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ORIGINAL ARTICLE

Is repeated childhood fracture related to areal bone density or body composition in middle age?

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Abstract

Summary Childhood fracture is common, but whether it predicts adult fracture is not clear. Repeat childhood fracture was associated with adult (≤45 years) fracture, and in women, lower areal bone density was associated with repeat childhood fracture. Identifying fracture-prone children can modify adult fracture risk management.

Introduction A quarter of boys and 15% of girls will suffer multiple fractures, but it is not clear whether multiple fractures during growth predict fracture risk and areal bone density in adulthood. This study evaluated whether children who repeatedly fracture were at increased risk of low areal bone density, abnormal body composition, and fractures by age 45.

Methods A subsample of a large birth cohort study with childhood fracture cases had areal bone density assessed at age 45 years. Participants were questioned regularly across their lifetime about fractures during childhood (ages 0–18 years of age) and adulthood (any fracture between 18 and 45 years). The number of fractures was collapsed into three categories: no fractures; 1 fracture; and > 1 fracture, separately for child and adult groups.

Results At age 45 years, areal bone mineral density (g/cm^2) and body composition were measured with dual X-ray absorptiometry in $n=555$ participants. Compared to no fractures, twice as many girls (14% vs 7%, $P=0.156$) and boys (31.4% vs 14.1%, $P=0.004$) who repeatedly fractured in childhood sustained multiple fractures as adults. Both girls and boys who were fracture-free tended to remain fracture-free as adults (79.8% compared with 62.8%, $P=0.045$, and 64.8% compared with 51.4%, $P=0.025$, in males and females, respectively). Participants were more than twice as likely to fracture repeatedly as adults if they had sustained multiple fractures as a child (*OR* 2.5 95% *CI*: 1.4, 4.6). Women who repeatedly fractured during childhood had lower areal bone density, whereas repeated fracturing during childhood was not associated with areal bone density or body composition in men, even after adjustment for other factors known to influence fracture history.

Conclusion Childhood fracture history is associated with persistent skeletal fragility in adulthood (≤45 years), even after adjustment for behavioral and demographic factors known to influence fracture history.

Keywords Adult · Areal bone density · Body composition · DXA · Fracture · Longitudinal

Introduction

History of prior fracture is one of the strongest predictors of future fractures [1], yet current guidelines, including commonly used osteoporosis risk scores, ignore fractures that occur during childhood, despite their high frequency [2]. Approximately one in two children sustains a fracture during childhood, with almost a quarter of boys and 15% of girls suffering *multiple* fractures [3]. The background of repeated fractures in healthy children is insufficiently understood. Studies have shown associations between childhood fracture and higher levels of socioeconomic deprivation [4], high levels of vigorous exercise [5], high body mass

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index (BMI) and overweight status [6], vitamin D insufficiency [7], low calcium intakes, and physical abuse [8]. Children who fracture repeatedly may also have especially fragile skeletons, or they may be "accident-prone," or they may occur due to sport or physical activity that actually improves bone strength during growth [3]. It is unclear if childhood fractures are related to temporary reductions in bone strength during rapid growth or to skeletal weaknesses that persist into adulthood. Because achieving peak bone mass early in life is likely to reduce fracture risk later in life [9], it is important to identify factors during childhood that predict suboptimal peak bone mass in adulthood.

If low adult bone density has its antecedents in childhood, so too could abnormal body composition such as low muscle mass or low muscle and low bone and high fat mass. Recent research has demonstrated a close relation between skeletal muscle mass and bone mass across the lifecourse [10]. Children who fractured tended to have lower muscle mass and higher fat mass [11, 12] and during growth, bone mineral content is predominantly associated with changes in lean mass. Among adults, age-related loss of muscle mass is intricately linked with changes in bone mass [13] such that a fracture event promotes the decline in muscle function and the declining muscle function in older adults further increases the risk of falls and fractures [14].

Although some observational studies have demonstrated that bone size and shape tend to track through time [15, 16], and cross-sectional studies that have shown that volumetric bone mineral density and bone structure are less favorable in young adults with prior fracture [17, 18], no longitudinal study has investigated whether individuals who repeatedly fracture in childhood have altered bone density and/or body composition in adulthood.

The aims of the current study were to (1) compare adult (age 45 years) areal bone density, body composition, and adult fracture rates in those who did not repeatedly fracture during childhood to those who sustained more than one fracture during childhood (at age < 18 years) in a subsample of childhood fracture cases who were part of a birth cohort study and (2) examine the associations between demographic and behavioral factors (history of low birthweight, child and adult deprivation, sport participation, low self-control, and physical abuse) and fracture history.

Methods

Study design and population

Birth cohort

Participants in the current study consisted of a sample of childhood fracture cases identified from members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behavior in a representative birth cohort. The 1037 participants (91% of eligible births) who were born between April 1972 and March 1973 in Dunedin, New Zealand, became eligible for enrolment on the basis of residence in the province at the first assessment at age 3 years [19]. The cohort represents the full range of socioeconomic status (SES) in the general population of New Zealand's South Island and, as adults, matches the New Zealand National Health and Nutrition Survey on key adult health indicators (e.g., body mass index, smoking, and general practitioner visits) and the New Zealand Census of citizens of the same age on educational attainment [19]. Assessments, including questions about injuries and fractures, were performed at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 32, and 38 years and most recently (completed April 2019) at age 45 years, when 938 of the 997 participants (94.1%) still alive participated. Typically each participant was brought to the research unit for interviews and examinations. The Dunedin Study was approved by the NZ-Health and Disability Ethics Committee. Study members (or their parent/guardian for childhood data) gave informed consent before participating.

