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ORIGINAL ARTICLE

Measured height loss predicts incident clinical fractures independently from FRAX: a registry-based cohort study

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Abstract

Summary During median follow-up 6.0 years in 11,495 individuals, prior absolute and annualized measured height loss was significantly greater in those with subsequent incident fracture compared with those without incident fracture.

Purpose FRAX® accepts baseline height and weight as input variables, but does not consider change in these parameters over time.

Aim To evaluate the association between measured height or weight loss on subsequent fracture risk adjusted for FRAX scores, risk factors, and competing mortality.

Methods Using a dual-energy x-ray absorptiometry (DXA) registry for the Province of Manitoba, Canada, we identified women and men age 40 years or older with height and weight measured at the time of two DXA scans. Cox regression analyses were performed to test for a covariate-adjusted association between prior height and weight loss with incident fractures occurring after the second scan using linked population-based healthcare data.

Results The study population consisted of 11,495 individuals (average age 68.0 ± 9.9 years, 94.6% women). During median follow-up 6.0 years, records demonstrated incident major osteoporotic fracture (MOF) in 869 individuals, hip fractures in 265, clinical vertebral fractures in 207, and any fracture in 1203. Prior height loss was significantly greater in individuals with fracture compared with those without fracture, regardless of fracture site. Mortality was greater in those with prior height loss (HR per SD 1.11, 95% CI 1.06–1.17) or weight loss (HR per SD 1.26, 95% CI 1.19–1.32). Each SD in height loss was associated with increased fracture risk (MOF 12–17%, hip 8–19%, clinical vertebral 28–37%, any fracture 14–19%). Prior weight loss was associated with 21–30% increased risk for hip fracture, but did not increase risk for other fractures. Height loss of 3.0 cm or greater more than doubled the risk for subsequent fracture.

Conclusions Prior height loss is associated with a small but significant increase in risk of incident fracture at all skeletal sites independent of other clinical risk factors and competing mortality as considered by FRAX. Prior weight loss only increases risk for subsequent hip fracture.

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Keywords Dual-energy x-ray absorptiometry · Fractures · FRAX · Height · Osteoporosis

Introduction

Osteoporosis is characterized by low bone mass and deterioration of bone tissue, leading to an increase in bone fragility and susceptibility to fracture, with substantial health consequences for the individual and society [1]. Identification of easily assessed risk factors is important in clinical practice to distinguish those at increased fracture risk to initiate treatments capable of reducing that risk and preventing fracture. In addition to bone mineral density (BMD) and other clinical risk factors, taller height, lower weight, and lower body mass index (BMI) at baseline are associated with increased fracture risk, particularly those affecting the hip [2–5].

The fracture risk assessment tool (FRAX®) is widely used to assess fracture risk and need for anti-osteoporosis therapy [6]. FRAX accepts baseline height and weight as input variables, but does not consider change in these parameters over time. Documented prior weight loss has been associated with increased fracture risk [3, 7]. Height loss can be a sign of clinically unrecognized vertebral compression fractures [8–11]. Thresholds have been proposed, based upon self-reported or measured height loss, as a guide for spine imaging to identify previously undiagnosed vertebral compression fractures [12, 13]. Beyond the association with vertebral fractures, some data indicate that even modest height loss is associated with excess non-vertebral fractures, particularly hip fractures, in women and men [14, 15].

Clinical guidelines often recommend serial measurements of height and/or weight as part of routine fracture risk assessment [12, 16]. Whether the documentation of prior height or weight loss in routine clinical practice modifies fracture risk independent of FRAX scores is currently unknown. To address this question, we used a large clinical dual-energy x-ray absorptiometry (DXA) registry for the Province of Manitoba, Canada, where height and weight were routinely measured in conjunction with BMD. Our objective was to evaluate the association between measured height and weight loss on subsequent fracture risk adjusted for FRAX scores, FRAX risk factors, and competing mortality.

Methods

Study population

In the Canadian Province of Manitoba (population 1.3 million, 2017), health services are provided to virtually all residents through a public healthcare system. DXA-based BMD testing has been managed as an integrated clinical program since 1997; criteria for testing have been published and include screening at age 65 years for women and in men and younger women with additional risk factors [17]. The program maintains a database of all DXA results, which can be linked with other provincial population-based computerized health databases through an anonymous personal identifier. The DXA database has completeness and accuracy in excess of 99% [18].

