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Original Article

Association of body size at birth and childhood growth with hip fractures in older age: an exploratory follow-up of the Helsinki Birth Cohort Study†

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DISCLOSURES

The authors have no conflicts of interest to declare.

ABSTRACT

Childhood growth has been linked with bone properties in adulthood while less is known about the contribution of early growth to bone fracture risk. We investigated the association of body size at birth and childhood growth with hip fractures and pharmacotherapy for osteoporosis in older age. Men and women, born full term, from the Helsinki Birth Cohort Study (n=8,345) were followed up until the age of 68 to 80 years. Height and weight from birth to 11 years were obtained from health care records and diagnoses of hip fractures and osteoporosis drug purchases from national registers. Independent associations of each age period were analyzed using Cox models adjusted for age, childhood and adulthood socioeconomic status, and drugs affecting bone metabolism. In men, the risk of hip fractures was non-linearly associated with childhood growth. Compared to intermediate increase, low and high increase in height between 2 and 7 years ($p<0.001$) were associated with all hip fractures and hip fractures sustained after the age of 50 years. Further, compared to intermediate gain, low and high gain in BMI between 7 and 11 years ($p=0.001$) were associated with greater risk of hip fractures in men. In women, growth was not associated with the risk of hip fractures but greater weight (hazard ratio [HR]=0.85; 95% CI 0.77-0.94, $p=0.001$) and BMI (HR 0.86; 95% CI 0.78-0.95, $p=0.003$) gain between ages 2 and 7 years were associated with a decreased risk of pharmacotherapy for osteoporosis. In men, growth was not associated with the risk of pharmacotherapy for osteoporosis. In conclusion, growth during childhood may contribute to the risk of hip fractures in later life among men.

Key words: Aging, General population studies, Developmental modeling, Osteoporosis, Therapeutics

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INTRODUCTION

In osteoporosis research, it has long been understood that earlier phases of life may have an important role in determining bone health in later life. Many studies have focused on the effects of puberty and menopause but recently more focus has been set on the importance of early life influences on bone health in adulthood and older age.[1] The Developmental Origins of Health and Disease (DOHaD) hypothesis has been widely applied when studying risk factors for cardiovascular health and metabolic diseases.[2-5] DOHaD studies have shown that early life conditions, as reflected by body size at birth and childhood growth, are consistently associated with health in midlife and older age. These results have been interpreted to be consequences of programming taking place during early life, the aim of which is to adapt body systems to prevailing conditions but this may also have adverse health effects later in life.[6]

Evidence on the association between body size at birth and early growth and bone mineral density and bone structure measured across the life course is accumulating.[1] Lower birth weight and slower childhood growth have been linked to lower bone mineral mass[7-9] and weaker bone structure[10] in older age. Early growth may also be associated with other modifiable risk factors for hip fractures, such as muscle strength and general physical capacity.[11,12]

Only a few studies have so far explored the association of early growth with fractures in later life. They have found no associations between body size at birth and fractures in later life.[13-15] However, one previous study including men and women from the Helsinki Birth Cohort Study (HBCS) born 1924-1933 with follow-up up to 70 years showed that children with poorest height or weight gain during the school years (7-15 yrs.) were more likely to sustain hip fractures than those with highest gain.[13] Further, our study among HBCS women born

1934-1944 showed that greater increase in height and lower BMI gain between 1 and 12 years of age was associated with greater risk of a hip fracture in later life.[14]

Slow growth may indicate adverse environment or health, which may, during sensitive periods, compromise bone development or affect factors protecting from falls, such as muscle mass. Fast growth throughout the growth period leads obviously to large skeletal size in adulthood which translates into more robust bone structure. On the other hand, tall stature in adulthood is a risk factor for hip fractures.[16,17] Further, an earlier growth spurt indicates earlier maturation, which has beneficial influence on bone properties[18] and hence, possibly also on hip fractures.

