Aus der Kinderklinik und Kinderpoliklinik im Dr. von Haunerschen Kinderspital

Klinik der Universität München

Direktor: Prof. Dr. Dr. Christoph Klein

Long-term weight development in offspring exposed to obesity in pregnancy

Dissertation

zum Erwerb des Doktorgrades der Humanbiologie

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

vorgelegt von

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aus

New Delhi, Indien

im Jahr

2023

Mit Genehmigung der Medizinischen Fakultät

der Universität München

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Affidavit

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Munich, 24.11.2022
(Place, date)

Delphina Gomes
(Doctoral candidate)

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List of abbreviations

AGA	Average-for-gestational age
AUROC	Area under the receiver operating characteristic
BMI	Body mass index
CI	Confidence interval
DEGS	German Health Interview and Examination Survey for Adults
DOHAD	Developmental origins of health and disease
GDM	Gestational diabetes mellitus
GLUT	Glucose transporter
GWG	Gestational weight gain
HbA_{1c}	Glycated hemoglobin
HR	Hazards ratio
IADPSG	International Association of Diabetes in Pregnancy Study Groups
IPD	Individual participant data
IQTiG	Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (Institute for Quality Assurance and Transparency in Healthcare)
KiGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (German Health Interview and Examination Survey for Children and Adolescents)
LAT	Large neutral amino acid transporter
LGA	Large-for-gestational age
MGRS	Multicentre Growth Reference Study
NCD	Non-communicable disease
OR	Odds ratio
PEACHES	Programming of Enhanced Adiposity Risk in CHildhood - Early Screening
PEPO	PErinatal Prevention of Obesity
RR	Relative risk
SD	Standard deviation
SGA	Small-for-gestational age
SNAT	Sodium-coupled neutral amino acid transporter
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
WAZ	Weight-for-age
WHO	World Health Organization

List of publications

Two research articles are presented:

1. **Late-pregnancy dysglycemia in obese pregnancies after negative testing for gestational diabetes and risk of future childhood overweight: An interim analysis from a longitudinal mother–child cohort study. Delphina Gomes**, Rüdiger von Kries, Maria Delius, Ulrich Mansmann, Martha Nast, Martina Stubert, Lena Langhammer, Nikolaus A. Haas, Heinrich Netz, Viola Obermeier, Stefan Kuhle, Lesca M. Holdt, Daniel Teupser, Uwe Hasbargen, Adelbert A. Roscher, Regina Ensenauer. PMCID: PMC6205663. DOI: https://doi.org/10.1371/journal.pmed.1002681.

2. **Predicting the earliest deviation in weight gain in the course towards manifest overweight in offspring exposed to obesity in pregnancy: a longitudinal cohort study. Delphina Gomes**, Lien Le, Sarah Perschbacher, Nikolaus A Haas, Heinrich Netz, Uwe Hasbargen, Maria Delius, Kristin Lange, Uta Nennstiel-Ratzel, Adelbert A Roscher, Ulrich Mansmann, Regina Ensenauer. PMID: 35418073. https://doi.org/10.1186/s12916-022-02318-z.

I. Description of author's contribution to the publications

1. Contribution to publication 1

The doctoral candidate performed extensive background research to identify current strategies to manage gestational diabetes in women with obesity. As the main research area, she focused on existing strategies to manage third-trimester hyperglycemia after exclusion of gestational diabetes at the end of the second trimester in women with obesity. She defined several maternal groups based on their glycemia status during pregnancy. Subsequently, she analysed the data in R and prepared tables and figures. She wrote the first draft of the paper and identified potential journals for publication. As a part of publication 1, she gave several talks and presentations in national and international conferences. She was constantly supported by her supervisor Prof. Dr. med. Regina Ensenauer. She collaborated with co-authors in order to respond to specific reviewer comments and implemented all suggestions for changes to the manuscript.

2. Contribution to publication 2

The doctoral candidate independently did background research to identify the various outcomes and influencing factors of childhood overweight and obesity. She next searched for existing prediction tools and methods to identify young children who will become overweight or obese during school years. This initial step guided her to recognize research gaps in terms of both methods and outcomes. Subsequently, a novel outcome was defined and used in this work. Furthermore, the methological uniqueness was the development of a sequential prediction approach starting at the beginning of life. She performed data management and data analysis in R together with Lien Le. The candidate independently prepared tables and figures. She wrote the first draft of the paper under the supervision of Prof. Dr. med. Regina Ensenauer. During the review process she responded to and implemented all suggestions for changes to the manuscript. Prof. Dr. med. Regina Ensenauer and Prof. Dr. Ulrich Mansmann provided feedback and guidance throughout the entire process.

II. Introduction

1. Childhood obesity

1.1 Background and prevalence

Childhood overweight or obesity has increased drastically (1, 2). Childhood obesity affects nearly 108 million children (<20 years) worldwide (3). Between 1975 and 2016, there was a global rise in age adjusted mean body mass index (BMI) of 0.32 kg/m² per decade for girls and 0.40 kg/m² per decade for boys, leading to an increased prevalence of obesity in childhood (5 to 19 years) in both sexes (girls: 5.6%; boys: 7.8%) (4). At present, up to 46% of children between 5 and 17 years of age are overweight or obese in the USA (defined as BMI ≥85th percentile) during the coronavirus disease pandemic in year 2020 (5). In Germany, results from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS Wave 2, 2014 to 2017) indicated that 15.4% of children between ages 3 and 17 years are overweight or obese (defined as BMI >90th percentile) (2). Although there are no representative data relating to BMI changes in German children after coronavirus disease pandemic, a regional study has shown an increase in BMI gain in children aged 1 to 18 years (6).

There is now clear evidence showing that many of these children with obesity are likely to become obese adults (7). A simulation study on 41,567 American children aged 2 to 19 years found that at 2 years of age, children with severe obesity (defined as BMI ≥120% of the 95th percentile by the Center for Disease Control and Prevention (8)) have a 4-in-5 chance of being obese by the age of 35 years (7). This study demonstrated that obesity in the initial years of life was related to a persistent persistent risk of adult obesity and highlights the importance of promoting a healthy weight development throughout childhood (7). Evidence from Germany, which is based on more than 51,000 children aged 0 to 14 years, has also shown that rapid versus stable BMI gains between 2 and 6 years was associated with a 40% higher risk of overweight or obesity in adolescence (9). Even prior to age 2 years, accelerated BMI growth in the first years has been found to quadruple the risk of childhood obesity, as recently shown in a meta-analysis of 17 studies (10). Therefore, higher deviations in BMI growth in the early postnatal life could have long-term influence on the development of adiposity later.

1.2 Physiological weight development in early life

Growth is a multifaceted physiological process which includes modifications in body proportions and composition encompassing both (i) an increase in cell number and size and (ii) programmed cell death (11). Growth patterns in early life including fetal life and infancy (birth to age 2 years) is linked to later health in both children and young adults (12, 13).

Birth weight can be used to classify fetal growth according to gestational age into small-for-gestational-age birth weight (SGA, <10th percentile), average-for-gestational-age birth weight (AGA, ≥10th to ≤90th percentile), and large-for-gestational-age birth weight (LGA, >90th percentile) (14). Data from the German perinatal survey of 2007–2011 on more than 3.1 million children from all 16 states of Germany resulted in updated percentile values to classify birth weight adjusted for gestational age and sex in German children (15).

The first 2 years after birth is a phase of rapid BMI growth (16) and is critical for the development of obesity later (10). Typically, rapid BMI growth in infants is a change of more than 0.67 standard deviation (SD) in weight-for-age z-scores (WAZ) from birth to age 2 years (17) and may be clinically interpreted as upward centile crossing through at least one of the centile bands (18, 19). Infants with a high rapid weight gain (WAZ >0.67 SD) during this period have an almost 4-fold higher odds of later overweight (10).

After the physiological increases in BMI growth (presumed to represent an increase in cell size) during infancy (birth to age 2 years), there is a decline in growth (presumed to represent a decrease in cell size) until the BMI of the child reaches the lowest point in the BMI growth curve, known as “nadir” (20). The age corresponding to the nadir can be considered as a critical point for developing adiposity (20). Adiposity rebound, which is a typical physiological process, is the second rise in BMI curve (21). This second rise after the “nadir” is postulated to correspond to an increase in the number of fat cells (21). Data from the KiGGS study, which comprised 17,641 German children and adolescents between 0 and 17 years of age, have shown that adiposity rebound occurs at approximately age 6 years among German boys and girls (22). In children at risk of overweight, such as those of mothers with pre-conception obesity, adiposity rebound was observed at an earlier age of around 5 years (23).

1.3 Classification of weight status in young children

Since BMI varies by age, BMI values for children are compared with age- and sex-specific reference values. A child’s BMI is frequently transformed into a z-score or categorized by percentiles based on the underlying population distribution of BMI-for-age (24).

A z-score is the distance from the median in units of SD. It can be used to indicate where a child’s anthropometric measurement such as BMI falls in the reference population relative to other children of the same age and sex. For an individual, a z-score is calculated as the difference between the specific child’s value and the reference population’s median value for the same age and sex, divided by the SD of the reference population (25). A positive z-score value indicates that the value is greater than the median, whereas a negative z-score indicates that the value is less than the median (26). In a normal distribution, z-scores and percentiles are equivalent indicating that a percentile can be converted to a z-score and vice versa (24). However, the use of cut-points based on rounded percentiles as an alternative to exact z-scores may misclassify children’s BMI growth status (27). Therefore, it is recommended to use z-scores to evaluate a child’s growth status (27).

The assessment of overweight in children relies on plotting BMI on a standard BMI growth chart and using a cut-off point for increased age and sex-specific BMI (26). The World Health Organization (WHO) recommends that particularly all infants and young children aged ≤5 years should have both weight and length/height measured, in order to evaluate their growth status (28). Therefore, the WHO conducted a population-based study (The Multicentre Growth Reference Study [MGRS] Study) from July 1997 to December 2003 of 8,440 healthy, fully breastfed children from USA, Oman, Norway, Brazil, Ghana, and India (29). The study objective was to develop a ‘novel approach’ of classifying the nutritional status of children from birth to age 5 years based on the degrees of deviation from normality (30). Figure 1 shows the WHO cut-offs of BMI-for-age z-score cut-offs on a normally distributed population of children to define the growth status based on age- and sex-standardized data provided by the WHO (31, 32).

While the WHO Child Growth Standards are widely used as international standards to classify the nutritional status of children, other criteria - both international (33) and country-specific (22, 34, 35) - are also available (36). In Germany, the KiGGS study provides BMI percentiles for weight assessment in children (22) and defines overweight as BMI >90th percentile and obesity as BMI >97th percentile for children aged between 3 and 18 years (2).

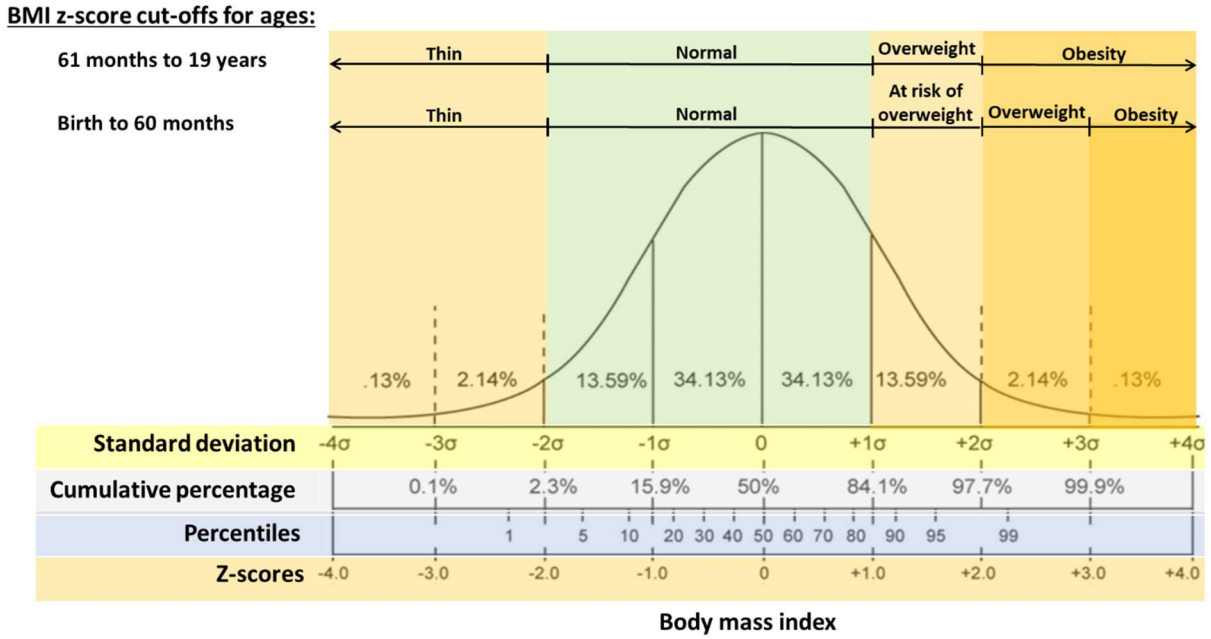

Figure 1: The WHO cut-offs for BMI z-scores in children between birth and 19 years.
BMI, body mass index. WHO, World Health Organization. Population-based age- and sex-specific BMI tables to calculate BMI z-scores for an individual child are provided on the WHO website and can be assessed using the link in the references (31, 32). Source: Figure adapted and modified from Ward 1999 (37), and shown BMI z-scores categories are based on cut-offs provided by the WHO (38).

