Early childhood growth and risk of adult cerebrovascular disease

-The Northern Finland Birth Cohort 1966

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Abstract

Background and purpose

Low birth weight is associated with an increased risk of adulthood cerebrovascular disease (CVD). Not much is known about effects of early childhood growth. We studied whether the risk of adult CVD is associated with growth or nutritional factors during early childhood.

Methods

Within the Northern Finland Birth Cohort 1966, 11,991 persons were followed from birth to 52 years of age. CVD diagnoses were extracted from national hospital and death registers with diagnostic coding based on the World Health Organization recommendations. Cox proportional hazard models were used to estimate associations of childhood growth variables, growth trajectories (by Latent Class Growth Modelling) and nutritional factors with adult CVD,e.g. ischemic and haemorrhagic strokes. The analyses were adjusted for childhood socioeconomic status and birth weight.

Results

A total of 453 (3.8%) CVDs were recorded during follow-up. Among females, groups with low early childhood weight and height had an increased risk for adulthood ischemic CVDs, with an adjusted hazard ratio (aHR) of 1.97 (95% confidence interval (CI) 1.21-3.20) and 2.05 (CI 1.11-3.81) respectively. In addition, females with BMI over 1 SD at BMI rebound had an increased risk for ischemic CVDs (aHR 1.90;CI 1.19-3.04) compared to females with BMI -1 to +1 SD. These associations were not found among males.

Conclusion

The findings suggest that timing of weight gain during childhood is of significance for development of CVD risk among females.

NON-STANDARD ABBREVIATIONS:

Cerebrovascular disease (CVD), Adjusted hazard ratio (aHR), Body Mass Index (BMI), confidence interval (CI), International Classification of Diseases (ICD), Northern Finland Birth Cohort 1966 (NFBC1966), standard deviation (SD).

INTRODUCTION

Cerebrovascular disease (CVD) is a leading cause of death and loss in productive life years worldwide([1]). To its devastating effects adds the rising incidence of ischemic CVDs among young adults in many populations. This could be related to earlier, even childhood, exposure to risk factors([2,3]).

Low birth weight is a risk factor for adult CVD, but so is childhood obesity([4,5]). Previous studies examining adult CVD and growth during early childhood are scarce. One study reported low weight gain between birth and 2 years and a low BMI at 2 years to be associated with later hemorrhagic and ischemic CVD([6]). Two studies have found thinness and short height in the first years of childhood to associate with increased risk of later CVD among males([7,8]). In a study of growth between ages 7 and 13 years, researchers found that among females an increase in BMI was associated with early adult ischemic CVD, regardless of baseline or attained BMI([9]).

In the Northern Finland Birth Cohort 1966 (NFBC1966), we have previously established a relationship of low maternal weight gain during pregnancy and thinness at birth with increased risk for offspring CVD([10]). The first 2 years of life are increasingly recognized as a critical period for development of adult non-communicable diseases([11]). Still, growth during this important period and later risk of CVD has not been thoroughly studied. In the present study, we used the same cohort to investigate if height, weight, and BMI during childhood are associated with increased risk of adulthood CVD. We focused on growth rates between birth and 2 years, which we refer to as early childhood. We also examined if nutritional factors, *e.g.*, duration of breastfeeding, vitamin D, iron intake or anemia, explained growth related risk associations for adult CVD.

METHODS

Data availability statement

NFBC1966 data is available from the University of Oulu, Infrastructure for Population Studies. Permission to use the data can be applied for research purposes from www.oulu.fi/nfbc.

Design of Study and Sample

NFBC1966 is a prospective, general population-based birth cohort containing data on 12,068 pregnant females and their 12,058 children born alive in the provinces of Oulu and Lapland with an expected date of birth in 1966([12]).

Excluded from the study were the subjects who declined use of their data(n=59) and persons who had a CVD under the age of 15 years(n=8). The current sample included 11,991 subjects who were followed from birth to their first CVD, death, moving abroad, or until the end of year 2018, whichever came first. The 84 persons who had moved abroad but whose moving date was unknown were censored on their day of birth.

Permission to gather register data was obtained from the Ministry of Social Affairs and Health, and the study was approved by the Ethical Committee of Northern Ostrobothnia Hospital District, Finland. Informed consent was inquired from all the participants.

This study was performed and reported in accordance with STROBE checklist(Supplement 1).

Growth and nutritional data

Finnish health clinic nurses record regular and multiple growth measurements during infancy and childhood. Height, weight, and head circumference were directly measured and recorded with an accuracy of 0.1cm for height, 1cm for head circumference and 0.01 kg for weight([13]). BMI was calculated as weight(kg)/height(m) squared. Height, weight, and BMI values were converted to Z-scores within the cohort data age and sex specifically([14]).

BMI peak is the first rise in BMI occurring at around nine months of age. Data was obtained from random effects models fitted from age 2 weeks to 18 months. BMI rebound is the second rise in BMI occurring at around 6 years and data was obtained from random effects models fitted from age 1.5 to 13 years. Detailed methods are described elsewhere([15]). Peak height velocity and peak weight velocity were derived from parametric growth curves as described elsewhere([16]).

Nutritional details were reported by mothers in questionnaire at 1-year follow-up. More information on variable collection is provided in Supplement 1.

CVD

Strokes and transient ischemic attacks were identified from the nationwide registers based on medical records. CVDs were classified by first primary diagnosis: subarachnoid hemorrhages, intracerebral hemorrhages, ischemic strokes, transient ischemic attacks and other CVDs. More detailed information is found in Supplement 1. The linkage to other data with pseudonymization was fully complete for stroke diagnoses. Ischemic strokes and transient ischemic attacks were defined as ischemic CVD and subarachnoid hemorrhages and intracerebral hemorrhages as hemorrhagic CVD. For analyses of any CVD, ischemic, hemorrhagic, and other CVDs were combined.

Covariates

Covariates were socioeconomic status of family and birth weight corrected for gestational age. More information is found in Supplement 1.

