

Association between change in body weight after midlife and risk of hip fracture—the Singapore Chinese Health Study

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Abstract

Summary The relationship between change in body weight and risk of fractures is inconsistent in epidemiologic studies. In this cohort of middle-aged to elderly Chinese in Singapore, compared to stable weight, weight loss $\geq 10\%$ over an average of 6 years is associated with nearly 40 % increase in risk of hip fracture.

Introduction Findings on the relationship between change in body weight and risk of hip fracture are inconsistent. In this study, we examined this association among middle-aged and elderly Chinese in Singapore.

Methods We used prospective data from the Singapore Chinese Health Study, a population-based cohort of 63,257

Chinese men and women aged 45–74 years at recruitment in 1993–1998. Body weight and height were self-reported at recruitment and reassessed during follow-up interview in 1999–2004. Percent in weight change was computed based on the weight difference over an average of 6 years, and categorized as loss $\geq 10\%$, loss 5 to $< 10\%$, loss or gain $< 5\%$ (stable weight), gain 5 to $< 10\%$, and gain $\geq 10\%$. Multivariable Cox proportional hazards regression model was applied with adjustment for risk factors for hip fracture and body mass index (BMI) reported at follow-up interview. **Results** About 12 % experienced weight loss $\geq 10\%$, and another 12 % had weight gain $\geq 10\%$. After a mean follow-up of 9.0 years, we identified 775 incident hip fractures among 42,149 eligible participants. Compared to stable weight, weight loss $\geq 10\%$ was associated with 39 % increased risk (hazard ratio 1.39; 95 % confidence interval 1.14, 1.69). Such elevated risk with weight loss $\geq 10\%$ was observed in both genders and age groups at follow-up (≤ 65 and > 65 years) and in those with baseline BMI ≥ 20 kg/m². There was no significant association with weight gain.

Conclusions Our findings provide evidence that substantial weight loss is an important risk factor for osteoporotic hip fractures among the middle-aged to elderly Chinese.

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Keywords Body weight · Chinese · Hip fracture · Weight change

Introduction

Weight loss due to reduced lean mass during aging is common among elderly [1–3]. Previous studies conducted in Western populations suggested that weight loss was significantly associated with bone loss in women [4, 5] and increased fracture risk among middle-aged to elderly men and women [6–13]. However, results on weight gain were inconclusive. While

most of the studies did not show statistically significant association between weight gain and bone health outcomes, one study among Norwegian men and women reported that weight gain over 5.6 kg significantly increased hip fracture risk in women [10], while another study showed weight loss $\geq 10\%$ reduced risk of hip fracture of borderline statistical significance among Caucasian men in the USA [9].

Leanness is an established independent risk factor of hip fracture in a previous meta-analysis [14]. We have also reported that low body mass index (BMI) increased the risk of hip fracture among men in our cohort of middle-aged and elderly Chinese in Singapore [15]. Asian populations have lower BMI and possibly different weight change patterns during aging as compared to their Western counterparts. In the present study, we used prospective data from the same cohort to examine the association between body weight changes over an average of 6 years with risk of hip fracture.

Methods

Study population

The present study was conducted in the Singapore Chinese Health Study, a population-based cohort prospective study established to investigate dietary and lifestyle factors in relation to risk of chronic diseases. We recruited 63,257 aged 45–74 years men ($n=27,959$) and women ($n=35,298$) between April 1993 and December 1998. The study participants were restricted to two dialect groups of Hokkiens and Cantonese who originated from Fujian and Guangdong provinces in southern China. During the enrollment period, all of our study participants were residents of government housing estates, where 86 % of the Singapore population was residing at the time of recruitment [16]. Participants were recontacted for a telephone interview between July 1999 and October 2004 [17]. After excluding those who had died, were noncontactable, or who were no longer able to participate in the follow-up interview due to disability, a total of 52,322 participants (82.7 % of the original cohort) were reinterviewed. The Institutional Review Board at the National University of Singapore approved this study. All study participants gave written informed consent.