In order to disentangle which growth periods are important for older age bone health we explored the associations of birth size and childhood growth, until the age 11, with the risk of hip fractures in HBCS men and women with a follow-up up to the age of 80 years. We also explored the associations of birth size and childhood growth with the use of pharmacotherapy for osteoporosis as a proxy for osteoporosis. It was hypothesized that body size at birth is not associated with the risk of hip fractures in later life while greater prepubertal growth is associated with a reduced risk of hip fractures.

MATERIALS AND METHODS

The Helsinki Birth Cohort Study (HBCS) comprises 13,345 individuals born in Helsinki, Finland, at Helsinki University Central Hospital or Helsinki City Maternity Hospital between 1934 and 1944 for whom data on body size at birth and in childhood have been retrieved from healthcare records.[3,19] As individuals born preterm may present abnormalities in growth and bone health, participants born before 37 weeks of gestation (n=800) as well as those with missing data on gestational age (n=532) were excluded. Because the children were not measured exactly on their birthdays, we obtained a z score at each birthday by

interpolation if measurements had been made within 2 y of that age. Interpolation was carried out between successive z scores with a piecewise linear function. After that, individuals with missing height/weight at any of the ages 0, 2, 7 or 11 years were excluded (n=3,668), leaving 8,345 individuals in the analyses. The register data were linked to the participants using a personal identification number assigned to all Finnish residents in 1971. The study was approved by the Ethics Committee of Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa and that of the National Public Health Institute, Helsinki.

Infant and childhood measures

Birth date, weight, and length of the newborns were retrieved from hospital birth records, and infancy and childhood weight and height from child welfare clinic and school healthcare records, described in detail previously.[20,21] Date of the mothers' last menstrual period prior to pregnancy was also extracted from hospital birth records and was used to calculate gestational age. Childhood socio-economic status was ascertained based on father's highest occupational status extracted from birth, child welfare, and school healthcare records, coded as upper middle class, lower middle class, and manual workers based on the original social classification system issued by Statistics of Finland.[22] Using the highest occupational status we minimized the number of missing data.

Hip fractures

Information on hip fractures was obtained from the national Care register for Health Care (formerly Hospital Discharge Register) for the years 1971-2013. The maximum age at follow-up was 80 years. The register contains information of all hospital admissions in Finland. From the register, first hospital admissions due to femoral neck, trochanteric or subtrochanteric fractures (ICD-8 and ICD-9 codes 820.0-820.9; ICD-10 codes S72.0-S72.2) were identified. Mortality dates from January 1, 1971 to December 31, 2013 were obtained

from the National Death Register. Date of migration from Finland was obtained from the population register and was available until year 2000.

Pharmacotherapy for osteoporosis

Information on drug purchase for osteoporosis was obtained from the register of the Social Insurance Institution of Finland for the years 1995-2011. Purchases of all prescription drugs partly or fully reimbursed, classified using Anatomical Therapeutic Chemical (ATC) classification codes, are recorded in the register. Dates of the first purchases with ATC code M05B (i.e. Drugs affecting bone structure and mineralization including: Bisphosphonates alone and in combinations, Bone morphogenetic proteins, and Other drugs affecting bone structure and mineralization), H05AA02 (Teriparatide), H05BA (Calcitonin preparations), or G03XC01 (Raloxifene) were identified from the register.

Potential confounders

Register data from Statistics Finland were used to indicate adult socioeconomic status. The highest occupational status at five-year intervals between 1970 and 2000 was coded as upper middle class, lower middle class, self-employed, and laborers.[22] This definition captures most of the lifetime occupational history for all subjects and minimizes missing data.

Corticosteroid users were identified from the drug register described above. A person with 2 or more purchases of corticosteroids for systemic use (ATC code H02) prior to the possible first hip fracture/ first purchase of osteoporosis drugs were considered to be corticosteroid users. We also identified female users of hormone therapy using ATC code G03C (Estrogens) and G03F (Progestogens and estrogens in combination). A woman was classified as an estrogen user if she had more than six purchases of estrogen and if estrogen use had started prior to possible first hip fracture/ first purchase of osteoporosis drugs. Use of osteoporosis

medication prior to the possible hip fracture was used as a potential confounder for hip fracture.

