Childhood growth patterns and cardiovascular autonomic modulation in midlife - Northern Finland 1966 Birth Cohort Study

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Running title: Early growth and adult cardiac autonomic function

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Abstract

Objectives: To test the hypothesis that age and body mass index (BMI) at BMI peak during infancy and at BMI rebound in childhood are related to cardiovascular autonomic modulation in adulthood.

Methods: At the age of 46, a sample (n=5 861) of the participants of the Northern Finland Birth Cohort 1966 took part in follow-up examinations. Heart rate variability (HRV), baroreflex sensitivity (BRS) and low-frequency oscillations of systolic blood pressure (LF_{SBP}) were measured during sympathetic stimulus by standing. BMI at various ages was calculated from frequent anthropometric measurements collected from child welfare clinical records. BRS and LF_{SBP} were available for 1243 participants with BMI peak data and 1524 participants with BMI rebound data, and HRV for 2137 participants with BMI peak data and 2688 participants with BMI rebound data.

Results: Age at BMI rebound had a significant inverse association with LF_{SBP} (Beta=-0.071, p=0.006) after all adjustments (p<0.001) and was also directly associated with BRS (Beta=0.082, p=0.001) independently of birth and maternal factors (p=0.023). BMI at BMI peak and at BMI rebound was inversely associated with high frequency component of HRV (HF) (Beta=-0.045, p=0.036 for BMI at peak; Beta=-0.043, p=0.024 for BMI at rebound) and directly associated with the ratio of low- and high-frequency components of HRV (LF/HF ratio) (Beta=0.084, p=<0.001 for BMI at peak; Beta=0.069, p<0.001 for BMI at rebound). These associations remained significant after all adjustments (p<0.05 for all).

Conclusions: This novel study shows that younger age at BMI rebound and higher BMI at BMI peak and at BMI rebound are associated with higher levels in markers

suggestive of augmented sympathetic and reduced vagal cardiovascular modulation in midlife.

Introduction

Several recent studies have observed impaired cardiovascular autonomic modulation in children with obesity (1-8). Most of these studies have shown reduced vagal parasympathetic cardiovascular modulation (1-6) and some also increased sympathetic cardiovascular modulation or a shift of the sympatho-vagal balance towards sympathetic predominance (1, 2, 5) assessed by heart rate variability (HRV) and baroreflex sensitivity (BRS). Also, a reduction of both parasympathetic and sympathetic cardiovascular modulation in children with obesity has been reported (7, 8). It is well known that impaired cardiovascular autonomic regulation is an important risk factor associated with future cardiovascular and metabolic morbidity and mortality (9-12). It seems that the normal maturation of cardiovascular autonomic modulation is disrupted by childhood obesity and these individuals may be placed at a higher cardiovascular risk in adulthood. However, to the best of our knowledge no prior studies have explored whether childhood growth patterns are associated with cardiovascular autonomic regulation in adulthood.

During infancy and early childhood, one's growth curve usually follows a typical pattern. First, body mass index (BMI) increases from birth until the BMI peak of infancy, which typically occurs before one year of age. Thereafter BMI decreases before increasing again in later childhood. (13) This nadir of BMI is often referred to as BMI rebound or adiposity rebound, which usually takes place at the age of 5 to 6 years. Prior evidence shows that younger age at childhood BMI rebound is associated with obesity as well as other cardiovascular risk factors such as elevated blood pressure and insulin resistance in later life (14-18). Some studies have suggested that earlier BMI rebound is associated with later BMI and other cardiometabolic risk factors simply because it

identifies children with a high BMI or who are crossing over to a higher percentile, and the strong tracking of childhood BMI into adulthood (19-21). Indeed, childhood BMI has been associated with obesity and cardiovascular morbidity in adulthood, and the associations seem to be largely mediated by adult BMI (20, 21). However, as timing of BMI rebound involves the examination of several points in growth, it may give further insight into BMI patterns leading to future overweight and cardiometabolic risk (22). The long-term effects of BMI peak have been less studied. Higher BMI at BMI peak has been related to a higher BMI in later life (18, 23). Later BMI peak has also been associated with later overweight (18, 23). However, the latter correlation is weaker and partly controversial, suggesting that timing of BMI peak has a less important role in the tracking of future obesity than BMI at BMI peak (18, 23, 24).

The aim of the present study was to explore the associations between growth in infancy and childhood, specifically BMI and age at BMI peak and at BMI rebound, and markers of cardiovascular autonomic function in midlife (46 years of age) in males and females in the Northern Finland Birth Cohort 1966 (NFBC1966) (25). The NFBC1966 is a large prospective study with extensive data on the participants from the fetal period to midlife. Our hypothesis was that later BMI peak, earlier BMI rebound and higher BMI at BMI peak and at BMI rebound are associated with poorer cardiovascular autonomic regulation in later life.

Materials and Methods

Participants: All pregnant mothers whose expected date of delivery fell between January 1st and December 31st 1966 in the two northernmost provinces of Finland (Oulu and Lapland) were invited to the prospective NFBC 1966 study. The cohort covers

96.3% of all births in 1966 in this area (n = 12 058 live births). Starting from their mothers' recruitment during their first visit to maternity health centers on average on the 16th gestational week, data has been collected on the participants' growth, health, life style and socioeconomic status until middle age. The study has been conducted according to the Declaration of Helsinki and approved by the Ethical Committee of the Northern Ostrobothnia Hospital District in Oulu, Finland. The participants have provided their written informed consent for the study.

Birth and maternal variables: Birth and maternal variables that were considered in the analyses as possible confounding factors include birth weight, gestational age, paternal (maternal if mother was single) socioeconomic status, mother's age at delivery, pre-pregnancy weight, height, parity and maternal smoking during pregnancy. Paternal socioeconomic status (high, middle, low, farmer), parity (1, 2–3 and ≥4) and maternal smoking status (smoking ≥1 cigarette/day after 2nd month of pregnancy) were categorized using cutoffs adapted from Järvelin et al. 2004 (25).

