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# Early growth, stress, and socioeconomic factors as predictors of the rate of multimorbidity accumulation across the life course: a longitudinal birth cohort study



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## Summary

**Background** Early growth, stress, and socioeconomic factors are associated with future risk of individual chronic diseases. It is uncertain whether they also affect the rate of multimorbidity accumulation later in life. This study aimed to explore whether early life factors are associated with the rate at which chronic diseases are accumulated across older age.

**Methods** In this national birth cohort study, we studied people born at Helsinki University Central Hospital, Helsinki, Finland between Jan 1, 1934, and Dec 31, 1944, who attended child welfare clinics in the city, and were living in Finland in 1971. Individuals who had died or emigrated from Finland before 1987 were excluded, alongside participants without any registry data and who died before the end of the registry follow-up on Dec 31, 2017. Early anthropometry, growth, wartime parental separation, and socioeconomic factors were recorded from birth, child welfare clinic, or school health-care records, and Finnish National Archives. International Classification of Diseases codes of diagnoses for chronic diseases were obtained from the Care Register for Health Care starting from 1987 (when participants were aged 42–53 years) until 2017. Linear mixed models were used to study the association between early-life factors and the rate of change in the number of chronic diseases over 10-year periods.

**Findings** From Jan 1, 1934, to Dec 31, 2017, 11 689 people (6064 [51·9%] men and 5625 [48·1%] women) were included in the study. Individuals born to mothers younger than 25 years ( $\beta$  0·09; 95% CI 0·06–0·12), mothers with a BMI of 25–30 kg/m<sup>2</sup> (0·08; 0·05–0·10), and mothers with a BMI more than 30 kg/m<sup>2</sup> (0·26; 0·21–0·31) in late pregnancy accumulated chronic diseases faster than those born to older mothers (25–30 years) and those with a BMI of less than 25 kg/m<sup>2</sup>. Individuals with a birthweight less than 2·5 kg (0·17; 0·10–0·25) and those with a rapid growth in height and weight from birth until age 11 years accumulated chronic diseases faster during their life course. Additionally, paternal occupational class (manual workers vs upper-middle class 0·27; 0·23–0·30) and wartime parental separation (0·24; 0·19–0·29 for boys; 0·31; 0·25–0·36 for girls) were associated with a faster rate of chronic disease accumulation.

**Interpretation** Our findings suggest that the foundation for accumulating chronic diseases is established early in life. Early interventions might be needed for vulnerable populations, including war evacuee children and children with lower socioeconomic status.

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## Introduction

The risk of developing chronic diseases is not only influenced by genetics and lifestyle, but also by individual and environmental factors during the periconceptional, fetal, and infant phases of life.<sup>1,2</sup> The Developmental Origins of Health and Disease (DOHaD) hypothesis suggests that early-life factors (eg, undernutrition, growth patterns, or stress) could shape future health outcomes through suboptimal organ development, altered metabolic and hormonal pathways, and epigenetic changes.<sup>1,2</sup> This theory is well established for individual diseases, including diabetes and ischaemic heart disease,<sup>2–4</sup> but the evidence remains scarce regarding the

association between early life factors and multimorbidity (ie, the co-occurrence of multiple chronic diseases in the same individual) in later life.<sup>5–12</sup> Multimorbidity is associated with premature mortality, poorer functioning, and higher use of health-care services.<sup>13</sup> The rate of multimorbidity accumulation over time reflects the speed at which an individual is ageing,<sup>14</sup> and consequently predicts the future development of frailty<sup>15</sup> and use of health-care services.<sup>13</sup>

Previous studies on early life factors and multimorbidity are characterised by a small number of studies and conflicting findings. A previous study reported an association between lower birthweight and

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For the Finnish translation of the abstract see Online for appendix 1

For the Swedish translation of the abstract see Online for appendix 2

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See Online for appendix 3

## Research in context

### Evidence before this study

We searched PubMed for studies published from the inception of the database to Dec 1, 2022, using the search terms “multimorbidity” AND (“birth weight” OR “early growth” OR “childhood adversity” OR “childhood socioeconomic status”) along with all the synonyms (appendix 3 p 28). We only included studies published in English. We specifically looked for studies that defined multimorbidity in late adulthood or old age. Although survival rates have improved, the globally ageing population and unhealthy lifestyle factors have been identified as contributing factors to the rising prevalence of multimorbidity. Our comprehensive understanding of how earlier life phases affect this phenomenon remains poor. Early growth, stress, and socioeconomic factors have been shown to influence the future risk of individual chronic diseases in adults. However, when it comes to multimorbidity, the evidence is both scarce and characterised by conflicting findings. It is uncertain whether factors in the

periconceptional, fetal, and infant phases of life affect the rate of multimorbidity during the life course.

### Added value of this study

Our study suggests that younger maternal age and higher BMI, small body size at birth, rapid childhood growth in height and weight, adverse socioeconomic circumstances, and wartime parental separation influence the speed of accumulation of chronic diseases in later life.

### Implications of all the available evidence

The influence of early life characteristics on multimorbidity accumulation is broader and more consistent than what previous studies suggest. To improve the long-term health of future generations, interventions should focus on preventing maternal obesity, optimising maternal health during pregnancy, and preventing childhood obesity on a global scale. Groups at a high risk of accumulating chronic diseases during adulthood, such as war evacuee children and those with lower socioeconomic status, might require targeted early interventions.

multimorbidity at 46–48 years,<sup>5</sup> but no such association has been observed in old age.<sup>6</sup> Scarce findings on early growth (birth to 1 year) reported no association with multimorbidity risk.<sup>6</sup> Parental socioeconomic status and childhood health have shown varying degrees of association with multimorbidity risk,<sup>6–9</sup> but not with multimorbidity accumulation.<sup>7,9,10</sup> Still, adequacy of childhood nutrition has been associated with slower multimorbidity accumulation.<sup>9</sup> Childhood adverse experiences have been associated with multimorbidity more consistently,<sup>11,12</sup> particularly parental physical abuse, which was associated with faster disease accumulation.<sup>9</sup> Yet, evidence remains scarce regarding the effect of severe early stress resulting from war, conflicts, and migration movements on multimorbidity.

