Maternal and infant prediction of the child BMI trajectories; studies across two generations of Northern Finland birth cohorts

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Abstract:

Background/objective: Children BMI is a longitudinal phenotype, developing through interplays between genetic and environmental factors. Whilst childhood obesity is escalating, we require a better understanding of its early origins and variation across generations to prevent it.

Subjects/Methods: We designed a cross-cohort study including 12,040 Finnish children from the Northern Finland Birth Cohorts 1966 and 1986 (NFBC1966 and NFBC1986) born before or at the start of the obesity epidemic. We used group-based trajectory modelling to identify BMI trajectories from 2 to 20 years. We subsequently tested their associations with early determinants (mother and child) and the possible difference between generations, adjusted for relevant biological and socioeconomic confounders.

Results: We identified four BMI trajectories, 'stable-low' (34.8%), 'normal' (44.0%), 'stable-high' (17.5%) and 'early-increase' (3.7%). The 'early-increase' trajectory represented the highest risk for obesity. We analysed a dose-response association of maternal pre-pregnancy BMI and smoking with BMI trajectories. The directions of effect were consistent across generations and the effect sizes tended to increase from earlier generation to later. Respectively for NFBC1966 and NFBC1986, the adjusted risk ratios of being in the early-increase group were 1.08 (1.06-1.10) and 1.12 (1.09-1.15) per unit of pre-pregnancy BMI and 1.44 (1.05-1.96) and 1.48 (1.17-1.87) in offspring of smoking mothers compared to non-smokers. We observed similar relations with infant factors including birthweight for gestational age and peak weight velocity. In contrast, the age at adiposity peak in infancy was associated with the BMI trajectories in NFBC1966 but did not replicate in NFBC1986.

Conclusion: Exposures to adverse maternal predictors were associated with a higher risk obesity trajectory and were consistent across generations. However, we found a discordant association for the timing of adiposity peak over a 20-year period. This suggest the role of residual environmental factors, such as nutrition, and warrants additional research to understand the underlying gene-environment interplay.

Key words: Epidemiology, life-course, BMI trajectories, adiposity peak, obesity

INTRODUCTION

In 2016, the World Health Organisation (WHO) reported a global prevalence of 41 million children under the age of five and 340 million between 5 and 19 years old with overweight or obesity [1]. Over the last four decades, obesity in the latter age category has increased tenfold [2]. Obesity, including during childhood, is currently being explained by interplays between a polygenetic build-up [3,4] and interrelated environmental risk factors acting upon body composition (epidemiologically proxied from BMI). Whilst the polygenetic structure has remained stable over the last four decades, including in the population studied in the current research [5], we are observing major changes in the set of environmental risk factors affecting the risk of obesity, with growing evidence to support the role of the environment in the early years of life. At the population level, BMI and changes in BMI during childhood are therefore highly heterogeneous and different paths to obesity may coexist throughout the life-course, some of them starting very early and influencing child's growth patterns [6-8].

So far, a vast majority of studies have considered childhood BMI from a cross-sectional manner without accounting for the longitudinal effect such as changes over time. Various analytical strategies have been proposed to study child BMI development. Conventional growth modelling methods assume that a single growth trajectory approximates the entire population and that covariates influence each individual in the same manner [9]. However, these models cannot account for the heterogeneity of BMI development over longer periods [10,11]. In contrast, in growth mixture models (GMM), the attention is put on relationships among individuals and the longitudinal characteristics of the measures. They assume that the population is made of latent groups, sharing the same pattern over time. GMM is a flexible modelling approach that can provide quantitative insights in the longitudinal aspect of BMI changes throughout the life course.

Previous longitudinal studies have described multiple BMI trajectories defined from latent growth trajectory analysis supporting more than one BMI trajectories in childhood [12-15]. As to whether early biological and/or psychosocial factors, classically associated with the child BMI [16], influenced each BMI trajectory in a comparative manner and whether the strength of such association is affected from one generation to another remains a debatable area of research. In the current study, we hypothesized that maternal and early childhood factors are determinants of the BMI trajectory a child embarks. We further hypothesized that the strength (*i.e.* effect size) of the associations linking a risk factor to the child BMI trajectory could be modified from one generation to another. Testing such hypotheses might help identify potential shared and generation specific risk factors and further advance the understanding of child BMI development.

To study the association of early risk factors with childhood BMI trajectories and its evolution over time, we performed a BMI trajectory analysis in two birth cohorts about one generation apart, using GBTM (Group

Based Trajectory Modelling) in SAS PROC TRAJ [10]. Importantly, we studied the Northern Finland Birth Cohort (NFBC)1966, pre-dating the obesity epidemic and the NFBC1986, born 20 years later, with prospective recruitment at the start of the obesity epidemic in Finland. While consistent evidence supports replicability of effects of early life factors on the child BMI and the risk of obesity [17], we may anticipate important generational effects depending on contextual differences in terms of feeding and nurturing practices and changes in the environmental exposures.

METHODS

Study population

The study was based on the two Northern Finland Birth Cohorts initiated 20 years apart from the same region (the two northernmost provinces of Finland: Oulu and Lapland) and founder population. NFBC1966 recruited pregnant women with a due date between the 1st of January and the 31st of December 1966 (12 055 mothers, 12 231 babies, 96.3% of all births from this period in the region). NFBC1986 included pregnant women with an expected delivery date between 1st of July 1985 and 30th of June 1986 (9362 mothers, 9479 babies, 99% of all births from this period in the region). A total of 12 058 and 9432 babies were born alive in the NFBC1966 and 1986 respectively.

Data collection of the child BMI measures

The mothers entered the study around the 16th gestational week for NBC1966 and the 10th to 12th gestational weeks for NFBC1986. Pregnant mothers were followed throughout pregnancy. Children's height and weight measures were collected by linking data from questionnaires, Health and Welfare records, clinical examination and national registers. Briefly, in Finland, a child welfare nurse checks up on infants every month during the first few months and then once a year, usually around their birthday. When they start school at seven years of age, the school nurse takes over the yearly check-ups. Children's measurements data were completed by self-reported measurements at 14 years for NFBC1966 and 7-8 years for NFBC1986. At 16 years old, NFBC1986 members were invited to a clinical examination with a trained nurse.

Exclusion criteria

We excluded preterm babies (<37 gestational weeks) and multiple births (N=2 199) (Supplementary Figure S1). We calculated BMI (kg/m^2) from height and weight. It is recommended and customary to use weight-for-length rather than BMI to measure growth during the first two years of life [18]. Therefore, we chose to model BMI in 16 age-windows, one per year from two to 16.9 years-old and, due to the scarcity of the data in late adolescence, the last group comprised ages from 17 to 20. Individuals with less than three repeated

BMI measurements, required for model stability, were excluded (N=7 159 altogether in NFBCs). Attrition in the data could be due either to non-attendance to check-ups or to non-retrieved or lost records. There were little differences between the children included from the model and those excluded: the mothers of the excluded children were more often single and less educated than the mothers of the included children (Supplementary table S1).

The study comprised 12 040 individuals (51.9% male), 6864 from NFBC1966 (53.7% male) and 5176 from NFBC1986 (49.4% male).

Maternal data

In the pregnancy questionnaire, mothers were asked to report their pre-pregnancy weight. The corresponding BMI was calculated using height measurement from the first prenatal visit. Maternal education was categorised as elementary, vocational or secondary, matriculation level, matriculation and beyond. Maternal smoking status at eight weeks of pregnancy was categorized as smokers and no smokers and their marital status as married or cohabitating, single, widowed or divorced.