Childhood fracture cohort

This subsample included in the current study consists of fracture cases who were originally identified in a study investigating the proportion of children who remain fracture-free in childhood [3]. Of the 1037 participants in the Dunedin Study birth cohort, 601 were seen and interviewed about their injury status at every phase up to age 18 years. There was no evidence that the participants who were not seen at every phase differed from the 601 who were seen at every phase for either sex or SES [3].

Fracture history

Parents were asked to provide information about all injuries requiring medical attention during the first 5 years of their child's life. This request covered inpatient, outpatient, and general practitioner treatment. Thereafter, injury information was collected at each phase and covered the period of time since the previous assessment. Information was obtained about the nature of the injury and the age of the participant when the injury occurred. All fractures were given a separate code and the site of fracture was identified. Childhood fractures were defined as any fracture between ages 0 and 18 years of age, and adult fractures were defined as any fracture from 19 years onward. The number of reported fractures was collapsed into three categories: no fractures; one fracture; and more than one fracture, separately for child and adult fracture groups. No information concerning the

severity of trauma associated with individual fractures was available. We did not investigate the potential contribution of underlying medical conditions or medication use to fracture occurrence.

Bone parameters and body composition

At age 45 years, areal bone density at the proximal femur (femoral neck and total hip) and body composition, including total body fat and lean mass, were measured by DXA by one experienced operator after removing any jewelery and metal objects. Total body and hip scans were conducted according to manufacturer instructions (GE Lunar Prodigy; Madison, WI, USA; 16.0 enCore software version with CoreScan™) and areal bone density aBMD (g/cm^2), bone mineral content (BMC (g)), and area (cm^2) of the total hip and femoral neck were determined. Densitometry results were also reported as Z-scores for the total hip and femoral neck calculated using the combined US National Health and Nutrition Examination Survey (NHANES) III/Lunar reference database. The scanner was calibrated daily with bone phantoms provided by the manufacturer for quality assurance. Our DXA laboratory coefficients of variation (CVs) for repeat in vivo scans in adults for BMC (g) and area (g/cm^2), respectively, are 1.6% and 1.9% total body, 1.8% for total fat mass, 1.8% for percentage fat, and 1.0% for bone-free lean tissue mass.

Covariates

Childhood maltreatment

As previously described [20], the measure of childhood maltreatment included [1] maternal rejection assessed at age 3 years by observational ratings of mothers' interaction with the study children; [2] harsh discipline assessed at ages 7 and 9 years by parental report of disciplinary behaviors; [3] 2 or more changes in the child's primary caregiver; and [4] physical abuse and [5] sexual abuse reported by study members once they reached adulthood (and were able to give informed consent). For each child, the cumulative index counts the number of maltreatment indicators during the first decade of life.

Childhood self-control

The child's sustained self-control style was defined using an omnibus measure of self-control that comprised reports collected at ages 3, 5, 7, 9, and 11 years. These reports by researcher-observers, parents, teachers, and the children themselves assessed capacities including lack of control, impulsive aggression, hyperactivity, lack of persistence, inattention, and impulsivity. They were combined into a highly reliable composite measure for each study child (Cronbach's $\alpha = 0.86$) [21].

Club sport participation

Participation in sport was assessed in face-to-face interviews at ages 7 and 9 years. Parents of study members reported if their child was a member of and regularly attended a sports, dance, or gymnastics club, and study members reported their participation directly at ages 15, 18, and 21 years.

Socioeconomic status

Childhood SES was measured on a six-point scale assessing parents' self-reported occupational status [22]. The scale places each occupation into one of six categories (1 = professional, 6 = unskilled laborer) based upon the educational level and income associated with that occupation in data from the New Zealand census. The variable used in our analyses, childhood SES, was the average of the highest SES level of either parent, assessed repeatedly from the study members' birth through age 15 years [23]. At age 45 years, the SES of the study members was measured on a six-point scale that assessed self-reported occupational status and allocates each occupation to 1 of 6 categories (1 = unskilled laborer, 6 = professional). Homemakers and those not working were pro-rated based on their educational status according to criteria included in the New Zealand Socioeconomic Index 2006 (NZSEI-06) [24].

Anthropometry

BMI was calculated in kilograms per square meter (weight (kg)/height (m)^2) at age 45. Weight and height were measured at the research unit. Weight was recorded to the nearest 0.1 kg by using calibrated scales with the participants wearing only light clothing. Height was measured to the nearest millimeter by the Seca 264 Wireless Stadiometer (Seca™, Hanover, MD, USA).

Biomarkers

Blood samples were collected at age 45 years. The collection was performed between 4:15 pm and 4:45 pm for all participants. Blood samples were centrifuged at 3500 × g for 10 min. Serum was divided into aliquots and stored at (2–8 °C) until analysis. Serum 25 (OH) D was assessed by chemiluminescent microparticle immunoassay using Abbott Architect 25-OH vitamin D assay reagent. Serum calcium level was analyzed photometrically (5-nitro-5′-methyl-BAPTA and EDTA) using the cobas Calcium Gen.2 assay (Roche Diagnostics).