Growth variables: The growth modelling methods used in this study have been described in detail elsewhere (18). Briefly, BMI at various ages was calculated from frequent anthropometric measurements during infancy and childhood collected from child welfare clinical records. The average of 22 height and weight measurements per person were collected from 0 years until adulthood. Growth variables were derived from random effect models fitted at 0-1.5 years (n=3,265) and >1.5-13 years (n=4,121).

Protocol at age of 46: A postal questionnaire-based data collection on the participant's health status and life style was conducted in 2012-2014 (response rate 66%, n=6 825). Smoking status, alcohol consumption, total sitting time during waking hours, nocturnal items of Athens Insomnia Scale (26) and physical activity were

inquired. Participants were invited to clinical examinations at the Center for Life Course Health Research (University of Oulu) with three laboratory units (Oulu, Southern and Northern Finland). A total of 5 861 (57%) participants participated in clinical examinations between April 2012 and March 2014. The participants entered the laboratory between 7:00 and 11:00 a.m. after an overnight fasting period (12 hours). Participants were instructed to avoid smoking and drinking coffee during the examination day. Venous blood samples were drawn from an antecubital vein for the analysis of glycemic and lipid status. Serum glucose, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides and glycated hemoglobin were analyzed as previously described (27). Systolic (SBP) and diastolic blood pressure (DBP) were measured three times in 1-minute periods (the two lowest systolic values and the corresponding diastolic values averaged) with an automated sphygmomanometer (Omron M10, Omron Healthcare, Kyoto, Japan) in a seated position from the right arm after 15 minutes of rest. After various measurements, including anthropometry, the participants had a light meal 60-90 min before the assessments of cardiovascular autonomic function.

Measurement and analysis of cardiovascular autonomic function: The protocol and analyses have been described elsewhere in detail (27). Briefly, the participant sat on a chair for instrumentation and review of the protocol. A heart rate (HR) monitor (RS800CX, Polar Electro Oy, Kempele, Finland) was used to record R-R intervals with an accuracy of 1 ms. In about half of the participants (Oulu laboratory unit only) spontaneous BRS was also assessed. Standard lead-II electrocardiography (ECG) (Cardiolife, Nihon Kohden, Tokyo, Japan), breathing frequency (MLT415/D, Nasal Temperature Probe, ADInstruments, Bella Vista, New South Wales, Australia),

and blood pressure by finger plethysmography (Nexfin, BMEYE Medical Systems, Amsterdam, the Netherlands) were recorded during the protocol with a sampling frequency of 1,000 Hz (PowerLab 8/35, ADInstruments). After 3 min recording in a seated position, the participant stood up and remained still in a standing position for 3 min while breathing spontaneously. The first 150 s of recording in seated position and the last 150 s in standing position were analyzed. A total of 5 679 participants attended R-R interval recordings of whom 5 473 (96%) had eligible HRV data for both phases of the protocol (seated and standing). Mean HR, root mean square of successive differences in R-R intervals (rMSSD, ms), spectral power densities (fast Fourier transform, length 512 beats) at low (LF, 0.04-0.15 Hz, ms^2) and high frequency (HF, 0.15–0.40 Hz, ms^2) components of HRV, and their ratio (LF/HF) were analyzed (28). For the BRS analysis, a fast Fourier transform (Welch method, segments of 128 samples with 50% overlap, length 1024 samples) was performed to analyze the LF power of R-R interval and SBP oscillations (LF ms^2, LF_{SBP} $mmHg^2$) for subsequent analysis of BRS by the alpha method if sufficient coherence (≥0.5) between LF oscillations in R-R interval and SBP was verified (29, 30). Out of 2 726 recordings, BRS was successfully calculated for 2 641 participants in the seated position and 2 617 while they were standing. We focused on assessment of autonomic function in a standing position based on previous findings suggesting that LF/HF ratio and LF_{SBP} would estimate sympathetic modulation during sympathetic stimulus by upright position (31).

Inclusions/Exclusions: All participants with early growth and HRV or BRS data were included in the analyses. BRS and LF_{SBP} were available for 1243 participants with BMI peak data and 1524 participants with BMI rebound data, and HRV for 2137

participants with BMI peak data and 2688 participants with BMI rebound data. (Figure 1).

Statistical analyses

The data were analyzed using SPSS software (IBM SPSS Statistics 24, IBM Corp., New York, USA). A p-value <0.05 was considered as statistically significant. The distributions of the dependent variables were assessed by analyzing the skewness of the data and by visual inspection of histograms. In the case of skewed distribution (BMI at BMI peak and at BMI rebound, LF, HF, LF/HF, rMSSD, BRS, LF_{SBP}), variables were transformed into natural logarithm (ln). These transformed variables were visually verified for normality (Gaussian distribution). Two-tailed t-test for independent samples was performed to compare men and women. Gender-interactions in the associations between early growth variables and cardiovascular autonomic function were tested by ANCOVA (gender*early growth variable [in tertiles]). Univariate linear regression models were used to assess the relationships between early growth variables and adult cardiovascular autonomic function (HR, LF, HF, LF/HF, rMSSD, BRS, LF_{SBP} measured in seated and standing positions).

All significant associations between early growth variables and cardiovascular autonomic function in univariate analysis were further adjusted for potential confounders in multiple linear regression models. First for birth (gender, birth weight, gestational age) and maternal factors (socioeconomics, age, height, weight, smoking after 2nd month of pregnancy and parity), and, subsequently, also for continuous adult anthropometric (weight, height and waist-hip ratio) and cardiometabolic variables (HR, SBP, DBP, glycated hemoglobin, total cholesterol, high density cholesterol and triglycerides) as well as adult life style variables (smoking,

sitting time, alcohol consumption, Athens insomnia scale and physical activity). Finally, the significant univariate associations were further adjusted for diabetes based on previous or new diagnosis according to the criteria issued by the World Health Organization (fasting plasma glucose ≥7.0 mmol/l or 2-hour glucose ≥11.1 mmol/l in oral glucose test or glycated hemoglobin ≥ 6.5 %) (32), cardiac and respiratory disease, and antihypertensive medication. Variables were continuous where applicable. No significant collinearity between the independent variables was present (variance inflation factor <5 for all independent variables in the final models). Second degree polynomial terms were added for maternal age, height and weight to account for their nonlinear relationships with dependent variables. Among the included participants, there were some missing data in independent variables and covariates. We used maximum available participant-approach and the variation in the number of participants in specific analyses are noted in the results.