The study population consisted of all women and men age 40 years or older with height and weight measured at the time of two DXA scans performed by the program at least 1 year apart. We excluded those with missing height or weight measurements, outliers (> 2.5 cm height increase or > 10 cm height loss presumed to represent data entry errors) and those with missing covariates. For those with more than one qualifying examination, only the first was included. The study was approved by the Health Research Ethics Board for the University of Manitoba.

Height and weight loss

Weight and height were measured and recorded at the time of DXA as weight (in kilograms, floor scale) and height (in meters, wall-mounted stadiometer). Change was calculated as the absolute difference (visit 2–visit 1) in height (cm) and weight (kg). Annualized rates of height loss and BMD loss (cm/year and kg/year, respectively) were also calculated.

Incident fracture ascertainment

Manitoba Health records were assessed for the presence of fracture diagnostic codes occurring after the visit 2 BMD assessment (index date) up to March 31, 2017. Fractures were assessed through a combination of hospital discharge abstracts (diagnoses and procedures coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) prior to 2004 and International Classification of Diseases, Tenth Revision, Canadian Enhancements (ICD-10-CA) thereafter) and physician billing claims (coded using ICD-9-CM) using previously validated algorithms [19, 20]. Analysis was based upon hip, clinical vertebral, forearm, and humerus fracture diagnostic codes (collectively designated major osteoporotic fractures (MOF)), hip fracture alone, clinical vertebral alone, and any fracture (excluding head/neck, hands, feet, and ankle). Incident fractures with high-trauma codes were excluded from the analysis. To minimize potential misclassification of prior incident fractures, we conservatively required that there be no

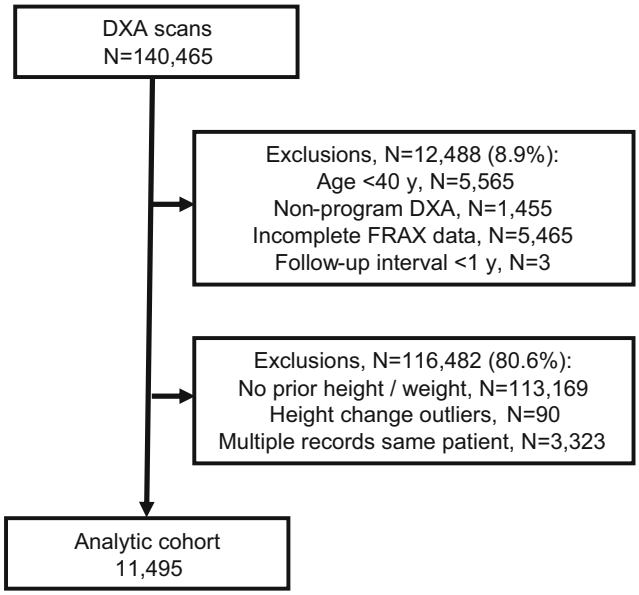

Fig. 1 Population selection flowchart

hospitalization or physician visit(s) with the same fracture type in the 6 months preceding an incident fracture diagnosis.

Relevant covariates

We adjusted for multiple covariates assessed at visit 2 that could affect fracture risk independent of BMD. Ten-year probability of a MOF and hip fracture was calculated using the Canadian FRAX tool (FRAX® Desktop Multi-Patient Entry, version 3.8). The Canadian FRAX tool was calibrated using nationwide hip fracture and mortality data [21] and independently validated in the general population [18, 19]. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Prior fracture and other FRAX input variables were assessed using linkage to the population-based research registry that includes hospital discharge abstracts and physician billing claims as previously described [22]. We defined prior fragility fracture as any non-traumatic MOF that occurred before the baseline DXA test examining medical records back to 1987. Parental hip fracture and current smoking was self-reported. High alcohol use was by self-report from 2012 onwards and from a proxy variable in earlier years (alcohol substance abuse diagnosis codes). Rheumatoid arthritis diagnosis was from health service diagnoses. Prolonged oral corticosteroid use (> 90 days dispensed in the 1 year prior to DXA) was obtained from the provincial pharmacy system. Hip DXA scans were performed and analyzed in accordance with manufacturer recommendations. Femur neck T-scores were calculated from Third National Health and Nutrition Examination Surveys (NHANES III) white female reference values [23]. The cross-calibrated instruments used for this study (Prodigy, iDXA, GE/Lunar