The prevalence of multimorbidity has increased over the past two decades.<sup>16</sup> Understanding factors connected with this trend is crucial, especially modifiable early risk factors, because chronic disease accumulation poses a substantial challenge to individuals, their caregivers, and health-care systems. To address previous gaps in research, we aimed to provide a comprehensive overview of early factors covering physical, psychosocial, and socioeconomic aspects from developmentally important life stages. Recent evidence from this cohort highlighted the importance of earlier life phases on healthy ageing.<sup>17</sup> With the DOHaD hypothesis<sup>12</sup> as our theoretical framework, our study investigated whether factors during gestation, birth, infancy, and childhood predict the rate of chronic disease accumulation over a 30-year period. We hypothesised that adverse early life circumstances would accelerate the depletion of physiological reserves and the ageing process, leading to faster chronic disease accumulation.

## Methods

### Study design and participants

This national birth cohort study used the Helsinki Birth Cohort, which includes 6975 men and 6370 women who were born at Helsinki University Central Hospital, Helsinki, Finland between Jan 1, 1934, and Dec 31, 1944, attended child welfare clinics in the city, and were living in Finland in 1971 when unique identification numbers were assigned to all Finnish residents (appendix 3 p 25).<sup>3</sup> Early life characteristics, spanning from birth to 11 years old, were extracted from records held at the hospitals, child welfare and school health-care clinics, and the Finnish National Archives.<sup>3,4,18</sup> After excluding individuals who had died (n=404) or emigrated from Finland (n=895) before 1987, we used the participants' unique identification number to integrate clinical data from the Care Register for Health Care<sup>19</sup> from Jan 1, 1987. We excluded an additional 357 participants without any registry data and those who died before the end of the registry follow-up on Dec 31, 2017, resulting in an analytical sample of 11 689 individuals. Follow-up ended with participant death, emigration, or on Dec 31, 2017, whichever occurred first.

The study was approved by the Ethics Committees of the Hospital District of Helsinki and Uusimaa and that of the National Public Health Institute, Helsinki, Finland.

### Procedures

Multimorbidity was quantified as the sum of chronic diseases, serving as a proxy measure of accelerated ageing.<sup>14</sup> Chronic diseases were defined as conditions with prolonged duration, resulting in residual disability or requiring extended care, treatment, or rehabilitation.<sup>20</sup> Each chronic disease was categorised into one of the

60 chronic disease categories proposed by Calderón-Larrañaga and colleagues.<sup>20</sup> To this end, all hospital inpatient and outpatient health-care records from Jan 1, 1987, until Dec 31, 2017, were extracted from the Care Register for Health Care,<sup>19</sup> including visit or admission dates and diagnostic codes, transitioning from International Classification of Diseases (ICD)-9 to ICD-10 in 1995 (appendix 3 pp 2–20). Age at visit or admission indicated the onset of each chronic disease, and when a disease was present, it persisted in all subsequent data points. The primary outcome variable for this study was the changing sum of chronic disease groups a person had over time.

In accordance with the DOHaD hypothesis,<sup>1,2</sup> we chose physical, psychosocial, and socioeconomic factors from different developmental stages to comprehensively capture the participants' early life circumstances. Birth records from the Helsinki University Central Hospital provided data on maternal age, parity, height, weight at giving birth, and last menstrual period. Gestational age was calculated as the time in weeks between the last menstrual period and date of birth. Parity information was used to dichotomise the participants as first born or not. The birth records for newborns included information on birthweight and length. The mother's BMI (in kg/m<sup>2</sup>) and the BMI (in kg/m<sup>2</sup>) and ponderal index (in kg/m<sup>3</sup>) of the newborn were calculated. The children had been regularly measured in child welfare clinics and school health care, archived by the Helsinki City archives. For each child, we estimated their height, weight, and BMI at each birthday from 1 to 11 years. Measurements within 2 years of the specific age were considered. These values were converted into Z scores to indicate the deviation from the cohort mean. Fewer measurements were made between age of 2 years and enrolment at school than the number measured before 2 years of age. Conditional growth (0–2 years for infancy; 2–7 years for early childhood; and 7–11 years for childhood) was determined by examining the residuals from linear regression to indicate how body size at each age differed from the predicted size based on an earlier age. Childhood socioeconomic status (SES) was coded as manual workers, lower-middle class, and upper-middle class based on the father's highest occupational status reported in birth, child welfare clinic, or school health-care records. Information on separations during World War 2, when participants were sent abroad without their families to protect them from the war, was obtained from the Finnish National Archives and included details on the age at and duration of the separation.<sup>18</sup>

### Statistical analysis

Our analysis aimed to explore and quantify the association between early life factors and the change in chronic diseases with age. As disease accumulation was linear in this sample (appendix 3 p 26), we used separate linear mixed models for each early life factor. Hypothesised

relationships between early life factors and chronic disease accumulation are reported in appendix 3 (p 27). We centred age at 42 years, the youngest age in our dataset, and other continuous variables at their means. Model comparisons, including assessments of model fit, residual plots, and plotted model predictions, showed no evidence of quadratic time effects or interactions with early-life factors. Furthermore, overall assessment of the comparisons supported a Gaussian distribution over a Poisson distribution for the number of chronic diseases. We determined fixed effects based on the literature, including covariate–age interactions due to their significant associations with chronic disease accumulation. To account for individual variability, we included random intercepts for each individual, determining the compound symmetry within-individual variance–covariance structure.

Age-adjusted and sex-adjusted models were controlled for sex and its interaction with age, with age serving as the underlying time scale. Fully adjusted models were additionally controlled for childhood SES and its interaction with age (appendix 3 p 21). Inter-relationships between early life factors (appendix 3 p 22) were considered, such as including gestational age in models of weight, length, and BMI at birth, and birthweight in models including maternal BMI. We incorporated quadratic terms for early life factors to test for non-linear relationships and included them if significant.