Statistical analyses

We used Latent Class Growth Modeling from the PROC TRAJ macro in SAS 9.4(SAS Institute Inc,USA) to determine height and weight growth trajectories. The aim was to reveal subgroups which share a similar growth pattern from age 0 to 2 years. We modeled growth trajectories for males and females separately adjusted for gestational age([17]). More detailed information is found in Supplement 1.

For both sexes, Group 2 of weight and Group 3 of height trajectories was used as reference group according to size and growth tendency close to point 0 SD. We refer to weight trajectory Group 1 as 'stable-low' and Group 2 as 'average', Group 3 as 'high-normal' and Group 4 as 'stable-high'. For height trajectories we refer to Group 1 as 'stable-low' and Group 2 as 'low-normal', Group 3 as 'average' and Group 4 as 'stable-high'.

Cox proportional hazards model was used to estimate the associations of childhood and infancy growth variables, nutritional variables, and ischemic and haemorrhagic CVD during follow-up. All models were performed by sex and included adjustment for family socioeconomic status and birth weight corrected for gestational age.

Analyses were carried out using IBM SPSS Statistics 27.0 for Windows(IBM Corp,USA).

RESULTS

The length of follow-up was 568,821 person-years. Population characteristics are shown in Table 1 and characteristics of growth measurements in Supplemental Table 1. During follow-up, 453 (3.8%) persons had a CVD. Of them, 144 (31.8%) were ischemic strokes, 164 (36.2%) transient ischemic attacks, 59 (13.0%) subarachnoid hemorrhages, 36 (7.9%) intracerebral hemorrhages, and 50 (11.0%) other cerebrovascular events. The median age at onset was 46.4 (SD 7.2) years for ischemic stroke, 47.3 (SD 5.0) years for transient ischemic attack, 45.7 (SD 8.7) years for intracerebral hemorrhage, and 43.6 (SD 9.7) years for subarachnoid hemorrhage.

Early growth and risk of CVD

The growth trajectories showed a stable growth tendency from 0 to 2 years closely following the SD point determined at birth(Fig.1). Among females, low (≤-1 SD) weight, height and BMI at 6 months associated with an increased risk for CVD, with an aHR of 1.54 (CI 1.02-2.33), an aHR of 1.57 (CI 1.00-2.45) and an aHR of 1.56 (CI 1.01-2.40), respectively(Table 2,Fig.2A). The group with low (≤-1 SD) height at 6 months was associated with an increased risk of especially ischemic CVD (aHR=1.74;CI 1.05-2.89) as was the group with low BMI (≤-1 SD) at 6 months (aHR=1.76;CI 1.07-2.88). The group with low weight at 1 year associated with an increased risk for ischemic CVD with an aHR of 1.65 (CI 1.05-2.60).

Among females, the group with high (≥+1 SD) BMI at time of BMI rebound was at increased risk for any CVD (aHR=1.55;CI 1.01-2.36), especially for ischemic CVD (aHR=1.90;CI 1.19-3.04).

Supporting the results for specific time point measurements, the ‘stable-low’ trajectory group showed an increased risk for ischemic CVD with an aHR of 1.97 (CI 1.21-3.20) for weight and 2.05 (CI 1.11-3.81) for height(Table 2,Fig.2A). The ‘stable-low’ weight group also had an increased risk for any CVD with an aHR of 1.60 (CI 1.05-2.46).

Among males, no associations for childhood growth variables or growth trajectory groups and CVD risk were found(Table 3,Fig.2B).

For either sex no associations were found for variables of head circumference at 1-year, peak height velocity in infancy, peak weight velocity in infancy, BMI at time of BMI peak, age at time of BMI peak or age at time of BMI rebound(Tables 2&3).

Nutrition and risk of CVD

Duration of breastfeeding, D vitamin or iron supplementation and anemia were not associated with CVD risk(Table 4).

DISCUSSION

We have examined the early childhood growth of a population-based cohort of 6139 males and 5860 females in respect to adult CVD. Females who had low weight, height, and BMI during the first year had as adults an increased risk of CVD. A similar relationship was apparent in weight and height growth trajectories between 0-2 years, where girls belonging to the group with stable low growth tendency were at an increased risk for later ischemic CVD. However, at time of BMI rebound, girls with a higher BMI had as adults an increased risk for later CVD, especially ischemic CVD.

To date, most of the studies that investigated the relation between childhood growth and CVD risk in adulthood have focused on growth after the infancy period. One study reported that short height during age 7-13 years is associated with an increased ischemic CVD risk([18]). To our knowledge, the current study is first to show that early childhood latent class growth trajectories associate with adult CVD risk.

Mechanisms that could underlie associations between early growth and later risk of CVD and its risk factors are mostly still unknown. Research on prenatal growth suggests that fetal adaptations in response to undernutrition lead to persisting changes in metabolism and organ structure to ensure survival with possible food shortage after birth([19,20]). This “Barker hypothesis” has been extended to propose that the period sensitive to adverse nutrition in early life would extend at least to first years after birth, with suboptimal growth increasing susceptibility to later metabolic syndrome and complications including CVD([21]).

One of the important factors between early childhood growth and adult disease, such as CVD, seems to be adiposity([22,23]). Studies have shown that an accelerated growth during infancy was associated with later metabolic disturbances and vascular disease, especially in individuals born small for gestational age([24,25]) or having low weight gain during infancy([26,27]). Furthermore, a few studies have established a relationship between low birth weight followed by rapid growth during childhood and later hypertension([28,29]). However, the findings of our study raise questions on sex differences in timing of critical stages concerning development of CVD risk factors. A study examining sex

differences on developmental programming of hypertension showed dependency on individual hormonal milieu, age, and age-related adiposity accumulation, which are all sex-specific and suggests different programming outcomes in males and females([30]).

Our findings that high BMI at rebound increased the risk of later cerebrovascular events support the notion that the CVD risk increase could at least in part be explained by later obesity or other obesity-associated conditions. In line with our findings, a previous cohort study reported that children defined as obese in childhood were at increased risk of CVD later in life([31]). It has been shown that higher BMI at rebound is related to higher BMI and obesity in later life([32]). Thus, the timing of weight gain during infancy and childhood seems to be of importance for later development of CVD. From a public health perspective, with childhood obesity steadily on the rise, the findings of this study are of importance for applying targeted primary preventative measures.