Plotting of consecutive BMI values on a BMI growth chart provides a visual display vital for clinical use and depicts a track of BMI growth up to a particular age (33). When expressed as centiles on BMI growth charts, average centile indicates average velocity, while upper or lower centile crossing indicates faster or slower than average velocity (33). Given the increasing prevalence of childhood overweight, it is becoming more important to characterize trajectories of BMI development for surveillance, etiology, and clinical practice (39). The evaluation of BMI growth trajectories in young children could provide a more precise identification of those at risk and could help to predict future health outcomes (39).

1.4 Long-term consequences of high weight status in infants and young children

A high birth weight and childhood overweight can have several implications on health later (40, 41). An overview is provided in Figure 2.

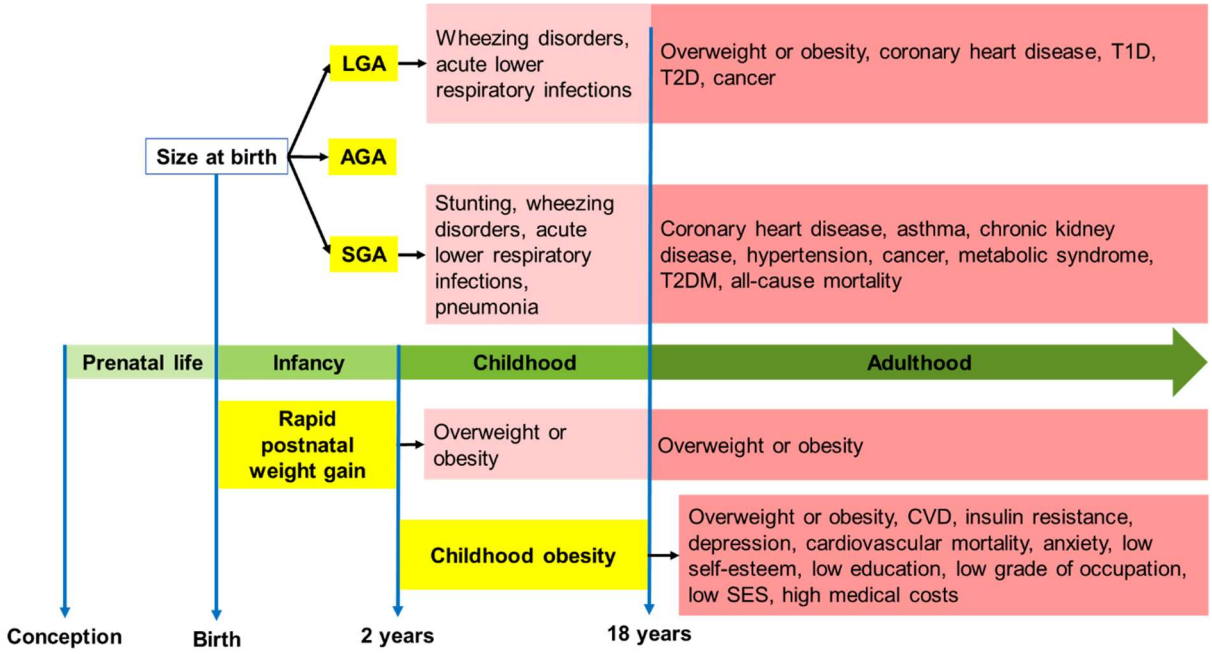

Figure 2: Consequences of prenatal and postnatal excessive BMI growth on later health.
Yellow boxes indicate exposures and red boxes indicate health outcomes in childhood or adulthood. AGA, average-for-gestational-age; CVD, cardiovascular disease; LGA, large-for-gestational-age; SES, socioeconomic status; SGA, small-for-gestational-age; T1D, type 1 diabetes; T2D, type 2 diabetes. Source: The figure presented here is self-made and based on data from meta-analyses from Umer et al, 2017 (42), Sharma et al, 2019 (43), Bellou et al, 2018 (44), Belbasis et al, 2016 (45), and Llewellyn et al, 2015 (46).

1.4.1 Consequences of LGA birth weight

A recent "umbrella" review of 39 systematic reviews and meta-analyses exploring the association of birth weight with 78 diverse outcomes showed that a high birth weight was suggestive of wheezing disorders and acute lower respiratory tract infections in childhood (45). The authors of this review also indicated that a high weight at birth was related to overweight or obesity and impaired glucose metabolism (type 1 diabetes [T1D], type 2 diabetes [T2D]) in adulthood (45). Evidence from other meta-analyses also shows that a high birth weight is strongly related to coronary heart disease and cancer in adulthood (43-45).

1.4.2 Consequences of rapid infancy weight gain

A recent systematic review which included 17 studies highlighted that rapid weight gain during infancy (birth until age 2 years) was related to a 3.7-fold increased odds of overweight at later ages (2 to 47 years) (10). Supporting the results of this systematic review, evidence from the Taiwan Birth Cohort study of 24,200 children demonstrated that regardless of the timing of weight gain between birth and two years of age, rapid weight gain increased the odds of overweight and obesity at ages 3, 5, and 8 years (47). Particularly, during the first 6 months after birth, rapid weight gain may predispose the young child to become obese and experience unfavorable cardiometabolic health in adolescence and early adulthood (18, 48, 49). Evidence from studies evaluating longitudinal BMI development across the first 18 years of life showed that the

"change in path" of BMI development occurred within the first 4 years and that the highest BMI growth trajectory was associated with adverse cardiometabolic outcomes at age 18 years (50). However, results of studies that closely investigated BMI development between birth and age 4 years found that distinct deviations from the physiological BMI growth trajectories become evident by 6 months of age (51-53). One study showed that rapid growth from birth to age 3 months was related to BMI increments until age 4 years (52). However, how patterns of BMI growth in early life periods contribute to preschool overweight in offspring of mothers with pre-conception obesity has not been evaluated. Such data could provide a starting point for predictive analyses of longitudinal BMI growth trajectories toward overweight manifestation, particularly in high-risk offspring exposed to gestational obesity.

1.4.3 Consequences of childhood overweight

Obesity in childhood has been shown to be linked with depression, anxiety, and low self-esteem (54). Data from a recent study of more than 12,000 American adults demonstrated that those who were overweight or obese as children were less likely of having a more advanced degree than those who had healthy weight in childhood (55). Academic achievements are very important because of the relation between educational accomplishment and employment prospects (55), subsequent socioeconomic status (56), and later health (56). A recent study on nearly 40,000 American youths aged 11 to 17 years showed that being obese and severely obese was related to 92% and 151% higher medical costs relative to being normal weight, respectively (57). This study also highlighted that medical expenses increase substantially with BMI and that obesity leads to high costs in all key categories of medical care such as costs of doctor visits, hospital care, and medication (57).

In addition, children with overweight or obesity are more susceptible to later diseases in adulthood including obesity (58), insulin resistance, and cardiovascular disease (46, 58). Evidence from a large population study of 2.3 million Israeli youth (16 and 19 years of age) showed that obesity during adolescent life contributed substantially to an increased risk of cardiovascular mortality in adulthood (hazards ratio [HR] 4.89, 95% confidence interval [CI] 3.91–6.12) (59). A dose-response relationship was also evident between increasing BMI percentile during adolescence and all-cause mortality in adulthood (59).

1.5 Risk factors of childhood overweight

The causes of obesity in children are multifactorial (60). A comprehensive review which included 282 prospective studies identified several prenatal and postnatal factors associated with childhood obesity (61). For instance, maternal obesity (62, 63), excessive gestational weight gain (GWG) (62, 64), GDM (65), early-life feeding (66, 67), and early BMI growth trajectories (7) may have implications on weight status throughout childhood. Figure 3 presents relevant factors associated with childhood overweight that are potentially modifiable. Only factors that are both in the focus of current scientific research related to childhood overweight and can be potentially modified were selected. Evidence of associations in Figure 3 is broad, and several studies have used either continuous or categorical outcomes. In the footnote of Figure 3, examples of associations are listed.

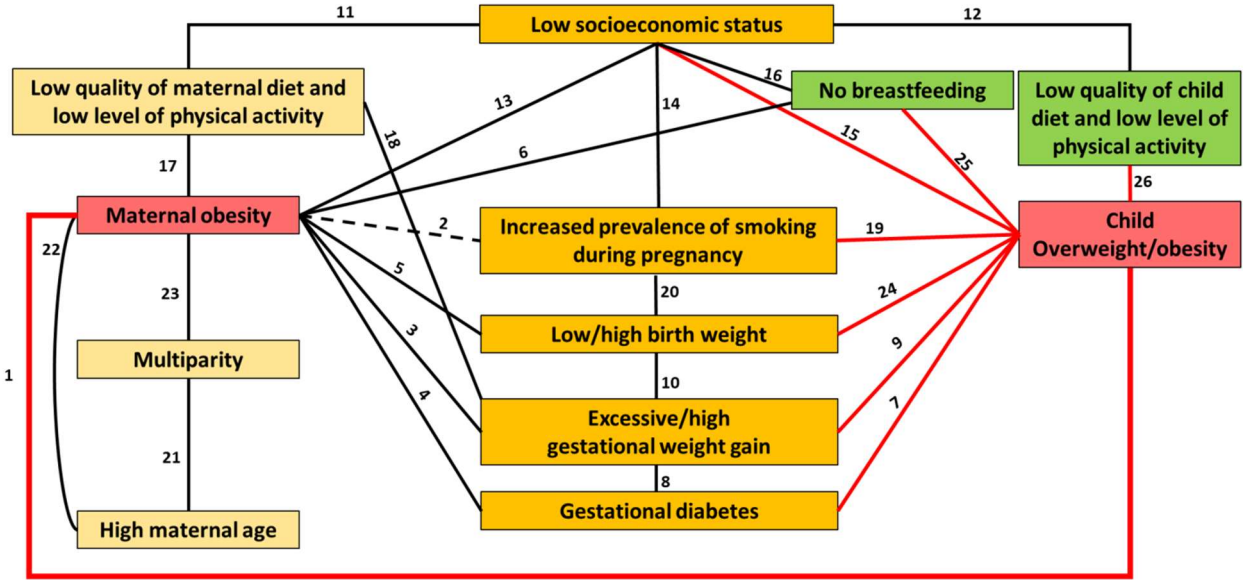

Figure 3: Relevant prenatal and postnatal potentially modifiable factors associated with childhood overweight and obesity.

Selected relevant factors that are in the focus of current scientific research on childhood overweight and can be potentially modified are shown. Orange boxes indicate pre- or perinatal factors, green boxes indicate postnatal factors, red boxes indicate main exposure or outcome, red lines indicate direct associations between maternal obesity and the relevant factor, black lines indicate indirect associations between maternal obesity and the relevant factor, and dashed line indicates increased prevalence/proportion of factor among mothers with obesity. Source: Figure adapted and modified from Josey et al. 2019 (68). The original figure from Josey et al published in BMC Public Health is licensed under the Creative Commons Attribution 4.0 International License (69) which "permits unrestricted use, distribution, modification, and reproduction in any medium". Associations from literature:

1. Maternal preconception obesity → childhood overweight and obesity (62, 63)
2. Maternal preconception obesity → increased prevalence of smoking during pregnancy (70)
3. Maternal preconception obesity → excessive gestational weight gain (71)
4. Maternal preconception obesity → gestational diabetes (72)
5. Maternal preconception obesity → high offspring birth weight (73)
6. Maternal preconception obesity → lack of breastfeeding (74)
7. Gestational diabetes → childhood overweight and obesity (65)
8. Gestational diabetes → lower gestational weight gain (75, 76)
9. Excessive gestational weight gain → childhood overweight and obesity (62)
10. High gestational weight gain → high offspring birth weight (77)
11. Low socioeconomic status → low quality of maternal diet (78) and low level of physical activity (79)
12. Low socioeconomic status: low maternal/parental education → low quality of diet (80) and low level of physical activity (81)
13. Low socioeconomic status → maternal preconception obesity (70)
14. Low socioeconomic status → smoking during pregnancy (82)
15. Low socioeconomic status → childhood obesity (83)
16. Low socioeconomic status → lack of breastfeeding (84)
17. Low quality of maternal diet → maternal preconception obesity (85)
18. Low quality of maternal diet: high fat content in maternal diet → excessive gestational weight gain (86)
19. Smoking during pregnancy → childhood overweight (87)
20. Smoking during pregnancy → low offspring birth weight (88)
21. High maternal age → multiparity (89)
22. High maternal age → maternal preconception obesity (90)
23. Multiparity → maternal preconception obesity (91)
24. Low/high birth weight → childhood obesity (92)
25. Lack of breastfeeding → childhood overweight and obesity (66, 93)
26. Low quality of child diet and low level of physical activity → childhood obesity (94)

2. Developmental programming

Over the past 3 decades, emerging emphasis has been given to the effect of alterations in the in-utero environment on the origins of non-communicable diseases (NCD) in adulthood (95-97). Initially termed as the “fetal origins hypothesis” or “fetal programming”, this concept was renamed to “developmental origins of health and disease” (DOHAD) to better reflect periods of both prenatal and postnatal life (97). Following the original work of Barker and Osmond more than 30 years ago who showed that an exposure to poor living standards in early childhood was related to heart diseases during adulthood (98), a number of studies were conducted to link early conditioning mechanisms and NCD in adulthood (95, 97). Intrauterine insults during the crucial periods of BMI growth and development could have long-lasting effects on the function and structure of organs and increase the susceptibility to cardiometabolic diseases in the future (99). Furthermore, there is evidence that the adverse impact of such functional and structural changes can be transmitted to future generations suggesting that there is a risk of intergenerational transmission of disease (100).