Infant and child data

The first rise in the BMI curve called adiposity peak (AP), around nine months of age and the nadir of the curve called adiposity rebound (AR) around six years were obtained from random effects models fitted from 0 to 18 months and from 18 months to 13 years as described elsewhere [19]. The peak height velocity (PHV) and peak weight velocity (PWV) in infancy were derived from parametric growth curves [20,21]. These methods are developed in the supplementary materials. Gestational age at birth was calculated from the mother's last menstrual period in NFBC1966, and ultrasound in priority before the last menstrual period in NFBC1986. Birthweight was adjusted for gestational age, sex and cohort. BMI measures were sex and cohort standardized, for each age-windows as described previously [3,4]. Briefly, the z-scores were calculated internally, derived from NFBC1966 and NFBC1986, comprising respectively 96% and 99% of all children born in the north of Finland at the time.

Statistical analysis

Developmental Growth trajectories

We used GBTM from the PROC TRAJ procedure in SAS software, based on Nagin's approach to group-based modelling [22], to determine BMI growth trajectories. This approach consists in fitting a mixture of parametric models to the data, using the maximum likelihood method, handling missing data under the missing at random assumption. PROC TRAJ fits longitudinal data to discern rather than assume two or more distinctive trajectories or latent groups of individuals and estimate their prevalence in the population. Group-based trajectory modelling has been successfully applied to BMI in large cohort studies [13,14,23].

We used PROC TRAJ with BMI modelled as censored normal to identify subgroups which share a similar BMI growth from two to 20 years in both cohorts modelled together. We started by fitting a quartic polynomial to the models, increasing one by one the number of groups up to 7. The first step of the modelling consisted in choosing the optimal model. Bayesian Information Criterions (BIC) values are compared and the model with the smallest absolute value is chosen. The second step consisted in determining the shape of each trajectory by identifying the best polynomial order. Model adequacy was evaluated by calculating the average posterior probabilities of belonging to each group, they should be at least 0.7 with the closest to 1 reflecting the best discrimination between groups. We also calculated the Odds of Correct Classification, they should be over 5, and sought for a close correspondence between the estimated and actual percentages for each group and a reasonably tight confidence intervals of each trajectory [10]. A group should represent at least 1% of the population [9]. Parsimony and a priori knowledge of the topic combined with an evaluation of the graphical shape of the trajectories should be taken into account.

Descriptive and association analysis

All analyses were performed using SAS software 9.4 (SAS Institute Inc, Cary, North Carolina). Characteristics of participants were presented as frequencies for categorical variables and means and SD for continuous variables. We used non-parametric tests for comparisons between groups and χ^2 test for categorical variables. Multivariate models were applied to calculate risk ratios (RR) and their 95% confidence intervals in associations between maternal, infancy and childhood predictors and BMI trajectories, trajectory two being the reference. The confounders for the models were selected according to existing literature and previous analyses [19]. We tested three models for the maternal parameters: unadjusted, adjusted for maternal education and adjusted for parity, maternal education, maternal age and smoking (Fig. 2a)/pre-pregnancy BMI (Fig. 2b). Birthweight was not included in model 2a-b as it might be in the causal pathway between prenatal factors and the BMI trajectories. For birthweight, we tested three models: unadjusted, adjusted for pre-pregnancy BMI and adjusted for parity, pre-pregnancy BMI, maternal age, maternal education, smoking. For childhood predictors, we tested four models: unadjusted, adjusted for birthweight z-scores, adjusted for pre-pregnancy BMI and the last model adjusted for parity, pre-pregnancy BMI, maternal age, maternal education, smoking and birthweight z-scores.

RESULTS

Characteristics of the study population

On average, mothers enrolled in the NFBC1986 cohort were 3 cm taller, 2 months younger and had a 0.9 BMI smaller in comparison to NFBC1966 mothers (Supplementary Table S2). In addition, they also had

fewer children, were more often smoker and better educated. Furthermore, offspring born to the NFBC1986 mothers were 86 grams heavier, had a 3.7% increase in PHV and a 2.3% decrease in PWV compared to their NFBC1966 counterparts. They were also younger at the time of AP by 3.6 weeks and AR by 7.7 months suggesting distinct early growth patterns.

BMI trajectories

In an exploratory analysis, we modelled the trajectories separately by cohort (Supplementary Fig. S2 and table S3). To compare the cohort effect, we modelled the pooled cohorts, controlling for sex in the modelling process. The model converged well using the default starting values (codes in Supplementary material). During the modelling of the trajectories, we could not identify the best number of trajectories based on the Bayesian Index Criterion (BIC), i.e. BIC continued decreasing through all seven tested models. In this situation Nagin advised to use more subjective criteria [10]. Between the visual analysis of the trajectory graphs, the objective of the study and the knowledge of the other goodness of fit criteria (Supplementary Fig. S3 and table S4), we were able to identify four trajectories (polynomials 4, 3, 4, 3) as the optimal model for the studied population (Fig. 1). The trajectories were named according to their position in the graph (low to high) as 1: 'stable-low' (34.8% of total population, 34.4% of NFBC1966 and 35.4% of NFBC1986), 2: 'normal' (44.0%, 44.9% of NFBC1966 and 42.9% of NFBC1986), 3: 'stable-high' (17.5%, 13.3% of NFBC1966 and 17.7% of NFBC1986), 4: 'early-increase' (3.7%, 3.4% of NFBC1966 and 4.0% of NFBC1986). We observed that, compared to the other trajectories, the early-increase trajectory started already at a higher point, with a steeper curve. The cohort and sex prevalence per group are presented in Supplementary table S5.

In both cohorts, from trajectory one to four, we observed a stepwise increase in pre-pregnancy BMI and smoking during pregnancy (Table 1). The effect was consistent between cohorts both in terms of direction and magnitude. Parity and maternal marital status were associated to trajectories in a stepwise manner in NFBC1966 only. We also noted a decrease in the proportion of non-instrumental vaginal deliveries from group one to four in both cohorts.

The early life determinants followed the same stepwise pattern described earlier (Table 2). Birthweight was on average higher in NFBC1986 for each group trajectory and increased gradually by 245 and 270g between trajectory one to four in NFBC1966 and NFBC1986 respectively. We observed the same trend in PHV with higher PHV in NFBC1986 and an increase of 1.1 cm/year from group one to four in NFBC1966 only. PWV increased by 2.13 and 1.99 kg/year, for NFBC1966 and NFBC1986 respectively. At AP, we observed a stepwise increase in BMI between trajectory one and four, 1.2 and 0.8 kg/m^2 in NFBC1966 and NFBC1986 respectively. Changes in age at AP showed the same trend with only one week increase for NFBC1966. AR occurred earlier in NFBC1986 than in NFBC1966 and we observed a dramatic stepwise decrease of 2.6 and

2.9 years between the low stable and the early increase trajectory for NFBC1966 and NFBC1986 respectively. It is interesting to notice that in trajectory four, BMI at AP and AR are high, above 18 kg/m^2 in both cohorts.

