Abstract

Background: There is evidence suggesting that several chronic diseases have their origins in utero and that development taking place during sensitive periods may affect the aging process. We investigated whether early life determinants would be associated with frailty in old age.

Methods: At a mean age of 71 years, 1078 participants belonging to the Helsinki Birth Cohort Study were assessed for frailty according to the Fried frailty criteria. Early life measurements (birth weight, length, mother body mass index [BMI] and parity) were obtained from birth, child welfare and school health records. Multinomial regression analysis was used to assess the association between early life determinants and frailty in old age.

Results: Weight, length and BMI at birth were all inversely associated with frailty in old age. A 1kg increase in birth weight was associated with a lower relative risk ratio (RRR) of frailty (age and sex adjusted RRR 0.40, 95% CI 0.19, 0.82) compared to non-frailty. Associations persisted after adjusting for several confounding factors. Compared to cohort members in the upper middle class, those who as adults worked as manual workers or belonged to the lower middle class, were at an increased risk of frailty.

Conclusions: Those who were small at birth were at an increased risk of developing frailty in old age, suggesting that frailty is at least partly programmed in early life. A less privileged socio-economic status in adulthood was associated with an increased risk of frailty in old age.

Key Words: Frailty – life course – birth weight – fetal programming – aging

Key points

- Evidence suggests that several chronic diseases may have their origins in utero
- There is evidence suggesting that a small body size at birth may be associated with certain sub-components of frailty
- Small body size at birth was associated with the syndrome of frailty as a whole
- A less privileged adult socio-economic status was associated with frailty in old age

Introduction

Globally, as the mean age is increasing with more people surviving into old age (1), the prevalence of frailty is increasing particularly among those aged 80 years and older (2). Frailty, the clinical condition that affects several organ systems predisposing an individual to poor recovery from minor changes in health status, is associated with adverse outcomes such as falls, hospitalization, disability, institutionalization and premature mortality (3,4)**.** Several factors such as poorer physical functioning, grip strength, sarcopenia and lower cognitive functioning can increase disturbances in homeostasis which may result in frailty (3,5,6).

Other factors such as underprivileged socio-economic background and lower educational attainment and income (7) as well as financial difficulties (8) have also been linked to frailty. Furthermore, an increased number of co-morbid diseases predisposes an individual to frailty (9).

The theoretical framework of life-course epidemiology suggests that development taking place during the course of one's life has long-lasting effects on future health (10). Within this framework, the concept of programming stresses the importance of exposure taking place at critical times during early development and their impact on future health (11). Besides associations between body size at birth and adult chronic diseases e.g. cardiovascular disease (12,13), studies on the associations between body size at birth and sub-components of frailty such as grip strength (14) and physical

activity (15) highlight the importance of prenatal exposures in determining later functioning. However, knowledge on how body size at birth affects the condition of frailty as a whole and whether these associations reach beyond those found previously for the individual sub-components, is scarce.

A recent study suggested that maternal undernutrition during pregnancy and a small body size at birth might predispose to frailty. However, that study did not have the statistical power to establish such an association (16). In the present study we explore the association between early life determinants; body size at birth, parity, maternal adiposity, socioeconomic status and frailty according to Fried's criteria (3) at an average age of 71 years.

Materials and methods

Study design

The present sub-study of the Helsinki Birth Cohort Study includes a sub-population of 8,760 individuals who were born in Helsinki between the years 1934 and 1944, had at that time visited child welfare clinics and who later lived in Finland in 1971 when a unique personal identification number was assigned to all Finnish residents (17). A random sample of participants (n=2003) were examined clinically between the years 2001 and 2004. At the time of the clinical follow-up in 2011-2013, 151 had died, 212 had declined their subsequent participation in the study and 236 lived further than 100km from Helsinki. Of the 1,404 remaining individuals who could be traced, 1,094 participated in a clinical follow-up during the years 2011-2013. Of these, 1078 individuals (603 women and 475 men) had adequate information on frailty criteria and were included in this study (18). The study complies with the guidelines of the Declaration of Helsinki. The clinical study protocol was approved by the Coordinating Ethics Committee of The Hospital District of Helsinki and Uusimaa. Written informed consent was acquired from each participant prior to initiating any study procedures.