Complete case results are presented for the entire sample. For wartime separation models, we present separate results for boys and girls due to significant sex interactions ( $p < 0.001$ ). 95% CIs were calculated using parametric bootstrapping. We set statistical significance as a p value of less than 0.05 and used Bonferroni correction for multiple comparisons. We performed all analyses using R<sup>21</sup> packages lme4<sup>22</sup> and lmerTest.<sup>23</sup>

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### Results

From Jan 1, 1934, to Dec 31, 2017, 11689 participants (6064 [51.9%] men and 5625 [48.1%] women) were included in the study. At birth, boys had a mean weight of 3.47 kg (SD 0.49) and measured 50.6 cm (SD 2.0), whereas girls had a mean weight of 3.34 kg (SD 0.46) and measured 49.9 cm (SD 1.8; table 1). Socio-economically, most participants came from manual working backgrounds. During World War 2, 1437 (12.5%) participants were evacuated. At the start of the follow-up on Jan 1, 1987, the mean age of participants was 45.8 years (SD 2.8). The proportion of participants with chronic diseases, and the number of chronic diseases individuals had, increased over time (figure 1). Participants were followed up for a median of 31 years (IQR 28–31), with the oldest participant reaching 84 years

	All (n=11 689)	Men (n=6064)	Women (n=5625)
<b>Birth characteristics</b>			
Weight, kg	11 689 (100%); 3·40 (0·48)	6064 (100%); 3·47 (0·49)	5625 (100%); 3·34 (0·46)
Length, cm	11 579 (99·1%); 50·2 (1·9)	6011 (99·1%); 50·6 (2·0)	5568 (99·0%); 49·9 (1·8)
BMI, kg/m <sup>2</sup>	11 579 (99·1%); 13·4 (1·2)	6011 (99·1%); 13·5 (1·2)	5568 (99·0%); 13·4 (1·2)
Ponderal index, kg/m <sup>3</sup>	11 579 (99·1%); 26·7 (2·2)	6011 (99·1%); 26·7 (2·3)	5568 (99·0%); 26·8 (2·2)
Gestational age, weeks	11 294 (96·6%); 39·9 (1·9)	5841 (96·3%); 39·9 (1·9)	5453 (96·9%); 40·0 (1·9)
First born	5705/11 686; (48·8%)	2994/6063 (49·4%)	2711/5623 (48·2%)
Second born or later	5981/11 686 (51·2%)	3069/6063 (50·6%)	2912/5623 (51·8%)
<b>Maternal characteristics</b>			
Age, years	11 682 (99·9%); 28·4 (5·4)	6060 (99·9%); 28·3 (5·4)	5622 (99·9%); 28·5 (5·5)
BMI, kg/m <sup>2</sup>	10 529 (90·1%); 26·2 (2·9)	5461 (90·1%); 26·2 (2·9)	5068 (90·1%); 26·2 (2·9)
<b>Childhood socioeconomic status</b>			
Manual worker	6648/11 392 (58·4%)	3412/5925 (57·6%)	3236/5467 (59·2%)
Lower-middle class	2763/11 392 (24·2%)	1433/5925 (24·2%)	1330/5467 (24·3%)
Upper-middle class	1981/11 392 (17·4%)	1080/5925 (18·2%)	901/5467 (16·5%)
<b>Wartime separation during World War 2</b>			
Separated	1437/11 500 (12·5%)	774/5995 (12·9%)	663/5505 (12·0%)
Age at separation, years	1297/1437 (90·3%); 4·6 (2·4)	704/774 (91·0%); 4·5 (2·4)	593/663 (89·4%); 4·8 (2·4)
Duration of separation, years	1266/1435 (88·2%); 1·7 (1·0)	685/774 (88·5%); 1·8 (1·1)	581/663 (87·6%); 1·7 (1·0)
<b>Serial measurements of body size</b>			
Height (cm) at age			
1 year	11 673 (99·9%); 75·7 (2·7)	6054 (99·8%); 76·5 (2·6)	5619 (99·9%); 74·8 (2·6)
2 years	11 676 (99·9%); 86·0 (3·2)	6056 (99·9%); 86·6 (3·2)	5620 (99·9%); 85·5 (3·2)
7 years	8763 (75·0%); 120·3 (4·8)	4554 (75·1%); 120·7 (4·9)	4209 (74·8%); 119·8 (4·7)
11 years	8582 (73·4%); 141·4 (6·2)	4476 (73·8%); 141·4 (6·0)	4106 (73·0%); 141·4 (6·4)
Weight (kg) at age			
1 year	11 683 (99·9%); 10·2 (1·1)	6059 (99·9%); 10·5 (1·1)	5624 (100%); 9·8 (1·0)
2 years	11 686 (100%); 12·1 (1·2)	6062 (100%); 12·4 (1·2)	5624 (100%); 11·9 (1·2)
7 years	8773 (75·1%); 22·3 (2·8)	4560 (75·2%); 22·5 (2·7)	4213 (74·9%); 22·1 (2·9)
11 years	8581 (73·4%); 34·0 (5·2)	4477 (73·8%); 33·7 (4·6)	4104 (73·0%); 34·3 (5·7)
BMI (kg/m <sup>2</sup> ) at age			
1 year	11 676 (99·9%); 17·7 (1·4)	6055 (99·9%); 17·9 (1·4)	5621 (99·9%); 17·5 (1·4)
2 years	11 680 (99·9%); 16·5 (1·2)	6058 (99·9%); 16·7 (1·2)	5622 (99·9%); 16·4 (1·2)
7 years	8748 (74·8%); 15·5 (1·2)	4548 (75·0%); 15·5 (1·1)	4200 (75·7%); 15·5 (1·3)
11 years	8571 (73·3%); 17·0 (1·7)	4471 (73·7%); 16·8 (1·5)	4100 (72·9%); 17·1 (1·9)
<b>Follow-up information</b>			
Age at the start of the follow-up, years	11 689 (100%); 45·8 (2·8)	6064 (100%); 45·8 (2·8)	5625 (100%); 45·9 (2·8)
Follow-up, years	11 689 (100%); 31 (28–31)	6064 (100%); 31 (25–31)	5625 (100%); 31 (31–31)
Multimorbidity accumulation,* diseases per 10 years	11 679 (99·9%); 1·9 (1·9)	6057 (99·9%); 2·0 (2·2)	5622 (99·9%); 1·8 (1·6)
Incidence of two or more diseases, incidence rate per 1000 person-years (95% CI)†	11 679 (99·9%); 29·8 (29·2–30·4)	6057 (99·9%); 29·0 (28·1–29·8)	5622 (99·9%); 30·7 (29·9–31·6)
Incidence of three or more diseases, incidence rate per 1000 person-years (95% CI)†	11 679 (99·9%); 25·4 (24·8–25·9)	6057 (99·9%); 24·4 (23·6–25·2)	5622 (99·9%); 26·3 (25·5–27·1)
Died between 1987 and 2017	2887/11 689 (24·7%)	1845/6064 (30·4%)	1042/5625 (18·5%)

Data are n (%), n/N (%), mean (SD), or median (IQR), unless otherwise stated. \*Calculated by dividing the difference between the number of chronic disease groups each participant had at death or the end of the follow-up and at baseline by the individual follow-up time of each participant in years. †Confidence intervals are exact 95% Poisson confidence intervals.

