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Infant and childhood growth and frailty in old age: the Helsinki Birth Cohort Study

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Abstract

Background: Evidence from life course studies highlights the importance of infant and childhood growth as risk factors for adulthood chronic diseases.

Methods: In this sub-study of the Helsinki Birth Cohort Study we studied 1078 individuals who had both information on body size from birth to 12 years of age and who were assessed for frailty according to the Fried criteria at the mean age of 71 years.

Results: Greater BMI gain between 2 and 11 years in boys was associated with frailty in old age (age-adjusted RRR 2.36, 95% CI 1.21, 4.63). No similar associations were observed in girls.

Conclusions: Men who were frail in old age experienced accelerated BMI gain in childhood compared with those men who were not frail. This was not observed in women, which suggests that the patterns of early growth predisposing to frailty may vary by sex.

Key Words: growth, frailty, life-course, risk factor.

Introduction

Frailty, the clinical condition that affects several organ systems leading to incomplete recovery from changes in health status and of which the prevalence increases on average from 3.2 at age 65-70 years to 16.3% at age 80-84 years, is associated with adverse health outcomes including falls, fractures, difficulties in activities of daily living, hospitalization and premature mortality (1,2). Prevention and treatment of frailty, which have been addressed as a public health priority (3), require a life course perspective for the understanding of its long-term dynamic development (4).

Life course studies have indicated that chronic diseases such as hypertension, cardiovascular disease and type 2 diabetes, have in addition to risk factors related to adult lifestyle, risk factors originating from infancy and childhood as a consequence of the phenomenon known as “programming” (5,6). Although studies examining the associations of early growth and the individual components of frailty such as grip strength and physical performance exist, research into the early life origins of the condition as a whole are scarce (7–9). An association between body size at birth and frailty at the mean age of 71 years has been reported previously in the Helsinki Birth Cohort Study (HBCS) (10), yet little is known whether size and growth later in infancy and childhood are associated with frailty. Therefore, using unique data on growth, we investigated the association between size and growth in infancy and childhood and frailty in the HBCS.

Materials and methods

Study design

HBCS has been described in detail previously (5,11). The present sub-study includes 1078 participants (603 women and 475 men) born between 1934 and 1944. There were on average 17 measurements on body size available for each individual from birth to 12 years of age (12). The participants were examined clinically at baseline between the years 2001 and 2004 and followed up between 2011 and 2013.

Measurements

Child welfare and school healthcare records provided information on the serial measurements of the participants' weight and height and their socio-economic status (SES) in childhood (father's highest occupational status coded as manual workers, lower middle class and upper middle class). SES in adulthood, based on the highest attained occupational status, was obtained from Statistics Finland (manual workers, self-employed, lower middle class and upper middle class). Measurements of the participants' weight and height and self-reported data on smoking status and the prevalence of hypertension and diabetes were obtained at the clinical baseline examination between the years 2001-2004. Body mass index (BMI) was calculated as weight in kilograms divided by square of height in meters (kg/m^2).

Frailty

Frailty was assessed in 2011-2013 using five criteria: weight loss, exhaustion, low physical activity, slowness and weakness as in a previous publication (1,10). Briefly, weight loss, exhaustion and low physical activity were assessed using questionnaires. Slowness and weakness were defined according to objective measurements of maximal walking speed and grip strength, respectively. Cohort members were classified as frail if they met three or more, pre-frail if they met one or two and non-frail if none of the criteria were met.

Statistics

The measurements of size for each child every month from birth to 2 years of age and then at each birthday thereafter until 12 years of age were converted into z scores representing the difference from the mean value of the cohort, expressed in standard deviations (13). We examined how body size at each age differed from that predicted by size at an earlier age using the residuals from linear regression, which we refer to as conditional growth. Age at minimum BMI between the ages from 1 to 12 years was used to calculate the age at BMI rebound. Birth weight was divided into thirds (cut-

offs 3.22 kg and 3.60 kg). For consistency with previous studies (14), BMI at age 11 was grouped into three categories ($<16.0 \text{ kg/m}^2$, $16.0\text{-}17.5 \text{ kg/m}^2$ and $>17.5 \text{ kg/m}^2$) and body size at 1, 2, 7 and 11 years was used in the analyses. Multinomial regression analyses were used to investigate the association between body size at birth, 1, 2, 7 and 11 years, conditional growth and BMI rebound and frailty in old age. Conditional BMI gain was analysed separately for men and women due to an interaction between sex and conditional BMI gain from 2-11 years on frailty ($p=0.05$). We first adjusted for age and sex, and further for childhood and adulthood SES, adulthood BMI, smoking, hypertension and diabetes. The analyses were carried out with IBM SPSS version 23.0.