Associations between maternal factors and BMI trajectories

We observed differences between trajectories, showing positive associations of pre-pregnancy BMI and maternal smoking with stable high and early increase trajectories (Fig. 2). In Figure 2a, in the fully adjusted model compared to the normal trajectory, pre-pregnancy BMI was associated to a lower risk of belonging to the stable-low trajectory in both NFBC1966 and NFBC1986. From high-stable to early-increase trajectories, the risk steadily increased up to a RR of 1.08 (95% CI 1.06-1.10) for NFBC1966 and 1.12 (95% CI 1.09-1.15) for NFBC1986. Maternal smoking was associated to a 34% (adjusted-RR (aRR): 1.34, 95% CI 1.14-1.59) and 42% (aRR: 1.42, 95% CI 1.22-1.64) higher risk of being in the high-stable trajectory for NFBC1966 and NFBC1986 respectively (Fig. 2b). The risk increased up to 44% (aRR: 1.44, 95% CI 1.05-1.96) and 48% (aRR: 1.48, 95% CI 1.17-1.87) in the early-increase trajectory for NFBC1966 and NFBC1986 respectively.

Associations between early life factors and BMI trajectories

The association between BW z-score and BMI trajectories (Fig. 3a) showed, in both cohorts, the stepwise pattern described in Fig. 2. A higher BW z-score was associated to a higher risk of belonging to the highest trajectory, with an aRR of 1.18 (95% CI 1.05-1.33) in NFBC1966 and 1.28 (95% CI: 1.12-1.46) in NFBC1986 (Fig. 3a). PWV (Fig. 3b) was associated with a decreased risk of belonging to the low-stable trajectory (aRR: 0.92, 95% CI 0.92-0.93 in NFBC1966 and aRR: 0.89, 95% CI: 0.88-0.90 in NFBC1986). High PWV was associated with an 8% and 7% higher risk of being in the early-increase trajectory, for NFBC1966 and NFBC1986 respectively. Regarding PHV, the pattern was divergent between the cohorts (Fig. 3c). PHV was positively associated with trajectory four (aRR:1.014, 95% CI: 1.002-1.026) in NFBC1966, but no association was found in NFBC1986. The stepwise pattern described earlier was maintained in the association between age at AP and the four trajectories in NFBC1966. The adjusted RR were ranging from 0.989 (95% CI: 0.986-0-991) in the lowest trajectory to 1.015 (95% CI: 1.008-1.022) in the early-increase trajectory (Fig. 3d). However, there was no association in NFBC1986.

DISCUSSION

To our knowledge, this is the first time that BMI latent growth trajectories were modelled in two birth cohorts set 20 years apart. The specific study design relied on using two separate prospective birth cohorts from the same founder population born 20 years apart. Whilst the causal genomic factors affecting BMI development are highly likely to be stable from one generation to another, we have observed important changes in the environmental risk factors associated to BMI development from the mid 60's and mid 80's in

Europe. We identified four BMI z-scores trajectories from 2 to 20 years in the combined NFBC studies. Our findings suggested that, in both cohorts, offspring of high pre-pregnancy BMI or smoking mothers had more chances of belonging to the more adverse childhood BMI trajectory. Conversely, children of low pre-pregnancy BMI or non-smoking mothers had better chances in following more favourable trajectories. Our results also suggested that the child's faster weight and height gains in infancy associated with adverse trajectories in both cohorts. Furthermore, we uncovered that age at AP was associated with every BMI trajectory in NFBC1966, but the association was lost in NFBC1986, suggesting that adiposity measured around 9 months of age might not be a stable determinant of later adiposity during childhood.

Our findings about the association of adverse maternal factors and BMI trajectories were in line with others [15,25]. The age of adiposity rebound decreased in a stepwise manner from group trajectories one to four, consistent with a higher risk of obesity. We observed the same pattern between the two cohorts which suggests that the effect associated to the variation of pre-pregnancy BMI and smoking remained over 20 years. They are important factors to consider in future generations and cohort studies. Interestingly, we observed that the amplitude of the effect differed. Although the average pre-pregnancy BMI was lower in NFBC1986 than in NFBC1966, its effect on the trajectories appeared stronger in the early increase trajectory. The association of birthweight with the trajectories was reflecting the strong link shown with pre-pregnancy BMI, unchanged over a 20-year period. A Danish study showed a stable association between birthweight and childhood overweight across almost 50 years [26], those results were supported by a study comparing both NFBC studies [27]. Infancy peak velocities occurred around the first month of life and were associated with BMI trajectories in both cohorts. Birthweight as an indicator of foetal growth and the peak velocities as indicators of early postnatal growth could be expected to be associated with the trajectories. However, there are still some important areas of debate pertained by mismatched findings between epidemiological observations and the causal inference made by Mendelian randomisation [28,29] or the measures of genetic overlap between these early adiposity phenotypes [30]. The relationship between these early growth phenotypes (BW, PWV and PHV) and the child BMI trajectory from 2 years onwards may still need clarifications as highlighted by our present observations. Possible inter-individuals and -generational differences in childcare and early nutrition may be important sources of moderation of the above relationships. These inter-individual and generational factors might explain the large confidence intervals and differential effect size or the lack of replication as these observed for PHV.

One of the main findings of this study was that the age at AP followed a different pattern of association between the two cohorts with a stepwise association observed between the age at AP and BMI trajectories in NFBC1966 only. The current literature in the field shows contrasting findings. Evidence from Swedish and Dutch birth cohorts supported a positive association between the BMI at adiposity peak and the later risk of obesity [31,32]. However, the generalisation of such association is currently being debated by two recent

GWAS supporting distinct molecular factors regulating infant and child BMI [30,33]. Furthermore, in western populations, it was reported that BMI at adiposity peak is getting lower in more contemporary cohorts. This may seem counterintuitive with the increasing prevalence of childhood obesity during the last decades but it aligned with a study based on European cohorts establishing that children from contemporary cohorts had a lower BMI at two years, a greater BMI growth velocity and earlier age at AR than children from older cohorts [34]. Altogether, these findings warrant a better understanding of the nature of the association linking the BMI of a child in infancy and during childhood to support evidence-based recommendations for parents and health care professionals. The present observation for an inconsistent effect between two generations of birth cohort from the same founder population may allow us to speculate about an indirect (confounded), association between the timing of the adiposity peak and the risk of being in an adverse BMI trajectory.

Although, we are lacking quantitative or qualitative indicators to explain this generational difference in the age at AP and PHV in infancy, it was meaningful, and it might highlight important moderating factors. The Finnish society underwent a massive change between 1966 and 1986, from agricultural to high-tech society. This transformation was accompanied with better pre- and post-natal care, but it also brought convenient energy-dense food affecting both adult and children nutrition. We might speculate that the differences in PHV and AP between cohorts, observed so soon after birth, might be due to early nutrition. Although, breastfeeding data in NFBC was incomplete, when included in the model (data not shown), it did not alter the results. The changes in PHV and AP between the cohorts might also indicate some residual confounding that we were unable to analyse. Historically, breastfeeding in Finland, like in other European countries, decreased from the second World War to its record low in the 1960s and 1970s until it started to increase again [35,36]. Following this trend, it is likely that NFBC1966 infants were less often breastfed than the NFBC1986. Exclusive breastfeeding for five months has been shown to modulate the timing of AP and AR and BMI velocities in Avon Longitudinal Study of Parents And Children study [37]. Exclusive breastfeeding for six months reduced the associations of birthweight and early weight gain on fat mass in three year old children in a Danish cohort [38].