Throughout childhood, nutrition and growth are interrelated([33]). We examined possible nutritional etiologies between childhood growth and later CVD risk. Breastfeeding has been reported to provide protection against chronic diseases, but results are inconclusive and not sustained in a large, randomized trial([34,35]). Higher D vitamin status and intake have been shown to decrease risk of CVD, whereas childhood iron-deficiency anemia is a reported risk factor for ischemic CVD([36,37]). In this study, we found no associations between risk of adult ischemic or hemorrhagic CVD and the duration of breastfeeding, D vitamin supplementation, iron supplementation or anemia in childhood. Performing a thorough study of nutritional factors and CVD would need accounting for more confounding factors than was possible within the scope of our study and data. These nutritional factors did not, however, explain our findings between small body size in early childhood and adulthood risk of CVD.

It should be considered that the present study had some limitations, the main one being the small sample size of stroke groups. CVD in early adulthood is rare([38]) and even though we had a large-scale cohort with comprehensive follow-up data, only 453 CVDs were recorded. We have no data on body composition in childhood and were unable to test whether the associations with BMI are due to lean mass, fat mass, or both. We were limited to accuracy of data collected in the 1960's and for example

head circumference was recorded with only an accuracy of 1 cm. Although attendance to child welfare clinics in Finland is generally good, the visits are voluntary and sample sizes of weight and height measurements grew notably smaller after children turned 1 year old. This study also has the limitations of an epidemiological cohort study setting and we were not able to use medical records during our study. We performed all analyses with adjustments for family socioeconomic status and birth weight corrected for gestational age, but otherwise the population was assumed to be homogenous. Unidentified or residual confounders are a limitation of population-based research. Finally, we performed several comparisons, which increases the possibility of false positive associations.

This study also had several important strengths, one of them is the use of a large, unselected, population-based birth cohort with almost 12,000 participants and nearly 570000 person years of follow-up. Data collection started from the second trimester of the antenatal period and the cohort members have been followed-up regularly ever since. We were also able to perform analyzes separately for both sexes. Information on CVD diagnoses was complete for the entire cohort from nationwide registers. We had comprehensive data on the cohort member's early growth and were able to model growth in several different ways. We believe the results of this population-based data set are generalizable to most Western societies.

SUMMARY

Independent of birth weight, consistently low weight, and height during the first two years of life and high BMI at time of rebound showed a relationship with later CVD among females. Our findings add to the evidence that modification of infant and early childhood growth may serve as a window of opportunity for prevention of CVD.

TABLE 1.Population Characteristics		
All(N=11,991)	**N**	**%/Mean(SD)**
Sex		
Female	5860	48.8%
Male	6139	51.2%
Person years in follow-up	568821	47.4(12.0)
Highest occupational status in family	11871	
Professional	4429	36.9%
Skilled worker	4080	34.0%
Unskilled worker	3263	27.2%
No occupation	99	0.8%

TABLE 2.Results for growth variables among females.

	Any CVD		**Ischemic CVD**		**Hemorrhagic CVD**	
	N(%)	HR(95%CI)	N(%)	HR(95%CI)	N(%)	HR(95%CI)
At 6 months						
Weight (n=4224)						
-0.99–0.99 SD (n=3003)	103 (3.4%)	ref.	76 (2.6%)	ref.	20 (0.7%)	ref.
≤-1.00 SD (n=614)	32 (5.2%)	**1.54 (1.02-2.33)**	25 (4.1%)	1.57 (0.97-2.52)	3 (0.5%)	0.91 (0.27-3.13)
≥1.00 SD (n=607)	21 (3.5%)	0.95 (0.58-1.54)	15 (2.5%)	0.97 (0.55-1.70)	3 (0.5%)	0.69 (0.20-2.36)
Height (n=3804)						
-0.99–0.99 SD (n=2543)	83 (3.3%)	ref	59 (2.3%)	ref	16 (0.6%)	ref
≤-1.00 SD (n=548)	28 (5.1%)	**1.57 (1.00-2.45)**	23 (4.2%)	**1.74 (1.05-2.89)**	3 (0.6%)	1.09 (0.31-3.79)
≥1.00 SD (n=713)	30 (4.2%)	1.28 (0.83-1.98)	22 (3.1%)	1.38 (0.84-2.27)	6 (0.9%)	1.26 (0.50-3.30)
BMI (n=3804)						
-0.99–0.99 SD (n=2684)	91 (3.4%)	ref	62 (2.3%)	ref	21 (0.8%)	ref
≤-1.00 SD (n=560)	28 (5.0%)	**1.56 (1.01-2.40)**	22 (4.0%)	**1.76 (1.07-2.88)**	4 (0.7%)	1.12 (0.38-3.31)
≥1.00 SD (n=560)	24 (4.3%)	1.26 (0.79-2.03)	20 (3.6%)	1.57 (0.93-2.65)	1 (0.2%)	0.24 (0.03-1.82)
At 1 year						
Weight (n=4941)						