Statistics

To obtain body size at birth adjusted for gestational age, we fitted, separately for males and females, a polynomial function for gestational age as a predictor of body size at birth. The highest degree with $p<0.05$ was chosen for each variable and sex (2^{nd} and 3^{rd} degree) and graphs were used to check that the functions were biologically plausible. The residuals from this model were symmetrical about zero. We then fitted a 1^{st} or 2^{nd} degree (highest degree with $p<0.05$) polynomial to the absolute values of these residuals. Following Royston,[23] we used the fitted values from these curves to define sex and gestational age-specific standardized scores (z-scores) for weight, length and BMI at birth. In each week of gestation we checked that these had mean and standard deviation close to zero and unity, respectively. The z-score at any age describes the number of standard deviations by which an observation differs from the mean for that particular (gestational) age. To measure how much size at any age differed from that predicted by the body size attained at an earlier age, we used the residuals from linear regression analysis, which we refer to as conditional growth. By this construction, conditional growth is uncorrelated with the earlier size and enables the effects of changes in body size during different growth periods to be distinguished.[24]

We used Cox proportional hazards regression to analyze the associations of birth size and childhood growth with hip fractures and use of pharmacotherapy for osteoporosis. Subjects were censored in the analysis when they had the event (first hip fracture or first purchase of osteoporosis drugs), migrated from Finland, died, or reached the end of the follow-up (Supplemental Table 1). The analyses were conducted separately for men and women as there were significant interactions between sex and growth on hip fractures and osteoporosis. Full adjustment included the following covariates: age, childhood and adulthood socioeconomic

status, corticosteroid user, estrogen user and user of pharmacotherapy for osteoporosis (only for the analysis of hip fractures). Hazard ratios (HR) are given per one standard deviation increase in the independent variable (i.e. conditional body size). We tested the proportionality assumption by introducing time-dependent covariates (i.e. interaction term time*growth variable) into the models. There was no evidence of violation of this assumption (i.e. no statistically significant interaction terms). We also conducted a sensitivity analysis by excluding those with hip fractures before age of 50. The analyses were carried out using IBM SPSS Statistics version 22.

RESULTS

Full term individuals belonging to the HBCS included and excluded from the analysis did not differ in early growth, socioeconomic status, corticosteroid use, or estrogen use (Table 1). Those included were taller and heavier compared to the excluded at the age of 11 years. Individuals included in the analysis were also slightly younger at the start of the follow-up.

Altogether, the participants were followed up for 308,032 person-years for the analysis of hip fractures and 109,224 person-years for the analysis of pharmacotherapy for osteoporosis. Men sustained more hip fractures than women (103 men and 86 women) while more women than men started using pharmacotherapy for osteoporosis during the follow-up (138 men and 455 women) (Supplemental Table 1). The number of hip fractures sustained at the age of 50 or older was similar among men and women (82 men and 81 women).

In men, growth in height between the ages 2 and 7 years, conditional on previous growth, was non-linearly associated with the hip fracture risk in older age; those with small or large gains in height were more likely to sustain a hip fracture than those with intermediate gain in height (fully adjusted model $p<0.001$) (Figure 1, Table 2, Supplemental Figure 1). Growth in BMI between the ages of 7 and 11 years was also non-linearly associated with the risk of hip

fracture. Men with small and large increase in BMI from age 7 to 11 were more likely to sustain a hip fracture than men with intermediate increase in BMI (fully adjusted model p=0.001). Further, men with greater weight gain between birth and 2 years were more likely to sustain a hip fracture (fully adjusted model HR 1.24 95% CI 1.02-1.52, p=0.036). In women, body size at birth or childhood growth were not associated with the risk of hip fractures.

When excluding hip fractures sustained before the age of 50 years, the hazard ratios did not markedly change (Table 2). In men, the association between conditional growth in BMI between the ages of 7 and 11 years and hip fractures in old age was parallel but no longer statistically significant.