Early life factors and socio-economic status

Data on the mothers consisted of parity together with body weight measured on admission in labor. Gestational age at delivery was estimated from the date of the last menstrual period. Data on their newborn babies consisted of birth weight and length extracted from hospital birth records. Childhood socio-economic status (SES) was assessed based on the father's occupation as indicated by the highest occupational class extracted from birth, child welfare and school records. Socio-economic status in adulthood, based on occupational status, was obtained from Statistics Finland. As in previous publications, we used the maximum occupational status attained at 5-year intervals between 1970 and 2000, grouped into upper and lower middle class, self-employed and manual workers.

Frailty

Frailty was assessed using five criteria including weight loss, exhaustion, low physical activity, slowness and weakness at the clinical examination between the years 2011 and 2013 (3). Weight loss was assessed using a question from the Beck Depression Inventory (19) inquiring about recent weight loss. Those who reported losing at least 5kg met the criterion. Exhaustion was evaluated using the following question: "How many times during the last week have you felt unusually tired or weak?" The criterion was met if the response was "On three days or more". Low physical activity was assessed using the validated KIHD (Kuopio Ischaemic Heart Disease Risk Study) leisure time physical activity (LTPA) questionnaire (20). Those whose total physical activity time (including e.g. walking, resistance training and gardening) was 1 hour or less per week met the criterion. If KIHD LTPA data were missing (n=42), physical activity was assessed using the question: "In total, how many hours a week do you do the following sports (walking, jogging, cycling, swimming, gymnastics, group exercise)?" The criterion was met if the total duration of physical activity was 1 hour per week at the most. Slowness was assessed based on maximal walking speed over a 4.57 meter distance. For walking speed, sex-specific cut-offs for medium height (for men ≤175.9 cm cut-off was 1.65 m/sec and >175.9 cm 1.83 m/sec and for women ≤162.2 cm cut-off was 1.47 m/sec and >162.2 cm 1.55 m/sec) were used to identify the slowest 20% that met the criterion. Weakness was assessed based on

the isometric grip strength of the dominant hand using an adjustable dynamometer chair (Good Strength, Metitur Ltd, Jyväskylä, Finland). For grip strength, sex-specific quartiles of BMI were used to identify the weakest 20% that met the criterion. 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.

Covariates

The participants' baseline characteristics including height and weight were measured at the clinical follow-ups. Body mass index (BMI) was calculated as weight in kilograms divided by square of height in meters (kg/m^2). Participants' smoking status (smoker, former smoker, never smoked) and self-reported diabetes and hypertension were assessed using questionnaires at the clinical examination.

Statistical methods

Results are expressed as means and standard deviations (SD) in case of continuous and as proportions for dichotomous or categorical values. Differences in the background information were tested using one-way ANOVA in case of continuous and cross tabulation in case of categorical values. We used multinomial regression analysis to assess the association between early life determinants and frailty in old age. We first adjusted for sex and age. In Model 2, further adjustments were made for gestational age, childhood and adulthood SES. In Model 3, the analyses were further adjuster for adulthood BMI, smoking, hypertension and diabetes. Since no significant interactions were observed between sex and body size at birth on frailty (p=0.899), we report results pooled by sex. In order to obtain a dataset with complete data on all main variables and covariates, we imputed values for covariates using multiple imputations (gestational age n=33, childhood SES n=4, adult BMI n=13, physical activity n=9, smoking n=7, hypertension n=3 and diabetes n=3; maximum proportion of data missing was 3,1%). A total of 10 imputed datasets were created using all variables in the analyses. Regression models were first performed using complete data available for all main variables and

covariates and then using multiply imputed datasets combining the effect estimates using Rubin's rules. While these results were very similar, we present findings on imputed data. The analyses were carried out with SPSS (IBM SPSS Statistics for Windows, Version 23.0 IBM Corp. Released 2015, Armonk, NY).

Results

General characteristics

Characteristics of the 1078 men and women included in the study are shown in Table 1. The mean birth weight and birth length of frail individuals were smaller than those of non-frail individuals (3.25 kg vs 3.45 kg and 49.5 cm vs 50.5 cm; both p-values $\leq$0.003). The majority of frail participants were manual workers during their working careers, and at the average age of 62 years, self-reported hypertension and diabetes as well as a higher measured BMI were more common among frail cohort members than their non-frail counterparts (all p-values for covariates <0.001).