Exposure assessment

Baseline assessment was conducted between 1993 and 1998 through a face-to-face interview with a trained interviewer using a structured questionnaire, which included demographics, medical history, cigarette smoking, alcohol consumption, physical activity, detailed menstrual and reproductive history (women only), and habitual diet recorded by a validated semi-quantitative food frequency questionnaire. History of cancer prior to the follow-up interview was self-reported and also assessed via linkage with the

national cancer registry. At the follow-up interview from 1999 to 2004, smoking and drinking behavior, medical and health history, and menstrual and reproductive history (women only) were reassessed. Current body weight and height were self-reported at both of the baseline and the follow-up assessments with an average of 5.7 years apart. BMI is calculated as weight in kilograms divided by height in meters squared (kg/m^2). We excluded participants with missing body weight and height at both baseline and follow-up interviews ($n=9994$). We further excluded 41 participants who developed hip fracture prior to baseline and 138 participants who developed hip fracture prior to the follow-up interview, thus leaving 42,149 participants in this study for the final analysis. Compared to the participants included in this study, the 9994 participants excluded from this study were older, had a higher proportion of women and were less educated. They were also more likely to be current smokers, and had higher prevalence of diabetes mellitus, stroke, and cancer.

Weight change

Percent weight change was computed as weight difference divided by baseline body weight $[(\text{weight at follow-up} - \text{weight at baseline}) / \text{weight at baseline}] \times 100\%$. Weight change was then categorized as follows: loss $\geq 10\%$, loss 5 to $<10\%$, stable weight (loss or gain $<5\%$), gain 5 to $<10\%$, and gain $\geq 10\%$. These categories of weight change were suggested to be clinically relevant and meaningful comparison among participants with wide range of weight variation in previous studies [7, 18].

Case ascertainment

Incident cases of hip fracture were identified through December 31, 2010, via the record linkage with the national hospital discharge database, which captures inpatient discharge information from all public and private hospitals in Singapore. All hip fracture cases were verified by surgical or medical records. Only 47 participants from this cohort (0.07 %) were known to be lost to follow-up due to migration out of Singapore or for other reasons. The survival status of all cohort participants was ascertained via the record linkage with the population-based Singapore Registry of Births and Deaths.

Statistical analysis

Differences in characteristics among weight change groups were tested for statistical significance using chi-squared tests for categorical variables and ANOVA for continuous variables. For each study subject, person-years were counted from the date of the follow-up interview to the date of diagnosis of hip fracture, death, migration or December 31, 2010, whichever occurred first. Multivariable Cox proportional hazards

regression model was applied to assess the association between weight change and risk of hip fracture for the whole cohort and for subgroup analyses. The strength of the association between weight change and hip fracture risk was estimated by hazard ratios (HRs) and their corresponding 95 % confidence intervals (CI), using participants with stable weight (loss or gain <5 %) as the reference group. We did not identify any violation of the proportional hazard assumption or multicollinearity among the covariates that were included in the models.

We examined the association between weight change and risk of hip fracture using three models. Model 1 was adjusted for the following covariates: age at follow-up interview (years), time interval between baseline and follow-up assessments (years), dialect group (Hokkien, Cantonese), level of education (no formal education, primary school, secondary school or higher), smoking status at follow-up interview (never smokers, ex-smokers, current smokers), current use of hormone replacement at follow-up interview (women only; yes, no), and gender (for the whole cohort). The time interval between baseline and follow-up defined the period when weight change occurred, since weight and height were assessed at these two occasions. The mean (standard deviation (SD)) time interval was 5.7 years (1.4), and the interquartile range was 4.5 to 8.8 years. This variable was included as a covariate in the regression model because the duration of the time interval could influence the degree of weight change and thus confound the relationship between weight change and the risk of hip fracture. Model 2 was adjusted for the abovementioned covariates plus self-reported physician-diagnosed history of diabetes mellitus (yes, no), stroke (yes, no), coronary heart disease (yes, no), cancer (yes, no), and other fractures (yes, no) prior to baseline or the follow-up interview. Model 3 was further adjusted for BMI (<20, 20–23.9, 24–27.9, ≥ 28 kg/m²) reported at the follow-up interview. We also conducted stratified analysis by gender (men and women), age group at follow-up (≤ 65 and > 65 years) and baseline BMI category (BMI <20, 20 to <25, and ≥ 25 kg/m²). Finally, we tested interactions between weight change categories and gender, age groups, or baseline BMI categories using the likelihood ratio test. The test was done by including five product terms in the model between these two sets of variables.