Table 1 Baseline characteristics

Characteristic	All subjects $N = 11,495$
Age (years)	68.0 ± 9.9
Gender (woman)	10,875 (94.6)
Height baseline (cm)	160.4 ± 7.2
Weight baseline (kg)	67.4 ± 14.4
FRAX MOF percent (without BMD)	14.6 ± 9.7
FRAX hip percent (without BMD)	5.1 ± 6.9
FRAX MOF percent (with BMD)	12.4 ± 7.7
FRAX hip percent (with BMD)	3.3 ± 4.9
Prior interval (years)	3.8 ± 1.7
Height loss (cm)	0.6 ± 1.0
Weight loss (kg)	0.8 ± 5.1
Height loss rate (cm per year)	0.16 ± 0.33
Weight loss rate (kg per year)	0.21 ± 1.75

Data expressed as mean (SD) or *N* (percent). *MOF*, major osteoporotic fracture

Table 2 Unadjusted mean (± standard deviation) height and weight loss according to incident fracture status

	No fracture	Fracture	*p* value*
Incident MOF	10,626	869	
Height loss (cm)	0.58 ± 0.98	0.79 ± 1.27	< 0.001
Weight loss (kg)	0.76 ± 5.09	1.42 ± 5.21	< 0.001
Height loss rate (cm per year)	0.16 ± 0.32	0.23 ± 0.42	< 0.001
Weight loss rate (kg per year)	0.19 ± 1.74	0.41 ± 1.86	< 0.001
Incident hip	11,230	265	
Height loss (cm)	0.59 ± 0.99	0.97 ± 1.32	< 0.001
Weight loss (kg)	0.77 ± 5.08	2.76 ± 5.65	< 0.001
Height loss rate (cm per year)	0.16 ± 0.33	0.29 ± 0.40	< 0.001
Weight loss rate (kg per year)	0.20 ± 1.75	0.72 ± 1.79	< 0.001
Incident clinical vertebral	11,288	207	
Height loss (cm)	0.59 ± 0.99	1.17 ± 1.55	< 0.001
Weight loss (kg)	0.80 ± 5.1	1.70 ± 5.13	0.012
Height loss rate (cm per year)	0.16 ± 0.32	0.35 ± 0.48	< 0.001
Weight loss rate (kg per year)	0.21 ± 1.75	0.43 ± 1.91	0.068
Incident any fracture	10,292	1203	
Height loss (cm)	0.58 ± 0.98	0.77 ± 1.21	< 0.001
Weight loss (kg)	0.77 ± 5.06	1.16 ± 5.42	0.014
Height loss rate (cm per year)	0.15 ± 0.32	0.22 ± 0.40	< 0.001
Weight loss rate (kg per year)	0.20 ± 1.73	0.30 ± 1.97	0.067

MOF, major osteoporotic fracture

**t* test, no fracture vs fracture

Table 3 Multivariable adjusted hazard ratios (HR) with 95% confidence interval (CI) for incident fracture according to prior height loss (per SD = 1 cm) and weight loss (per SD = 5 kg)

	Incident MOF		Incident hip		Incident clinical vertebral		Incident any fracture	
Adjusted for:	Height loss HR (95% CI)	Weight loss HR (95% CI)	Height loss HR (95% CI)	Weight loss HR (95% CI)	Height loss HR (95% CI)	Weight loss HR (95% CI)	Height loss HR (95% CI)	Weight loss HR (95% CI)
FRAX without BMD, no competing mortality	*1.17 (1.11–1.-24)*	1.04 (0.96–1.-11)	*1.19 (1.09–1.-3)0*	*1.25 (1.11–1.-4)*	*1.37 (1.26–1.-49)*	1.00 (0.87–1.-15)	*1.19 (1.13–1.-25)*	0.99 (0.93–1.-05)
FRAX with BMD, no competing mortality	*1.15 (1.08–1.-21)*	1.06 (0.99–1.-13)	*1.14 (1.04–1.-25)*	*1.27 (1.14–1.-42)*	*1.35 (1.24–1.-47)*	1.03 (0.90–1.-18)	*1.16 (1.11–1.-22)*	1.01 (0.95–1.-07)
FRAX without BMD, includes competing mortality	*1.15 (1.09–1.-22)*	1.01 (0.95–1.-09)	*1.17 (1.07–1.-28)*	*1.21 (1.08–1.-36)*	*1.35 (1.24–1.-47)*	0.98 (0.85–1.-13)	*1.16 (1.11–1.-22)*	0.97 (0.91–1.-03)
FRAX with BMD, includes competing mortality	*1.12 (1.06–1.-19)*	1.03 (0.96–1.-11)	*1.12 (1.02–1.-23)*	*1.24 (1.11–1.-39)*	*1.32 (1.21–1.-44)*	1.01 (0.88–1.-16)	*1.14 (1.08–1.-19)*	0.99 (0.93–1.-05)
FRAX risk factors with BMD	*1.12 (1.05–1.-18)*	1.06 (0.99–1.-14)	1.08 (0.98–1.-19)	*1.30 (1.16–1.-46)*	*1.28 (1.17–1.-40)*	1.02 (0.89–1.-16)	*1.14 (1.08–1.-20)*	1.01 (0.95–1.-08)