Results

Characteristics of the study population

Table 1 describes the growth parameters, cardiometabolic profile and measures of cardiovascular autonomic modulation of the study population and their distribution by sex. Some sex differences were observed. Males were born larger and heavier than females and their BMI at BMI peak and at BMI rebound was significantly higher than in females. The timing of BMI rebound was earlier in females than in males. At 46 years of age males had a more disadvantageous cardiometabolic profile than females. Regarding measures of cardiovascular autonomic modulation, males had higher values of LF, LF/HF ratio and LF_{SBP}. HF and rMSSD values were similar for males and

females. BRS values were higher in males. Heart diseases were more common in males, and females were more frequently on antihypertensive medication.

Table 2 shows the correlations between early growth measures. Birth weight was moderately positively associated with BMI at BMI peak and at BMI rebound. Birth weight was inversely associated with age at BMI peak and at BMI rebound; though these associations were weak. Ages at BMI peak and BMI rebound were not correlated. Age at BMI peak was weakly associated with BMI at the same time, whereas its correlation to BMI at BMI rebound was slightly stronger. Age at BMI rebound had a moderate to strong inverse correlation with BMI at rebound. BMI at BMI peak and at BMI rebound were strongly positively correlated.

Early growth and adult cardiovascular autonomic function

No gender interactions in the associations between early growth and later cardiovascular autonomic modulation were observed. Table 3 reports the statistically significant associations between early growth and adult markers of cardiovascular autonomic modulation measured in a standing position. For the associations between early growth and HR, also non-significant correlations are shown. None of the early growth variables were associated with adult rMSSD or LF. Adjustment for birth and maternal factors are shown in Table 3. Further adjustment for adult anthropometrics, lifestyle and cardiometabolic risk and morbidity are shown in Table 4. Partly corresponding results were seen in associations between early growth and adult cardiovascular autonomic function measured in a seated position, though less associations were observed (data not shown).

Infant BMI growth

Age at BMI peak was not related to measures of cardiovascular autonomic modulation in adulthood. Higher BMI at BMI peak was associated with lower HF and higher LF/HF ratio. These associations remained statistically significant after all adjustments. (Table 3, Table 4).

Childhood BMI growth

Univariate analysis showed that earlier BMI rebound correlated with higher LF_{SBP} and lower BRS (Table 3). Both of these associations remained statistically significant after adjustments for birth and maternal variables, and the association between age at BMI rebound and LF_{SBP} even after further adjustment for adult variables (Table 3, Table 4). We also observed insignificant tendencies in the associations between age at BMI rebound and HF (standardized beta (Beta)=0.037, unstandardized beta (B)=0.05 [-0.001, 0.1], p=0.056) and LF/HF ratio (Beta=-0.033, B=-0.03 [-0.07, 0.005], p=0.089). The relationship between age at BMI rebound and HF attenuated after adjustment for maternal and birth variables. The association between timing of BMI rebound and LF/HF ratio was independent of birth and maternal as well as adult factors (R^2=0.159, Beta=-0.074, B=-0.07 [-0.1, -0.03], p=0.001 in final multivariate model). HR was not associated with timing of BMI rebound. BMI at BMI rebound was directly associated with LF/HF ratio and inversely associated with HF and HR (Table 3). All of these correlations remained statistically significant after adjustments for all confounders (Table 3, Table 4). BMI at BMI rebound tended to associate with LF_{SBP} (Beta=0.050, B=0.6 [-0.004, 1.2], p=0.052), and this association was not explained by birth and maternal and adult factors (R^2=0.101, Beta=0.086, B=1.0 [0.3, 1.7], p=0.006 in final multivariate model).

Discussion

Our main findings were that timing of BMI rebound and BMI in infancy and childhood were associated with markers of cardiovascular autonomic regulation in adulthood. Earlier BMI rebound was independently related to higher values of LF_{SBP} and lower BRS suggesting that lower age at BMI rebound is associated with deteriorated cardiovascular autonomic regulation in adulthood. BMI at infant BMI peak and at childhood BMI rebound were inversely associated with HF and directly with LF/HF indicating that higher BMI in infancy and childhood is related to reduced vagal cardiovascular modulation and shift of the sympatho-vagal balance towards sympathetic predominance. These findings support our hypothesis that earlier age at BMI rebound and higher infant and childhood BMI are associated with poorer cardiovascular autonomic modulation in adults. No associations between age at BMI peak and later autonomic regulation were observed.

Previous studies have suggested that childhood obesity disturbs the normal maturation of cardiovascular autonomic regulation (1-8). However, most of these studies are case control studies with relatively small sample sizes and therefore larger studies in a longitudinal setting are needed. Also, most studies have used BMI at fixed ages as a predictor, which does not take into account the heterogeneity in the developmental patterns of infancy and childhood. In our study, frequent anthropometric measurements in infancy and childhood enabled modeling of individual growth trajectories. From the growth trajectories, we derived points in infant and childhood growth, BMI peak and BMI rebound, which have been related to future overweight and obesity (14, 16-18, 23, 24). Our study is the first to explore associations between childhood BMI growth patterns and cardiovascular autonomic modulation in adulthood.