-0.99–0.99 SD (n=3518)	130 (3.7%)	ref	86 (2.5%)	Ref	28 (0.8%)	
≤-1.00 SD (n=669)	30 (4.5%)	1.30 (0.87-1.96)	26 (3.9%)	**1.65 (1.05-2.60)**	2 (0.3%)	0.46 (0.12-1.96)
≥1.00 SD (n=754)	33 (4.4%)	1.23 (0.83-1.82)	25 (3.4%)	1.45 (0.92-2.29)	2 (0.6%)	0.64 (0.22-1.85)
Height (n=4923)						
-0.99–0.99 SD (n=3207)	126 (3.9%)	ref	87 (2.7%)	Ref	25 (0.8%)	ref
≤-1.00 SD (n=863)	28 (3.2%)	0.84 (0.55-1.28)	23 (2.7%)	0.99 (0.62-1.58)	1 (0.1%)	0.17 (0.02-1.26)
≥1.00 SD (n=853)	36 (4.2%)	1.10 (0.75-1.61)	26 (3.1%)	1.20 (0.76-1.88)	7 (0.8%)	0.82 (0.33-2.02)
BMI (n=4882)						
-0.99–0.99 SD (n=3509)	128 (3.6%)	ref	86 (2.5%)	ref	27 (0.8%)	ref
≤-1.00 SD (n=693)	25 (3.6%)	0.99 (0.65-1.53)	21 (3.0%)	1.21 (0.75-1.96)	2 (0.3%)	0.40 (0.10-1.68)
≥1.00 SD (n=680)	33 (4.9%)	1.33 (0.90-1.96)	26 (3.9%)	1.60 (1.03-2.50)	4 (0.6%)	0.75 (0.26-2.17)
Head circumference (n=5060)						
-0.99–0.99 SD (n=3753)	144 (3.8%)	ref	102 (2.7%)	ref	27 (0.7%)	ref
≤-1.00 SD (n=471)	14 (3.0%)	0.81 (0.47-1.41)	11 (2.4%)	0.86 (0.46-1.61)	1 (0.2%)	0.34 (0.05-2.51)
≥1.00 SD (n=836)	37 (3.9%)	1.17 (0.81-1.69)	26 (3.2%)	1.15 (0.74-1.79)	7 (0.9%)	1.15 (0.50-2.66)
At 2 years						
Weight (n=916)						
-0.99–0.99 SD (n=643)	26 (4.0%)	ref	19 (3.0%)	ref	4 (0.6%)	ref

≤-1.00 SD (n=124)	6 (4.8%)	1.31 (0.53-3.25)	5 (4.1%)	1.44 (0.52-3.97)	1 (0.8%)	1.44 (0.15-13.35)
≥1.00 SD (n=149)	7 (4.7%)	1.12 (0.48-2.65)	5 (3.4%)	1.19 (0.43-3.29)	2 (0.4%)	1.73 (0.31-9.73)
Height (n=900)						
-0.99–0.99 SD (n=653)	26 (4.0%)	ref	20 (3.1%)	ref	4 (0.6%)	ref
≤-1.00 SD (n=124)	6 (4.8%)	1.04 (0.39-2.76)	5 (4.1%)	1.05 (0.35-3.16)	0	n.a.
≥1.00 SD (n=123)	7 (5.7%)	1.40 (0.60-3.28)	4 (3.3%)	1.10 (0.37-3.27)	3 (2.5%)	3.78 (0.81-17.56)
BMI (n=897)						
-0.99–0.99 SD (n=621)	27 (4.3%)	ref	21 (3.4%)	ref	4 (0.7%)	ref
≤-1.00 SD (n=137)	5 (3.6%)	0.83 (0.32-2.17)	4 (2.9%)	0.82 (0.28-2.41)	1 (0.8%)	1.15 (0.13-10.35)
≥1.00 SD (n=139)	7 (5.0%)	0.94 (0.39-2.29)	4 (2.9%)	0.63 (0.19-2.13)	2 (1.5%)	1.87 (0.34-10.39)
At BMI Peak						
BMI (n=2842)						
-0.99–0.99 SD (n=2014)	73 (3.6%)	ref	54 (2.7%)	ref	15 (0.8%)	ref
≤-1.00 SD (n=412)	21 (5.1%)	1.40 (0.85-2.29)	18 (4.4%)	1.61 (0.93-2.79)	1 (0.3%)	0.36 (0.05-2.76)
≥1.00 SD (n=416)	17 (4.1%)	1.21 (0.71-2.07)	13 (3.2%)	1.29 (0.70-2.38)	2 (0.5%)	0.62 (0.14-2.73)
Age (n=2843)						
-0.99–0.99 SD (n=1963)	74 (3.8%)	ref	56 (2.9%)	ref	12 (0.6%)	ref
≤-1.00 SD (n=203)	7 (3.4%)	1.00 (0.46-2.19)	6 (3.0%)	1.14 (0.49-2.66)	1 (0.5%)	0.84 (0.11-6.49)
≥1.00 SD (n=677)	31 (4.6%)	1.26 (0.82-1.94)	23 (3.4%)	1.20 (0.73-1.97)	5 (0.8%)	1.37 (0.48-3.91)

At BMI rebound						
BMI (n=3450)						
-0.99–0.99 SD (n=2489)	100 (4.0%)	ref	70 (2.8%)	ref	19 (0.8%)	ref
≤-1.00 SD (n=475)	17 (3.6%)	0.88 (0.52-1.47)	11 (2.3%)	0.78 (0.41-1.48)	3 (0.7%)	0.83 (0.25-2.82)
≥1.00 SD (n=486)	29 (6.0%)	**1.55 (1.01-2.36)**	25 (5.2%)	**1.90 (1.19-3.04)**	3 (0.7%)	0.80 (0.24-2.74)
Age (n=3450)						
-0.99–0.99 SD (n=2479)	100 (4.0%)	ref	73 (3.0%)	ref	18 (0.8%)	ref
≤-1.00 SD (n=501)	28 (5.6%)	1.43 (0.94-2.18)	22 (4.4%)	1.54 (0.95-2.48)	5 (1.0%)	1.34 (0.50-3.61)
≥1.00 SD (n=470)	18 (3.8%)	0.98 (0.59-1.62)	11 (2.4%)	0.81 (0.43-1.53)	2 (0.4%)	0.58 (0.14-2.52)
Peak Height Velocity in infancy (n=2096)						
-0.99–0.99 SD (n=1500)	56 (3.7%)	ref	44 (3.0%)	ref	6 (0.4%)	ref
≤-1.00 SD (n=291)	16 (5.5%)	1.49 (0.85-2.60)	11 (3.8%)	1.31 (0.68-2.54)	3 (1.1%)	2.50 (0.62-10.16)
≥1.00 SD (n=305)	14 (4.6%)	1.27 (0.71-2.29)	10 (3.3%)	1.15 (0.58-2.30)	3 (1.0%)	2.73 (0.68-11.00)
Peak Weight Velocity in infancy (n=2097)						
-0.99–0.99 SD (n=1501)	61 (4.1%)	ref	44 (3.0%)	ref	10 (0.7%)	ref
≤-1.00 SD (n=297)	12 (4.0%)	1.00 (0.54-1.83)	9 (3.1%)	1.02 (0.50-2.09)	2 (0.7%)	1.12 (0.24-5.13)
≥1.00 SD (n=299)	13 (4.3%)	1.08 (0.59-1.96)	12 (4.0%)	1.39 (0.73-2.64)	0	n.a.
Weight trajectory (n=5583)						