Results from Cox regression models with height loss and weight loss both included in the models. Significant effects are in italics. *MOF*, major osteoporotic fracture; *BMD*, bone mineral density (femur neck). FRAX hip fracture probability was used for covariate adjustment in the incident hip fracture analysis; FRAX MOF probability was used for all other incident fracture analyses

Healthcare, Madison WI) exhibited stable long-term performance (coefficient of variation < 0.5%).

Statistical analysis

Statistical analyses were performed with Statistica (Version 13.0, StatSoft Inc., Tulsa, OK). Descriptive statistics for demographic and baseline characteristics are presented as mean ± SD for continuous variables or number (%) for categorical variables. Time to incident fracture following the DXA scan (index date) was studied using Cox proportional hazards regression. Observations were censored for death (vital statistics), migration out of province (Manitoba Health registry file), or end of follow-up (March 31, 2017). Absolute prior height loss and weight loss as continuous measures were the primary predictor variables (both included in the analytic models), with annualized change assessed as secondary predictor variables. Graphical analyses confirmed that these approximated a normal distribution. Models were sequentially adjusted for FRAX score without BMD, FRAX with BMD, and individual FRAX risk factors including BMD. Models that included competing mortality were also assessed [24]. FRAX scores were log-transformed due to a skewed distribution. Proportionality of hazards was confirmed by testing scaled Schoenfeld residuals versus time. Secondary analyses also evaluated prior height loss as a categorical predictor variable (less than 1.0 cm loss (referent), 1.0–1.9 cm loss, 2.0–2.9 cm loss, and ≥ 3.0 cm loss) using the Kaplan-Meier method (with log-rank comparisons) and Cox regression (adjusted for age-sex alone and FRAX score).

Results

The study population selection flowchart appears in Fig. 1. The entire BMD registry contained 140,465 scans (1990–2017). We excluded 12,488 (8.9%) in individuals < 40 years at baseline, non-program DXA, incomplete FRAX data, or follow-up interval < 1 year. We next excluded 116,482 (80.6%) of the individuals without a prior measurement of height and/or weight, height change outliers, or with multiple qualifying records (only the first recorded change in height/weight was used for analysis). The final study population consisted of 11,495 individuals, average age 68.0 ± 9.9 years, 94.6% women (Table 1). Average height loss was 0.6 ± 1.0 cm and weight loss 0.8 ± 5.1 kg prior to the index date (mean time interval 3.8 ± 1.7 years between visit 1 and visit 2).

During median follow-up 6.0 years (interquartile range 4.5–7.4) after the index date (visit 2), records demonstrated one or more incident MOF in 869 individuals, hip fractures in 265, clinical vertebral fractures in 207, and any fracture in 1203. Height loss (both absolute and annualized) that occurred between visit 1 and visit 2 was significantly greater in

individuals with subsequent fracture compared with those without fracture, regardless of fracture site (Table 2). Absolute weight loss was also associated with incident fractures regardless of site, but when expressed as an annualized measure, this was only statistically significant for MOF and hip fracture.