**Table 1: Characteristics of the study population**

old. During follow-up, the entire cohort accumulated 1·9 more diseases every 10 years (table 1). The incidence rate of two or more chronic diseases was 29·8 (95% CI 29·2–30·4) per 1000 person-years and the incidence rate

of three or more chronic diseases was 25·4 (24·8–25·9) per 1000 person-years (table 1). Between Jan 1, 1987, and Dec 31, 2017, 2887 (24·7%) participants of the original cohort died (table 1). However, birth and maternal factors



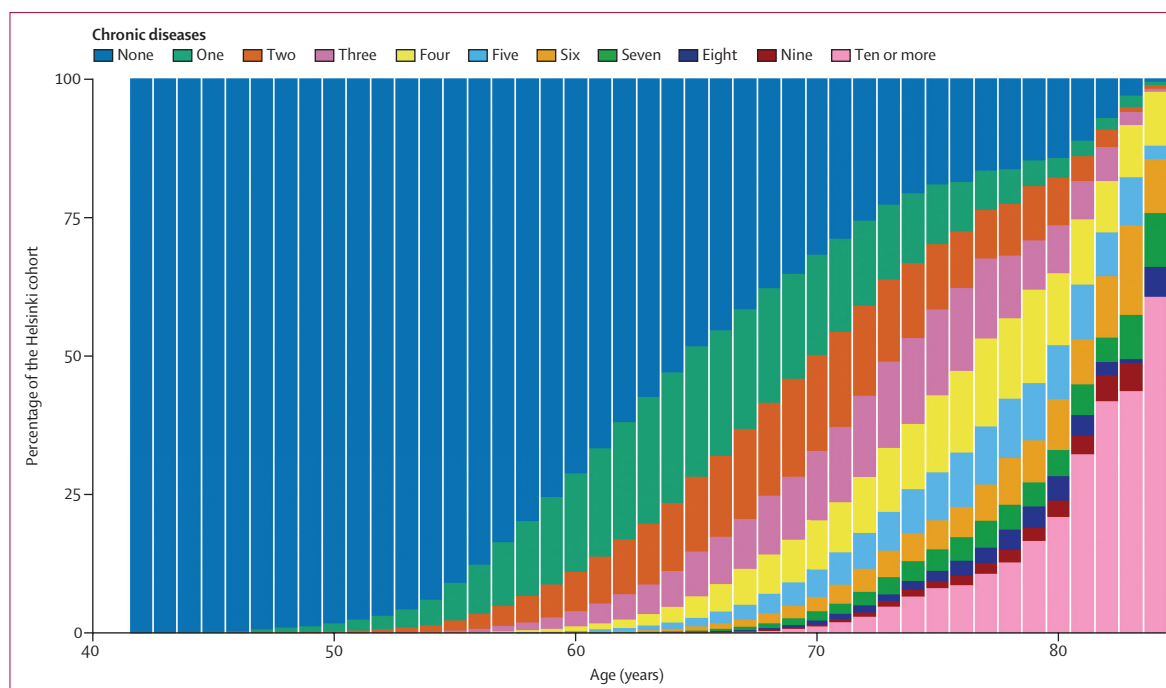


Figure 1: Distribution of the number of chronic diseases from age 42 to 84 years

were not significant predictors of all-cause mortality (appendix 3 p 23).

Smaller body size at birth and later birth order were linked to faster multimorbidity accumulation from the age of 42 years onwards, even after adjusting for sex, childhood SES, and their interactions with age (table 2). One-unit higher birthweight in kg was associated with 0.05 (95% CI 0.02 to 0.08) fewer chronic disease groups per 10 years and one-unit longer birth length in cm was associated with 0.02 (0.01 to 0.02) fewer chronic disease groups per 10 years. Additionally, the children of younger mothers (<25 years vs 25–30 years;  $\beta$  0.09; 95% CI 0.06 to 0.12; table 2), mothers with BMI in the overweight range (25–30 kg/m<sup>2</sup> vs <25 kg/m<sup>2</sup>; 0.08; 0.05 to 0.10), or mothers with BMI in the obese range (>30 kg/m<sup>2</sup> vs <25 kg/m<sup>2</sup>; 0.26; 0.21 to 0.31) in late pregnancy had a faster rate of chronic disease accumulation (table 2). We standardised birth and maternal factors for better comparability and found that an increase of one standard deviation in maternal BMI ( $\beta$  0.07; 95% CI 0.06 to 0.08) and maternal age (−0.06; −0.07 to −0.04) exhibited the strongest associations with an accelerated rate of chronic disease accumulation, followed by birth length (−0.03; −0.04 to −0.02) and birthweight (−0.02; −0.04 to −0.01; appendix 3 p 24).

Participants from manual worker and lower-middle class backgrounds experienced faster rates of chronic disease accumulation (table 2). Compared with participants from upper-middle class backgrounds, those from a manual worker background were associated with 0.27 (95% CI 0.23–0.30) more disease groups per

10 years and those from lower-middle class backgrounds were associated with 0.15 (0.12–0.19) more disease groups per 10 years.

Boys and girls who grew more rapidly in height, weight, and BMI from birth until 11 years had faster chronic disease accumulation (table 2). In particular, those with a faster weight (per 1 SD  $\beta$  0.08; 95% CI 0.07–0.09) and BMI (per 1 SD 0.08; 0.07–0.10) growth from age 7 to 11 years were associated with faster chronic disease accumulation. Boys and girls who as adults were in the highest third of chronic disease accumulation grew more rapidly in height, weight, and BMI during infancy, which then accelerated in childhood (figure 2).