Crude models (Supplemental Table 2) for the associations between growth and hip fractures did not markedly differ from the adjusted models.

In men, body size at birth and childhood growth were not associated with the risk of pharmacotherapy for osteoporosis in older age (Supplemental Table 3). In women, greater weight (fully adjusted HR 0.85; 95% CI 0.77-0.94) and BMI (fully adjusted HR 0.86; 95% CI 0.78-0.95) gain between ages 2 and 7 years were associated with decreased risk of pharmacotherapy for osteoporosis in older age.

DISCUSSION

The present study showed that the contributions of childhood growth to hip fracture risk and pharmacotherapy for osteoporosis in later life differed between men and women. In men, the risk of hip fractures was driven by increase in height between 2 and 7 years of age, and gain in BMI between 7 and 11 years of age. In women, early growth was not associated with the risk of hip fractures. Growth was not associated with pharmacotherapy for osteoporosis in

men while in women, greater increase in weight and BMI between 2 and 7 years were associated with lower risk of pharmacotherapy for osteoporosis.

It is not surprising that men and women differ in the developmental origins of bone fragility. Gender-specific programming of health and disease has been widely described in relation to other health outcomes as well.[25,26] Further, bone structure demonstrates sexual dimorphism across the life course[27] and differences between the sexes are apparent already in newborn babies, females having smaller vertebral bodies than men even when adjusted for body size.[28] Our findings are in agreement with previous studies,[13-15] in which no associations between body size at birth and hip fractures in either sex were observed. Greater body size at birth has been found to predict higher bone mineral density[7-9] and more robust bone structure[10] in older age, which could, in theory, lead to lower risk of hip fractures. However, other risk factors for hip fractures that are not affected by birth weight may obscure the modest contribution of birth weight mediating through bone properties. Indeed falls, an important risk factor for hip fractures in old age, has been found to be unrelated to birth weight. [11]

Men with high or low conditional gain in height between 2 and 7 years had greater risk of hip fractures than those with intermediate height gain. Conditional height gain during this age period correlated with final adult height (r=0.455). Consequently, the fact that taller stature in adulthood is a risk factor for hip fractures,[17] may explain our finding. The higher risk of hip fracture in those with small gain in height compared to those with intermediate gain are supported by findings that higher height velocities both between 2 and 4 years and 4 and 7 years were associated with greater bone strength index in older age.[10] Slow height gain may indicate poor nutrition which compromises normal bone development and increases bone fragility. The World War II and related rationing that continued in Finland several years after the end of the war is likely to have markedly influenced the nutrition of the HBCS cohort at

the age of 2 to 7 years. A recent systematic review suggested that some aspects of nutrition, such as milk avoidance and high-energy diet, may be associated with increased fracture risk in growing children.[29] Poor nutrition may also underlie the association observed between low weight and BMI gain between 2 and 7 years of age and the risk of pharmacotherapy for osteoporosis in women. Another explanation may lie in lean body mass. Girls with small gains in weight and BMI are likely to have poor accumulation of muscle mass and in such case, the level of mechanical stimulation from muscles to bone is low, leading to suboptimal bone mass accrual.[30]

The present study showed that men with high or low conditional gain in BMI between 7 and 11 years of age were more likely to sustain a hip fracture. The results from an older cohort, that included men and women in the same models, showed that poor height or weight gain between 7 and 15 years of age was associated with increased hip fracture risk.[13] These results may be explained by fat and/or lean mass accumulation. Excess accumulation of adipose tissue has been shown predict both earlier[31] and later maturation in boys.[32] Later maturation is detrimental for the skeleton, resulting in lower peak bone mass and weaker bone structure in later adolescence.[18] On the other hand, adiposity is often found to be positively associated with bone health.[33] A recent study suggested that this association is largely accounted for by higher lean mass that accompanies excess fat accumulation in adolescents.[34] High lean mass and associated exercise during prepuberty are likely to be particularly important for later bone health because during prepuberty bones seem to be very sensitive for exercise-induced loading.[35] Boys with the lowest BMIs are likely to have low muscle mass which may impede them from obtaining high peak bone mass, which further results in higher risk for hip fractures in later life. As growth spurt in height precedes pubertal maturation, participants with early maturation have also had earlier onset of growth spurt in height. Hence, it would be expected that greater increase in height between 7 and 11 years

