Midlife Obesity and Risk of Frailty in Old Age During a 22-Year Follow-up in Men and Women: The Mini-Finland Follow-up Survey

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Background. Long-term predictors of geriatric syndrome of frailty are unclear. Several obesity-related conditions are associated with frailty. This study examines the predictive role of midlife overweight and obesity on development of frailty more than 22 years of follow-up.

Methods. Data are from 1,119 men and women aged 30 or older without frailty at baseline participating in a population-based Mini-Finland Health Examination Survey (1978–1980) with follow-up measurement in 2000–2001. At baseline (1978–1980), body weight and height were measured. At follow-up (2000–2001), the dependent variable prefrailty was defined as the presence of one or two of five frailty indicators (shrinking, weakness, exhaustion, slowness, and low physical activity) and frailty was defined as three or more indicators.

Results. The mean age at the baseline was 43.6 (SD 9.7) years, and majority of the participants (95%) were 30–60 years old. Incidence of prefrailty was 5% and frailty 36%. Based on adjusted multinominal logistic regression, persons with overweight (body mass index 25–29.9 kg/m²) and obesity (body mass index ≥ 30 kg/m²) at baseline had increased risk of prefrailty (odds ratio 1.45, 95% CI 1.08, 1.96; odds ratio 2.36, 95% CI 1.41, 3.93) and frailty (odds ratio 2.49, 95% CI 1.22, 5.06; odds ratio 5.02, 95% CI 1.89, 13.33) at follow-up in comparison to normal-weight persons after adjusting for age, sex, lifestyle factors and chronic conditions.

Conclusions. Development of frailty may start already in midlife, and obesity is one of the underlying causes of frailty.

Key Words: Aging—Epidemiology—Frailty—Life course—Obesity.

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Frailty is a common geriatric condition characterized by decreased reserve and diminished resistance to stress predisposing older adults for many adverse outcomes such as disability, falls, fractures, institutionalization, and mortality (1). Although there is not yet uniform conceptual and operational definition of frailty (2,3), the biological model of Fried and colleagues (4) is commonly used consisting of five criteria: shrinking, weakness, exhaustion, slowness, and low physical activity.

The common clinical perception of frail person is small and thin. However, recent cross-sectional studies have detected a new subgroup of frail persons—fat and frail. This shows that frailty can coexist with obesity and that expanded view of frailty and its risk factors may be warranted (5–8). Although there are several potential obesity-related conditions, including low-grade inflammation, insulin resistance, type 2 diabetes, and low physical activity that could serve as risk factors for frailty, only few prospective studies have examined the effect of obesity on development of frailty. Based on 3-year follow-up study by Woods and colleagues (9) reported that obesity predicted frailty among postmenopausal women and Strandberg and colleagues (10) showed that obesity in clinically healthy middle-aged men predicted old-age frailty 26 years later.

Despite the emerging evidence, there is need for further studies examining the consequences of midlife obesity on development of frailty based on representative samples including both men and women. Thus, the aim of this study was to examine the predictive role of midlife overweight and obesity on development of frailty over 22-year follow-up.
**Materials and Methods**

**Study Population**

The study population comprises persons who participated in the population-based Mini-Finland Health Examination Survey in 1978–1980 (n = 8,000) (11). Altogether, 1,278 of these participants are still alive and living in one of the seven selected municipalities across the country were invited to take part in the follow-up study carried out in conjunction with the Health 2000 Survey in 2000–2001 (12). Frailty status at the follow-up was available for 1,122 persons (88% of those invited), aged 30–75 years at baseline (median age 42 years). The average follow-up time was 22.2 years (SD 20.5–23.2 years).

Details of the design and implementation of the Mini-Finland Health Examination Survey (11,13), as well as the Health 2000 Survey (12), have been reported elsewhere. At the re-examination survey, all participants signed a written informed consent, and the study was approved by the Ethical Committee for epidemiology and public health in the hospital district of Helsinki and Uusimaa in Finland.