Strengths and limitations

One of the great strengths of this study was the richness of data, we were able to closely follow any variation in childhood BMI through 16 age-windows. Another highly valuable strength resided in the use of two birth cohorts, born before and at the start of the obesity epidemic, originating from the same geographic area of Finland and characterised by a genetically homogeneous population. Nevertheless, limitations should be considered. One limitation of this study would reside in the harmonization of variables between cohorts, such as paternal data, type of infant feeding or maternal weight gain during pregnancy which could not be reciprocated in both cohorts. Due to model requirements, many individuals

from both cohorts were excluded. In addition, we should acknowledge that BMI measures the ratio between weight and height. Each of these two measures are susceptible to describe their own trajectories during childhood which might affect the BMI trajectories described in this report. One of the future steps to undertake, to grow our understanding of the biological and environmental mechanisms being at play would be the development of analytical strategy modelling child height and weight trajectory simultaneously.

There are few statistical methods available to model children BMI. Modelling approaches using mixed-effect models, latent curve analysis, hierarchical modelling or growth-curve modelling are offering measures of individual growth profiles against the mean and may provide a health professional with derived phenotypes such as the age at adiposity rebound. In contrast, the GBTM used in this study, is a person-centred data-driven process and assumes that the population is composed of latent groups, they do not assume the one-size-fits-all approach. These subgroups are homogeneous within their trajectory but distinct from other trajectories, each following the same behaviour over time. This latent approach captures more information, especially the longitudinal relationships at the child level but, is specific to the modelled population. Unlike growth models, GBTM are limited in the obtention of distinct phenotypes that could be directly translated as clinical measures. Nonetheless, they seem to present a new set of tools to study individual variation in response to clinical interventions and randomized trials [39].

Conclusion

Our results add new insights to the study of childhood obesity by using two generations of Finnish birth cohorts, initiated before and at the start of the obesity epidemic. In both cohorts, detrimental maternal factors were associated to adverse BMI trajectories, independent of time. However, we were observing a larger amplitude of the effects in the younger cohort suggesting moderation by a more obesogenic environment. Our findings support evidence for very early mechanisms in the first months of life linked to childhood obesity and affected over the course of a generation. Finally, the cross-cohort design exemplified by this research might be a powerful way to detect indirect associations such as the one linking early variation at the time of the adiposity peak and later BMI trajectories. Further research, and methodological development are warranted to identify the intergenerational changes that might help revealing gene-environment interplays.

Data Availability Statement: Data is available from the Northern Finland Birth Cohort (NFBC) for researchers who meet the criteria for accessing confidential data. Please, contact NFBC project center (NFBCprojectcenter@oulu.fi) and visit the cohort website (www.oulu.fi/nfbc) for more information.

Ethical approval: All procedures performed were in accordance with the 1964 Helsinki declaration. The Ethics Committee of the Northern Ostrobothnia Hospital District has approved the NFBC1966 and NFBC1986 studies.

Informed consent: Mothers gave their informed consent in the beginning of the NFBC1966 and 1986 data collections. Written informed consent has been obtained from the cohort participants in the 31- and 46-year data collections.

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Conflict of Interest

The authors, RN, JM, MM, MRJ and SS declare that they have no competing interest.

References

1. WHO. Obesity and overweight, Fact sheet

. 2018; Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight, 2018.

2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet 2017 December 16;390(10113):2627-2642.

3. Bradfield JP, Vogelezang S, Felix JF, Chesi A, Helgeland O, Horikoshi M, et al. A Trans-ancestral Meta-Analysis of Genome-Wide Association Studies Reveals Loci Associated with Childhood Obesity. Hum Mol Genet 2019 July 05.

4. Felix JF, Bradfield JP, Monnereau C, van der Valk, R J, Stergiakouli E, Chesi A, et al. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. Hum Mol Genet 2016 January 15;25(2):389-403.

5. Bond TA, Karhunen V, Wielscher M, Auvinen J, Mannikko M, Keinanen-Kiukaanniemi S, et al. Exploring the role of genetic confounding in the association between maternal and offspring body mass index: evidence from three birth cohorts. Int J Epidemiol 2019 May 10.

6. Araujo J, Severo M, Barros H, Mishra GD, Guimaraes JT, Ramos E. Developmental trajectories of adiposity from birth until early adulthood and association with cardiometabolic risk factors. Int J Obes (Lond) 2015 Oct;39(10):1443-1449.

7. Rolland-Cachera MF, Deheeger M, Bellisle F, Sempe M, Guilloud-Bataille M, Patois E. Adiposity rebound in children: a simple indicator for predicting obesity. Am J Clin Nutr 1984 Jan;39(1):129-135.

8. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ 2005 October 22;331(7522):929.

9. Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. Social and Personality Psychology Compass 2008;2(1):302-317.

10. Daniel Nagin. Group-based modeling of development. US: Harvard University Press; 2005.

11. Randall E. Schumacker, George A. Marcoulides. Latent variable mixture modeling. In: New Developments And Techniques In Structural Equation Modeling. 2 ed. ed. GB: Routledge Ltd; 2001.

12. Ziyab AH, Karmaus W, Kurukulaaratchy RJ, Zhang H, Arshad SH. Developmental trajectories of Body Mass Index from infancy to 18 years of age: prenatal determinants and health consequences. J Epidemiol Community Health 2014 Oct;68(10):934-941.

13. Stuart B, Panico L. Early-childhood BMI trajectories: evidence from a prospective, nationally representative British cohort study. Nutr Diabetes 2016 Mar 7;6:e198.

14. Peneau S, Giudici KV, Gusto G, Goxe D, Lantieri O, Hercberg S, et al. Growth Trajectories of Body Mass Index during Childhood: Associated Factors and Health Outcome at Adulthood. J Pediatr 2017 Mar 7.

15. Tu AW, Masse LC, Lear SA, Gotay CC, Richardson CG. Body mass index trajectories from ages 1 to 20: Results from two nationally representative canadian longitudinal cohorts. Obesity (Silver Spring) 2015 August 01;23(8):1703-1711.

16. Voerman E, Santos S, Patro Golab B, Amiano P, Ballester F, Barros H, et al. Maternal body mass index, gestational weight gain, and the risk of overweight and obesity across childhood: An individual participant data meta-analysis. PLoS Med 2019 February 11;16(2):e1002744.

17. Gaillard R, Wright J, Jaddoe VWV. Lifestyle intervention strategies in early life to improve pregnancy outcomes and long-term health of offspring: a narrative review. J Dev Orig Health Dis 2018 November 09:1-8.

18. de Onis M, Onyango A, Borghi E, Siyam A, Blossner M, Lutter C, et al. Worldwide implementation of the WHO Child Growth Standards. Public Health Nutr 2012 September 01;15(9):1603-1610.

19. Sovio U, Kaakinen M, Tzoulaki I, Das S, Ruokonen A, Pouta A, et al. How do changes in body mass index in infancy and childhood associate with cardiometabolic profile in adulthood? Findings from the Northern Finland Birth Cohort 1966 Study. Int J Obes (Lond) 2014 Jan;38(1):53-59.

20. Tzoulaki I, Sovio U, Pillas D, Hartikainen AL, Pouta A, Laitinen J, et al. Relation of immediate postnatal growth with obesity and related metabolic risk factors in adulthood: the northern Finland birth cohort 1966 study. Am J Epidemiol 2010 May 1;171(9):989-998.

21. Berkey CS, Reed RB. A model for describing normal and abnormal growth in early childhood. Hum Biol 1987 Dec;59(6):973-987.

22. Nagin D, Tremblay RE. Trajectories of boys' physical aggression, opposition, and hyperactivity on the path to physically violent and nonviolent juvenile delinquency. Child Dev 1999 October 01;70(5):1181-1196.

