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Frailty in Midlife as a Predictor of Changes in Body Composition from Midlife into Old Age: A Longitudinal Birth Cohort Study

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Keywords
Frailty · Body composition · Fat mass · Lean mass · Longitudinal study

Abstract
Introduction: Few studies have investigated the association between frailty and subsequent body composition. ***Methods:*** We performed separate linear mixed model analyses to study the associations between changes in the participant frailty status assessed by a frailty index (FI) and subsequent body mass index (BMI), lean mass index (LMI), fat mass index (FMI), and FMI to LMI ratio values assessed on three occasions over 17 years. The analyses were carried out among 996 participants spanning from age 57 to 84 years. ***Results:*** With advancing age, LMI and BMI decreased, whereas FMI and FMI to LMI ratio increased. Participants with "stable frailty," followed by those with "increasing frailty" experienced faster decreases in LMI and faster increases in FMI and FMI to LMI ratio values from midlife into old age relative to those in the group "stable not frail." Contrastingly, those in the highest third of absolute annual increase in FMI and FMI to LMI ratio became more frail faster from midlife into old age relative to those in the lowest third. ***Conclusions:*** We found evidence of an adverse health outcome of frailty where lean indices declined faster and fat indices and fat-to-lean ratios increased faster from midlife into old age. The changes resembled those that occurred with aging, but at a faster pace. The relationship between body composition and frailty is likely bidirectional, where high or increasing levels of fat are associated with the risk of becoming more frail earlier, but where a longer duration of frailty may increase the risk of faster age-related changes to body composition.

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Introduction

Frailty describes decline across multiple physiological systems and shows increased vulnerability to stressors [1, 2]. Altered inflammatory and hormonal functions, a lower level of energy metabolism, and reduced skeletal muscle mass and quality are some of the potential mechanisms that enable and sustain physiological and functional decline among those with frailty [3]. Body composition may change partly related to the aging process and an advancing degree of frailty, as suggested in weight loss used to define physical frailty itself [2]. Thus far, we have a more thorough understanding of body composition predisposing to subsequent frailty [4] than vice versa [5].

Aging accompanies changes to body composition which includes a reduction in lean mass, increasing fat mass, and their altered distribution [6]. However, the changes that individuals with higher levels of frailty undergo may be accelerated, i.e., a faster decline in lean mass and increases in fat mass, thus resulting in premature aging. The hypothesis regarding lean mass was tested by Jung et al. [5] among community-dwelling Koreans aged 65 years and older (n = 341). They observed that the likelihood of significant lean mass decline (>5%) over 5 years was higher with increasing phenotypic frailty classification. This field is relevant, as body anthropometry and sarcopenia have been shown to modify the risk of adverse outcomes among those with frailty, including disability [7] and all-cause mortality [8, 9]. Therefore, a deeper understanding of the interplay between frailty and body composition has the potential to inform clinical practice and interventions targeting middle-aged and older adults' health.

To address this knowledge gap, we studied community-dwelling participants of the Helsinki Birth Cohort Study (HBCS; n = 996; aged 57–69 years at baseline) with up to three assessments of both frailty and body composition over 17 years from midlife into old age (ages 57–84 years). Both lean and fat indices were measured to capture body composition more comprehensively. The level of frailty was assessed using a frailty index (FI) based on deficit accumulation because it has shown the ability to detect frailty even in individuals aged under 65 years [10, 11]. We hypothesize that a longer duration of frailty would be associated with a faster decline in lean mass and faster increases in fat mass. In addition, we hypothesize that there is a bidirectional association between frailty and body composition, where higher levels of fat during the life course may be associated with increased risk of frailty, but where frailty itself would be associated with declining lean and increasing fat mass.

Materials and Methods

Study Design

The HBCS is a longitudinal birth cohort of participants born in Helsinki during 1934–1944 who visited child welfare clinics in the city and had been allocated personal ID numbers as Finnish residents in the year 1971 [12]. Figure 1 presents a flowchart of the HBCS [13]. This sub-study uses information from the clinical baseline (years 2001–2004; n = 2,003; mean age = 61.5 years; range = 57–69 years) and two clinical follow-ups (years 2011–2013; n = 1,094; mean age = 71.1 years; range = 67–79 years and years 2017–2018; n = 815; mean age = 75.9 years; range = 72–84 years). We included participants (n = 996) who had at least two measurements of both frailty and body composition to be able to account for their change with aging.