Boys and girls evacuated during World War 2 accumulated diseases faster during their life course than those who had not been evacuated (table 3). Separated boys presented with 0.24 (95% CI 0.19–0.29) and separated girls with 0.31 (0.25–0.36) more chronic disease groups per 10 years compared with those who were not separated. Girls and boys separated at an older age (older than 7 years) were associated with faster chronic disease accumulation (table 3). The duration of the separation was not associated with chronic disease accumulation.

## Discussion

We found that the rate at which chronic diseases were accumulated was influenced by factors during gestation, birth, infancy, and childhood. The children of younger mothers and mothers with BMI in the overweight and obese ranges in late pregnancy had a faster accumulation

	Age and sex adjusted*		Fully adjusted†	
	Number of participants (n=11 689)	β × time (95% CI; p value)	Number of participants (n=11 392)	β × time (95% CI; p value)
<b>Birth factors‡</b>				
Birthweight, kg§	11 689 (100%)	-0.08 (-0.10 to -0.05; <0.0001)	11 009 (96.6%)	-0.05 (-0.08 to -0.02; 0.0070)
<2.5 kg	386/11 689 (3.3%)	0.20 (0.14 to 0.27; <0.0001)	329/11 009 (3.0%)	0.17 (0.10 to 0.25; 0.0002)
2.5 to <3.0 kg	1822/11 689 (15.6%)	0.07 (0.03 to 0.10; 0.0009)	1672/11 009 (15.2%)	0.07 (0.04 to 0.11; 0.0012)
3.0 to <3.5 kg	4725/11 689 (40.4%)	1 (ref)	4483/11 009 (40.7%)	1 (ref)
3.5 to <4.0 kg	3669/11 689 (31.4%)	-0.01 (-0.03 to 0.02; 0.99)	3480/11 009 (31.6%)	0.02 (-0.01 to 0.05; 0.99)
≥4.0 kg	1087/11 689 (9.3%)	-0.05 (-0.09 to -0.01; 0.79)	1045/11 009 (9.5%)	-0.04 (-0.09 to 0.01; 0.99)
Birth length, cm§	11579 (99.1%)	-0.02 (-0.03 to -0.01; 0.0001)	10913 (95.8%)	-0.02 (-0.02 to -0.01; 0.0003)
Birth length, cm§¶	11579 (99.1%)	-0.02 (-0.03 to -0.01; 0.0001)	10913 (95.8%)	-0.02 (-0.02 to -0.01; 0.0006)
Birth BMI, kg/m²§	11579 (99.1%)	-0.02 (-0.03 to -0.01; 0.0001)	10913 (95.8%)	-0.01 (-0.02 to 0.00; 0.99)
Ponderal index, kg/m³§	11579 (99.1%)	-0.01 (-0.01 to -0.00; 0.64)	11288 (99.1%)	-0.01 (-0.01 to -0.00; 0.99)
Gestational age, weeks	11294 (96.6%)	-0.01 (-0.01 to 0.00; 0.99)	11 009 (96.6%)	-0.01 (-0.01 to -0.00; 0.35)
Parity				
First born	5705/11 686 (48.8%)	1 (ref)	5464/11 389 (48.0%)	1 (ref)
Second or later	5981/11 686 (51.2%)	0.08 (0.06 to 0.11; <0.0001)	5925/11 389 (52.0%)	0.07 (0.05 to 0.10; <0.0001)
<b>Maternal factors‡</b>				
Age (continuous; years)	11 682 (99.9%)	-0.01 (-0.01 to -0.01; <0.0001)	11 385 (99.9%)	-0.01 (-0.01 to -0.01; <0.0001)
<25 years	3886/11 682 (33.3%)	0.09 (0.07 to 0.12; <0.0001)	3732/11 385 (32.8%)	0.09 (0.06 to 0.12; <0.0001)
25 to <30 years	3789/11 682 (32.4%)	1 (ref)	3719/11 385 (32.7%)	1 (ref)
≥30 years	4007/11 682 (34.3%)	-0.03 (-0.06 to -0.01; 0.80)	3934/11 385 (34.5%)	-0.03 (-0.06 to -0.00; 0.73)
BMI (continuous; kg/m²)	10 529 (90.1%)	0.02 (0.02 to 0.03; <0.0001)	10 262 (90.1%)	0.02 (0.02 to 0.03; <0.0001)
BMI (kg/m²)  ¶	10 529 (90.1%)	0.02 (0.02 to 0.03; <0.0001)	10 262 (90.1%)	0.02 (0.02 to 0.03; <0.0001)
BMI				
<25 kg/m²	3823/10 529 (36.3%)	1 (ref)	3725/10 262 (36.3%)	1 (ref)
25 to 30 kg/m²§	5745/10 529 (54.6%)	0.06 (0.03 to 0.09; 0.0002)	5596/10 262 (54.5%)	0.08 (0.05 to 0.10; <0.0001)
>30 kg/m²§	961/10 529 (9.1%)	0.22 (0.17 to 0.26; <0.0001)	941/10 262 (9.2%)	0.26 (0.21 to 0.31; <0.0001)
<b>Childhood socioeconomic status‡</b>				
Upper-middle	1981/11 392 (17.4%)	1 (ref)	..	..
Lower-middle	2763/11 392 (24.2%)	0.15 (0.12 to 0.19; <0.0001)	..	..
Manual worker	6648/11 392 (58.4%)	0.27 (0.23 to 0.30; <0.0001)	..	..
<b>Conditional growth from birth to age 2 years</b>				
Weight growth, per SD	8243 (70.5%)	0.04 (0.02 to 0.05; <0.0001)	8133 (71.4%)	0.04 (0.03 to 0.05; <0.0001)
Height growth, per SD	8165 (69.9%)	0.03 (0.02 to 0.05; 0.0003)	8057 (70.7%)	0.04 (0.03 to 0.05; <0.0001)
BMI growth, per SD	8144 (69.7%)	0.01 (0.01 to 0.03; 0.035)	8036 (70.5%)	0.01 (0.00 to 0.03; 0.99)
<b>Conditional growth from 2 years to 7 years</b>				
Weight growth, per SD	8243 (70.5%)	0.02 (0.01 to 0.04; 0.0004)	8133 (71.4%)	0.03 (0.01 to 0.04; 0.0011)
Height growth, per SD	8165 (69.9%)	0.02 (0.01 to 0.03; 0.032)	8057 (70.7%)	0.02 (0.01 to 0.03; 0.062)
BMI growth, per SD	8144 (69.7%)	0.03 (0.01 to 0.04; 0.0006)	8036 (70.5%)	0.03 (0.01 to 0.04; 0.0030)
<b>Conditional growth from 7 years to 11 years</b>				
Weight growth, per SD	8243 (70.5%)	0.08 (0.07 to 0.10; <0.0001)	8133 (71.4%)	0.08 (0.07 to 0.09; <0.0001)
Height growth, per SD	8165 (69.9%)	0.03 (0.02 to 0.05; 0.0001)	8057 (70.7%)	0.03 (0.02 to 0.04; 0.0002)
BMI growth, per SD	8144 (69.7%)	0.09 (0.07 to 0.10; <0.0001)	8036 (70.5%)	0.08 (0.07 to 0.10; <0.0001)

