

# Growth in childhood predicts hip fracture risk in later life

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## Abstract

**Summary** The incidence of hip fracture was estimated in 6,370 women born in Helsinki between 1934 and 1944. Women in the lowest quarter of adiposity gain had an 8.2-fold increase in hip fracture risk compared with those in the highest quarter ( $p < 0.001$ ). These data point to a relationship between childhood growth and fracture risk during later life.

**Introduction** Previous findings show that discordance between childhood increase in height and weight is associated with an increased risk of osteoporotic fractures during later life.

**Methods** We studied 6,370 women born in Helsinki between 1934 and 1944. Each woman's birth weight and length at birth was recorded, as well as her height and weight through childhood. We identified the occurrence of hip fracture through the National Finnish Hospital discharge register.

**Results** There were 49 hip fractures in the 6,370 women over 187,238 person-years of follow-up. Hip fracture was associated with increasing Z-scores for height between 1 and 12 years, not matched by a corresponding increase in weight. Therefore, reduction in the Z-score for body mass index was associated with increased risk of hip fracture. Women in the lowest quarter of change in Z-scores for body mass index had an 8.2-fold increase in hip fracture risk (95% CI 1.9 to 35), compared with those in the highest quarter ( $p < 0.001$ ).

**Conclusion** Thinness in childhood is a risk factor for hip fracture in later life. This could be a direct effect of low fat mass on bone mineralization, or represent the influence of altered timing of pubertal maturation.

**Keywords** Developmental origins · Epidemiology · Hip fracture · Osteoporosis

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## Introduction

Osteoporosis and its related fractures are an important cause of morbidity and mortality worldwide [1–3], and there is an urgent need to develop strategies that prevent or delay their onset. The risk of hip fracture is dependent upon bone mass at the proximal femur [4], which tracks throughout adult life [5]. It has been estimated that peak bone mass during young adulthood accounts for around 60% of the variation in bone mass through adult life [6]. Measures to enhance bone mineralization during childhood and augment peak bone mass, for example by dietary supplementation with calcium and exercise programmes, have been widely proposed as preventive measures against osteoporotic fracture [7–9]. However, there are few published data directly linking growth rates in childhood with the later risk of osteoporosis, and in particular with the later risk of hip fracture, the most important clinical consequence of the disorder.

Recent studies suggest that the intrauterine and early postnatal environment may influence the incidence of osteoporotic fracture. Maternal smoking, nutrition and physical activity have all been linked with bone mass of the offspring at birth [10] and during childhood [11]. Retrospective cohort studies have also demonstrated that weight in infancy is positively correlated with bone mass in adulthood. In a previous cohort study, we reported that reduced childhood growth between age 7 and 15 years is associated with an increased risk of hip fracture in later life [12]. We here extend these findings, by describing the associations between hip fracture and growth from birth to age 12 years.

## Subjects and methods

We studied 6,370 women born in Helsinki University Central Hospital or the Helsinki City Maternity Hospital between 1934 and 1944, who visited child welfare clinics, who went to school in the city and who were still resident in Finland in 1971. The birth records included neonatal length and weight as well as maternal age, parity, height and weight at the time of delivery. The study methods and growth measurements have been described in detail [13]. The median number of visits to the clinic was eight in the first year of life, two more before age 6. There was a median of eight recordings of height and weight at school between 7 and 12 years.

In 1971, all residents of Finland were assigned a unique personal identification number. Using this number, we linked the girl's growth data to the national hospital discharge register from 1971 to 2003. The maximal age at follow-up was 70 years. Using the personal identification number, we identified the first hospital admission for hip fracture according to ICD 9 code 820 and ICD 10 code

S72. Using the father's occupation, which was present on the birth, welfare and school records, we divided the cohort into upper middle class, lower middle class and manual worker according to an original social classification made by Statistics Finland.