FI Assessed Three Times over 17 Years during 2001–2018

We included diseases, clinical measurements, laboratory test values, functioning measures, and general health information in the 41-item FI [13], which was created following the standard procedure [14]. The FI in HBCS shares similar characteristics with other published deficit accumulation-based FIs [15, 16]. Deficits related to body composition (body mass index [BMI] and waist-to-hip ratio) were removed from the index as they were related to the outcome variables; online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000539204) presents the resulting 39 variables and their scoring into deficits. The FI could be calculated for 99.6%, 99.9%, and 99.1% of participants participating at the three clinical visits; 306 participants had two and 776 participants had three FI measurements. The FI level of ≥0.25 was used to indicate the "frail" state [17] at each visit. To account for temporal change in the participants' frailty status during the study (frail/not frail at each visit), we grouped participants as "stable not frail" (n = 611, 56.47%), "increasing frailty" (n = 249, 23.01%), "decreasing frailty" (n = 44, 4.07%), and "stable frail" (n = 178, 16.45%). The group "decreasing frailty" had few observations and was merged with the group "stable not frail."

Body Composition Assessed Three Times over 17 Years during 2001–2018

Measured weight rounded to the nearest 0.1 kg and height to the nearest 0.1 cm was used in the calculation of BMI at each clinical visit. Fat mass was estimated by bioelectrical impedance analysis [18] using the InBody 720 eight-polar system (Biospace Co., Ltd., Seoul, Korea). Lean mass was calculated by subtracting fat mass from total body mass. Fat mass index (FMI) and lean mass index (LMI) were calculated as fat/lean mass in kilograms divided by height in meters to the power of two. FMI to LMI ratio was calculated to account for joint effects of fat/lean mass. Full information on body composition was recorded twice for 292 participants and 3 times for 757 participants. Absolute annual changes in BMI, LMI, FMI, and FMI to LMI ratio were calculated to account for their change with aging. Thirds of absolute change in BMI per year (tertiles −0.08 and 0.03 kg/m^2/year) were coded as "decreasing," "stable," or "increasing." Changes in LMI (tertiles −0.11 and −0.05 kg/m^2/year) were coded as "rapidly decreasing," "slowly decreasing," or "stable or increasing." Changes in FMI (tertiles 0.01 and 0.11 kg/m^2/year) were coded as "stable or decreasing," "slowly increasing," or "rapidly increasing." Changes