BMI rebound seems to be an interesting period in childhood growth. Early BMI rebound has been shown to reflect increased weight gain in childhood with the weight gain being essentially due to accumulation of body fat rather than lean mass (33, 34). Accumulation of fat mass has been related to alterations in adipose tissue function in early childhood (35). Together the excess fat, adipose tissue dysfunction and other obesity related changes cause the development of vascular changes already in childhood (36-38). Timing of BMI rebound considers several BMI measurements of infancy and childhood, giving insight into early developmental patterns. A recent large study showed that early childhood is indeed a critical age for development of sustained obesity and that an increase in the BMI standard-deviation score between ages 2 and 6 years is the most powerful predictor of adolescence obesity. Thus, it seems that patterns of BMI growth in early childhood, rather than the absolute BMI, may be important in identifying children with future cardiometabolic risk. (39) However, also absolute BMI values in childhood may be associated with future cardiometabolic outcome as obesity tends to persist into adulthood from as early as 3 years of age. (39) Our results show that early BMI rebound was associated with higher level in a marker considered to describe peripheral sympathetic modulation (LF_{SBP}) (40) and we also observed a similar tendency regarding sympatho-vagal balance (LF/HF) (28, 40). Early BMI rebound was also associated with reduced vagal modulation. Similar features in markers of adult cardiovascular autonomic modulation were observed in children and even infants with higher BMI. Higher BMI at rebound (on average at 5.7 years) and at BMI peak (on average at 9 months of age) in childhood were related to lower parasympathetic cardiovascular regulation and sympathetic predominance in adulthood. These

associations were not attenuated by adjustment for birth and maternal factors or adult cardiometabolic factors and lifestyle.

The alterations in adult HRV that we observed with earlier BMI rebound and higher infant and childhood BMI are similar to HRV alterations previously reported in children with obesity (1-8). This suggests that alterations in the maturation of cardiovascular autonomic function related to obesity may affect cardiovascular autonomic modulation in adulthood. Childhood BMI has a strong tendency to track into adulthood and the association between childhood obesity and adult cardiovascular morbidity seems to be in large part mediated by high adult BMI (20, 21). However, there is evidence of alterations of the cardiovascular system (vascular alterations and changes in the morphology of the heart) related to childhood obesity, which may place children with obesity at predisposition to cardiometabolic diseases (36-38, 41). In our study the associations between early growth and adult cardiovascular autonomic modulation were not attenuated after adjustment for adult weight status, suggesting that childhood growth patterns may contribute to later cardiovascular autonomic modulation even independently of the strong tracking of BMI into adulthood.

In a previous study, we found that mothers' overweight prior to pregnancy, excess gestational weight gain and birth weight are associated with cardiovascular autonomic regulation in adulthood (27). Maternal overweight prior to pregnancy has also been shown to be associated with adverse childhood growth patterns, e.g., early adiposity rebound (42, 43). Based on these previous observations it could be speculated that prenatal influences may also have contributed to our present findings concerning the relationship between infant and childhood BMI growth patterns

and adult cardiovascular autonomic regulation. These notions emphasize the importance of maternal and childhood weight development and control.

Many factors have been shown to influence cardiovascular autonomic modulation including cardiometabolic risk factors and lifestyle. However, these factors explain surprisingly little of the inter-individual variance in cardiovascular autonomic function. (44, 45) In our study childhood BMI growth patterns remained significant determinants of cardiovascular autonomic regulation in adulthood. However, relatively low R^2 levels in the final models suggest that even if birth and maternal factors, early growth as well as adult cardiometabolic profile and lifestyle are combined together, they only partly explain cardiovascular autonomic regulation in adulthood suggesting a contribution of genetic and still unknown factors.

Study strengths and limitations

The present study is unique in that it has the longest follow-up from early pregnancy until middle age ever reported on these measures. Large general population sample, longitudinal setting and comprehensive high-quality data on the study participants ensure quality of reported results. However, there are also some limitations. Our study sample did not fully represent the whole NFBC 1966, which should be taken into account when interpreting the results. The recordings for R-R interval and blood pressure data were relatively short. Cardiovascular autonomic function is affected by, e.g., the time from the previous meal, which although controlled, was relatively short in the present study. Nicotine and caffeine withdrawal may also have affected the measures of cardiac autonomic function. Also, spontaneous breathing may confound the spectral analysis of cardiovascular oscillations. The role of LF/HF ratio and LF_{SBP} as markers of sympathetic autonomic regulation is less well established when measured at

rest or exercise (46, 47). However, we used the measurements obtained in standing position as they better reflect sympathetic autonomic modulation.

Conclusions

Our study provides novel information on an association between timing of BMI rebound, early childhood BMI and cardiovascular autonomic regulation in adulthood suggesting that early effects in the maturation of cardiovascular autonomic function may reflect into adulthood.

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Competing interests

The authors have no conflicts of interest to disclose.

References

1. Taşçılar ME, Yokuşoğlu M, Boyraz M, Baysan O, Köz C, Dündaröz R. Cardiac autonomic functions in obese children. J Clin Res Pediatr Endocrinol 2011; 3:60–64.

2. Kaufman CL, Kaiser DR, Steinberger J, Dengel DR. Relationships between heart rate variability, vascular function, and adiposity in children. Clin Auton Res 2007; 17:165–171.

3. Birch SL, Duncan MJ, Franklin C. Overweight and reduced heart rate variability in British children: an exploratory study. Prev Med 2012; 55:430–32.

4. Zhou Y, Xie G, Wang J, Yang S. Cardiovascular risk factors significantly correlate with autonomic nervous system activity in children. Can J Cardiol 2012; 28:477–82.

5. Rodríguez-Colón SM, Bixler EO, Li X, Vgontzas AN, Liao D. Obesity is associated with impaired cardiac autonomic modulation in children. Int J Pediatr Obes 2011; 6:128–34.

6. Dangardt F, Volkmann R, Chen Y, Osika W, Marild S, Friberg P. Reduced cardiac vagal activity in obese children and adolescents. Clin Physiol Funct Imaging 2011; 31:108–13.