23. Ostbye T, Malhotra R, Landerman LR. Body mass trajectories through adulthood: results from the National Longitudinal Survey of Youth 1979 Cohort (1981-2006). Int J Epidemiol 2011 Feb;40(1):240-250.

24. Hejazi S, Dahinten VS, Marshall SK, Ratner PA. Developmental pathways leading to obesity in childhood. Health Rep 2009 Sep;20(3):63-69.

25. Montazeri P, Vrijheid M, Martinez D, Basterrechea M, Fernandez-Somoano A, Guxens M, et al. Maternal Metabolic Health Parameters During Pregnancy in Relation to Early Childhood BMI Trajectories. Obesity (Silver Spring) 2018 March 01;26(3):588-596.

26. Rugholm S, Baker JL, Olsen LW, Schack-Nielsen L, Bua J, Sorensen TI. Stability of the association between birth weight and childhood overweight during the development of the obesity epidemic. Obes Res 2005 December 01;13(12):2187-2194.

27. Graversen L, Sorensen TI, Petersen L, Sovio U, Kaakinen M, Sandbaek A, et al. Stability of the associations between early life risk indicators and adolescent overweight over the evolving obesity epidemic. PLoS One 2014 April 18;9(4):e95314.

28. Tyrrell J, Richmond RC, Palmer TM, Feenstra B, Rangarajan J, Metrustry S, et al. Genetic Evidence for Causal Relationships Between Maternal Obesity-Related Traits and Birth Weight. JAMA 2016 March 15;315(11):1129-1140.

443 29. Richmond RC, Timpson NJ, Felix JF, Palmer T, Gaillard R, McMahon G, et al. Using Genetic Variation to
444 Explore the Causal Effect of Maternal Pregnancy Adiposity on Future Offspring Adiposity: A Mendelian
445 Randomisation Study. PLoS Med 2017 January 24;14(1):e1002221.

446 30. Couto Alves A, De Silva, N. Maneka G, Karhunen V, Sovio U, Das S, Taal HR, et al. GWAS on longitudinal
447 growth traits reveals different genetic factors influencing infant, child, and adult BMI. Science Advances
448 2019 Sep;5(9):eaaw3095.

449 31. Silverwood RJ, De Stavola BL, Cole TJ, Leon DA. BMI peak in infancy as a predictor for later BMI in the
450 Uppsala Family Study. Int J Obes (Lond) 2009 August 01;33(8):929-937.

451 32. Kruithof CJ, Gishti O, Hofman A, Gaillard R, Jaddoe VW. Infant weight growth velocity patterns and
452 general and abdominal adiposity in school-age children. The Generation R Study. Eur J Clin Nutr 2016
453 October 01;70(10):1144-1150.

454 33. Helgeland O, Vaudel M, Juliusson PB, Lingaas Holmen O, Juodakis J, Bacelis J, et al. Genome-wide
455 association study reveals dynamic role of genetic variation in infant and early childhood growth. Nat
456 Commun 2019 October 01;10(1):4448-0.

457 34. Johnson W, Soloway LE, Erickson D, Choh AC, Lee M, Chumlea WC, et al. A changing pattern of
458 childhood BMI growth during the 20th century: 70 y of data from the Fels Longitudinal Study. Am J Clin
459 Nutr 2012 May;95(5):1136-1143.

460 35. Hultin H, Opas R, Sarna S. Breast feeding of babies in Finland in the seventies. Katilolehti 1974
461 Oct;79(10):365.

462 36. Uusitalo, L., Nyberg, H., Pelkonen, M., Sarlio - Lähteenkorva, S., Hakulinen - Viitanen, T. & Virtanen, S.
463 Imeväisikäisten ruoki
464 nta Suomessa vuonna 2012. THL 2012.

465 37. Wu YY, Lye S, Briollais L. The role of early life growth development, the FTO gene and exclusive
466 breastfeeding on child BMI trajectories. Int J Epidemiol 2017 October 01;46(5):1512-1522.

467 38. Ejlerskov KT, Christensen LB, Ritz C, Jensen SM, Molgaard C, Michaelsen KF. The impact of early growth
468 patterns and infant feeding on body composition at 3 years of age. Br J Nutr 2015 July 01;114(2):316-327.

469 39. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol
470 2010;6:109-138.

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Table 1. Characteristic of maternal variables according to the group trajectories. BMI: Body Mass Index. Statistical tests performed between trajectories by cohorts and between cohorts by trajectories.

Table 2. Characteristics of infancy and childhood variables according to the group trajectories. PHV: Peak Height Velocity, PWV: Peak Weight Velocity, AP: Adiposity Peak, AR: Adiposity Rebound. Statistical tests performed between trajectories by cohorts and between cohorts by trajectories.

Fig. 1: BMI z-scores trajectories of NFBC studies from 2 to 20 years. Solid lines represent the trajectories and dashed lines the 95% confidence intervals. Group trajectories, 1: Stable-low (34.8%, N=4195), 2: Normal (44.0%, N=5299), 3: Stable-high (17.5%, N=2106) ND 4: Early-increase (3.7%, N=440).

Fig. 2: Forest-plot of unadjusted and adjusted Risk Ratios (RR) between maternal parameters and BMI z-scores trajectory classes. Fig. 2a: pre-pregnancy BMI (kg/m^2), Fig. 2b: maternal smoking during pregnancy. RR with 95% confidence intervals. ●: unadjusted; ▲: adjusted for maternal education; ■: adjusted for pre-pregnancy BMI (Fig. 2b); ▼: adjusted for parity, maternal age, maternal education, maternal smoking (Fig. 2a) / maternal age, parity, maternal education and pre-pregnancy BMI (Fig. 2b). G1: Stable Low group trajectory; G2: Normal group trajectory (reference); G3; Stable high group trajectory; G4; Early Increase group trajectory.

Fig. 3: Forest-plot of unadjusted and adjusted Risk Ratios (RR) between early growth parameters and BMI z-scores trajectory classes. Fig. 3a: birthweight z-scores, Fig. 3b: peak weight velocity in infancy (kg/year), Fig. 3c: peak height velocity in infancy (cm/year), Fig. 3d: age at adiposity peak (years). RR with 95% confidence intervals. ●: unadjusted; ▲: adjusted for birthweight z-score (Fig. 3b, 3c and 3d); ■: adjusted for pre-pregnancy BMI; ▼: adjusted for parity, pre-pregnancy BMI, maternal age, maternal education, maternal smoking (Fig. 3a) / birthweight z-score, parity, pre-pregnancy BMI, maternal age, maternal education, maternal smoking (Fig. 3b, 3c and 3d). G1: Stable Low group trajectory; G2: Normal group trajectory (reference); G3; Stable high group trajectory; G4; Early Increase group trajectory.