Statistical analyses

The final analytic dataset comprised of 555 (92.4%) study members who were included in the original childhood fracture subsample ($n = 601$) and had data collected on bone parameters and body composition at Phase 45. In total, 46 study members were excluded from this analysis because they were missing DXA data at age 45 years. Data on the complete birth cohort sample is included in Supplementary Table 1. To determine if those participants in the birth cohort who were not included in this analysis were different from those who were included, differences in demographic, anthropometric, childhood fractures, and total bone mass were assessed by a two-tailed *t*-test for continuous variables, chi-squared test for categorical variables, and Fisher's exact test for categorical variables with less than 10 in any cell. Statistically significant differences were present if $P < 0.05$.

All subsequent analyses were stratified by sex. The number of childhood fractures was collapsed into three categories: no fractures; one fracture; and more than one fracture. Differences between these fracture groups were assessed in terms of variables measured in childhood (childhood SES, sport participation, childhood self-control, childhood maltreatment) and adulthood (adult fractures between ages 19 and 45 years, SES, BMI, weight status, serum vitamin D and calcium at age 45 years). Differences were assessed by an *F*-test from a oneway ANOVA for continuous variables, chi-squared test for categorical variables, and Fisher's exact test for categorical variables with less than 10 in any cell.

Differences in body composition variables between fracture groups (both childhood and adult) were estimated using a linear regression model with the body composition variable as the dependent variable and fracture group as the independent variable. All analyses were adjusted for the pre-specified covariates of childhood maltreatment, low self-control in childhood, and sports participation. Mean (SD) of the body composition variable in the no fracture group was reported, then the mean difference (95% *CI*) from this group was reported for the one fracture and multiple fracture groups. As the objective was to estimate differences between the groups, *P*-values were not reported for associations with body composition [25] and no adjustment for multiple tests was applied [26]. Residuals of all models were plotted and assessed for homogeneity of variance and normality.

To determine the odds of having no, one, or multiple fractures up to age 45 years if one or multiple fractures occurred in childhood, logistic regression models were used for each adult fracture group (using dummy variables). The first model did not include any covariates; the second model aimed to assess if the relationship between child and adult fractures was independent of childhood maltreatment, low self-control in childhood, sports participation, and areal bone density (assessed using total body Z-score) by including these variables as covariates. Odds ratios and 95% *CI* were reported. For illustrative purposes, adjusted odds ratios and 95% *CI* for male and female participants together were plotted as a forest plot. All analyses were checked for reproducibility by an independent data analyst, who recreated the code by working from the manuscript and applied it to a fresh copy of the dataset. Statistical analyses were performed with Stata (16.1, StataCorp, College Station, TX). The project and analysis plan were preregistered (2018; https://dunedinstudy.otago.ac.nz/for-investigators).

Results

There was no evidence that included ($n = 555$) and excluded ($n = 482$) birth cohort study members differed in terms of demographic or anthropometric measures, childhood fractures, or total bone mass (all $P > 0.05$). Three fracture groups were created, children who did not fracture ($n = 286$), those who suffered 1 fracture ($n = 156$), and those who suffered more than 1 fracture ($n = 113$).

There was no evidence for differences between serum vitamin D, calcium, or any social, demographic, or physiological factor among females and males that did not fracture in childhood compared to those that sustained only one fracture or those that repeatedly fractured (Tables 1 and 2). However, among females (albeit not statistically significant), about twice as many girls who repeatedly fractured in childhood sustained multiple fractures as adults (14.0% vs 7.0%, $P = 0.156$). Similarly, those who did not sustain a fracture in childhood also tended to remain fracture-free as adults (Table 1). Among males, a similar pattern emerged, with more than twice as many males repeatedly fracturing in childhood also repeatedly fracturing as adults (31.4% vs 14.1%, $P = 0.004$). Those who did not sustain a fracture in childhood also tended to remain fracture-free as adults (64.8% compared with 51.4% in those with repeated fractures, $P = 0.025$) (Table 2).

Although body composition was similar between fracture groups among females (Table 3), those who sustained multiple fractures in childhood had significantly lower bone mineral density at the total hip and neck of femur (Table 3) and significantly lower Z-scores at these sites at age 45 years (Table 3). Females who sustained a single fracture in up to age 45 years had significantly lower total hip areal bone mineral density and lower Z-scores at the total hip (Table 3) than females with no childhood fractures. Body composition and areal bone density were not significantly different between any of the male fracture groups in childhood and at age 45 years (Table 4).

As the patterns were similar between males and females (Supplementary Table 2), the groups were combined to determine the odds of having no adult fractures

Table 1 Characteristics of female participants by fracture history in childhood ($n = 274$)