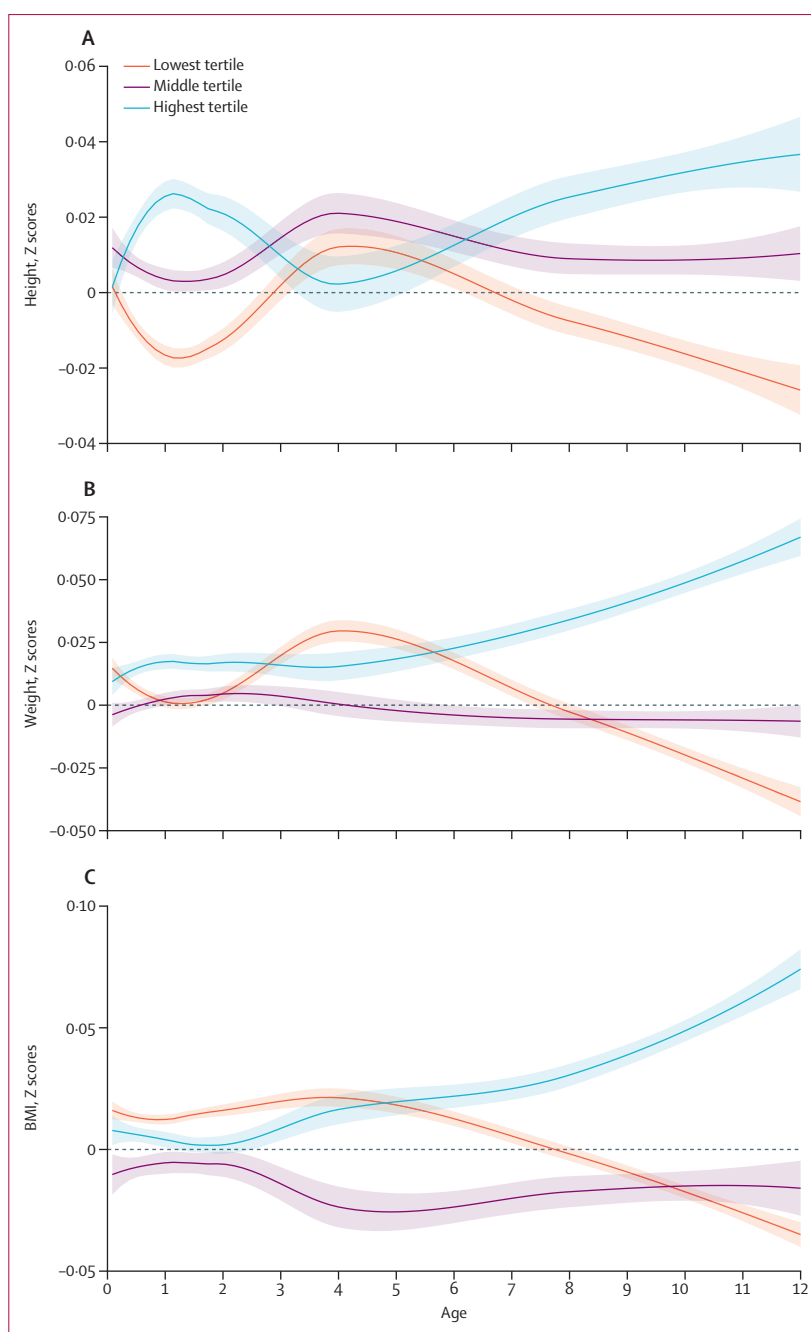
p values are Bonferroni adjusted. \*Linear mixed model adjusted with sex and its interaction with age. Age was treated as the underlying time scale and was therefore inherently adjusted for. Positive estimates (unstandardised β × time) indicate a faster increase in chronic diseases per 10 years, whereas negative estimates refer to a slower increase. †Linear mixed model adjusted with sex, childhood socioeconomic status, and their interactions with age. Age was treated as the underlying time scale and was therefore inherently adjusted for. Positive estimates (unstandardised β × time) indicate a faster increase in chronic diseases per 10 years, whereas negative estimates refer to a slower increase. ‡Analysed in separate models. §Fully adjusted model adjusted additionally with gestational age. ¶Quadratic term included. ||Fully adjusted model adjusted additionally with birthweight.

**Table 2: The association between early life factors and the rate of multimorbidity accumulation over 31 years**

of chronic diseases. Participants who had been born small or who grew faster in size during infancy and childhood accumulated chronic diseases faster during the life course. Childhood socioeconomic factors and wartime parental separation had similar long-lasting associations with chronic disease accumulation. The negative effect of wartime parental separation was more severe overall for girls compared with boys regardless of age at separation, but the largest effect was in boys separated at an older age. The findings persisted when other determinants of health, including sex and childhood socioeconomic status, were accounted for. In accordance with the DOHaD hypothesis,<sup>1,2</sup> the findings show that the pace of multimorbidity accumulation could be programmed early by factors during sensitive developmental periods and have long-lasting effects on later health. Our results provide an overview of early life factors and reveal that their influence on chronic disease accumulation is broader and more consistent across biological, psychological, and socioeconomic factors than that suggested in previous studies.<sup>5-12</sup>

Maternal obesity affects around one in six pregnant mothers,<sup>24</sup> and it has been linked to higher levels of proinflammatory and dysmetabolic signalling<sup>25</sup> as well as risk of cardiovascular disease in their children.<sup>26</sup> Our study suggests that a higher maternal BMI was one of the strongest predictors of morbidity in their children. Those born to obese mothers accumulated 0.26 more diseases per decade than those born to mothers with a BMI of less than 25 kg/m<sup>2</sup>, taking about 40 years to acquire one additional chronic disease. It is unclear whether these associations are solely attributable to maternal BMI or if maternal BMI acts as a surrogate for potential confounding factors, such as maternal education or lifestyle. We also found that the children of younger mothers (younger than 25 years) had faster chronic diseases accumulation. This aligns with previously reported U-shaped associations between maternal age and health of their children<sup>27</sup> and might indirectly reflect access to parenting skills and resources. However, advanced maternal age could not be studied due to its rarity in this cohort.

