fracture in the general population is well known, this general population will include both frail and non-frail women. Therefore, it was problematic to estimate fracture incidence in an unexposed group i.e. non-frail women, a requirement for power calculations. There is simply no known incidence for this group. Similarly, post hoc analysis are generally agreed to have limitations and not recommended (158), but are reported here to give an indication of the power of this study.

Based on the 5-year incidence of any fracture (19.1%) in non-frail women in the cohort, our study had >80% power to detect a 1.45 difference in relative risk (RR) (alpha 5%) between frail and non-frail women. This indicating that the study was sufficiently powered to detect a true difference. However, with these known limitations the confidence intervals are a better indication of the reliability of the associations.

Statistical analyses

Descriptive data are presented as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables are reported as number (n) and percentage (%).

Analyses were performed using SPSS version 22 (SPSS, Inc., Chicago, IL), JMP SAS (SAS Institute, Cary, NC, USA) and RStudio v1.2.5042 (159, 160). P values of < 0.05 were considered nominally significant.

Study 1

This study explored the distribution of frailty in community-dwelling older women, the association to death and the association with BMD. The frailty index was used both as a continuous variable and stratified into quartiles (Q1 = lowest level of frailty; Q4 = highest level of frailty) and comparisons were done overall or Q1 vs Q4. To compare how frailty associated to bone related variables and mortality, quartiles were compared using ANOVA, t-test, Fisher's exact test, Chi-square or Kruskal-Wallis test as appropriate.

To calculate the progress of frailty over 10 years the mean values of the whole cohort were used and averaged as an annual linear progression. Mortality risk was estimated using Cox proportional hazard regression at 5 years, 10 years or end of study (October 2012). Hazard ratios (HR) and 95% confidence intervals (95%CI) were calculated using Q1 (healthiest group) as reference and presented unadjusted.

Study 2

This study investigated how frailty and falls propensity interact. For primary analysis an empirical cut-off suggested by other studies was used (55, 127) to define 'non-frail' (≤ 0.25) and 'frail' (> 0.25) groups. Frailty was also analysed in quintiles to explore the association to number of previous falls or future falls (5 and 10 years).

Falls were defined both as 'at least one fall' and 'recurrent falls' (i.e., 2 or more falls) during the previous 12 months. Furthermore, we also analysed the number of falls stratified into 4 groups (no falls, 1 fall, 2 falls, 3 or more falls). Only participants with valid data on falls were included (75y n= 914; 80y n= 711; 85y n= 382).

Binary logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals, of future falls (5 and 10 years) comparing frail women to non-frail. This was also performed at age 80 with frailty status reassessed. In a sensitivity analysis and to distinguish the effect of a previous fall, the same analyses were performed comparing those *with* or *without* a previous fall. Models were unadjusted and adjusted for vitamin D (25(OH)D), BMI, smoking and previous fractures (between age 50 and 75).

To explore the association between gradients of baseline frailty (quintiles) and number of future falls (4 groups) cross-tabulations and Chi-square was used. At age 80 frailty status was reassessed and the same analyses were performed.

Study 3

This study aimed to investigate how frailty status affected timeframes for fracture risk, fracture types and fracture risk.

Women were categorized as frail or non-frail ($FI \leq 0.25$ or > 0.25) and in quartiles (Q1 least frail; Q4 most frail) to investigate the relation of lower frailty to fracture risk.

Fracture risk was assessed over short (1 and 2 years) and long terms (5 and 10 years). Frailty status was reassessed at age 80 and the relationship re-analysed over the same timeframes. Fracture risk was defined for any fracture, major osteoporotic fractures (MOFs), hip and vertebral fracture. Occurrence of a first fracture was used as primary outcome.

When analysing risk in longitudinal studies of the elderly with high mortality there is a risk of overestimation because of the competing risk of death. Therefore, statistical models accounting for competing risk were used, minimizing potential bias. The probability of fracture was calculated as a cumulative incidence function (CIF) using Gray's test to determine significance. For calculations of fracture risk proportional subdistribution hazard ratios (SHR) and 95% CI for a first fracture were estimated using a model proposed by Fine and Gray (161). To determine if frailty independently predicts fracture risk, BMD was included as a covariate.

To estimate the effect of multiple fractures, incidence rates (fractures/1000 person-years) using *all fractures* were calculated and compared (incidence rate ratio; IRR)

Study 4

This study explored the relationship between a brief subjective visual estimation of general health (VPH) and an objective estimation (FI) and examined the implications on mortality when they are discordant.

The visual perception of health scores were stratified into tertiles (poor/intermediate/good health). The frailty index (FI) (scored 0.0–1.0) was stratified into tertiles: 'frail' (≥ 0.22), 'pre-frail'(0.13–0-21) and 'non-frail' (≤ 0.12).

The association between tertiles of VPH and individual variables in the FI were tested using Kruskal–Wallis test, Chi-squared and ANOVA, as appropriate.

Correlation between subjective and objective assessments was tested in the cohort as a whole and in each tertile of VPH using Spearman's Rho. To test to what degree the VPH mirrored the variation in the frailty index, linear regression analysis was performed after logarithmic and square root transformations. The effect of significant outliers (> 3 SD, n= 5) was tested with or without these included.

Discordance between VPH and FI was defined as being in the opposite tertiles of VPH and frailty, i.e., *visually* perceived to be in *good* health but *measured as frail* by frailty index or someone *visually* in *bad* health but *measured as non-frail*.

To test the clinical relevance of both VPH and FI scores, difference in 10-year mortality between tertiles were explored using Kaplan-Meyer analysis with log-rank for assessing significance. Cox regression analyses were used to estimate hazard ratios. To explore the implications of 'misjudging' (discordance) cox regression analysis was performed separately in 'good' and 'poor' tertiles of VPH.

Results

Study 1 - Frailty in the OPRA cohort

Context

In the osteoporosis field frailty has not been extensively researched. One hurdle has been that cohorts designed to specifically address osteoporosis have not been designed to specifically capture frailty. In the same way, cohorts designed to address frailty generally lack osteoporosis outcomes. Of existent frailty studies comparatively few are in older community-dwelling women or designed to provide long-term data.

To address this, our initial step was to find a way to construct a measure of frailty. As described in detail in the methods, a 40-variable frailty index was constructed for 5 and 10-year follow-ups, and from this a 13-variable index was derived that could be followed across all time-points (Figure 13). The indices were compared by correlation and validated by association to mortality. From these analyses it was judged that the indices are valid measurements of frailty.

The next step was to longitudinally investigate frailty, aiming to understand the distribution of frailty and how this progressed over 10 years. The association between frailty, mortality and osteoporosis was also investigated.

Methods and subjects

A frailty score (FI) was calculated for participants from the OPRA cohort at ages 75 (n=1044), 80 (n=715) and 85 (n=392). For analyses this score was used both as a continuous variable and stratified into quartiles (Q1 =lowest level of frailty; Q4 = highest level of frailty). For survival analyses, hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated using Cox proportional hazard regression with the healthiest quartile (Q1) as the reference category. Time to death was 5 years and 10 years.

Results

Characteristics of the OPRA cohort

Table 8 shows the most relevant characteristics of the OPRA cohort at ages 75, 80 and 85. It can be seen how all the components of the frailty index, apart from p-CRP, gets "worse" over time. At baseline 53.7% of the women were living alone, 91.7% had been married, 85.3% had had children and 73.2 % were living in a one level apartment or house.

Table 8. Key clinical characteristics of the OPRA cohort at age 75, 80 and 85
All the components of the FI except P-CRP change to a "worse" state with age.

Variable	Age 75 (Baseline) n=1044		Age 80 (5 year) n=715		Age 85 (10 year) n=382	
	Mean or N°	SD or %	Mean or N°	SD or %	Mean or N°	SD or %
Age (y)	75.2	(0.2)	80.2	(0.2)	85.2	(0.1)
Height (cm)	160.5	(5.7)	159.2	(5.8)	158.3	(5.8)
Weight (kg)	67.8	(11.7)	66.0	(11.6)	63.95	(10.9)
BMI (kg/m^2)	26.3	(4.2)	26.1	(4.2)	25.5	(4.0)
Frailty Index	0.17	(0.17)	0.24	(0.18)	0.32	(0.19)
Variables in the FI						
Daily activity[1]	0.06	(0.19)	0.11	(0.23)	0.20	(0.26)
Average time outdoors (hrs)	2.73	(1.33)	1.84	(0.87)	1.66	(0.78)
Gait - Speed 2 x 15m (m/s)	1.31	(0.30)	1.20	(0.33)	1.10	(0.32)
Gait - Steps taken, 2 x 15m	49.4	(9.8)	53.6	(11.7)	55.8	(12.3)
Balance (2 legs, eyes closed)(s)*	57.8	(10.6)	54.8	(14.6)	52.1	(17.5)
Balance (N°. failing 60s test)	47	(4.6%)	91	(12.7%)	75	(20.3%)
Muscle strength[2] (nms)	267.9	(79.5)	247.3	(71.2)	218.3	(63.6)
Diabetes/Cancer (%)	219	(21.0 %)	178	(24.9%)	91	(24.1%)
Disease affecting balance (%)	201	(22.6%)	256	(35.8%)	184	(48.2%)
Self-estimated fall risk						
Low (categories 1-2)	681	(75.4%)	491	(62.1%)	240	(63.8%)
Medium (category 3)	126	(14.0%)	129	(18.9%)	94	(25.0%)
High (categories 4-5)	98	(10.6%)	61	(8.9%)	42	(11.2%)
Polypharmacy[3] (%)	210	(20.1%)	175	(24.5%)	165	(43.2%)
P-CRP (mg/L)	3.9	(6.8)	3.7	(5.1)	3.4	(5.8)
P-Creatinine (umol/L)	69.9	(0.60)	74.3	(19.9)	82.2	(1.20)

Mean (SD) unless otherwise stated. [1]Daily activity calculated from the frailty threshold categories; [2]Voluntary maximal isometric muscle strength of the right knee (knee extension at 90o) measured using a Biodex computerized dynamometer; [3]Five or more medications; *not used in index.

Frailty, prevalence and progression

Frailty increased with age and those who survived and attended at 5-year visit had in retrospect been less frail at baseline than the non-attenders (mean FI 0.13 vs 0.25)

(Figure 17). In non-attenders a similar difference was seen for those still alive and those that died during the five years (mean FI 0.23 vs 0.30). The same pattern was seen when comparing mean frailty at 10-year visit to 5-year visit. Initial baseline frailty score was lowest in those who attended 10-year follow-up (mean FI 0.11)

Overall, the typical characteristics of the frail 75-year-old women, based on the descriptives from studies 1, 2 and 3, demonstrate that frail women had more previous falls and fractures, lower education, more were current or previous smokers and used glucocorticoids and bisphosphonates, as summarised in Figure 18.

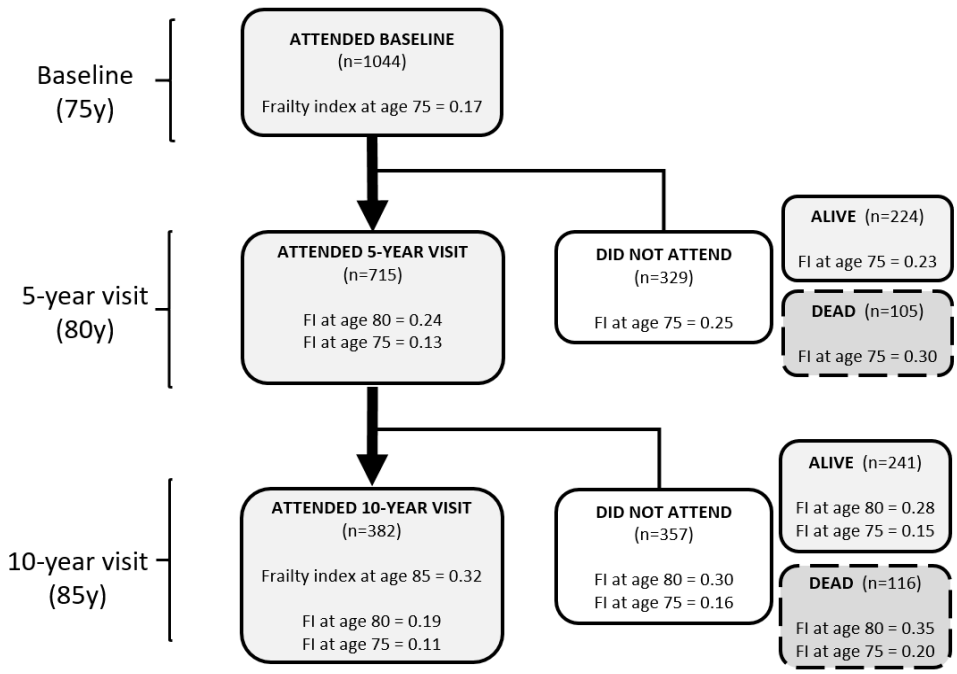


Figure 17. Frailty index across participation at each visit
Mean frailty index is reported for attendees and those who were non-attenders, dead or alive.

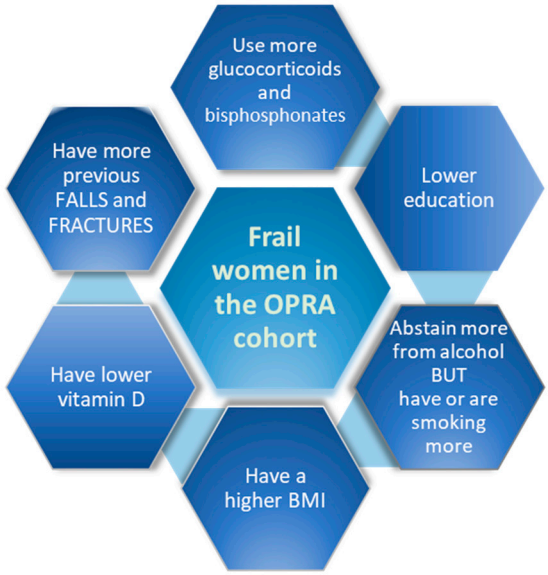


Figure 18. General characteristics of frail women in the OPRA cohort at age 75

Prevalence and progression of frailty

With a frail state defined as FI ≥0.25, 23.5% of the women were already frail at baseline. After 5 years the prevalence increased to 39.3% and after 10 years more than half of the women were frail (56.8%) (study 2).

For 75-year-old women the mean frailty index was 0.17 and this was almost doubled at age 85 (0.32). Over 10 years this approximated an annual progression of 6–7% (Figure 19, see also fig. 15 a and b).

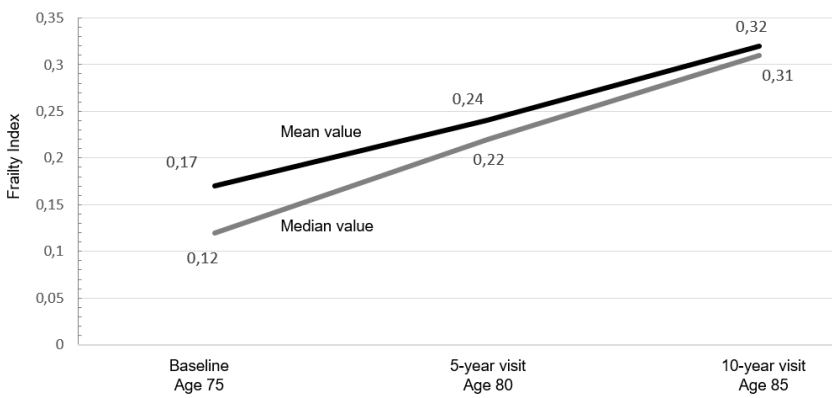


Figure 19. Frailty index in the **OPRA cohort at ages 75, 80 and 85 years of age**

The progression towards higher frailty is further illustrated in Figure 20 where women were stratified in quartiles by their frailty status at baseline. After 10 years, only 4.7% of the women remained in the least frail quartile.

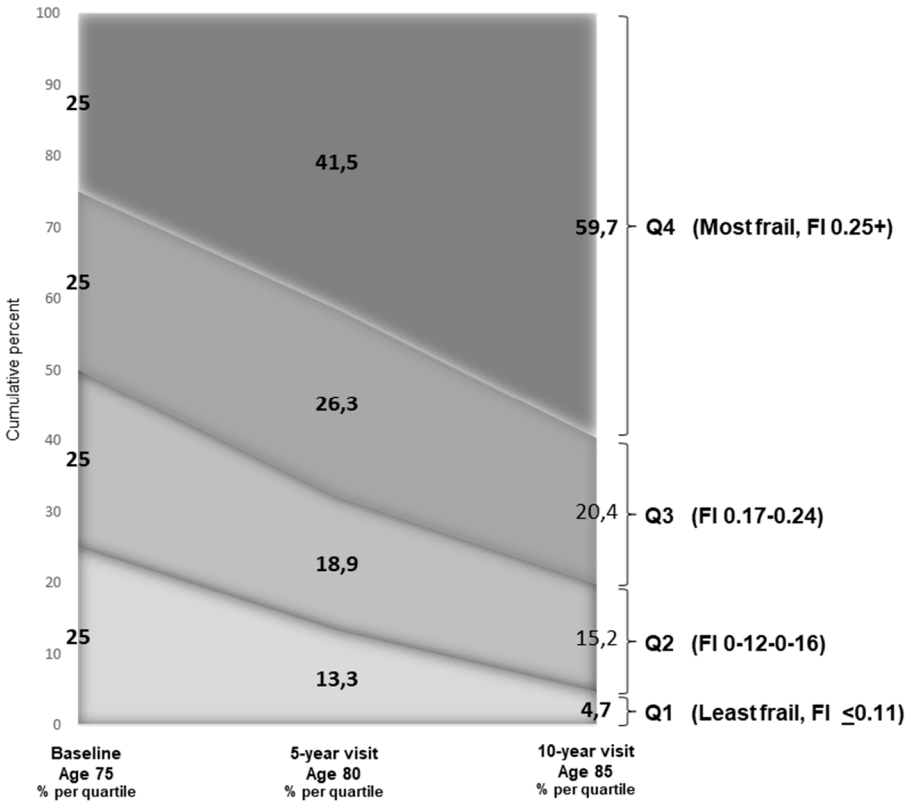


Figure 20. Ageing and the progression of frailty over time
At baseline the distribution of quartiles of frailty are identical (25%). Over 10 years the proportion of "most frail" individuals increases substantially while the proportion "least frail" diminishes. The same thresholds are used at every timepoint (13-variable $_{refined}$ ≤0.02; 0.03 – 0.12; 0.13 – 0.27; ≥ 0.28) (n=1044, 715, 382).

To determine how frailty dispersed over time we defined a group of "super robust" women (FI 0.0–0.1). Over time their proportion diminished, from 48% initially, dropping to 25% at age 80 and 14% at age 85. Over 10 years of study, only 11% of these initially super robust women, remained unaffected (Figure 21).

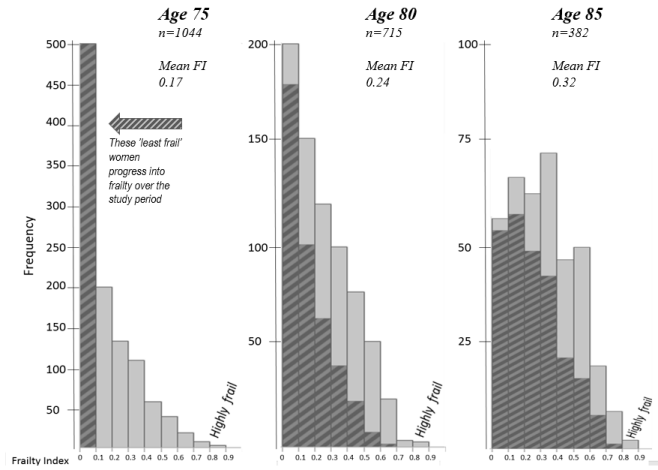


Figure 21. Frailty and change of frailty over time in older women assessed at baseline, 5-year and 10-year follow-up, tracking progression in those most robust at baseline (hatched area)
The three histograms show the distribution of frailty index scores at each visit (baseline, 5 years,10 years). The index is presented in decentiles (0.0–1.0). The hatched area in the histogram on the left hand side represents the LEAST frail women at baseline, and their progression towards increasing frailty over the course of the study (center panel 80y; right hand side panel 85y).

Change in frailty

By definition frailty is a dynamic state and ageing generally leads to higher frailty, but a reversal is possible. In OPRA the majority of women progressed towards a frailer state, but for a small minority their frailty index did not increase. From baseline to 5-year follow-up 32.4% had a FI which increased by 0.10 units or more, compared to only 2.2% whose FI decreased by 0.10 or more. Between 5 and 10-year follow-up the changes were similar with 39.1% and 3.6% respectively (Figure 22 a and b).

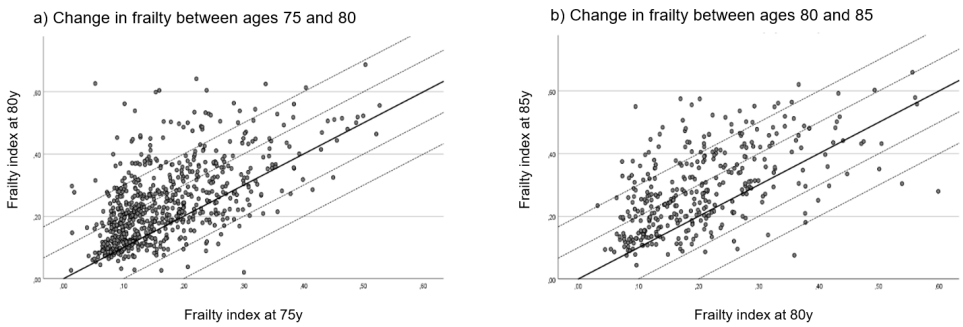


Figure 22. Change in frailty over 5-year time-windows between a) 75y to 80y and b) 80y to 85y
Dots around the zero-line have experienced little or no change since baseline follow-up. Dotted lines indicate change upwards or downwards of 0.1 and 0.2 frailty index points.

Mortality

The women that died during the first 5-year time-window (75-80y) also had the highest average frailty score at baseline (n=105; mean 0.30, median 0.29) which was approximately the same as the mean frailty index of women at age 85 (Figure 23). Mortality was substantially higher among those in the highest quartile (Q4) compared to the lowest (Q1) based on baseline FI. After 10 years almost half of these had died compared to only one sixth of the least frail (49.1% vs 17.2%; p <0.001). Expressed as risk, these frail women had more than three times higher risk of dying within 5 years (Q4 vs Q1; HR_{unadj} 3.26 [1.86–5.73]; p <0.001). The pattern was similar in a 10-year perspective (HR_{unadj} 3.58 [2.55–5.03]; p < 0.001).

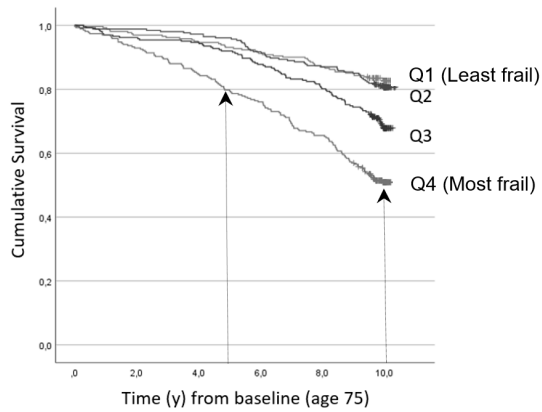


Figure 23. Kaplan Meier analysis showing cumulative survival based on quartiles of frailty at age 75. Mortality was highest in Q4, the highest quartile of frailty compared to the lowest. At 10 years mortality was also higher in Q3. The corresponding mortality risk over the first five years (75-80y) and second five years (80-85y) was highest in the frailest women.

Frailty association with BMD

The proportion of women with osteoporosis increased with age; at baseline, 28.1% were osteoporotic rising to 49.0% after 10 years. At age 75, BMD was 0.773 g/cm^2 (SD 0.131) in the least frail compared to 0.759 (SD 0.150) in the frailest, but not statistically different. However, with adjustment for BMI (which is strongly associated to BMD), the association was significant (overall; p=0.0006 and Q1 vs Q4 p=0.0003). At age 80 the pattern was similar across the quartiles of frailty, but at age 85 no difference was seen, even after adjusting for BMI.

Conclusion

In a cohort designed to assess osteoporosis risk, we showed that is possible to use the variables available to construct an informative frailty index. Frailty increases with age and only one in ten older women escaped the progression of frailty. As expected, being frail was associated with increased mortality, and also with low bone density.

Study 2 - Frailty and falls

Context

Falls are a leading cause of morbidity and fracture. A previous fall is a major risk factor for having more falls, and with more falls comes higher frailty. Study 2 addressed some of the gaps in understanding of how patterns of frailty and falls interact, particularly in those who have not yet entered the falls-frailty cycle.

Methods and subjects

For these analyses the number with information on falls was, at age 75 (n=914) and age 80 (n=704) and 85 (n=371). Information on falls was self-reported and included having had a recent fall (in the previous 12m) and the number of times in this period. Fall outcomes analysed were "at least one fall" and "recurrent falls" (i.e., 2 or more falls). These analyses used the refined frailty index and women were stratified into groups of non-frail (<0.25) and frail (≥0.25) and also divided into quintiles.

Results

Falls incidence

The overall incidence of women reporting having fallen at least once increased at each successive follow-up; from 28.4%, to 31.0% and, at age 85, 44.7%, as did the incidence of *recurrent falls* which almost doubles from age 75–85 (14.7%; 17.6%; 26.4%.). See Figure 24.