Based on the identified correlations between low birth weight and T2D development (101, 102), it was speculated that intrauterine exposure to low-quality maternal nutrition could lead to permanent glucometabolic alterations, which increases the risk of cardiometabolic disease later (101). More recent studies have also shown that fetuses who receive excessive nutrient supply during pregnancy are likely to have high birth weight (103), thereby contributing to a long-term risk of NCD (104). During the postnatal life, offspring experiencing an affluent postnatal environment may have a high BMI growth velocity leading to an increased susceptibility to obesity and metabolic syndrome (105). Figure 4 shows the effect of gestational programming on the origins and longitudinal development of cardiometabolic disease in offspring.

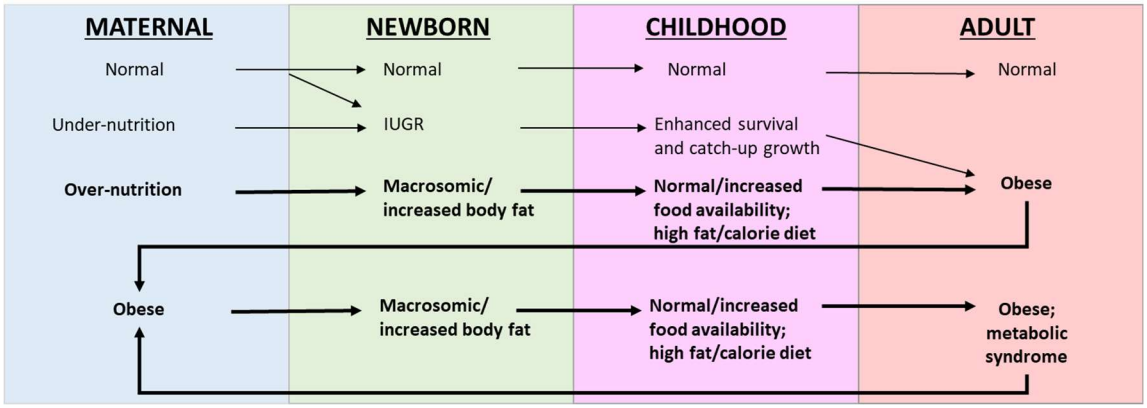

Figure 4: Gestational programming and longitudinal development of cardiometabolic diseases in offspring.
Source: Figure adapted and modified from Desai et al. 2015 (105). Permission for the reproduction of this figure was given by Springer Nature (Macmillan Publishers Limited).

3. Maternal pre-conception obesity

3.1 Background and prevalence

The definition of obesity refers to “abnormal or excessive fat accumulation that may impair health” (106). Obesity is measured using BMI, which is currently the best available anthropometric estimate of fatness (107) and is expressed as weight-for-height by applying the following formula:

$$BMI\ (kg/m^2) = \frac{weight\ (kg)}{height\ (m)^2}$$

The WHO provides BMI categories to measure weight status in adults (108) (Table 1):

Table 1: Body mass index categories for adults

BMI (kg/m^2)	Weight Status
<18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight
30.0-34.9	Obesity Class I
35.0-39.9	Obesity Class II
≥40.0	Obesity Class III

Obesity in pregnancy is of substantial importance to public health since it affects a vast majority of women today. In 2014, the NCD Risk Factor Collaboration which included an international population of 9.3 million women (≥18 years) reported an incidence of 14.9% for obesity in this population (109). In the US alone, overweight and obesity affects 2-in-3 women of fertile age (110) and nearly 40% of these are obese (110). The Euro-Peristat Network which examines health data of pregnant women and their newborn offspring from 29 European countries demonstrated that the prevalence of maternal obesity is up to 25% in Europe (111). Results from the nationally representative German Health Interview and Examination Survey for Adults (DEGS) indicate that 38.1% of German women of reproductive age are overweight or obese (obese: 15.4%) (112). Further, the “Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (IQTiG)” which conducts analysis of hospital data in Germany reported that in 2020, 39.4% of pregnant women were overweight or obese (obesity: 15.5%) (113).

Recent demographic forecasts suggest that given the current trends in obesity, nearly 1 in 2 women aged 18 to 39 years will be obese by the year 2030 in the United States (114). Similar projections have been made for European women predicting that almost 1 in 5 women in Germany will be obese by the year 2025 (115).

3.2 Effect of maternal obesity on childhood overweight and obesity

A large number of studies have concluded that maternal pre-conception obesity is a strong trigger factor of childhood obesity (63, 73, 116). An individual participant data (IPD) meta-analysis of 162,129 mothers and their children demonstrated that pre-gestational obesity increased the risk of overweight or obesity throughout childhood by 2.43 to 4.47-folds (62). This IPD found that the risks of childhood overweight or

obesity increased progressively with higher grades of maternal obesity (class I, class II, and class III obesity) (62). The authors suggested that maternal obesity may have a long-lasting impact on offspring fat development (62). Evidence from cohort studies has also found a 4.25-fold (95% CI 2.86 to 6.32) to 5.02-fold (95% CI 2.97 to 8.45) increase in risk of obesity in the 4-year-old (117) and of overweight or obesity in the 7-year-old (118) offspring of mothers with pre-conception obesity, respectively.

Another study evaluated the effect of the distinct and combined exposure of maternal and paternal pre-gravid BMI on weight status of 4,871 6-year-old offspring (119). This study found that offspring exposed to mothers with versus without pre-conception obesity were at a high risk of overweight (OR 3.84; 95% CI 3.01 to 4.90) and of having an unfavorable cardiometabolic risk score comprising an increased fat mass, high blood pressure, and high concentrations of triglycerides and insulin (OR 3.00; 95% CI 2.09 to 4.34). By identifying a stronger influence of maternal pre-conception obesity than paternal obesity, this study further reinforces the intrauterine origins of unfavorable health later in life (119), similar to other studies (120). Particularly, data from an extensive meta-analysis which included 20 randomised controlled trials and cohort studies showed that offspring of mothers with pre-pregnancy overweight and obesity had a 31% increased body fat percentage between birth and age 11 years in comparison to offspring born of mothers who were normal weight at conception (121).

3.3 Additional prenatal and postnatal risk factors in pregnancies with obesity

Additional factors emerging from prenatal and postnatal periods in women with preconception obesity could further predispose offspring to overweight and might be important targets for developing preventive interventions. Figure 5 depicts examples of such associated factors likely to influence long-term BMI growth in offspring of mothers with obesity. Potentially modifiable factors that are considered as scientifically particularly relevant and have been studied in our research group were extracted from Figure 3 mostly and are shown in Figure 5.

3.3.1 Gestational diabetes

Diabetes that was not evident prior to pregnancy and is diagnosed only in the second or third trimester of gestation is called gestational diabetes (GDM) (122). A recent meta-analysis which included more than 5 million pregnant women enrolled in 51 studies showed that, irrespective of screening classification thresholds, the global prevalence of GDM was 4.4% (95% CI 4.3–4.4%) (123). With regards to the widely used diagnostic thresholds of International Association of Diabetes in Pregnancy Study Groups (IADPSG) criteria, the pooled GDM prevalence was 10.6% (95% CI 10.5–10.6%) (123).

Obesity in pregnancy is an independent factor influencing the development of GDM since mothers with obesity are up to 6-fold more likely to develop GDM (72). According to the diagnostic definitions used, GDM affects up to 30% of women with obesity (124, 125). While pregnancy is a phase of a 40% to 50% reduction in insulin sensitivity (126), women with obesity have decreased insulin sensitivity even before pregnancy (127) and are therefore more prone to develop GDM.

3.3.2 Gestational weight gain

Despite the availability of GWG recommendations specific to mother's BMI at conception (128), mothers with obesity have an up to 6-fold higher risk of gaining excessive GWG during pregnancy (129). A large cohort study of German mothers also found that nearly 2-in-3 women with obesity in pregnancy had excessive GWG (130). Numerous studies have reported that excessive GWG is linked to unfavourable birth outcomes such as preterm birth, LGA birth weight, SGA birth weight, macrosomia, and caesarean section delivery (131, 132). A large IPD meta-analysis of mothers with obesity at conception (n = 162,129 mother-child pairs) evaluated the additional influence of excessive GWG on offspring overweight and obesity during childhood (62). The study showed that the odds of overweight and obesity in offspring were up to 6-fold higher when offspring experience a combined exposure to maternal pre-conception obesity and excessive GWG. Interestingly, 21.7% to 41.7% of the prevalence of overweight and obesity in children was attributed to maternal overweight and obesity, whereas 11.4% to 19.2% could be ascribed to excessive GWG alone. In support of this large meta-analysis, previous studies have also recommended that interventions to reduce the adverse effects of maternal overnutrition factors including both pre-conception BMI and excessive GWG should be initiated even before conception (133, 134). Pregnant women with obesity have increased levels of circulating glucose, lipids, inflammatory cytokines, and insulin resistance which potentially result in increased nutrient transport to the fetus (135). This seems to result in steady alterations in metabolism, behavior, and appetite regulation in offspring subsequently contributing to overweight, and metabolic and behavioral issues in adulthood (135).

3.3.3 Smoking during pregnancy

Smoking of women during pregnancy increases the offsprings' risk of obesity (136, 137). A large IPD meta-analysis consisting of 238,340 mother–child-pairs has shown that the risk of offspring overweight or obesity increases linearly by the number of cigarettes smoked by the mother during gestation, with the highest risk between ages 5 and 8 years (87). Even though the proportion of mothers who smoke during gestation rises with an increasing maternal pre-conception BMI (72), this meta-analysis aimed at assessing smoking effects regardless of maternal BMI at conception (87). Previous studies have also shown that prenatal smoking is related to a higher chance of developing a rapid-growth trajectory during preschool ages in offspring (138) and that infants of mothers who smoked during gestation showed higher BMI growth velocity until age 2 years in comparison to offspring of non-smoking mothers (139).

An intrauterine exposure to nicotine could result in an unphysiological proliferation of adipocytes and persistent alterations in central autonomic pathways which lead to stable and negative consequences for the control of food intake and energy expenditure in the hypothalamus (140). Interestingly, only one recent study assessed the impact of smoking behavior of pregnant women with obesity on offspring birth weight but lacked long-term BMI growth assessment (141). Nevertheless, this study, which included 3,241 infants born at term from the PIAMA birth cohort, showed that the simultaneous effects of prenatal smoking and maternal pre-gravid obesity on birth weight in offspring seemed to be nullified (141). It could be speculated that the effect of smoking during pregnancy on later offspring overweight may take time to emerge since women who smoked during gestation are likely to restart smoking in the postpartum phase and hence

abstain from breastfeeding more often (142, 143), which might contribute to offspring overweight development (66). Further, not only are the nicotine levels 3 times higher in breast milk of smoking mothers than those in plasma, but there are also reductions in breast milk volumes, the duration of lactation periods, nutritional properties of breast milk, and infants' response to breast feeding and to breast milk (142). Together, these postnatal effects of maternal smoking might additionally impact offspring long-term weight development.