Average (n=3447)	116 (3.4%)	ref	75 (2.2%)	ref	23 (0.7%)	ref
Stable-low (n=500)	26 (5.2%)	**1.60 (1.05-2.46)**	21 (4.2%)	**1.97 (1.21-3.20)**	2 (0.4%)	0.63 (0.15-2.67)
High-normal (n=1328)	57 (4.3%)	1.24 (0.90-1.71)	41 (3.1%)	1.37 (0.94-2.00)	14 (1.1%)	1.52 (0.78-2.96)
Stable-high (n=308)	16 (5.2%)	1.50 (0.89-2.52)	11 (3.6%)	1.58 (0.84-2.97)	4 (1.4%)	1.87 (0.65-5.41)
Height trajectory (n=5800)						
Average (n=2837)	104 (3.7%)	ref	64 (2.3%)	ref	29 (1.0%)	ref
Stable-low (n=303)	15 (5.0%)	1.61 (0.94-2.77)	12 (4.0%)	**2.05 (1.11-3.81)**	1 (0.3%)	0.39 (0.05-2.87)
Low-normal (n=1942)	72 (3.7%)	1.04 (0.77-1.41)	53 (2.8%)	1.23 (0.85-1.76)	8 (0.4%)	0.41 (0.19-0.91)
Stable-high (n=718)	29 (4.0%)	1.12 (0.74-1.69)	22 (3.1%)	1.38 (0.85-2.24)	6 (0.9%)	0.82 (0.34-1.99)

Cox regression adjusted for socioeconomic status and birth weight for gestational age. N=number;HR=hazard ratio;CI=confidence interval;n.a.=not applicable;Ref=reference group. Boldface indicates statistical significance.

TABLE 3.Results for growth variables among males.

	Any CVD		Ischemic CVD		Hemorrhagic CVD	
	N(%)	HR(95%CI)	N(%)	HR(95%CI)	N(%)	HR(95%CI)
At 6 months						
Weight (n=4349)						
-0.99–0.99 SD (n=3123)	121 (3.9%)	ref.	84 (2.7%)	ref.	22 (0.7%)	ref.
≤-1.00 SD (n=591)	18 (3.0%)	0.68 (0.40-1.17)	15 (2.6%)	0.77 (0.42-1.41)	3 (0.3%)	0.48 (0.11-2.10)
≥1.00 SD (n=635)	17 (2.7%)	0.46 (0.46-1.30)	13 (2.1%)	0.87 (0.48-1.58)	2 (0.3%)	0.50 (0.12-2.17)
Height (n=3924)						
-0.99–0.99 SD (n=2614)	95 (3.6%)	ref	71 (2.7%)	ref	16 (0.6%)	ref
≤-1.00 SD (n=647)	22 (3.4%)	0.85 (0.52-1.38)	18 (2.8%)	0.93 (0.54-1.61)	2 (0.3%)	0.44 (0.10-1.96)
≥1.00 SD (n=663)	25 (3.8%)	1.11 (0.70-1.74)	15 (2.3%)	0.95 (0.54-1.67)	3 (0.5%)	0.80 (0.23-2.78)
BMI (n=3915)						
-0.99–0.99 SD (n=2717)	100 (3.7%)	ref	72 (2.7%)	ref	13 (0.5%)	ref
≤-1.00 SD (n=578)	25 (4.3%)	1.07 (0.67-1.69)	18 (3.2%)	1.02 (0.59-1.76)	6 (1.1%)	2.10 (0.79-5.61)
≥1.00 SD (n=620)	17 (2.7%)	0.82 (0.49-1.37)	14 (2.3%)	0.96 (0.54-1.70)	2 (0.3%)	0.68 (0.15-3.02)
At 1 year						

Weight (n=5084)						
-0.99–0.99 SD (n=3511)	134 (3.8%)	ref	92 (2.7%)	ref	25 (0.7%)	
≤-1.00 SD (n=771)	28 (3.6%)	0.90 (0.59-1.39)	21 (2.7%)	0.93 (0.56-1.55)	6 (0.8%)	1.18 (0.47-2.95)
≥1.00 SD (n=802)	27 (3.4%)	0.91 (0.59-1.39)	18 (2.3%)	0.87 (0.51-1.47)	5 (0.6%)	0.92 (0.34-2.44)
Height (n=5063)						
-0.99–0.99 SD (n=3740)	147 (3.9%)	ref	101 (2.7%)	ref	29 (0.8%)	ref
≤-1.00 SD (n=600)	18 (3.0%)	0.84 (0.51-1.37)	13 (2.2%)	0.88 (0.50-1.58)	4 (0.7%)	0.91 (0.32-2.62)
≥1.00 SD (n=723)	21 (2.9%)	0.79 (0.49-1.25)	14 (2.0%)	0.77 (0.44-1.35)	3 (0.4%)	0.56 (0.17-1.88)
BMI (n=5017)						
-0.99–0.99 SD (n=3513)	128 (3.6%)	ref	89 (2.6%)	ref	24 (0.7%)	ref
≤-1.00 SD (n=738)	30 (4.1%)	1.06 (0.70-1.60)	19 (2.6%)	0.90 (0.54-1.53)	7 (1.0%)	1.45 (0.62-3.41)
≥1.00 SD (n=766)	26 (3.4%)	0.97 (0.63-1.49)	19 (2.5%)	1.02 (0.61-1.69)	4 (0.5%)	0.81 (0.28-2.35)
Head circumference (n=5195)						
-0.99–0.99 SD (n=3777)	143 (3.8%)	ref	101 (2.7%)	ref	27 (0.7%)	ref
≤-1.00 SD (n=420)	15 (3.6%)	0.93 (0.53-1.62)	10 (2.4%)	0.85 (0.43-1.70)	3 (0.7%)	1.02 (0.31-3.41)
≥1.00 SD (n=998)	33 (3.3%)	0.89 (0.61-1.31)	21 (2.1%)	0.84 (0.52-1.35)	8 (0.8%)	0.96 (0.41-2.22)
At 2 years						
Weight (n=1017)						