would indicate earlier maturation and therefore greater increase in height during this age period would be associated with reduced risk of hip fractures. However, this was not the case. This may be explained by the fact that the onset of the growth spurt (and pubertal maturation) has occurred later in those born in 1930's and 1940's than it occurs nowadays.[36] Consequently, the age period from 7 to 11 years may not capture the timing of the growth spurt very well in this cohort.

We also found an association between greater weight gain between birth and 2 years of age and hip fractures among men. However, given that we carried out multiple statistical tests and the confidence intervals for this association were wide and the p-value high, there is a high likelihood that this association occurred only by chance.

This study has several strengths. The cohort was large and it was followed up until old age. Although hip fractures were not ascertained from the hospital medical records by the authors, the data in the national register, especially on hip fractures, have been shown to be of high quality and highly suitable for research purposes.[37-40] The quality of the register data, however, has been lower during the first years of the follow-up [39] but considering the participants' age at that time this is unlikely to have resulted in missing a marked number of hip fracture cases. In addition to data on body size at birth, we had detailed data on childhood physical growth and thus were able to model growth during several periods in childhood conditional on preceding growth. This allowed us to determine the independent influences of each age period. A limitation in this study was that we were not able to analyze other fractures than hip fractures, as a marked proportion of other fractures do not necessarily require overnight care and hence, these other fractures are not captured by the care register. Further, purchases of osteoporosis drugs is not a perfect surrogate for osteoporosis as not all with low BMD receive osteoporosis treatment. It has been estimated that 27% of those eligible for osteoporosis treatment were actually treated in Finland in 2010.[41] In men, the

number of users of osteoporosis medication was rather low which may have led to inadequate statistical power in men. Lack of data on bone properties and falls limited investigating potential pathways underlying the associations between growth, hip fractures and pharmacotherapy for osteoporosis. It should be noticed that the follow-up of in this study was until the age of 68 to 80 years. Hence, these results may not be generalizable to oldest old persons. Although we attempted to control for confounding factors there may be residual confounding affecting the results.

This study suggests that childhood growth is associated with hip fractures and pharmacotherapy for osteoporosis in later life. However, the associations were sex-specific implying that the timing and possibly also underlying mechanisms, of these sensitive growth periods are at least partly different in men and women. When developing early-life interventions to promote bone health in older age, optimal time windows and means should be considered according to sex.

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FIGURE LEGENDS

FIGURE 1. Hazard ratios (HR) and 95% CIs for hip fractures per 1 SD increase in body size conditional on previous growth during each age period. Analyses are adjusted for age at the start of the follow-up, father's occupational status, socioeconomic status in adulthood, use of systemic corticosteroids, use of osteoporosis medication, and in women with estrogen use. *quadratic association

TABLES

Table 1. Characteristics of men and women born full term (≥37 weeks of gestation) in the Helsinki Birth Cohort Study

	Included in the analyses				Not included in the analyses			
	Men (n=4378)		Women (n=3967)		Men (n=1873)		Women (n=1795)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Gestational age, weeks	4378	40.1 (1.4)	3967	40.1 (1.4)	1873	40.1 (1.4)	1795	40.2 (1.4)
Age, years[a]	4378	29.6 (2.7)	3967	29.6 (2.7)	1873	30.4 (2.9)	1795	30.4 (3)
Height, cm								
Birth	4353	50.7 (1.8)	3931	50 (1.7)	1859	50.7 (1.8)	1785	50 (1.7)
2 years	4377	86.7 (3.1)	3964	85.5 (3.1)	1871	86.6 (3.3)	1794	85.5 (3.3)
7 years	4374	120.8 (4.8)	3965	119.9 (4.7)	291	120.5 (5)	269	119.8 (4.9)
11 years	4374	141.4 (5.9)	3966	141.5 (6.4)	182	140.3 (5.9)	160	141.2 (6.3)
Weight, kg								
Birth	4378	3.51 (0.46)	3967	3.37 (0.44)	1873	3.49 (0.45)	1795	3.35 (0.43)
2 years	4378	12.4 (1.1)	3967	11.9 (1.2)	1873	12.3 (1.2)	1794	11.9 (1.2)