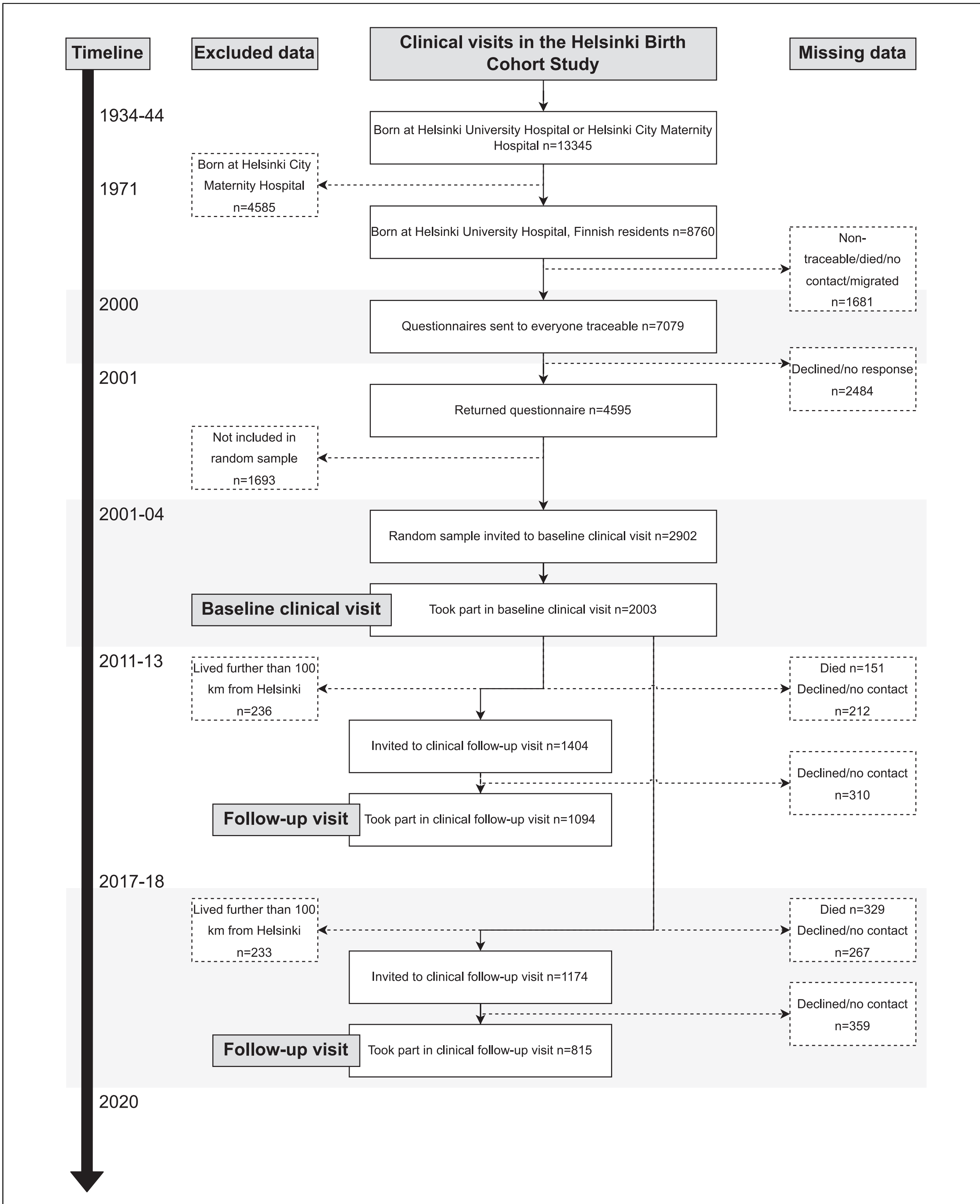

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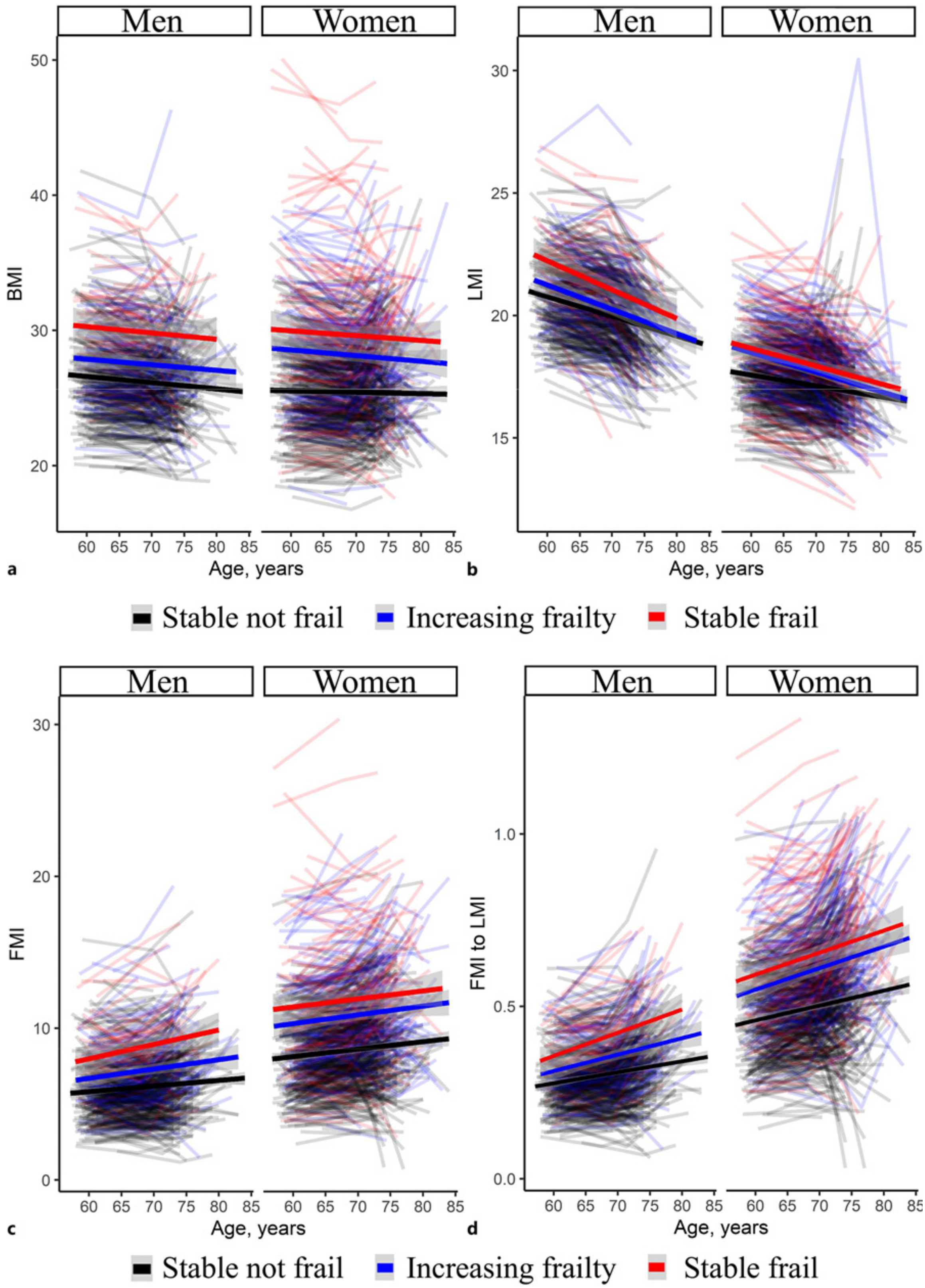
Table 1. Characteristics of the study participants