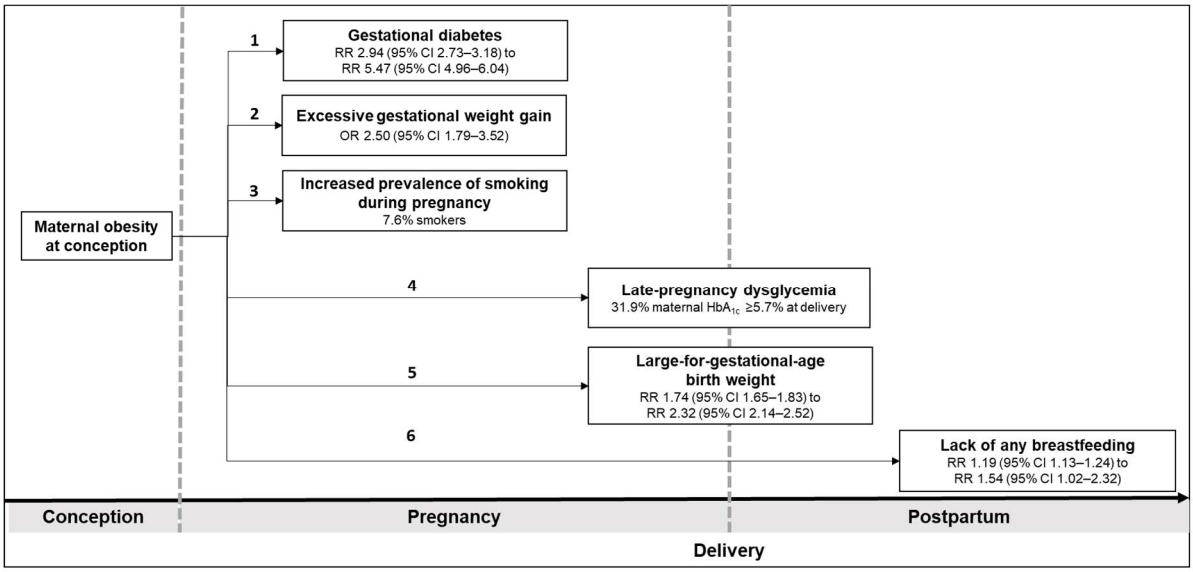

Figure 5: Relevant prenatal and postnatal risk factors of childhood overweight in mothers with obesity from conception to early postpartum life.
Factors shown are extracted from Figure 3, considered as scientifically particularly relevant and in the focus of our research group and can be potentially modified. CI, confidence interval; RR, relative risk; OR, odds ratio. Source: The figure presented here is self- made based on literature and shows relative risks, odds ratios, or prevalences of the relevant factors in mothers exposed to obesity in pregnancy:

1. Maternal preconception obesity → gestational diabetes (72)
2. Maternal preconception obesity → excessive gestational weight gain (129)
3. Maternal preconception obesity → increased prevalence of smoking during pregnancy (70)
4. Maternal preconception obesity → late-pregnancy dysglycemia (144)
5. Maternal preconception obesity →offspring LGA birth weight (73)
6. Maternal preconception obesity →lack of any breastfeeding (74)

3.3.4 Late-pregnancy dysglycemia

Data from our longitudinal Programming of Enhanced Adiposity Risk in CHildhood - Early Screening (PEACHES) mother-child cohort have shown that despite negative GDM testing at the end of the second trimenon, approximately one-third of women with obesity developed late-pregnancy dysglycemia (maternal glycated hemoglobin [HbA_{1c}] ≥5.7% at delivery) (144, 145). The high HbA_{1c} levels measured at delivery indicate development of hyperglycemia in the third trimenon, hypothesized to be due to the lack of close monitoring of women with obesity previously tested negative for GDM at the end of the second trimenon. In previous work of our research group, late-pregnancy dysglycemia in women with obesity and without GDM contributed to a higher chance of having an LGA birth weight, a higher concentration of cord-blood C-peptide, and increased maternal fasting glucose levels 3 years postpartum. Nonetheless, whether late-

pregnancy dysglycemia is related to adverse longitudinal BMI growth in offspring of mothers with obesity and without GDM remained unclear.

3.3.5 High birth weight

Birth weight is an indicator of prenatal developmental conditions and is linked with type 2 diabetes, hypertension, brain tumors, and breast cancer (146, 147). Children with an increased birth weight (>4000g) or those with an LGA birth weight are at a 66% (147) and 51% (148) higher risk of overweight and obesity in adulthood, respectively. Similarly, children born with an SGA birth weight may experience very rapid catch-up growth leading to a persistent risk of overweight until age 5 years (149). However, LGA birth weight occurs more frequently than SGA birth weight in children of mothers with obesity (LGA birth weight: 27.3% versus SGA birth weight: 4%) (150). Depending on the grade of maternal pre-gravid obesity, the risk of LGA birth weight ranges from 1.74 to 2.32-fold (72). Insulin resistance in pregnant women with obesity leads to higher transplacental transfer of glucose (hyperinsulinemia) stimulating an increase in fetal growth (151). Pregnant women with obesity also show a high concentration of blood triglycerides which are transported to the fetus, thus delivering higher amounts of energy to the fetus (152, 153). These disturbances are potential mechanisms underlying the manifestation of macrosomia and LGA birth weight (151). Animal studies have shown that there is an increase in the protein expression of specific placental nutrient transporter isoforms, including glucose transporter 1 and 3 (GLUT1 and GLUT3), sodium-coupled neutral amino acid transporter 2 (SNAT2), and large neutral amino acid transporter 1 (LAT1) which may influence fetal overgrowth in mothers with obesity (154).

3.3.6 Lack of full breastfeeding

Full breastfeeding comprises of both exclusive and predominant breastfeeding (155). An infant is exclusively breastfed when he/she is fed exclusively with breastmilk (156, 157). On the other hand, predominant breastfeeding means that the infant's key source of nourishment is breast milk and that the infant may also get water, water-based drinks, fruit juice, drops, or syrups (157). The major source of nourishment for a formula-fed infant is any type of commercially-produced infant formula but not breastmilk (156).

Breastfed and formula-fed infants have varying BMI growth trajectories which may modulate the risk of obesity in the future (66, 138, 158). Offspring of women with obesity are at a much greater risk of overweight development throughout the life course due to several unfavourable factors which include lower initiation rates and breastfeeding duration in mothers with obesity compared to women who are normal weight at conception (159).

Analysis of data from 4 prospective cohort studies/trials revealed that, following prenatal programming of adipose tissue, the first months of life (first 3 months of full breastfeeding) constitute an important growth phase for the postnatal development of adipose tissue (138, 160). Supporting this finding, a recent study showed that compared to infants who were not breastfed at all, a longer duration of any breastfeeding (6 to 12 months or >12 months) in infants was related to a better lipid profile throughout childhood (161). It is speculated that the beneficial composition of breast milk (162) may support healthy adipose tissue development (163). In contrast, the high protein intake from formula milk could promote rapid BMI growth

acceleration leading to an earlier adiposity rebound in children (164). On the other hand, infants with lower BMI growth have lower energy requirements (165) and might be satisfied with breastfeeding for a longer period (166, 167).

Further, a longer duration of breastfeeding during infancy is also crucial for later weight status in offspring. A recent meta-analysis confirmed results of previous systematic reviews (168, 169) by showing a dose-response relationship between ever breastfeeding (versus never breastfeeding) and risk of childhood obesity (ages 6 months to 14 years) (93). Interestingly, each additional month of any breastfeeding reduces the risk of childhood obesity by 4% (170).

4. Research gap and aims

Research gaps and aims are published in my research papers (Gomes 2018 and Gomes 2022) and are here summarized. For details, please see papers included in Section V and Section VI in this thesis document.

Maternal pre-conception obesity is one of the strongest factors of overweight and obesity in the offspring (171). However, data are lacking on (i) patterns of early BMI growth of offspring from pregnancies of mothers with obesity and how these patterns differ compared to those of offspring from pregnancies of mothers without obesity and on (ii) underlying factors which trigger these differences. Elucidating the earliest deviation in BMI growth patterns eventually leading to preschool overweight could help to identify crucial time points for early intervention after birth. Furthermore, pinpointing risk factors that influence "higher-than-normal BMI growth" could aid in developing a risk score and prediction system for children who are at high risk after exposure to gestational obesity.

Regarding exposures and potential risk factors relating to prenatal life, previous data of our research group have shown that dysglycemia towards the end of gestation (maternal HbA_{1c} ≥5.7% at delivery) in pregnancies of mothers with obesity, particularly in those women who had a negative GDM test at the end of the second trimester, could induce adverse birth outcomes (144, 145). These adverse birth outcomes included an increased risk of a high birth weight (LGA) and higher concentrations of cord blood C-peptide compared to newborns of women with obesity who also were tested negative for GDM and did not have dysglycemia at the end of gestation (144). Given its adverse influence on outcomes at birth in babies of mothers with obesity and a negative GDM test, we hypothesized that the presence of late-pregnancy dysglycemia might also pose a long-term risk for children of women with obesity to become overweight in the future. Specifically, we hypothesized that late-pregnancy dysglycemia could be a previously unidentified but important exposure factor of excessive BMI growth emerging from the prenatal phase in offspring of mothers with obesity.

Besides prenatal factors, exposures emerging from the first postnatal years in life could also be crucial for future weight status. The importance of postnatal life is magnified because mothers with obesity are likely to experience more adverse risk factors compared to their normal weight counterparts. Furthermore, since one or more risk factors already exist during pregnancy and in the first months after birth in mothers with obesity (such as excessive GWG and/or lack of breastfeeding), recognition of such risks could help to identify "high-risk" offspring as soon as possible. However, current tools to identify manifest overweight in offspring are inadequate as they have not focused on children exposed to gestational obesity and have not addressed the very early deviations in BMI gain in the track leading to overweight. Therefore, we aimed to develop a systematic approach for quantifying risk early in life and segregation of offspring who are particularly susceptible to gaining more weight than expected. A prevention strategy comprising sequential risk assessments was hypothesized as being helpful to enable monitoring of BMI growth, particularly in "high-risk" children, from age 3 months onwards.

Overall aim

To understand the role and predictive capability of both prenatal and postnatal influences for the development of concepts to prevent early excessive weight gain patterns in “high-risk” children, particularly those exposed to gestational obesity.

Specific aims

1. To study the role of late-pregnancy dysglycemia (HbA_{1c} ≥5.7% at delivery) as a prenatal risk factor on longitudinal weight development in children of women with obesity who were tested negative for GDM, aiming at improving third-trimester care of pregnant mothers with obesity (172).
2. To evaluate and compare “higher-than-normal” patterns of BMI growth in children of women with obesity compared to those of women without pre-conception obesity and the contribution of underlying prenatal and postnatal risk factors (173).
3. To assess the potential of such early-life risk factors as predictors of excessive weight gain in children of women with obesity compared to those of women without pre-conception obesity (173).
4. To develop a sequential risk prediction system for utilization in the well-child care setting to implement prevention measures in early life (173).

5. Methods

This section contains an overview of the methods. For details, please see my published papers and relevant supplements (Gomes 2018 and Gomes 2022) included in Section V and Section VI in this thesis document.

For work included in the present thesis, we used data from the PEACHES cohort study. This unique prospective PEACHES study is a cohort comprising a large number of mothers with obesity at conception (and normal weight controls) and their children (n = 1,707) and contains comprehensive data on prenatal and postnatal risk factors and various offspring and maternal outcomes including repeated BMI data in offspring.

For analysis of data in the present thesis, a total of 1,671 mother-child pairs were used following exclusion of mothers who gave birth in the year 2016/2017 (n = 20), had a second child enrolled in the PEACHES study (n = 15), and had a GDM test in late pregnancy (>32 weeks 6 days of gestation) (n = 1). Prenatal and postnatal risk factors included e.g. maternal pre-pregnancy BMI, smoking in pregnancy, GDM, total GWG, late-pregnancy dysglycemia (maternal HbA_{1c} ≥5.7% at delivery), SES at birth, and birth weight categories for gestational age and sex (172, 173). Offspring's measurements of height and weight at several ages including at birth, 1, 3, 6, 12, 24, 36, 48, and 60 months were used to calculate BMI which were compared to the WHO Growth Standards using BMI z-scores.

Robust statistical procedures were used to achieve the aims of this thesis. Offspring BMI growth outcomes included weight status at birth, BMI z-score change per year from birth until age 4 years, BMI growth clusters from birth to 5 years of age, "higher-than-normal BMI growth" in early (between age 6 months and 2 years) and late (between age 3 and 5 years) phases of growth, and manifest overweight at age 4 and/or 5 years (173). We compared prenatal and postnatal characteristics between maternal or offspring groups by use of Student's t test or 1-way analysis of variance and $\chi 2$ test as suitable (172, 173). We conducted multivariable linear, log-binomial regression, and/or logistic regressions to evaluate the associations between various pre- and/or postnatal influences and offspring outcomes related to BMI growth. In order to authenticate that maternal weight data collected at the first antenatal visit could approximate the mother's weight data at conception, we evaluated the agreement between measured weight and self-reported pre-conception weight collected at the first antenatal visit using the Bland-Altman method and the Pearson product-moment correlation (173). In the analyses, results were compared to the group of glucometabolically healthy women with obesity and/or to the group of mothers with normal weight. Mediation analysis was performed to evaluate the role of dysglycemia at the end of gestation for its contribution to the effect of maternal pre-pregnancy obesity on BMI z-scores in the 4-year-old offspring (172).