7. Vanderlei LC, Pastre CM, Freitas IF, Jr, Godoy MF. Analysis of cardiac autonomic modulation in obese and eutrophic children. Clinics 2010; 65:789–92.

8. Nagai N, Matsumoto T, Kita H, Moritani T. Autonomic nervous system activity and the state and development of obesity in Japanese school children. Obes Res 2003; 11:25–32.

9. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and

412 mortality from several causes: the ARIC Study. Atherosclerosis Risk In Communities.
413 Circulation 2000; 102(11):1239-44.

414 10. Liao D, Cai J, Brancati FL, Folsom A, Barnes RW, Tyroler HA, et al. Association
415 of vagal tone with serum insulin, glucose, and diabetes mellitus--The ARIC Study.
416 Diabetes Res Clin Pract 1995; 30(3):211-21.

417 11. Tsuji H, Larson MG, Venditti FJ, Manders ES, Evans JC, Feldman CL, et al. Impact
418 of reduced heart rate variability on risk for cardiac events. The Framingham Heart
419 Study. Circulation 1996; 94:2850-55.

420 12. Kiviniemi AM, Tulppo MP, Hautala AJ, Perkiomaki JS, Ylitalo A, Kesaniemi YA,
421 et al. Prognostic significance of impaired baroreflex sensitivity assessed from phase IV
422 of the valsalva maneuver in a population-based sample of middle-aged subjects. Am J
423 Cardiol 2014; 114:571-76.

424 13. Rolland-Cachera MF, Deheeger M, Bellisle F, Sempé M, Guilloud-Bataille M,
425 Patois E. Adiposity rebound in children: a simple indicator for predicting obesity. Am J
426 Clin Nutr. 1984; 39(1):129-35.

427 14. Hughes AR, Sherriff A, Ness AR, Reilly JJ. Timing of adiposity rebound and
428 adiposity in adolescence. Pediatrics 2014; 134, e1354-61.

429 15. Mo-Suwan L, McNeil E, Sangsupawanich P, Chittchang U, Choprapawon C.
430 Adiposity rebound from three to six years of age was associated with a higher insulin
431 resistance risk at eight-and-a-half years in a birth cohort study. Acta Paediatr 2017;
432 106:128-34.

433 16. Peneau S, Gonzalez-Carrascosa R, Gusto G, Goxe D, Lantieri O, Fezeu L, et al. Age
434 at adiposity rebound: Determinants and association with nutritional status and the
435 metabolic syndrome at adulthood. Int J Obes 2016; 40:1150-56.

436 17. Taylor RW, Grant AM, Goulding A, Williams SM. Early adiposity rebound:
437 Review of papers linking this to subsequent obesity in children and adults. Curr Opin
438 Clin Nutr Metab Care 2005; 8:607-12.
439 18. Sovio U, Kaakinen M, Tzoulaki I, Das S, Ruokonen A, Pouta A., et al. How do
440 changes in body mass index in infancy and childhood associate with cardiometabolic
441 profile in adulthood? Findings from the Northern Finland Birth Cohort 1966 Study. Int J
442 Obes 2014; 38:53-59.
443 19. Cole TJ. Children grow and horses race: Is the adiposity rebound a critical period
444 for later obesity? BMC Pediatr 2004; 4:6.
445 20. Lloyd LJ, Langley-Evans SC, McMullen S. Childhood obesity and risk of the adult
446 metabolic syndrome: a systematic review. Int J Obes 2012; 36:1–11.
447 21. Lloyd LJ, Langley-Evans SC, McMullen S. Childhood obesity and adult
448 cardiovascular disease risk: a systematic review. Int J Obes 2010; 34:18-28.
449 22. Rolland-Cachera MF, Deheeger M, Maillot M, Bellisle F. Early adiposity rebound:
450 causes and consequences for obesity in children and adults. Int J Obes 2006; 30:11–17.
451 23. Silverwood RJ, De Stavola BL, Cole TJ, Leon DA. BMI peak in infancy as a
452 predictor for later BMI in the Uppsala Family Study. Int J Obes 2009; 33:929–37.
453 24. Wen X, Kleinman K, Gillman MW, Rifas-Shiman SL, Taveras EM. Childhood
454 body mass index trajectories: modeling, characterizing, pairwise correlations and socio-
455 demographic predictors of trajectory characteristics. BMC Med Res Methodol 2012;
456 12:38.
457 25. Jarvelin MR, Sovio U, King V, Lauren L, Xu B, McCarthy MI, et al. Early life
458 factors and blood pressure at age 31 years in the 1966 Northern Finland birth cohort.
459 Hypertension 2004; 44:838-46.

460 26. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. The diagnostic validity of the Athens
461 insomnia scale. J Psychosom Res 2003; 55:263-67.
462 27. Perkiomaki N, Auvinen J, Tulppo MP, Hautala AJ, Perkiomaki J, Karhunen V, et al.
463 Association between birth characteristics and cardiovascular autonomic function at mid-
464 life. PLoS One 2016; 11:e0161604
465 28. Task Force of the European society of cardiology and the North American society of
466 pacing and electrophysiology. Heart rate variability: standards of measurement,
467 physiological interpretation, and clinical use. Eur Heart J 1996; 17:354-81.
468 29. Kiviniemi AM, Hautala AJ, Karjalainen JJ, Piira OP, Lepojarvi S, Tiinanen S, et al.
469 Impact of type 2 diabetes on cardiac autonomic responses to sympathetic stimuli in
470 patients with coronary artery disease. Auton Neurosci 2013; 179:142-47.
471 30. Kiviniemi AM, Hintsala H, Hautala AJ, Ikaheimo TM, Jaakkola JJ, Tiinanen S, et
472 al. Impact and management of physiological calibration in spectral analysis of blood
473 pressure variability. Front Physiol 2014; 5:473.
474 31. Furlan R, Porta A, Costa F, Tank J, Baker L, Schiavi R, et al. Oscillatory patterns in
475 sympathetic neural discharge and cardiovascular variables during orthostatic stimulus.
476 Circulation 2000; 101: 886-92.
477 32. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus
478 and its complications. Part 1: diagnosis and classification of diabetes mellitus
479 provisional report of a WHO consultation. Diabet Med 1998; 15:539-53.
480 33. Taylor RW, Goulding A, Lewis-Barned NJ, Williams SM. Rate of fat gain is faster
481 in girls undergoing early adiposity rebound. Obes Res 2004; 12:1228-30.
482 34. Williams SM. Weight and height growth rate and the timing of adiposity rebound.
483 Obes Res 2005; 13:1123-30.