	Total study population (n = 2,003)	Women (n = 1,075)	Men (n = 928)	p value
	mean (SD)	mean (SD)	mean (SD)	
Participant characteristics assessed at baseline				
Age, years	61.5 (2.9), range 57–69	61.5 (2.8)	61.5 (3.0)	0.694
Current smoker, N (%)	475 (23.9)	221 (20.7)	254 (27.5)	<0.001
Adult socioeconomic status				
Manual worker, N (%)	669 (33.6)	70 (16.3)	114 (33.9)	<0.001
Self-employed, N (%)	186 (9.3)	37 (8.6)	33 (9.8)	
Lower official, N (%)	853 (42.8)	265 (61.8)	99 (29.5)	
Upper official, N (%)	286 (14.3)	57 (13.3)	90 (26.8)	
FI assessed three times				
Baseline visit in 2001–2004[a]	0.20 (0.10)	0.21 (0.10)	0.20 (0.10)	0.120
Follow-up visit in 2011–2013[b]	0.21 (0.10)	0.23 (0.10)	0.19 (0.10)	<0.001
Follow-up visit in 2017–2018[c]	0.23 (0.11)	0.24 (0.11)	0.21 (0.10)	<0.001
Change in frailty				
Stable not frail, N (%)	655 (60.5)	332 (54.4)	323 (68.4)	<0.001
Increasing frailty, N (%)	249 (23.0)	152 (24.9)	97 (20.6)	
Stable frail, N (%)	178 (16.5)	126 (20.7)	52 (11.0)	
BMI assessed three times, kg/m^2				
Baseline visit in 2001–2004[a]	27.6 (4.7)	27.7 (5.0)	27.5 (4.2)	0.783
Follow-up visit in 2011–2013[b]	26.5 (3.9)	26.4 (4.3)	26.6 (3.3)	0.050
Follow-up visit in 2017–2018[c]	26.9 (4.5)	27.2 (4.8)	26.6 (3.9)	0.130
Mean absolute change per year, kg/m^2	−0.028 (0.166)	−0.017 (0.178)	−0.043 (0.148)	0.016
Mean relative change per year, %	−0.089 (0.589)	−0.044 (0.636)	−0.146 (0.519)	0.015
LMI assessed three times, kg/m^2				
Baseline visit in 2001–2004[a]	19.3 (2.3)	18.0 (1.7)	20.8 (1.9)	<0.001
Follow-up visit in 2011–2013[b]	18.7 (2.2)	17.5 (1.7)	20.3 (1.8)	<0.001
Follow-up visit in 2017–2018[c]	17.9 (2.1)	16.8 (1.8)	19.3 (1.7)	<0.001
Mean absolute change per year, kg/m^2	−0.078 (0.094)	−0.066 (0.095)	−0.094 (0.092)	<0.001
Mean relative change per year, %	−0.397 (0.487)	−0.362 (0.526)	−0.443 (0.427)	0.140
FMI assessed three times, kg/m^2				
Baseline visit in 2001–2004[a]	8.3 (3.6)	9.7 (3.7)	6.7 (2.8)	<0.001
Follow-up visit in 2011–2013[b]	8.4 (3.7)	9.8 (3.7)	6.5 (2.5)	<0.001
Follow-up visit in 2017–2018[c]	9.0 (3.9)	10.3 (3.9)	7.2 (2.9)	<0.001
Mean absolute change per year, kg/m^2	0.062 (0.161)	0.071 (0.174)	0.049 (0.142)	0.012
Mean relative change per year, %	0.883 (2.124)	0.856 (1.977)	0.920 (2.302)	0.973
FMI to LMI assessed three times, kg/m^2				
Baseline visit in 2001–2004[a]	0.43 (0.18)	0.53 (0.16)	0.32 (0.11)	<0.001
Follow-up visit in 2011–2013[b]	0.45 (0.19)	0.55 (0.17)	0.32 (0.11)	<0.001
Follow-up visit in 2017–2018[c]	0.51 (0.22)	0.61 (0.21)	0.37 (0.14)	<0.001
Mean absolute change per year, kg/m^2	0.005 (0.009)	0.006 (0.010)	0.004 (0.007)	<0.001
Mean relative change per year, %	1.382 (2.223)	1.317 (2.063)	1.466 (2.430)	0.607