## Statistical analysis

Mother's body mass index (BMI) was skewed and log-transformed. We generated growth curves for height, weight and BMI using the method of Royston [14]. We used linear interpolation to generate Z-scores at each birthday from birth to 12 years only when there was an observation within 2 years. We back-transformed these Z-scores to obtain the corresponding height, weight and BMI. We analysed the predictors of adult hip fracture by Cox proportional hazard models, using age at hip fracture as the outcome. Subjects were censored in the analysis when they had a hip fracture ( $n=49$ ), migrated from Finland ( $n=732$ ), died ( $n=450$ ) or reached the end of 2003 ( $n=5,139$ ).

## Results

The anthropometric and medical characteristics of the cohort are shown in Table 1. The distribution of paternal

**Table 1** Anthropometric and fracture characteristics of the 6,370 women

Characteristic	Mean	SD
<b>Anthropometry</b>		
Birth length (cm)	49.9	1.8
Birth weight (kg)	3.34	0.46
Birth BMI (kg/m <sup>2</sup> )	13.4	1.2
Height at 1 year (cm)	74.8	2.6
Weight at 1 year (kg)	9.8	1.0
BMI at 1 year (kg/m <sup>2</sup> )	17.5	1.4
Height at 12 years (cm)	147.6	6.8
Weight at 12 years (kg)	39.2	7.0
BMI at 12 years (kg/m <sup>2</sup> )	17.7	2.2
<b>Fractures</b>		
Age at censoring (years)	58.8	10.2
Age at first hip fracture	Number	Rate per million person years
–50 years	5	41
50–54 years	8	293
55–59 years	17	659
60–64 years	13	1,181
>65 years	6	3,190
All ages	49	

socio-economic status was as follows: upper middle class, 16.5%; lower middle class, 24.5%; and labourers, 59%. Forty-nine incident hip fractures were recorded (Table 1), of which only five occurred below the age of 50 years.

#### Post-natal growth and risk of future fracture

At birth, there was little difference in size between subjects who did and did not sustain a fracture in adulthood (Table 2). At 1 year of age, BMI was slightly higher among women who had hip fractures. By age 12, these women had lower BMI than other women (Table 2). We analysed the relationship between postnatal growth and the risk of hip fracture by studying the change in height, weight and BMI Z-score within two age ranges: infancy (birth-1 year) and childhood (age 1-12 years). During infancy, there was no association between changes in height, weight or BMI Z-score and fracture risk ( $p$  values 0.7, 0.4, 0.3, respectively). Hazard ratios for hip fracture per Z-score increase in childhood body size were: 1.43 (95% confidence interval (CI) 0.98-2.09,  $p=0.06$ ) for height; 0.76 (0.53-1.07,  $p=0.12$ ) for weight and 0.55 (0.39-0.77,  $p=0.0004$ ) for BMI (Table 3, Fig. 1). These relationships remained after excluding hip fractures that occurred before the age of 50 years (hazard ratio for BMI 0.58 {0.40-0.83},  $p=0.003$ ); before the age of 55 years (0.61 {0.40-0.93},  $p=0.023$ ); and before age 60 years (0.64 {0.38-1.09},  $p=0.103$ ).

#### Maternal anthropometry and hip fracture in the offspring

The mean height of the mothers was 160.0 cm (SD 5.6), median weight 66 kg (interquartile range (IQR) 61-72) and BMI 25.9 kg/m<sup>2</sup> (IQR 24.2 to 27.7). Hip fracture was associated with increasing maternal weight (hazard ratio (HR) 1.31 per SD,  $p=0.05$ ) and increasing maternal BMI

(HR 1.35 per SD,  $p=0.03$ ). In a simultaneous regression both high maternal BMI and low BMI gain between age 1 and 12 years were associated with increased fracture risk ( $p=0.04$  and 0.0003, respectively).

The relationships between change in SD score in childhood anthropometry and adult hip fracture remained unchanged after adjusting for social class at birth, infancy or childhood.