Table 1

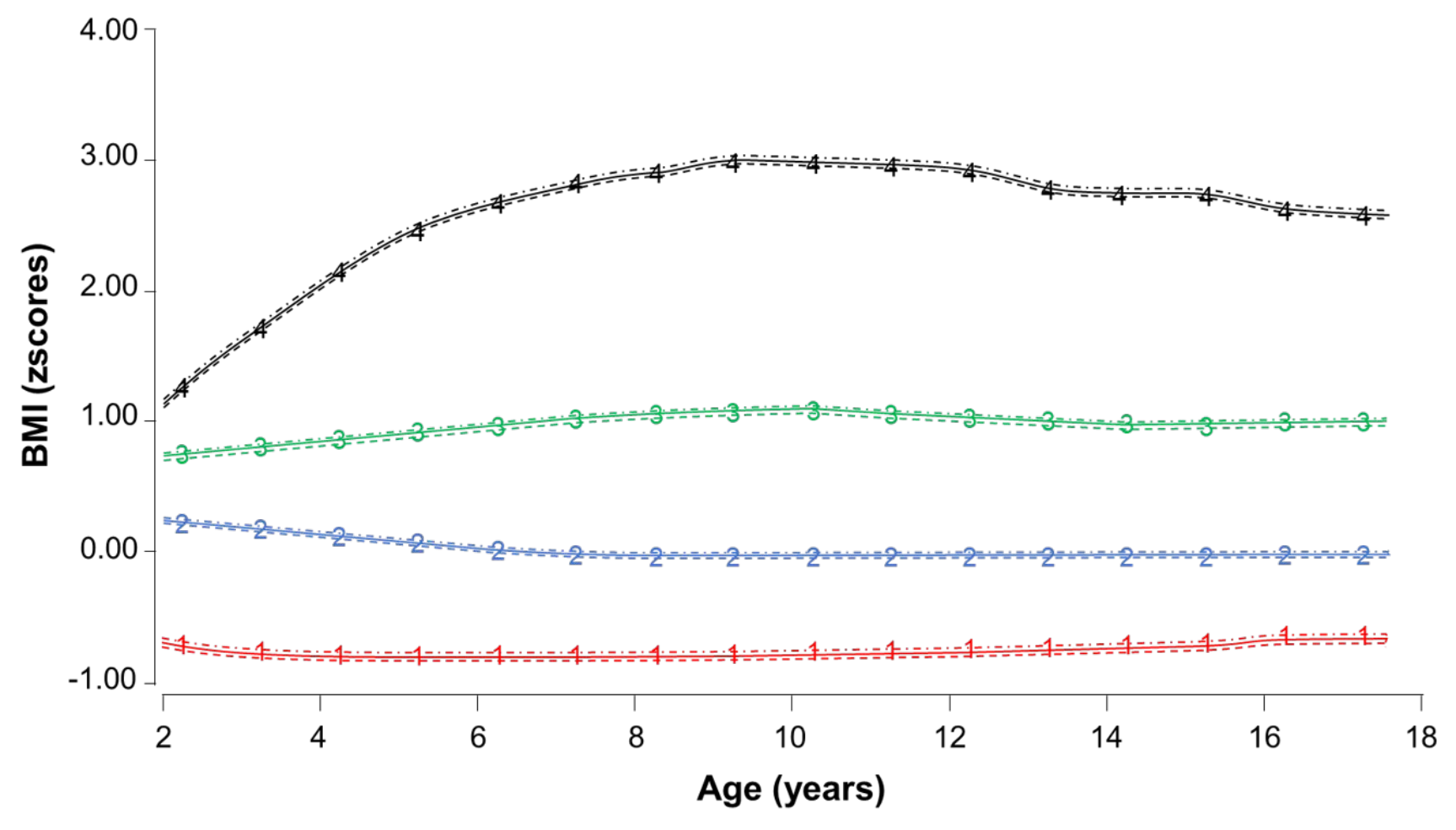
	Trajectories								
	1: Stable-low		2: Normal		3: Stable-high		4: Early-increase		
	N=4195		N=5299		N=2106		N=440		
	N	mean±SD	N	mean±SD	N	mean±SD	N	mean±SD	***p* value**
Maternal pre-pregnancy weight (kg)									
NFBC1966	2250	57.8 ± 8.2	2933	59.9 ± 8.9	1136	61.4 ± 9.8	223	63.6 ± 10.1	**<0.0001**
NFBC1986	1801	57.2 ± 8.5	2187	59.5 ± 9.1	895	62.4 ± 10.3	201	66.6 ± 14.0	**<0.0001**
***p* value**		**0.0187**		**0.0440**		0.775		0.325	
Maternal pre-pregnancy BMI (kg/m^2)									
NFBC1966	2171	22.5 ± 3.0	2814	23.3 ± 3.2	1091	24.2 ± 3.5	215	25.1 ± 3.8	**<0.0001**
NFBC1986	1795	21.5 ± 3.0	2175	22.3 ± 3.2	891	23.3 ± 3.6	201	25.1 ± 5.1	**<0.0001**
***p* value**		**<0.0001**		**<0.0001**		**<0.0001**		0.295	
Parity									
NFBC1966	2358	3.0 ± 2.2	3078	3.0 ± 2.2	1188	2.8 ± 2.1	234	2.6 ± 2.1	**0.0006**
NFBC1986	1828	1.6 ± 2.0	2212	1.5 ± 1.9	914	1.3 ± 1.7	206	1.4 ± 1.7	0.1
***p* value**		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
	N	%	N	%	N	%	N	%	***p* value**
Maternal Smoking									
NFBC1966	2321		3008		1167		230		**0.0038**
Smoker	309	13.3	388	12.9	194	16.6	41	17.8	
No smoker	2012	86.7	2620	87.1	973	83.4	189	82.2	
NFBC1986	1827		2208		912		205		**<0.0001**
Smoker	302	16.5	400	18.1	236	25.9	62	30.2	
No smoker	1525	83.5	1808	81.9	676	74.1	143	69.8	
***p* value**		**0.0037**		**<0.0001**		**<0.0001**		**0.0024**	
Maternal marital status									
NFBC1966	2358		3078		1185		234		**0.0419**
Married/Cohabiting	2291	97.1	2995	97.3	1139	96.1	222	94.9	
Single	56	2.4	71	2.3	35	3.0	8	3.4	
Widowed /Divorced	11	0.5	12	0.4	11	0.9	4	1.7	
NFBC1986	1831		2213		917		206		0.13
Married/Cohabiting	1750	95.6	2124	96.0	881	96.1	194	94.2	
Single	56	3.0	73	3.3	32	3.5	8	3.9	
Widowed /Divorced	25	1.4	16	0.7	4	0.4	4	1.9	

***p* value**		**0.0028**		**0.0225**		0.33		0.95	
Operative delivery									
NFBC1966	839		1087		441		97		**0.0009**
Non-instrumental vaginal deliveries	642	76.5	822	75.6	323	73.2	59	60.8	
Caesarian Section	90	10.7	131	12.1	54	12.3	26	26.8	
Others (vacuum extraction, forceps)	107	12.8	134	12.3	64	14.5	12	12.4	
NFBC1986	1834		2218		918		206		**<0.0001**
Non-instrumental vaginal deliveries	1545	84.2	1828	82.4	714	77.8	158	76.7	
Caesarian Section	177	9.7	278	12.5	133	14.5	31	15.1	
Others (vacuum extraction, forceps)	112	6.1	112	5.1	71	7.7	17	8.3	
***p* value**		**<0.0001**		**<0.0001**		**0.0004**		**0.0155**	