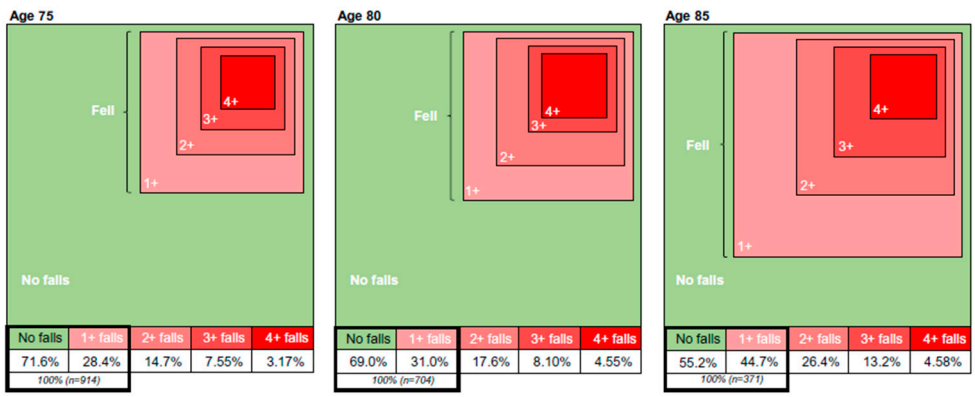


Figure 24. Proportional representation of women who reported no falls, a single fall, or multiple falls in the previous 12 months at each of the three visits (ages 75, 80 and 85)
With advancing age the proportion of women falling increases and the green area, representing non-fallers, shrinks. The fallers are represented with deepening shades of red. At each visit the proportion who had fallen once or more in the previous 12 months increased from 28.4% to 31% to 44.7%. Multiple fallers increase over time as the proportion falling increases.

Frailty and previous and future falls

Being frail at age 75 was associated with having sustained more falls in the recent past i.e. previous 12 months. Already one third (32.6%) of women in the frail group had already suffered recurrent falls during this period and this was almost four times more common than in the non-frail group (8.9%).

Tracking the fall pattern of these women that were frail at age 75, we saw that they continue to have more recurrent falls over 5 and 10 years (Figure 25). Analogue to this, baseline frailty was a significant predictor of recurrent falls (OR_{5yr} 2.55 (1.62-3.99); OR_{10yr} 3.04 (1.63-5.67)). When frailty status was reassessed at age 80 the results were similar (data not shown).

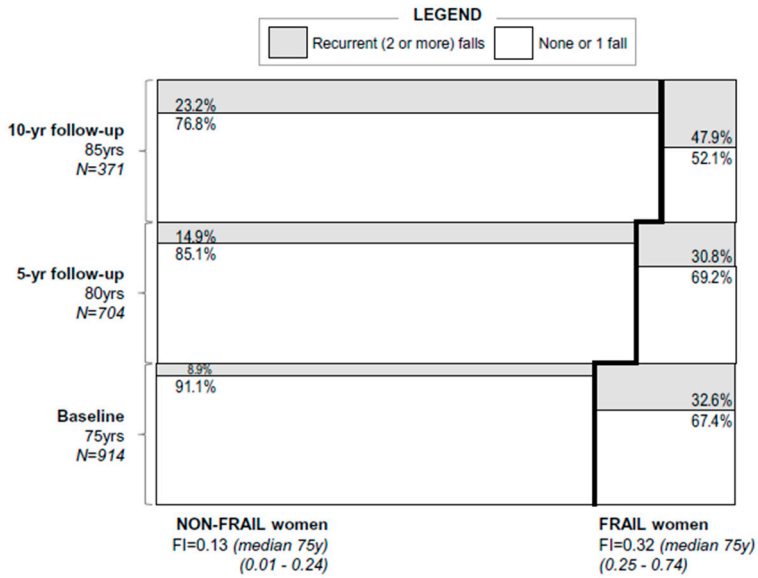


Figure 25. Proportional representation of non-frail and frail women women reporting recurrent falls at at each of the three visits (ages 75, 80 and 85) based on frailty status at age 75.
Women are defined as frail (≥ 0.25) or non-frail (< 0.25) at baseline and we show the proportion at each visit who reported recurrent falls in the previous 12 months. Among FRAIL women, proportionally more reported recurrent falls, compared to non-frail (32.6 vs. 8.9 at 75 y; 30.8 vs. 14.9 at 80 y; 47.9 vs. 23.2 at 85 y). Width of the frail segments narrows with successive visits, reflecting the proportionally higher loss-to-death and nonattendancein the most frail

Impact of grades of frailty on number of falls

Level of baseline frailty (in quintiles) corresponded with the number of falls and there was an almost stepwise increase from Q1 (least frail) to Q5 (most frail), proportionally in the number of falls, both in retrospect (prior to inclusion in the study at 75) and prospectively.

At age 75, women in the highest frailty quintile already had a high proportion (20.2%) who reported multiple falls. In the highest frailty quintile at age 80, 15.7%

had sustained 3 or more falls, compared to only 5.7% in the lowest quintile (p=0.001). At age 85, more than one-quarter of women in the highest frailty quintile had sustained 3 or more falls (26.7% vs. 4.0%; p=0.012) (Figure 26).

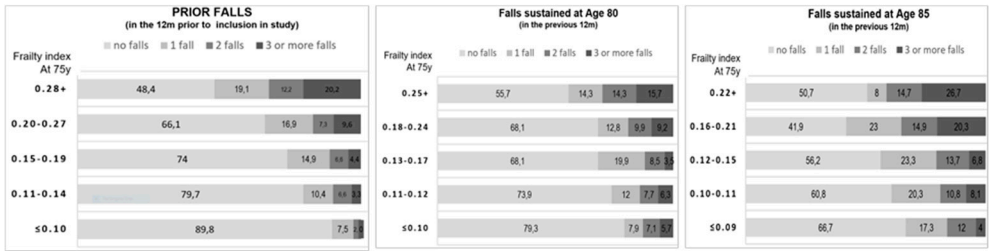


Figure 26. The level of frailty at baseline (age 75) and proportion of prior and future falls
The number of reported falls were stratified into four group (no falls, 1 fall, 2 falls and 3 or more falls). The proportions of these groups were examined in each quintile of frailty, both prior to baseline examination and prospectively after 5 years.

Impact of frailty in women with or without prior falls

To evaluate the independent effect of frailty in women with *no history of falls*, women were grouped into fallers and non-faller.

For those with no fall history at 75y, frailty was a strong predictor of recurrent falls [OR_{5yr} 3.06 (1.59–5.89)] and much more so than for women who already had a fall history [OR_{5yr} 1.02 (0.51–2.06)]. However, with reassessment at age 80, frail women in both groups fell more, and the difference was only significant in women with a previous fall.

The combination of being *both* frail and a faller conferred a significantly higher risk of recurrent falls within 5-years compared to robust (non-faller, non-frail) women (age 75: OR_{5yr} 4.54 (2.35–8.71); age 80: OR_{5yr} 5.82 (2.79–12.56)).

Conclusion

This population-based cohort of identically aged elderly women highlighted that frailty plays a significant role in the aetiology of falls and the reciprocal increase in falls propensity and frailty status. Being frail is a significant predictor of recurrent falls. Interestingly, frailty is a particularly strong predictor of future falls in women who have not yet experienced a fall.

Study 3 - Frailty and fractures

Context

Osteoporosis related fractures are common and preventing them is an important aspect of successful aging.

In study 3 we wanted to explore the association between frailty and fracture, addressing the knowledge gaps including whether frailty can independently predict fracture and if so which fracture types and over what time periods. Specifically, we investigated whether a frail person was at increased short-term risk i.e., over 1 and 2 years as well as longer term (5-10 years).

In older individuals, hip fracture is of predominant interest, but other fracture types were also explored since these may precede a hip fracture. Furthermore, we investigated if early stages of frailty and progression of frailty interact with fracture risk.

Methods and subjects

For these analyses the number with information on fractures was, at age 75 (n=1044) and age 80 (n=715) and 85 (n=382).

Frailty was analysed as frail (≥0.25) and non-frail (<0.25) categories and in quartiles (Q1 least frail; Q4 most frail). Frailty status was assessed at age 75 and reassessed at age 80. The fractures assessed were any, hip, major osteoporotic fractures (MOF) and vertebral fractures. Fracture status was examined in relation to baseline frailty in short (1 and 2 years) and long (5 and 10 years) time-windows, from age 75 and then from age 80 (Figure 16). Fracture risk used models accounting for the competing risk of death.

Results

At baseline almost one quarter (23.5%, n=245) of the women were classified as frail (FI ≥0.25) and these had higher BMI and more glucocorticoid/bisphosphonate use. These frail women had also suffered more previous fractures and falls (p>0.05) (Figure 18). In total 524 (50.2%) women suffered at least one fracture during the total study period (13-17 years) and a quarter 268 (25.7%) women had had two or more fractures at any site.

Frailty at age 75 and short- and long-term fracture risk

Frail women at 75y had a three times higher risk for experiencing a hip fracture during the next two years (Table 9). Proportionally, 4.5% fractured compared with 1.5% of non-frail women (p<0.05). Looking at major osteoporotic fractures the risk was doubled in the same 2-year timeframe (10.6% vs. 5.8%; frail vs. non-frail).

Adjusting for BMD did not alter these results. In frail, but not the non-frail women, smoking further increased the risk of early fractures (data not shown).

In the 5-year perspective frailty continued to associate with increased fracture risk; with frail women having double the risk of a hip fracture. Overall, a greater proportion of frail women had at least one fracture at any site (24.9% vs. 19.1%, p=0.051).

Table 9. Relative risk of fracture for frail women across timeframes of 1-, 2- and 5-years based on being frail at A) age 75 and B) age 80

A) Frail at age 75	1-year risk		2-year risk		5-year risk	
	SHR*	95% CI	SHR	95% CI	SHR	95% CI
Any	1.55	(0.87 - 2.76)	1.70	(1.11 - 2.60)	1.38	(1.02 - 1.86)
Major osteoporotic	1.71	(0.90 - 3.25)	1.89	(1.17 - 3.06)	1.38	(0.99 - 1.93)
Hip	3.94	(1.20 - 12.9)	3.04	(1.34 - 6.88)	2.03	(1.13 - 3.63)
Vertebral	1.19	(0.38 - 3.74)	1.88	(0.79 - 4.46)	1.83	(1.10 - 3.04)
B) Frail at age 80						
Any	1.85	(0.95 - 3.59)	1.59	(1.02 - 2.48)	1.52	(1.13 - 2.04)
Major osteoporotic	1.89	(0.93 - 3.83)	1.79	(1.12 - 2.86)	1.53	(1.12 - 2.09)
Hip	5.43	(1.13 - 26.2)	2.0	(0.91 - 4.39)	1.48	(0.90 - 2.44)
Vertebral	1.86	(0.57 - 6.09)	1.43	(0.63 - 3.24)	1.97	(1.21 - 3.21)

*Subdistribution hazard ratios (reference category non-frail). Frailty status was assessed at each age (75 and 80).

When analysing the cumulative incidence of any fracture, the trajectories of frail and non-frail women at age 75 differed, with the greatest difference observed at 2 to 5 years. The probability of a fracture continued to be elevated after this but across the extended observation period baseline frailty did not discriminate the probability of fracturing, as can be seen by comparable slopes (Figure 27 a).

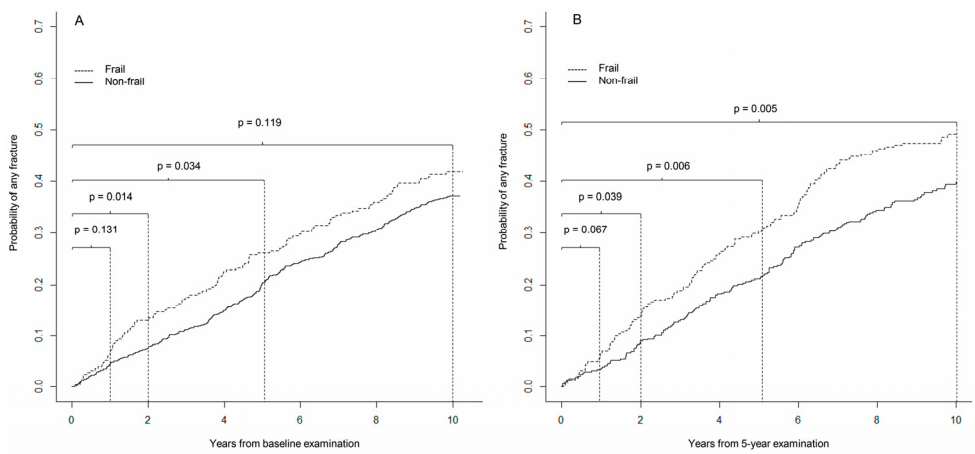


Figure 27. Cumulative incidence of any fracture stratified by frailty status at a) age 75 and b) age 80
For a woman who is frail at age 75 the the greatest difference in fracture trajectory is apparent at 2-5 yrs. Differences in cumulative incidence rates are calculated in the presence of the competing risk of death. For a woman who is frail at age 80 the probability of fracture is higher for the remaining lifetime. Frail (FI ≥ 25) and non-frail (FI< 0.25FI).

Frailty at age 80 and short- and long-term fracture risk

For women aged 80, the short-term association between frailty and fracture was similar in terms of MOF and any fracture (table 1B). Frail women had an elevated risk of hip fracture through the first year but the proportion who fractured was low (2.5% of frail vs. 0.5% of non-frail; p=0.017). After 2 years the hip fracture risk was elevated but not statistically significant.

In the 5-year perspective frailty was less predictive of hip fractures but continued to be associated with a higher risk of any fracture and MOF. For frail women the risk of a vertebral fracture was also doubled. Adjustment for BMD did not change the results. Looking at the incidence trajectories when frailty status was reassessed at age 80 (Figure 27 b) frail women again had a higher probability of an early fracture (any fracture) which continued to be elevated up to 10 years (essentially the remaining lifetime).

Grades of frailty and fracture risk

When stratifying participants frailty in quartiles we saw a clear stepwise association between increasing frailty and the 10-year probability of a first fracture of any type (Q4 to Q1, p=0.03) (Figure 28 a). For a fracture of any type (minor or major), the most frail accumulated their fractures more rapidly – while for the least frail the accumulation was slower, and it took another 2.5 years to reach the same incidence (10%). For hip fracture this difference was even more pronounced – the least frail women took almost five years longer to reach the same incidence (5%) (Figure 28 b). This highlights that frail women are highly at risk, beyond what is expected for their chronological age. As the figure demonstrates, fracture-free time was longer among the least frail women.

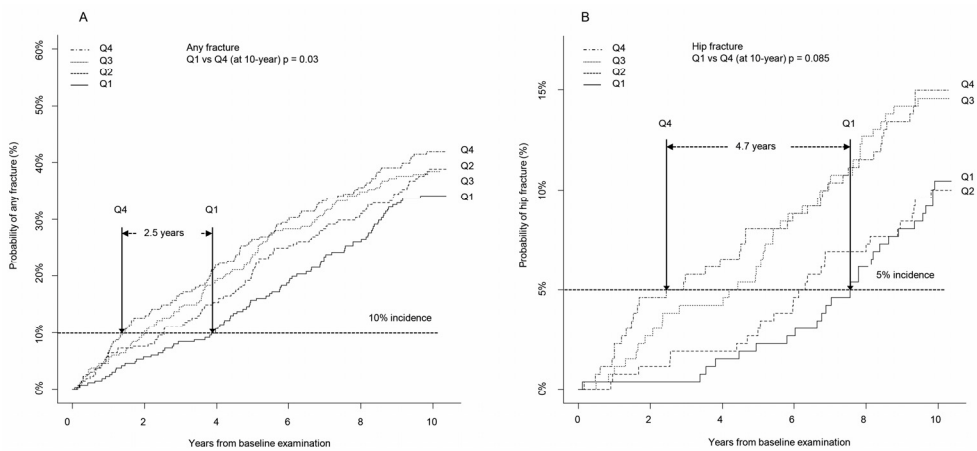


Figure 28. Cumulative incidence of a) any fracture and b) hip fracture, stratified by quartiles of frailty at age 75
The least frail women (Q1) remain fracture free for longer compared to the most frail (Q4) women. This equates to 2.5 years (any fracture) and 4.7 years (hip fracture). Differences are calculated in the presence of the competing risk of death.*Frailty quartiles Q1 (FI ≤ 0.11), Q2 (FI 0.12–0.16), Q3 (FI 0.17-0.24), and Q4 (FI ≥ 25).

Conclusion

For 75-year-old women being frail is a risk factor for fractures in the very near future, within 12–24 months. The risk is most marked for hip fractures and is higher regardless of bone density. Frail women continue to be at higher risk over subsequent years, but frailty status needs to be reassessed regularly since health status can rapidly change with advancing age, which influences fracture risk.

Study 4 - Frailty and the visual perception of health

Context

In clinic, a subjective visual estimation of a patient's general health often guides interventions, yet little is known of how this assessment relates to objectively measured frailty This study aimed to characterise the relationship between the subjective "clinical eye" with a quantitative measure of health i.e. a frailty index. Few studies of this type are available in the literature, and most involve specific patient groups. Furthermore, we examined the conditions under which these measures were concordant or discordant and what the implications were for mortality.

Methods and subjects

At baseline participants were subjected to a visual estimation of general health (VPH). Data on both VPH and FI was available for 1004 participants. Scores were used both as continuous variables in linear regression analysis and in tertiles defining groups who looked to be in "Poor", "Intermediate" and "Good" health (VPH), and for frailty as tertiles equivalent to "Frail" (FI>0.22), "Pre-frail" (0.13-0.21) and "Robust" (≤0.12).

Results

Women in the poor tertile had the highest frailty index (median 0.22; mean 0.25) and also the widest range in values (FI 0.02-0.66). Using an empirical cut-off for defining frail (FI ≥0.25) almost 40% in the poor VPH tertile were classified as frail, compared to only 9% of women perceived to be in the good VPH tertile were actually frail.

VPH correlated with frailty but was strongest in those looking unhealthy (r_s=0.424, p<0.001) and weakest in those looking healthy (r_s=0.129, p=0.021). Women with poor VPH had higher BMI, poorer visual acuity and had reported more previous falls and fractures (Table 10).

Table 10. General characteristics of the OPRA participants overall and stratified by visual perception of health tertiles

		Visual Perception of Health (VPH) tertile		
	OVERALL *(n=1004)*	**GOOD** *(n=365)*	**INTERMED** *(n=311)*	**POOR** *(n=328)*
VPH Range (0-100)	29.4 - 98.9	29.4 - 47.4	47.4 - 50.1	50.4 - 98.9
Frailty Index (median, IQR)	0.16 (0.13)	0.12 (0.10)	0.15 (0.12)	0.22 (0.16)
Frailty Index (Mean, SD)	0.19 (0.11)	0.14 (0.07)	0.18 (0.09)	0.25 (0.13)
Frailty Index (Range 0.00-1.00)	(0.01-0.66)	(0.01-0.40)	(0.01-0.53)	(0.02-0.66)
Proportion Frail (FI $\geq$0.25) % (n)	223 (22.2%)	33 (9.0%)	60 (19.3%)	130 (39.6%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
BMI (kg/m^2)	26.3 (4.19)	24.9 (3.13)	26.7 (4.06)	27.5 (4.85)
Height (cm)	160 (5.8)	161 (5.4)	160 (5.8)	160 (6.1)
Body weight (kg)	67.7 (11.5)	64.6 (8.9)	68.5 (11.0)	70.9 (13.5)
Visual acuity (average both eyes)	0.50 (0.22)	0.54 (0.22)	0.51 (0.21)	0.46 (0.23)
	n (%)	n (%)	n (%)	n (%)
Smoker (current/previous)	334 (33.6)	122 (33.5)	95 (31.0)	117 (36.2)
Alcohol (each week)	174 (17.5)	91 (25.0)	48 (15.6)	35 (10.9)
Education (elementary school level)	546 (54.5)	170 (46.4)	182 (58.9)	194 (59.1)
Fallen in previous 12 months	250 (28.2)	76 (23.1)	74 (25.1)	100 (38.3)
Any fracture between ages 50-75	367 (37.0)	124 (34.3)	101 (33.0)	142 (44.0)
Surgery within last 5 years	218 (23.6)	64 (19.0)	64 (21.8)	90 (30.9)

Concordance and discordance between VPH and FI

Figure 29 shows the distribution of frailty scores within the good and the poor VPH tertile. In the “Poor” and “Good” tertiles of VPH approximately 50% also belonged to the reciprocal frailty tertiles, while 16% were discordant i.e. visually perceived to be in good health but measured as frail by the frailty index or vice versa. In those allocated as good VPH, no one had a FI above 0.40.

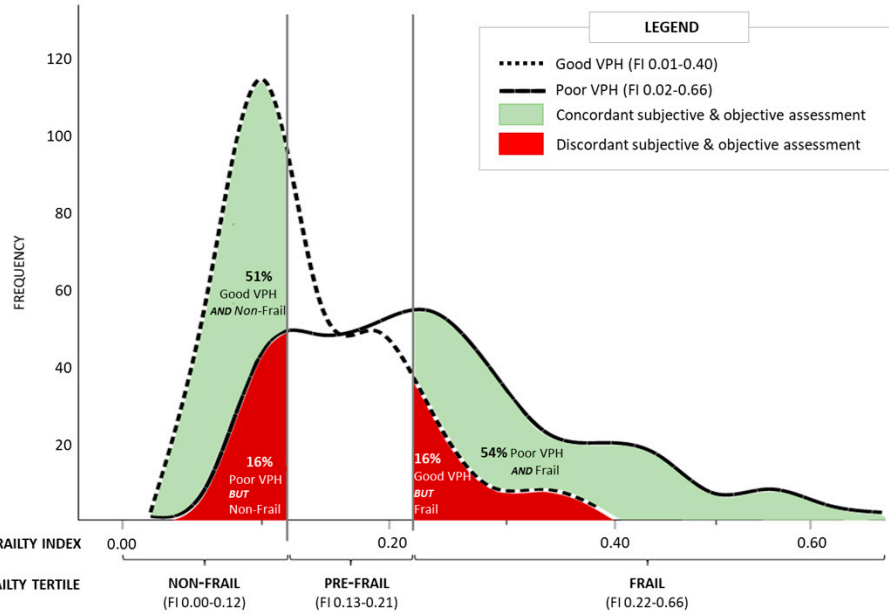


Figure 29. Distribution of frailty scores within the poor and good tertiles of Visual Perception of Health.
The green area represents agreement been the subjective visual estimate and measured frailty status. The red area represents disagreement i.e. how the individual looks does not reflect their measured frailty status. By 'eyeballing' it is easiest to correctly judge an individuals health if they look to be in very obviously good health or very poor health, but pre-frail can't be identified.

VPH and the components of the frailty index

To understand which factors in the frailty index that contributed to the visual perception of health we analysed the individual components of the frailty index within the tertiles of VPH. The majority of the frailty index variables showed an association to VPH (11/13) with overall better musculoskeletal performance (gait, strength and balance) in those perceived in good health and conversely for those in bad health.

Mortality outcomes for subjective and objectively measured health

Poor health, regardless of whether subjective (VPH) or objective (FI), was associated with increased 10-year mortality, but the discriminative abilities differed. In those that visually looked to be in good or intermediate health there was no difference in mortality. By contrast, in the reciprocal tertiles of FI discrimination was seen; where pre-frail women had a higher risk of mortality than non-frail (Figure 30 a and b).

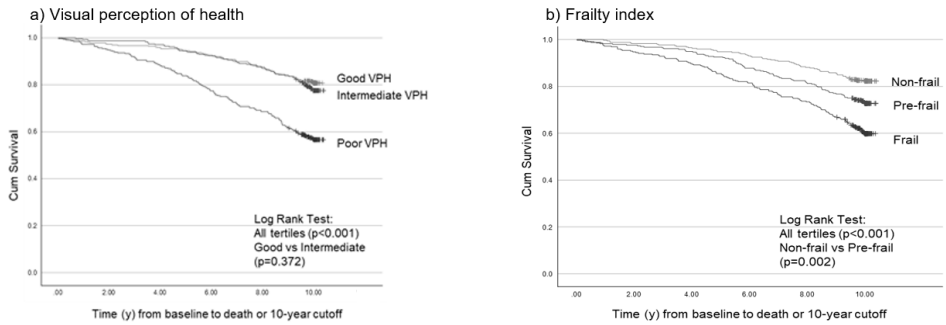


Figure 30 a and b. Ten-year mortality stratified by tertiles of a) visual perception of health and b) frailty index
Individuals who were classified into the tertiles 'poor VPH' ' or 'frail' had an associated higher 10-year mortality. As can been seen in b) only by objectively measuring frailty is it possible to see that those who are pre-frail also have an associated higher mortality.

Looking at the possible long-term implications of discordance between the two scores, women appearing to be in good health but were quantifiably pre-frail had a higher mortality than those non-frail (log rank test; p=0.015). However, frail women (n=58) in this group did not significantly differ from non-frail. Conversely, in the group of women that appeared to be in poor health, being objectively non-frail was associated with a lower mortality risk (HR 0.57 (0.34-0.95)).

Conclusion

A brief 'snap-shot' estimation of general health was associated with quantified frailty, predominantly in women looking unhealthy. When estimating good or poor health, every second time the observer's classification agreed with the classification of a frailty index.

Although a mere eye-balling recognizes frailty fairly well, in one in six women these classifications were diametrically opposite. One implication of this was that women that *looked* as in poor health but were in fact *measured* non-frail or pre-frail, had lower 10-year mortality.

Pre-frailty cannot be captured by a subjective visual estimation. To capture this clinically important sub-group quantitative assessments of frailty are advisable. Finding pre-frail individuals in those looking healthy could pinpoint a group with a steeper trajectory into frailty, and in need for intervention.

Discussion

With increased age comes increased risk of age-related conditions, in this instance osteoporosis related fragility fractures. But above and beyond chronological age, this thesis investigates how taking biological age into consideration could add to our understanding of musculoskeletal adverse outcomes.

Construction of a frailty index

Frailty in the context of osteoporosis and musculoskeletal health is still in its infancy. An instrumental gap in knowledge addressed was "Can a measurement of frailty be created in a cohort that was not originally designed to address frailty?"

The most widely used operationalization by Fried (30) could not be used because of the lack of "weight loss" and "exhaustion" variables, therefore a deficit accumulation index (FI) less dependent on specific variables was created (56). A FI is recommended to include 30-40 variables, but this study showed that a 13-variable index (available at all three ages) was comparable to a 40-variable index. Validation confirmed similar distribution of the index values cross sectionally, similar accumulation over time, and an almost identical association to mortality. With a high correlation and close similarities, this demonstrated that the smaller index indeed captured the same construct, equivalent to a more extensive FI. The wider implication from this is that it opens up the field for future research in frailty in other existing osteoporosis cohorts.