484 35. Landgraf K, Rockstroh D, Wagner IV, Weise S, Tauscher R, Schwartze JT, et al.
485 Evidence of early alterations in adipose tissue biology and function and its association
486 with obesity-related inflammation and insulin resistance in children. Diabetes 2015;
487 64(4):1249-61.
488 36. Freemark M. Predictors of childhood obesity and pathogenesis of comorbidities.
489 Pediatr Ann 2014; 43:357-60.
490 37. Freedman DS, Patel DA, Srinivasan SR, Chen W, Tang R, Bond MG, et al. The
491 contribution of childhood obesity to adult carotid intima-media thickness: the Bogalusa
492 Heart Study. Int J Obes 2008; 32:749–56.
493 38. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA.
494 Association between multiple cardiovascular risk factors and atherosclerosis in children
495 and young adults. The Bogalusa Heart Study. N Engl J Med 1998; 338:1650–6.
496 39. Geserick M, Vogel M, Gausche R, Lipek T, Spielau U, Keller E, et al. Acceleration
497 of BMI in Early Childhood and Risk of Sustained Obesity. N Engl J Med 2018;
498 379:1303-12.
499 40. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation
500 explored in the frequency domain. Circulation 1991; 84:482–92.
501 41. Liao D, Rodríguez-Colón SM, He F, Bixler EO. Childhood obesity and autonomic
502 dysfunction: risk for cardiac morbidity and mortality. Curr Treat Options Cardiovasc
503 Med. 2014; 16(10):342.
504 42. Ip EH, Marshall SA, Saldana S, Skelton JA, Suerken CK, Arcury TA, et al.
505 Determinants of Adiposity Rebound Timing in Children. J Pediatr. 2017; 184:151-6.

506 43. Linares J, Corvalán C, Galleguillos B, Kain J, González L, Uauy R, et al. The
507 effects of pre-pregnancy BMI and maternal factors on the timing of adiposity rebound
508 in offspring. Obesity (Silver Spring) 2016; 24(6):1313-9.
509 44. Kardos A, Watterich G, de Menezes R, Csanady M, Casadei B, Rudas L.
510 Determinants of spontaneous baroreflex sensitivity in a healthy working population.
511 Hypertension 200; 37(3):911–16.
512 45. Tsuji H, Venditti FJ Jr, Manders ES, Evans JC, Larson MG, Feldman CL, et al.
513 Determinants of heart rate variability. J Am Coll Cardiol 1996; 28(6):1539–46.
514 46. Billman GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal
515 balance. Front Physiol 2013; 4:26
516 47. Tulppo MP, Mäkikallio TH, Takala TE, Seppänen T, Huikuri HV. Quantitative
517 beat-to-beat analysis of heart rate dynamics during exercise. Am J Physiol 1996. 271(1
518 Pt 2):H244-52.

Table 1. Characteristics of the study population

	Male	Female	p-value
Growth variables			
Gestational age (weeks)	40.1 (1.9)	40.2 (1.8)	0.174
Birth weight (grams)	3587 (518)	3448 (475)	<0.001
Birth length (cm)	50.9 (2.1)	50.0 (2.0)	<0.001
Age at BMI peak (years)*	0.74 (0.06)	0.75 (0.06)	0.080
Age at BMI rebound (years)	5.8 (0.9)	5.6 (0.9)	<0.001
BMI at BMI peak (kg/m^2)*	18.3 (1.1)	17.9 (1.1)	<0.001
BMI at BMI rebound (kg/m^2)	15.4 (1.0)	15.3 (1.2)	0.023
Cardiometabolic outcomes at 46 years			
Weight (kg)	86.6 (14)	72 (15)	<0.001
Height (cm)	178 (6.3)	165 (6.1)	<0.001
BMI (kg/m^2)	27.2 (4.2)	26.6 (5.2)	0.001
Waist-hip ratio	0.98 (0.06)	0.87 (0.06)	<0.001
SBP (mmHg)	129 (14)	119 (15)	<0.001
DBP (mmHg)	86 (10)	82 (11)	<0.001
HbA1c (%)	5.6 (0.6)	5.4 (0.5)	<0.001
Total cholesterol (mmol/l)	5.6 (1.0)	5.2 (0.9)	<0.001
HDL cholesterol(mmol/l)	1.4 (0.3)	1.7 (0.4)	<0.001
LDL cholesterol (mmol/l)	3.7 (0.9)	3.2 (0.8)	<0.001
Triglycerides (mmol/l)	1.5 (1.0)	1.1 (0.6)	<0.001
Diabetes (n)	85 (7%)	83 (6%)	0.087
Heart diseases (n)	33 (3%)	24 (2%)	<0.001
Antihypertensive medication (n)	141 (12%)	195 (13%)	<0.001
Cardiac autonomic function at 46 years			
HR (bpm)	81 (73-90)	83 (75-92)	<0.001
rMSSD (ms)	12.2 (8.1-19)	12.1 (7.9-18)	0.412
BRS (ms/mmHg)**	4.66 (3.2-6.7)	4.13 (3.0-5.8)	<0.001
LF_{SBP} ($mmHg^2$)**	9.39 (5.3-16)	7.57 (4.5-13)	<0.001
LF (ms^2)	269 (134-546)	191 (101-354)	<0.001
HF (ms^2)	64.0 (27-144)	72.0 (29-160)	0.107
LF/HF	4.41 (2.4-7.6)	2.81 (1.6-5.0)	<0.001