Characteristic		Mean (SD) or *n* (%) as specified				*P*-value for difference between fracture groups[a]
		All ($n = 274$)	No fractures in childhood ($n = 158$)	One fracture in childhood ($n = 73$)	Multiple fractures in childhood ($n = 43$)	
Age (years), mean (SD)		44.7 (0.6)	44.7 (0.6)	44.7 (0.6)	44.8 (0.5)	0.637
Average SES at 15 years of age[b], *n* (%)						
	Low	55 (20.2)	31 (19.6)	16 (22.2)	8 (18.6)	0.891
	Medium	177 (64.8)	105 (66.5)	44 (61.1)	28 (65.1)	0.733
	High	41 (15.0)	22 (13.9)	12 (16.7)	7 (16.3)	0.840
Average SES at 45 years of age[b], *n* (%)						
	Low	43 (15.7)	25 (15.8)	13 (17.8)	5 (11.6)	0.695
	Medium	128 (46.7)	72 (45.6)	34 (46.6)	22 (51.2)	0.808
	High	103 (37.6)	61 (38.6)	26 (35.6)	16 (37.2)	0.908
Birthweight (kg), mean (SD)		3.33 (0.50)	3.32 (0.49)	3.32 (0.50)	3.37 (0.52)	0.849
BMI (kg/m^2), mean (SD)		28.4 (6.4)	28.2 (6.1)	29.3 (7.1)	27.6 (6.3)	0.341
Weight status, *n* (%)						
	Underweight (BMI < 18.5 kg/m^2)	2 (0.7)	0	1 (1.4)	1 (2.3)	
	Healthy weight (BMI ≥ 18.5 and < 25 kg/m^2)	94 (34.3)	57 (36.1)	21 (28.8)	16 (37.2)	0.503
	Overweight (BMI ≥ 25 and < 30 kg/m^2)	82 (29.9)	48 (30.4)	20 (27.4)	14 (36.6)	0.827
	Obese (BMI ≥ 25 kg/m^2)	96 (35.0)	53 (33.5)	31 (42.5)	12 (27.9)	0.236
Childhood abuse, *n* (%)						
	None	178 (65.0)	108 (68.4)	43 (58.9)	27 (62.8)	0.356
	Probable	65 (23.7)	34 (21.5)	20 (27.4)	11 (25.6)	0.591
	Severe	31 (11.3)	16 (10.1)	10 (13.7)	5 (11.6)	0.719
Low self-control[d], mean (SD)		−0.24 (0.77)	−0.26 (0.75)	−0.30 (0.67)	−0.08 (0.97)	0.296
Participation in sports, *n* (%)		233 (85.0)	136 (86.1)	60 (82.2)	37 (86.1)	0.707
Adult fractures to 45 years, *n* (%)						
	No adult fractures	204 (74.5)	126 (79.8)	51 (69.9)	27 (62.8)	0.045
	One adult fracture	43 (15.7)	21 (13.3)	12 (16.4)	10 (23.3)	0.281
	More than one adult fractures	27 (9.9)	11 (7.0)	10 (13.7)	6 (14.0)	0.156

[a]*P*-value from ANOVA *F*-test for continous variables, chi-squared test for categorical variables, and Fisher's exact test for categorical variables with less than 10 in any cell. [b]*SES*, socio-economic status; low: category 1 or 2; medium: category 3 or 4; high: category 5 or 6. [d]Children's self-control measured using nine measures of self-control: observational ratings of children's lack of control (3 and 5 years of age) and parent, teacher, and self-reports of impulsive aggression, hyperactivity, lack of persistence, inattention, and impulsivity (5, 7, 9, and 11 years of age)[26] (continuous scale used). [e]Collected at age 45 years. [f]Evidence of childhood maltreatment during the first decade of life (ages 3 to 11 years and retrospectively at age 26 years)[59]. [g]Participation in sport, dance, or gymnastics as part of a club or group (outside of school) assessed at ages 7, 9, 15, 18, and 21 years

(≤ 45 years), one adult fracture (≤ 45 years), or multiple adult fractures (≤ 45 years) by childhood fracture history. These were illustrated in a forest plot (Fig. 1), which shows that, compared to having no fractures in childhood, there was an increased odds of having multiple fractures in adulthood (≤ 45 years) with either one or multiple childhood fractures (*OR* 2.5, 95% *CI* 1.4, 4.3 and *OR* 2.5, 95% *CI* 1.4, 4.6, respectively).

Table 2 Characteristics of male participants by fracture history in childhood ($n=281$)