All statistical analysis was conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC). A *P* value <0.05 is considered to be statistically significant. All reported *P* values are two-sided.

Results

We identified 775 incident cases of hip fracture among 42,149 eligible cohort participants during a mean survival time of 9.0 years (SD 2.1). The time interval between the two assessments of body weight at baseline and follow-up interviews

was 5.7 years (SD 1.4). Among the incident cases of hip fracture, the mean age at fracture was 75.3 years (SD 7.3). Women accounted for 69.2 % of all hip fracture cases. The incidence rate of hip fractures in women standardized to the age structure of the whole cohort was 256 per 100,000 person-years, which was nearly two times that in men (143 per 100,000 person-years).

The characteristics of participants according to weight change are shown in Table 1. About half of the cohort participants had weight change less than 5 %, and the mean of the absolute weight change was -0.08 kg (SD 6.36). For the other half of participants, the proportion of weight loss and weight gain was distributed similarly, with 11.6 % of the cohort reporting extreme weight loss and 12.2 % reporting extreme weight gain ≥ 10 %. The mean (SD) for extreme weight change was -10.7 kg (7.4) for weight loss ≥ 10 % and 9.8 kg (5.1) for weight gain ≥ 10 %, respectively. Compared to those with stable weight, participants with weight loss ≥ 10 % were older at follow-up interview, more likely to be men, had higher weight and BMI at baseline; they also had lower education level, were more likely to be current smokers, and had a higher prevalence of diabetes, stroke, coronary heart disease, and cancer. Among the women, they were more likely to be postmenopausal and less likely to use hormone replacement therapy. By contrast, relative to those with stable weight, participants who had weight gain ≥ 10 % were more likely to be women, slightly older at follow-up interview, and had lower weight and BMI at baseline; they were also less educated and had a higher proportion of current smokers. Among the women, they were also more likely to be postmenopausal and less likely to use hormone replacement therapy (Table 1).

The association between body weight change and risk of hip fracture is shown in Table 2. Compared to stable weight (loss or gain <5 %), individuals with weight loss ≥ 10 % experienced a statistically significant 56 % increase in risk of hip fracture after adjustment for demographic and lifestyle factors (model 1). Further adjustment for comorbidities including history of diabetes, stroke, coronary heart disease, cancer, and other bone fractures (model 2) and BMI reported at the follow-up assessment (model 3) did not materially alter the results. In the final model, compared to stable weight, weight loss ≥ 10 % was associated with 39 % increased risk of hip fracture (HR 1.39; 95 % CI 1.14, 1.69). Conversely, no association was found between weight gain and hip fracture risk. The results were materially the same in a simpler model that included only age, gender, and BMI at follow-up as covariates (Supplemental Table S1). In this simpler model, the HR (95 % CI) associated with weight loss ≥ 10 % was 1.55 (1.28, 1.88) and that with weight gain ≥ 10 % was 1.00 (0.78, 1.26). The association between weight change and risk of hip fractures did not differ by gender (all *P* for interaction > 0.30).

Table 1 Characteristics of participants [% for categorical variables and mean (SD) for continuous variables] according to weight change categories, the Singapore Chinese Health Study (1999–2010)