In the literature there are many operationalizations of frailty and the number of variables used range from one single to 92 (17, 47). When reflecting on the sufficient number of variables needed to capture frailty, it is important to point out that many variables interconnect, and a deficit in one variable often affects others. When somebody has problems with arthritis this will also affect their ability to tie their shoelaces or lead to lesser time spent outdoors, and somebody with advanced colon cancer would answer "yes" to a question about weight loss. No single variable is an independent entity, therefore, for a specific domain and if there are no available variables in the data set, other variables in other domains can still capture this. A notable example of using few variables that interconnect (but still captures a wider picture) would be the frequently used Fried frailty phenotype, comprising of only

five variables (30). In the extreme end is also handgrip strength, which is frequently used alone as a proxy for frailty.

There are pros and cons for using many or few variables. Using an operationalization requiring many variables can be problematic; many frailty indices depend on self-reported data. This is very convenient when studying cohorts but could be a weakness in terms of accuracy and potential bias. The Fried Frailty Phenotype and even more the Clinical Frailty Scale (162), developed for purely clinical settings, are on the other hand simple to use, but might lack the ability to detect minor impairments, making them too crude to sufficiently detect pre-frailty.

Frailty in community-dwelling older women

The true population prevalence of frailty is difficult to pinpoint. A systematic review suggests that among community-dwelling older populations the range is between 4.0 – 59.1% (10). In the OPRA cohort the prevalence of frailty doubled over 10 years - from one of four women at age 75 to more than half of the women at age 85. One similar study in a mixed Dutch population (75+) (163) showed a somewhat slower accumulation with a doubling of the number of deficits over 12.5 years. These findings together indicate that a fast progression takes place after age 75 and highlights the definite need to address and prevent the development of frailty even before this age. Due to the single-age design of the OPRA cohort, there are few comparable studies that can capture this precise age-specific change in prevalence. In the longer term this data could provide important information for future health care policies.

There was a linear increase of frailty by 6-7 % per year, which was higher compared to two other studies (17, 56). Knowing that the progress of frailty reaches a critical state where the physical reserve capacity is too low to respond to a stressor, it is reasonable to believe that frailty accelerates in a population once a threshold has been passed. This acceleration into frailty is however not homogenous. In study 1 the progression of a least frail category (0.0-0.1) at baseline was tracked. Here we saw that these women diverged over time and followed different trajectories into frailty. After 5 years half of these women had not progressed to a worse state of health, but after 10 years only around 10% had managed to maintain their initial health and escape frailty. What factors that determine this “super group” was beyond the scope of this thesis but poses interesting questions for further research.

Mortality was not surprisingly highest in the frailest (up to 3 times higher) but pre-frail women also had a higher risk. Frailty increments lead to gradually higher mortality demonstrating the sensitivity and utility of the frailty index. The strong association to mortality and incapacity was further demonstrated when comparing groups that survived to those who died or couldn’t attend. Those 75-year-olds who

died within 5 years of baseline had a mean FI equivalent to women 10-years older, this indicates that their biological age at age 75 was equivalent to a woman aged 85. Those who were still alive five years after baseline but unable to participate in the study were biologically only 5-years older than their attending counterparts.

The osteoporotic patient is assumed to be more frail, therefore, we hypothesized that the frailest women would have lower bone density. This was also the case, but only after adjustment for BMI. Interestingly BMI was higher in those with higher frailty, indicative of an accumulation of conditions resulting in an overall decreased health status and reduced activity. The most typical patient with osteoporosis often has a small frame and low body fat, but this study demonstrates that bone health should be considered in women with higher body weight, because if they are frail they are likely to have lower than expected bone density.

Frailty and falls

In the elderly falls are common, but what makes someone "a faller"? To understand patterns and propensity to fall, this study investigated frailty, falls and their interaction.

Estimates of falls propensity that relate to age are instrumental for understanding associated injuries, where fractures are perhaps the most relevant. In OPRA falls incidence increased between 75 y and 85 y (from one-third to almost half), with the most drastic change between 80 and 85. These changes also affected the number of falls women had. In other mixed-age studies this precise change was difficult to capture (127, 164, 165). In the National health and Aging Trends Study fall rates from 29 - 38% were reported in a slightly younger population including men, but among those 85-89 years old rates were 42%, which was similar to our findings (166).

A primary interest was to study frailty in relation to recurrent falls rather than the arbitrary nature of a single fall, on the assumption that frequent falling stems from age-related intrinsic changes and failure of multiple physiologic systems, potentially captured by frailty.

For 75-year-old women, being frail was a significant risk factor for frequent falls for more or less the rest of their life. This provides long-term evidence far beyond the one-to-3-year perspectives of previous studies (30, 134, 164, 167, 168). Such women are in a dangerous falls-frailty cycle which is difficult to depart from, and therefore these findings emphasize the importance of *not* entering this cycle to maintain a good quality of life.

A previous fall is a strong risk factor for future falls (169), and a high falls propensity may well be a good indicator of high frailty. This mutuality was also apparent at all

investigations in our study; those with highest frailty also had had most falls in the previous year.

To dissect the contribution of frailty, its effect on future falls was examined in women *with* or *without* previous falls. Fallers and non-fallers had distinctly different future-falls pattern and the impact of frailty varied with age. At age 75 frailty was an important risk factor for women *without* a history of previous falls, conferring a three times higher odds for recurring falls in the future. For those that already had a history, the fall was more of a proxy for frailty than the index, and the FI was less predictive. We speculate that this is a consequence of having entered the falls-frailty cycle and the high correlation between falls and frailty. Interestingly and conversely, at age 80 frailty was a similarly important risk factor but for women *with* a history of falls. The falls-frailty relationship is complex and almost impossible to fully dissect since other major factors contribute. In a mixed-sex population (mean 70.1y) one study showed how frailty was more predictive in non-fallers, but in another only-female study (mean 69.4y) the opposite was reported (168, 170); implying that risk factors could be both age and gender-specific.

One important objective of frailty research is identifying individuals before they become frail. Our study demonstrates that a stepwise increase in frailty associates with an increasing number of falls, both at age 80 and 85. These findings demonstrates that even lesser frailty is important in terms of the risk of future falls - implying that careful assessment of frailty in the elderly would be beneficial for fall prevention and possibly forestall the cycle of frailty and falls.

Frailty and fractures

Fractures play an important role in the transition from independence to dependency, but still today it is notoriously difficult to predict who will fracture. The role of frailty as a risk factor is little investigated and this study aimed to add further knowledge.

In accordance with previous findings (171, 172), frailty was associated with a higher risk of fractures. An important clinical feature that was identified in the study was that that the elevated risk was present already within the following 12-24 months. At age 75 frail women had a 2 to 4 times higher risk of a hip fracture than non-frail, already within the first year. Within two years the risk of having a major osteoporotic fracture (MOF) and indeed any type of fracture was also almost doubled, independently of BMD status. At age 80 frail women were at high risk of sustaining a fracture of any type within the short-term, but not specifically hip fracture.

In terms for understanding risk for hip fracture we know that risk increases as age increases. But being frail confers a risk that goes beyond what is expected for chronological age, particularly in the early seventies. By the ninth decade everyone has become more frail and the associated fracture risk is similar. Another study finds similar results where the association between frailty and hip fracture is lost in participants aged 65 or older (173). Whether this is explained by the wide age range, a transition to less physical activity, impaired mobility, or that the impact of frailty manifests differently (174) is unclear.

As age increases risk factors for fracture accumulate and health can rapidly change. Since frailty progresses at different trajectories and is dynamic it is most meaningful to use over short time windows. Its value deflates over long durations. We saw that over five years a higher fracture risk persisted, but over 10 years both frail and non-frail women were similarly at risk. Long-term projections are therefore less meaningful and the value of assessing frailty status lies in its relationship to immediate fracture risk. Therefore, it needs to be reassessed regularly. This is illustrated by the fact that when frailty was reassessed at age 80, it was again predictive of short-term fracture risk. Even if other studies suggests long-term associations with fracture (164, 173, 175, 176) the immediate implications of being frail are considerably more important, given the relatively short remaining life time in the elderly.

With age more fractures accumulate in the population but frailty status will affect the rate of accumulation. In the most frail group, we saw that the incidence for any fracture was also higher. Essentially this means that for the group of most robust women it takes two and a half years longer to accumulate the same number of fractures as frail women. Looking at hip fractures this delay was even longer, almost 5 years. To put this in a more clinical context, this means that for a hip fracture, within 2 years 5% of frail 75-year-old women will have had a hip fracture, while for non-frail women it would take 7 years to reach the same incidence. This important evidence could be acquired because of the unique single-age design of the study and demonstrates that frailty assessment provides valuable information about fracture risk that goes beyond chronological age alone.

This study corroborates that frailty leads to fracture, and that fractures leads to higher frailty (177), highlighting just how critical the musculoskeletal component is within frailty since fractures leads to functional decline. Fracture prevention, primary or secondary can influence the trajectory of frailty. In OPRA, even women who had suffered a fracture prior to the age of 75, but thereafter managed to remain fracture free for 10 years, could have the same frailty trajectory as women that never fractured. This finding advocates the benefits of secondary prevention. Based on the data from this study, clinically it is essential to initiate interventions with immediate effect (preventing falls through home environment adjustments, initiate medication reconciliation and balance training etc.) (178, 179) in conjunction with antiosteoporosis medication, which have a longer time to take effect.

Frailty and the visual perception of health

In clinic situations a mere "eye-balling" often serves as an estimation of a patient's health. Quantifying frailty status, on the other hand can be time consuming. We tried to answer the questions: "Do these two approaches capture the same thing?" and "when is relevant to perform a frailty assessment?".

In women estimated visually to be in good or poor health, more than half were also correctly classified as quantitatively non-frail or frail. However, the visual assessment (VPH) was not fully reliable with as many as 1 in 6 women incorrectly judged. The relevance of this is that women who appear on the surface to be in good health could already be frail or pre-frail and on the verge of a trajectory into frailty. A similar poor reliability has also been shown in other studies, although these were performed in specific patient groups rather than in a population-based study (139, 141, 142).

Overall, there was a moderate correlation between VPH and FI but stronger in those that looked in poor health i.e., presumably because of displaying more visual cues. Examining the separate components of the frailty index to understand which are the most important visual cues, VPH was associated to almost every variable, particularly walking ability, muscle strength and balance. Previous falls and fracture, which affect walking ability and balance, were more common in those that looked most obviously in poor health. This association between visual perception and mobility is also reported in other studies, with the strongest visual cue being the use of mobility aids (139, 140, 142). Although these may be the most obvious signs of frailty numerous other signs influence judgement, including overall presentation, general coherence, facial expression, and perhaps even smell. Interestingly VPH also associated with inflammation, polypharmacy and diabetes which indicates the importance of the "clinical eye" in making assumptions from all possible cues.

Previous studies, including in the OPRA cohort, have shown that a subjective health assessment predicts mortality (136, 140, 143, 180). In the current study, being frail or looking in poor health were both associated with higher 10-year mortality, but only the FI could discriminate a pre-frail group whose mortality risk was also higher.

Misjudgement of health had clinical implications, women appearing to be in good health but who were quantifiably pre-frail had a higher mortality than might otherwise be expected from a visual estimation alone. The reverse side of this was that there were also women who looked to be in poor health but actually measured as non-frail, whose mortality risk was lower than expected from a visual estimation.

This study showed that "eye-balling" reflects frailty fairly well and undoubtedly provides valuable complimentary information. However, the findings from this study together indicate that an objective measurement of frailty has the sensitivity to identify women with a worse outlook, but also better outlook, which could have

implications for treatment strategies, for overall health and for fracture management.

Clinical implications

This thesis makes an important contribution to the field of frailty and musculoskeletal research, describing the clinical consequences of frailty in a representative, relatively healthy population of women on the verge of old age. 75-years is a pivotal age where many experience a transition from an independent to a dependent life. Maintaining musculoskeletal health is a vital for preventing dependency and in a broader sense a key factor for a successful ageing. This thesis demonstrates that frailty, both overt but also earlier stages, is strongly associated with musculoskeletal health, both in terms of falls propensity and fracture risk. While frailty assessment is becoming increasingly common in clinic, and especially so during the recent COVID pandemic, this thesis supports that frailty, affecting many aspects of health, should be part of the standard examinations in the older population.

- In terms of falls, even early stages frailty are important to detect, since they are associated with a higher number of future falls. Therefore, the sensitivity of subjectively measured frailty could be utilised in falls prevention and possibly avert the cycle of frailty and falls.
- Frail women are at higher risk of fragility fracture, particularly hip fractures already within the coming two years. This means that interventions that have immediate effect (preventing falls) have an even higher priority and should be implemented alongside antiosteoporosis medication.
- A quick visual estimation can give valuable information of an individual's general health, but is less efficient when declines have just begun and are not yet visible. Assessing frailty could help in finding individuals that are in need of early interventions, to stop or delay the trajectory into frailty.
- Frailty should be evaluated as a part of the general practitioner's routine because it is a feasible assessment of general health that, better than separate single diagnoses, prognosticates healthy aging and future adverse events.
- Frailty is better indicator of "true" age than chronological age and therefore an important consideration in clinical decision-making e.g. whether a new medication or a surgical procedure is likely to be tolerated.

Strengths and limitations

Strengths

The primary strength of the studies lies in the OPRA cohort itself; the relatively large scale and the extensive follow-up time, more than 15 years, allowed investigation of frailty and musculoskeletal outcomes in different timeframes, from the old to the very old. With re-assessments after 5 and 10 years the consistency of associations over time could be tested and changes in frailty status with advancing age followed. Thus, offering a long-term viewpoint on the significance of frailty for successful aging.

Another strength of the OPRA cohort is that the participants are randomly selected community-dwelling older women. Covering one third of all 75-year-old women in Malmö at the time of inclusion this provides a representative cross section of women in a pivotal phase where harmful changes, including falls and fractures, accumulate at higher rates. Thus, the findings from our studies provide essential data for prevention strategies aiming to reduce the impact and consequences of frailty. Furthermore, the unique identical-age design of the cohort enabled us to separate the frailty component (biological age) from the chronological age, and thereby avoid age-adjustments.

Additionally, we show that a meaningful frailty index can be constructed from a cohort not necessarily designed for the purpose. Using available data, we created an index with the same discriminatory ability as a larger more comprehensive frailty index. This could potentially be applied to other cohorts with similar limitations and therefore beneficial to future research in osteoporosis.

A common problem in longitudinal studies of the elderly is the competing risk of death. To minimize the potential for bias or overestimation we used statistical models to account for this.

Limitations

There are also limitations to acknowledge. One potential weakness in the construction of the OPRA-specific frailty index is that it was applied to the same population that it was derived from, and that it has not been validated externally. However, the subsequent refined index we created used variables but without dichotomization thereby making it less dependent on derived thresholds. Since these indices are highly correlated this could be considered a pseudo-validation.

Although our frailty index used fewer variables than the recommended 30-40, we demonstrated that the 13-variable index correlated highly and was almost identical in predicting mortality. The is due to a high interrelationship between variables, where a single variable captures almost the same construct as multiple other

variables. The frailty index was also strongly associated with a number of deficits in ADL and IADL, commonly utilized in larger frailty indices.

Lately there have been calls to include *social* and *psychological* factor to capture the vulnerability of an individual in its full context. Such data was not available in the OPRA cohort because it was not designed to specifically address frailty. Even if these factors were not directly measured, the frailty index showed a clear association with variables e.g. “life satisfaction”, “experience of mental stress or disease” or “feeling of deterioration in health”, available at follow-ups.

Potential sources of bias need to be considered: in longitudinal studies of older persons there is an inherent difficulty with loss to follow-up and therefore a potential selection bias of healthier participants remaining in the study (181). This was also apparent in our studies with those continuing in the study being less frail than those who were lost. The reduced number of participants could potentially lead to a loss of power; however, for outcomes like falls and fractures the incidence increases with age and therefore the study is likely to be sufficiently powered.

When using self-reported data there is a risk for recall bias. With falls there is a danger that the participants cannot sufficiently remember how many falls they have had. Although we employed a 12-month time-window, deemed as a sufficient period to accurately recall, an even shorter timeframe might have increased reliability (182).

As for all studies, caution should be exercised in terms of extrapolating the results outside the population of elderly women studied. The results may not be directly applicable to younger women, men or other ethnicities. In addition, the diversity of frailty instruments and operationalisations used in the literature makes direct comparison with other studies difficult. The results are in general agreement, but it illustrates the need for a consensus on frailty should be defined and measured.

Conclusions

This thesis investigated how a multi-component measurement of frailty is associated to musculoskeletal outcomes in elderly community-dwelling women. We showed that:

- It is feasible to construct a frailty index from standard data collected in a typical osteoporosis cohort.
- At age 75 frailty progresses at around 6-7% every year and only 1 in 10 of robust women maintained their healthy status over 10 years. Frailty was associated with a higher mortality, both in a short and long perspectives.
- Frailty is key-player in the aetiology of falls and the reciprocal relationship leads to a falls-frailty cycle with recurrent falls and increasing frailty over the remaining lifetime.
- Frailty increases fracture risk beyond what could be expected by age alone. In a two-year perspective frail women have an elevated risk of hip and major osteoporotic fractures.
- A visual estimation of health can identify the most or least frail and could provide complementary information on health. It is however less accurate than an objective frailty assessment in finding pre-frail individuals.

A frail individual risks low bone density, falls and fractures. Identifying individuals before they pass a threshold of depleted reserve, from which it is difficult to recover, requires a holistic approach - one part of which should be maintaining musculoskeletal integrity.

Future perspectives

Frailty – Interventions

Worldwide, people are living longer, and in every country there is an expected change in demography towards an even older population. By 2050 the number of persons aged 80 years or older is estimated to reach over 400 million (183). With vast social, economic and personal consequences, preventing frailty is a critical issue. Frailty is thought of as a dynamic condition, with changes to the worse but also to the better (something that is also seen in our studies). Therefore, intervention would be possible, at least in theory. Many studies exist, with different strategies and settings, but also with very mixed results.

Exercise is probably the most explored intervention which is reasonable considering the close connection of frailty to decreased mobility. Most studies are small with very specific interventions and outcomes, and reviews and meta-analyses provides the clearest overview.

In a systematic review using nine randomized control studies (n=1067 older people, 71.8% women, mean age 82.3) de Labra et al examined the effect of strength training, multicomponent exercise and physical comprehensive training in frail older adults (184). The longest intervention lasted one year but the majority less than 6 months. The frequency of the training varied from 2-5 times a week. A positive effect from exercises on falls was found in 3 of 5 studies. The effect was less decisive on balance performance, with only one third of the studies showing an effect. The majority (5/7) of studies saw an effect on muscle strength, and one study reported an association to becoming less frail (using a Fried score). The review summarises that a decisive conclusion about the optimal program remains unclear.

Another meta-analysis by de Vries et al including non-frail and pre-frail elderly and focusing patients with problems with mobility, disability and/or multi-morbidity, showed that physical exercise had a positive effect on mobility and physical functioning (185), and that high-intensity exercise could be more effective than low-intensity. One important consideration is whether the effect of exercise is sustained after the intervention has ended. This is less studied, and de Vries finds only one study, using a personalised approach, that showed significant effects 6 months after (186).

This question of a sustained effect is addressed in a Cochrane review on mobility training (187). Treacy et al looks at frail community-dwelling elderly (65+) and evaluates the effect of mobility training on two outcomes: *function* and *mobility*. Training improved the level of *mobility* during the intervention, and the effects were maintained 6 months after completion. For *function* the results were less clear and most likely not sustained. The training had uncertain or no effect on adverse outcomes such as admission to nursing care facilities, and no effect on falls and mortality.

Poor nutritional status has often been mentioned as key element of developing frailty. This is especially true when frailty is defined by the phenotypic frailty of Fried et al (30), describing a vicious cycle of dysregulated energetics leading into frailty. The resulting typical "shrinking" in the elderly is not fully understood and many changes such as muscle wasting (sarcopenia), changed dietary intake and metabolic/inflammatory changes could be involved (188). As nutrition poses a clearly modifiable risk factor it has been the subject of many studies, but studies focusing on interventions and frailty outcomes are fewer.

In a review by Manal et al (189) the effectiveness of nutritional interventions on older adults with frailty was reported (n= 2216; frail and pre-frail). Twenty-four studies (16 RCTs) were used that reported the outcome of the trial as changes in frailty or frailty indicators. Four groups of interventions were identified: specific nutritional supplements, fortifications of daily food with protein, nutritional counselling/education, and supplementation of micronutrients (Vit D, Omega 3 and multivitamin). Studies using energy supplements showed significant improvements in frailty indicators, while counselling/nutritional advice was ineffective. In general, modifications by supplements or improved diet intake improved strength and walking speed of pre-frail and frail older adults in the majority of studies. Studies that combined nutrition with exercise showed a stronger effect from exercise, suggesting a combination of the two may be the most effective intervention (190).

Other possible interventions have been suggested including lifestyle and behavioural changes (191), cognitive health maintenance and perhaps most interesting, individually tailored interventions (192). From systematic reviews we have seen that results vary greatly and no single intervention seems effective for all. Many of the suggested interventions are general in character and often include the above-mentioned strategies. However, with these results there is some doubt over how effectively these interventions target the sources of frailty, and one reason for this could lie in how we define a frail person.

With a great number of frailty scales containing vastly different variables it is apparent that frail individuals have heterogeneous deficits defining them as frail. To give an example, the frequently used Fried operationalisation of frailty uses five typical traits or manifestations: slowness, weakness, exhaustion, weight loss and low physical activity. If someone is deficient in three of these, they will be counted

as being frail. However, the physiological underpinnings of these traits can be very diverse e.g. reasons for low physical activity could be a fracture, neurological problems, heart failure or a number of other ailments (Figure 31). This is also true for other manifestations. Therefore, the underlying physiological problems or pathophysiological profile will not be the same for all frail and it is possible that interventions will miss the target, or at worst, even be harmful. Moving from a disease-specific towards a holistic view on human health, there might also be a need for frailty research to take a personalised approach on interventions.

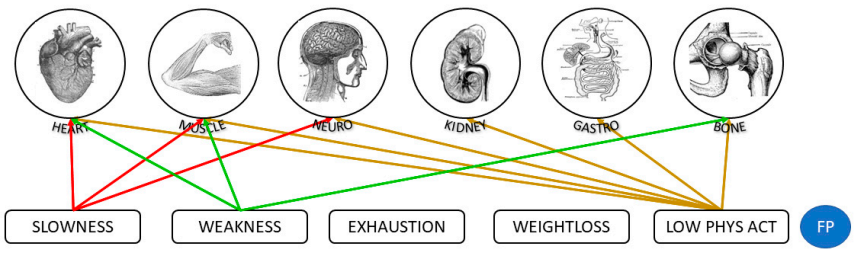


Figure 31. The five manifestations of frailty in the Phenotypic frailty (FP) model suggested by Fried et al. A deficiency in a manifestation could have different physiological explanations and consequently require different interventions.

Pre-frailty

Pre-frailty denotes an intermediate state of accumulated age-related deficits that portends clinically identifiable frailty (193). The pathophysiology of pre-frailty is not yet clearly understood (194) but often described as an early stage in the continuum of extrinsic and intrinsic changes in the whole body, that eventually leads up to frailty. While difficult to correctly assess, the global prevalence of pre-frailty has been estimated at 42% in community-dwelling adults aged 65 or more (195).

This early stage of frailty could be clinically silent. Detecting it is however important, especially in a still healthy and independent population, because pre-frailty is a primary contributor to the trajectory into overt frailty (137, 138), and the pre-frail have a more than double the risk than non-frail of becoming frail (30). Current thinking also suggests that interventions for the reversal of frailty would be more effective in the pre-frail, rather than in those that are already frail (196-198). Because of less disability in the pre-frail group, it is also possible that these could be submitted to more rigorous interventions.

Pre-frailty is also a risk factor for other adverse events. In the current thesis the focus was not explicitly investigating pre-frailty as a risk. However, during the course of

research it became gradually clearer that this state is also important and poses a higher risk to many outcomes, when compared to robust women. In the studies we found that only moderately frail women (Quartile 2) had double the risk of a vertebral fracture over 10 years; that pre-frail women had a higher number of future falls and also a higher mortality. We also saw that quantified pre-frail women had higher mortality in a group of women that visually appeared to be healthy, and that a visual inspection wouldn't sufficiently capture pre-frailty.

How do we find pre-frail individuals? The answer is not straight forward, and it is possible that current frailty scores are not sensible enough. The Fried phenotypic frailty uses five physical trait and when a deficit is present in one or two of these an individual is considered pre-frail. Considering the categorical nature of this method, plus the above-mentioned reasoning on different pathophysiological profiles, it is unlikely that this would suffice to capture the small and sometimes silent changes of pre-frailty. A better option would be the deficit accumulation index or frailty index, which creates a continuous scale where earlier changes could be captured. However, most frailty indices rely on visible signs and symptoms of frailty so invisible signs would not be found. Another more interesting approach is the use of biomarkers, that has the potential to detect age-related cellular changes already at an early age, before any organ dysfunction is detectable (29) (Figure 32). There are a number of potential advantages using biomarkers such as simplicity (if only using blood sample), high potential for early screening, providing "cleaner" data by avoiding often biased self-reported data and a potential use of big data analytics. Depending on for what purpose frailty is assessed, there are of course also disadvantages. When assessing the needs and risks of an older population already on the verge of frailty, where social and psychological factors are important, it is unlikely that biomarkers would add anything.

Only few studies have been performed in this field and there is still great uncertainty on which biomarkers would reflect frailty. Howlett et al showed that a frailty index based on standard laboratory data could find older adults with higher mortality risk (199). Mitnitski et al combined biomarkers of cellular ageing, haematology, immunosenescence and inflammation that could discriminate a higher mortality risk over seven years (44). However, a combination of the bio-FI and a standard-FI provided the best discriminative ability. Research is also currently being done in the "omics" field (200), and in our own research group we have identified 8 pro-inflammatory proteins in the OPRA cohort, highly interesting for continued investigation (Mitchell et al, *in revision*). From my own point of view this area poses one of the most interesting and promising aspects of frailty, and in the future I hope there will be possibilities to gain further knowledge.