Results

The anthropometric measurements of the 475 boys and 603 girls and their characteristics in old age are shown in the Supplementary Table. The boys were heavier and taller than the girls at 1, 2 and 7 years, after which the sex differences in size levelled off. A greater proportion of girls experienced BMI rebound before 5 years of age compared to the boys (21.4% and 15.2%, $p=0.03$). The prevalence of frailty was 2.7% and 4.3%, respectively for men and women at the mean age of 71 years.

Body size at 1, 2, 7 and 11 years, BMI rebound and frailty in old age

No associations between size at 1, 2, 7 or 11 years, age at BMI rebound and frailty were observed. However, the prevalence of frailty was higher (8.6%) than the cohort average (2.7%) in boys who at birth belonged to the lowest tertile of birth weight and at 11 years of age to the group with the highest ($>17.5 \text{ kg/m}^2$) body mass index (4.2% and 4.3% respectively for girls).

Infant and childhood growth and frailty

Infant and childhood growth of the boys and girls who were frail in old age is expressed as mean Z scores in Figure 1. A child maintaining size in relation to other children in the cohort would follow a horizontal path in the figure. Boys who later developed frailty, however, having been small in size at birth, had accelerated BMI and weight gain starting approximately from the age of 1 year. In

childhood, the boys' BMI and weight measurements increased further so that they were well above the cohort average. In contrast, their heights increased rapidly after birth but remained slightly below the cohort average thereafter. This was not observed in women, who despite being slightly below the cohort average at birth, experienced accelerated growth in early life. However, in childhood their mean measurements of weight, height and BMI regressed towards the horizontal line indicating the cohort average.

Conditional growth was calculated for the age periods of 0-6 months (early infancy), 6-24 months (late infancy) and 2-11 years (childhood). No associations were observed between BMI gain in infancy and frailty. However, in analyses conducted separately for men and women, greater BMI gain during the period of 2-11 years was associated with frailty in boys (age-adjusted RRR 2.36, 95% CI 1.21, 4.63). The association was attenuated after additional adjustment for childhood and adulthood SES, adulthood BMI, smoking, hypertension and diabetes (adjusted RRR 2.07, 95% CI 0.94, 4.56). Exclusion of adulthood BMI from the adjustments had little effect on the association (adjusted RRR 2.16, 95% CI 0.98, 4.73). Infant and childhood weight and height gain were not associated with frailty in old age.

Discussion

Previously, a pattern of thinness both at birth and at 2 years followed by rapid growth thereafter, with boys being more sensitive to weight and girls more sensitive to height gain, has been associated with chronic diseases such as cardiovascular disease and type 2 diabetes (6). Using unique data on growth in the Helsinki Birth Cohort Study, we are the first to report that men who were frail at the mean age of 71 years had on average experienced accelerated BMI gain between the ages of 2 and 11 years. Furthermore, frailty was most prevalent in the boys who at birth belonged to the lowest third of birth weight and later at 11 years to the group with the highest BMI, a finding which is in line with previous findings on physical functioning (14).

Possible mechanisms underlying the association between childhood growth and frailty in old age could include besides environmental, genetic as well as epigenetic mechanisms, early programming. An unfavourable pre-natal environment may result in the trade-off of muscle tissue at the expense of the development of vital organs such as the brain (15). Early infancy is of major importance for muscle development, and as a result of this trade-off, babies born small lack muscle tissue which can persist into later life and manifest as decreased muscle strength (16). Thus, the observed BMI gain in the present study may have been attributed to increases in primarily adipose tissue. Although greater rates of frailty have been observed among individuals with both high and low BMI, a higher waist circumference indicating abdominal obesity was associated with frailty even within normal ranges of BMI (17). Furthermore, BMI has also been found to mediate certain factors that are associated with frailty, namely markers of systemic inflammation (18), the role of which in aging-related chronic disease pathogenesis has been established (19). Besides inflammation, certain abnormal patterns of early growth have also been found to contribute to adult chronic disease risk (6). A greater simultaneous prevalence of these diseases may result in diminished functional capacity to cope with stressors that are characteristic of frailty (20).