Data on menarcheal age and pubertal status were not available. However, we were able to estimate height at age 14 years for 787 girls and compare this with postal questionnaire data on adult height [15]. We used the difference in height as an index of pubertal maturation. Girls who sustained a hip fracture in later life had an 8.6 cm average deficit, compared with only 5.2 cm among those who did not (difference 3.5 cm, 95% CI -0.2 to 7.1,  $p=0.06$ ).

## Discussion

In this study of 6,370 women born in Helsinki, Finland, we have shown that decline in Z-scores for BMI between 1 and 12 years of age and higher maternal BMI were associated with an increased risk of hip fracture in later life.

There is a growing body of evidence showing that bone fragility in old age is partly determined during early life [16, 17]. Retrospective cohort studies from Europe [17–20], Australia [21] and Northern America [22] have demonstrated that reduced growth in early life is associated with reduced proximal femoral bone mineral density and altered hip geometry in adulthood [23]. However, these outcomes are surrogate markers for the most important complication of osteoporosis, which is hip fracture. We have previously shown that faltering height and weight gain during late childhood are associated with an increased risk of later hip fracture [12]. This study confirms the importance of poor growth during late childhood as a risk factor for future hip fracture. Unlike our previous study, we did not find that women who sustained hip fractures were smaller at birth, when compared with women who did not have hip fractures. Our data suggest that it is the rate of change in BMI, rather than the absolute BMI at any age during childhood that is the key determinant of later hip fracture. Reduction in z-scores for BMI may reflect a relative loss of fat mass, but could also reflect a relative reduction in muscle mass [24]. Recent work on the Helsinki cohort has demonstrated that while BMI gain in infancy predicts lean mass in adulthood, BMI gain in childhood predicts adult fat mass [25].

There are two potential explanations for the link between reduction in Z-scores for BMI and later fracture risk. First, it might reflect differences in the timing of puberty. Unfortunately, direct estimates of pubertal status during growth were not available in this cohort and estimates of

**Table 2** Mean body size of women with and without hip fractures

	No fracture ( <i>n</i> =6,321)	Fracture ( <i>n</i> =49)	<i>p</i> for difference
Birth			
Length (cm)	49.9	49.8	0.69
Weight (kg)	3.34	3.33	0.89
BMI (kg/m <sup>2</sup> )	13.4	13.4	0.84
1 year			
Height (cm)	74.8	74.5	0.50
Weight (kg)	9.8	10.0	0.40
BMI (kg/m <sup>2</sup> )	17.5	17.8	0.13
12 years			
Height (cm)	147.6	147.3	0.84
Weight (kg)	39.2	37.0	0.09
BMI (kg/m <sup>2</sup> )	17.8	16.9	0.04

**Table 3** Hazard ratios (95% confidence interval) for hip fracture incidence according to fourths of change in Z-score of BMI during infancy and childhood

Age range	Fourth of change in BMI Z-score	Cases/women	HR (95% CI)
Infancy (0-1 year)	Lowest	13/1,577	0.8 (0.4-1.7)
	Low	8/1,578	0.5 (0.2-1.1)
	High	12/1,578	0.7 (0.3-1.5)
	Highest	16/1,577	1.0 (baseline)
	<i>p</i> for trend		0.3
	Hazard ratio per unit Z-score increase		1.13 (0.89-1.43)
Childhood (1-12 years)	Lowest	18/1,067	8.2 (1.9-35)
	Low	7/1,069	3.2 (0.7-15)
	High	3/1,069	1.5 (0.2-8.8)
	Highest	2/1,068	1.0 (baseline)
	<i>p</i> for trend		0.0004
	Hazard ratio per unit Z-score increase		1.82 (1.31-2.54)