SD, standard deviation. [a]$n_{\text{frailty index}}$ = 2,003; $n_{\text{body mass index}}$ = 2,001; $n_{\text{lean mass index}}$ = 1,918; $n_{\text{fat mass index}}$ = 1,918. [b]$n_{\text{frailty index}}$ = 1,082; $n_{\text{body mass index}}$ = 1,065; $n_{\text{lean mass index}}$ = 1,059; $n_{\text{fat mass index}}$ = 1,059. [c]$n_{\text{frailty index}}$ = 813; $n_{\text{body mass index}}$ = 810; $n_{\text{lean mass index}}$ = 790; $n_{\text{fat mass index}}$ = 790.

Fig. 1. Flowchart of participants in the Helsinki Birth Cohort Study. The present study reports data from baseline visit and follow-up visits conducted between 2011–2013 and 2017–2018.



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in FMI to LMI ratio (tertiles 0.0019 and 0.0081 units/year) were coded as "stable or decreasing," "slowly increasing," or "rapidly increasing."

Clinical Covariate Data Assessed at Baseline

Self-reported smoking status was assessed using questionnaires and coded into never, former, and current smoker. Socioeconomic status was assessed by grouping occupational status according to the classification provided by Statistics Finland [19].

Statistical Methods

We constructed separate linear mixed models for BMI, LMI, FMI, and FMI to LMI ratio to study associations between changes in frailty and subsequent body composition from midlife into old age. To better understand possible bidirectional associations, further linear mixed models were constructed to study associations between changes in body composition and subsequent levels of frailty from midlife into old age. The analyses were performed for men and women separately since LMI and FMI values show significant differences between men and women [20]. The underlying time scale was age, and it was centered at 57 years (the youngest age in our data). We adjusted the models for key lifestyle and socioeconomic factors which were not already included in the FI or among the studied variables: smoking, adult socioeconomic status, and their interactions with age. Estimates of the rate in body composition correspond to faster/slower absolute annual increase in BMI, LMI, FMI, and FMI to LMI ratio values from midlife into old age, where statistically significant values describe significant age × frailty interactions on these studied variables. Regarding our model of subsequent levels of frailty from midlife into old age, we multiplied our estimates by 100 and treat them as a percentage. Here the estimates of the rate of change correspond to faster/slower percentage point rate of change compared to the mean change per year from midlife into old age. p value <0.05 was used as the threshold for statistical significance. Additional analyses were conducted to assess covariate-adjusted absolute annual changes in body composition across older age within each frailty change category. We performed the analyses and visualized the data with the R software [21] packages ggplot2, lme4 [22], and lmerTest [23].

Results

General Characteristics

Our sample included 996 individuals who all had at least two measurements of frailty and body composition starting from midlife. This sample was younger, healthier, and less frail than those who participated at the baseline visit only (online suppl. Table 2). With advancing age, mean levels of frailty of both men and women increased, with women being more frail than men at the clinical follow-ups (Table 1).

Subsequent measurements of BMI, LMI, and FMI showed moderate to very strong bivariate correlations with each other that were similar among men and women (online suppl. Table 3). Both men and women had similar mean BMI in midlife (27.5 and 27.7 kg/m^2), which decreased by −0.15%/year among men and by −0.04%/year among women (Table 1). Mean LMI was consistently greater among men than women, and it decreased by −0.44%/year among men and by −0.36%/year among women. Mean FMI was consistently higher among women, and it increased by 0.92%/year among men and by 0.86%/year among women, respectively (Table 1).