The capability of prenatal and postnatal influences to predict a "higher-than-normal BMI growth" pattern in young children at three pediatric visits (ages 3 months, 1 year, and 2 years) was studied with the help of penalized logistic regression in cooperation with Prof. Mansmann, IBE, LMU München. Models for prediction were validated in an independent cohort of large size (n = 11,730), the PErinatal Prevention of Obesity (PEPO) cohort (64). Detailed information on the statistical procedures are mentioned in the respective publications (172, 173).

6. Results

A summary of the results is presented here. For detailed results, please see my published papers (Gomes 2018 and Gomes 2022) included in Section V and Section VI in this thesis document.

Using the large longitudinal dataset of the PEACHES cohort study, we found that children of women with obesity are at risk to develop a “higher-than-normal” pattern of BMI growth already in the first years of life. In order to define early-life strategies to prevent the development of such a “higher-than-normal” pattern of BMI growth, we pursued research relating to two sensitive phases in life, including (i) the third trimester of gestation and (ii) the early months and years of a child’s life.

In Paper 1 (172), we show that among mothers with preconception obesity and without GDM (n = 448), nearly 1-in-3 women developed dysglycemia in late pregnancy as defined by their HbA_{1c} ≥5.7% at delivery (n = 135, 30.1%). In children of women with obesity who tested negative for GDM at the end of the second trimester, the presence of dysglycemia in late pregnancy was related to adverse birth and long-term outcomes. These birth outcomes included in average a higher weight at birth (mean increment 192 g, 95% CI 100 to 284) and a higher C-peptide concentration in cord blood (mean increment 0.10 ng/ml, 95% CI 0.02 to 0.17). Further, long-term outcomes included a higher gain in weight in young children (BMI change per year between ages 2 and 4 years: 0.18, 95% CI 0.06 to 0.30) and a higher 4-year BMI z-score (mean increment 0.58, 95% CI 0.18 to 0.99). Our results showed that 29% of the effect of pre-gravid obesity in mothers who tested negative for GDM on BMI z-score in the 4-year-old offspring was contributed by late-pregnancy dysglycemia (172).

In these children’s mothers, dysglycemia in late pregnancy was associated with higher postpartum concentrations of HbA_{1c} as well as glucose (both fasting and 1-h post-load) resulting in a 4-fold elevated risk of T2DM or prediabetes a few years later. Interestingly, in contrast to offspring of mothers with obesity who had received a diagnosis of GDM and were subsequently treated, newborns of women with obesity who had a GDM-negative test but developed dysglycemia in late pregnancy (untreated) had an increased weight status at birth (mean increment 134 g, 95% CI 28 to 239) and at age 4 years (mean increment 0.52, 95% CI 0.07 to 0.97) and a marginally increased BMI z-score change per year (mean annual increment 0.13, 95% CI −0.02 to 0.27) (172).

The identification of late-pregnancy dysglycemia as a previously undervalued risk factor for a high childhood weight status led us to proceed with evaluating the contribution of additional risk factors occurring early in life to “higher-than-normal” longitudinal BMI gain in offspring (Paper 2). For this purpose, we conducted comprehensive analyses in several steps which resulted in the development of a sequential strategy to predict early deviations in BMI gain in the track leading to manifest overweight. First, we identified different BMI growth curves in children after exposure to obesity in pregnancy versus those of offspring from pregnancies of mothers without obesity. By comparing the uppermost offspring BMI growth curves by the presence or absence of maternal preconception obesity, we found that in children of women with pre-gestational obesity, the pattern of “higher-than-normal BMI growth” was more severe than that in children of women without obesity. This pattern in children exposed to obesity in pregnancy was characterized by multiple crossings of the upper cut-off value of the BMI z-score for “risk of overweight” of >1 SD (≥5 times)

from the age of 6 months until age 5 years. Indeed, in this group of offspring, the presence of maternal obesity (versus absence) was related to overweight at ages 4 years (Odds ratio [OR] 7.38; 95% confidence interval [CI] 3.68 to 14.81) and 5 years (OR 4.90, 95% CI 2.80 to 8.59) (173).

After identifying such a sub-population of children at risk who are vulnerable to deviate from healthy BMI gain patterns, we evaluated the contribution of well-documented risk associations from prenatal and early-postnatal life phases. Offspring of women with pre-gravid obesity experienced several obesity-related risk factors which contributed to excess BMI growth outcomes compared to only a limited number of factors in children not exposed to obesity in pregnancy. Such extra exposures in children of women with obesity included e.g. excessive GWG, as defined by the Institute of Medicine (now known as the National Academy of Medicine)/National Research Council (128), and smoking during pregnancy. Interestingly, we also found that exposures emerging from life phases spanning from pre-gestation to the perinatal phase contributed differently during consecutive early-life stages following birth.

Next, we used those prenatal and postnatal influences to develop a novel risk quantification strategy to evaluate the possibilities of identifying offspring with the greatest odds of excess BMI gain way before overweight development at preschool age. The novel models of prediction at age 1 and 2 years were externally validated using available data from the PEPO cohort. The PEPO cohort comprises extensive prenatal and postnatal data of 11,730 German mother-child pairs recruited just before the mandatory school entry health examinations. Our prediction-guided prevention strategy allowed assessments as early as at 3 months of age and opportunities to re-evaluate at 1 and 2 years of age in children of both women with obesity and those without obesity separately. The sequential prediction times at ages 3 months, 1 year, and 2 years allows integration in the current system of well-child care in Germany. The well-child visits are performed by qualified pediatricians of the pediatric health care system in order to detect developmental delays or health issues at an early stage.

7. Conclusions

Overall, our data show that the third trimester appears to be a crucial window of opportunity for maintaining glucometabolic control in mothers with obesity and thus for developing improved obstetrics care concepts for certain populations of women. Close third-trimester follow-up of pregnant women with obesity is likely to be beneficial for both long-term weight outcomes in offspring and glucometabolic outcomes in the mother years after delivery. After birth, the first months of life are critical as offspring exposed to obesity in pregnancy should be stratified before the onset of upper deviations in weight development in the course towards overweight. Such close risk assessments in offspring could be embedded in the already existing infrastructure of the health system of the well-child visits. A graphical scheme showing an overview of the results of our work is provided in Figure 6.

To summarize, within the field of overweight prevention, pregnancy and the early months and years of life are most critical for developing and implementing concepts to avoid early excessive BMI growth patterns in offspring at risk, particularly those exposed to gestational obesity.

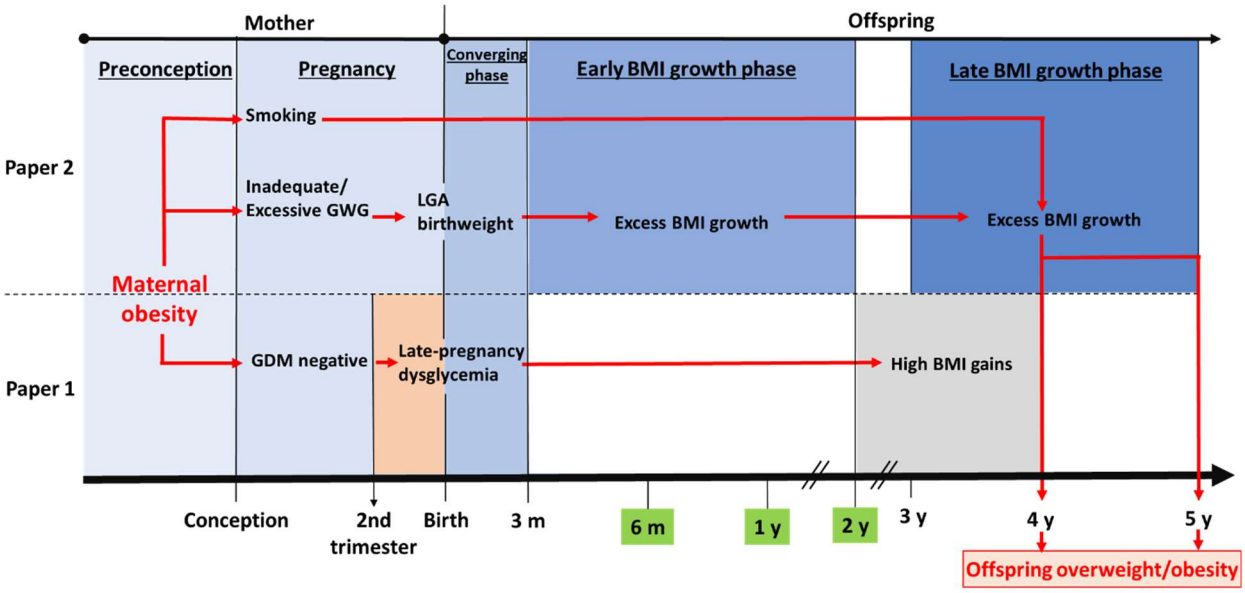

Figure 6: Early-life growth leading to preschool overweight or obesity in offspring of mothers with pre-conception obesity and underlying risk factors. Orange box indicates development of late-pregnancy dysglycemia in the third trimester (Paper 1) and green boxes indicate time points of risk prediction and re-assessments at the pediatricians' well-child visits (Paper 2).

III. Summary

I present here a summary of my work. For details, please see my published papers (Gomes 2018 and Gomes 2022) included in Section V and Section VI in this thesis document.

The prevalence of childhood overweight has increased drastically, and weight development in preschool years is linked to future obesity. A greater risk of overweight at preschool age is conferred by a higher maternal preconception body mass index (BMI), an urgent public health issue, since overweight or obesity occurs in up to two-thirds of child-bearing women today, frequently developing metabolic complications. In fact, our research group previously found that women with obesity may develop dysglycemia towards the end of pregnancy, despite a negative test for gestational diabetes (GDM). Therefore, we hypothesized that late-pregnancy dysglycemia could also contribute to adverse longitudinal BMI development in their offspring. For prevention, such offspring should be identified at a time prior to the first upper divergence in BMI gain in the trajectory towards overweight manifestation. However, prediction of early deviations in weight gain has not been achieved on an individual level as a prerequisite for implementation in the public health setting, because data on weight trajectories in children who had exposure to gestational overnutrition and the contribution of "obesogenic influences" are lacking.

Using comprehensive and longitudinal data from different gestational and postnatal phases of the large Programming of Enhanced Adiposity Risk in CHildhood - Early Screening (PEACHES) cohort study of women with obesity and their children (n = 1,707), we performed linear mixed-effects models and mediation analysis to evaluate the long-term (from age 2 to 4 years) effect and contribution of obesity-related dysglycemia at the end of gestation (women's HbA_{1c} [glycated hemoglobin] at delivery ≥5.7%) on preschool BMI (at 4 years of age), respectively. We also identified specific patterns of BMI growth from birth until 5 years of age following exposure to obesity in pregnancy, assessed various BMI outcomes, and evaluated their underlying contributors in offspring using k-means cluster analysis and a series of multivariable regression models. Subsequently, a serial approach of individual risk score assessment, prediction, and re-assessments was developed using penalized logistic regressions. Data from an independent mother-child cohort (PErinatal Prevention of Obesity [PEPO], n = 11,730) were available for data validation.

In the analysis of children exposed to gestational obesity, a diagnosis of GDM did not influence offspring BMI at age 4 years. However, within the group of mothers with obesity who tested negative for GDM towards the end of the second trimester, dysglycemia in late pregnancy was associated with high BMI gains between ages 2 and 4 years in offspring (mean annual increment Δ 0.18, 95% confidence interval [CI] 0.06–0.30). Overall, it accounted for almost one-quarter of the contribution of gestational obesity on offspring BMI z-score at age 4 years. In these mothers, the presence of late-pregnancy dysglycemia was related to a risk of prediabetes or type 2 diabetes (T2D) a few years later that was four times higher than in mothers with normal HbA_{1c} at delivery (relative risk [RR] 4.01, 95% CI 1.97–8.17). Excessive third-trimester weight gain was related to a mean increase in the risk of dysglycemia in late pregnancy by 72% (RR 1.72, 95% CI 1.12–2.65) in mothers with obesity who had a negative GDM test. Next, we focused on a "pre-symptomatic" offspring BMI outcome and identified a "high-risk" subgroup of children (21%) likely to undergo early upper

divergence from a healthy BMI growth track after exposure to gestational overnutrition. Belonging to this upper BMI cluster was associated with a high risk of preschool overweight/obesity (odds ratio [OR] 16.13; 95% CI 9.98–26.05). Underlying pre- and perinatal influences such as high maternal weight gain (OR 2.08, 95% CI 1.25–3.45) and smoking in pregnancy (OR 1.94, 95% CI 1.27–2.95) were essential to predict a subsequent “higher-than-normal BMI growth” pattern in the 3-month-old, 1-year-old, and 2-year-old offspring. Sequential prediction models showed adequate predictive performances (area under the receiver operating characteristic [AUROC] 0.69–0.79, specificity 64.7–78.1%, sensitivity 70.7–76.0%), and findings were confirmed in the cohort PEPO.