Frailty criteria

The prevalence of frailty was 2.7% for men and 4.3% for women with no significant sex differences (p=0.383) as indicated in Supplementary Table 1. The most commonly met criteria for frailty were slowness and weakness accounting for 20.1% and 19.9%, respectively, of the cohort members. Other met criteria were low physical activity (9.7%), exhaustion (7.6%) and weight loss (5.6%). Women reported exhaustion and low physical activity more frequently (p=0.005 and p=0.02, respectively) whereas no significant sex differences were seen for weight loss.

Small body size at birth and frailty

The mean birth weight varied according to frailty in old age, as illustrated in Figure 1. A smaller body size at birth was associated with frailty in old age: the birth weight and length of frail cohort members were lower than those of non-frail participants (p=0.018 and p=0.004, respectively). The mean birth

weight and length of pre-frail participants were also lower than those of non-frail participants (p=0.031 and p=0.02, respectively). Birth BMI or gestational age were not associated with frailty.

Table 2 shows the relative risk ratios (RRR's) for pre-frailty and frailty according to selected early life factors. Birth weight was associated with frailty: a 1kg increase in birth weight was associated with a lower RRR of frailty (age and sex adjusted RRR 0.40, 95% CI 0.19, 0.82) compared to non-frailty. Further adjustment for adult BMI, socioeconomic status, adult lifestyle and main chronic diseases strengthened the association. Similarly, a 1cm increase in birth length decreased the RRR of frailty, age and sex adjusted RRR 0.78, 95% CI 0.66, 0.91 compared to non-frailty. Further adjustments did not significantly alter the association. Similarly, birth BMI was associated with frailty: a one-unit increase in birth BMI resulted in a RRR of 0.02, (95% CI 0.003, 0.25). The associations for birth weight and birth length and pre-frailty were similar. Birth order and maternal BMI were not significantly associated with frailty at age 71 years.

Socio-economic status and frailty

The RRR's for pre-frailty and frailty according to childhood and adult socio-economic status are shown in Supplementary Table 2. In general, an increase in the RRR's for pre-frailty and frailty according to lower SES in adulthood and childhood relative to the highest SES were observed. Those who grew up in a family of manual workers compared to those who came from a upper middle class background, had a greater RRR for pre-frailty when non-frailty was the reference group. In a sex and age adjusted regression analysis the observed RRR was 1.46 (95% CI 1.05, 2.04). The results became non-significant after adjustment for adult SES, adult BMI and health behaviors. The lower the SES in adulthood, the higher was the observed RRR for pre-frailty and frailty in comparison with cohort members in the highest SES. For manual workers compared to those belonging to the upper middle class, the RRR's for pre-frailty and frailty in comparison with non-frailty were 1.82 (95% CI 1.23, 2.68) and 3.18 (95% CI 1.15, 8.80), respectively, in an age- and sex-adjusted analysis, but became

statistically non-significant after further adjustments. Similarly, those who as adults belonged to the lower middle class relative to those in upper middle class, had increasing RRR's for pre-frailty and frailty. The associations remained significant after adjusting for other confounding factors.

Discussion

We found that small body size at birth, as indicated by birth weight, length and body mass index, was associated with an increased risk of frailty at a mean age of 71 years in this well-characterized birth cohort. There was no significant association between other early life determinants such as birth order or mother's BMI and frailty in old age. Further, relative to the participants with the highest SES in adulthood, cohort members with a lower SES had an increased risk of developing frailty in old age. Childhood SES was only associated with pre-frailty in those from a family of manual workers relative to those from an upper middle class background in analyses adjusted by sex and age.

This is the first study to our knowledge that studies the effects of early life determinants on frailty as a whole. We had sufficient power to study the association which was addressed in a previous study that lacked the statistical power to establish this association (16). Due to limited power we report analyses pooled by sex, however, the results were similar in analyses performed separately for men and women. The observed prevalence of frailty among men (2.7%) and women (4.3%) was lower than that reported in previous studies (21,22). Our findings are in line with previous studies linking adult SES and frailty (23), however, we were not able to confirm previous findings on childhood SES and frailty (7).

Possible mechanisms through which a small body size at birth would predispose to frailty could include, besides genetic and environmental factors, early programming (11). First, unfavorable conditions during fetal life may lead to inadequate development of the musculoskeletal system. This can manifest as diminished fat-free mass (24) or sarcopenia (25) and consequently, to a lowered muscle strength (26) and physical activity (27). Second, small body size at birth has been associated

with depressive disorders later in life (28). This might in turn contribute to diminished activity, self-reported exhaustion and weight loss (19). Lastly, a small body size at birth may alter organ function and excretion in ways that accelerate physiological aging and therefore promote the onset of frailty (29).