Cox regression analyses were performed to test for independent associations between prior height and weight loss (per SD, 1 cm and 5 kg, respectively) on incident fractures adjusted for multiple covariates and for each other. Adjusted for FRAX risk factors including BMD, mortality was greater in those with prior height loss (HR per SD 1.11, 95% CI 1.06–1.17) or weight loss (HR per SD 1.26, 95% CI 1.19–1.32); competing mortality was also considered in the analyses (Table 3). Each SD of height loss was associated with increased fracture risk across all sites, despite a range of covariate adjustments (MOF 12–17%, hip 8–19%, clinical vertebral 28–37%, any fracture 14–19%). Prior weight loss was associated with 21–30% increased risk for hip fracture, but did not increase risk for other fractures. Results were similar for annualized height and weight loss (Supplementary Table 1).

Prior height loss was also studied as a categorical measure. Kaplan-Meier curves (Fig. 2) showing statistically significant curve separation for all fracture types (all log-rank $p < 0.001$). There was a general gradient of increasing fracture risk for greater height loss (all p-linear trend < 0.001), with height loss of 3.0 cm or greater more than doubling the risk for subsequent fracture (Table 4). The strength of association was greatest with incident clinical vertebral fractures (more than fivefold risk for height loss of 3.0 cm or greater). Results were similar when age and sex adjusted or adjusted for FRAX score.