Characteristic		Mean (SD) or *n* (%) as specified				*P*-value for difference between fracture groups[a]
		All ($n=281$)	No fractures in childhood ($n=128$)	One fracture in childhood ($n=83$)	Multiple fractures in childhood ($n=70$)	
Age (years), mean (SD)		44.8 (0.6)	44.7 (0.6)	44.8 (0.6)	44.9 (0.6)	0.230
Average SES at 15 years of age[b], *n* (%)						
	Low	47 (16.7)	21 (16.4)	15 (18.1)	11 (15.7)	0.919
	Medium	189 (67.3)	85 (66.4)	55 (66.3)	49 (70.0)	0.853
	High	45 (16.0)	22 (17.2)	13 (15.7)	10 (14.3)	0.863
Average SES at 45 years of age[b], *n* (%)						
	Low	57 (20.3)	27 (21.1)	20 (24.1)	10 (14.3)	0.308
	Medium	136 (48.4)	62 (48.4)	37 (44.6)	37 (52.9)	0.594
	High	88 (31.3)	39 (30.5)	26 (31.3)	23 (32.9)	0.942
Birthweight (kg), mean (SD)		3.46 (0.54)	3.43 (0.53)	3.44 (0.52)	3.54 (0.56)	0.385
BMI[e] (kg/m^2), mean (SD)		28.5 (4.6)	28.5 (4.9)	28.1 (4.2)	28.9 (4.5)	0.572
Weight status, *n* (%)						
	Underweight (BMI < 18.5 kg/m^2)	0	0	0	0	
	Healthy weight (BMI ≥ 18.5 and < 25 kg/m^2)	62 (22.1)	31 (24.2)	19 (22.9)	12 (17.1)	0.505
	Overweight (BMI ≥ 25 and < 30 kg/m^2)	125 (44.5)	56 (43.8)	38 (45.8)	31 (44.3)	0.958
	Obese (BMI ≥ 25 kg/m^2)	94 (33.5)	41 (32.0)	26 (31.3)	27 (38.6)	0.574
Childhood abuse[f], *n* (%)						
	None	192 (68.3)	86 (67.2)	52 (62.7)	54 (77.1)	0.148
	Probable	73 (26.0)	35 (27.3)	25 (30.1)	13 (18.6)	0.239
	Severe	16 (5.7)	7 (5.5)	6 (7.2)	3 (4.3)	0.801
Low self-control[d], mean (SD)		0.07 (0.97)	−0.04 (0.88)	0.18 (1.05)	0.14 (1.02)	0.225
Sports participation[g], *n* (%)		247 (87.9)	110 (85.9)	73 (88.0)	64 (91.4)	0.564
Adult fractures to 45 years, *n* (%)						
	No adult fractures	158 (56.2)	83 (64.8)	39 (47.0)	36 (51.4)	0.025
	One adult fracture	58 (20.6)	27 (21.1)	19 (22.9)	12 (17.1)	0.672
	More than one adult fracture	65 (23.1)	18 (14.1)	25 (30.1)	22 (31.4)	0.004

[a]*P*-value from ANOVA *F*-test for continous variables, chi-squared test for categorical variables, and Fisher's exact test for categorical variables with less than 10 in any cell. [b]*SES*, socio-economic status; low: category 1 or 2; medium: category 3 or 4; high: category 5 or 6. [d] Children's self-control was measured using nine measures of self-control: observational ratings of children's lack of control (3 and 5 years of age) and parent, teacher, and self-reports of impulsive aggression, hyperactivity, lack of persistence, inattention, and impulsivity (5, 7, 9, and 11 years of age)[(26)] (continuous scale used). [e]Collected at age 45 years. [f]Evidence of childhood maltreatment during the first decade of life (ages 3 to 11 years and retrospectively at age 26 years)[(59)]. [g]Participation in sport, dance, or gymnastics as part of a club or group (outside of school) assessed at ages 7, 9, 15, 18, and 21 years

Discussion

Children who sustained multiple fractures before the age of 18 years suffered more fractures as adults up to age 45 years, with the converse also being true; those who were fracture-free as children also tended to remain fracture-free as adults (≤45 years). However, repeated fracturing during childhood was not associated with areal bone density or body composition in men, even after adjustment for other factors known to influence fracture history. In contrast, women who repeatedly fracture during childhood had lower areal bone density at the hip in early middle age. Because the relation between child and adult fracture (≤45 years) history does not appear to be influenced by differences in areal bone

Table 3 Differences in body composition and bone density at age 45 years between women with and without single or multiple fractures in childhood (upper half) and adulthood (lower half, $n=274$) compared to those who did not fracture