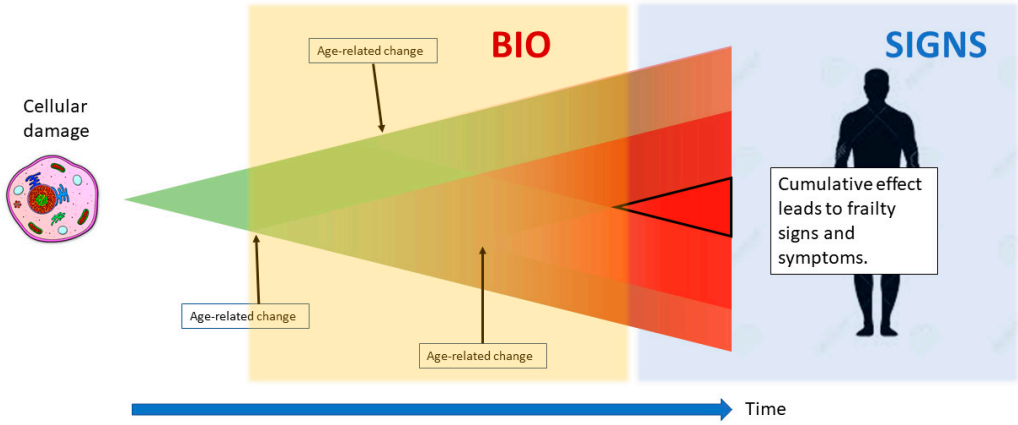


Figure 32. Biomarkers of frailty has a potential to detect biological ageing before overt signs and symptoms.
The figure suggests how age-related cellular damage accumulate over time in different body systems - eventually leading to organ dysfunction and overt signs of frailty.

Svensk sammanfattning

Alla åldras olika. Det är något som var och en lätt kan observera, både på andra och kanske även när man tittar på sig själv. För kliniker inom vården är detta välkänt och man har länge sett att det finns en särskild grupp gamla som är skröpligare och blir mycket sämre än andra om de drabbas av en infektion, ramlar eller något annat stressande. Dessa gamla repar sig inte lika bra som andra, utan förblir dåliga. Hos yngre människor finns en slags reservkapacitet i våra organ för att möta påfrestningar, men i denna grupp menar man att den inte längre räcker till. Dessa benämns ofta som sköra, och inom forskningen använder man det engelska begreppet ”frail” eller ”frailty” när man tänker sig det som något mätbart. När man mäter frailty försöker man få en bild av tillståndet i alla delar av kroppen. På det viset kan man säga att frailty är ett holistiskt mått på vårt biologiska åldrande.

Det har visat sig att frailty är en viktig riskfaktor för många olika sjukdomar och även död. Därför är det viktigt att vi kan mäta det på något sätt så att vi kan hitta dem som är i behov av hjälp. Men hur man mäter detta råder det stor oenighet om: visa forskare menar att mäta handstyrkan räcker, medan andra använder en stor mängd variabler.

Denna avhandling består av fyra delar och är först och främst gjord för att undersöka vilken betydelse frailty har för frakturer och fall, men den vill också undersöka hur vår visuella uppfattning av en persons hälsa förhåller sig till den uppmätta skörheten. Visar de samma sak och om inte, finns det en risk att vi missbedömer hälsotillståndet? Om de mäter samma sak varför behöver vi då mäta frailty?

Dessa samband ville vi undersöka i en kohort med 75-åriga kvinnor från Malmö som följts i tio år. Detta är en viktig ålder då både antalet frakturer och frailty ökar. Som det ser ut idag är det svårt att förutsäga vilka som riskerar att ramla och få en fraktur och därför behövs mer forskning.

I den första studien visade vi hur man kunde skapa ett frailty index (FI) som gick att följa under dessa tio år. Genom att mäta detta kunde vi se att graden av frailty var starkt kopplad till risken att dö. Vi visade också hur frailty utvecklades olika fort hos dessa kvinnor och att bara en av tio kvinnor som var väldigt friska som 75-åringar var lika friska efter 10 år.

Den andra studien visade att de kvinnor som var sköra hade mycket större risk att falla i framtiden, och om man är skör och har fallit, är risken stor att man kommer att fortsätta falla under i stort sett resten av livet.

Den tredje studien visade vi att frailty är en riskfaktor för frakturer. Om man är skör har man nästan tre gånger så hög risk för att få en fraktur de närmast 1-2 åren, än den som inte är skör. Den allra störst risken har man för att få en höftfraktur, och detta var oberoende av vilken bentäthet man hade.

I den fjärde studien tittade vi på hur en kort visuell uppskattning av hälsan ”det kliniska ögat” förhöll sig till den uppskattning som vi mätte med vår frailty index. Vi såg att båda måtten kunde förutsäga en högre risk för död. Hos dem som såg ut att vara i bra hälsa kunde vi dock visa, om man mätte med vårt frailty index, att det fanns en grupp som hade större risk att dö. Därför tror vi att vårt index är bättre på att fånga upp små förändringar i hälsan som man kanske inte kan se.

Sammantaget visar vi att den som är skör riskerar att ha lägre bentäthet, flera fall och frakturer än vad som kan förväntas om man bara tittar på den kronologiska åldern. Eftersom benskörhet och skörhetsfrakturer är starkt relaterade till ålder tror vi att uppskattningar av frailty kan vara viktiga hjälpmedel för att få en hälsosam ålderdom.

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Appendix

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Paper I

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ORIGINAL ARTICLE

Progression of frailty and prevalence of osteoporosis in a community cohort of older women—a 10-year longitudinal study

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Abstract

Summary In community dwelling, 75-year-old women followed 10 years, a frailty index was created at each of three visits. Frailty score increased by ~ 6–7% annually. A higher frailty score was equivalent to being 5–10 years chronologically older. Frailty was associated with low bone density and higher risk of dying.

Introduction To understand the distribution of frailty among a population-based sample of older community-dwelling women, progression over 10 years, and association with mortality and osteoporosis.

Methods The study is performed in a cohort designed to investigate osteoporosis. The OPRA cohort consists of 75-year-old women, $n = 1044$ at baseline, and follow-up at age 80 and 85. A frailty index (scored from 0.0–1.0) based on deficits in health across multiple domains was created at all time-points; outcomes were mortality up to 15 years and femoral neck bone density.

Results At baseline, the proportion least frail, i.e., most robust (FI 0.0–0.1) constituted 48%, dropping to 25 and 14% at age 80 and 85. On average, over 10 years, the annual linear frailty score progression was approximately 6–7%. Among the least frail, 11% remained robust over 10 years. A higher frailty score was equivalent to being 5 to 10 years older. Mortality was substantially higher in the highest quartile compared to the lowest based on baseline frailty score; after 10 years, 48.7% had died vs 17.2% ($p = 1.7 \times 10^{-14}$). Mortality risk over the first 5 years was highest in the frailest (Q4 vs Q1; HR_{unadj} 3.26 [1.86–5.73]; $p < 0.001$) and continued to be elevated at 10 years (HR_{unadj} 3.58 [2.55–5.03]; $p < 0.001$). Frailty was associated with BMD after adjusting for BMI (overall $p = 0.006$; Q1 vs Q4 $p = 0.003$).

Conclusions The frailty index was highly predictive of mortality showing a threefold increased risk of death in the frailest both in a shorter and longer perspective. Only one in ten older women escaped progression after 10 years. Frailty and osteoporosis were associated.

Keywords Bone density · Community-dwelling · Frailty · Mortality · Women

Introduction

The expected demographic change towards an increasingly elderly population [1] indicates the importance of understanding frailty and the clinical implications of frailty for successful aging. Frailty has become central in geriatric medicine, contributing as it does to a higher risk for many adverse health outcomes [2] and institutionalization [3]. Frailty encompasses the functional decline in multiple physiological systems, among others, neurodegeneration, sarcopenia, and cognitive changes [4–6]. However, perhaps the most dramatic declines, in terms of function and structure, are in the musculoskeletal system, affecting balance, mobility, disability, and ultimately the ability to live independently. In the field of osteoporosis, research into frailty is still not a major focus, despite being potentially highly relevant since the most severe fractures occur in the old, hip fractures in particular. The few studies available suggest an association with osteoporosis outcomes [7–12].

Frailty as a concept has been most extensively studied in order to understand factors associated with rapid decline in health status ultimately leading to death, and in addition identify targets for intervention [13, 14]. However, a gap in

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knowledge still exists since comparatively few frailty studies are designed to provide long-term data on older community-dwelling women [15], especially its pattern of progression. Furthermore, despite the prevalence of osteoporosis and its consequences in older populations, cohorts designed to specifically address osteoporosis may not have sufficient data to adequately capture frailty. Likewise, cohorts designed to address frailty or other conditions may lack osteoporosis outcomes.

To address this, an initial step is to longitudinally investigate frailty in a large population-based osteoporosis cohort of older women. To this end, using the Osteoporosis Risk Assessment study (OPRA) of women all aged 75 years at inclusion with reassessment at ages 80 and 85, the purpose of this initial study is to understand the distribution of frailty among older community-dwelling women and progression rate over 10 years, but also potential prediction of mortality and osteoporosis.

Materials and methods

Subjects

In this study, we investigate 75-year-old community-dwelling women (the OPRA cohort) [16]. The cohort was randomly selected from population registries and women invited on their 75th birthday. No exclusion criteria were applied. A total of 1044 women participated in the baseline investigation between 1995 and 1999, representing a participation rate of 67%. Reasons for non-attendance have previously been detailed [17]. Follow-up investigations were performed at 5 years (age 80, $n = 715$ attended) and at 10 years (age 85, $n = 382$ attended). Similarly, reasons for non-attendance have been detailed [18] (Fig. 1).

The participants were extensively investigated at each visit. A questionnaire provided information on lifestyle (education, work, physical activity, smoking, and alcohol), health (medications, surgery, injuries, other diseases, food/nutrition, and hormonal function) falls, and fractures. The questionnaire was revised at follow-up to include supplemental information and events over the intervening 5 years. Self-estimated risk of falling was assessed using a Likert scale with 5 as the highest risk.

Physical assessment included balance (modified Romberg method), gait speed, and number of steps (30-m walk, 2 × 15 m with one turn) and thigh muscle strength (Biodex Medical Systems®, v4.5.0, Biodex Corporation, Shirley, N.Y., USA) as previously described [19]. Biochemical markers (CRP and creatinine) were assayed as described [18, 20]. BMD was measured using dual-energy x-ray absorptiometry (DXA) (GE Lunar, Madison, WI) [19] and the same machine used throughout. In this study, femoral neck BMD is used with osteoporosis being defined as a T-score below − 2.5.

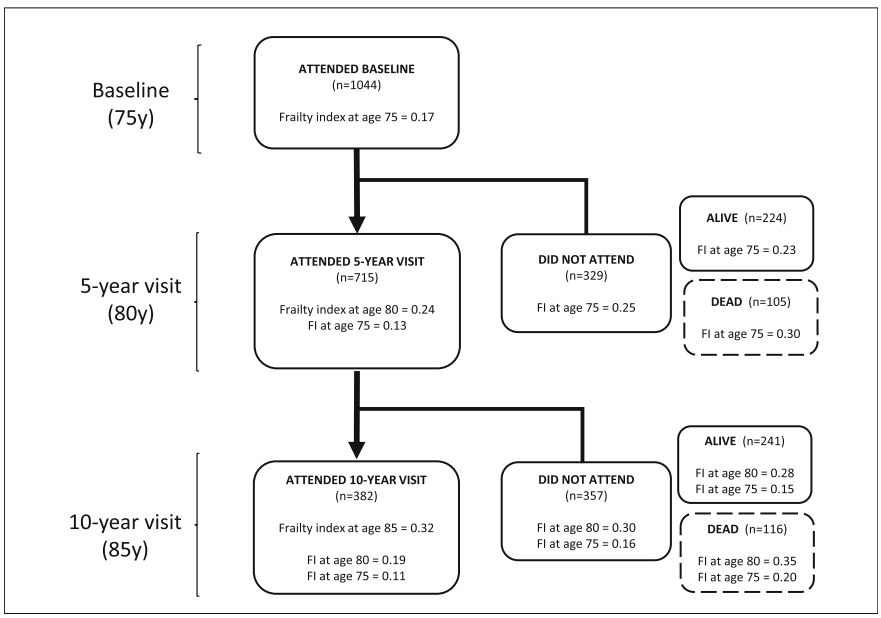

Fig. 1 Frailty across participation at each visit; frailty index reported for attendees and non-attendees, dead or alive

Precision of DXA was assessed by duplicate measurements on healthy individuals (precision error was 0.009–0.010 g/cm2 at FN). No drifts in phantom measured results were observed [21].

Mortality as date of death was acquired in October 2012, from the Swedish National Population Register (individuals still alive were a maximum 91.5 years of age).

Participants provided written informed consent, and the regional ethical review board at Lund University approved the study, which was performed according to the principles of the Helsinki Declaration.

Study-specific frailty index

Being an osteoporosis cohort, we were unable to define frailty according to the most commonly used frailty phenotype [5]. Instead, using the principles of Searle et al. [22], we followed a stepwise process to construct an index with available data that allowed us to capture frailty across all assessment points.

As described in detail below, the final frailty index (FI) used in these analyses consists of 13 variables at all visits (Table 1). Covering a number of physiological domains, e.g., mobility, strength, co-ordination, and poly-medication, the index represents, for each OPRA participant, the number of "deficits in health." The FI was calculated by dividing the number of deficits present by the total number of deficits examined, giving a score from 0.0–1.0, where a higher score indicates a higher frailty status. Where an individual had missing information for a particular variable, the total deficits were reduced by one.

To score variables (deficit present/non-present), we used either clinically relevant cut-points or identified the cut-off values by plotting the variable against an interim FI [22]. Categorical values were converted to binary values 1 (=deficit present) and 0 (=deficit absent); those with more than two categories were scored between 0 and 1 (e.g., high = 1.0; medium = 0.5; low = 0.0). To estimate cut-points of continuous data for dichotomization, curve estimation regression was performed, plotting potential frailty index variables against an intermediate frailty index. The resulting categories were then tested for differences in survival using Cox proportional hazard regression [22].

Frailty index development, construction, and validation

Searle et al. [22] recommend an index consisting of 30–40 variables. Since the availability of suitable data was limited at baseline, we constructed the index using the following approach.

Using data collected at the 5-year follow-up (age 80), a 40-variable index was first constructed, then to validate the method, prediction of mortality risk was tested using Cox regression (mortality risk HR 3.5 [95% CI, 2.5–4.8]). In the next step, the 40 variables were reduced to 10, considering availability at all time-points, and a 10-variable index was constructed (using data at age 80) and found equally predictive of mortality (HR 3.1 [2.4–3.9]). In an additional step, to ensure a wider coverage of biological domains essential for a measurement of frailty, additional variables (such as biomarkers) were added as covariates in logistic regression analysis to identify further variables associated with mortality risk.

Table 1 Components included in the OPRA-specific Frailty Index constructed at ages 75, 80, and 85

	OPRA-specific Frailty Index	Measurement units	Scoring or cut point
1	Daily physical activity	Categories 1–6 (1 = lowest; 6 highest)	Cat 1–3 = 1; cat 4 = 0.5; cat 5–6 = 0
2	Average time spent outdoors	Hours	< 1 h = 1; ≥ 1 h = 0
3	Gait—walking speed for 2 × 15 m	m/s	> 1.20 = 1; < 1.20 = 0
4	Gait—steps taken walking 2 × 15 m	No. of steps	< 54 = 0; > 54 = 1
5	Balance (2 legs, eyes closed)	Seconds	Failed test = 1; passed test = 0
6	Muscle strength—knee extension*	Nms	> 213 = 0; < 213 = 1
7	Diabetes	Yes/No	Yes = 1; No = 0
8	Cancer	Yes/No	Yes = 1; No = 0
9	Diseases affecting balance	Yes/No	Yes = 1; No = 0
10	Polypharmacy, using 5 or more medications	Yes/No	Yes = 1; No = 0
11	Self-estimated risk of falling	Categories 1–5 (1 = lowest; 5 highest)	Cat 1–5: 0.0; 0.25; 0.5; 0.75; 1.0
12	P-CRP	mg/L	> = 4.21 = 1; < 4.21 = 0
13	P-creatinine	umol/L	> = 82.02 = 1; < 82.02

*Voluntary maximal, isometric muscle strength of the right knee (knee extension at 90°) measured using a Biodex computerized dynamometer

This resulted in the creation of a 15-variable index, which could be compared longitudinally across the complete duration of follow-up (full details available on request). For the purpose of the present analyses, the BMD variables was subsequently removed from the index, since it is the study outcome, as was BMI due to its strong correlation to BMD. Correlation between the 40- and 13-variable indices was high (Spearman's $r^2 = 0.846$). All indices were equivalently predictive of mortality.

Statistical analyses

Descriptive statistics are reported as mean and standard deviation (SD), median, and IQR or frequency and percentage.

The frailty index, which shows a typically positively skewed (gamma) distribution [22], was used both as a continuous variable and stratified into quartiles (Q1 = lowest level of frailty; Q4 = highest level of frailty). Statistical comparisons were calculated overall or for Q1 vs Q4 as appropriate.

Annual linear progression of frailty over 10 years was calculated as the average, based on mean values of the whole cohort. For mortality, hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated using Cox proportional hazard regression with the healthiest quartile (Q1) as the reference category. Time to death was 5 years, 10 years, or until end of study (i.e., October 2012). HRs are presented unadjusted.

For osteoporosis, differences in T-score between the frailty categories were estimated using the non-parametric Kruskal Wallis test.

Analyses were performed using SPSS version 22 (SPSS, Inc., Chicago, IL) and JMP SAS (SAS Institute, Cary, NC, USA). p values of < 0.05 were considered nominally significant.

Results

Characteristics of the OPRA cohort, including frailty score components at ages 75, 80, and 85, are presented in Table 2. In general, the frailest women typically had poorer gait, balance and muscle strength, the highest CRP, more frequent polypharmacy, and the lowest albumin (a proxy for nutritional status) levels (data not shown).

Table 2 Key clinical characteristics of the OPRA cohort at age 75, 80, and 85

All variables at 75 years	Age 75 (baseline) $n = 1044$		Age 80 (5 year) $n = 715$		Age 85 (10 year) $n = 382$	
	Mean or No.	SD or %	Mean or No.	SD or %	Mean or No.	SD or %
Age (years)	75.2	(0.2)	80.2	(0.2)	85.2	(0.1)
Height (cm)	160.5	(5.7)	159.2	(5.8)	158.3	(5.8)
Weight (kg)	67.8	(11.7)	66.0	(11.6)	63.95	(10.9)
BMI (kg/m^2)	26.3	(4.2)	26.1	(4.2)	25.5	(4.0)
OPRA-specific Frailty Score	0.17	(0.17)	0.24	(0.18)	0.32	(0.19)
Distribution of FI components						
Daily activity[1]	0.06	(0.19)	0.11	(0.23)	0.20	(0.26)
Average time spent outdoors (hours)	2.73	(1.33)	1.84	(0.87)	1.66	(0.78)
Gait—walking speed for 2 × 15 m (m/s)	1.31	(0.30)	1.20	(0.33)	1.10	(0.32)
Gait—steps taken walking 2 × 15 m	49.4	(9.8)	53.6	(11.7)	55.8	(12.3)
Balance (2 legs, eyes closed)(s)*	57.8	(10.6)	54.8	(14.6)	52.1	(17.5)
Balance (No. failing 60-s test)	47	(4.6%)	91	(12.7%)	75	(20.3%)
Muscle strength[2] (nms)	267.9	(79.5)	247.3	(71.2)	218.3	(63.6)
Diabetes/cancer (%)	219	(21.0%)	178	(24.9%)	91	(24.1%)
Disease affecting balance (%)	201	(22.6%)	256	(35.8%)	184	(48.2%)
Self-estimated risk of falling (cat1–5)						
Low (1–2)	681	(75.4%)	491	(62.1%)	240	(63.8%)
Medium (3)	126	(14.0%)	129	(18.9%)	94	(25.0%)
High (4–5)	98	(10.6%)	61	(8.9%)	42	(11.2%)
Polypharmacy[3] (%)	210	(20.1%)	175	(24.5%)	165	(43.2%)
P-CRP (mg/L)	3.9	(6.8)	3.7	(5.1)	3.4	(5.8)
P-creatinine (umol/L)	69.9	(0.60)	74.3	(19.9)	82.2	(1.20)

Mean (SD) unless otherwise stated. [1] Daily activity calculated from the frailty threshold categories; [2] voluntary maximal isometric muscle strength of the right knee (knee extension at 90°) measured using a Biodex computerized dynamometer; [3] five or more medications; *not used in index

Progression of frailty

Over 10 years of follow-up, mean frailty increased giving an approximate annual linear frailty score progression of 6–7% (Table 2, Fig. 1). At baseline, the proportion scoring least frail (FI 0.0–0.1), i.e., most robust, constituted 48% of the cohort. At age 80 and 85, that proportion dropped to 25 and 14%, respectively. Among those rated least frail at age 75, although they progressed in frailty, the majority only reached intermediate levels (FI 0.2–0.6). As many as 11% had no change in frailty status and remained robust during the 10 years. Figure 2 illustrates the progression towards increased frailty among the participants.

Mortality

Those who died during the first 5-year period had the highest average frailty scores at baseline ($n = 105$; mean FI 0.30, median 0.29); approximately similar to the mean FI at age 85. The same trend was observed tracing those who attended the 5-year visit and comparing their frailty score at the 10-year follow-up (Fig. 1).

Mortality was substantially higher in the highest quartile of frailty compared to the lowest based on their baseline frailty score; after 10 years, 49.1% had died compared to 17.2% ($p = 8.4 \times 10^{-15}$). At 10 years, mortality was also higher in Q3 and 70% of those dead contained in Q3–Q4 (Table 3). The corresponding mortality risk over the first 5 years was highest in the frailest women (Q4 vs Q1; HR_{unadj} 3.26 [1.86–5.73]; $p < 0.001$) and continued to be elevated at 10 years (HR_{unadj} 3.58 [2.55–5.03]; $p < 0.001$) (Fig. 3). At age 85, only the least frail (i.e., most robust) had 2–3 times lower mortality, compared to the other quartiles.

Participation

Study participation may serve as an indicator of societal participation. Women who were alive but did *not* attend 5-year follow-up at age 80 were more frail at baseline than those who attended again (mean FI 0.23, median 0.19 vs FI 0.13, median 0.09). Further demonstrating the applicability of this frailty index in a long-term perspective, initial baseline frailty score was lowest in those who attended 10-year follow-up (FI 0.11, median 0.08), and increased stepwise in those who were alive but did not attend (FI 0.15, median 0.10) and those who had died (FI 0.20, median 0.18) (Fig. 1).

Osteoporosis and frailty

Aging is associated with osteoporosis and since this cohort was specifically designed for this purpose, we tested the association between frailty and osteoporosis. The proportion with osteoporosis increased with age as expected in the population overall; at baseline, 28.1% were osteoporotic rising to 49.0%

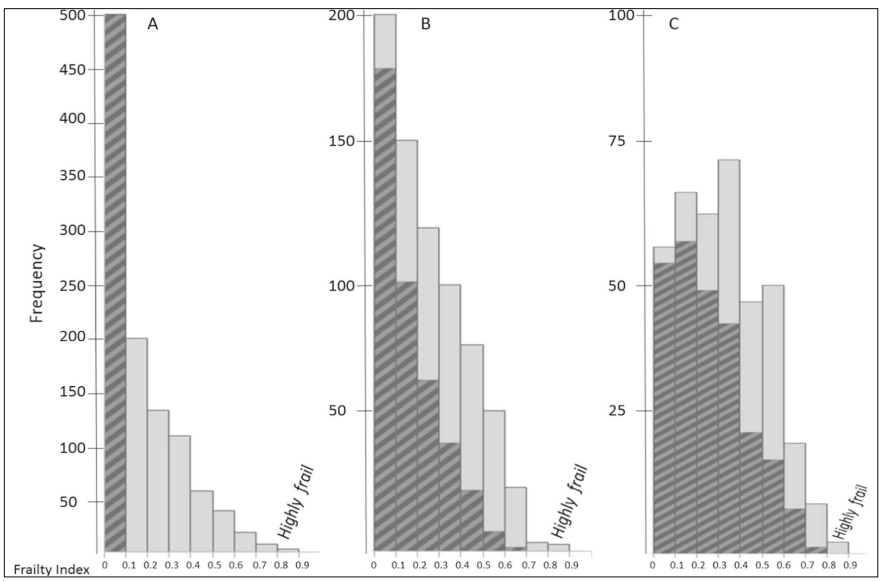

Fig. 2 Frailty and change of frailty over time in older women assessed at baseline, 5-year and 10-year follow-up, tracking progression in those most robust at baseline (hatched area). The three histograms show the distribution of frailty index scores at each visit (baseline, 5 years, 10 years). The index is presented in decentiles (0.0–1.0). The hatched area in (**a**) represents the LEAST frail women at baseline, and their progression towards increasing frailty over the course of the study (panels **b** and **c**)

Table 3 Frailty by quartiles at age 75, 80, and 85 and distribution of mortality and bone mineral density

	Low frailty (Q1)	Frailty (Q2)	Frailty (Q3)	Highly frail (Q4)	*p* value[#] overall	*p* value Q1 vs Q4
All variables at 75 years ($n = 1044$)	$n = 261$	$n = 254$	$n = 262$	$n = 267$		
OPRA-specific Frailty Index (range)	0.00–0.02	0.03–0.12	0.13–0.27	0.28–0.88		
No. dead at 5 years (age 80 follow-up) (%)	18 (6.9)	11 (4.3)	21 (8.0)	55 (20.6)	5×10^{-10}	1.1×10^{-5}
No. dead at 10 years (age 85 follow-up) (%)	45 (17.2)	49 (19.3)	84 (32.1)	131 (49.1)	1×10^{-5}	8.4×10^{-15}
BMD—Femoral neck g/cm^3	0.773 (0.131)	0.770 (0.136)	0.756 (0.136)	0.759 (0.150)	0.460	0.280
Bone density—femoral neck T-score	− 1.72 (1.09)	− 1.75 (1.13)	− 1.86 (1.14)	− 1.84 (1.25)	0.460	0.280
Osteoporosis—FN T-score < − 2.5 (*n*/%)	61 (24.6)	69 (28.3)	74 (30.3)	62 (29.4)	0.516	0.290
All variables at 80 years ($n = 715$)	$n = 196$	$n = 158$	$n = 187$	$n = 174$		
OPRA-specific Frailty Index (range)	0.00–0.10	0.11–0.22	0.23–0.38	0.39–0.85		
No. dead at 5 years (age 85 follow-up) *n* (%)	14 (7.1)	17 (10.8)	32 (17.1)	53 (30.5)	< 0.001	9.8×10^{-9}
No. dead at end of study (%)	64 (32.7)	55 (34.8)	97 (51.9)	115 (66.1)	2×10^{-11}	1×10^{-10}
BMD—femoral neck g/cm^3	0.720 (0.114)	0.713 (0.123)	0.714 (0.126)	0.702 (0.153)	0.652	0.221
Bone density—femoral neck T-score	− 2.17 (0.95)	− 2.23 (1.03)	− 2.22 (1.05)	− 2.31 (1.27)	0.652	0.221
Osteoporosis—FN T-score < − 2.5 (*n*/%)	74 (38.3)	68 (44.2)	81 (45.8)	75 (47.5)	0.323	0.103
All variables at 85 years ($n = 382$)	$n = 102$	$n = 95$	$n = 100$	$n = 85$		
OPRA-specific Frailty Index (range)	0.00–0.17	0.18–0.31	0.32–0.46	0.47–0.83		
No. dead at end of study (%)	14 (13.7)	27 (28.4)	27 (27.0)	37 (43.5)	1.2×10^{-4}	6×10^{-6}
BMD—femoral neck g/cm^3	0.699 (0.128)	0.700 (0.145)	0.662 (0.125)	0.699 (0.148)	0.154	0.974
Bone density—femoral neck T-score	− 2.34 (1.06)	− 2.34 (1.21)	− 2.65 (1.04)	− 2.34 (1.23)	0.154	0.974
Osteoporosis—FN T-score < − 2.5 (*n*/%)	50 (49.5)	42 (45.7)	53 (55.8)	35 (44.3)	0.412	0.548

Reported values are means, unless otherwise stated. [#] *p* values calculated by ANOVA, *t* test, Fisher's exact test, or Chi-square as appropriate

after 10 years. At age 75, femoral neck BMD was 0.773 g/cm^2 (SD 0.131) in the least frail compared to 0.759 (SD 0.150) in the frailest, and not statistically different. After adjustment for BMI, BMD was significantly associated with frailty (overall; $p = 0.0006$ and Q1 vs Q4 $p = 0.0003$). The pattern was similar at age 80, while femoral neck BMD at age 85 was similar across frailty quartiles (Table 3), adjustment for BMI did not result in a statistically significant difference (data not shown).