	Weight change				
	Loss ≥ 10 %	Loss 5 to <10 %	Stable weight (loss or gain <5 %)	Gain 5 to <10 %	Gain ≥ 10 %
Number of participants (% of cohort)	4872 (11.6)	5259 (12.5)	21,565 (51.2)	5292 (12.5)	5161 (12.2)
Gender					
Men (%)	45.5	44.7	44.7	42.7	43.3
Women (%)	54.5	55.3	55.3	57.3	56.7
Age at follow-up, mean (SD)	63.5 (8.0)	61.7 (7.7)	60.2 (7.5)	59.9 (7.5)	61.2 (7.9)
BMI (kg/m^2), mean (SD)					
At baseline	24.6 (4.4)	23.9 (3.5)	23.2 (3.3)	22.6 (3.2)	21.4 (3.1)
At follow-up	20.7 (3.2)	22.3 (3.3)	23.2 (3.4)	24.2 (3.4)	25.1 (3.8)
Weight (kg), mean (SD)					
At baseline	62.7 (12.1)	61.1 (10.3)	59.4 (9.9)	57.7 (9.3)	54.4 (8.9)
At follow-up	52.0 (9.0)	56.7 (9.5)	59.4 (9.9)	61.8 (9.9)	64.1 (10.7)
Weight change (kg), median (IQR)	-9 (-12, -7)	-4 (-5, -4)	0 (-1, 1)	4 (3, 5)	8 (7, 11)
Secondary school or higher (%)	25.6	31.0	36.9	36.7	28.9
Current smoker (%)	21.2	17.7	15.7	15.9	19.9
History of diabetes mellitus (%)	20.9	18.9	13.1	9.9	11.2
History of stroke (%)	5.3	3.9	2.7	3.0	3.4
History of coronary heart disease (%)	9.4	8.0	6.8	6.2	7.1
History of cancer (%)	7.2	5.6	4.1	4.0	4.8
History of other fractures (%)	7.0	8.5	8.0	8.4	8.0
Postmenopausal (women only) (%)	95.3	93.3	88.5	87.6	90.1
Current use of hormone replacement among postmenopausal women (%)	3.4	5.1	7.8	7.6	5.5

All *P* values for differences in categorical variables (chi-squared) and continuous variables (ANOVA) were <0.05

We further analyzed the data after excluding participants with history of diabetes, stroke, coronary heart disease, and cancer reported at the follow-up interview, because they would be more likely to experience greater weight loss than those without such diseases. Among the 31,875 participants without the abovementioned comorbidities, there were 468 incident cases of hip fracture. Compared to stable weight, weight loss ≥ 10 % was significantly associated with a statistically significant 55 % increase in risk of hip fracture (HR 1.55; 95 % CI 1.20, 2.01), whereas no apparent association was found for those with weight gain ≥ 10 % (HR 1.14; 95 % CI 0.85, 1.53).

Table 3 shows the association between weight change and risk of hip fracture stratified by baseline BMI in three categories (<20 , 20 to <25 , and ≥ 25 kg/m^2) and age group at follow-up (≤ 65 and >65 years). We used BMI <20 kg/m^2 as the cutoff for leanness, because it was a significant risk factor for hip fracture in this cohort [15] as well as in a meta-analysis that examined BMI and fracture risk [14]. We used the current recommendation by the World Health Organization of BMI ≥ 25 kg/m^2 as the cutoff for the overweight category [19]. In the stratification by baseline BMI, there was a marginal

significant difference in the risk estimates associated with weight loss ≥ 10 % between the BMI <20 kg/m^2 and BMI 20 to <25 kg/m^2 categories ($P=0.09$), and also between the BMI <20 kg/m^2 and BMI ≥ 25 kg/m^2 categories ($P=0.06$). Weight loss ≥ 10 % was not significantly associated with hip fracture risk in participants with baseline BMI <20 kg/m^2 . Conversely, among those with baseline BMI ≥ 20 kg/m^2 , there was a 48 % increase in hip fracture risk (HR 1.48; 95 % CI 1.18, 1.84). The highest risk was observed among those who were overweight (BMI ≥ 25 kg/m^2) at baseline (HR 1.55; 95 % CI 1.02, 2.37). The risk estimates for hip fracture associated with weight gain ≥ 10 % between the three baseline BMI categories were not statistically different (all *P*s for interaction >0.18). Compared to stable weight, weight loss ≥ 10 % was associated with increased risk of hip fracture similarly in both age groups. There was no apparent difference in the relationship between weight change and risk of hip fracture by age group (all *P*s for interaction >0.59).