**Measurement of Obesity at Baseline**

At baseline, body weight and height were measured in light indoor clothing without shoes. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m²) and categorized as normal weight (BMI < 25 kg/m²), overweight (BMI 25–29.9 kg/m²), and obesity (BMI ≥ 30 kg/m²) as suggested by the World Health Organization (14).

**Measurement of Frailty at the Baseline and Follow-up**

In this study, the frailty status was operationally defined by a modification of the method described by Fried and colleagues (4). The concept frailty was not yet operationalized at baseline in the 1970s. However, by using data available, following indicators were used to define frailty at baseline: (a) “Shrinking”: self-reported unintentional weight loss of greater than 3 kg during the last 3 months due to poor appetite (part of present state examination) (15,16) or body mass index (BMI) less than 18.5 kg/m². (b) “Weakness”: handgrip strength in the lowest gender- and BMI-specific quintile. Maximal handgrip strength was measured with a handheld dynamometer based on strain gage sensors (Good Strength, IGS01, Mettur Oy, Jyväskylä, Finland) using a standard method (18). (c) “Exhaustion”: self-reported tiredness in the Beck Depression Inventory. Participants answering “I get tired from doing almost anything” and “I am too tired to do anything” were considered positive for exhaustion criterion. (d) “Slowness”: slow walking speed in the lowest gender- and height-specific quintile. Maximal walking speed over a distance of 6.1 m was measured using a stopwatch (19). Walking aids were allowed if the person normally used them when walking. (e) “Low physical activity”: self-reported sedentary behavior (eg, reading, watching television). This was based on a physical activity questionnaire in which participants were asked to indicate their average level of physical activity. Frailty was very rare at baseline. Only three persons were categorized as frail and they have been excluded from the further analysis.

At follow-up, following diagnostic criteria for frailty were used. (a) “Shrinking”: self-reported recent unintentional weight loss of greater than 5 kg (part of Beck Depression Inventory) or BMI less than 18.5 kg/m². (b) “Weakness”: handgrip strength in the lowest gender- and BMI-specific quintile. Maximal handgrip strength was measured with a handheld dynamometer based on strain gage sensors (Good Strength, IGS01, Mettur Oy, Jyväskylä, Finland) using a standard method (18). (c) “Exhaustion”: self-reported tiredness in the Beck Depression Inventory. Participants answering “I get tired from doing almost anything” and “I am too tired to do anything” were considered positive for exhaustion criterion. (d) “Slowness”: slow walking speed in the lowest gender- and height-specific quintile. Maximal walking speed over a distance of 6.1 m was measured using a stopwatch (19). Walking aids were allowed if the person normally used them when walking. (e) “Low physical activity”: self-reported sedentary behavior (eg, reading, watching television). This was based on a physical activity questionnaire in which participants were asked to indicate their average level of physical activity. Frailty was very rare at baseline. Only three persons were categorized as frail and they have been excluded from the further analysis.

**Potential Confounding Factors at Baseline**

Education was based on the highest completed degree and was dichotomized as less than 9 years and greater than or equal to 9 years of education. Leisure-time physical activity was assessed with a questionnaire in which participants were asked to indicate their average level of physical activity. Physical activity was classified as regular exercise activity (eg, running, biking, gymnastics), occasional physical exercise or lifestyle activity (eg, gardening, hunting, outdoor recreation), and sedentary (eg, reading, watching television). Work-related physical activity was categorized as light, moderate, or strenuous based on the work description. Smoking behavior was classified as never smokers, ex-smokers, and current smokers. Average weekly alcohol consumption (g/week) during the preceding month was calculated, and the limit for heavy alcohol use was set at 280 g/week for men and 140 g/week for women (20).

Standardized clinical examinations were carried out by specially trained physicians who diagnosed chronic conditions on the basis of clinical findings, symptoms, disease histories, and related documentation using uniform criteria (11,13,21). Chronic conditions analyzed in this study were
hypertension defined as systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg, coronary heart disease (angina pectoris or myocardial infarction), other cardiovascular diseases (heart failure, peripheral artery disease, stroke, arrhythmia, valvular heart disease, or congenital heart disease), diabetes, osteoarthritis (hip, knee, or hand), inflammatory arthritis, and chronic mental disorders (depression, neurosis, or other mental diseases).