7 years	4376	22.5 (2.7)	3966	22.2 (2.9)	294	22.5 (2.6)	274	22 (2.7)
11 years	4375	33.7 (4.6)	3964	34.3 (5.8)	183	33.2 (4.5)	160	33.7 (5.3)
Body mass index, kgm^{-2}								
Birth	4353	13.6 (1.2)	3931	13.4 (1.2)	1859	13.5 (1.2)	1785	13.4 (1.2)
2 years	4377	16.7 (1.2)	3964	16.4 (1.2)	1871	16.6 (1.2)	1795	16.4 (1.3)
7 years	4369	15.5 (1.1)	3958	15.5 (1.3)	290	15.5 (1.1)	267	15.4 (1.3)
11 years	4368	16.8 (1.5)	3961	17.1 (1.9)	183	16.9 (1.5)	159	16.9 (1.8)
	N	%	N	%	N	%	N	%
Father's highest occupational status	4325		3915		1791		1679	
Upper middle		18		16		20		18
Lower middle		24		25		24		25
Laborer		58		59		57		58
Maximum social class in adulthood	4134		3645		1639		1518	
Upper middle		15		10		18		10
Lower middle		24		54		24		48

Self-employed		10		9		11		11
Laborer		51		28		47		31
Corticosteroid user[b]	4378	10	3967	16	1873	10	1795	13
Estrogen user[c]	4378	NA	3967	51	1873	NA	1795	47

Note. SD, standard deviation; NA, not applicable

[a]at the start of the follow-up in 1971

[b]a person with 2 or more purchases of oral corticosteroids (prior to hip fracture)

[c]a person with 7 or more purchases of estrogens (prior to hip fracture)

Table 2. Adjusted hazard ratios (HR) for all hip fractures and hip fractures sustained at the age of 50 or older per one SD increase in conditional growth.

	Men						Women					
	All hip fractures			Hip fractures at 50+ years			All hip fractures			Hip fractures at 50+ years		
	HR	**95%CI**	p	HR	**95%CI**	p	HR	95%CI	p	HR	95%CI	p
Height												
Birth	1.01	0.84-1.2	0.940	1.02	0.83-1.25	0.849	1.00	0.82-1.22	0.988	1.01	0.82-1.24	0.950
Birth quadratic	1.07	0.99-1.16	0.110	1.04	0.94-1.16	0.419	NA			NA		
0 to 2 years	1.16	0.95-1.41	0.155	1.15	0.92-1.43	0.231	1.06	0.86-1.31	0.590	1.08	0.87-1.34	0.505
2 to 7 years	1.21	1.02-1.42	0.026	1.21	1.01-1.45	0.045	1.14	0.92-1.41	0.228	1.14	0.92-1.42	0.234
2 to 7 years quadratic	**1.18**	**1.09-1.27**	**0.000**	**1.18**	**1.08-1.29**	**0.000**	NA			NA		
7 to 11 years	1.12	0.91-1.38	0.275	1.01	0.80-1.28	0.935	0.97	0.8-1.18	0.767	1.00	0.82-1.22	0.998
Weight												
Birth	0.99	0.81-1.21	0.926	1.02	0.81-1.27	0.896	0.89	0.72-1.1	0.289	0.91	0.73-1.14	0.407
0 to 2 years	**1.24**	**1.02-1.52**	**0.036**	**1.26**	**1.00-1.58**	**0.048**	1.18	0.95-1.47	0.128	1.20	0.96-1.50	0.104