Furthermore, in the stratum of participants with baseline BMI <20 kg/m^2 , we excluded those who died before the cutoff date of December 31, 2010 ($n=1036$), leaving 6513 surviving participants with 148 hip fracture incident cases and 6365

Table 2 Association between change in body weight and risk of hip fracture, the Singapore Chinese Health Study (1999–2010)

		Weight change				
		Loss ≥ 10 %	Loss 5 to <10 %	Stable weight (weight change <5 %)	Gain 5 to <10 %	Gain ≥ 10 %
Overall ($n=42,149$)						
Hip fracture cases		165	106	337	80	87
Person-years		40,553	46,638	196,262	48,275	45,876
HR ^a	(95 % CI)	1.56 (1.29, 1.89)	1.10 (0.88, 1.37)	Reference	0.99 (0.78, 1.27)	0.92 (0.73, 1.17)
HR ^b	(95 % CI)	1.51 (1.25, 1.83)	1.07 (0.86, 1.33)	Reference	1.01 (0.79, 1.29)	0.94 (0.74, 1.20)
HR ^c	(95 % CI)	1.39 (1.14, 1.69)	1.03 (0.83, 1.28)	Reference	1.05 (0.82, 1.34)	0.99 (0.78, 1.26)
Men ($n=18,704$)						
Hip fracture cases		43	38	106	28	24
Person-years		17,640	20,242	85,630	20,100	19,259
HR ^a	(95 % CI)	1.45 (1.01, 2.07)	1.27 (0.88, 1.84)	Reference	1.16 (0.76, 1.76)	0.88 (0.57, 1.38)
HR ^b	(95 % CI)	1.42 (0.99, 2.03)	1.26 (0.87, 1.83)	Reference	1.19 (0.78, 1.81)	0.90 (0.58, 1.40)
HR ^c	(95 % CI)	1.28 (0.89, 1.86)	1.22 (0.84, 1.77)	Reference	1.22 (0.81, 1.86)	0.94 (0.60, 1.48)
Women ($n=23,445$)						
Hip fracture cases		122	68	231	52	63
Person-years		22,913	26,396	110,632	28,175	26,617
HR ^a	(95 % CI)	1.62 (1.29, 2.02)	1.02 (0.78, 1.34)	Reference	0.92 (0.68, 1.24)	0.94 (0.71, 1.25)
HR ^b	(95 % CI)	1.56 (1.25, 1.94)	0.98 (0.75, 1.28)	Reference	0.93 (0.69, 1.26)	0.97 (0.73, 1.28)
HR ^c	(95 % CI)	1.44 (1.14, 1.82)	0.95 (0.72, 1.24)	Reference	0.96 (0.71, 1.30)	1.01 (0.76, 1.34)

CI confidence interval

^a HR adjusted for gender (for the whole cohort), age at follow-up interview (years), time interval between baseline and follow-up assessment (years), dialect group (Hokkien, Cantonese), level of education (no formal education, primary school, secondary school or higher), smoking status at follow-up interview (never smokers, ex-smokers, current smokers), current use of hormone replacement at follow-up interview (women only; yes, no)

^b HR adjusted for covariates in model 1 and diabetes mellitus, stroke, CHD, cancer, and other fractures

^c HR adjusted for covariates in model 2 and follow-up body mass index (<20 , 20 – 23.9 , 24 – 27.9 , ≥ 28 kg/m²)

non-cases. Although those who remained alive before the cut-off date were likely to be healthier than those who had died, the risk estimates for the 6513 surviving participants remained materially the same. Neither weight loss ≥ 10 % (HR 1.01; 95 % CI 0.56, 1.82) nor weight gain ≥ 10 % (HR 0.81; 95 % CI 0.52, 1.25) was associated with risk of hip fracture.

Discussion

In this study, we observed a significant increase in risk of hip fracture among those who sustained a weight loss of 10 % and above. Conversely, no significant association was found between weight gain and risk of hip fracture. Results were similar in both men and women.