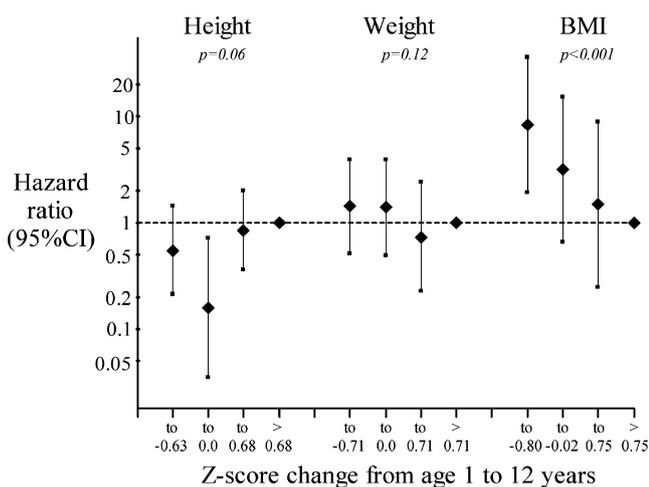
*BMI* body mass index; *HR* hazard ratio; *CI* confidence interval

peak height velocity could not be derived because of the small number of subjects who were measured after age 12 years. We were, however, able to use a proxy measure of maturation—the difference between height at age 14 years and in adult life. Although not statistically significant, and clearly compromised by the relatively small number of fracture cases, it was interesting to note that girls who went on to fracture (five cases) appeared further from skeletal maturity than those who did not fracture. Second, it might reflect a slowing of growth in response to adverse environmental influences. Our previous analyses in an older cohort from Helsinki [12] showed pronounced discordance between the trajectories of height and weight gain between ages 7 and 15 years in people who later developed hip fracture, which led us to conclude that delayed puberty was the explanation for the association between childhood growth and hip fracture. The present study also shows discordance between the trajectories of

height and weight gain (Fig. 1), which is reflected in a reduction in Z-scores for body mass index.

Contemporary studies of childhood bone strength have demonstrated that higher adiposity is associated with greater proximal femoral strength [26], due to an increase in femoral cortical thickness and cross-sectional area. It is possible that attenuated adiposity gain during childhood might be associated with a specific reduction in proximal femoral section modulus, tracking through to late adulthood and leading to a higher risk of hip fracture. This is supported by recent evidence from an adult cohort, demonstrating a positive association between weight gain in infancy and distal radius cortical thickness as assessed by quantitative computed tomography [27].

There are several limitations to our study. Only 60% of children born in Helsinki and still living there attended child welfare clinics at the time of our study. Subjects were recruited on the basis of attendance, so we have no direct comparison group. However, the socio-economic status of this sample does not differ appreciably from the Helsinki population as a whole, and hip fracture incidence rates derived from the sample are similar to those for Finland as a whole [28]. Second, we reported growth trajectories from birth to 1 year and from 1-12 years. The precedent for this subdivision of age emerges from analyses of linear growth, which distinguish infant and childhood phases before puberty [29]. When these two phases are combined, relationships with later health outcomes, such as fracture, are blunted due to opposite directions of effect; these can be observed in Table 3. Third, we were unable to identify the level of trauma associated with hip fracture. It is likely that fractures occurring among younger women were due to high-energy trauma, and a recent study has suggested that low BMD may operate as a risk factor for fracture even below age 60 years [30]. Nevertheless, we were able to conduct stratified analyses relating childhood change in BMI Z-score to hip fracture risk at ages above 55 and



**Fig. 1** Relationship between childhood growth from age 1-12 years and hazard ratios for adult hip fracture. The women are divided according to fourths of childhood growth. The group showing the greatest increase is the baseline for each analysis

60 years, respectively. Despite the compromised statistical power of these analyses, we observed only very slightly attenuated hazard ratios in different age strata. In addition, we had no direct assessment of puberty and instead used the difference between height at age 14 years and adult height in a subset of the cohort. Finally, we were unable to take account of several adult determinants of hip fracture risk, including impaired nutrition and physical inactivity.

In conclusion, this study suggests that thinness in childhood might be a risk factor for hip fracture in later life. This association might result from a direct effect of low fat mass on bone mineralization.

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**Conflicts of interest** None.

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