	No fractures in **childhood**, mean (SD) ($n=158$)	Mean difference (95% *CI*) for those with a single fracture in **childhood** ($n=73$) compared to no fractures	Mean difference (95% *CI*) for those with multiple fractures in **childhood** ($n=43$) compared to no fractures
Total fat mass (kg)	29.2 (12.8)	2.0 (−1.8, 5.8)	−1.2 (−5.8, 3.4)
Total lean mass (kg)	45.3 (6.1)	0.1 (−1.5, 1.8)	−0.2 (−2.2, 1.8)
Total body %fat	0.36 (0.08)	0.01 (−0.02, 0.03)	−0.01 (−0.04, 0.02)
Total body BMD (g/cm^2)	1.24 (0.12)	−0.02 (−0.05, 0.02)	−0.02 (−0.06, 0.02)
Total body BMC (g)	2521 (337)	−57 (−147, 33)	−43 (−152, 67)
Total Z-score	1.56 (1.14)	−0.17 (−0.47, 0.14)	−0.21 (−0.59, 0.16)
Total hip BMD (g/cm^2)	1.07 (0.15)	−0.03 (−0.07, 0.01)	**−0.05 (−0.10, −0.005)**
Neck BMD (g/cm^2)	1.02 (0.14)	−0.03 (−0.07, 0.001)	**−0.05 (−0.09, −0.003)**
Neck BMC (g)	4.96 (0.74)	**−0.22 (−0.41, −0.02)**	−0.14 (−0.38, 0.10)
Total hip BMC (g)	33.6 (5.6)	−1.3 (−2.7, 0.2)	−1.7 (−3.4, 0.1)
Neck Z-score	0.47 (1.00)	−0.25 (−0.51, 0.01)	**−0.34 (−0.65, −0.02)**
Total hip Z-score	0.74 (1.16)	−0.26 (−0.56, 0.05)	**−0.40 (−0.78, −0.03)**
LMI (kg/m^2)	16.6 (1.9)	0.2 (−0.3, 0.8)	−0.2 (−0.9, 0.4)
FMI (kg/m^2)	10.7 (4.7)	0.8 (−0.6, 2.2)	−0.6 (−2.2, 1.1)
App lean (kg)	20.4 (3.4)	0.1 (−0.8, 1.1)	−0.2 (−1.4, 0.9)
App LMI(kg/m^2)	7.5 (1.1)	0.1 (−0.2, 0.4)	−0.2 (−0.5, 0.2)
	No fractures in **adulthood**, mean (SD) ($n=158$)	Mean difference (95% *CI*) for those with a single fracture in **adulthood** ($n=73$) compared to no fractures	Mean difference (95% *CI*) for those with multiple fractures in **adulthood** ($n=43$) compared to no fractures
Total bone mass (g)	2484 (310)	6 (−98, 109)	62 (−65, 189)
Total fat mass (kg)	28.8 (13.0)	3.5 (−1.0, 8.0)	2.6 (−2.9, 8.1)
Total lean mass (kg)	44.9 (5.9)	0.9 (−1.1, 2.9)	1.8 (−0.6, 4.2)
Total region %fat	0.36 (0.09)	0.02 (−0.01, 0.05)	0.01 (−0.03, 0.04)
Total body BMD (g/cm^2)	1.23 (0.11)	−0.01 (−0.05, 0.03)	0.00 (−0.04, 0.05)
Total body BMC (g)	2484 (310)	30 (−76, 137)	63 (−68, 193)
Total Z-score	1.5 (1.1)	−0.2 (−0.5, 0.2)	0.0 (−0.4, 0.5)
Total hip BMD (g/cm^2)	1.05 (0.14)	**−0.05 (−0.09, −0.003)**	0.02 (−0.03, 0.08)
Neck BMD (g/cm^2)	1.01 (0.13)	−0.04 (−0.08, 0.01)	0.02 (−0.03, 0.07)
Neck BMC (g)	4.9 (0.7)	−0.1 (−0.3, 0.2)	0.1 (−0.2, 0.4)
Total hip BMC (g)	32.9 (5.4)	−0.8 (−2.6, 0.9)	1.5 (−0.6, 3.7)
Neck Z-score	0.4 (1.0)	−0.3 (−0.6, 0.02)	0.1 (−0.3, 0.5)
Total hip Z-score	0.6 (1.1)	**−0.4 (−0.8, −0.1)**	0.2 (−0.3, 0.6)
LMI (kg/m^2)	16.5 (1.9)	0.1 (−0.5, 0.7)	0.6 (−0.2, 1.3)
FMI (kg/m^2)	10.6 (4.8)	1.2 (−0.5, 2.8)	0.9 (−1.1, 2.9)
App lean (kg)	20.2 (3.3)	0.6 (−0.5, 1.7)	1.0 (−0.4, 2.4)
App LMI (kg/m^2)	7.4 (1.1)	0.1 (−0.2, 0.5)	0.3 (−0.1, 0.8)

[a]Estimated with a regression model adjusted for childhood maltreatment, low self-control, and sports participation. Bolded numbers represent significant differences. *LMI*, lean mass index; *FMI*, fat mass index; *App lean*, appendicular lean mass; *App LMI*, appendicular lean mass index

density, demographics, psychosocial factors, or participation in sports, our results suggest that persistent skeletal fragility can track into early middle age.

Previous work has consistently demonstrated that the bones of children and adolescents who fracture during growth have an intrinsic structural deficit compared with their counterparts who do not fracture [11, 27, 28]. Studies suggest these children are more accident prone [6], engage in higher risk activities [29], and have lower bone mineral density at baseline than fracture-free children or children who suffer only a single fracture [6]. Whatever the reason, there is increasing evidence that children who have multiple fractures become adults with low bone density and increased risk for further fractures [30]. Although several studies have

Table 4 Differences in body composition and bone density at age 45 years between men with and without single or multiple fractures in childhood and adulthood ($n = 281$)