Table 2

	Trajectories								
	1 Stable-low		2 Normal		3 Stable-high		4 Early-increase		
	N=4195		N=5299		N=2106		N=440		
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	***p* value**
Sex (%male)									
NFBC1966	2361	51.8	3081	56.2	1188	50.6	234	54.7	**0.0010**
NFBC1986	1834	48.7	2218	51.4	918	45.7	206	50.5	**0.0286**
p value		**0.0458**		**0.0005**		**0.0276**		0.38	
	N	**mean±SD**	**N**	**mean±SD**	**N**	**mean±SD**	**N**	**mean±SD**	***p* value**
Birthweight (grams)									
NFBC1966	2361	3450 ± 467	3081	3568 ± 481	1188	3642 ± 520	234	3695 ± 465	**<0.0001**
NFBC1986	1834	3519 ± 440	2218	3662 ± 460	918	3739 ± 479	206	3789 ± 517	**<0.0001**
p value		**0.0001**		**<0.0001**		**<0.0001**		**0.0369**	
Birthweight z-score									
NFBC1966	2361	-0.14 ± 0.94	3081	0.08 ± 0.95	1188	0.25 ± 1.03	234	0.35 ± 0.94	**<0.0001**
NFBC1986	1834	-0.19 ± 0.93	2218	0.10 ± 0.96	918	0.27 ± 1.00	206	0.36 ± 1.11	**<0.0001**
p value		0.063		0.49		0.46		0.93	
PHV in Infancy (cm/year)									
NFBC1966	2081	50.31 ± 3.72	2726	50.67 ± 3.71	1069	50.92 ± 3.90	209	51.41 ± 4.06	**<0.0001**
NFBC1986	1785	52.42 ± 6.72	2150	52.49 ± 6.74	893	52.61 ± 6.83	199	52.28 ± 6.54	0.95
p value		**<0.0001**		**<0.0001**		**<0.0001**		0.2705	
PWV in infancy (kg/year)									
NFBC1966	2145	12.03 ± 1.43	2806	13.07 ± 1.56	1096	13.65 ± 1.89	213	14.16 ± 2.07	**<0.0001**
NFBC1986	1798	11.65 ± 2.39	2167	13.01 ± 2.85	898	13.42 ± 3.05	200	13.64 ± 3.40	**<0.0001**
p value		**<0.0001**		**<0.0001**		**<0.0001**		**0.0029**	
Age AP (years)									
NFBC1966	1817	0.75 ± 0.03	2427	0.76 ± 0.03	959	0.77 ± 0.04	188	0.77 ± 0.04	**<0.0001**
NFBC1986	1753	0.70 ± 0.02	2114	0.69 ± 0.02	882	0.69 ± 0.02	195	0.69 ± 0.02	**<0.0001**
p value		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
BMI AP (kg/m^2)									
NFBC1966	1817	17.5 ± 0.7	2427	18.1 ± 0.7	959	18.4 ± 0.8	188	18.7 ± 0.9	**<0.0001**
NFBC1986	1753	17.2 ± 0.6	2114	17.7 ± 0.6	882	17.9 ± 0.7	195	18.0 ± 0.8	**<0.0001**

p value		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
Age AR (years)									
NFBC1966	2323	6.20 ± 0.59	3033	5.67 ± 0.60	1168	4.79 ± 0.71	231	3.59 ± 0.71	**<0.0001**
NFBC1986	1822	5.72 ± 0.72	2197	5.02 ± 0.73	911	3.92 ± 0.71	200	2.83 ± 0.42	**<0.0001**
p value		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
BMI AR (kg/m^2)									
NFBC1966	2323	14.4 ± 0.5	3033	15.5 ± 0.4	1168	16.6 ± 0.6	231	18.1 ± 1.1	**<0.0001**
NFBC1986	1822	14.6 ± 0.5	2197	15.8 ± 0.4	911	16.95 ± 0.6	200	18.3 ± 1.1	**<0.0001**
p value		**<0.0001**		**<0.0001**		**<0.0001**		**0.0503**	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BMI (zscores)
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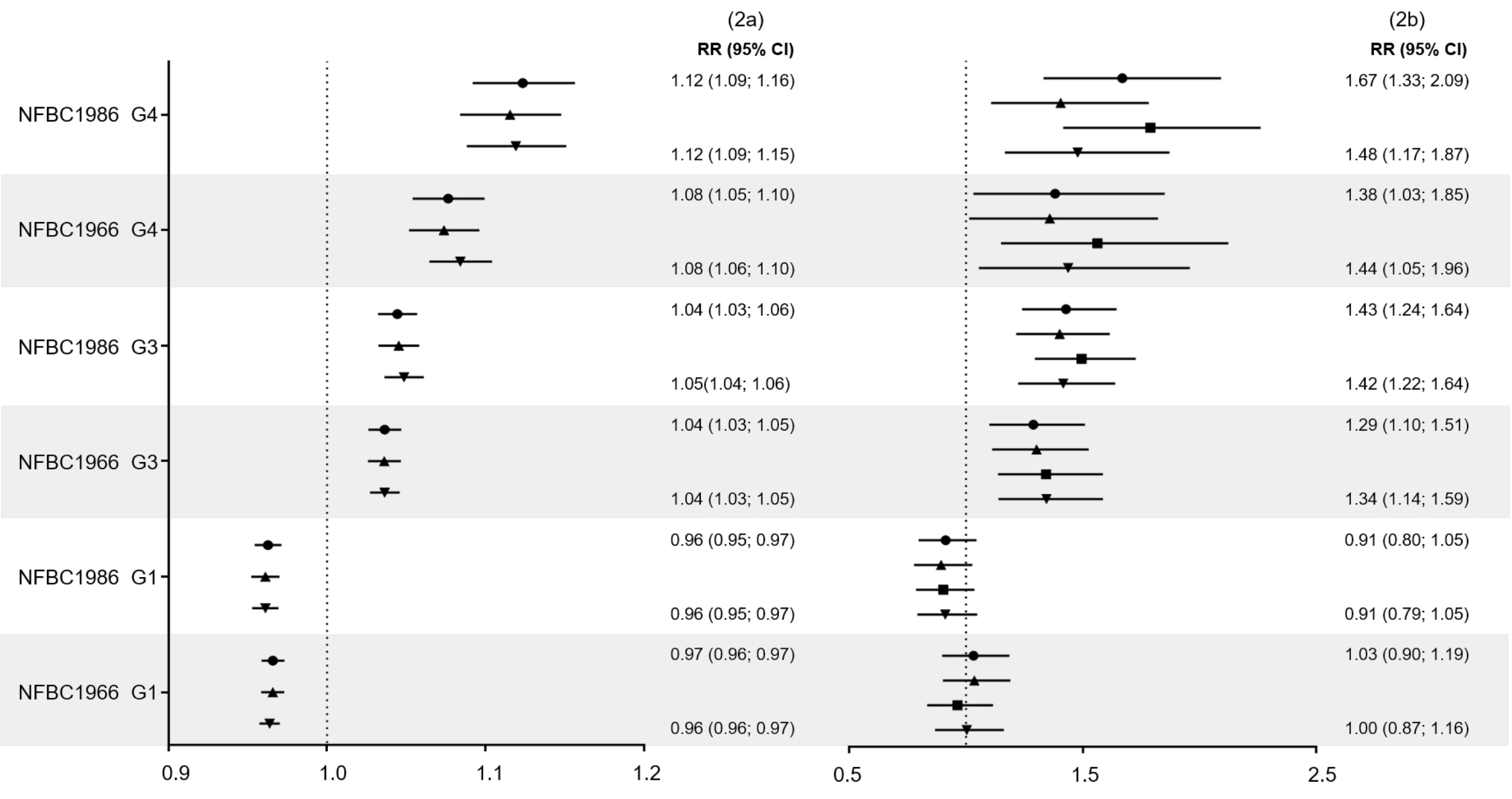
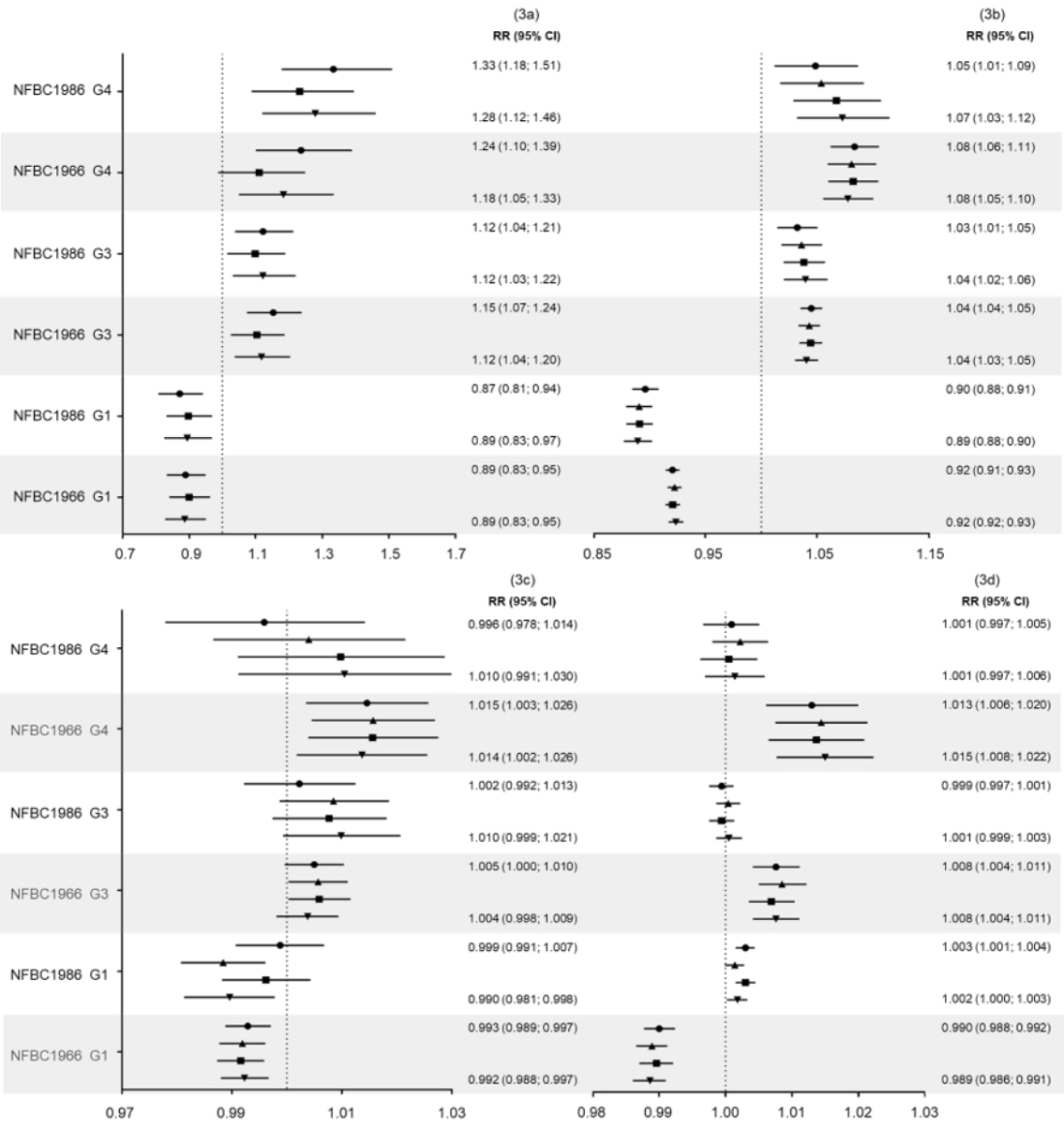
Age (years)