Our findings suggest that individuals who were born small are more likely to have a faster pace of chronic disease accumulation. Individuals with a low birthweight (<2.5 kg) accumulated 0.17 more diseases per decade and were estimated to acquire one additional chronic disease after 60 years compared with those weighing 3.0–3.5 kg at birth. According to the DOHaD hypothesis,<sup>1,2</sup> disturbances during prenatal life can programme physiological systems and metabolism, leading to long-term changes in the structure and function of organs and tissues. Individuals with lower birthweights have an increased risk of chronic diseases, including cardiovascular disease and diabetes, in adulthood.<sup>2-4</sup> The underlying mechanisms have been suggested to involve insulin resistance and other



**Figure 2:** The patterns of infant and childhood growth in individuals stratified by their rate of chronic disease accumulation

Height (A), weight (B), and BMI (C) growth curves from infancy to childhood according to thirds of chronic disease accumulation speed. Values above the dashed line indicate faster growth than the cohort average, whereas values below the dashed line indicate slower growth. Chronic disease accumulation speed was calculated by dividing the difference between the number of chronic disease groups each participant had at death or the end of the follow-up and at baseline by the individual follow-up time of each participant in years. Tertile cutoffs were at 0.97 and 1.94 disease groups increase per 10 years. Shaded areas represent 95% CI regions.

metabolic alterations,<sup>3</sup> inflammation,<sup>28</sup> and epigenetic changes.<sup>29</sup>

Boys and girls who had rapid height and weight growth accumulated chronic diseases faster during their life



	Age adjusted*		Fully adjusted†	
	Number of boys; $\beta \times \text{time}$ (95% CI); p value	Number of girls; $\beta \times \text{time}$ (95% CI); p value	Number of boys; $\beta \times \text{time}$ (95% CI); p value	Number of girls; $\beta \times \text{time}$ (95% CI); p value
<b>Wartime separation from both parents‡</b>				
Not separated	5221/5995 (87.1%); 1 (ref)	4842/5505 (88.0%); 1 (ref)	5104/5857 (87.1%); 1 (ref)	4700/5347 (87.9%); 1 (ref)
Separated	774/5995 (12.9%); 0.26 (0.21 to 0.31); <0.0001	663/5505 (12.0%); 0.32 (0.27 to 0.37); <0.0001	753/5857 (12.9%); 0.24 (0.19 to 0.29); <0.0001	647/5347 (12.1%); 0.31 (0.25 to 0.36); <0.0001
<b>Age at separation‡</b>				
1 to <2 years	108/704 (15.3%); 1 (ref)	76/593 (12.8%); 1 (ref)	102/687 (14.8%); 1 (ref)	72/580 (12.4%); 1 (ref)
2 to <4 years	238/704 (33.8%); 0.27 (0.10 to 0.42); 0.0073	185/593 (31.2%); -0.09 (-0.27 to 0.08); 0.99	235/687 (34.2%); 0.28 (0.12 to 0.45); 0.0053	183/580 (31.6%); -0.13 (-0.30 to 0.03); 0.99
4 to <7 years	229/704 (32.6%); 0.54 (0.38 to 0.71); <0.0001	212/593 (35.8%); -0.07 (-0.25 to 0.10); 0.99	226/687 (32.9%); 0.55 (0.38 to 0.71); <0.0001	207/580 (35.7%); -0.13 (-0.30 to 0.05); 0.98
>7 years	129/704 (18.3%); 0.41 (0.21 to 0.59); 0.0001	120/593 (20.2%); 0.28 (0.09 to 0.47); 0.021	124/687 (18.1%); 0.45 (0.27 to 0.62); <0.0001	118/580 (20.3%); 0.22 (0.04 to 0.42); 0.18
<b>Duration of the separation‡</b>				
0 to <1 year	149/685 (21.8%); 1 (ref)	132/593 (22.3%); 1 (ref)	147/668 (22.0%); 1 (ref)	131/568 (23.1%); 1 (ref)
1 to <2 years	328/685 (47.8%); -0.03 (-0.16 to 0.11); 0.99	285/593 (48.1%); 0.02 (-0.12 to 0.15); 0.99	320/668 (47.9%); 0.02 (-0.12 to 0.15); 0.99	277/568 (48.8%); 0.01 (-0.14 to 0.15); 0.99
2 to <3 years	112/685 (16.4%); 0.13 (-0.02 to 0.30); 0.79	102/593 (17.2%); -0.20 (-0.36 to -0.01); 0.99	108/668 (16.2%); 0.19 (-0.05 to 0.37); 0.16	99/568 (17.4%); -0.23 (-0.38 to -0.06); 0.082
>3 years	96/685 (14.0%); 0.14 (-0.03 to 0.30); 0.81	62/593 (10.4%); 0.12 (-0.08 to 0.33); 0.99	93/668 (13.9%); 0.20 (0.01 to 0.38); 0.19	61/568 (10.7%); 0.11 (-0.09 to 0.30); 0.99

p values are Bonferroni-adjusted. \*Age was treated as the underlying time scale and was therefore inherently adjusted for. †Linear mixed model adjusted with childhood socioeconomic status and its interactions with age; age was treated as the underlying time scale and was therefore inherently adjusted for; positive estimates (unstandardised  $\beta \times \text{time}$ ) indicate a faster increase in chronic diseases per 10 years, whereas negative estimates refer to a slower increase. ‡Analysed in separate models.