**Statistical Analysis**

Baseline characteristics of the study population are reported as age- and sex-adjusted mean values for continuous variables and percentages for categorical variables. Comparisons across groups were examined with the generalized linear model. Adjusted incidence values for prefrailty and frailty in each BMI category were calculated, and the differences between groups were tested with the generalized linear model. Multinomial logistic regression was used to examine whether baseline BMI is associated with different stages of frailty (nonfrail, prefrail, and frail) at follow-up. Odds ratios (ORs) are presented for prefrail and frail groups in different levels of BMI, using BMI less than 25 as the reference. Series of multinomial logistic regression models were sequentially adjusted for all variables hypothesized as potential confounders or mediators of the association between BMI and frailty and which were independently associated with obesity and frailty status. No statistically significant sex × BMI and age × BMI interactions on frailty were observed and therefore no sex or age-stratified analyses were conducted.

Finally, to analyze the effect of loss to follow-up, persons without follow-up information were compared with those who had follow-up information on frailty status with t test for continuous variables and chi-square test for categorical variables. All analyses were performed using the SAS System for Windows, version 9.3 (SAS Institute, Inc., Cary, NC).

**RESULTS**

The mean age at the baseline was 43.6 (SD 9.7) years and majority of the participants (95%) were 30–60 years old. At follow-up, 5% of the participants were frail, 36% prefrail, and 59% nonfrail. Baseline characteristics of the study population are shown in **Table 1**. Several lifestyle factors and chronic conditions at baseline were associated with frailty status at follow-up. The proportion of normal-weight participants at baseline was higher among those categorized as nonfrail at follow-up than those among prefrail or frail participants (65%, 49%, and 28%, respectively, p < .0001), whereas overweight and obesity at baseline were more common among prefrail and frail participants at follow-up.

Participants who did not participate in the follow-up measurements (n = 156, 12%) were older (48.6 vs 43.6, p < .0001) and had higher BMI (26.0 vs 24.8 kg/m², p < .05) at baseline than those with follow-up information on frailty status. Women also had lower handgrip strength (261 vs 292 N, p < .001), used less alcohol (p < .001), were more often sedentary (p = .04), had lower education (p < .001), and had more comorbidities (p = .007). Especially musculoskeletal problems, such as osteoarthritis and chronic back syndrome, were more common among those who did not participate in the follow-up measurements (data not shown).

To examine the role of BMI on different stages of frailty, multinomial logistic regression with three-level outcome variable was used (**Table 2 and Figure 1**). Baseline overweight and obesity were strongly associated with prefrailty and frailty at follow-up in comparison to nonfrail at the follow-up after adjusting for age, sex, education, and lifestyle factors (**Table 2, Model 1**). The risks for prefrailty were 1.46 (95% confidence interval [CI] 1.09, 1.95) for overweight and 2.47 (95% CI 1.50, 4.07) for obesity, and the risks for frailty were 2.52 (95% CI 1.28, 5.00) for overweight and 5.43 (95% CI 2.13, 13.80) for obesity compared with normal-weight persons. Further adjustments for several chronic conditions did not markedly decrease the odds ratios for prefrailty and frailty among overweight and obese participants (**Table 2, Model 2**). In the final model baseline age, physical activity, alcohol use, and inflammatory arthritis remained independently associated with frailty status in addition to BMI.

Finally, the effect of preliminary steps of frailty (ie, baseline prefrail status) on the association between obesity and frailty in old age was examined by including only robust individuals at the baseline. Overweight and obesity at the baseline were associated with higher risk of frailty, OR = 1.87, 95% CI 1.07–4.50 and OR = 5.24, 95% CI 1.64–16.79, respectively. However, overweight and obesity at the baseline were not associated with higher risk of prefrailty, OR = 1.15, 95% CI 0.72–1.84 and OR = 1.72, 95% CI 0.79–3.76, respectively.