(2a)
RR (95% CI)
(2b)
RR (95% CI)
NFBC1986 G4
1.12 (1.09; 1.16)
1.12 (1.09; 1.15)
1.67 (1.33; 2.09)
1.48 (1.17; 1.87)
NFBC1966 G4
1.08 (1.05; 1.10)
1.08 (1.06; 1.10)
1.38 (1.03; 1.85)
1.44 (1.05; 1.96)
NFBC1986 G3
1.04 (1.03; 1.06)
1.05(1.04; 1.06)
1.43 (1.24; 1.64)
1.42 (1.22; 1.64)
NFBC1966 G3
1.04 (1.03; 1.05)
1.04 (1.03; 1.05)
1.29 (1.10; 1.51)
1.34 (1.14; 1.59)
NFBC1986 G1
0.96 (0.95; 0.97)
0.96 (0.95; 0.97)
0.91 (0.80; 1.05)
0.91 (0.79; 1.05)
NFBC1966 G1
0.97 (0.96; 0.97)
0.96 (0.96; 0.97)
1.03 (0.90; 1.19)
1.00 (0.87; 1.16)
0.9
1.0
1.1
1.2
0.5
1.5
2.5


(3a)
RR (95% CI)
NFBC1986 G4
1.33 (1.18; 1.51)
1.28 (1.12; 1.46)
NFBC1966 G4
1.24 (1.10; 1.39)
1.18 (1.05; 1.33)
NFBC1986 G3
1.12 (1.04; 1.21)
1.12 (1.03; 1.22)
NFBC1966 G3
1.15 (1.07; 1.24)
1.12 (1.04; 1.20)
NFBC1986 G1
0.87 (0.81; 0.94)
0.89 (0.83; 0.97)
NFBC1966 G1
0.89 (0.83; 0.95)
0.89 (0.83; 0.95)
0.7
0.9
1.1
1.3
1.5
1.7
(3b)
RR (95% CI)
1.05 (1.01; 1.09)
1.07 (1.03; 1.12)
1.08 (1.06; 1.11)
1.08 (1.05; 1.10)
1.03 (1.01; 1.05)
1.04 (1.02; 1.06)
1.04 (1.04; 1.05)
1.04 (1.03; 1.05)
0.90 (0.88; 0.91)
0.89 (0.88; 0.90)
0.92 (0.91; 0.93)
0.92 (0.92; 0.93)
0.85
0.95
1.05
1.15
(3c)
RR (95% CI)
NFBC1986 G4
0.996 (0.978; 1.014)
1.010 (0.991; 1.030)
NFBC1966 G4
1.015 (1.003; 1.026)
1.014 (1.002; 1.026)
NFBC1986 G3
1.002 (0.992; 1.013)
1.010 (0.999; 1.021)
NFBC1966 G3
1.005 (1.000; 1.010)
1.004 (0.998; 1.009)
NFBC1986 G1
0.999 (0.991; 1.007)
0.990 (0.981; 0.998)
NFBC1966 G1
0.993 (0.989; 0.997)
0.992 (0.988; 0.997)
0.97
0.99
1.01
1.03
(3d)
RR (95% CI)
1.001 (0.997; 1.005)
1.001 (0.997; 1.006)
1.013 (1.006; 1.020)
1.015 (1.008; 1.022)
0.999 (0.997; 1.001)
1.001 (0.999; 1.003)
1.008 (1.004; 1.011)
1.008 (1.004; 1.011)
1.003 (1.001; 1.004)
1.002 (1.000; 1.003)
0.990 (0.988; 0.992)
0.989 (0.986; 0.991)
0.98
0.99
1.00
1.01
1.02
1.03