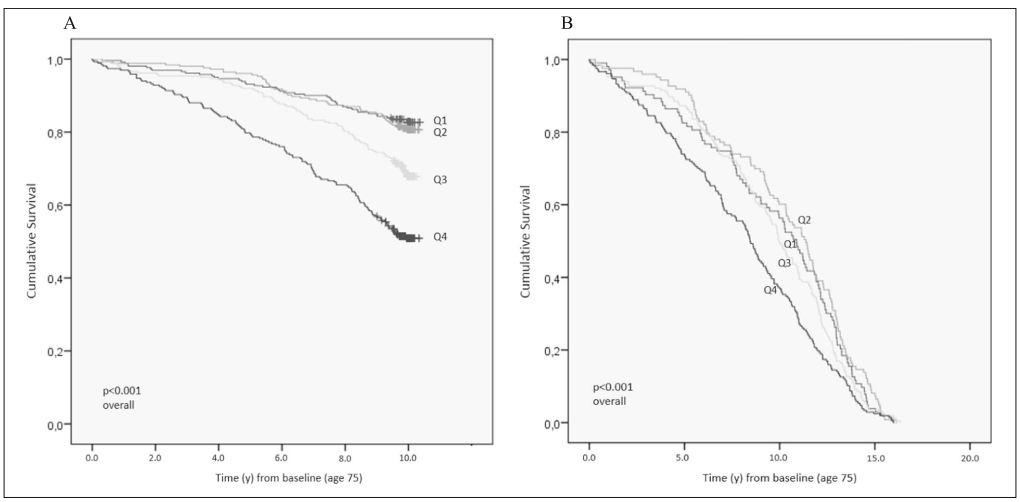

Fig. 3 Mortality risk according to quartiles of frailty at age 75. **a** 10 years. **b** End of study

Discussion

In this study, we show how frailty is distributed in a population-based cohort of older community-dwelling women where the majority are still in relatively good health at age 75. We also show the progression of frailty with advancing age, noteworthy being the pattern of change among those initially least frail, while the higher mortality among the most frail is as expected. Our findings highlight the possibility of, and also the value of, estimating overall health in older people by objectively evaluating frailty as part of prognosticating healthy aging and future adverse events.

How to best measure frailty is widely discussed and many instruments have been suggested [4, 23]. Our frailty index was developed according to the fairly simple philosophy of "The more individuals have wrong with them, the higher the likelihood that they will be frail" suggested by Rockwood and Mitnitski; meaning that these "wrongs" or deficits will mirror impaired and aging-associated processes at a cellular level, and that more deficits within different physiological systems are reflecting the generalized syndrome considered essential for frailty [6, 22, 24]. Our cohort was designed to assess osteoporosis risk in older women and not for estimating frailty; however, we show that is possible to use the variables available to construct an informative frailty index highly predictive of mortality. In accordance with the stated principles, the method allows for a varying number and types of variables to be used as long as they follow the basic rules [22].

Approximately half of the women were in the least frail category (FI 0.0–0.1) (i.e., were most robust) at age 75. Five years later, this was halved and at age 85 halved again as deficits accumulate. Frailty increased by 6 to 7% per year, which is higher than in some studies, most likely because we are assessing same-aged individuals as they age while other studies compare the difference by chronological year [22, 24–26]. Furthermore, recognizing frailty as a state where reserve capabilities are reduced, it is reasonable to assume that, once a threshold has been passed, frailty evolves at a faster pace. Such a threshold has not yet been defined, but our data indicate a clinical cut-off of approximately 0.27. Given our data describing the pattern of progression over many years in older women and given that frailty is considered dynamic and hence potentially reversible, our findings highlight the need to observe frailty status together with advancing age to ensure timely interventions. Currently, the evidence supporting interventions to reverse or minimize the rate of decline are varied but most rely on nutrition and training [27–31].

Mortality was highest in the most frail; at age 75 and during the following 5 years half of all those dead were among the frailest and the risk of dying more than three times that of the least frail. But those in the next quartile (Q3) also had a higher mortality over 10 years, suggesting their pre-frailty status. The same pattern was apparent when frailty was assessed at age 80. In contrast, and mirroring the age-related shift towards increased frailty, at age 85, all but the most robust (i.e., least frail) had a 2–3 times higher mortality. One interpretation of this is that it is most useful to identify signs of frailty at earlier ages to allow for appropriate intervention. To put this into perspective, those who died within 5 years of baseline (between age 75 and 80) had a mean FI equivalent to someone 10 years older, i.e., comparable to those attending at age 85, meaning they were 10 years more frail. Those who did not attend the 5-year follow-up had a baseline FI similar to those attended at age 80, suggesting they were 5 years more frail.

The osteoporotic patient is assumed to be more frail. Therefore, we hypothesized that the frailest women would have lower bone density and a higher proportion with osteoporosis. This was the case, but after adjustment for BMI. Frailty in relation to bone density is only addressed in a few studies and with inconsistent results as a consequence of small sample, diverse populations, and frailty definitions [32, 33], yet frailty is very relevant to osteoporosis since its clinical outcome of fracture encompasses a wider spectrum than BMD alone (which we are addressing in another study). Furthermore, an additional observation among these community-dwelling women is that BMI was higher in those with higher frailty, indicative of an accumulation of conditions resulting in an overall decreased health status and reduced activity. This also suggests that assessment of bone should not be overlooked in women with higher body weight, but overall poor health status.

Limitations and strengths

Firstly, one potential limitation is that our frailty index was derived and applied in the same population and external validation of the index has not been performed. While validation would be valuable, this is however, part of the problem in the emerging field of frailty and mirrors the lack of consensus and inconsistency across studies in terms of collected information. Further to this, making direct comparison with other studies is difficult; however, in our index, the cut-off for frailty coincides with the lower limit of Q4 and while a consensus threshold is lacking; this is close to the empirical cut-off point of > 0.25 for a frailty index based on accumulated deficits as described by Rockwood [6].

Secondly, our index has fewer variables than the suggestion of 30–40; however, in its development, we demonstrate a very high correlation and an almost identical ability to predict mortality between a 40-item index and the 13-item index used in this study. This most likely reflects the high interrelationship between the included variables, whereby one variable can capture and substitute multiple variables. It can also be argued that this high redundancy between variables is an advantage as it indicates the possibility to use simpler

constructs and facilitate use. Thirdly, due to constraints from the original study design and subsequent lack of information in certain domains, data on social and mental factors are unfortunately not included. Fourth, being a longitudinal study of older persons, there is an inherent problem of loss to follow-up and a potential bias of healthy participants. Indeed, we also show that those continuing in the study are less frail, and with regard to mortality, this is not problematic, but a loss of power may occur for other outcomes, although the descriptive information is still robust. Fifth, caution should be exercised in terms of generalizing the findings to other populations such as younger women or other ethnicities.

Strengths of this study include that the participants are 75-year-old community-dwelling rather than institutionalized women, representing a pivotal period for continued healthy aging or deteriorating health. The fact that all women were at the same age at inclusion is advantageous as it minimizes the influence of chronological age on accumulated health deficits. Another strength is the provision of longitudinal data for up to 15 years allowing us to quantitatively assess change in frailty status with advancing age. Additionally, we demonstrate that it is possible to develop a meaningful frailty index from available data and with the same discriminatory ability as a more comprehensive, larger item index. This is important since research on frailty in relation to osteoporosis is still in its infancy but potentially beneficial for future research. Taken together, this study contributes with data on frailty in averagely healthy older women including tracking over time and its association to bone health.

In conclusion, the relevance of this study lies in demonstrating the pattern of frailty longitudinally in older community-dwelling women and its association to mortality up to 15 years. Frailty was associated with a threefold increased risk of death in both a short and longer perspective with a higher frailty score being equivalent to being chronologically five to 10 years older. Conversely, only one in ten older women escaped progression of frailty. In addition, higher frailty is associated with osteoporosis, despite the fact that the frailest individuals may have a higher BMI.

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Authors' roles Patrik Bartosh (PB), Fiona McGuigan (FM), Kristina Åkesson (KA)

1. Conception or design, or analysis and interpretation of data, or both (PB, FM, KA).
2. Drafting and revising the article (PB, FM, KA)
3. Providing intellectual content of critical importance to the work (PB, FM, KA)
4. Final approval of the version to be published (PB, FM, KA)
5. Agree to be accountable for accuracy and integrity of the work (PB, FM, KA)

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Compliance with ethical standards

Participants provided written informed consent, and the regional ethical review board at Lund University approved the study, which was performed according to the principles of the Helsinki Declaration.

Conflicts of interest None.

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Paper II

Aging Clinical and Experimental Research
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ORIGINAL ARTICLE

Frailty and prediction of recurrent falls over 10 years in a community cohort of 75-year-old women

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Abstract

Background Frailty captures the age-related declines in health leading to increased vulnerability, including falls which are commonplace in older women. The relationship between frailty and falls is complex, with one leading to the other in a vicious cycle.

Aims This study addresses the gap in understanding how patterns of frailty and falls propensity interact, particularly in those who have *not yet* entered the falls-frailty cycle.

Methods The Osteoporosis Risk Assessment cohort consists of 1044 community-dwelling women aged 75, with 10 years of follow-up. Investigations were performed and a frailty index constructed at baseline, 5 and 10 years. Falls were self-reported for each previous 12 months. Analysis was two-directional, firstly based on frailty status and second, based on falls status. Recurrent falls was the primary outcome.

Results Baseline frailty was a significant predictor of recurrent falls after 5 and 10 years [(OR 2.55 (1.62–3.99); 3.04 (1.63–5.67)]. Among women who had *no history* of falls at age 75, frailty was a stronger predictor of falls at 5 years [OR 3.06 (1.59–5.89)] than among women who had previously fallen.

Discussion Frailty is significantly associated with recurrent falls and most pronounced in those who are frail but have not yet fallen.

Conclusions This suggests that frailty should be an integral part of falls-risk assessment to improve identification of those at risk of becoming fallers.

Keywords Frailty · Falls · Women · Community-dwelling

Introduction

Frailty, the age-related decline in reserve capacity and resilience, is associated with a multitude of adverse outcomes [1]. Deficits in musculoskeletal health contributes to frailty with gait problems, weakness, reduced reaction time and balance, factors also leading to falls risk [2, 3]. The consequences of falls leads to extensive costs from injuries and fractures, disability and nursing home placement [4]. Given the demographic shift towards an older population and anticipated high care burden, frailty is a research priority.

The relationship between frailty and falls is demonstrated by observations that in community-dwelling populations aged 65 and over, every third person experiences at least one fall annually; fifteen percent leading to significant injury [5–7]. In those over 80, the proportion increases to every second person. Causes of falling are complex and the combination of general health status, environmental circumstances and chance makes prediction difficult [8]. Fall specific scales have been developed; however, their predictive ability is limited and the clinical utilization neither consistent or widespread [9, 10].

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Assessment of frailty may capture the multi-factorial aspects of falls propensity. Since an important objective is identifying individuals *before* they become frail, this opens the possibility to capture an elevated falls risk before it manifests clinically.

Previous falls are important predictors of future falls [3]; however, the correlation between *frailty* and falls is also high [11, 12], although difficult to untangle as they are reciprocal. This 'vicious cycle' of functional decline with frailty leading to falls, greater frailty and more falls, makes it imperative to understand *if* and *how* frailty affects those who have *not yet* suffered a fall compared to those already in the falls-frailty cycle. Regardless if frailty precedes falls or vice versa, interventions, whether physical or nutritional, are more likely to be effective before a point-of-no-return is reached [13].

A clear picture of the frailty–falls relationship is difficult to obtain, not least due to differences in study design and frailty and falls measures. Most studies utilize a categorical frailty definition [1]; however, this could hamper assessment of a gradually higher frailty and its association to falls. Therefore, the ambition of this study was to create a continuous deficit accumulation frailty index [14] with which to investigate this relationship.

An additional gap-in-knowledge is the time frame of prediction; 3 months to 5 years is well studied [6, 15], while little is known in a longer perspective. This is an important aspect since maintaining a good quality of life during aging is related to *not* entering the frailty–falls cycle. In a previous study we followed the progression of frailty over 10 years in the Osteoporosis Risk Assessment (OPRA) cohort and its association with osteoporosis [16].

In the present study the overall aim is to understand frailty and its relationship to fall propensity in short and longer perspectives. Seventy-five is a pivotal age at which most are still physically active and relatively healthy; therefore, the consequences of a fall, especially if a fracture results, often marks the beginning of a more dependent state.

Our specific aims were to (1) describe the proportion who are frail at age 75, 80 and 85 and the number reporting recent falls, (2) determine the association between frailty and risk of recurrent falls, (3) determine if a gradual increase in frailty is associated with the number of future falls and (4) explore the relationship of frailty to future falls in women with or without previous falls.

Materials and methods

Subjects

The OPRA cohort consists of 75-year-old community-dwelling women (75.2 ± 0.2) as described in detail [17]. $N = 1044$ attended baseline. Detailed follow-up investigations including questionnaires, physical and falls assessment were performed at 5 years ($n = 715$, age 80.2 ± 0.2) and 10 years ($n = 382$, age 85 ± 0.1) [18, 19].

Participants provided written informed consent. The regional ethical review board in Lund approved the study (Dnr:2014804), which was performed according to the Helsinki Declaration principles.

Frailty index

We constructed a frailty index [16, 17] adhering to the principles of Searle et al. [20]. Briefly, the index includes thirteen variables covering a number of physiological domains (daily physical activity, time spent out-doors, walking speed, number of steps taken, balance, muscle strength, diabetes, cancer, diseases affecting balance, self-reported fall risk, polypharmacy, CRP and creatinine). The index represents the number of 'deficits in health' (scored 0.0–1.0); a higher score indicating higher frailty.

Since some variables in the index are dichotomized, loss-of-discrimination is possible (due to many individuals having identical values), therefore, as a refinement we reclassified each applicable variable as continuous between 0.0 and 1.0, i.e., providing a range. For example, "number of steps taken to walk 30 m". Dichotomized, cut-points were < 54 steps = 0 or ≥ 54 steps = 1. Reclassifying this as a continuous variable, fewer steps indicates a longer stride, hence a healthier state and a score closer to zero. To implement this we examined the range of values across the entire cohort (in this case 21–160) and, after excluding extreme outliers, the highest (V_{max}) and lowest (V_{min}) values were set to 1 and 0, respectively. The original values (V_x) were then reclassified using $\frac{(V_x - V_{min})}{(V_{max} - V_{min})}$.

To test how this 13-variable index related to a more typical index comprising dichotomized variables, we compared it to a 40-variable frailty index that had been created for the two follow-up visits [16]. The refined 13-variable index was highly correlated to the full 40-variable index ($r = 0.80$) and distributions were comparable (5 years: 0.24 vs. 0.23, $_{median}$0.21 vs. 0.21; 10 years: 0.27 vs. 0.29, $_{median}$0.26 vs. 0.27).

We used an empirical cutoff ≥ 0.25 to define frail individuals. This is suggested by others [21, 22] and supported through calculations in our cohort; plotting differences in 10-year mortality using 0.02 increments, the beginning of a steeper slope in the curve occurs at approximately 0.25.

Falls

At baseline, 5-year and 10-year follow-up visits participants provided information on whether they had fallen in the previous 12 months and if they had fallen, how many times they

fell during that period. In the analysis we define falls variously: at least one fall, recurrent falls (i.e., 2 or more falls) during the previous 12 months, the rationale being that multiple falls are more likely due to a frail disposition, mirroring a "falling-phenotype". We also define women as 'fallers' and 'non-fallers' and we use 'number of falls'. Only participants with valid data on falls were included (75 y $n=914$; 80 y $n=711$; 85 y $n=382$).

Statistical analyses

Descriptives are reported as mean (SD), median (IQR) and frequency (%). Comparisons of demographic characteristics, overall and between frail/non-frail categories, used Student's *T* test and Chi square. The frailty index showed a typical skewed distribution at all timepoints [14] (tending towards normality at 10-year follow-up); non-parametric analyses were performed when appropriate.

Frailty was analysed primarily as 'non-frail' (≤ 0.25); 'frail' (>0.25). To facilitate comparison with other studies, frailty was also used as a continuous variable in 0.01 increments. To explore a gradual increase in frailty, frailty quintiles were created.

To explore the relationship between frailty, at least one fall and recurrent falls, odds ratios (OR) with 95% confidence intervals were calculated using binary logistic regression, with adjustment for 25(OH)D, BMI, smoking and previous fractures (between 50 and 75 y) also performed.

To explore the relationship between frailty and falls status, we defined 'fallers' as those reporting at least one fall during the 12 months prior to baseline. We combined this with frailty status to give four groups (faller/frail; faller/non-frail; non-faller/frail; non-faller/non-frail); compared using cross tabulation, Chi square and regression analysis.

To explore the association between frailty at baseline (75 y) and number of future falls at 5-year follow-up, four groups were used (no falls, 1 fall, 2 falls, 3 or more falls). The same groups were used for comparison of frailty at age 80 and number of future falls at the next 5-year follow-up (85 y). Frailty was also binned into equal-sized quintiles and compared using cross tabulation. Only individuals who participated *and* had fall data at follow-up were included.

Analyses were performed using SPSS v25 and JMP (SAS Institute, USA). $P<0.05$ was considered nominally significant.

Results

Table 1 presents key clinical characteristics of the OPRA cohort at ages 75, 80 and 85. Table 2 presents key baseline characteristics of frail and non-frail women. The prevalence of frailty increased from 23.5% at baseline to 39.3% and 56.8% at 5 and 10-year follow-up, respectively. This is reflected in the median frailty score increasing with age; baseline 0.16 ($_{mean}$0.19) and 0.21 ($_{mean}$0.24) and 0.27 ($_{mean}$0.29) at the 5- and 10-year follow-up.

The overall incidence of women reporting falls at each visit is illustrated in Fig. 1. At baseline, the proportion reporting at least one fall was 28.4% ($n=260$), increasing to 31.0% ($n=218$) and 44.7% ($n=166$) at subsequent visits. A similar pattern is seen for recurrent falls; incidence almost doubles from age 75–85 (14.7%; 17.6%; 26.4%). Online_Resource _Figure 1 shows frailty score in relation to fall status at each visit.

Based on frailty status at 75, Fig. 2 illustrates the proportion of women who *did* or *did not* report recurrent falls in the previous 12-month period at 75, 80 and 85. At age 75, recurrent falls were almost four times more common among frail compared to non-frail women (32.6% vs. 8.9%; $p<0.001$). Frail women continued to report recurrent falls across follow-up (5 y 30.8% vs. 14.9%; 10 y 47.9% vs. 23.2%, both $p\leq 0.001$).

Baseline frailty was a significant predictor of recurrent falls. Calculating falls odds risk in relation to frailty status showed that being frail at age 75 was associated with

Table 1 Key clinical characteristics of the OPRA cohort at age 75, 80 and 85

All variables at 75 y	Age 75 (Baseline) $n=1044$		Age 80 (5 years) $n=715$		Age 85 (10 years) $n=382$	
	Mean	SD	Mean	SD	Mean	SD
Age (y)	75.2	(0.2)	80.2	(0.2)	85.2	(0.1)
Height (cm)	160.5	(5.7)	159.2	(5.8)	158.3	(5.8)
Weight (kg)	67.8	(11.7)	66.0	(11.6)	63.95	(10.9)
BMI (kg/m^2)	26.3	(4.2)	26.1	(4.2)	25.5	(4.0)
S-25(OH)D (nmol/L)	62	(19)	78	(30)	79	(26)
Femoral Neck (T-score)	−1.8	(1.1)	−2.2	(1.1)	−2.4	(1.1)
	Median	IQR	Median	IQR	Median	IQR
Frailty index (FI)	0.16	(0.14)	0.21	(0.17)	0.27	(0.20)

Table 2 Baseline characteristics of frail and non-frail women

All variables at 75 y	Non-frail (< 0.25)		Frail (≥ 0.25)		All Women	
	n = 799		*n* = 245		*n* = 1044	
	Median	IQR	Median	IQR	Median	IQR
Frailty index (FI)	0.14	(0.09)	0.32	(0.49)	0.16	(0.73)
	Mean	SD	Mean	SD	Mean	SD
BMI (Kg/m^2)	26.0	(3.88)	27.0	(5.05)	26.3	(4.19)
S-25(OH)D (nmol/L)	63.1	(18.9)	57.7	(20.4)	61.8	(19.4)
	No	(%)	No	(%)	No	(%)
Falls in previous 12 months (n = 914)						
1 fall	84	(12.2)	42	(19.0)	126	(13.8)
2 or more falls	62	(8.9)	72	(32.6)	134	(14.7)
No falls	547	(78.9)	107	(48.4)	654	(62.6)
Prior fractures						
Any (50–75 y)	278	(35.1)	105	(43.9)	383	(37.1)
Major osteoporotic (50–75 y)	187	(23.6)	53	(22.2)	240	(23.3)
Education						
Lower education	587	(73.6)	185	(76.4)	772	(74.2)
Higher education	211	(26.4)	58	(23.9)	269	(25.8)
Smoking						
Non-smoker	535	(67.6)	144	(59.8)	679	(65.7)
Previous	150	(18.9)	59	(24.5)	209	(20.2)
Current	107	(13.5)	38	(15.8)	145	(14.0)
Alcohol						
Abstainer	141	(17.8)	61	(25.6)	202	(19.6)
A few times a month	489	(61.2)	140	(58.8)	629	(60.9)
Weekly	149	(18.8)	31	(13.0	180	(17.4)
Almost daily	15	(1.9)	6	(2.5)	21	(2.0)

increased falls risk up to 5 and 10 years; recurrent falls were 2.5–3 times more likely in frail vs. non-frail women [OR 2.55 (CI 1.62–3.99); 3.04 (1.63–5.67)] (Online_Resource_ Table 1). Similar results were also observed assessing the relationship between frailty status at age 80 and fall risk after 5 years (85 years), with a two times higher OR compared to non-frail women.

At age 75 an increment of 0.01 in the index significantly increased the odds for at least one fall (1.04, 1.03–1.06) and recurrent falls (1.05, 1.03–1.07) after 5 years. Similarly, after 10-year follow-up (1.04, 1.01–1.07 and 1.07, 1.04–1.10; all $p < 0.001$). Increase in frailty at age 80, was similarly associated with an increased risk of falls after 5 years (1.04, 1.02–1.07, $p < 0.001$).

To understand how gradations of frailty associate with number of falls, we used frailty quintiles and four fall groups (Table 3). Already at baseline, the increment is stepwise between increasing frailty and number of falls, particularly pronounced for women having 2 and 3 or more falls within the 12 months prior to study inclusion.

For the association between baseline frailty and future falls at age 80 and 85 the pattern is similar. With increasing frailty, the proportion of women falling increases, almost stepwise. In the highest frailty quintile, 15.7% had 3 or more falls at age 80, compared to 5.7% in the lowest quintile. After 10 years, more than one-quarter of women in the highest quintile sustained 3 or more falls (26.7% vs. 4.0%).

The association between frailty at age 80 and future falls at age 85 follows a similar pattern.

We combined and grouped women into fallers and non-fallers, investigating how frailty status affected their future-falls pattern. Among fallers at age 75, *regardless* of frailty status, approximately half had fallen at least once and one-third had recurrent falls at 5 years (Table 4). However, with reassessment at age 80, fallers who were *also frail*, fell more. Apart from a generally higher incidence at this age, frail women reported higher fall rates than non-frail, for at least one fall (76.9% vs. 57.3%) and recurrent falls (57.1% vs. 32.4%).