In conclusion, in order to achieve healthy weight development at the beginning of life, efforts should be made to optimize maternal weight gain and glucose metabolism as well as fetal growth also in the 3rd trimester of pregnancy, particularly if the mother with obesity had a prior GDM-negative test result. After birth, children of women with obesity should be closely sequentially assessed for risk quantification and individual detection of an increased risk of “higher-than-normal” BMI growth at the established well-child care visits for intensified prevention measures. A “continuum” of targeted management strategies in the very early stages of life could help reduce intergenerational transmission of obesity.

IV. Zusammenfassung

Die Prävalenz von Übergewicht im Kindes- bzw. Vorschulalter ist in den vergangenen Dekaden stark angestiegen und geht häufig mit Adipositas im späteren Leben einher. Ein höherer mütterlicher body mass index (BMI) bei Konzeption ist mit einem höheren Risiko für Übergewicht der Nachkommen im Vorschulalter assoziiert. Da weltweit inzwischen bis zu zwei Drittel der Frauen im gebärfähigen Alter an Übergewicht oder Adipositas leiden und häufig Stoffwechselkomplikationen in der Schwangerschaft entwickeln, stellt dies ein Problem für zwei Generationen mit immensen Auswirkungen für das Gesundheitssystem dar.

Unsere Arbeitsgruppe konnte in Vorarbeiten zeigen, dass auch Schwangere mit Adipositas, die ursprünglich negativ auf Gestationsdiabetes (GDM) getestet wurden, im 3. Trimenon der Schwangerschaft Dysglykämien entwickeln können. Daher stellten wir die Hypothese auf, dass auch Dysglykämien in der Spätschwangerschaft zu einer ungünstigen longitudinalen BMI-Entwicklung bei den Nachkommen beitragen könnte. Aus präventivmedizinischer Sicht sollten diese Kinder zum Zeitpunkt der frühesten Abweichung vom physiologischen Wachstum und Gewichtszuwachs und vor der Manifestation von Übergewicht identifiziert werden. Die Vorhersage einer abweichenden Gewichtsentwicklung ist derzeit auf individueller Ebene noch nicht möglich, was jedoch eine Voraussetzung für die Umsetzung in entsprechenden Kinder-Vorsorgemaßnahmen im Gesundheitswesen (Public Health Sektor) wäre. Auch fehlen bisher Daten zu den BMI-Wachstumsverläufen der Nachkommen, die während der Schwangerschaft gegenüber einer mütterlichen Adipositas exponiert waren, sowie zum Beitrag dieser "adipogenen“ Einflüsse für das frühkindliche Wachstum.

Unter Verwendung von umfassenden, longitudinalen Daten aus verschiedenen Schwangerschafts- und Nachgeburtsphasen von Müttern mit Adipositas und ihren Kindern aus der Programming of Enhanced Adiposity Risk in CHildhood - Early Screening (PEACHES)-Kohorte (n = 1.707) haben wir Analysen mittels linearer gemischter Modelle vorgenommen. Wir führten zudem eine Mediationsanalyse durch, um den longitudinalen Effekt (zwischen 2 und 4 Jahren) und den Beitrag von Adipositas-assoziierten Dysglykämien in der Spätschwangerschaft (mütterlicher HbA_{1c} [glykiertes Hämoglobin]-Wert bei Geburt ≥5,7%) auf den BMI der Nachkommen (mit 4 Jahren) zu bewerten. Neben der Identifizierung unterschiedlicher kindlicher BMI-Wachstumsmuster ab dem Zeitpunkt Geburt bis hin zum Alter von 5 Jahren nach Exposition gegenüber Adipositas in der Schwangerschaft mithilfe von „K-Means“-Clusteranalysen, bewerteten wir verschiedene BMI-abhängige Endpunkte und evaluierten die ihnen zugrundeliegenden Faktoren bei den Nachkommen mit einer Reihe von multivariablen Regressionsmodellen. Anschließend wurde eine sequenzielle Strategie bestehend aus individueller Risikobewertung, -vorhersage und -neueinschätzung unter Verwendung eines speziellen „penalized“ logistischen Regressionsmodells entwickelt. Zur Validierung standen Daten aus einer weiteren unabhängigen Mutter-Kind-Kohorte (PErinatal Prevention of Obesity [PEPO], n = 11.730) zur Verfügung.

Die Analyse der Nachkommen von Müttern mit Adipositas ergab, dass die Diagnose eines GDM keinen Einfluss auf deren BMI im Alter von 4 Jahren hatte. Jedoch waren in der Gruppe der Mütter mit Adipositas, die im 2. Trimenon zunächst negativ auf GDM getestet worden waren, Dysglykämien in der Spätschwangerschaft mit einem hohen BMI-Zuwachs zwischen dem 2. und 4. Lebensjahr der Nachkommen verbunden (mittlerer jährlicher Zuwachs: Δ 0,18; 95%- Konfidenzintervall [KI] 0,06-0,30). Das

Auftreten von Dysglykämien am Ende der Schwangerschaft war für fast ein Viertel des Effekts der mütterlichen Adipositas auf den 4-Jahres-BMI-Z-Score der Nachkommen verantwortlich. Bei den Müttern selbst war das Auftreten von Dysglykämien in der Spätschwangerschaft mit einem 4-fach höheren Risiko (relatives Risiko [RR] 4,01; 95%-KI 1,97-8,17) für Prädiabetes oder Typ-2-Diabetes (T1D) einige Jahre später verbunden. Bei Müttern mit Adipositas, die negativ auf GDM getestet wurden, war eine übermäßige Gewichtszunahme im 3. Trimenon mit einem mittleren Anstieg des Risikos von Dysglykämien in der Spätschwangerschaft um 72% verbunden (RR 1,72; 95%-KI 1,12-2,65).

Weiterhin konzentrierten wir uns auf die Definition eines „präsymptomatischen“ Endpunkts bei den Nachkommen vor der Manifestation von Übergewicht und identifizierten eine "Hochrisiko"-Population von Nachkommen (21%), die nach der Exposition gegenüber Adipositas in der Schwangerschaft ein höheres Risiko hatten, vom normalen BMI-Wachstumsverlauf nach oben abzuweichen. Die Zugehörigkeit zu diesem oberen „BMI-Wachstumscluster“ war mit einem hohen Risiko für Übergewicht/Adipositas im Vorschulalter verbunden (Odds Ratio [OR] 16,13; 95%-KI 9,98-26,05). Zugrundeliegende prä- und perinatale Faktoren wie eine exzessive Gewichtszunahme in der Schwangerschaft (OR 2,08; 95%-KI 1,25-3,45) und Rauchen in der Schwangerschaft (OR 1,94; 95%-KI 1,27-2,95) waren entscheidend für die Vorhersage für einen überdurchschnittlich hohen BMI-Wachstumsverlauf („higher-than-normal BMI growth pattern“) im Alter von 3 Monaten, 1 Jahr und 2 Jahren. Die sequenziellen Prädiktionsmodelle zeigten eine adäquate Vorhersage (Fläche unter ROC-Kurve [AUROC] 0,69-0,79, Sensitivität 70,7-76,0%, Spezifität 64,7-78,1%) und wurden anhand der PEPO-Kohorte extern validiert.

Um eine gesunde Gewichtsentwicklung zu Beginn des Lebens zu erreichen, sollten Anstrengungen unternommen werden, die Gewichtszunahme und den Glukosestoffwechsel der Schwangeren sowie das fetale Wachstum auch im 3. Trimenon der Schwangerschaft zu optimieren, insbesondere wenn die Schwangere mit Adipositas zuvor ein negatives Testergebnis auf Gestationsdiabetes hatte. Nach der Entbindung sollten die Nachkommen, die während der Schwangerschaft einem adipogenen Milieu ausgesetzt waren, engmaschig nachuntersucht werden, um mittels Risikoquantifizierung ein hohes Risiko für eine überdurchschnittliche Gewichtszunahme im Rahmen der Kindervorsorgeuntersuchungen (U-Untersuchungen) zu identifizieren. Ein „Kontinuum“ an „gezielten“ Managementstrategien in den ersten Phasen des Lebens könnte dazu beitragen, die intergenerationelle Übertragung bzw. Prägung von Adipositas zu verringern.

V. Paper 1

PLOS MEDICINE

RESEARCH ARTICLE

Late-pregnancy dysglycemia in obese pregnancies after negative testing for gestational diabetes and risk of future childhood overweight: An interim analysis from a longitudinal mother–child cohort study

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Citation: Gomes D, von Kries R, Delius M, Mansmann U, Nast M, Stubert M, et al. (2018) Late-pregnancy dysglycemia in obese pregnancies after negative testing for gestational diabetes and risk of future childhood overweight: An interim analysis from a longitudinal mother–child cohort study. PLoS Med 15(10): e1002681. https://doi.org/10.1371/journal.pmed.1002681

Academic Editor: Jenny E. Myers, University of Manchester, UNITED KINGDOM

Received: February 4, 2018

Accepted: September 25, 2018

Published: October 29, 2018

Data Availability Statement: Data cannot be shared publicly because participants did not explicitly consent to the sharing of their data as per European Union's General Data Protection Regulation and the corresponding German privacy laws. Data are available through the Research Ethics Board of the Ludwig-Maximilians-Universität München, Munich/Germany for researchers who meet the criteria for access to

Abstract

Background

Maternal pre-conception obesity is a strong risk factor for childhood overweight. However, prenatal mechanisms and their effects in susceptible gestational periods that contribute to this risk are not well understood. We aimed to assess the impact of late-pregnancy dysglycemia in obese pregnancies with negative testing for gestational diabetes mellitus (GDM) on long-term mother–child outcomes.

Methods and findings

The prospective cohort study Programming of Enhanced Adiposity Risk in Childhood–Early Screening (PEACHES) ($n = 1,671$) enrolled obese and normal weight mothers from August 2010 to December 2015 with trimester-specific data on glucose metabolism including GDM status at the end of the second trimester and maternal glycated hemoglobin (HbA_{1c}) at delivery as a marker for late-pregnancy dysglycemia ($HbA_{1c} \geq 5.7\%$ [39 mmol/mol]). We assessed offspring short- and long-term outcomes up to 4 years, and maternal glucose metabolism 3.5 years postpartum. Multivariable linear and log-binomial regression with effects presented as mean increments (Δ) or relative risks (RRs) with 95% confidence

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Funding: This study was supported by the German Federal Ministry of Education and Research grant 01EA1307 to RE and the Foundation for Cardiovascular Prevention in Childhood, Ludwig-Maximilians-Universität München, Munich, Germany. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; CI, confidence interval; GCT, glucose challenge test; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HbA_{1c}, glycated hemoglobin; HPLC, high performance liquid chromatography; IADPSG, International Association of Diabetes and Pregnancy Study Groups; IQR, interquartile range; LGA, large-for-gestational-age; OGTT, oral glucose tolerance test; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening; RR, relative risk; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

intervals (CIs) were used to examine the association between late-pregnancy dysglycemia and outcomes. Linear mixed-effects models were used to study the longitudinal development of offspring body mass index (BMI) *z*-scores. The contribution of late-pregnancy dysglycemia to the association between maternal pre-conception obesity and offspring BMI was estimated using mediation analysis. In all, 898 mother–child pairs were included in this unplanned interim analysis. Among obese mothers with negative testing for GDM ($n = 448$), those with late-pregnancy dysglycemia ($n = 135$, 30.1%) had higher proportions of excessive total gestational weight gain (GWG), excessive third-trimester GWG, and offspring with large-for-gestational-age birth weight than those without. Besides higher birth weight (Δ 192 g, 95% CI 100–284) and cord-blood C-peptide concentration (Δ 0.10 ng/ml, 95% CI 0.02–0.17), offspring of these women had greater weight gain during early childhood (Δ BMI *z*-score per year 0.18, 95% CI 0.06–0.30, $n = 262$) and higher BMI *z*-score at 4 years (Δ 0.58, 95% CI 0.18–0.99, $n = 43$) than offspring of the obese, GDM-negative mothers with normal HbA_{1c} values at delivery. Late-pregnancy dysglycemia in GDM-negative mothers accounted for about one-quarter of the association of maternal obesity with offspring BMI at age 4 years ($n = 151$). In contrast, childhood BMI *z*-scores were not affected by a diagnosis of GDM in obese pregnancies (GDM-positive: 0.58, 95% CI 0.36–0.79, versus GDM-negative: 0.62, 95% CI 0.44–0.79). One mechanism triggering late-pregnancy dysglycemia in obese, GDM-negative mothers was related to excessive third-trimester weight gain (RR 1.72, 95% CI 1.12–2.65). Furthermore, in the maternal population, we found a 4-fold (RR 4.01, 95% CI 1.97–8.17) increased risk of future prediabetes or diabetes if obese, GDM-negative women had a high versus normal HbA_{1c} at delivery (absolute risk: 43.2% versus 10.5%). There is a potential for misclassification bias as the predominantly used GDM test procedure changed over the enrollment period. Further studies are required to validate the findings and elucidate the possible third-trimester factors contributing to future mother–child health status.