It is known that a small body size at birth is a risk factor for several chronic illnesses such as cardiovascular disease and hypertension (12,13). These conditions may either directly weaken the functional capacity of organ systems or indirectly through comorbidity, predispose to frailty in old age (9). The presence of several chronic conditions may involve systemic inflammation which in turn might contribute to the onset of frailty (30).

The study had several strengths. Data on body size at birth and socio-economic status were extracted from reliable sources such as national registers. Frailty was defined according to Fried (3) using standardized methods. However, caution should be taken when interpreting the results. The prevalence of frailty, which was lower than the population average, resulted in few frail individuals consequently limiting our ability to detect associations between early life determinants and frailty. The clinical check-ups might be missing the cohort members in poor health and we also cannot exclude that this may be partly due to survival effect. Although the analyses were adjusted for several confounding factors, some confounding particularly due to frailty and other simultaneous co-morbidities that might be insightful in understanding possible mechanisms by which factors in early life may increase the risk of frailty, was unaccounted for. The applicability of the results to other populations is limited because the data is based on people born in Helsinki between the years 1934 and 1944 and who at that time went to child welfare clinics.

In conclusion, this study extends previous knowledge linking early life factors and individual sub-components of frailty to the clinical syndrome of frailty as a whole. Small body size at birth was associated with frailty in old age and adjusting for several confounding factors did not alter the

association. Our findings highlight the importance of early life factors in determining health in old age and suggest interventions targeted to improve the health of women already at childbearing age.

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Conflict of interest

The authors have no competing interests to declare.

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Legend for tables

Table 1. Characteristics of the study cohort according to frailty classification.

	Non-frail n=608 Mean (SD)	**Pre-frail n=431 Mean (SD)**	**Frail n=39 Mean (SD)**	**p[a]**
Birth characteristics				
Women, n (%)	339 (55.8)	238 (55.2)	26 (66.7)	0.383
Birth weight (kg)	3.45 (0.45)	3.38 (0.47)	3.25 (0.50)	0.003
Birth length (cm)	50.5 (1.9)	50.2 (1.9)	49.5 (2.2)	0.001
Birth BMI (kg/m^2)	13.5 (1.2)	13.3 (1.2)	13.3 (1.9)	0.122
Gestational age (weeks)	39.5 (1.7)	39.2 (1.9)	39.3 (2.4)	0.097
Mother's BMI in late pregnancy (kg/m^2)	26.6 (2.8)	26.4 (2.9)	27.0 (2.6)	0.278
Parity				0.220
First born, n (%)	268 (44.1)	205 (47.6)	22 (56.4)	
Second born or later, n (%)	340 (55.9)	226 (52.4)	17 (43.6)	
Childhood socio-economic status				0.118
Manual workers, n (%)	335 (55.3)	262 (61.1)	27 (69.2)	
Lower middle class, n (%)	138 (22.8)	96 (22.4)	7 (17.9)	
Upper middle class, n (%)	133 (21.9)	71 (16.6)	5 (12.8)	
Adult characteristics				
Age (years)	70.6 (2.5)	71.4 (3.0)	71.2 (2.3)	<0.001
Height (cm)	168.9 (9.0)	168.0 (9.1)	165.4 (8.9)	0.042
Weight (kg)	75.8 (13.3)	78.2 (15.3)	77.0 (16.9)	0.030
BMI (kg/m^2)	25.9 (3.5)	27.1 (4.2)	28.1 (4.8)	<0.001
Current smoker, n (%)	95 (15.7)	98 (22.9)	12 (30.8)	0.006

Hypertension, n (%)	171 (28.2)	145 (33.7)	26 (66.7)	<0.001
Diabetes, n (%)	21 (3.5)	28 (6.5)	7 (17.9)	<0.001
Adult socio-economic status				0.001
Manual workers, n (%)	146 (24.0)	143 (33.2)	20 (51.3)	
Self-employed, n (%)	58 (9.5)	32 (7.4)	2 (5.1)	
Lower middle class, n (%)	292 (48.0)	192 (44.5)	12 (30.8)	
Upper middle class (%)	112 (18.4)	64 (14.8)	5 (12.8)	

Note. BMI=body mass index. [a] Trend across frailty classification.

Table 2. Multivariate regression analyses of frailty.