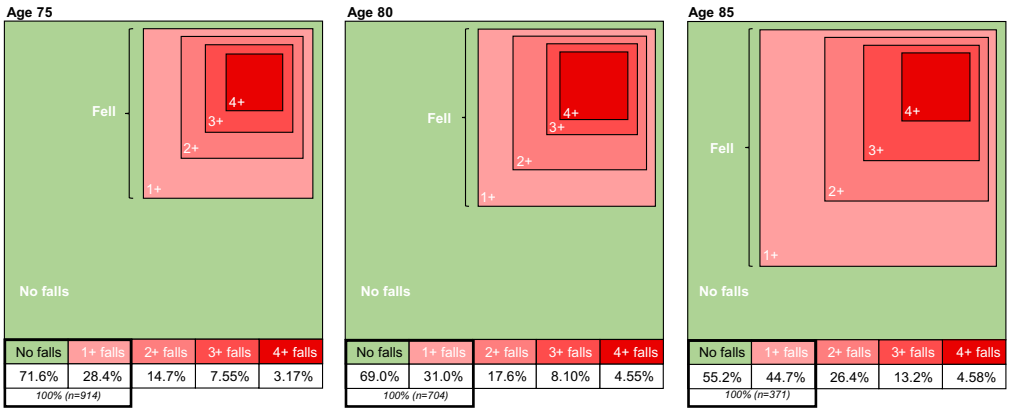

Fig. 1 Proportion of women attending each visit who reported none, one or multiple falls in the previous 12 months. This figure shows how, with advancing age the proportion of women falling increases. At each visit (ages 75, 80 and 85) the proportion of women reporting haven fallen once or more in the previous 12 months increases from 28.4 to 31% to 44.7%. The green area represents non-fallers and shrinks as the proportion of women reporting falls increases. The fallers are represented with deepening shades of red to illustrate the multiple fallers; these increase over time as the proportion falling increases. Missing falls data: 75 y ($n=130$); 80 y ($n=82$)

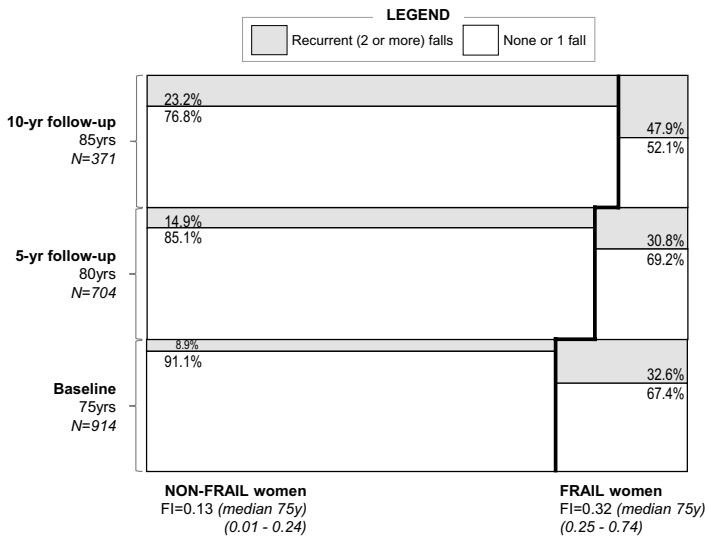

Fig. 2 Proportion of non-frail and frail women women reporting recurrent falls at all visits based on frailty status at age 75. Women are defined as frail (≥ 0.25) or non-frail (<0.25) at baseline and we show the proportion at each visit who reported recurrent falls in the previous 12 months. Among FRAIL women, proportionally more reported recurrent falls, compared to non-frail (32.6 vs. 8.9 at 75 y; 30.8 vs. 14.9 at 80 y; 47.9 vs. 23.2 at 85 y). Width of the frail segments narrows with successive visits, reflecting the proportionally higher loss-to-death and non-attendance in the most frail

In a 10-year perspective (but not 5 years), women who were fallers *and* frail at age 75 were more likely to have recurrent falls at age 85 than their non-frail counterparts [2.92 (1.08–7.91)] (Table 4). *Fallers* at age 80 who were also frail had an increased risk for at least one fall [2.48 (1.03–5.95)] and for recurrent falls at age 85 [2.78 (1.21–6.41)].

Among non-fallers, frailty significantly impacts future falls. For non-fallers but frail at age 75, at least one fall and recurrent falls were both more frequent at age 80 (37.3% frail vs. 24.4% non-frail; 27.6% vs. 11.1%) (Table 4). The trend was similar, for women at age 80 and falls reported at 85. Estimating the risk, women who were non-fallers and frail at age 75 were three times more likely to have recurrent falls at age 80

Table 3 Gradients of frailty and number of women reporting none, one or multiple falls in different time perspectives. Frailty in quintiles at age 75 and falls[#] prior to baseline, 5 and 10 years; frailty at age 80 and falls[#] at 5 years

Frailty age 75 and incidence of women falling immediately prior to baseline*								
Frailty score at 75 y	No falls age 75		1 fall age 75		2 falls age 75		3 or more falls age 75	
≤0.10	167	(89.8)	14	(7.5)	5	(2.7)	0	(0.0)
0.11–0.14	145	(79.7)	19	(10.4)	12	(6.6)	6	(3.3)
0.15–0.19	134	(74.0)	27	(14.9)	12	(6.6)	8	(4.4)
0.20–0.27	117	(66.1)	30	(16.9)	13	(7.3)	17	(9.6)
0.28+	91	(48.4)	36	(19.1)	23	(12.2)	38	(20.2)
Frailty age 75 and incidence of women falling after 5 years**								
Frailty score at 75 y	No falls age 80		1 fall age 80		2 falls age 80		3 or more falls age 80	
≤0.10	111	(79.3)	11	(7.9)	10	(7.1)	8	(5.7)
0.11–0.12	105	(73.9)	17	(12.0)	11	(7.7)	9	(6.3)
0.13–0.17	95	(68.1)	28	(19.9)	12	(8.5)	5	(3.5)
0.18–0.24	96	(68.1)	18	(12.8)	14	(9.9)	13	(9.2)
0.25+	78	(55.7)	20	(14.3)	20	(14.3)	22	(15.7)
Frailty age 75 and incidence of women falling after 10 years**								
Frailty score at 75 y	No falls age 85		1 fall age 85		2 falls age 85		3 or more falls age 85	
≤0.09	50	(66.7)	13	(17.3)	9	(12.0)	3	(4.0)
0.10–0.11	45	(60.8)	15	(20.3)	8	(10.8)	6	(8.1)
0.12–0.15	41	(56.2)	17	(23.3)	10	(13.7)	5	(6.8)
0.16–0.21	31	(41.9)	17	(23.0)	11	(14.9)	15	(20.3)
0.22+	38	(50.7)	6	(8.0)	11	(14.7)	20	(26.7)
Frailty age 80 and incidence of women falling after 5 years***								
Frailty score at 80 y	NO FALLS age 85		1 fall age 85		2 falls age 85		3 or more falls age 8 y	
≤0.11	47	(68.1)	9	(13.0)	8	(11.6)	5	(7.2)
0.12–0.16	38	(54.3)	16	(22.9)	10	(14.3)	6	(8.6)
0.17–0.21	40	(58.0)	13	(18.8)	11	(15.9)	5	(7.2)
0.22–0.28	32	(45.7)	18	(25.7)	9	(12.9)	11	(15.7)
0.29+	30	(43.5)	10	(14.5)	10	(14.5)	19	(27.5)

[#]Falls occurring during the previous 12 months prior to each visit. Reported values, number(%). Chi-squared overall: *$p<0.001$; **$p=0.001$; ***$p=0.012$

[3.06 (1.59–5.89)] (Table 4). At age 80, the 5-year association between frailty and recurrent falls was, however, also non-significant [1.71 (0.88–3.31)].

The combination of being both frail and faller conferred a significantly higher risk of recurrent falls within 5 years compared to robust (non-faller, non-frail) women (age 75: 4.54, 2.35–8.71; age 80: 5.82, 2.79–12.56) in regression analysis using all four groups.

Table 4 Combined fall-frailty status and the relationship with frequency and odds risk of future falls in different time perspectives. Fall-frailty status at age 75 and falls[#] at 5 and 10 years; fall-frailty status at age 80 and falls at 5 years

Combined falls-frailty and PROPORTION reporting falls[#]					
	At least 1 fall at 80 y			Recurrent falls at 80 y	
Fall-frailty status at 75 y	No(%) $n=631$[a]		P^*	No (%) $n=625$[a]	P^*
1. Faller *and* Frail	27 (54.0)	Group		18 (36.0)	
2. Faller *and* Non-Frail	53 (47.3)	1 v 2	0.432	39 (35.5)	0.947
3. Non-faller *and* Frail	22 (37.3)	3 v 4	0.035	16 (27.6)	0.0014
4. Non-faller *and* Non-Frail	100 (24.4)	1 v 4	<0.0001	45 (11.1)	<0.0001
	At least 1 fall at 85 y[#]			Recurrent falls at 85 y	
Fall-frailty status at 80 y	No (%) $n=358$[a]		P^*	No(%) $n=347$[a]	P^*
1. Faller *and* Frail	30 (76.9)	Group		20 (57.1)	
2. Faller *and* Non-Frail	43 (57.3)	1 v 2	0.039	23 (32.4)	0.015
3. Non-Faller *and* Frail	31 (48.4)	3 v 4	0.116	18 (28.1)	0.112
4. Non-Faller *and* Non-Frail	67 (37.2)	1 v 4	<0.0001	33 (18.6)	<0.0001

Combined falls-frailty and ODDS RISK of future falls				
	At least 1 fall[#]		Recurrent falls[#]	
	OR (CI 95%)	OR_{adj} (CI 95%)	OR (CI 95%)	OR_{adj} (CI 95%)
FALLER and Frail at 75 y				
Risk of falling, 5 years (80 years)	1.31 (0.67–2.55)	1.14 (0.56–2.32)	1.02 (0.51–2.06)	0.83 (0.39–1.76)
Risk of falling, 10 years (85 years)	1.39 (0.51–3.82)	1.48 (0.49–0.46)	2.92 (1.08–7.91)	2.99 (1.03–8.67)
NON-Faller and Frail at 75 y				
Risk of falling, 5 years (80 years)	1.84 (1.04–3.27)	1.95 (1.08–3.54)	3.06 (1.59–5.89)	3.24 (1.62–6.45)
Risk of falling, 10 years (85 years)	0.92 (0.37–2.30)	0.88 (0.33–2.35)	1.33 (0.46–3.86)	1.60 (0.53–4.82)
FALLER and Frail at 80 years[b]				
Risk of falling, 5 years (85 years)	2.48 (1.03–5.95)	3.11 (1.10–8.78)	2.78 (1.21–6.41)	3.54 (1.37–9.12)
NON-Faller and Frail at 80 years[b]				
Risk of falling, 5 years (85 years)	1.58 (0.89–2.82)	1.54 (0.83–2.87)	1.71 (0.88–3.31)	1.91 (0.94–3.87)

[#]Falls occurring during the previous 12 months prior to each visit

[a]Number of total cases with complete data

[b]Based on women age 80 and falls reported in the previous 12 months

*p values, Chi-squared. Odds ratios (OR) use non-frail category as reference. $OR_{adjusted}$ for BMI, 25(OH)D, fractures, smoking

Discussion

This study shows that in women, being frail at age 75 is a significant risk factor for recurrent falls both in five and 10-year perspectives. Frailty is a particularly strong predictor of future falls in women who have not yet experienced a fall, suggesting that if someone is frail, this is a time to intervene to avoid falls and fall-related injuries. In contrast, for women who have already experienced falls, frailty is secondary to prediction, most likely since they are already in the frailty–falls cycle.

The falls incidence increased between 75 y and 85 y (from one-third to almost half), with the most drastic change between 80 and 85, when the number of *individuals* falling increases, as does the number of *falls*. This precise change is difficult to capture in other studies [11, 22, 23]. Fall rates from 28.7 to 37.5% are observed in the National Health and Aging Trends Study, and while this is for somewhat younger ages including men, the 42.4% for age group 85–89 is consistent with our findings [24]. Age-related estimates of falls propensity are a foundation for understanding associated injuries; fractures being among the most important, although not part of this report.

The primary interest of this study is on recurrent falls as a sign of cumulative intrinsic age-related falls propensity. This is based on the assumption that frequent falling stems from failure of multiple physiologic systems, potentially captured by frailty, in contrast with the more arbitrary nature of one

fall which may be accidental. To facilitate comparison with the existing literature, however, we also report 'any fall'.

The reciprocity between frailty and falls is a major challenge to aging. With frailty increasing at each assessment age, those with the highest frailty had more falls in the previous year; and if highly frail, a higher incidence of future falls was also more likely.

Most studies find association between frailty and falls [1, 11, 15, 25, 26], although the relationship is unclear at the less-pronounced stages of frailty, reflecting the complexity in defining the transition from robust to pre-frail and frail. The strength of the association also varies depending on the age ranges, sex and setting of the studied populations [6]. An advantage in our setting is the single-age inclusion and duration of follow-up, which allows us to combine frailty and falls history to improve understanding of the interaction, albeit by 5-year increments. Hence, frailty has a long-term impact on falls, far beyond the one-to-3-year perspectives of existing studies, with women frail at age 75 having a continued higher falls propensity after 10 years compared to their non-frail counterparts.

A previous fall is a strong risk factor for future falls [3] which others have either adjusted for or performed subgroup analyses [25, 27]. To dissect the respective contribution from previous falls and frailty on the risk of future falls, we combined participants into fallers and non-fallers with or without frailty. Fallers and non-fallers have a distinctly different future-falls pattern. At age 75 frailty appears to be an important risk factor for women *without* a history of previous falls but not for women *with* falls. Conversely, at older ages frailty is a risk factor among *fallers* though not among *non-fallers*. We speculate that this is a consequence of the frailty–falls–frailty cycle and an indication of accumulated frailty with age. This is also obvious from the very different frailty score between frail and non-frail *non-fallers* at age 75 which is reflected in a higher recurrent falls risk after 5 years among the frail. Also, when reassessing frailty at age 80, the frailty score has a more normal distribution; the higher mean possibly reducing predictivity. One exisiting study of a mixed-sex population (mean 70.1 y) also reports that frailty is a stronger predictor in non-fallers, but another all-female survey (mean 69.4 y) reports the opposite [25, 28]; a likely explanation being that risk factors are both sex and age-specific.

As a way of understanding the transition to greater frailty and the association with falls, we examined initial frailty as a gradient, demonstrating a stepwise gradient in frailty quantifiable as an increasing number of falls at age 80 and 85. Although these women represent a relatively healthy susbset (having all survived 10 years and predominantly 'non-frail' or 'pre-frail'), nevertheless differences in frailty are mirrored in the high proportion of recurrent fallers. This implies that a careful assessment of frailty in the elderly might be beneficial for fall prevention and possibly forestall the cycle of frailty and falls.

Strengths of this study include first that the participants are community-dwelling, older women of average health, at a pivotal phase, where detrimental changes accumulate at a higher rate. Therefore, this study also provides information essential for prevention strategies to reduce the impact and consequences of frailty. Second, since all women were identically aged at inclusion, confounding from chronological age is reduced and age-adjustment unnecessary. Third, the availability of data for 10 years and beyond allows us to assess fall risk with increasing frailty, providing a long-term perspective on the consequences of frailty for successful aging.

Limitations of the study are also acknowledged. First, for direct comparison to other studies use of the most widely used phenotypic definition of frailty by Fried et al. [1] would be preferable. However, since the cohort was designed to investigate bone health, not general health, in aging, this was impossible. Instead, following the rules of Searle et al. [20] we developed a frailty index which performs well [16, 17]. Second, one of the variables included in the index was 'self-estimated fall risk', since the index was constructed for use with multiple outcomes. However, this did not appreciably affect the results, without it associations were a little lower but still significant. Third, there is a risk for recall bias, since falls were self-reported. A 12-month period was decided to be an acceptable recall period, since the times between follow-up visits were long. It has, however, been suggested that a narrower time frame increases internal validity and that participants should be questioned about the past month [29] and the results should be interpreted with this in mind. In retrospect a design involving mailing post-cards or frequent telephone calls could potentially have decreased the risk of bias. Further to this, exact fall dates were not collected hence it is impossible to determine how many falls directly resulted in fracture or injury. Fall outcome was, however, beyond the scope of this study. Cognitive function and whether it affected fall recall was not specifically tested in the cohort. Fourth, longitudinal studies following older people have an inherent limitation of loss-to-follow-up, mainly because of morbidity, relocation or mortality. Among survivors, reasons for non-attendance in OPRA are described in detail elsewhere [19, 30] but briefly at 5-year follow-up this was primarily due to illness (31%), while other reasons included moving to a senior home, moving abroad, social reasons, mobility problems (16%). The remainder did not specify a reason. At 10-year follow-up illness accounted for 56% of those not attending, moving or other reasons (21%). We acknowledge that the length of follow-up and high age of the participants reduces the number of participants at each follow-up, an inherent problem in all stuch studies. However,

since the incidence of falls increases with age the study is sufficiently powered.

In this population-based cohort of identically aged elderly women, frailty plays a significant role in the etiology of falls, most pronounced in those who are frail but have not yet reported a fall. It also emphasizes the connectivity between frailty and falls and the reciprocal increase in falls propensity and frailty status. These findings could be important in formulating prevention strategies, since it indicates that frailty assessment should be initiated early on.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The regional ethical review board in Lund approved the study (Dnr:2014804), which was performed according to the Helsinki Declaration principles.

Informed consent Participants provided written informed consent.

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Paper III

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ORIGINAL ARTICLE

In community-dwelling women frailty is associated with imminent risk of osteoporotic fractures

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Abstract

Summary Frailty reflects an accelerated health decline. Frailty is a consequence of fracture and contributes to fracture. Greater frailty was associated with higher fracture risk. Frail women were at immediate risk (within 24 months) of a hip or major fracture. Fracture prevention could be improved by considering frailty status.

Introduction Frailty encompasses the functional decline in multiple systems, particularly the musculoskeletal system. Frailty can be a consequence of and contribute to fracture, leading to a cycle of further fractures and greater frailty. This study investigates this association, specifically time frames for risk, associated fracture types, and how grade of frailty affects risk.

Methods The study is performed in the OPRA cohort of 1044, 75-year-old women. A frailty index was created at baseline and 5 and 10 years. Women were categorized as frail or nonfrail and in quartiles (Q1 least frail; Q4 most frail). Fracture risk was assessed over short (1 and 2 years) and long terms (5 and 10 years). Fracture risk was defined for any fracture, major osteoporotic fractures (MOFs), and hip and vertebral fracture, using models including bone mineral density (BMD) and death as a competing risk.

Results For women aged 75, frailty was associated with higher risk of fracture within 2 years (Hip $SHR_{adj.}$ 3.16 (1.34–7.47)) and MOF (2 years $SHR_{adj.}$ 1.88 (1.12–3.16)). The increased risk continued for up to 5 years (Hip $SHR_{adj.}$ 2.02 (1.07–3.82)); (MOF $SHR_{adj.}$ 1.43 (0.99–2.05)). Grade of frailty was associated with increased 10-year probability of fracture ($p = 0.03$). Frailty predicted fracture independently of BMD. For women aged 80, frailty was similarly associated with fracture.

Conclusion Frail elderly women are at immediate risk of fracture, regardless of bone density and continue to be at risk over subsequent years compared to identically aged nonfrail women. Incorporating regular frailty assessment into fracture management could improve identification of women at high fracture risk.

Keywords BMD · Community dwelling · Fracture · Frailty · Women

Introduction

Osteoporosis, which causes low bone mass and microarchitectural deterioration, is responsible for 3.5 million fractures annually in Europe [1]. These fragility fractures occur typically at the hip, wrist, and vertebra and are a significant cause of disability, pain, and reduced quality of life [2]. Fractures are also associated with mortality [3, 4]. In addition to the personal toll, they account for increased health care costs, particularly after hip fracture [5].

As a consequence of aging, and the inevitable functional decline in the musculoskeletal system, almost every second, woman in Sweden will suffer a fracture by the age of 80 [4]. Since demography changes towards an elderly population [6], the 50% lifetime fracture risk for women over the age of 50 makes prevention of osteoporotic fracture not only a challenge but a must.

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One way to identify individuals at high risk of osteoporotic fracture could be frailty. Frailty encompasses the functional decline in multiple physiological systems, with perhaps the most dramatic changes in the musculoskeletal system [7, 8]. Frailty is both a consequence of and a contributing factor to fracture. Consequently, this association can lead to a vicious cycle of further fractures and greater frailty [9, 10] and a wide range of adverse outcomes [8].

Fracture prevention, whether primary or secondary, is an important aspect for successful aging [11], and one of the most significant obstacles is the difficulty in correctly identifying those at high risk of fracture [4]. Of the standard tools, neither bone density measurements nor fracture risk assessment by FRAX can fully capture and adequately identify all those at risk. In particular, there are limitations when applied in the very old [12]. With these limitations, new aids to improve risk assessment are needed; one such possibility is to evaluate frailty.

Although earlier studies have investigated frailty and fracture [13, 14], few have been performed in cohorts specifically designed to address osteoporosis-related outcomes. The knowledge gaps include whether frailty can independently predict fracture and if so which fracture types and over what time periods. In older individuals, hip fracture is the predominant fracture of interest, but can other types of fractures be predicted by frailty since these might precede a hip fracture? Furthermore, with advancing age, it is not known how frailty and fracture interact.

We have previously followed the progression of frailty over 10 years and reported that frailty is associated with osteoporosis, falls, and mortality in a population of community-dwelling elderly women [15, 16]. In the present study, the overall aim was to explore the association between frailty and fracture. Firstly, we investigated the time frame over which a frail person is at increased risk, focusing on imminent risk, i.e., over 1 and 2 years and longer term, over 5 and 10 years. Secondly, we investigated if frailty is independently predictive of specific fracture types with advancing age. Thirdly, we investigated if early stages of frailty and progression interact with fracture risk. Ultimately, this knowledge may contribute to the understanding of how frailty assessment can serve as an integral part in fracture prevention protocols.

Materials and methods

Subjects

The Osteoporosis Prospective Risk Assessment (OPRA) cohort is an observational study designed to study risk factors related to bone health. Community-dwelling women, 75 years old (75.2 ± 0.2 years), were randomly selected, without exclusion criteria, from the population register for Malmö, Sweden [17]. Of those invited, 1044 attended baseline investigation (1995–1999), 67% attendance rate. At follow-up, 715 attended (age 80.2 ± 0.2) at 5 years and 382 (age 85 ± 0.1) at 10 years. Reasons for nonparticipation have been previously described in full [18].

At each visit, detailed investigations were performed: physical assessment (balance, gait, and muscle strength), biomarkers, and measurements of femoral neck bone mineral density (BMD) together with questionnaires to capture information related to lifestyle, health, and other risk factors [15, 17].

Using the unique personal identification number allocated to every Swedish citizen, date of death was acquired from the Swedish National Population Register (October 2012, when the maximum age of those women still alive was 91.5 years).

All procedures performed were in accordance with the ethical standards of the regional ethical review board in Lund (Dnr: 2014804), and the study was performed according to the principles of the Helsinki Declaration. All women provided written informed consent.

Assessment of frailty

A deficit accumulation frailty index (FI) was constructed adhering to the principles suggested by Searle et al. [19], i.e., all variables were associated with health, increased with age, did not saturate too early, and covered a wide range of domains. Briefly, all continuous and categorical variables were reclassified into the range 0.0 and 1.0 and then summed and divided by the numbers of variables included (Online Resource 1). The thirteen variable index, including treatment of missing values, has been described previously [16]. The index represents "deficits in health," where a higher score indicates higher frailty. The index of frailty was calculated for each age (75, 80, and 85). An empirical threshold of ≥ 0.25 was used to define frail individuals [16, 20, 21].

Fractures

Incident fractures were prospectively followed until October 2012 (up to 15 years) through the X-ray files at the Radiology Department, Malmö, Skåne University Hospital [18]. Information loss during follow-up was exceptionally low since the Department of Orthopaedics is the sole unit treating fractures in the catchment area. Fractures resulting from pathology and high energy were excluded. Fractures occurring prior to inclusion (specifically, between ages 50 and 75) were also registered [22].

Statistical analyses

Descriptives for continuous variables are reported as mean and standard deviation (SD) or median and interquartile range

(IQ) where appropriate. Categorical variables are reported as number (*n*) and percentage (%).

Frailty was analyzed as categories "frail" (≥ 0.25) or "nonfrail" (< 0.25) and in quartiles (Q1 least frail; Q4 most frail) to visualize progression of frailty and changes in fracture risk. Fractures are reported as any fracture, major osteoporotic fractures (MOFs) as defined by FRAX (http://www.shef.ac.uk/FRAX), and hip and vertebral fracture.

The temporal association between frailty and fracture was explored in different time frames. From age 75, we estimated short-term (1 and 2 years) fracture risk (i.e., frailty at age 75 and incident fractures between ages 75–76 and 75–77) and long-term (5 or 10 years) risk (fractures between ages 75–80 and 75–85). To evaluate this association in the very old, we then "reset" baseline and, based on frailty at age 80, estimated fracture risk over the same time frames.

Demographic characteristics of frail/nonfrail women were compared using Student's T-test and chi-square or Mann–Whitney *U* test for nonparametric distributions.

Fracture incidence was defined as the number of women sustaining at least one fracture during the specified time frame. Incidence rate is presented as number of fractures per 1000 person-years, calculated using *all* registered fractures. Incidence rate ratios (IRRs) with 95% confidence intervals (95% CI) were estimated by Poisson distribution to compare fracture rates between frail/nonfrail women.

To investigate the association between frailty and fracture with death as a competing event, we estimated the probability of fracture, calculated as a cumulative incidence function (CIF) with Gray's test to assess statistical significance. To predict fracture risk, we used the model proposed by Fine and Gray [23] estimating proportional subdistribution hazard ratios (SHR) and 95% CI for a first fracture. To determine if frailty independently predicts fracture risk, BMD was included as a covariate. Subgroup analysis further assessed the additive effect of smoking.

The study is estimated to have > 80% power to detect a 1.45 difference in relative risk (RR) for any fracture (alpha 5%), between frail and nonfrail women. This is based on the 5-year incidence of any fracture (19.1%) in nonfrail women from the cohort. However, acknowledging the limitations of post hoc power calculations [24], confidence intervals indicate the reliability of the associations. Analyses were performed using SPSS v25 and RStudio v1.2.5042 [25, 26]. $p < 0.05$ was considered nominally significant.

Results

The characteristics of the OPRA cohort have been reported in detail previously [15], while those relevant to this study are shown in Table 1. On inclusion in the study at age 75, the median FI of the population was 0.16 (range 0.01–0.74). Almost one quarter (23.5%, $n = 245$) of the women were classified as frail (FI ≥ 0.25). For women having sustained a fracture prior to baseline, about half of the individual variables comprising the FI differed between frail and nonfrail women, predominantly those related to musculoskeletal function, while there was no difference in disease incidence or biomarkers. Frail women had higher BMI, higher bisphosphonate and glucocorticoid usage, and more previous fracture and falls ($p < 0.05$).