Conclusions

Findings from this interim analysis suggest that offspring of obese mothers treated because of a diagnosis of GDM appeared to have a better BMI outcome in childhood than those of obese mothers who—following negative GDM testing—remained untreated in the last trimester and developed dysglycemia. Late-pregnancy dysglycemia related to uncontrolled weight gain may contribute to the development of child overweight and maternal diabetes. Our data suggest that negative GDM testing in obese pregnancies is not an "all-clear signal" and should not lead to reduced attention and risk awareness of physicians and obese women. Effective strategies are needed to maintain third-trimester glycemic and weight gain control among otherwise healthy obese pregnant women.

Author summary

Why was this study done?

- Pre-conception obesity is associated with an increased risk of pregnancy complications and adverse long-term health outcomes for the mother and her child.

- Obese pregnant women can develop impairments in glucose metabolism in late pregnancy despite prior negative testing for gestational diabetes mellitus (GDM).
- Yet, to date, guidelines on obesity in pregnancy and GDM have focused only on early glucose screening rather than targeting factors relevant to the last trimester of pregnancy.
- To evaluate whether recommendations on management of obese pregnancies require optimization, additional evidence is needed on the consequences of late-pregnancy dysglycemia for long-term childhood and maternal outcomes.

What did the researchers do and find?

- We performed an interim analysis of 898 obese and normal weight mothers and their offspring from the Programming of Enhanced Adiposity Risk in Childhood–Early Screening (PEACHES) cohort study (total $n = 1,671$) that recruited pregnant women in Germany from 2010 to 2015.
- Late-pregnancy dysglycemia predisposed the offspring of obese, GDM-negative mothers to higher weight gain in early childhood and a higher body mass index at age 4 years.
- Children of obese mothers treated because of a diagnosis of GDM appeared to have a better weight outcome than those of obese mothers who remained untreated following a negative GDM test and developed late-pregnancy dysglycemia.
- Obese, GDM-negative women with late-pregnancy dysglycemia also had a 4-fold higher risk of prediabetes or diabetes several years after delivery compared to those with normal glucometabolic status in late pregnancy.

What do these findings mean?

- We suggest that a negative GDM test at the end of the second trimester should not be understood as an "all-clear signal" and should not result in reduced attention of caregivers and a false sense of security in the mothers.
- Guidelines to manage and maintain third-trimester glycemic and weight gain control are needed for "high risk" obese women.
- Further analyses and studies should validate the findings and investigate the possible role of third-trimester factors for future mother–child health.

Introduction

Since up to two-thirds of women of reproductive age are now overweight or obese in European countries and the US [1,2], obesity in pregnancy and its consequences represent a major public health challenge [3]. In Germany, the prevalence of overweight and obesity is 38.1% (obesity: 15.4%) among women of childbearing age [4] and 35.8% (obesity: 14.2%) among pregnant women [5]. Obese women are 3 to 5.5 times more likely to develop gestational diabetes mellitus (GDM) than normal weight women [6], leading to an approximately 3- to 10-fold

increased risk of developing type 2 diabetes mellitus (T2DM) later in life [7,8]. In addition, in offspring of obese women, the risk of adverse health outcomes such as the development of adiposity, T2DM, cardiovascular disease, and asthma is higher [9,10].

Despite maternal oral glucose tolerance test (OGTT) values within the reference range during pregnancy, children of mothers with pre-conception obesity are reported to have a higher rate of overweight [11]. Evidence from recent systematic reviews and meta-analyses even suggests a greater contribution to child overweight from maternal pre-conception obesity than from GDM [12,13]. Apart from genetic background and lifestyle factors related to maternal obesity, prenatal metabolic influences of an adipogenic intrauterine milieu seem to play a relevant role, as evident from higher rates of increased offspring body fat at birth [14,15]. Potentially modifiable factors in the relationship between maternal gestational obesity and offspring childhood overweight may be linked to mechanisms of intrauterine lipotoxicity, including inflammatory changes and oxidative stress, and/or glucometabolic alterations that could exert effects during sensitive gestational periods.

We previously found high glycated hemoglobin (HbA_{1c}) levels (≥5.7% [39 mmol/mol]) at delivery in about one-third of obese pregnant women [16,17], despite negative testing for GDM according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria at the end of the second trimester [18]. This finding suggested the presence of relevant dysglycemia in late pregnancy, which was in turn associated with persistently abnormal glucose metabolism in the obese women postpartum and a higher rate of macrosomia in their offspring at birth [17]. However, assessing dysglycemia in the last trimester of pregnancy is not part of routine healthcare for obese women to date, and available guidelines on obesity in pregnancy have focused only on early glucose screening rather than addressing factors pertinent to the last third of pregnancy [19,20].

Therefore, in order to evaluate whether recommendations on gestational management of otherwise healthy obese women need to be optimized, further evidence is required as to whether such dysglycemia in late pregnancy could represent a long-term risk for offspring developing overweight later in childhood. In the prospective Programming of Enhanced Adiposity Risk in Childhood–Early Screening (PEACHES) cohort study, we had a unique set of longitudinal data on "high risk" obese mothers and their children including trimester-specific data on glucose metabolism that allowed us to address this question. Such clarification is of particular relevance to designing efficacious intervention and prevention strategies in the susceptible time window of late pregnancy.

Methods

Study design and participants

PEACHES is an ongoing prospective mother–child cohort study (n = 1,671) on pregnant women recruited between August 2010 and December 2015 during their first contact at maternity clinics (4–6 weeks before due date) in 23 departments of obstetrics and gynecology in the Munich area, Bavaria (southern Germany); the University Hospital of Düsseldorf (western Germany); and parts of northern Germany. In brief, the long-term effect of pre-conception maternal obesity on the development of overweight and associated metabolic diseases in both mothers and their offspring is being assessed, as described elsewhere [16,17]. The entire cohort comprises pre-conceptionally obese (body mass index [BMI] ≥ 30 kg/m^2) or normal weight (BMI 18.5–24.9 kg/m^2) women without preexisting diseases including type 1 diabetes mellitus (T1DM) or T2DM. The study was approved by the local ethics committee of the Ludwig-Maximilians-Universität München, Germany (protocol no. 165–10). Written informed consent was obtained from all participants. The study protocol is provided as S1 Study Protocol. This study

is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (S1 STROBE Checklist). Data for this unplanned interim analysis were retrieved from the PEACHES database in August 2017.

Procedures

Inclusion criteria for analysis. We included women in the data analysis if they were preconceptionally obese, were white, had a singleton live birth, and had not been diagnosed with T1DM or T2DM. Normal weight women who tested negative for GDM and had normal levels of HbA_{1c} at delivery were also eligible to be included in the analysis. Women with incomplete data on pre-conception BMI, GDM status, maternal HbA_{1c} at delivery, or confounding variables were excluded from the analysis.

Exposure variables. Obese and normal weight women who met the inclusion criteria for the analysis had GDM testing (50-g glucose challenge test [GCT] or 75-g OGTT) between 12 weeks and 1 day and 32 weeks and 6 days of gestation (median 25 weeks and 3 days, interquartile range [IQR] 3 weeks and 4 days). We included women with a negative GDM test performed before 23 weeks and 1 day [21] if absence of GDM was confirmed later in pregnancy (according to the IADPSG recommendation [18]). Blood glucose concentrations were obtained either from the pregnancy record booklet ("Mutterpass") issued to every pregnant woman at her first antenatal visit in Germany or requested directly from the gynecologist. The pregnancy record booklet contains comprehensive information on ultrasound checkups, laboratory assessments, and weight measurements at multiple times collected by the gynecologist during antenatal care visits. GDM testing was defined as negative when none, and positive when 1 or more, of the 3 glucose concentrations of a 75-g OGTT met or exceeded the reference values according to the IADPSG criteria (1-step procedure): fasting glucose $\geq$ 5.1 mmol/l, 1-h post-load glucose $\geq$ 10 mmol/l, or 2-h post-load glucose $\geq$ 8.5 mmol/l [18]. In the 2-step procedure, a positive 50-g GCT, defined as 1-h post-load glucose concentration $\geq$ 7.8 mmol/l [22], was followed by a 75-g OGTT according to IADPSG diagnostic criteria [18]. In contrast to women with a negative test result (GDM-negative), those diagnosed with GDM (GDM-positive) received recommendations on treatment with insulin and/or diet, obtained advice on weight gain goals, and were monitored until the end of pregnancy.

Maternal HbA_{1c} concentration at delivery was measured in venous blood, following prompt transportation to a central laboratory, using high performance liquid chromatography (HPLC) via cation-exchange chromatography with a Tosoh G8 HPLC Analyzer (Tosoh Bioscience, Stuttgart, Germany) (interassay coefficient of variation $\leq$ 2.0%, analytic bias $\leq$ 0.05% HbA_{1c} at a target value of 5.33% [35 mmol/mol]). We used the term "late-pregnancy dysglycemia" when the maternal HbA_{1c} value at delivery was greater than or equal to the cut-off 5.7% (39 mmol/mol), as defined previously [17]. Information on the women's iron supplementation and their red blood cell indices were used to exclude iron deficiency anemia as a potential cause of HbA_{1c} elevation [23].

Outcome variables: Offspring weight and metabolic outcomes. Short-term offspring outcomes included both absolute birth weight and large-for-gestational-age (LGA) birth weight, defined as >90th percentile [24], and were extracted from birth records. Cord blood was centrifuged (2,500*g*, 22˚C) and sent to a central laboratory for analysis of C-peptide by a chemiluminescence immunoassay (Architect i2000, Abbott Wiesbaden, Germany). C-peptide values were dichotomized based on the 90th-percentile cutoff of the distribution among offspring from the normal weight, healthy (GDM-negative and HbA_{1c} < 5.7% at delivery) mothers in the PEACHES cohort ($\geq$0.94 ng/ml [0.31 nmol/l]). Long-term outcomes in children included offspring's BMI *z*-scores at 2, 3, and 4 years. Anthropometric data were obtained

from records of the regular well-child care visits conducted by trained professionals of the preventive health program offered to all children in Germany. Age- and sex-specific BMI *z*-scores were calculated according to World Health Organization (WHO) Child Growth Standards [25].

Outcome variables: Maternal postpartum follow-up. At a follow-up visit several years postpartum, to which women were consecutively invited for evaluation of their metabolic health and body composition [17], maternal HbA_{1c} and glucose concentrations of an OGTT were measured. Postpartum maternal body weight and height were determined using a digital scale (Clara 803, Seca, Hamburg, Germany) with an accuracy of 0.1 kg and a stadiometer (model 213, Seca) with an accuracy of 0.1 cm. Body fat mass was determined by bioelectrical impedance analysis (BIA) (body composition analyzer BC-420 MA, Tanita, Sindelfingen, Germany). Waist and hip circumferences were measured to the nearest 0.1 cm using standardized protocols as recommended by WHO [26], and waist-to-hip ratio was calculated. Each anthropometric measurement was carried out 3 times consecutively by the same trained investigator and averaged for analysis.

Follow-up maternal HbA_{1c} was measured in EDTA plasma by HPLC via cation-exchange chromatography with a Variant II Turbo (BioRad, Hercules, California, US). Analysis of serum glucose concentrations was performed using the hexokinase method on an AU 5800 analyzer (Beckman Coulter, Krefeld, Germany). The presence of T2DM (fasting glucose $\geq$ 7.0 mmol/l or 2-h post-load glucose of a 75-g OGTT $\geq$ 11.1 mmol/l or $HbA_{1c} \geq 6.5\%$ [48 mmol/mol]) and prediabetes (fasting glucose 5.6 mmol/l to 6.9 mmol/l or 2-h post-load glucose of a 75-g OGTT 7.8 mmol/l to 11.0 mmol/l or HbA_{1c} 5.7% to 6.4% [39 to 47 mmol/mol]) was determined [22].

Confounders. We extracted information on maternal age at conception and weight measurements from the mothers' pregnancy record booklets. Pre-conception BMI was based on data measured at the first antenatal visit if the visit was before 12 weeks and 6 days of gestation (92.5% of participants). When the first antenatal visit was later than the 13th week of gestation (7.5% of participants), pre-conception weight was used as reported by the woman at this first visit and documented in the pregnancy record booklet. Pre-conception BMI groups were defined according to WHO categories [27].

Total gestational weight gain (GWG) in pregnancy was defined as the difference between the last measured weight before delivery and pre-conception weight and classified as inadequate, adequate, or excessive according to the BMI-specific recommendations of the Institute of Medicine [28]. Third-trimester GWG (i.e., between 27 weeks of gestation and delivery) was calculated using the difference between the first (mean 28 weeks and 3 days [standard deviation (SD) 1 week and 2 days]) and last (mean 38 weeks and 4 days [SD 2 weeks and 2 days]) documented weight in the third trimester. To categorize third-trimester GWG as excessive or non-excessive for each woman, we calculated the average third-trimester weight gain per week (third-trimester GWG divided by weeks between the 2 weight measurements) [29] and compared it to the respective BMI-specific recommendations for weight gain per week of the Institute of Medicine [28].