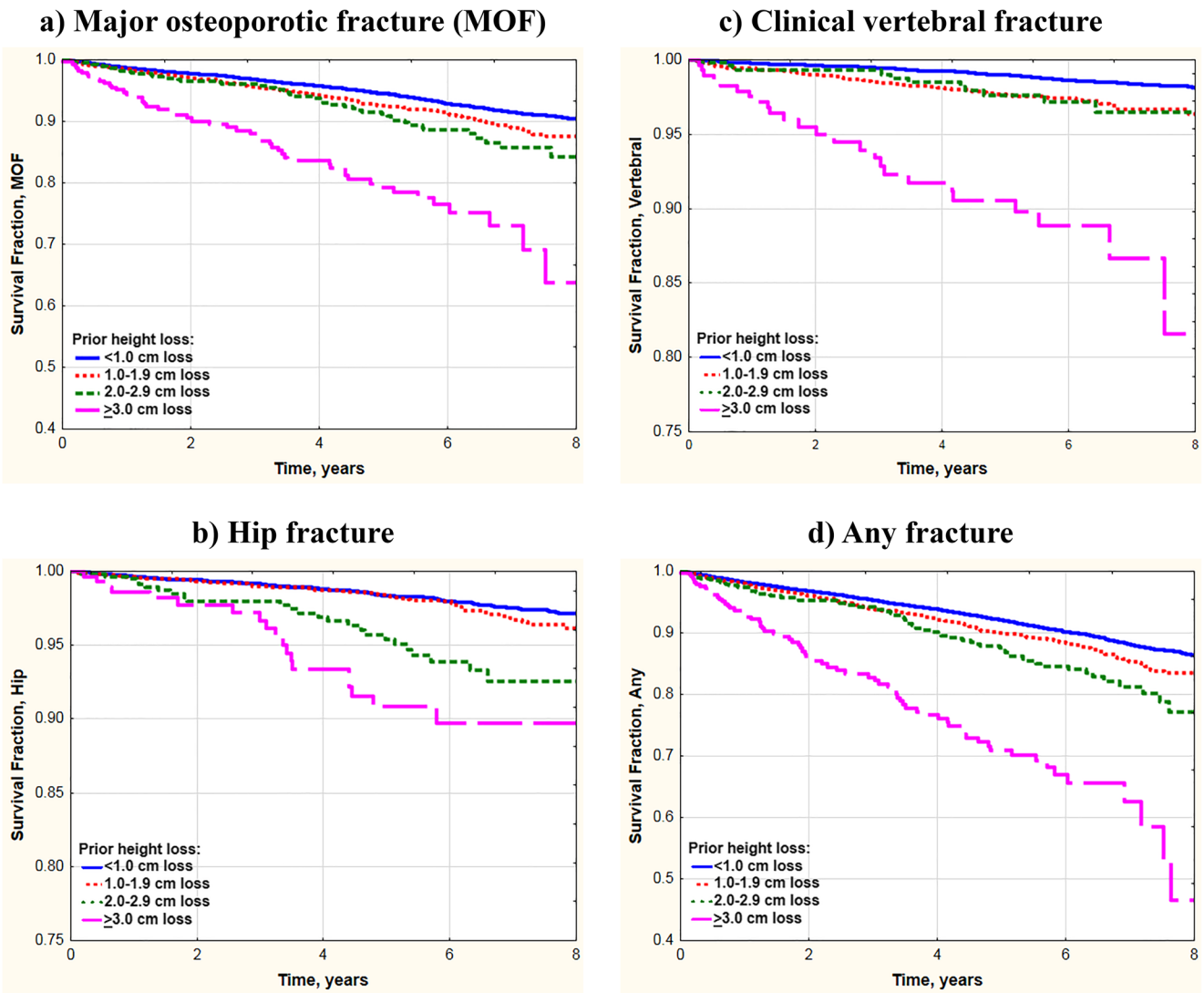

Fig. 2 Kaplan-Meier curves for fracture-free survival for incident fracture according to prior height loss as a categorical measure (**a**–**d**)

Table 4 Multivariable adjusted hazard ratios (HR) with 95% confidence interval (CI) for incident fracture according to prior height loss as categorical measure

	Incident MOF		Incident hip		Incident clinical vertebral		Incident any fracture	
Prior height loss	Age and sex adjusted HR (95% CI)	FRAX adjusted HR (95% CI)	Age and sex adjusted HR (95% CI)	FRAX adjusted HR (95% CI)	Age and sex adjusted HR (95% CI)	FRAX adjusted HR (95% CI)	Age and sex adjusted HR (95% CI)	FRAX adjusted HR (95% CI)
Less than 1.0 cm loss	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)
1.0–1.9 cm loss	*1.20 (1.02–1.41)*	*1.18 (1.01–1.39)*	1.00 (0.74–1.36)	1.03 (0.76–1.39)	*1.81 (1.32–2.47)*	*1.82 (1.33–2.49)*	1.14 (0.99–1.31)	1.12 (0.98–1.29)
2.0–2.9 cm loss	*1.40 (1.05–1.88)*	1.32 (0.99–1.77)	*2.05 (1.35–3.12)*	*2.00 (1.32–3.04)*	1.59 (0.87–2.9)	1.53 (0.84–2.79)	*1.41 (1.10–1.80)*	*1.34 (1.05–1.71)*
≥ 3.0 cm loss	*2.92 (2.18–3.91)*	*2.48 (1.85–3.31)*	*2.48 (1.52–4.04)*	*2.20 (1.35–3.57)*	*5.92 (3.75–9.35)*	*5.30 (3.37–8.35)*	*3.05 (2.38–3.91)*	*2.67 (2.08–3.42)*

Results from Cox regression models with height loss and weight loss both included in the models. Significant effects are in italics. *MOF*, major osteoporotic fracture; *BMD*, bone mineral density (femur neck). FRAX hip fracture probability was used for covariate adjustment in the incident hip fracture analysis; FRAX MOF probability was used for all other incident fracture analyses

Discussion

Our findings demonstrate a small but statistically significant increase in fracture risk related to previous height loss that was independent of other risk factors including the FRAX score and the association of height loss with increased mortality. This association was seen for a variety of fracture sites, and was strongest for incident clinical vertebral fractures. Height loss of 3.0 cm or greater more than doubled the risk for subsequent fracture. In contrast, previous weight loss was only significantly associated with incident hip fractures.

The association of height loss with vertebral fractures is well recognized and interpreted as vertebral fracture causing height loss, although most age-related height loss is actually not attributable to fractures [8–11]. The stronger association between prior height loss and clinical vertebral fracture in our study in part likely reflects height loss related to the vertebral fracture prior to its clinical recognition or as part of a vertebral fracture cascade, but this would not account for the associations with non-vertebral fractures, where the incident fracture event occurs subsequent to the height loss.

Height loss may also reflect increased kyphosis from loss of back extensor strength and/or degenerative disc disease, which then shifts moment arm of axial weight bearing more anteriorly, increasing compressive force on adjacent vertebrae that could lead to clinical vertebral fracture [25–27]. In addition, age-related hyperkyphosis and loss of back extensor muscle strength have been associated with significantly increased risk for falls [28–30]. The extent to which non-vertebral fracture risk reflects the risk associated with prior vertebral fracture versus other mechanisms cannot be answered from our study and would be an interesting area for future research.