**DISCUSSION**

This 22-year follow-up study provides evidence that the development of geriatric syndrome of frailty may start as early as in midlife and that obesity is one of the underlying risk factors for frailty. According to our study, those with obesity in midlife have more than two times higher risk for prefrailty and five times higher risk for frailty two decades later compared with normal-weight peers independent of age, sex, education, lifestyle factors, and chronic conditions.
It is widely recognized that frailty is characterized as dysregulation of multiple physiological systems that fail to maintain the homeostatic equilibrium. Although the pathway from obesity to frailty may seem paradoxical, there are several potential mechanisms through which midlife obesity may lead to development of frailty in later years. First, obesity often precedes conditions such as insulin resistance, diabetes, and cardiovascular diseases, which are known risk factors for frailty (22,23). Second, obesity and above-mentioned diseases are all associated with low-grade inflammation (22,24), which has detrimental effects on muscles (25–27) and shares a common pathway for multiple impairments. Third, increased adiposity is also related with decreased level of anabolic hormones, such as growth hormone and testosterone (28,29), which contribute to muscle impairment in the long run (30,31). Further, anabolic hormones are needed to maintain the integrity and function of many physiological systems contributing...
to frailty, including bones, central nervous system, energy production, and delivery. Further research is certainly needed, with appropriate study designs, to confirm these pathways.

Over the last decade, the prevalence of obesity has increased markedly among younger and middle-aged persons. Thus, it is expected that long-term consequences of obesity, such as metabolic diseases and frailty, will increase in the future. Previous research has shown that extended duration of obesity is more harmful on health and physical functioning than that of recently acquired obesity (32,33). Unfortunately, in this study, we were not able to determine the duration of obesity and to examine its consequences on frailty. However, it was observed that many people who were frail at the follow-up were also obese at the follow-up measurement (25%). This supports earlier findings that frailty can coexist with obesity (6–8). No data exist, but the mismatch between the amount of fat and muscle in the body, that is, sarcopenic obesity (34) is likely in the pathway leading from obesity to frailty. Finally, to prevent and alleviate disability, recognizing these “fat and frail” persons in the health care is very important, and health care professionals should not discard the possibility of frailty among obese persons.

Major strengths of this study are the unique longitudinal data with extensive objectively measured health and functional measurements 22 years apart. In addition, we were able to exclude persons with frailty at baseline, thus enabling us to examine the incidence of frailty. However, the survey measurements and questionnaires related to frailty definition were not exactly same at baseline and follow-up visits and therefore we had to use slightly modified frailty criteria at baseline. Because the participants were mostly middle aged (median age 42 years) at the baseline, the prevalence of frailty components was still very rare. Therefore, the misclassification of frailty and potential exclusion from the follow-up analysis is likely very small and its effect on results is minor. To take into account the effect of preliminary steps of frailty (ie, baseline prefrailty status), we also conducted a sensitivity analysis by including only robust participants at the baseline. It was found that overweight and obesity at baseline predicted development of frailty but not of prefrailty. These results confirm that midlife weight status has independent effect on the development of frailty, per se, and it is not only predictor of worsening health status.

Because a fair proportion of the initial cohort had died during the 22 years and because only persons alive at the time of the follow-up and living in seven selected municipalities across the country were invited to the follow-up examination, the effects of selection could not be controlled in this study and the results cannot be generalized to the general population. However, the participation rate was high (88%) among those who were invited to the follow-up. Moreover, we were able to capture well the most frail and weak persons in the sample because home health examination was carried out for those who were not able to visit the study center. Another limitation is that we did not have objectively measured data about body composition (eg, percent body fat and lean mass) or fat distribution (specifically abdominal obesity), which all may be relevant indicators of subsequent frailty.

In conclusion, based on a 22-year follow-up study, midlife obesity was associated with development of frailty in old age. Preventing weight gain among middle-aged may help to prevent or delay the onset of frailty.

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**References**