**Table 3: The association between wartime separation with the rate of multimorbidity accumulation over 31 years**

course. Such patterns of growth have been suggested to increase the risk of type 2 diabetes<sup>4</sup> and cardiovascular disease.<sup>3</sup> Babies who are small have less muscle, and, because of little muscle replication during childhood, the added weight could be disproportionately attributed to adipose tissue, predisposing to insulin resistance.<sup>3</sup> Our findings suggest that rapid growth, particularly in BMI, from ages 7 to 11 years could increase chronic disease accumulation. We have previously shown that faster BMI growth in this age range predicts adiposity<sup>30</sup> and obesity<sup>31</sup> in late midlife. In our study, these factors could affect the causal pathway connecting early growth to multimorbidity development.

During World War 2, around 70 000 Finnish children were evacuated without their parents to temporary foster care abroad—primarily to Sweden—to protect them from the war.<sup>18</sup> This created a unique natural experiment to study the association between wartime parental separation and later health in this cohort.<sup>32,33</sup> Although severe stress probably followed wartime parental separation, a double separation trauma could have occurred when the child returned home from foster care years later. Separated boys (0.24) and girls (0.31) accumulated more diseases each decade, taking 40 years in boys and 35 years in girls for one additional chronic disease. Following the DOHaD hypothesis,<sup>1,2</sup> early exposure to severe stress when the hypothalamic-pituitary-adrenal axis is developing can affect or alter subsequent stress responses, predisposing

to adult morbidity.<sup>32,34</sup> The negative effect of wartime parental separation was more pronounced in boys separated at an older age. We have previously described higher cortisol and adrenocorticotrophic hormone concentrations in late adulthood in children who were separated, with separated boys showing higher reactivity in a stress test.<sup>18</sup> Similar sex differences have also been shown for other adult chronic diseases<sup>32</sup> and frailty in old age.<sup>33</sup>

Worse childhood socioeconomic status predicted faster chronic disease accumulation in our study. Children in the lowest socioeconomic group accumulated 0.27 more diseases per decade than the highest group, requiring 40 years to acquire one additional chronic disease. Previously, some,<sup>8,9</sup> but not all,<sup>6,7</sup> studies reported that poorer childhood SES was associated with an increased multimorbidity risk, with little evidence of childhood or birth SES affecting disease accumulation.<sup>7,9,10</sup> This heterogeneity could result from how childhood SES (parental education, occupation, or childhood health) and multimorbidity (seven, 14, or 60 conditions) are operationalised. Our results suggest that childhood socioeconomic circumstances, defined with parental occupation, contribute to inequalities in chronic disease accumulation. Socioeconomic factors are structurally embedded in early life factors, suggesting that individuals with a higher SES might have more opportunities for accessing education and income, potentially improving maternal and child health.

Our study emphasises the significance of early life factors, spanning gestation, infancy, and childhood, in influencing lifelong chronic disease burden. Interventions targeting maternal health, pregnancy outcomes, and early nutrition (such as providing access to nutrient-rich foods during infancy) could help prevent maternal obesity, pregnancy complications, and chronic disease in their children. Addressing childhood obesity and mitigating the effect of wartime parental separation by improving social support and access to mental health services might also decrease chronic disease burden. Infants and children involved in war conflicts and massive migration movements might experience earlier pathological ageing associated with faster chronic disease accumulation. Reducing early socioeconomic inequalities might prevent differences in later chronic disease accumulation.

This study followed up more than 11500 individuals from their forties up to the age of 84 years to investigate the association between early life factors, including growth and wartime parental separation, and chronic disease accumulation. However, multimorbidity was defined using physician-defined ICD codes alone, possibly leading to misclassification or under-reporting. The registry data only captured specialist-driven health care provided in hospitals, omitting primary health care, resulting in an underestimation of multimorbidity. Exclusion of individuals who died before the study might underestimate multimorbidity due to a healthy survivor effect. Maternal BMI was calculated using predelivery weight, making it difficult to differentiate between the effects of pre-pregnancy weight and weight gain during pregnancy on multimorbidity in their children. However, mothers who are overweight or obese before giving birth tend to have already been overweight before becoming pregnant.<sup>35</sup> The National Archives documented official wartime evacuations, excluding private routes. False controls would probably diminish, not amplify, differences between those who were separated and those who were not. Despite controlling for socioeconomic factors, residual confounding remains possible, particularly because early life factors might serve as indicators of socioeconomic circumstances not accounted for by parental occupation. Finally, the study focused on a historical cohort including only White people born in Helsinki between 1934 and 1944, of whom only a clear minority underwent wartime evacuations, restricting the generalisability of the results.

We have shown that individuals who experienced an accelerated accumulation of chronic diseases during their lifespan had a higher probability of being born to mothers who either had a higher BMI or were younger. Furthermore, these individuals were more likely to be short and thin at birth or displayed rapid increases in height and weight after birth. Of note, the rate of multimorbidity accumulation was higher in wartime evacuees than non-evacuees. Poorer childhood socioeconomic conditions were also associated with faster

chronic disease accumulation. The findings suggest that factors during gestation, infancy, and childhood can more broadly and consistently affect the lifelong rate of chronic diseases accumulation than previously thought.

#### Contributors

MJH, MBvB, EK, and JGE conceptualised the study. MJH searched the literature, performed the formal analysis, and visualised the data. MJH and DLV designed the methods and wrote the original draft. MJH, DLV, TMM, AC-L, SD, EK, JGE, and MBvB interpreted the data. MJH, DLV, TMM, AC-L, SD, EK, JGE, and MBvB critically reviewed and edited the manuscript. MJH and MBvB directly accessed and verified the data. All authors had full access to all the data in the study. All authors had final responsibility for the decision to submit for publication.

#### Declaration of interests

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#### Data sharing

The data obtained from national registers, databases, and health records that support the findings of this study are available from the Finnish Institute for Health and Welfare, although restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. All data are available from the authors (markus.haapanen@helsinki.fi) upon reasonable request, and after the authors have applied for permission to share the data from the Finnish Institute for Health and Welfare. For the register data, additional licences are needed from the Finnish Institute for Health and Welfare. R code used to fit linear mixed models is in appendix 3 (pp 28–30).

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