Previous cohort studies have shown that height loss is associated with excess non-vertebral fractures, particularly hip fractures, in women and men [14, 15]. In 14,921 men and women from the Norfolk cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk) with two sets of height measurements (1993–1997 and 1997–2000), incident fractures during a mean follow-up period of 7.1 years to 2006 were significantly associated with annual height loss > 0.5 cm (age- and sex-adjusted HR for any fracture 1.76, 95% CI, 1.16–2.67, and for hip fracture 2.08, 95% CI, 1.07–4.05) compared with those with no height loss [14]. Each centimeter per year height loss was associated with a HR of 1.86 (95% CI, 1.28–2.72) for all fractures and 2.24 (95% CI, 1.23–4.09) for hip fracture after multivariate adjustment including heel ultrasound. A prospective study of 3145 community-dwelling Chinese women and men aged ≥ 65 years assessed height at baseline and 4 years later [15]. Height loss > 2 cm was associated with all fractures and hip fractures in women (adjusted HR 2.86 and 4.74, respectively) and hip fractures and all-cause mortality in men (adjusted HR 4.93 and 5.64, respectively). Our study shows that these findings are also applicable to height measurements collected in routine clinical practice. Moreover, absolute height change predicted fracture risk and annualized change, which may be more convenient for clinical application.

Ensrud et al. [31] have previously shown that older women experiencing weight loss have increased rates of BMD loss at the hip and a twofold greater risk of subsequent hip fracture. Crandall et al. [32] reported that weight loss was strongly

associated with hip fractures (medical record) in Women's Health Initiative (Observational and Clinical Trials), but had weaker and variable effects on other fractures (self-reported). These studies did not adjust for the effect of height loss. We confirmed the effect of prior weight loss on hip fracture risk, but found no consistent evidence for increased risk at other skeletal sites when adjusted for height loss and other covariates. Unintentional weight loss is considered part of the frailty phenotype, in addition to muscle weakness, slow walking speed, exhaustion, and low physical activity [33]. Frailty instruments based upon these parameters have been associated with increased risk for fracture including non-hip fracture [34, 35]. One day, the frailty phenotype could include height loss as part of a broader concept of "shrinkage."

Strengths of our study include the large population size, long-term follow-up, and large number of clinical fracture events observed. Limitations include reliance on linked administrative data for ascertainment of fractures, although the procedures used have been directly validated against x-ray confirmed fractures and adopted for a national osteoporosis surveillance program [19, 20, 36]. As a clinical registry, referral bias in baseline and subsequent DXA testing is to be expected. However, our cohort selection likely reflects routine clinical practice and therefore complements previous population-based cohort studies. We did not adjust for effects of anti-osteoporosis medication use since our objective was to examine FRAX-independent effects and we have previously found that treatment did not significantly affect predictions from FRAX [37]. Moreover, we saw no significant association between prior height loss and anti-osteoporosis medication use (data not shown). Lifestyle factors, including diet and exercise, are unavailable through administrative data. We also cannot determine whether weight loss was intentional or unintentional, though previous data suggest that these have similar effects on fracture risk [31, 32]. The study cohort was over ~95% women and ~98% of European ancestry, and it was therefore not possible to study subgroup differences related to sex or race/ethnicity.

In summary, prior height loss is associated with a small but significant increase in risk of fracture at all skeletal sites independent of other clinical risk factors and competing mortality as considered by FRAX. The strongest effect was on incident clinical vertebral fracture diagnosis. Prior weight loss only increases risk for subsequent hip fracture. Research is needed to delineate the pathogenetic pathways that explain why height loss is a marker for higher fracture risk. Meanwhile, this work supports a role for routine use of height measurement in clinical practice to identify individuals at increased risk for both vertebral and non-vertebral fracture.

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Compliance with ethical standards

Conflicts of interest Suzanne Morin: Nothing to declare for the context of this paper, but has received research grants: Amgen.

Eugene McCloskey: Nothing to declare for the context of this paper, but numerous ad hoc consultancies/speaking honoraria and/or research funding from Amgen, Bayer, General Electric, GSK, Hologic, Lilly, Merck Research Labs, Novartis, Novo Nordisk, Nycomed, Ono, Pfizer, ProStrakan, Roche, Sanofi-Aventis, Servier, Tethys, UBS, and Warner-Chilcott.

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Disclaimer The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, Seniors and Active Living, or other data providers is intended or should be inferred. This article has been reviewed and approved by the members of the Manitoba Bone Density Program Committee.

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