	No fractures in **childhood**, mean (SD) ($n = 128$)	Mean difference (95% *CI*)[a] for those with a single fracture in **childhood** ($n = 83$) compared to no fractures	Mean difference (95% *CI*)[a] for those with multiple fractures in **childhood** ($n = 70$) compared to no fractures
Total fat mass (kg)	26.0 (10.4)	− 1.1 (− 3.9, 1.7)	0.6 (− 2.4, 3.5)
Total lean mass (kg)	61.1 (7.8)	− 0.7 (− 2.9, 1.4)	1.8 (− 0.5, 4.0)
Total body % fat	0.28 (0.07)	− 0.01 (− 0.02, 0.01)	0.00 (− 0.02, 0.02)
Total body BMD (g/cm^2)	1.35 (0.12)	− 0.01 (− 0.05, 0.02)	− 0.01 (− 0.04, 0.03)
Total body BMC (g)	3210 (402)	− 36 (− 152, 81)	34 (− 90, 157)
Total Z-score	1.50 (1.21)	− 0.15 (− 0.50, 0.19)	− 0.08 (− 0.45, 0.28)
Total hip BMD (g/cm^2)	1.08 (0.14)	0.00 (− 0.04, 0.04)	− 0.02 (− 0.06, 0.02)
Neck BMD (g/cm^2)	1.03 (0.14)	− 0.01 (− 0.05, 0.03)	− 0.02 (− 0.06, 0.02)
Neck BMC (g)	5.74 (0.89)	− 0.03 (− 0.28, 0.22)	− 0.07 (− 0.33, 0.20)
Total hip BMC (g)	40.6 (5.9)	0.7 (− 1.1, 2.4)	− 0.1 (− 1.9, 1.7)
Neck Z-score	0.16 (1.08)	− 0.09 (− 0.38, 0.21)	− 0.18 (− 0.49, 0.13)
Total hip Z-score	0.16 (0.97)	− 0.03 (− 0.31, 0.25)	− 0.15 (− 0.45, 0.14)
LMI (kg/m^2)	19.2 (2.1)	− 0.15 (− 0.71, 0.41)	0.41 (− 0.18, 1.01)
FMI (kg/m^2)	8.2 (3.3)	− 0.36 (− 1.23, 0.51)	0.12 (− 0.80, 1.05)
App lean (kg)	28.8 (4.3)	− 0.6 (− 1.8, 0.6)	1.1 (− 0.2, 2.3)
App LMI (kg/m^2)	9.0 (1.2)	− 0.2 (− 0.5, 0.2)	0.3 (− 0.1, 0.6)
	No fractures in **adulthood**, mean (SD) ($n = 158$)	Mean difference (95% *CI*)[a] for those with a single fracture in **adulthood** ($n = 58$) compared to no fractures	Mean difference (95% *CI*)[a] for those with multiple fractures in **adulthood** ($n = 65$) compared to no fractures
Total bone mass (g)	3241 (402)	− 57 (− 183, 70)	− 60 (− 181, 65)
Total fat mass (kg)	26.7 (10.2)	− 1.5 (− 4.6, 1.5)	− 2.0 (− 5.0, 0.9)
Total lean mass (kg)	61.6 (7.6)	− 1.5 (− 3.8, 0.9)	0.0 (− 2.3, 2.3)
Total region %fat	0.28 (0.07)	− 0.01 (− 0.03, 0.01)	− 0.02 (− 0.04, 0.003)
Total body BMD (g/cm^2)	1.35 (0.12)	− 0.02 (− 0.06, 0.02)	− 0.02 (− 0.05, 0.02)
Total body BMC (g)	3234 (401)	− 50 (− 176, 77)	− 51 (− 174, 73)
Total Z-score	1.52 (1.16)	− 0.19 (− 0.56, 0.19)	− 0.17 (− 0.54, 0.19)
Total hip BMD (g/cm^2)	1.08 (0.14)	0.01 (− 0.04, 0.05)	− 0.03 (− 0.07, 0.01)
Neck BMD (g/cm^2)	1.03 (0.14)	0.01 (− 0.04, 0.05)	− 0.03 (− 0.07, 0.01)
Neck BMC (g)	5.74 (0.86)	0.06 (− 0.21, 0.33)	− 0.14 (− 0.40, 0.12)
Total hip BMC (g)	41.0 (6.3)	0.0 (− 1.9, 1.9)	− 0.8 (− 2.6, 1.1)
Neck Z-score	0.14 (1.06)	0.04 (− 0.28, 0.36)	− 0.23 (− 0.54, 0.08)
Total hip Z-score	0.16 (1.00)	0.04 (− 0.26, 0.34)	− 0.21 (− 0.50, 0.08)
LMI (kg/m^2)	19.3 (2.0)	− 0.4 (− 1.0, 0.2)	0.2 (− 0.4, 0.8)
FMI (kg/m^2)	8.4 (3.2)	− 0.5 (− 1.4, 0.5)	− 0.6 (− 1.5, 0.4)
App lean (kg)	29.0 (4.2)	− 0.6 (− 1.9, 0.7)	0.0 (− 1.3, 1.3)
App LMI (kg/m^2)	9.1 (1.1)	− 0.2 (− 0.5, 0.2)	0.1 (− 0.2, 0.4)

[a] Estimated with a regression model adjusted for childhood maltreatment, low self-control, and sports participation. *LMI*, lean mass index; *FMI*, fat mass index; *App lean*, appendicular lean mass; *App LMI*, appendicular lean mass index

sought to determine whether children who sustain a single fracture during childhood have skeletal fragility that persists into adulthood [17, 31–36], ours is the first study to demonstrate an increased risk of adult fracture (≤ 45 years) in both males and females who *repeatedly* fracture in childhood.

Conflicting evidence has been published among the few studies that have shown an association between single fractures during growth and adult bone fragility, with some reports indicating that fractures sustained during growth are associated with an increased risk of fragility fractures in adulthood [31–33, 37, 38], whereas others found no associations [39, 40]. Further muddying the waters, reported associations have been found for both sexes [33], only for females [41], or only for males [17]. However, the

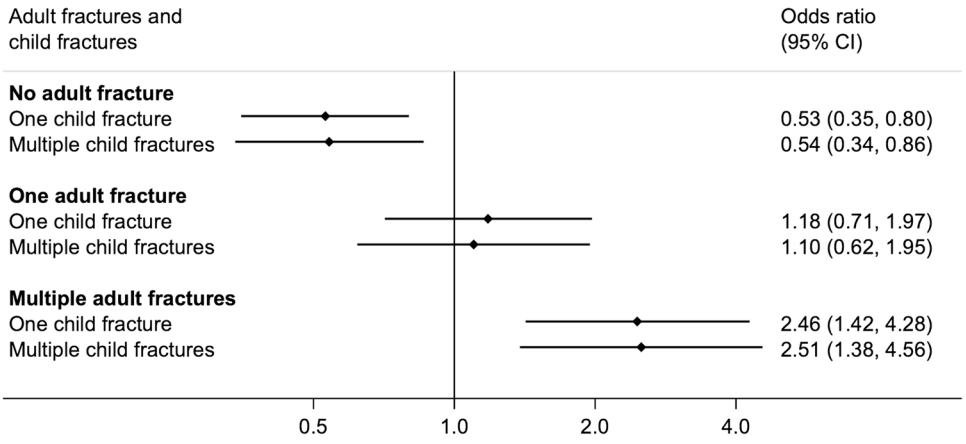

Fig. 1 Odds ratios (95% *CI*) of adult fractures by childhood fracture groups compared to those with no childhood fractures ($n=555$). Adjusted for child abuse, low self-control, sports participation, total hip T-score, and sex