-0.99–0.99 SD (n=715)	30 (4.2%)	ref	21 (3.0%)	ref	6 (0.9%)	ref
≤-1.00 SD (n=152)	9 (5.9%)	1.36 (0.61-3.03)	8 (5.3%)	1.63 (0.68-3.92)	1 (0.7%)	0.90 (0.10-7.96)
≥1.00 SD (n=150)	3 (2.0%)	0.51 (0.15-1.69)	2 (1.3%)	0.45 (0.10-1.92)	0	n.a.
Height (n=1002)						
-0.99–0.99 SD (n=665)	24 (3.6%)	ref	18 (2.7%)	ref	5 (0.8%)	ref
≤-1.00 SD (n=182)	11 (6.0%)	1.58 (0.74-3.38)	8 (4.5%)	1.45 (0.59-3.53)	2 (1.2%)	1.77 (0.31-10.09)
≥1.00 SD (n=155)	5 (3.2%)	0.72 (0.25-2.10)	3 (2.0%)	0.68 (0.20-2.31)	0	n.a.
BMI (n=998)						
-0.99–0.99 SD (n=709)	26 (3.7%)	ref	18 (2.6%)	ref	6 (0.9%)	ref
≤-1.00 SD (n=145)	8 (5.5%)	1.43 (0.61-3.32)	7 (4.9%)	1.64 (0.65-4.14)	1 (0.7%)	0.97 (0.11-8.38)
≥1.00 SD (n=144)	6 (4.2%)	1.28 (0.52-3.15)	4 (2.8%)	1.15 (0.39-3.41)	0	n.a.
At BMI Peak						
BMI (n=3227)						
-0.99–0.99 SD (n=2281)	92 (4.0%)	ref	64 (2.8%)	ref	18 (0.8%)	ref
≤-1.00 SD (n=470)	17 (3.6%)	0.78 (0.45-1.35)	14 (3.0%)	0.89 (0.47-1.67)	3 (0.7%)	0.78 (0.22-2.73)
≥1.00 SD (n=476)	9 (1.9%)	0.46 (0.22-0.96)	7 (1.5%)	0.59 (0.27-1.29)	0	n.a.
Age (n=3227)						
-0.99–0.99 SD (n=2261)	95 (4.2%)	ref	68 (3.0%)	ref	17 (0.8%)	ref

≤-1.00 SD (n=287)	8 (2.8%)	0.62 (0.29-1.34)	6 (2.1%)	0.62 (0.25-1.54)	2 (0.7%)	0.97 (0.22-4.24)
≥ 1.00 SD (n=679)	15 (2.2%)	0.55 (0.32-0.95)	11 (1.6%)	0.56 (0.29-1.06)	2 (0.3%)	0.40 (0.09-1.73)
At BMI Rebound						
BMI (n=3986)						
-0.99–0.99 SD (n=2871)	109 (3.8%)	ref	72 (2.5%)	ref	27 (1.0%)	ref
≤-1.00 SD (n=552)	23 (4.2%)	1.05 (0.66-1.70)	19 (3.5%)	1.29 (0.77-2.19)	2 (0.4%)	0.38 (0.09-1.61)
≥1.00 SD (n=563)	19 (3.4%)	0.89 (0.54-1.47)	15 (2.7%)	1.14 (0.65-1.99)	2 (0.4%)	0.40 (0.09-1.69)
Age (n=3986)						
-0.99–0.99 SD (n=2931)	111 (3.8%)	ref	75 (2.6%)	ref	27 (0.9%)	ref
≤-1.00 SD (n=545)	21 (3.9%)	1.07 (0.67-1.68)	15 (2.8%)	1.06 (0.61-1.85)	2 (0.4%)	0.62 (0.19-2.05)
≥1.00 SD (n=510)	19 (3.7%)	1.03 (0.64-1.67)	16 (3.2%)	1.21 (0.71-2.08)	2 (0.4%)	0.65 (0.20-2.16)
Peak Height Velocity in infancy (n=2095)						
-0.99–0.99 SD (n=1484)	54 (3.6%)	ref	42 (2.9%)	ref	8 (0.6%)	ref
≤-1.00 SD (n=314)	14 (4.5%)	1.33 (0.74-2.41)	10 (3.2%)	1.23 (0.61-2.47)	3 (1.0%)	2.05 (0.53-7.94)
≥1.00 SD (n=297)	7 (2.4%)	0.68 (0.31-1.51)	3 (1.0%)	0.37 (0.12-1.21)	1 (0.3%)	0.69 (0.09-5.66)
Peak Weight Velocity in infancy (n=2096)						
-0.99–0.99 SD (n=1778)	71 (4.0%)	ref	52 (3.0%)	ref	11 (0.6%)	ref
≤-1.00 SD (n=143)	2 (1.4%)	0.36 (0.09-1.47)	1 (0.7%)	0.25 (0.03-1.78)	1 (0.7%)	1.18 (0.15-9.24)

≥1.00 SD (n=175)	2 (1.1%)	0.31 (0.08-1.25)	2 (1.1%)	0.42 (0.10-1.74)	0	n.a.
Weight trajectories (n=5872)						
Average (n=3137)	127 (4.0%)	ref	78 (2.5%)	ref	34 (1.1%)	ref
Stable-low (n=661)	25 (3.8%)	0.93 (0.61-1.43)	20 (3.0)	1.21 (0.74-1.98)	5 (0.8%)	0.70 (0.27-1.78)
High-normal (n=1696)	61 (3.6%)	0.82 (0.60-1.11)	44 (2.6%)	0.95 (0.65-1.37)	9 (0.5%)	0.46 (0.22-0.96)
Stable-high (n=378)	5 (1.3%)	0.29 (0.12-0.72)	4 (1.1%)	0.38 (0.14-1.04)	0	n.a.
Height trajectories (n=6085)						
Average (n=2805)	104 (3.7%)	ref	66 (2.4%)	ref	22 (0.8%)	ref
Stable-low (n=341)	9 (2.6%)	0.91 (0.46-1.80)	9 (2.6%)	1.44 (0.72-2.90)	0	n.a.
Low-normal (n=2033)	84 (4.1%)	1.16 (0.87-1.55)	60 (3.0%)	1.31 (0.92-1.87)	19 (1.0%)	1.25 (0.67-2.33)
Stable-high (n=906)	30 (3.3%)	0.89 (0.59-1.33)	18 (2.0%)	0.83 (0.49-1.40)	8 (0.9%)	1.16 (0.51-2.61)

Cox regression adjusted for socioeconomic status and birth weight for gestational age. N=number;HR=hazard ratio;CI=confidence interval;n.a.=not applicable;Ref=reference group. Boldface indicates statistical significance.