	Model 1	**Model 2**	**Model 3**
	RRR (95% CI)	**RRR (95% CI)**	**RRR (95% CI)**
Birth weight n=1078[†]			
Non-frail	ref.	ref.	ref.
Pre-frail	0.73 (0.55 to 0.96)[*]	0.77 (0.57 to 1.04)	0.73 (0.53 to 0.99)[*]
Frail	0.40 (0.19 to 0.82)[*]	0.36 (0.16 to 0.81)[*]	0.36 (0.15 to 0.86)[*]
Birth length n=1066[†]			
Non-frail	ref.	ref.	ref.
Pre-frail	0.92 (0.86 to 0.98)[*]	0.93 (0.86 to 1.00)	0.92 (0.85 to 0.99)[*]
Frail	0.78 (0.66 to 0.91)[**]	0.76 (0.63 to 0.91)[**]	0.77 (0.63 to 0.94)[**]
Birth BMI n=1078[†‡]			
Non-frail	ref.	ref.	ref.
Pre-frail	0.43 (0.08 to 2.28)	0.56 (0.10 to 3.01)	0.77 (0.12 to 4.81)
Frail	0.02 (0.003 to 0.25)[**]	0.04 (0.004 to 0.34)[**]	0.03 (0.001 to 0.77)[*]
Birth order (first born vs. second or later) n=1078[†]			
Non-frail	ref.	ref.	ref.
Pre-frail	1.09 (0.85 to 1.41)	1.14 (0.88 to 1.46)	1.11 (0.85 to 1.44)
Frail	1.59 (0.82 to 3.06)	1.80 (0.94 to 3.47)	1.85 (0.93 to 3.70)
Mothers BMI in late pregnancy n=935[†]			
Non-frail	ref.	ref.	ref.
Pre-frail	0.97 (0.93 to 1.02)	0.97 (0.93 to 1.02)	0.96 (0.96 to 1.00)
Frail	1.04 (0.93 to 1.17)	1.04 (0.98 to 1.10)	1.00 (0.89 to 1.12)