Weight loss has been documented to be related to bone loss [4, 5] and increased fracture risk [6–9, 12] in previous studies among Western populations. Findings from the present study are generally consistent with the results reported earlier, where extreme weight loss was associated with increased fracture risk in both men and women [6–9, 12]. Similar to the findings in a community-dwelling prospective cohort study among US

Caucasian men [9] and women [7], whose weight change was measured between age of 50 years and older, weight loss ≥ 10 % compared to stable weight significantly increased risk of hip fracture by nearly threefold in men (HR 2.79; 95 % CI 1.62, 4.79) [9] and in women (HR 2.9; 95 % CI 2.0, 4.1) [7]. Another longitudinal study among Norwegian men and women also showed that weight loss of more than 3 kg was associated with a significant twofold increase in risk of hip fracture as compared to those who had body weight gain of 1.3–5.5 kg [10]. Furthermore, in this study, the significantly elevated risk with weight loss ≥ 10 % persisted in men and women combined, in elderly aged >65 years, in those whose baseline BMI ≥ 20 kg/m², and among participants without medical history of diabetes, stroke, cancer, and coronary heart disease. Thus, our data demonstrated the independent role of weight change in relation to risk of hip fracture. On the other hand, weight gain ≥ 10 % was not statistically significantly associated with hip fracture risk in this cohort, which is similar to the previous findings among Caucasian men [20] and women [12]. In line with these studies [6, 7, 9, 12], we did not find differences regarding weight change and hip fracture risk by gender or age group (≤ 65 and >65 years). Compared to the weight change

Table 3 Association between change in body weight and risk of hip fracture by BMI categories at baseline and age group at follow-up, the Singapore Chinese Health Study (1999–2010)

		Loss ≥ 10 %	Loss 5 to < 10 %	Stable weight (loss or gain < 5 %)	Gain 5 to < 10 %	Gain ≥ 10 %	Loss ≥ 10 %
BMI at baseline							
< 20 kg/m ² (<i>n</i> =7549)	Cases	14	16	66	22	30	
	Person-years	3814	5464	32,555	9917	15,287	
	HR ^a (95 % CI)	0.93 (0.51, 1.67)	1.08 (0.62, 1.86)	Reference	1.14 (0.70, 1.85)	0.82 (0.53, 1.26)	
	HR ^b (95 % CI)	0.91 (0.50, 1.64)	1.06 (0.61, 1.83)	Reference	1.18 (0.71, 1.95)	0.88 (0.53, 1.47)	
20 to < 25 kg/m ² (<i>n</i> =23,572)	Cases	86	61	197	43	45	
	Person-years	20,388	25,679	112,076	28,768	25,431	
	HR ^a (95 % CI)	1.60 (1.24, 2.06)	1.12 (0.84, 1.49)	Reference	0.88 (0.63, 1.22)	0.84 (0.61, 1.16)	
	HR ^b (95 % CI)	1.52 (1.13, 2.05)	1.11 (0.83, 1.49)	Reference	0.87 (0.62, 1.22)	0.81 (0.57, 1.16)	
≥ 25 kg/m ² (<i>n</i> =11,028)	Cases	65	29	74	15	12	
	Person-years	16,350	15,495	51,631	9,589	5,158	
	HR ^a (95 % CI)	1.85 (1.32, 2.59)	1.06 (0.69, 1.63)	Reference	1.07 (0.61, 1.86)	1.32 (0.72, 2.44)	
	HR ^b (95 % CI)	1.55 (1.02, 2.37)	0.98 (0.62, 1.53)	Reference	1.07 (0.61, 1.88)	1.29 (0.68, 2.47)	
Age at follow-up							
≤ 65 years (<i>n</i> =30,382)	Cases	39	28	111	30	27	
	Person-years	26,109	33,317	150,290	37,553	33,917	
	HR ^a (95 % CI)	1.50 (1.04, 2.17)	0.92 (0.61, 1.39)	Reference	1.14 (0.76, 1.70)	0.99 (0.65, 1.51)	
	HR ^b (95 % CI)	1.39 (0.94, 2.03)	0.90 (0.59, 1.36)	Reference	1.16 (0.77, 1.73)	1.01 (0.66, 1.55)	
> 65 years (<i>n</i> =11,767)	Cases	126	78	226	50	60	
	Person-years	14,444	13,321	45,972	10,722	11,959	
	HR ^a (95 % CI)	1.52 (1.22, 1.90)	1.12 (0.86, 1.45)	Reference	0.96 (0.71, 1.31)	0.94 (0.71, 1.25)	
	HR ^b (95 % CI)	1.39 (1.10, 1.75)	1.07 (0.83, 1.39)	Reference	1.00 (0.73, 1.36)	1.00 (0.75, 1.33)	