2 to 7 years	1.17	0.96-1.42	0.123	1.17	0.93-1.47	0.174	1.01	0.82-1.25	0.920	1.03	0.82-1.28	0.821
2 to 7 years quadratic	1.07	0.97-1.17	0.162	1.06	0.95-1.19	0.304	NA			NA		
7 to 11 years	1.02	0.85-1.22	0.849	0.99	0.78-1.25	0.902	0.85	0.69-1.04	0.117	0.88	0.71-1.09	0.240
7 to 11 years quadratic	1.06	0.99-1.14	0.092	1.00	0.88-1.13	0.951	NA			NA		
BMI												
Birth	1.00	0.81-1.22	0.977	1.00	0.80-1.26	0.972	0.87	0.7-1.07	0.190	0.89	0.71-1.11	0.303
0 to 2 years	1.13	0.92-1.39	0.228	1.15	0.92-1.44	0.215	1.15	0.92-1.43	0.222	1.15	0.92-1.44	0.224
2 to 7 years	1.14	0.93-1.4	0.207	1.18	0.94-1.48	0.164	0.95	0.77-1.18	0.648	0.97	0.78-1.21	0.778
7 to 11 years	0.99	0.84-1.16	0.867	0.99	0.81-1.20	0.881	0.87	0.7-1.08	0.210	0.90	0.72-1.12	0.337
7 to 11 years quadratic	**1.11**	**1.04-1.18**	**0.001**	1.07	0.98-1.16	0.162	NA			NA		

NA, not applicable

Hazard ratios are given for one standard deviation increase in the independent variable. Statistically significant ($p<.05$) associations are bolded.

Models are adjusted for age at the start of the follow-up, father's socioeconomic status, socioeconomic status in adulthood, use of systemic

corticosteroids, and in women with estrogen use.

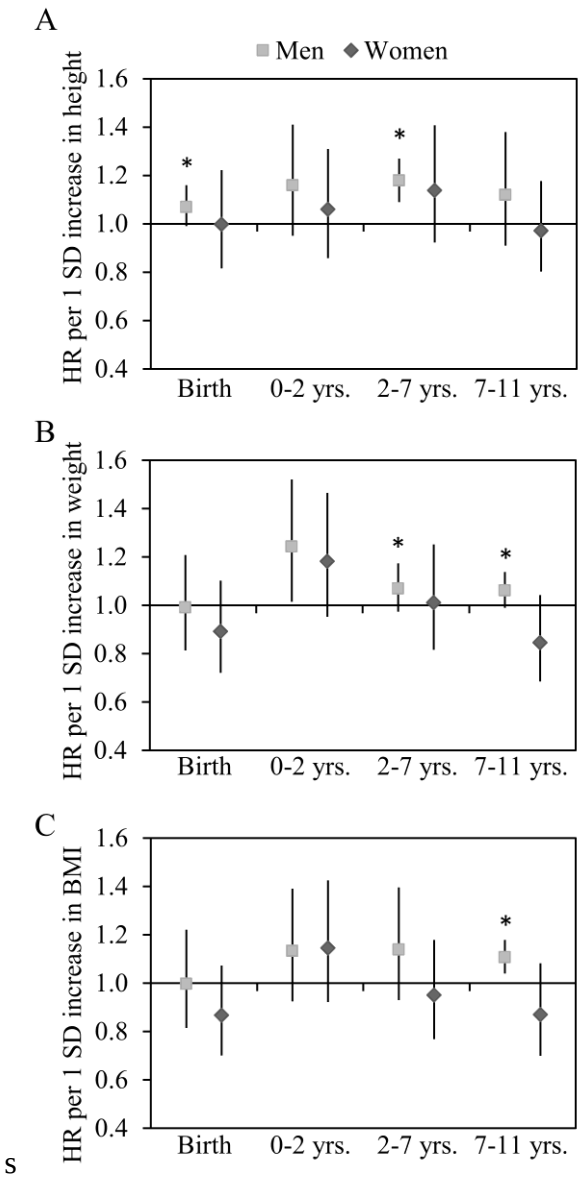

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Figure 1