At the end of the study (October 2012), half of the women (50.2%, $n = 524$) had sustained at least one fracture, and a quarter (25.7%, $n = 268$) had two or more fractures. Hip fracture occurred in 18.7% ($n = 195$) of the population and 20.5% ($n = 214$) had at least one vertebral fracture. The total fracture incidence increased regardless of frailty status over the observation period; between 75 and 80 ($n = 214$), the incidence of a first fracture was 20.5% and between 80 and 85 ($n = 177$) 24.8%.

The fracture incidence rate per 1000 person-years was higher among women who were frail at age 75, for any fracture (109.0 vs. 80.8; $p < 0.01$) and MOF (80.1 vs. 64.0; $p < 0.01$); reflected in an increased risk (IRRs 1.35 and 1.25), respectively. Hip fracture did not differ (23.1 vs. 18.0; $p = 0.13$).

The distribution of fracture types in frail and nonfrail women is shown in Online Resource 2.

Frailty at age 75 and short- and long-term fracture risk

Since age is an important factor for the elderly, we firstly investigate the short-term time frame and risk within the first 2 years. For a 75-year-old woman who is frail, the risk of hip fracture is elevated already within the first year compared to identically aged, nonfrail women (SHR 3.94, (1.20–12.9)). This is reflected in the proportion of women who fractured (2.4% vs. 0.6%; $p = 0.014$) (Table 2A and Supplementary Table 2). Adjustment for BMD did not significantly alter this association ($SHR_{adj.}$ 3.75 (1.11–12.71)). The risk of hip fracture continued to be elevated at two years (SHR 3.04 (1.34–6.88)). Indeed, the proportion of frail women who fractured was more than doubled compared to nonfrail (4.5% vs. 1.8%; $p = 0.005$). The frail also had a higher risk of any fracture and MOF within the first 2 years, SHR 1.70 (1.11–2.60) and 1.89 (1.17–3.06), respectively (Table 2A and Fig. 1a). Adjusting for BMD did not change these results. Being a current smoker and frail further increased the risk of fracture (Any HR 2.51 (1.15–5.48); MOF HR 2.89 (1.24–6.76); Hip HR 3.70 (1.04–13.1) compared to non-smoking frail women) while not apparent for the nonfrail. The proportion fractured were 13.1% vs. 7.9% ($p = 0.014$) for any fracture and 10.6% vs. 5.8%; ($p = 0.009$) for MOF (Online Resource 3).

In the 5-year perspective, frailty continues to associate with fracture (Table 2A and Table 3A). For hip fracture, the frail

Table 1 Characteristics of nonfrail and frail women at age 75

All variables at 75 years	Nonfrail (< 0.25) $n = 799$		Frail (≥ 0.25) $n = 245$	
	Mean	SD	Mean	SD
Frailty index (FI)	0.14	(0.05)	0.36	(0.10)
BMI (kg/m^2)	26.0	(3.88)	27.0	(5.05)
Femoral Neck BMD (g/cm^2)	0.764	(0.114)	0.770	(0.152)
Femoral Neck (T-score)	− 1.80	(1.12)	− 1.76	(1.27)
	No.	(%)	No.	(%)
Current smoker	107	(13.5)	38	(15.8)
Bisphosphonate user	20	(2.5)	13	(5.3)
Glucocorticoid user[a]	49	(6.1)	29	(11.9)
No. of women with prior fractures between 50 and 75	$n = 792$		$n = 239$	
At least one fracture	278	(35.1)	105	(43.9)
Major osteoporotic fracture	174	(22.0)	51	(21.3)
Hip	9	(1.1)	5	(2.1)
Radius	146	(18.4)	41	(17.2)
No. of women who fell in previous 12 months[b]	$n = 693$		$n = 221$	
At least one fall	146	(21.1)	114	(51.6)
No falls	547	(78.9)	107	(48.4)
Deceased at end of study (2012)	414	(51.8)	184	(75.1)
Deceased after 10 years	190	(23.8)	117	(47.8)

[a] Current or previous use for > 3 months

[b] Self-reported

75-year-old is at twice the risk compared to the nonfrail, even accounting for competing mortality (SHR 2.03 (1.13–3.64)) and similarly for incidence rate 17.5 vs. 8.1 per 1000 person-years. Overall, a greater proportion of frail women had at least one fracture at any site (24.9% vs. 19.1; $p = 0.051$), a higher fracture incidence rate (78.1 vs. 55.5 per 1000 person-years), and a higher risk even accounting for competing mortality. Vertebral fractures were more frequent in the frail (9.4% vs. 5.3%; $p = 0.019$), and risk was higher (SHR 1.83 (1.10–3.04)). With adjustment for BMD, the risk estimate just crossed below significance level ($SHR_{adj.}$ 1.75 (0.99–3.10)). In the same time frame, the IRR was almost doubled for vertebral fractures (1.79 (1.14–2.76)) (Table 3A).

For a woman who is frail at age 75, compared to the nonfrail, the cumulative incidence trajectories differ, with the greatest difference at 2 to 5 years (Fig. 1a). In a 10-year perspective, the probability of fracture continues to be elevated, although, with the extended observation period and

Table 2 Relative risk of fracture for frail women across time frames of 1, 2, and 5 years based on being frail at (A) age 75 and (B) age 80

	1-year risk		2-year risk		5-year risk	
	SHR[a]	95% CI	SHR	95% CI	SHR	95% CI
(A) Frail at age 75						
Any	1.55	(0.87–2.76)	1.70	(1.11–2.60)	1.38	(1.02–1.86)
Major osteoporotic	1.71	(0.90–3.25)	1.89	(1.17–3.06)	1.38	(0.99–1.93)
Hip	3.94	(1.20–12.9)	3.04	(1.34–6.88)	2.03	(1.13–3.63)
Vertebral	1.19	(0.38–3.74)	1.88	(0.79–4.46)	1.83	(1.10–3.04)
(B) Frail at age 80						
Any	1.85	(0.95–3.59)	1.59	(1.02–2.48)	1.52	(1.13–2.04)
Major osteoporotic	1.89	(0.93–3.83)	1.79	(1.12–2.86)	1.53	(1.12–2.09)
Hip	5.43	(1.13–26.2)	2.0	(0.91–4.39)	1.48	(0.90–2.44)
Vertebral	1.86	(0.57–6.09)	1.43	(0.63–3.24)	1.97	(1.21–3.21)

[a] Subdistribution hazard ratios with reference category nonfrail. Frailty status was assessed at beginning of each period calculated (ages 75 and 80)

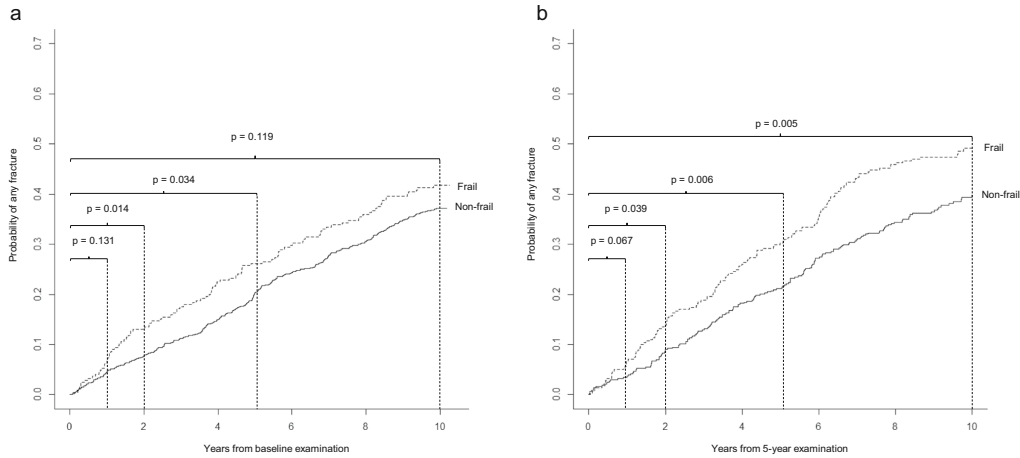

Fig. 1 Cumulative incidence of any fracture stratified by frailty status at **a** age 75 and **b** age 80, calculated in the presence of the competing risk of death. Differences in cumulative incidence rates between frail and nonfrail categories were tested using Gray's test

advancing age, baseline frailty status does not discriminate the probability of fracturing as is obvious by the comparable slopes.

Grade of frailty and fracture risk

Quartiles were used to further categorize frailty; (Q1 range ≤ 0.11; Q2 0.12–0.16; Q3 0.17–0.24; Q4 ≥ 0.25). There was a clear stepwise association between increasing frailty and the 10-year probability of a first fracture of any type (Q4 to Q1 (Gray's $p = 0.03$)) (Fig. 2a). For vertebral fractures, a significant difference was seen already between Q1 and Q2 ($p = 0.005$).

The time difference in fracture accumulation between the least frail and most frail (Q1 and Q4) is 2.5 years for any fracture and 4.7 years for hip fracture, i.e., the fracture free time is longer in the least frail (Fig. 2a, b).

Frailty at age 80 and short- and long-term fracture risk

For an 80-year-old woman who is frail, the risk of hip fracture is also elevated (SHR 5.43 (1.13–26.2)), although the proportion who fractured during this first year was low (2.5% vs. 0.5%; $p = 0.017$) (Table 2B). The risk continued to be elevated at 2 years; hip fracture (SHR 2.0 (0.91–4.39)) while not reaching statistical significance, any fracture (SHR 1.59 (1.02–2.48)) and MOF (SHR 1.79 (1.12–2.86)).

In the 5-year perspective, although frailty is less predictive for hip fracture (SHR 1.48 (0.90–2.44)), it continues to be associated with a higher risk of any fracture (SHR 1.52 (1.13–2.04)), MOF (SHR 1.53 (1.12–2.09)) and for vertebral fractures (SHR 1.97 (1.21–3.21)). Adjusting for BMD did not change the results.

The incidence trajectories for women who were frail and nonfrail at age 80 are illustrated in Fig. 1b. The probability of any fracture continues to be elevated for up to 10 years in the frail compared to the nonfrail.

Fracture leads to frailty

Having analyzed how frailty influences the risk of future fracture, we next investigated how a prior fracture, from age 50 to the baseline investigation, influenced frailty at age 75. Prior to the baseline, 37.1% ($n = 383$) of the women reported a fracture between ages 50 and 75. The mean frailty score was significantly higher compared to those with no prior fracture (0.21 vs. 0.18, $p < 0.01$). Furthermore, women with a fracture between ages 50 and 75 and in both later age intervals (75–80 and 80–85) were more frail compared to those who remain fracture free throughout, from ages 50 to 85 (0.38 vs. 0.27, $p = 0.038$). On the other hand, among those with a prior fracture, but no new fractures up to the age of 85, the frailty score was equivalent to those never experienced a fracture (0.27 vs. 0.27) (Fig. 3).

Discussion

This study of 75-year-old community-dwelling women indicated that frailty is an important, clinically feasible way to identify individuals at high fracture risk. Going beyond traditional risk factors such as BMD, frailty assessment takes a

Table 3 Number of *women* with incident fractures and number of *fractures* stratified by frailty status at (A) age 75 and (B) age 80

	No. of *women* with at least one fracture[a]					No. of *fractures*[b]				Incidence rate ratio
	Nonfrail		Frail			Nonfrail		Frail		
(A) Frailty status at age 75	*n* = 799		*n* = 245		*p* value					
Fractures in the 5 years between 75 and 80	No.	(%)	No.	(%)		No.	(fractures/1000 person-years)[c]	No.	(fractures/1000 person-years)[c]	IRR[d]
Any	153	(19.1)	61	(24.9)	0.051	213	(55.5)	85	(78.1)	1.41 (1.08–1.82)
Major osteoporotic	122	(15.3)	49	(20.0)	0.080	163	(42.5)	67	(61.6)	1.45 (1.07–1.99)
Hip	30	(3.8)	18	(7.3)	0.019	31	(8.1)	19	(17.5)	2.16 (1.15–3.95)
Vertebral	42	(5.3)	23	(9.4)	0.019	65	(16.9)	33	(30.3)	1.79 (1.14–2.76)
Frailty index (mean, SD)	0.14	(0.05)	0.36	(0.10)						
(B) Frailty status at age 80	*n* = 434		*n* = 281							
Fractures in the 5 years between 80 and 85	No.	(%)	No.	(%)		No.	(fractures/1000 person-years)	No.	(fractures/1000 person-years)	IRR
Any	92	(21.2)	85	(30.2)	0.006	143	(68.7)	132	(103.9)	1.51(1.18–1.93)
Major osteoporotic	81	(18.7)	76	(27.0)	0.008	121	(58.2)	110	(86.6)	1.46 (1.12–1.91)
Hip	32	(7.4)	30	(10.7)	0.125	36	(17.3)	33	(26.0)	1.50 (0.91–2.48)
Vertebral	29	(6.7)	36	(12.8)	0.005	38	(18.3)	53	(41.7)	2.28 (1.48–3.56)
Frailty index (mean, SD)	0.16	(0.05)	0.36	(0.09)						

[a] First fracture used as endpoint. A woman could be included in multiple categories if fractures at different sites were sustained during the follow-up

[b] Multiple fractures in the same woman are included in the count

[c] Incidence rate (IR)

[d] Incidence rate ratio, reference category nonfrail

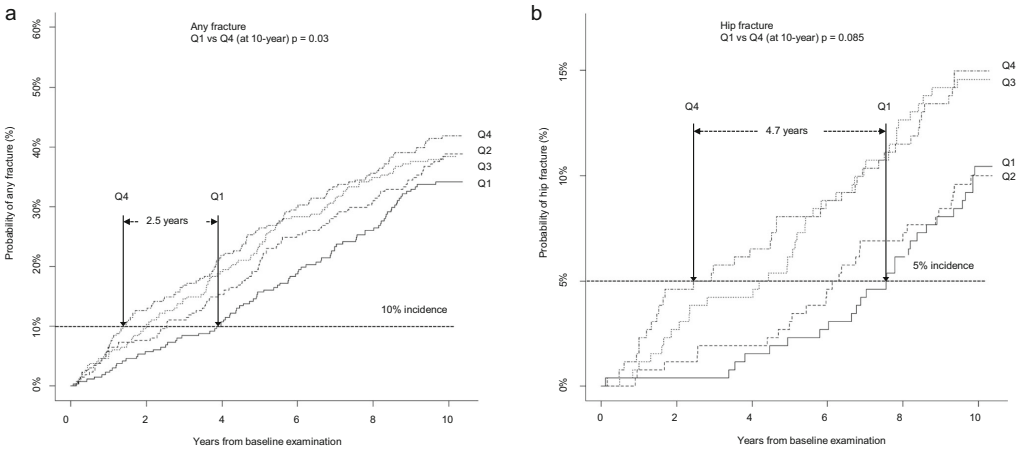

Fig. 2 Cumulative incidence of **a** any fracture and **b** hip fracture, stratified by quartiles of frailty at age 75, calculated in the presence of the competing risk of death. Differences in cumulative incidence rates between Q1 and Q4 was tested using Gray's test. The graphs show that among the least frail (Q1), fracture accumulation occurs between 2.5 (any fracture) and 4.7 years (hip fracture) later, i.e., they remain fracture free for longer compared to the most frail women (Q4). *Frailty quartiles Q1 (≤ 0.11), Q2 (0.12–0.16), Q3 (0.17-0.24), and Q4 (≥ 25)

much needed holistic approach to capturing fracture risk, making it a useful complement to existing assessment tools. Frailty is associated with fracture, and this study highlights that being frail presents a high risk of fracturing within the next 12–24 months. At entry into the study, frail women at the age of 75 had a two to four times higher risk of hip fracture already within the first year. These women continue to be at higher risk over the next 2 years for hip fracture, MOF, and indeed any type of fracture. The observed higher fracture risk within the first year is in agreement with two other studies,

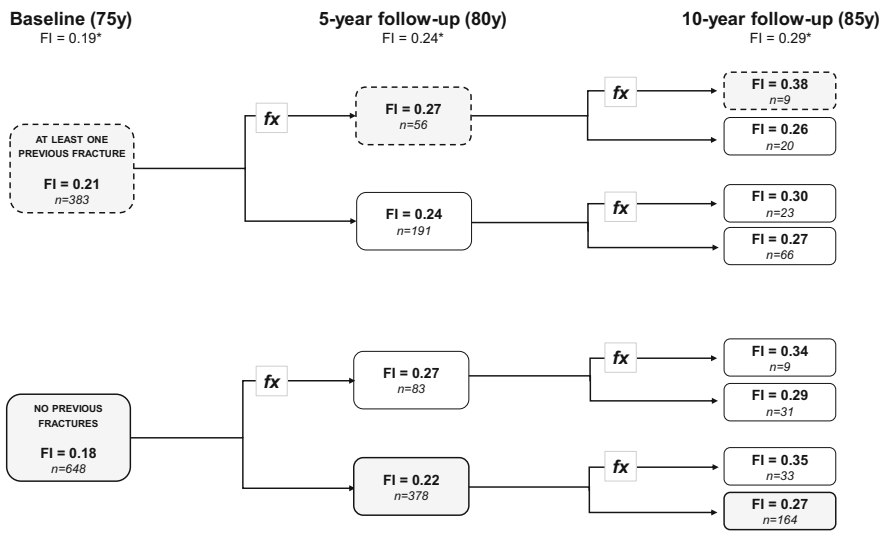

Fig. 3 Flowchart demonstrating how frailty score is affected by having had a fracture (at least one fracture of any type). At baseline, women were stratified based on whether they had at least one previous fracture between 50 and 75. Frailty score at 5- and 10-year visits is shown, based on fracture history during the intervening period. *FIs are population mean. The calculations were made on women that attended all follow-ups

albeit in younger individuals, confirming the value of frailty assessment by capturing health beyond chronological age [27, 28].

With increasing age, everyone becomes frailer, risk factors for fracture accumulate, and health status often rapidly changes. Since frailty is dynamic and accumulates at different rates, the value of an examination deflates over time. We showed that a higher fracture risk persisted over 5 years while after 10 years, frailty was no longer discriminative, because by age 85, almost everyone is frail. Long-term projections are therefore less meaningful and frailty should be reassessed regularly. Further demonstrating this, when frailty was reassessed at age 80, it again predicted high fracture risk within the short term. A number of studies have demonstrated association between frailty and fracture over 5–10 years [29–32] which is important in an epidemiological context, but given the short expected survival in the elderly, the immediate implications are more relevant. This association to imminent fracture risk has consequences for clinical decision making; most important is initiating interventions that have immediate effects, primarily to prevent falls leading to fracture, such as home environment adjustments, medication reconciliation, walking aids, and balance and strength training [33, 34]. Delayed-effect interventions such as antiosteoporosis medication can be implemented in parallel. Frailty and fractures are related to one another bidirectionally. Our study shows not only that frailty leads to fractures but also that fracture is associated with higher frailty, which is in line with other studies [35]. This reflects what a critical element the musculoskeletal system plays in the frailty syndrome and, in addition, the functional decline and disability that results particularly from a hip fracture. Prompt interventions may prevent the downward spiral into progressing frailty and subsequent recurrence of fracture [36]. The benefit of secondary fracture prevention is clearly seen in our study; even in the event of a postmenopausal fracture between 50 and 75, if a woman remains fracture free for 10 years, the trajectory of frailty will be similar to those who never fractured.

Not assessing frailty would be a missed opportunity in fracture prevention, since at age 75, one in ten women from the frailest quartile will suffer a fracture after little more than a year. Those who were nonfrail remain fracture free longer, delaying hip fracture for almost 5 years and any fracture for two and half years. This observation highlights the variability in risk between fracture types and age; frailty predicts hip fracture at 75, but less so after age 80, a finding in part supported by others. While not completely comparable in terms of demographics and follow-up, in the Canadian Multicentre study (CaMos), Kennedy et al. find a similar loss of association among participants aged 65 and older [29]. The present study allows us to further understand the temporal relationships between fracture type and age; from age 80, relative to nonfrail women, women who were frail had a larger increase in vertebral, shoulder, and pelvic fractures (data not shown) while the increase in hip and radius fractures was more pronounced among the nonfrail. Vertebral fracture was also associated with frailty. A novel finding was that even those who were only moderately frail (Q2) had double the risk of a vertebral fracture over 10 years. This is clinically relevant from two perspectives; (a) it emphasizes the utility of identifying prefrailty, and (b) since vertebral fractures are often symptom free and go undetected, it is possible that these "prefrail" women already have a vertebral fracture. Hence, it is a signal for investigation, and if warranted antiosteoporosis treatment, since if one has a vertebral fracture, one is likely to have another subsequent fracture [37].

We have shown that frailty captures multiple aspects of musculoskeletal aging in older women- osteoporosis, falls, and fracture - as well as mortality; therefore, it stands to reason that regular assessment of frailty has the capacity to be an additional tool in identifying those elderly at high risk of fracture [15, 16]. We can also speculate that a rapid change in frailty status could further impact on fracture risk. This also means that interventions to reduce the risk can be initiated at an earlier stage with a person-centered approach. Focusing on hip fracture, in the elderly, most hip fractures result from a simple fall. The association between being frail and having a hip fracture within a year indicates that frailty encompasses many physical changes related to fall propensity such as impaired balance, sarcopenia, and musculoskeletal dysfunction. To be effective, a proactive health service is essential, involving communication between multiple caregivers, including primary care, physiotherapists, and clinicians, preferably before a first fracture has occurred and definitely in any postfracture program.

The strengths of this study includes *firstly* that the OPRA cohort was specifically designed to investigate bone health and therefore has detailed information on time to fracture and fracture site. The extensive follow-up time allowed exploration of the effects of existing and emerging frailty on fracture risk in a clinically meaningful context. *Secondly*, this study is performed in randomly selected, community-dwelling older women at an age where fracture incidence is accelerating, and the implications of suffering a fracture or becoming frailer are severe. *Thirdly*, the identical age of all the participants allows us to clearly demonstrate that frailty, which reflects biological age, is additive, beyond chronological age in terms of correctly predicting fracture risk. The data show that being frail "accelerates" the normal expectation of when a fracture will occur, i.e., 2–5 years earlier. Being frail and a smoker confers an even higher risk of fracture. *Fourthly*, this study employed statistical modelling to account for the competing risk of death, a common problem in longitudinal studies of the elderly, therefore minimizing the potential for bias or overestimation. However, since Fine and Gray models give an approximate estimate of risk, the results should be interpreted with this in mind, and similarly that for all studies spanning decades, there is a loss of power from loss of participants beyond what is accountable by applying competing risk algorithms.

Limitations are acknowledged. It is difficult to make direct comparisons with other studies due to the diversity of frailty instruments used in the literature. However, overall, the results are in general agreement, which is in line with the high redundancy, whereby one variable captures many. Furthermore, there may be bias towards the participants being healthier compared to the general population; however, this is inherent to all longitudinal studies of older people and may be beyond even what can be accounted for. Nevertheless, we were able to follow the increasing fracture burden in the population through the stepwise gradient of risk when transitioning into greater frailty. We also recognize that our findings pertain to the population of elderly women studied and may not be directly transferrable to other ages, ethnicities or to men.

To summarize, our study demonstrates that frailty is associated with imminent fracture risk, in particular hip fracture and other MOFs. Frailty needs to be reassessed regularly since health status can rapidly change in the elderly and with advancing age, which influence fracture risk. This knowledge is important, with the temporal aspects of fracture risk potentially having implications in the choice of treatment strategy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-021-05886-7.

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Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Compliance with ethical standards The study was performed in accordance with the Helsinki declaration and approved by the Lund University Ethical Review Board. Participants provided written consent.

Conflicts of interest The authors Patrik Bartosch, Linnea Malmgren, Jimmie Kristensson, Fiona McGuigan, and Kristina Åkesson declare no potential conflicts of interest according to ICMJE requirements with respect to the research, authorship, and/or publication of this article.

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Paper IV

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ORIGINAL ARTICLE

A "snap-shot" visual estimation of health and objectively measured frailty: capturing general health in aging older women

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Abstract

Background In clinic, a subjective visual estimation of a patient's general health often guides interventions, yet little is known of how this assessment relates to objectively measured frailty.

Aims To characterize the relationship between these two assessments and explore the implication of discordance.

Methods The study was performed in the OPRA cohort of 75-year old community-dwelling women ($n = 1044$). Visual perception of health (VPH) was estimated within 15 s from first sight and stratified into tertiles (poor/intermediate/good health). Frailty was measured using a frailty index (FI) (scored 0.0–1.0) and stratified into tertiles: '*frail*' (≥ 0.22), '*pre-frail*' (0.13–0-21) and '*non-frail*' (≤ 0.12). Association between VPH and FI and with 10-year mortality was evaluated using Kaplan Meier curves and Cox proportional hazard models.

Results VPH and FI correlated, but was strongest in those perceived to be in poor health ($r_s = 0.424$, $p < 0.001$). Approximately half of these women were also objectively frail (53.7%). Similarly, 50.7% perceived to be in good health were also objectively non-frail. However, for one in ten, perceived health was discordant with measured frailty. Subjective and objective measures were associated with mortality, but VPH lacked discrimination in healthier looking women ($p = 0.372$) compared to FI ($p = 0.002$).

Discussion Detecting pre-frailty is important to prevent or slow the transition into a frail state. The frailest can be identified with a visual estimation, but only objective frailty assessments can reliably identity pre-frailty.

Conclusions A visual estimation of health provides valuable complementary information on health, whereas objective assessment of frailty has a broader applicability for health in aging.

Keywords Frailty · Visual perception · General health · Women · Community-dwelling

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Introduction

Frailty is a state of increased vulnerability to stressors, and intrinsically linked to age-related changes in general health. As such, it is superior to chronological age in reflecting a diminishing resilience in the aged [1]. Clinically, frailty is important because of its wide association to adverse outcomes such as hospitalisation, disability, treatment tolerance and mortality [2].

Detecting early progression of frailty or pre-frailty in the older population is important to prevent or slow down the transition into a frail state [3]. With the expected shift towards an older population, it is increasingly important to identify individuals at risk of developing frailty [4]. Early signs of frailty may be overlooked, either because of their subtle presentation, not yet visible to the eye, or at worst dismissed as normal signs of ageing [5].