majority of these studies were cross-sectional [31, 33, 37, 41, 42] and involved small samples [17, 33, 41, 42].

In the present study, the odds of sustaining multiple fractures as an adult (≤45 years) were significantly higher if a person had sustained at least one childhood fracture. Importantly, this risk did not appear to be explained by differences in areal bone density, demographics, psychosocial factors, or participation in sports. Large-scale studies in adults [43] and children [44] have shown that the best predictor of future fracture risk is prior fracture at any skeletal site, independent of bone mineral density and after adjustment for sex and several other confounders [44]. These conclusions have been based on studies predominantly limited to ages < 18 years or > 65 years, or studies using short endpoints when bones may not have reached peak bone mass.

In our study, areal bone density was not significantly different between any of the male fracture groups at age 45 years. However, among females, childhood fractures were related to lower areal bone mineral density at the hip. There was also a lower childhood fracture rate in females (42%) than in males (54%), which suggests that the determinants of fractures might differ between sexes. The occurrence of fractures in childhood or adolescence as an early marker of low aBMD in adulthood has been demonstrated in other studies [17, 32, 41]. Other studies that have prospectively followed children with fractures into young adulthood all suggest that low aBMD found at the time of fracture persists for years post-injury [17, 45]. However, again, the follow-up periods in these studies are short and often end before peak bone mass would be reached [45] or after age-related bone loss accelerates, typically at about age 50 [46].

In terms of body composition, our results contrast with recent research that has demonstrated a close relationship between skeletal muscle mass and bone mass that exists throughout the lifecourse [10]. However, only one other small study ($n=75$) has investigated the relation between childhood fracture and abnormal adult body composition and demonstrated relationships between moderate trauma distal forearm fracture and low body fat and high lean mass in females and high body fat in males compared to sex matched controls [33]. However, this was a small sample, restricting their investigation to distal forearm fractures, rather than fractures at any site. No information concerning the severity of trauma associated with individual fractures was available in the current study, which may limit our ability to make comparisons. Given previous research has demonstrated associations between childhood fracture and low muscle mass and high fat mass [6], and that in adults, age-related loss of muscle mass is associated with changes in bone mass [13], future research will be necessary to elucidate the role body composition plays in determining peak bone density and fracture risk.

Our study has several strengths. Although our results are based on self-report data, detailed face-to-face interviews were conducted with study members at 2 yearly intervals during childhood (or 3 year interval from age 15 years) to assess injury status throughout childhood which should reduce recall bias. Medical records were also checked against questionnaire reports when the study members were 13 years old [47] and again at age 45 years old; 86% of fractures were recalled at age 13 and 85% at age 45. At age 13, recall was inversely related to the number of injury events, suggesting that the number of fractures reported in the current study may be underestimated. Although only 55.6% of the children seen at age 5 years provided complete data about fracture history at every phase of the study, there was no evidence of selective attrition; specifically, study members did not differ in terms of demographic and anthropometricy measures, the frequency of childhood fractures, or total bone mass, which suggests that those with missing data were missing at random (MAR). This finding reduces the likelihood of bias when doing a complete case analysis to estimate the relationship between the number of fractures in childhood and bone outcomes (as measured by DXA) [48]. Our study also has some limitations. The study population is predominantly NZ

European but represents the full range of socioeconomic status of the general population of New Zealand's South Island. Although the sample differs slightly from the ethnic distribution for the New Zealand-wide population, average fracture rates for Europeans are approximately 30% higher than for Maori, Pacific, and Asian peoples and Maori and Pacific peoples tend to have greater bone density than people of NZ Europeans [49]. Although this is observational research and causal mechanisms cannot be directly inferred, causal studies on fractures cannot ethically be undertaken. Therefore, longitudinal evidence such as this provides important information to understanding the effects of fractures. We also did not include data on parity, age of menarche/menstrual status in females, or menopausal status and only assessed adult BMI and body composition. However, only 13 of the sample were menopausal and after further adjusting for menopause, no meaningful difference to the estimates was found (data not shown). However, we recognize that we are unable to account for all the possible confounders throughout life. Finally, our analyses are limited to age 45 years and therefore cannot address effects of childhood fracture on lifelong fracture risk or postmenopausal fracture risk for women.

Conclusion

The occurrence of multiple fractures in childhood more than doubles the odds of future fractures by middle age. The increased risk was independent of differences in psychosocial risk factors (e.g., childhood maltreatment and/or low self-control), participation in sports, body composition, or differences in areal bone density. Children who sustain multiple fractures before peak bone mass is attained should be informed about their risk for future fractures.

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Declarations

Conflicts of interest None.

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