A key strength of this well-characterised cohort is the unique data on infant and childhood growth. The participants were followed up into the seventh decade with register-based information on covariates including SES. A major limitation to the interpretation of the results is the small number of frail men (n=13). We consider these findings preliminary and expect an increase in the number of frail individuals as the cohort ages. Voluntary participation in the clinical visits may have resulted in selective survival and an underrepresentation of frail individuals. Similarly, participation in the child welfare clinics was voluntary which limits the generalizability of the results to those who did not attend these visits. The long follow-up period might have resulted in confounding during the life course that we were not able to account for in the analyses. This study was conducted on people who

were born in Helsinki in 1934-1944 and the results need to be addressed in more contemporary cohorts.

In conclusion, men who were frail at the mean age of 71 years had on average experienced greater BMI gain from 2 to 11 years than their non-frail peers independent of BMI measured in late adulthood. This was not observed among women, suggesting that the patterns of early growth that predispose to frailty in old age may differ by sex.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Coordinating Ethics Committee of The Hospital District of Helsinki and Uusimaa) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figure Caption

Fig. 1. Infant and childhood growth of the 13 men and 26 women who developed frailty in a cohort of 1078 participants born in Helsinki

Legend of Supplementary Material

Supplementary Table. Characteristics of the study cohort (n=1078).

	Men (n=475)		Women (n=603)		p ^a
	Means (SD)	n	Means (SD)	n	
Neonatal, infant and childhood characteristics					
Length (cm) at age					
1 year	76.7 (2.4)	475	75.0 (2.4)	603	<0.001
2 years	86.8 (2.9)	475	85.6 (2.9)	603	<0.001
7 years	121.1 (4.7)	461	120.1 (4.5)	577	0.001
11 years	141.8 (5.6)	459	141.7 (6.4)	581	0.80
Weight (kg) at age					
1 year	10.5 (1.0)	475	9.9 (1.0)	603	<0.001
2 years	12.4 (1.1)	475	11.9 (1.1)	603	<0.001
7 years	22.7 (2.5)	461	22.3 (2.8)	577	0.02
11 years	33.9 (4.3)	459	34.2 (5.5)	582	0.35
Body mass index (kg/m ²) at age					
1 year	17.9 (1.4)	475	17.5 (1.3)	603	<0.001
2 years	16.7 (1.2)	475	16.4 (1.2)	603	0.001
7 years	15.5 (1.1)	461	15.5 (1.3)	577	0.62
11 years	16.9 (1.4)	458	17.0 (1.9)	581	0.20
Childhood socio-economic status (n=1074)					0.07
Upper middle class (%)	22.4		17.2		
Lower middle class (%)	22.8		22.2		
Manual worker (%)	54.9		60.7		
BMI rebound (n=1078)					0.03
<5 years (%)	15.2		21.4		
5-6.9 years (%)	33.9		29.5		

≥ 7 years (%)	50.9	49.1
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Adulthood characteristics at the mean age of 61 years

Height (cm)	176.2 (6.0)	468	162.3 (5.7)	598	<0.001
Weight (kg)	83.3 (13.0)	468	71.7 (13.2)	598	<0.001
Body mass index (kg/m ²)	26.8 (3.8)	468	27.3 (5.0)	598	0.44
Current smoker (%)	20.8	471	17.8	600	<0.001
Hypertension (%)	32.1	473	31.6	602	0.84
Diabetes (%)	6.8	473	4.0	602	0.04

Adulthood socio-economic status (n=1078)	<0.001
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Upper middle class (%)	23.6	11.4
Lower middle class (%)	28.0	60.2
Self-employed (%)	9.3	8.0
Manual worker (%)	39.2	20.4

Characteristics in old age measured at the mean age of 71 years

Frailty (n=1078)	0.38
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Non-frail (%)	56.6	56.2
Pre-frail (%)	40.6	39.5
Frail (%)	2.7	4.3

Frailty criteria (n=1078)

Exhaustion (%)	5.1	9.6	0.01
Weight loss (%)	6.5	5.1	0.36
Low physical activity (%)	7.4	11.6	0.02
Slowness (%)	20.2	19.9	0.91
Weakness (%)	19.7	20.1	0.86

^aDifference between men and women.