To date, in the absence of a consensus on how best to measure, define and apply frailty, the clinician's judgement is commonly used. Often necessarily brief, a visual inspection by healthcare professionals frequently serves as an estimation of an individual's overall health [6]. This subjective "clinical eye" or visual perception of health (VPH) frequently guides further clinical decision-making albeit in conjunction with history and examination [7]. With this practice, there is nevertheless an inherent risk to misjudge a patients' health, and therefore, refrain from administering beneficial interventions [8] or indeed, subject them to treatments or medications that would actually be harmful. Assessing frailty objectively can be time-consuming, often encompassing physical testing e.g. measuring isometric muscle strength, gait speed and balance, therefore it is easy to understand the reliance on "the clinical eye".

It is not well established how closely subjective (i.e. VPH) and objective (i.e. frailty) estimates of general health relate to one another. A handful of studies has explored the subject in very specific patient groups, and with diverse, sometimes contradictory results [6–10]. At the population level, however, there are, to our knowledge, few or no existing studies. With limited resources in health care, it is also instrumental to know when an assessment of frailty status would actually add valuable information.

Therefore, in this exploratory study, our aim was to characterize the relationship between a subjective visual perception of health and objectively measured frailty, using a large cohort of older community-dwelling women with identical chronological age. This study explores the implications for mortality when these measures are concordant or discordant. In the study, we use a subjective visual perception of general health, which we have previously shown to be associated with fracture and 5-year mortality [11]. For comparison, we use a quantitative, cohort specific frailty index, which in the same cohort was associated with mortality, falls and fractures, [12–14].

Materials and methods

Subjects

This study is based on the Osteoporosis Prospective Risk Assessment (OPRA) cohort of 75 year old (75.2 ± 0.2 years) community-dwelling women. The women were randomly selected from the population register of Malmö, Sweden, at the age of 75. No exclusion criteria were applied. At baseline investigation (1995–1999), 1044 women of 1604 invited attended, giving a 65% attendance rate. At 5-year follow-up 715 attended (age 80.2 ± 0.2) and 382 (age 85 ± 0.1) at 10 years. Reasons for non-attendance are described in detail elsewhere [15]. At each visit, detailed data were collected from physical assessment (muscle strength, balance, gait, etc.), questionnaires on lifestyle and health, and blood samples [16, 17]. Date of death was acquired from the Swedish National Population Register. This study uses data from the baseline investigation only.

All procedures performed were in accordance with the ethical standards of the regional ethical review board in Lund (Dnr: 2014804), adhering to the principles of the Helsinki Declaration. All women provided written informed consent.

Quantitative frailty assessment

Following principles suggested by Searle et al. [18], a frailty index (FI) was constructed. In brief, 13 variables associated with health, increasing with age and covering a wide spectrum of physical domains were selected. These deficits in health were used to construct the index (scored 0.0–1.0, higher score indicating higher frailty) [13]. Where an individual lacked information for a variable, the total deficits were reduced by one. The majority of variables had less than 5% missing values, while 'self-estimated risk of falling' and 'diseases affecting balance' had 13.5 and 14.9% missing, respectively (supplementary Table 1). Overall, 80% of cases had valid data for at least 12 out of the 13 variables and formal testing of the effect of missing variables on the ability of the constructed index to predict mortality showed no appreciable differences (supplementary Table 2). Furthermore, the index correlates very highly to a full 40-variable index ($r = 0.80$) [13] that had been created for the two follow-up visits [12], and both these 13- and 40-variable indices have a similar ability to predict mortality [12].

Frailty was analysed as tertiles equating to non-frail (≤ 0.12), pre-frail (0.13–0.21) and frail (≥ 0.22). We also

used an empirical cut-off, where frail was defined as FI ≥ 0.25 [13].

Subjective visual perception of health

At baseline, the women (all chronologically identically aged) had a visual perception of health status (VPH) scored within the first 15 s of sight, as detailed earlier [16]. In brief, all women were estimated by two independent healthcare professionals (aware of the participants age), using an arbitrary scale ranging from 1 to 100, where "1" represented a very healthy appearance and "100" a very unhealthy appearance. The mean value of the two scores was used in calculations. The correlation between the observers was satisfactory ($r = 0.51–0.59$, $p < 0.0001$) [16]. VPH was analysed as tertiles equating to "good", "intermediate" and "poor" health.

The analyses in this study are based on a dataset of 1004 women for whom both FI and VPH were available. Forty women had missing VPH values; these 40 women had a higher FI compared to the cohort mean (0.31 vs 0.19, $p < 0.001$).

Statistics

Descriptive data are presented as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables are reported as number (n) and percentage (%). Association between tertiles of VPH and individual variables in the frailty index were tested using Kruskal–Wallis test, Chi-squared and ANOVA, as appropriate. Correlation between subjective and objective assessments in corresponding tertiles was tested using Spearman's Rho.

Linear regression was used to investigate the association between VPH and FI and to what degree the VPH mirrored variation in the frailty index. To adhere to the assumptions of normality in linear regression analysis, logarithmic and square root transformations were performed for VPH and FI, respectively. The effect of significant outliers (> 3 SD, $n = 5$) was tested with or without these included.

Concordance between subjective (VPH) and objective (FI) assessments was analysed using cross tabulation and chi^2, comparing the tertiles. Concordance was defined as being in the reciprocal tertile of both VPH and FI, i.e. visually perceived to be in good health *and* measured non-frail by frailty index or vice versa. Discordance was defined as being in the opposite tertiles of VPH and frailty, i.e. visually perceived to be in good health *but* measured as frail by frailty index or vice versa. For a visual representation of the density distribution of frailty within VPH tertiles, a spline function was used for smoothing the curves.

Using tertiles of VPH and FI, differences in 10-year mortality were assessed using Kaplan–Meier analysis with log rank. When assumptions were met, Cox regression analyses were used to calculate hazard ratios (HR). We also explored the implications for mortality when VPH and FI are not in accordance, aiming to identify in which situations VPH suffices and when an assessment of frailty adds to prediction. The results are reported without adjustments for multiple testing. For all calculations, alpha < 0.05 was considered nominally statistically significant. All calculations were performed using SPSS, IBM Corp, released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY.

Results

Participant characteristics stratified by visual perception of health

The characteristics of the OPRA cohort participants, stratified by subjective assessment (VPH) are presented in Table 1. Women in the poor VPH tertile had not only the highest frailty index (median 0.22; mean 0.25) but also the widest range in values (FI 0.02–0.66). Almost 40% of women who were perceived to be in poor health were objectively frail, with a FI > 0.25. By comparison, only 9% of women perceived to be in good health were objectively frail. Women in the poor VPH tertile, had higher BMI, poorer visual acuity, and more had reported having previous falls and fractures.

Correlation between visual perception of health and frailty index

There was a moderate but significant correlation between visual perception of health and frailty index ($r = 0.452$; $p < 0.001$). With removal of the five outliers, the correlation increased ($r = 0.474$). Not surprisingly, the correlation between subjective and objective assessments was highest in those perceived to be in poor health (Spearman's rho 0.403) and lowest in those perceived to be in good health (Spearman's rho 0.147). Approximately 20% ($r^2 = 0.204$) of the variation in VPH was explained by the frailty index.

Concordance and discordance between visual perception of health and frailty index

The distribution of frailty scores within the good VPH tertile (FI 0.01–0.40) and poor VPH tertile (FI 0.02–0.66) are shown in Fig. 1, with the areas concordant and discordant for VPH-FI highlighted. No one with an FI score above 0.40 was scored in the good VPH tertile. Across all tertiles, the overall concordance was 22.3% (i.e. an individual placed in the reciprocal tertile for both VPH and FI). As can be seen in Fig. 1, approximately half of the women perceived to be in poor health were also objectively frail (53.7%). Similarly,

Table 1 General characteristics of the OPRA participants overall and stratified by visual perception of health tertiles

	Visual perception of health (VPH) tertile			
	Overall ($n=1004$)	Good ($n=365$)	Intermed ($n=311$)	Poor ($n=328$)
VPH range (0–100)	29.4—98.9	29.4—47.4	47.4—50.1	50.4—98.9
Frailty index (median, IQR)	0.16 (0.13)	0.12 (0.10)	0.15 (0.12)	0.22 (0.16)
Frailty index (mean, SD)	0.19 (0.11)	0.14 (0.07)	0.18 (0.09)	0.25 (0.13)
Frailty index (range 0.00–1.00)	(0.01–0.66)	(0.01–0.40)	(0.01–0.53)	(0.02–0.66)
Proportion frail (FI ≥ 0.25) % (*n*)	223 (22.2%)	33 (9.0%)	60 (19.3%)	130 (39.6%)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
BMI (kg/m^2)	26.3 (4.19)	24.9 (3.13)	26.7 (4.06)	27.5 (4.85)
Height (cm)	160 (5.8)	161(5.4)	160 (5.8)	160 (6.1)
Body weight (kg)	67.7 (11.5)	64.6 (8.9)	68.5 (11.0)	70.9 (13.5)
Visual acuity (average both eyes)	0.50 (0.22)	0.54 (0.22)	0.51 (0.21)	0.46 (0.23)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Smoker (current/previous)	334 (33.6)	122 (33.5)	95 (31.0)	117 (36.2)
Alcohol (each week)	174 (17.5)	91 (25.0)	48 (15.6)	35 (10.9)
Education (elementary school level)	546 (54.5)	170 (46.4)	182 (58.9)	194 (59.1)
Fallen in previous 12 months	250 (28.2)	76 (23.1)	74 (25.1)	100 (38.3)
Any fracture between ages 50 and 75	367 (37.0)	124 (34.3)	101 (33.0)	142 (44.0)
Surgery within last 5 years	218 (23.6)	64 (19.0)	64 (21.8)	90 (30.9)

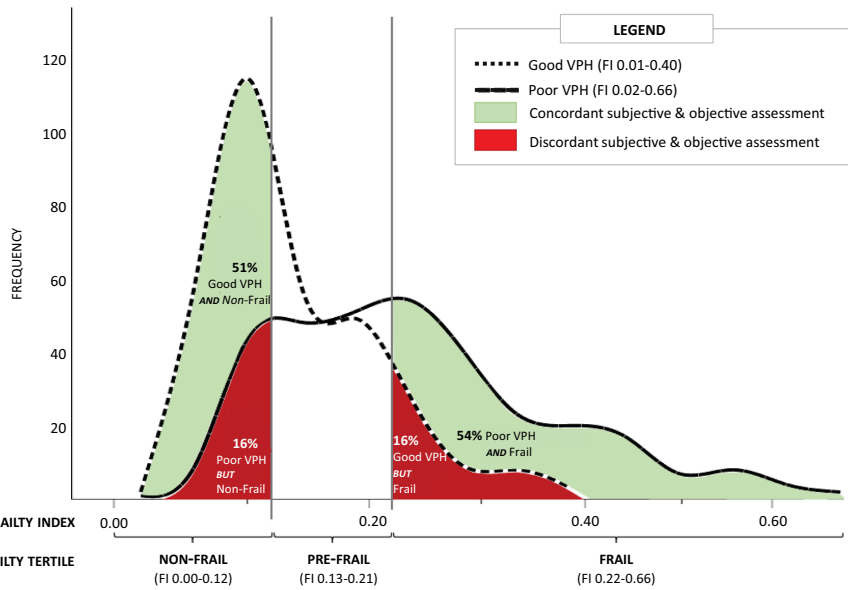

Fig. 1 Distribution of frailty scores within the poor and good VPH tertiles. Concordance between subjective and measured assessments is highlighted in green; discordance is highlighted in red

50.7% perceived to be in good health were also objectively non-frail. However for one in ten women, within each tertile, visually perceived health and measured frailty were discordant; specifically ~ 16% of women in the poor VPH tertile were actually non-frail and ~ 16% of women in the good VPH tertile were in fact frail.

Visual perception of health and components of the frailty index

To understand what contributes to the snap-shot estimation of health, we analysed association between VPH and the individual components constituting the frailty index. Of these, the majority (11/13) differed by increments or decrements, stepwise across the VPH tertiles (Table 2). Those perceived to be in good health had relatively better musculoskeletal performance (gait, strength and balance) and vice versa.

Mortality outcomes for subjective or objectively measured health

Poor health, regardless of whether subjective or objective was associated with increased mortality. Being classified in the poor VPH tertile or the frail tertile was associated with higher 10-year mortality ($p < 0.001$ for both) (Fig. 2a, b); and a similar proportion were dead (43 and 40%, respectively). However, only objectively measured frailty facilitated discrimination, in terms of mortality, between the frailest in addition to the non-frail and pre-frail individuals ($p = 0.002$), while with the visual estimate mortality only differed between good and poor VPH tertiles, but not the intermediate group.

Exploring the possible long-term implications when perceived and objectively measured health are not in accordance, we found that for women perceived to be in good health, mortality was similar regardless of frailty status ($p = 0.052$ overall) but was highest in the pre-frail women ($p = 0.015$) (Fig. 3a). Conversely, for those perceived to be in poor health, mortality differed by frailty status ($p = 0.013$ overall) and those who were actually non-frail by objective assessment had lower mortality (32.7 vs 50.0%; $p = 0.023$)

Table 2 Visual perception of health in relation to components of the Frailty Index

Components of frailty index[a]	Visual perception of health			
	Good ($n = 365$)	Intermed ($n = 311$)	Poor ($n = 328$)	Overall
	Mean (SD)	Mean (SD)	Mean (SD)	p value
Gait-walking speed (m/s, 2 × 15 m) $n = 972$	1.50 (0.22)	1.30 (0.22)	1.10 (0.31)	< 0.001[d]
Gait-walking steps taken (2 × 15 m) $n = 972$	45.0 (4.4)	48.5 (5.8)	55.5 (13.7)	< 0.001[d]
Muscle strength (knee extension, Nms) $n = 933$	291 (70)	267 (76)	240 (85)	< 0.001[d]
Average time spent outdoors (h), $n = 965$	3.0 (1.2)	2.7 (1.3)	2.5 (1.3)	< 0.001[d]
	Median (IQR)	Median (IQR)	Median (IQR)	
Balance[e] (s) $n = 978$	23.2 (15.5)	14.8 (16.5)	7.0 (16.0)	< 0.001[b]
P-CRP (mg/L), $n = 967$	1.6 (2.5)	1.9 (2.9)	2.2 (3.9)	0.001[b]
P-Creatinine (μmol/L), $n = 972$	66.2 (14.6)	66.7 (13.7)	67.1 (20.0)	0.592[b]
	n (%)	n (%)	n (%)	
Uses walking aid, $n = 998$	2 (0.5)	7 (2.3)	85 (26.1)	< 0.001[c]
Polypharmacy (≥ 5 medications), $n = 1004$	45 (12.3)	63 (20.3)	86 (26.2)	< 0.001[c]
High self-estimated risk of falling[f], $n = 876$	18 (5.5)	18 (6.3)	51 (19.6)	< 0.001[c]
Have diabetes, $n = 988$	8 (2.2)	26 (8.5)	30 (9.3)	< 0.001[c]
Have had cancer/severe disease, $n = 982$	50 (13.9)	54 (17.6)	53 (16.8)	0.393[c]
Have disease affecting balance, $n = 859$	52 (16.0)	47 (16.2)	83 (33.9)	< 0.001[c]

[a]Full details of the frailty index [12, 16]

[b]Kruskal–Wallis test

[c]Chi-squared overall

[d]ANOVA

[e]Mean of time (s) for left and right leg, eyes open

[f]Values 4 or 5, in a scale 1–5

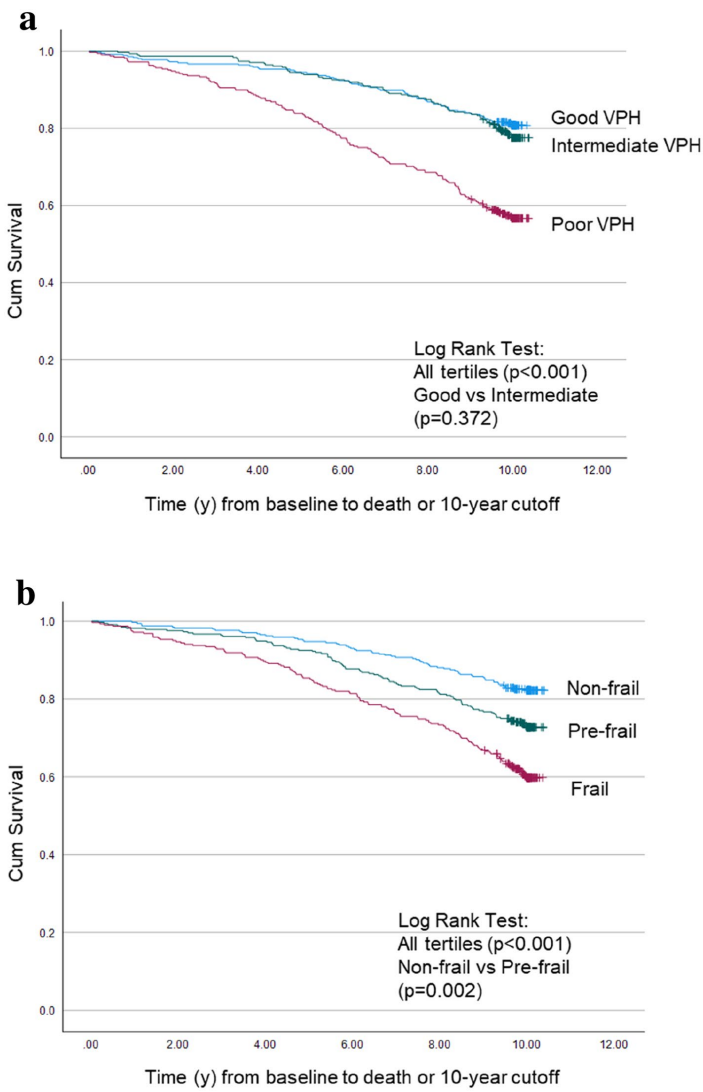

Fig. 2 Ten-year mortality stratified by tertiles of **a** visual perception of health and **b** frailty index

(Fig. 3b) and lower mortality risk [HR 0.57 (0.34–0.95), $p = 0.030$] compared to those who were frail.

Discussion

In this longitudinal study, we investigated the association between a subjective visual perception of health and an objective frailty index. The visual perception was associated with almost all individual components making up the frailty index, and subjective and objective assessments correlated. However, for one in six women, perceived and measured health was diametrically opposite, with the visual estimation being less able to identify women in the early stages of frailty. Nevertheless, both assessments were predictive of 10-year mortality.

Based on years of experience and thin-slicing, the clinician makes an instant visual assessment of a patient's

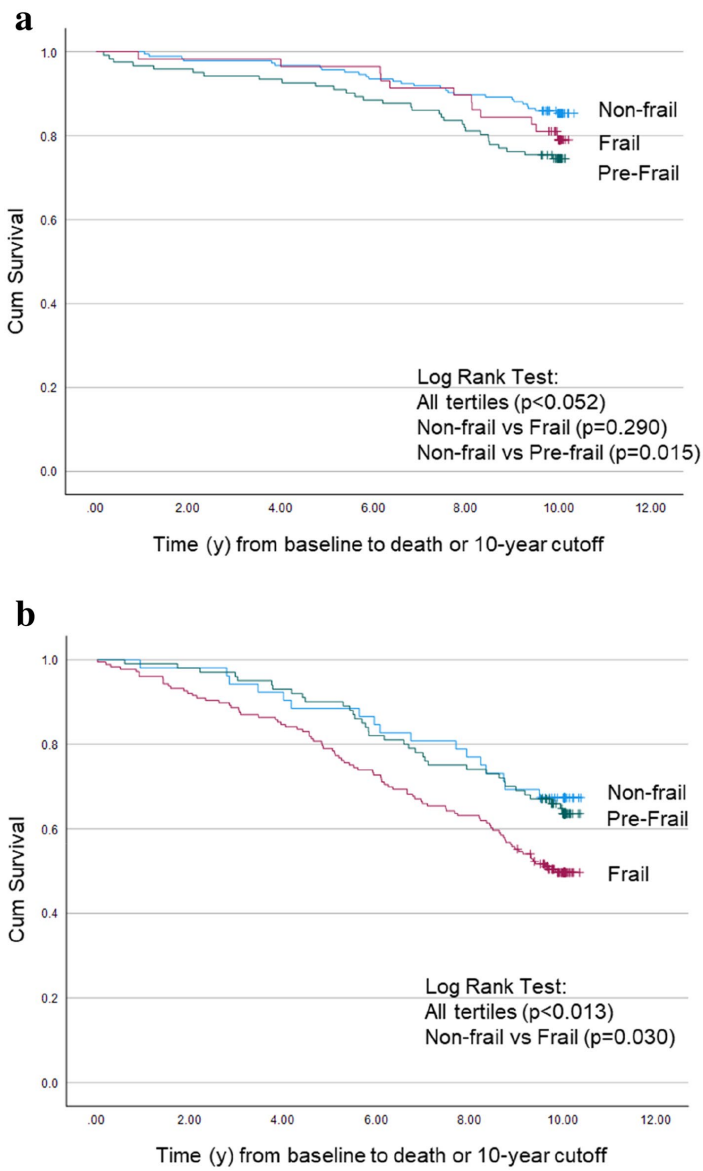

Fig. 3 Frailty associated differences in mortality based on visual perception **a** appeared in good health, **b** appeared in poor health

health and wellbeing. A subjective health perception can predict mortality [6, 7, 19] and in the OPRA cohort, 5-year [11] and as long as 10-year mortality was predicted by "just one look". While there is a moderate correlation between subjective and objective assessments, the visual perception more accurately mirrors actual frailty status in those looking most obviously in poor health.

For this visual assessment, made within 15 s of first sight, more than half of those 75-year-old women classified as visually good or poor were also quantitatively non-frail or frail.

Although visual perception may have its place in broadly categorizing individuals as robust or frail, it cannot reliably identify pre-frailty as many aspects may not yet be visible. Detecting the early stages of frailty is important, particularly in those that are still healthy and living independently, since pre-frailty is a major contributor to the trajectory into frailty [3, 20]. To identify and intervene with these risk individuals, as a way of delaying health declines and maintaining autonomy is now recognized as a public health and medical priority [21]. While frailty assessment is becoming increasingly common in clinic, it is not yet a standard part of the general practitioners routine, despite its potential implications for wisely choosing interventions.

We showed that almost all variables included in our frailty index, particularly walking ability, muscle strength and balance, are associated with the visual perception of health. Falls and fracture, which often affect walking ability and balance, were also more common in those that looked most obviously in poor health. This association between visual perception and mobility is also reported in other studies, with the strongest visual cue being the use of mobility aids [7, 9, 10]. Musculoskeletal competence may be the most obvious sign of frailty, but a multitude of other cues influence the judgement, such as general presentation, facial expression and coherence. In this study, around one-fifth of what an observer "sees" was explained by the frailty index, therefore, clinical observation provides valuable complimentary information. Hence, a combination of the observed status with a selection of a few of the most discriminating objective variables for frailty assessment might be the most sensible and least laborious use of the consultation time between patient and doctor.

However, it is important to recognize that the visual perception has its limitations and discordance with actual measured frailty has implications; in our study, women appearing to be in good health but who were quantifiably pre-frail had a higher mortality than might otherwise be expected. While we cannot fully explain this observation and we lack the data to address it, it indicates that only an objective assessment of frailty, using any of the available tools such as frailty index or frailty phenotype, has the sensitivity to discriminate those at pivotal junctures which would determine the individual frailty trajectory. It also argues for the need to identify frailty and intervene to maintain health, not just long-term but perhaps more relevantly in the short-term, since we have shown that in this cohort frailty is associated with falls [13] and fractures [14] within 1–3 years, all of which lead to increased frailty and disability. Given that every person's trajectory into becoming frail is individual, treatment could entail anything from sight-tests and home assessment, to appropriate pharmaceutical interventions.

This study has several strengths, among the most important is that, the women, all are of identical chronological age. In this respect, the visual estimation is relative to the typical presentation of a 75-year old, minimising bias from the influence of chronological age on appearance. To our knowledge, this study is the first using community-dwelling participants rather than patients, to compare a subjective estimation of health to objectively measured frailty and to assess 'real-life' consequences of discordancy between them. Compared to others, our study has a relatively large number of participants, but being exploratory, was not designed to detect effect sizes. Paired with a randomized selection and no exclusion criteria in cohort recruitment, the findings are likely to be generalizable to a typical population of older women. Caution should of course be exercised; whether this is also generalizable to women of other ages, ethnicities, specific patient groups or men, needs to be determined.

Limitations are acknowledged, such as the difficulty to make direct comparison with available literature due to differences in estimating frailty both objectively and subjectively. It would have been advantageous to include social and cognitive factors in the frailty index, since these could enhance discrimination of pre-frailty, however, such data were not available in our cohort and furthermore, beyond the remit of the study. The moderate correlation between the VPH and FI indicates that there are other complementary cues with which the clinician makes inference, and there is undoubtedly value in using both to improve outcome [6, 9]. Finally, the small number of women who did not have VPH assessed, and were therefore excluded, had a frailty index higher than the cohort mean (0.31 and 0.19). This, in conjunction with study participants possibly being healthier than non-participants, may result in a slight, but possible selection bias towards a healthier population, a not uncommon phenomenon in elderly populations [22].

Data from this cohort suggest that a visual estimation of health can identify the most or least frail, but only by objective frailty assessment can pre-frailty be captured. Given the clinical implications from misjudging, both over- and underestimating health, an objective frailty assessment provides a more tailored method to discriminate. This allows for using the most appropriate management strategies to maintain healthy ageing.

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Author contributions PB: study concept and design, data acquisition, analysis and interpretation, drafting and finalising manuscript. LM: interpretation of data, drafting and finalising manuscript PG:

acquisition of subjects, study design and preparation of final manuscript JK: interpretation of data and preparation of final manuscript. FMG: study concept and design, data acquisition, interpretation and manuscript preparation. KEA: study concept and design, acquisition of subjects and data, interpretation, and manuscript preparation.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The regional ethical review board in Lund approved the study (Dnr:2014804; LU200-95), which was performed according to the Helsinki Declaration principles.

Informed consent Participants provided written informed consent.

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