TABLE 4.Results for nutritional variables.

	MALES						FEMALES					
	Any CVD		**Ischemic CVD**		**Hemorrhagic CVD**		**Any CVD**		**Ischemic CVD**		**Hemorrhagic CVD**	
	N(%)	HR(95%CI)	N(%)	HR(95%CI)	N(%)	HR(95%CI)	N(%)	HR(95%CI)	N(%)	HR(95%CI)	N(%)	HR(95%CI)
D vitamin supplementation (n=10295)												
Regular (n=9060)	160 (3.5%)	ref.	113 (2.5%)	ref.	30 (0.7%)	ref.	175 (3.9%)	ref.	124 (2.8%)	ref.	33 (0.8%)	ref.
Irregular or not at all (n=1185)	32 (4.8%)	1.45 (0.99-2.14)	20 (3.1%)	1.32 (0.81-2.14)	8 (1.2%)	1.90 (0.86-4.22)	18 (3.2%)	0.81 (0.50-1.32)	14 (2.5%)	0.87 (0.50-1.52)	2 (0.4%)	0.48 (0.12-2.02)
Iron supplementation (n=10145)												
Not at all or irregularly (n=4150)	68 (3.3%)	Ref.	47 (2.3%)	Ref.	16 (0.8%)	Ref.	69 (3.3%)	ref	51 (2.5%)	ref	10 (0.5%)	ref
Regularly (n=5934)	121 (4.0%)	1.18 (0.88-1.60)	84 (2.8%)	1.19 (0.83-1.70)	21 (0.7%)	0.88 (0.45-1.69)	121 (4.2%)	1.29 (0.96-1.73)	85 (3.0%)	1.21 (0.86-1.72)	22 (0.8%)	1.59 (0.75-3.35)
Anemia (n=10135)												

No (n=9713)	175 (3.6%)	ref	121 (2.5%)	ref	35 (0.7%)	ref	187 (3.9%)	ref	132 (2.8%)	ref	35 (0.7%)	ref
Yes (n=422)	11 (4.4%)	1.21 (0.67-2.22)	8 (3.2%)	1.26 (0.62-2.58)	1 (0.4%)	0.57 (0.08-4.13)	4 (2.4%)	0.61 (0.23-1.64)	2 (1.2%)	0.43 (0.11-1.74)	1 (0.6%)	0.80 (0.11-5.87)
Duration of breastfeeding (n=2956)												
3 or 6 months (n=1741)	53 (3.0%)	ref	37 (2.1%)	ref	10 (0.6%)	ref	60 (4.0%)	ref	46 (3.1%)	ref	9 (0.6%)	ref
1 month or not at all (n=1215)	40 (3.3%)	1.04 (0.68-1.57)	30 (2.5%)	1.16 (0.71-1.88)	7 (0.6%)	0.81 (0.29-2.25)	46 (4.5%)	1.07 (0.73-1.58)	33 (3.3%)	0.97 (0.62-1.52)	9 (0.9%)	1.43 (0.56-3.64)

Cox regression adjusted for socioeconomic status and birth weight for gestational age.N=number;HR=hazard ratio;CI=confidence interval;n.a.=not applicable;Ref=reference group.Boldface indicates statistical significance.