Note. BMI=body mass index

[†]Exposures analyzed separately

‡Quadratic term included

$p<0.001^{***}$, $p<0.01^{**}$, $p<0.05^{*}$

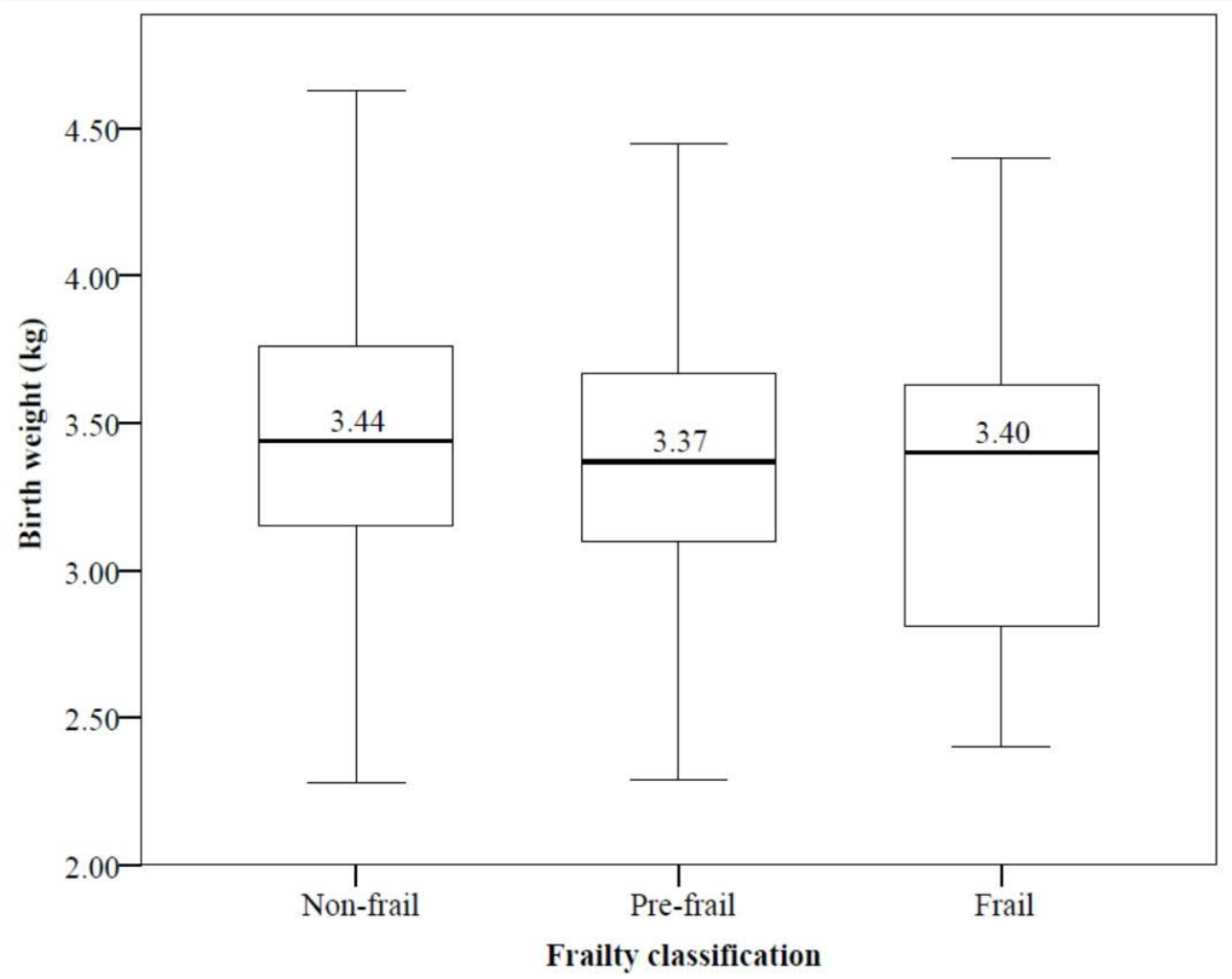
Model 1 adjusted for sex and age

Model 2 adjusted for Model 1 plus gestational age and childhood and adulthood SES

Model 3 adjusted for Model 2 plus adult BMI, smoking, hypertension and diabetes

Figure

Figure 1. Boxplot of birth weight according to frailty classification.



Appendices

Supplementary Table 1. Frailty criteria and classification according to sex.

	Male	**Female**	**p**[a]
Frailty sub-criteria			
Weight loss (%)	6.5	5.1	0.361
Exhaustion (%)	5.1	9.6	0.005
Low physical activity (%)	7.4	11.6	0.020
Slowness (%)	20.2	19.9	0.910
Weakness (%)	19.7	20.1	0.858
Frailty classification			0.383
Non-frail (%)	56.6	56.2	
Pre-frail (%)	40.6	39.5	
Frail (%)	2.7	4.3	

[a]Difference between sex

Supplementary Table 2. Relative risk ratios (RRR) and 95% confidence intervals for frailty status at age 71 years according to childhood and adult SES.

	Non-frailty (ref.)	**Pre-Frailty**		**Frailty**	
		Model 1	**Model 2**	**Model 1**	**Model 2**
		RRR (95% CI)		**RRR (95% CI)**	
Childhood socio-economic status[a]					
Upper middle class		Ref.	Ref.	Ref.	Ref.
Lower middle class		1.13 (0.83 to 1.55)	1.10 (0.79 to 1.53)	1.58 (0.67 to 3.72)	1.41 (0.56 to 3.52)
Manual workers		1.46 (1.05 to 2.04)*	1.22 (0.85 to 1.74)	2.05 (0.77 to 5.45)	1.13 (0.39 to 3.25)
Adulthood socio-economic status[b]					
Upper middle class		Ref.	Ref.	Ref.	Ref.
Lower middle class		1.50 (1.10 to 2.05)**	1.39 (0.99 to 1.93)*	4.26 (1.97 to 9.24)***	3.99 (1.76 to 9.02)**
Self-employed		1.73 (1.06 to 2.84)*	1.69 (0.99 to 2.86)	4.31 (0.97 to 19.17)	4.56 (0.97 to 21.36)
Manual workers		1.82 (1.23 to 2.68)**	1.47 (0.96 to 2.23)	3.18 (1.15 to 8.80)*	2.80 (0.91 to 8.63)

$p<0.001^{***}$, $p<0.01^{**}$, $p<0.05^{*}$

Model 1 adjusted for sex and age

[a]Model 2 adjusted for Model 1 plus adulthood SES, adult BMI, smoking, hypertension and diabetes

[b]Model 2 adjusted for Model 1 plus childhood SES, adult BMI, smoking, hypertension and diabetes