Values are mean (SD), median (1^{st}-3^{rd} quartile) and p-value for sex difference. *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol. *HR* heart rate, *rMSSD* root mean square of successive differences in R-R interval, *BRS* baroreflex sensitivity, LF_{SBP} low frequency power of systolic blood pressure variability, *LF* low frequency power of R-R interval variability, *HF* high frequency power of R-R interval variability, *LF/HF* ratio of low and high frequency power of R-R interval variability measured in a standing position. n= 1183-

1218/1419-1470 for men/women unless noted otherwise. *n=965/1172 and **696/828 for men/women

Table 2. Correlations between measures of early growth

	Birth weight	Age at BMI peak	Age at BMI rebound	BMI at BMI peak
Age at BMI peak	-0.082**	1		
Age at BMI rebound	-0.049**	0.004	1	
BMI at BMI peak	0.289**	0.114**	-0.012	1
BMI at BMI rebound	0.219**	0.219**	-0.526**	0.608**

Correlations are Pearson's correlation coefficients (r). *correlation is significant at the 0.05 level (two-tailed), **correlation is significant at the 0.01 level (two-tailed). *BMI* body mass index.

Table 3. Association between early growth and cardiovascular autonomic regulation in adulthood adjusted for birth and maternal variables

		Univariate				Multivariate			
		*				Adjusted Block 1**			
		R^2	Beta	B (95% CI)	p	R^2	Beta	B (95% CI)	p
Age at BMI peak	HR	0.000	-0.017	-3.7 [-13, 5.7]	0.435	0.009	-0.027	-6.0 [-16, 4.2]	0.248
Age at BMI rebound	HR	0.000	-0.008	-0.1 [-0.7, 0.4]	0.670	0.008	-0.002	-0.03 [-0.6, 0.6]	0.917
	BRS	0.007	0.082	0.05 [0.02, 0.08]	**0.001**	0.022	0.063	0.04 [0.005, 0.07]	**0.023**
	LF_{SBP}	0.005	-0.071	-0.06 [-0.1, -0.02]	**0.006**	0.037	-0.088	-0.08 [-0.1, -0.03]	**0.002**
BMI at BMI peak	HR	0.001	-0.034	-7.3 [-17, 1.9]	0.118	0.009	-0.024	-5.2 [-16, 5.2]	0.325
	HF	0.002	-0.045	-1.0 [-2.0, -0.07]	**0.036**	0.011	-0.053	-1.2 [-2.3, -0.1]	**0.029**
	LF/HF	0.007	0.084	1.2 [0.6, 1.8]	**<0.001**	0.074	0.062	0.9 [0.2, 1.6]	**0.009**
BMI at BMI rebound	HR	0.003	-0.052	-9.5 [-16, -2.6]	**0.007**	0.011	-0.056	-10 [-18, -2.5]	**0.009**
	HF	0.002	-0.043	-0.8 [-1.5, -0.1]	**0.024**	0.007	-0.045	-0.8 [-1.6, -0.05]	**0.037**
	LF/HF	0.005	0.069	0.9 [0.4, 1.3]	**<0.001**	0.067	0.069	0.8 [0.3, 1.3]	**0.001**

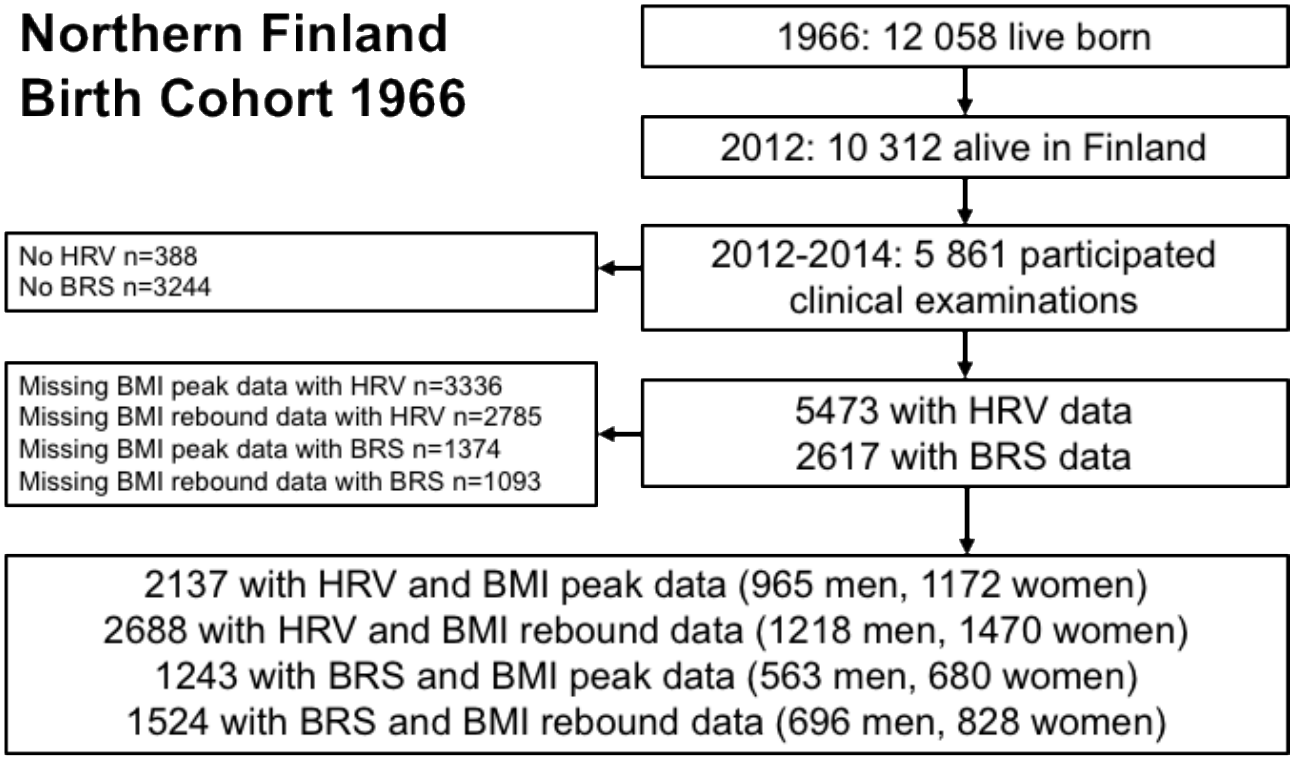
All significant associations between early growth and adult cardiovascular autonomic modulation measured in a standing position are shown. For associations between heart rate and adult cardiovascular autonomic modulation also insignificant correlations are shown. The values are statistical significances from linear regression models (p), explained variance of the model (R^2), and standardized beta (Beta) and unstandardized beta (B) with 95% confidence interval (95% CI) for the main independent variable. *BMI peak* peak of body mass index, *BMI rebound* rebound of body mass index. *HR* heart rate, *BRS* baroreflex sensitivity, LF_{SBP} low frequency power of systolic blood pressure variability, *LF* low frequency power of R-R interval variability, *HF* high frequency power of R-R interval variability, *LF/HF* ratio of low and high frequency power of R-R interval variability measured in a standing position. Because of skewed distributions variables BMI at BMI peak and at BMI rebound, BRS, LF_{SBP}, HF, LF/HF were transformed into natural logarithm (ln) before further analysis. Adjustments Block 1: gender, birthweight, gestational age, father's socioeconomic status, maternal age, height, weight, smoking after 2nd month of pregnancy and parity. *n=2137 for HRV at BMI peak; n=2688 for HRV and n=1524 for BRS/LF_{SBP} at BMI rebound. **n=1895 for HRV at BMI peak; n=2356 for HRV and n=1353 for BRS/LF_{SBP} at BMI rebound.