CI confidence interval

^a HR adjusted for gender, age at follow-up interview (years), time interval between baseline and follow-up assessment (years), dialect group (Hokkien, Cantonese), level of education (no formal education, primary school, secondary school or higher), smoking status at follow-up interview (never smokers, ex-smokers, current smokers), current use of hormone replacement at follow-up interview (women only; yes, no), history of cancer, coronary heart disease, diabetes mellitus, stroke, and other bone fractures

^b HR adjusted for covariates in model 2 and follow-up body mass index (< 20 , 20–23.9, 24–27.9, ≥ 28 kg/m²)

pattern in previous studies, the absolute change in weight among the participants in the extreme weight change category (≥ 10 %) in our study was about 4–5 kg less than that in the same category in two Caucasian studies [7, 9]. However, it should be noted that age, lifestyle factors, health conditions, and the time interval of weight change vary from one study to another.

This study is the first to examine weight change in relation to risk of hip fracture in lean participants with BMI < 20 kg/m², which is an independent risk factor for hip fracture [14, 15]. We found that weight loss ≥ 10 % did not further affect the risk of hip fracture among these lean individuals whose baseline BMI was already < 20 kg/m². Furthermore, after excluding who died between the follow-up assessment and December 31, 2010, in this subgroup, our results did not appear to bias toward to the healthier survivors. This suggested, at least in part, that in lean individuals who were already at risk of hip fracture due to their low BMI, extreme weight loss did not

confer additional risk for hip fracture. Nevertheless, this could be an observation by chance in our study due to the small numbers of participants and hip fracture cases in this group. In the previous studies among Caucasian populations, the lowest cutoff for baseline BMI was < 23 kg/m² among women in the USA [7] and was ≤ 22.6 kg/m² among men in Norway [20]. Hence, we are not able to compare our results for those with baseline BMI < 20 kg/m² with other populations. In the study among white women in the USA, weight loss ≥ 10 % was consistently associated with elevated risk of hip fracture in all strata of baseline BMI at 50 years of age. However, weight gain ≥ 10 % appeared to be associated with increased risk among those with baseline BMI < 23 kg/m², yet it was associated with reduced risk among those with baseline BMI ≥ 23 kg/m², although the relationship between weight gain ≥ 10 % and hip fracture risk did not reach statistical significance [7]. Conversely, in the study among Norwegian white men, compared to stable weight, weight loss ≤ 5 % decreased

bone mineral density (BMD) and weight gain ≥ 5 % increased BMD across all baseline BMI strata [20]. Further studies are needed to validate our finding of the null association between extreme weight loss and fracture risk in lean individuals with baseline BMI < 20 kg/m².

The potential mechanisms between weight loss and osteoporotic fractures have been proposed previously. Weight loss among elderly was suggested to decrease more lean mass, especially muscle mass [3, 21], resulting in weakened muscle strength and increased frailty [22]. This is particularly the case among elderly men [23], because men have more muscle mass than women [24]. In line with this, studies have shown that lean mass was an independent contributor to hip bone mineral density [25, 26], especially in men [26, 27]. Furthermore, decreased lean mass may reduce testosterone level [28, 29], which has been shown to be positively associated with muscle strength and bone mineral density [28]. In contrast, loss of fat mass following weight loss may play a more predominant role in bone mass among postmenopausal women [26, 27], possibly due to more fat tissue in women as compared to men [3]. Thus, loss of fat mass could contribute to a further decline of estrogen in postmenopausal women [30, 31], and reduced estrogen could have a negative impact on osteoblasts [32] and osteoclasts [33] through the expression of the pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, and TNF- α [34]. Other mechanisms underlying weight loss and hip fracture include decreased mechanical loading and weight bearing, and loss of fat around the hip, which in turn increase the risk of fractures during falls [35, 36]. Taken together, weight loss among elderly men and women may thus impair bone health and increase risk of fracture.