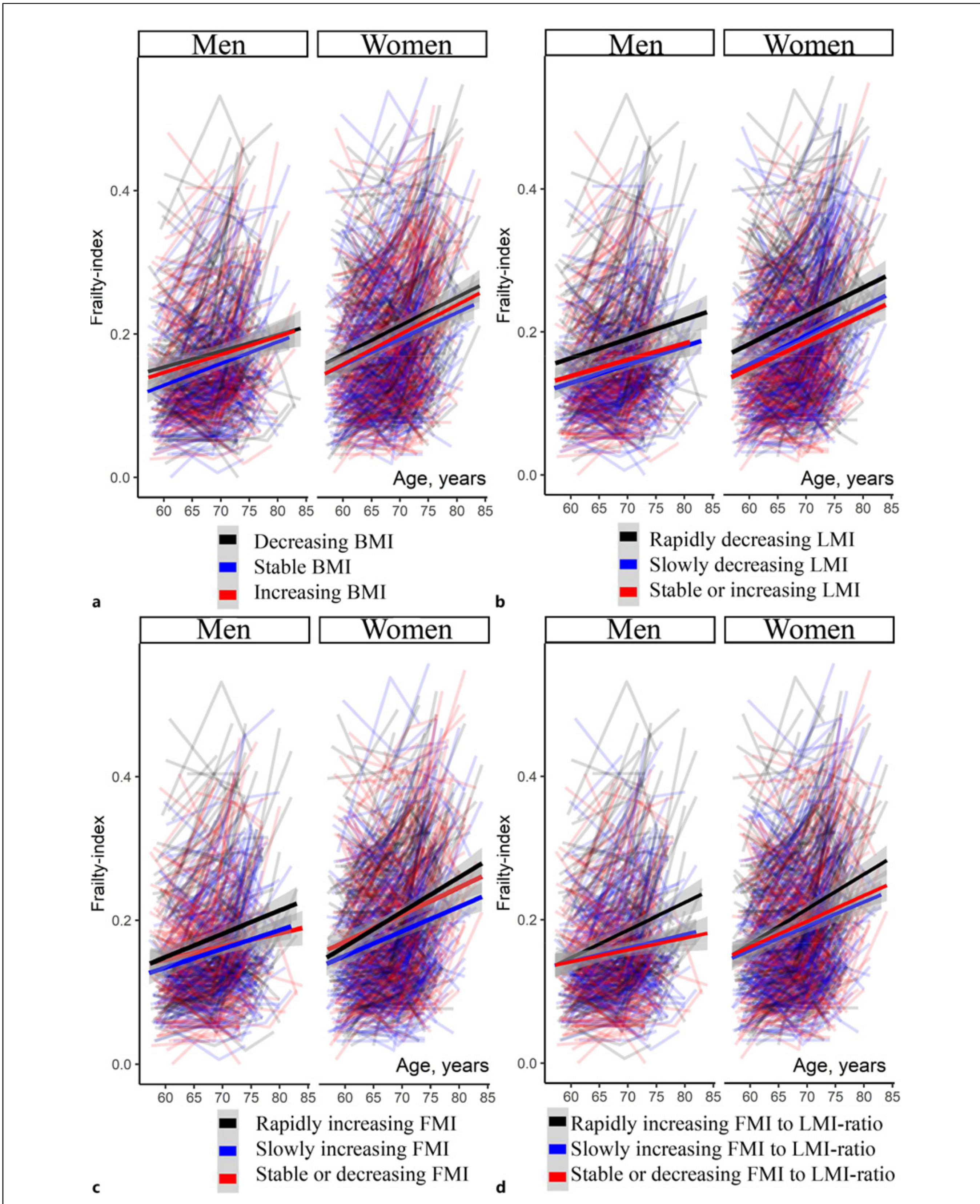
Changes in Frailty and the Rate of Change in BMI, LMI, FMI, and FMI to LMI Ratio Values from Midlife into Old Age

From the period of midlife into old age, body composition changed the least among participants in the group "stable not frail," followed by the group "increasing frailty," and changed the most among those in the group "stable frail" (Fig. 2 and online suppl. Table 4a, b). In the group "stable frail," LMI decreased faster and FMI together with FMI to LMI ratio increased faster per year from midlife into old age than in the group "stable not frail." The group "increasing frailty" showed similar but slightly weaker decreases in LMI and increases in FMI and FMI to LMI ratio from the period of midlife into old age. The results were similar among men and women.