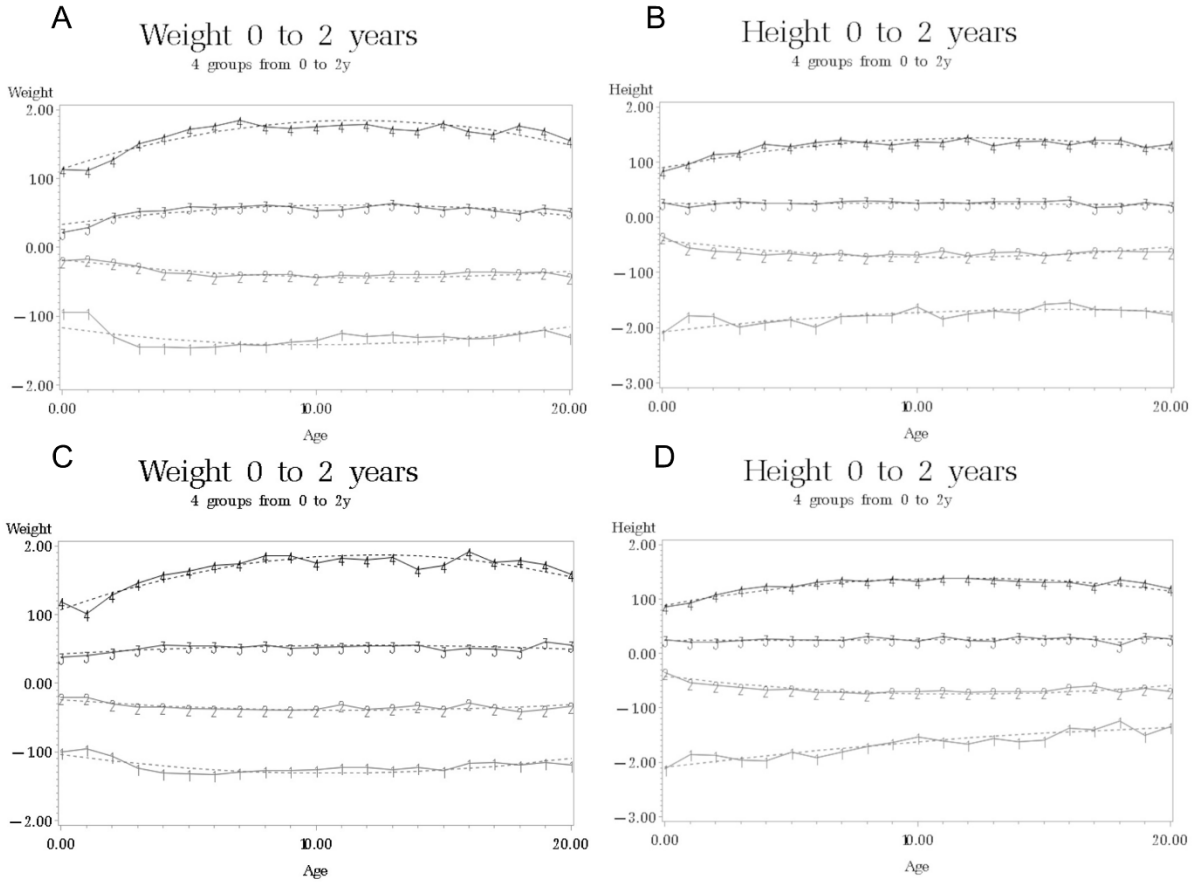

Figure 1A&B.Weight and height z-scores trajectories among females. Weight trajectory Group 1 'stable-low'(8.6%), Group 2 'average'(59.3%), Group 3 'high-normal'(23.8%), Group 4 'stable-high'(5.5%). Height trajectory Group 1'stable-low'(5.2%), Group 2 'low-normal'(33.5%), Group 3 'average'(48.9%), Group 4 'stable-high'(12.4%)**.C&B.Weight and height z-scores trajectories among males.**Weight trajectory Group 1 'stable-low'(11.3%), Group 2 'average'(53.4%), Group 3 'high-normal'(28.9%), Group 4 'stable-high'(6.4%). Height trajectory Group 1 'stable-low'(5.6%), Group 2 'low-normal'(33.4%), Group 3 'average'(46.1%), Group 4 'stable-high'(14.9%).

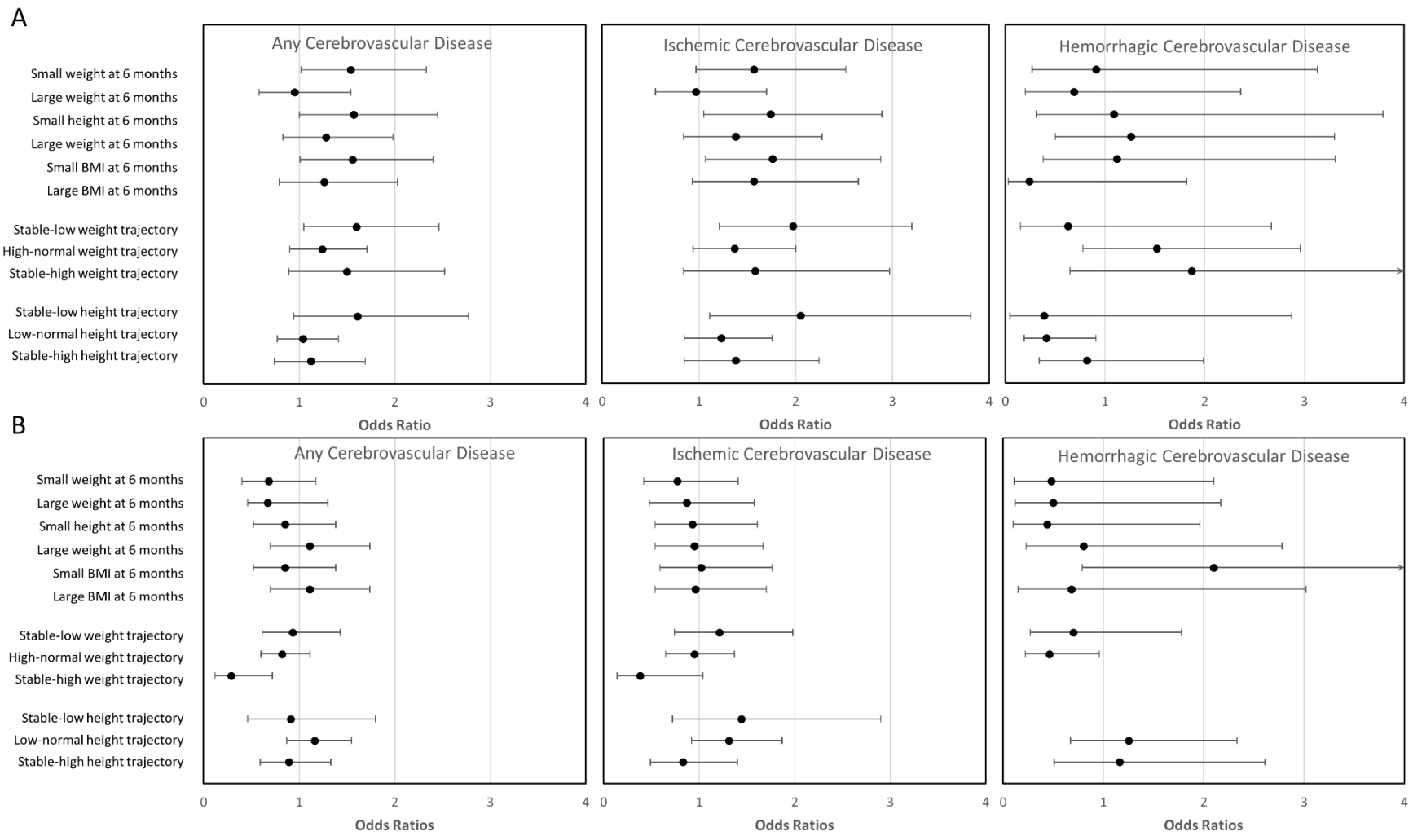

Figure 2 A.Forest plot of primary findings by CVD type, females. B.Forest plot of primary findings by CVD type, males.

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Supplemental Material

Supplemental Methods

Flowchart

Table S1

STROBE checklist

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