On the other hand, the benefit of weight gain in reducing risk of hip fracture is less certain. Although weight gain increased weight bearing, mechanical loading and padding around the hip [35, 36], all of which may protect against falls and fractures, there is generally little lean mass conservation with weight gain among elderly men and women [23, 37]. In the present study, although weight gain ≥ 10 % in those who were not overweight at baseline (BMI < 25 kg/m²) was associated with lower risk of hip fracture, it did not reach statistical significance. In contrast, weight gain ≥ 10 % in those who were overweight (BMI ≥ 25 kg/m²) at baseline was associated with a non-significant increase in risk. We speculate that extreme weight gain among overweight middle-aged to elderly may be associated with increased risk of other chronic diseases, such as cardiovascular disease and type 2 diabetes [38, 39], which are risk factors for hip fracture [40, 41]. In addition, body fat may redistribute with increased visceral fat in elderly [3], which in turn could impair insulin sensitivity and increase the expression of other pro-inflammatory cytokines [39]. Furthermore, serum vitamin D status was inversely related to adiposity [42], thus extreme weight gain may in turn decrease the circulation of vitamin D [43] and affect dietary

calcium absorption [44]. All of these are plausible explanations why weight gain may not protect against hip fracture among overweight participants in our study population.

The strength of this study is the large number of incident cases of hip fracture identified from a population-based prospective cohort with a long follow-up time. Another strength is the presumed lack of recall bias in body weight, height, and other potential confounding variables since they were reported by participants prior to hip fracture. Singapore is a small city-state with a system for easy access to specialized medical care. Since practically all hip fracture cases would seek medical attention immediately and be hospitalized, as well as a negligible proportion (0.07 %) of original cohort participants who migrated out of Singapore, our case ascertainment through the linkage with the comprehensive, nationwide hospital database can be considered complete. A limitation of our study is the lack of information on diet and physical activity at the follow-up interview, which did not allow us to further examine whether changes in these lifestyle factors may confound the association between weight change and risk of hip fracture. The use of self-reported body weight and height could be prone to non-differential misclassification, and thus, it would lead to underestimation of the association between weight change and risk of hip fracture. A systematic review of 64 studies [45] and a study among middle-aged and elderly Australian adults [46] suggested trends of underestimation for self-reported weight and overestimation for self-reported height. Furthermore, the systematic review also showed that the difference between the self-reported and objectively measured BMI was relatively small for those with BMI less than 30 kg/m² [45]. In line with this, there was a very high correlation between self-reported and measured height, weight, and BMI among the middle-aged and elderly Australians ($r \geq 0.95$), and those with higher measured BMI tend to have greater underestimation [46]. Nevertheless, self-report of body weight has been shown to be valid across many populations and specifically in Asians [47], and 96 % of our study population had BMI < 30 kg/m². We therefore speculated that the underestimation of self-reported weight and height was relatively small in our study population. Another limitation is that change of body composition, such as that of lean and fat mass, was not investigated in the current study. Therefore we were unable to evaluate whether the effect of weight change could be mediated by the variation of body composition in the development of osteoporosis. Finally, our study excluded those who could not report weight and/or height at either interview, and they were different in mean age and in the distribution of gender, education level, and prevalence of comorbidities from those included in this study. Nevertheless, all of our statistical models had included these factors as covariates to minimize possible confounding bias by these factors. Hence, even though differences between the participants included in the study and those who were excluded may affect the

generalizability of the results, we feel that the conclusions of the present study should be valid.

In conclusion, data from the present study demonstrate that weight loss of 10 % or more was associated with significant increased risk of hip fracture among middle-aged to elderly Chinese men and women in Singapore. Our findings highlight the importance of identifying risk of osteoporotic hip fracture in middle-aged to elderly with substantial weight loss in addition to low BMI.

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Conflicts of interest None

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