Changes in Body Composition and the Rate of Change in FI Levels from Midlife into Old Age

From the period of midlife into old age, men and women with "rapidly increasing" FMI or FMI to LMI ratio became more frail earlier than those in the group "stable or decreasing" FMI or FMI to LMI ratio (Fig. 3 and online suppl. Table 5). FI levels were consistently higher among men and women in the group "rapidly decreasing LMI" compared to the group "stable or increasing" LMI' (Fig. 3). However, thirds of absolute annual change in LMI or BMI were not associated with a faster or slower rate of change in FI levels from midlife into old age relative to the lowest third (online suppl. Table 5).

Fig. 2. a–d Body composition as a function of age according to changes in frailty (stable not frail [60.5%], increasing frailty [23.0%], and stable frail [16.5%]) from midlife into old age in the Helsinki Birth Cohort Study: body mass index (BMI) (**a**), lean mass index (LMI) (**b**), fat mass index (FMI) (**c**), and FMI to LMI ratio (**d**) (showing unadjusted data). Gray area indicates 95% confidence intervals.



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Discussion

Body composition has been studied as a risk factor of consequent frailty, where obesity has been shown to increase the risk of developing frailty [4]. However, there is only scarce evidence on the reverse association between frailty at baseline and subsequent body composition [5]. We found in community-dwelling adults that an earlier onset and a longer duration of frailty were associated with faster decreases in lean, faster increases in fat, and a faster increase in the ratio of fat-to-lean indices from the period of midlife into old age (ages 57–84 years). Community-dwelling men and women who were not frail at first but who became frail during the study also presented similar but slightly weaker associations. The observed changes in subsequent body composition resemble those that occur with aging, but they occurred at a faster pace. This suggests that a longer duration of frailty may be associated with faster body composition aging, where lean mass is lost, and fat is gained at a faster pace, starting as early as in late midlife. The results suggest that the onset of the aging process associated with changes in body composition and frailty may commence at an earlier stage of life than indicated previously [5]. The association between frailty and subsequent body composition.

The decline across physiological systems in frailty has been suggested to give rise to a negative cycle of health [2]. Some of the involved mechanisms have plausible consequences for body composition: a lower level of energy metabolism [3], impairments to the quality of lean tissue [24], and a multifactorial pro-inflammatory state [25], can all increase the likelihood of accelerated changes to body composition. A decline in lean mass indices is supported by the close overlap between frailty and sarcopenia, a reduction in muscle function and mass [26]. Our hypothesis, additionally based on previous findings of physical frailty [2] associating with subsequent LMI decline over 5 years [5], was that frail individuals would experience age-related changes to body composition at an accelerated pace. Not only did we find this to be true in our sample, but we were also able to extend our understanding of the association between frailty and subsequent body composition to younger community-dwelling populations. First, we now show that the onset and duration of frailty can differentially affect subsequent body composition, where an earlier onset and longer duration of frailty were associated with more notable decreases in lean and increases in fat mass indices. The decrease in lean mass indices may predispose individuals with frailty to adverse outcomes, including disability [7]. Second, we now show that not only lean mass is affected; frailty may be associated with increases in fat mass indices and higher amounts of fat relative to lean mass. Previously, a low body fat or a pronounced decline in adiposity was associated with higher mortality risk among frail older women [9].

The Bidirectional Association between Frailty and Body Composition

A bidirectional relationship between frailty and body composition is supported in published longitudinal studies. On one hand, weight gain [27] and obesity [28, 29] have been associated with an elevated risk of frailty in samples where the initial prevalence of frailty was low. On the other hand, individuals who are already frail are at risk of further decline in LMI [5], and as shown in our study, starting even as early on as in midlife. We have previously shown in this cohort that higher measures of adiposity among women (percent body fat) and abdominal obesity among men (waist-to-hip ratio) in midlife were associated with the participants becoming more frail faster from midlife into old age [30].