Table 4. Association between early growth and cardiovascular autonomic regulation in adulthood further adjusted for adult anthropometrics, lifestyle and cardiometabolic risk factors and morbidity

		Multivariate							
		Adjusted Block 2				Adjusted Block 3			
		R^2	Beta	B (95% CI)	p	R^2	Beta	B (95% CI)	p
Age at BMI peak	HR	0.130	-0.015	-3.4 [-14, 6.7]	0.507	0.132	-0.016	-3.7 [-14, 6.5]	0.479
Age at BMI rebound	HR	0.129	0.017	-0.2 [-0.4, 0.9]	0.463	0.131	0.019	0.3 [-0.4, 0.9]	0.428
	BRS	0.466	0.010	0.006 [-0.02, 0.04]	0.677	0.472	0.011	0.006 [-0.02, 0.04]	0.662
	LF_{SBP}	0.098	-0.111	-0.1 [-0.2, -0.04]	**0.001**	0.105	-0.113	-0.1 [-0.2, -0.05]	**<0.001**
BMI at BMI peak	HR	0.130	-0.021	-4.7 [-15, 5.9]	0.385	0.132	-0.024	-5.3 [-16, 5.3]	0.325
	HF	0.430	-0.073	-1.7 [-2.5, -0.8]	**<0.001**	0.435	-0.075	-1.7 [-2.6, -0.8]	**<0.001**
	LF/HF	0.169	0.062	0.9 [0.2, 1.6]	**0.010**	0.170	0.062	0.9 [0.2, 1.6]	**0.011**
BMI at BMI rebound	HR	0.132	-0.069	-13 [-21, -4.3]	**0.003**	0.135	-0.069	-13 [-21, -4.3]	**0.003**
	HF	0.421	-0.070	-1.3 [-2.0, -0.6]	**<0.001**	0.426	-0.069	-1.3 [-2.0, -0.6]	**<0.001**
	LF/HF	0.162	0.099	1.2 [0.7, 1.8]	**<0.001**	0.163	0.100	1.2 [0.7, 1.8]	**<0.001**

All significant associations between early growth and adult cardiovascular autonomic modulation measured in a standing position are shown. For associations between heart rate and adult cardiovascular autonomic modulation also insignificant correlations are shown. The values are statistical significances from linear regression models (p), explained variance of the model (R^2), and standardized beta (Beta) and unstandardized beta (B) with 95% confidence interval (95% CI) for the main independent variable. *BMI peak* peak of body mass index, *BMI rebound* rebound of body mass index. *HR* heart rate, *BRS* baroreflex sensitivity, LF_{SBP} low frequency power of systolic blood pressure variability, *LF* low frequency power of R-R interval variability, *HF* high frequency power of R-R interval variability, *LF/HF* ratio of low and high frequency power of R-R interval variability measured in a standing position. Because of skewed distributions variables BMI at BMI peak and at BMI rebound, BRS, LF_{SBP}, HF, LF/HF were transformed into natural logarithm (ln) before further analysis. Adjustments Block 2: Block 1(gender, birthweight, gestational age, father's socioeconomic status, maternal age, height, weight, smoking after 2nd month of pregnancy and parity) and adult anthropometrics and cardiometabolics: weight, height, heart rate, systolic and diastolic blood pressure, waist-hip ratio, glycated hemoglobin, total cholesterol, high density cholesterol, triglycerides; and lifestyle: current smoking, sitting time, sufficiency of sleep, physical activity and alcohol consumption. Block 3: Block 1, 2 and diabetes, respiratory diseases, heart diseases and antihypertensive medication. n=1698 for HRV at BMI peak; n=2116 for HRV and n=1234 for BRS/LF_{SBP} at BMI rebound.

Figure 1. Flowchart of study population, Northern Finland Birth Cohort 1966



HRV heart rate variability, *BRS* baroreflex sensitivity, *BMI* body mass index.