To address the potential bidirectional relationship between frailty and body composition, we studied changes in body composition and their associations with frailty and found evidence that faster increases in fat and the ratio of fat-to-lean indices were associated with participants becoming more frail faster from midlife into old age. There was no age interaction with changes in total body or lean mass indices per year on frailty from midlife into old age, although those with the greatest decrease in LMI per year had the highest FI levels. Taken together, this suggests that higher indices of fatness and their increase with time may predispose individuals to becoming more frail earlier. However, with the onset and longer duration of frailty, lean mass may be lost, and fat gained at a faster pace. In other words, there appears to be a bidirectional relationship between body composition and frailty, where high levels of fat and their increase were associated with the participants becoming more frail earlier. If frailty emerges, its longer duration may

Fig. 3. a–d FI levels as a function of age according to thirds of absolute annual change in body composition from midlife into old age in the Helsinki Birth Cohort Study: body mass index (BMI) (**a**), lean mass index (LMI) (**b**), fat mass index (FMI) (**c**), FMI to LMI ratio (**d**) (showing unadjusted data). Gray area indicates 95% confidence intervals.

predispose to faster decreases in lean and faster increases in fat indices. We found no evidence to support BMI or its annual change as a meaningful predictor of frailty. This suggests limited clinical applicability as BMI does not contain information on the proportion of lean relative to fat mass. Instead, our results underline the importance of more detailed information on fat and lean mass.

Implications

We now provide evidence of frailty associating with accelerated age-related changes to body composition, which include (1) decreasing lean, (2) increasing fat, and (3) increasing fat-to-lean ratio values. This phenomenon, which started as early as in late midlife among community-dwelling adults, was similar among both men and women. In other words, individuals with frailty are at higher risk of losing lean tissue and replacing some with fat tissue at a faster pace. Importantly, this can occur without showing dramatic changes in total BMI. The risk of this adverse health outcome likely increases with a longer duration of frailty. Clinical appraisal of body composition among frail patients should have a special focus on the distribution of fat and lean components. Our data support a bidirectional relationship with frailty and body composition: if frailty emerges, its longer duration may predispose to faster age-related changes to body composition. Conversely, higher levels of fat and their faster increase may put individuals at risk of becoming more frail faster. As we provide no direct longitudinal evidence of redistribution of fat/lean tissue in trunk/appendicular compartments, or adipose tissue infiltrating muscle, these areas can be areas of focus for future studies of frailty and body composition. Future studies may also address whether nutritional or physical activity interventions can mitigate negative body composition outcomes among those who are at risk of becoming frail or already are frail.

Strengths and Limitations

We were able to study the relationship between frailty and fat, lean, and total body mass indices across multiple measurement occasions from midlife into old age while simultaneously accounting for their change with aging. The following weaknesses should be considered when interpreting our results. First, although well-suited for large-scale epidemiological studies, bioimpedance analysis may overestimate lean and underestimate fat mass relative to dual-energy X-ray absorptiometry [31]. Second, our sample was younger, healthier, and less frail than those who did not have multiple measurements of body composition and frailty. This can potentially undermine rather than overestimate our findings. Finally, although we did corroborate previous findings reported on older Koreans [5], we present findings among relatively fit community-dwelling Caucasians and suggest caution in generalizing the results to other populations or ethnicities.

Conclusions

The relationship between frailty and body composition is likely bidirectional, where high or increasing levels of fat are associated with the risk of becoming more frail earlier. Contrastingly, we found that a longer duration of frailty was associated with a faster decline in lean and faster increases in fat indices and fat-to-lean ratios from midlife into old age. The changes resembled those that occurred with aging, but at a faster pace. The risk of this adverse health outcome likely increases with a longer duration of frailty.

Acknowledgments

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Statement of Ethics

The study was approved by the Coordinating and Epidemiology and Public Health Ethics Committees of the Hospital District of Helsinki and Uusimaa and that of the National Public Health Institute, Helsinki, approval number THL/101/6.02.00/2019. It was conducted in accordance with the Declaration of Helsinki. All participants have given their written informed consent before initiating any study procedures.

Conflict of Interest Statement

The authors have no conflicts of interest to report.

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Author Contributions

Concept and design: M.J.H., L.K., M.B.v.B., and J.G.E.; acquisition of data: T.M.M., M.S., N.S.W., E.K., and J.G.E.; analysis and interpretation of data: M.J.H. and L.K.; drafting the article: M.J.H.; and critical revision of the article: M.J.H., J.J., L.K., T.M.M., M.S., N.S.W., E.K., J.G.E., and M.B.v.B. All authors approved the article.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the authors (markus.haapanen@helsinki.fi) upon reasonable request.

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