Offspring sex and gestational age were extracted from birth records. Information on breastfeeding and treatment for GDM was collected using a questionnaire sent to each participant. Breastfeeding data were dichotomized as "$\geq$1 month exclusively without interruption" or "never or <1 month exclusively." Data on smoking and iron supplementation during pregnancy were obtained twice, via the questionnaire and via a standardized telephone interview shortly after delivery. Reported smoking at either assessment was categorized as maternal smoking at "any time during pregnancy" (versus "no time during pregnancy").

Statistical analysis

Aspects of the analysis plan were written prior to the analysis (S1 Study Protocol). However, there was no detailed prospective plan for the current interim analysis. The confounder adjustment and modeling strategy were modified in response to reviewers' suggestions. This unplanned analysis was triggered to present interim results that could potentially provide guidance on how to proceed with the future research of the cohort.

We compared gestational, offspring, and maternal characteristics by GDM status (negative or positive) and maternal HbA_{1c} level at delivery (high or normal) using Student's *t* test or 1-way analysis of variance (ANOVA) and χ^2 test as appropriate. After confirmation of a linear relationship between maternal HbA_{1c} at delivery and offspring BMI *z*-score at 4 years using B-splines [30], we performed linear regression to estimate the association between maternal HbA_{1c} at delivery (continuous) and offspring BMI *z*-score at 4 years.

The association of late-pregnancy dysglycemia with short- and long-term offspring and maternal outcomes among obese, GDM-negative mothers was examined using linear (continuous outcomes) and log-binomial (binary outcomes) regression; comparisons were relative to (i) obese, GDM-negative mothers with normal HbA_{1c} levels and (ii) obese, GDM-positive mothers. Effects are expressed as mean increments (Δ, linear regression) and relative risks (RRs, log-binomial regression) with 95% confidence intervals (CIs). In addition, the risk of developing late-pregnancy dysglycemia due to excessive third-trimester GWG was assessed in the group of obese, GDM-negative mothers using log-binomial regression. Models were adjusted for potential confounders including maternal pre-conception BMI, total GWG, maternal smoking at any time during pregnancy, and sex of the child; models for long-term childhood outcomes were additionally adjusted for exclusive breastfeeding $\geq$1 month. Potential confounders were chosen based on their demonstrated relationship to offspring childhood overweight [31]. The model for the maternal outcome prediabetes/T2DM was adjusted for maternal body fat percentage at 3.5 years postpartum.

To assess the longitudinal association of late-pregnancy dysglycemia (relative to the absence of late-pregnancy dysglycemia) with offspring BMI *z*-scores at ages 2, 3, and 4 years, we constructed linear mixed-effects models with random effects for intercept and time. Polynomial contrasts and interaction with group were tested to examine differential nonlinear time courses between both groups; the corresponding likelihood ratio test did not give strong evidence for a nonlinear time effect. Models were fitted using the R package "lme4" [32]. Missing data relate to the timing of recruitment into our cohort (i.e., offspring of mothers recruited after 2013 were too young to have their 4-year follow-up by August 2017) rather than loss to follow-up or withdrawal from participation. Thus, we assumed missingness at random for the follow-up data, which does not bias results of linear mixed-effects models.

Mediation analysis was conducted to assess whether late-pregnancy dysglycemia (as indicated by a high maternal HbA_{1c} at delivery) contributed to the association of maternal obesity with offspring BMI *z*-score in GDM-negative women [33]. First, we assessed the total effect of maternal pre-conceptional obesity on 4-year BMI *z*-score by comparing offspring of obese, GDM-negative women versus offspring of normal weight, GDM-negative women and adjusting for confounders as above. Subsequently, we adjusted for maternal HbA_{1c} at delivery (high versus normal) to estimate the direct effect of maternal pre-conceptional obesity on offspring 4-year BMI *z*-score. The difference between the total and direct effect provides a quantification of the potential contribution of late-pregnancy dysglycemia to increased 4-year BMI *z*-score. These analyses were conducted in all obese and normal weight women for whom information on offspring 4-year BMI *z*-score was available.

The sample size for the analysis is compatible with the sample size calculation provided in the original protocol as presented in S1 Study Protocol. Therefore, the data analyzed provide sufficient power to detect relevant effects.

We formally considered a p-value < 0.05 to be statistically significant, ignoring possible alpha inflation. The statistical analysis was carried out with the statistical software package R version 3.3.1 [34].

Results

Study population

A total of 898 women (749 obese and 149 normal weight) of the PEACHES cohort were eligible to be included in our analyses (Fig 1). Compared with women excluded from analysis due to missing data ($n = 259$), the included women were more likely to have a negative GDM test and had higher total GWG (S1 Table). Table 1 summarizes maternal and offspring characteristics of the study sample by GDM status and the presence or absence of late-pregnancy dysglycemia as indicated by a high or normal maternal HbA_{1c} level at delivery, respectively. More than one-third of obese women had a high HbA_{1c} value at delivery. In the subgroup of obese, GDM-negative women, 30% had a high HbA_{1c} value at delivery, whereas this proportion was 45% in the group of obese, GDM-positive women, who received various treatment regimens for their condition.

Testing for GDM was done using the 1-step procedure in 64% ($n = 571$) of obese and normal weight mothers, while 36% ($n = 327$) underwent the 2-step procedure. In the latter group, 66 had a positive GCT (1-h post-load glucose, median 10.2 mmol/l [IQR 2.5]), and 261 had a negative GCT (1-h post-load glucose, median 6.0 mmol/l [IQR 1.7]). A higher proportion of obese mothers diagnosed as GDM-negative underwent a 1-step compared to a 2-step GDM procedure (55.4%, 95% CI 50.8%–60.0%, versus 44.6%, 95% CI 40.0%–49.2%). However, despite the differences in the GDM test procedure used among these women, the proportion of obese, GDM-negative women who developed dysglycemia in late pregnancy was similar (1-step versus 2-step: 29.8%, 95% CI 24.1%–35.6%, versus 30.5%, 95% CI 24.1%–36.9%).

There was no noticeable difference in hemoglobin levels and red blood cell indices between obese, GDM-negative women with high compared to normal levels of HbA_{1c} at delivery (mean hemoglobin: 12.0 g/dl, 95% CI 11.8–12.2, versus 12.2 g/dl, 95% CI 12.0–12.4, and mean corpuscular hemoglobin: 28.6 pg, 95% CI 27.9–29.2, versus 28.9 pg, 95% CI 28.7–29.2). Those with high HbA_{1c} values at delivery had higher 75-g OGTT glucose concentrations, albeit below diagnostic cutoffs, at the time of GDM testing in pregnancy than those with normal HbA_{1c} values at delivery (S2 Table). Further, obese, GDM-negative women with a high HbA_{1c} at delivery had higher mean total and third-trimester GWG (Table 1). They were also more likely to have newborns with LGA birth weights, comparable to the proportion seen in obese, GDM-positive women with high HbA_{1c} values at delivery, and higher cord-blood C-peptide concentrations. In contrast to these women, obese, GDM-positive women had lower mean total and third-trimester GWG, irrespective of their HbA_{1c} level at delivery (Table 1), potentially due to risk awareness, treatment of GDM with insulin and/or diet, and tight supervised control.

Prenatal risk factors for increased childhood weight status

Offspring weight status was studied in children of obese and normal weight mothers until age 4 years (Fig 1). The follow-up rate in children was 88% at 4 years (S3 Table) without relevant differences in characteristics between those with and those without follow-up (S4 Table). Fig 2 shows the relation of prenatal risk factors with offspring BMI z-score at age 4 years. As expected, children of women with pre-conception obesity had a higher mean 4-year BMI z-score (0.60, 95% CI 0.46–0.74, versus 0.02, 95% CI −0.14 to 0.18) than children of normal weight women (Fig 2A). Surprisingly, further stratification by GDM status among obese mothers did not show any noticeable differences in offspring mean 4-year BMI z-score between the

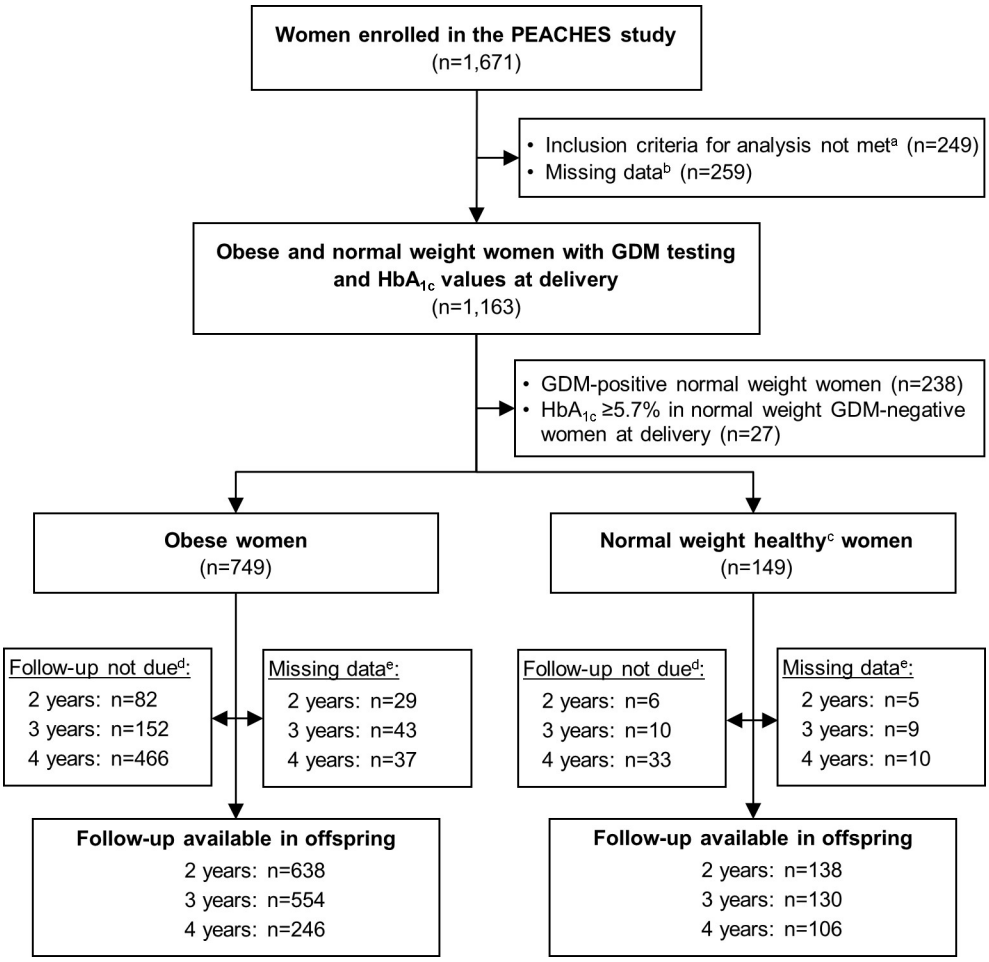

Fig 1. PEACHES study population and follow-up investigations of children. [a]Did not meet inclusion criteria for analysis including pre-conception obesity or normal weight, singleton live birth, and absence of type 1 diabetes and type 2 diabetes. [b]Missing information for at least 1 of the following variables: pre-conception body mass index group (normal weight or obese), GDM status (GDM-negative or GDM-positive), maternal HbA_{1c} at delivery (<5.7% [39 mmol/mol] or ≥5.7%), or confounding variables. [c]"Healthy" defined as GDM-negative and HbA_{1c} < 5.7% at delivery. [d]Offspring too young at the time of data retrieval from the PEACHES database. [e]Loss to follow-up or withdrawal from participation. GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening.

https://doi.org/10.1371/journal.pmed.1002681.g001

2 strata (0.62, 95% CI 0.44–0.79, versus 0.58, 95% CI 0.36–0.79) (Fig 2B). However, offspring of obese, GDM-negative women with high HbA_{1c} at delivery had a higher mean 4-year BMI *z*-score than offspring of obese, GDM-negative women with normal HbA_{1c} at delivery (1.01, 95% CI 0.68–1.35, versus 0.46, 95% CI 0.24–0.67) (Fig 2C). An analysis using HbA_{1c} as a continuous variable showed that among offspring of obese, GDM-negative mothers, the child's BMI *z*-score at 4 years increased by 0.07 (95% CI 0.01–0.12) for every 0.1% increase in maternal HbA_{1c} at delivery (S1 Fig).

Late-pregnancy dysglycemia and longitudinal offspring outcomes in early childhood

Offspring of obese, GDM-negative mothers with late-pregnancy dysglycemia had higher mean birth weight and cord-blood C-peptide concentration than newborns of the respective mothers with normal HbA_{1c} at delivery (Table 2). High (≥0.94 ng/ml [0.31 nmol/l]) cord-blood C-peptide

Table 1. Characteristics of the PEACHES study population: data on main exposure, maternal and offspring outcomes, and potential confounders.

Maternal/child characteristic	Normal weight mothers, GDM−, normal HbA_{1c}	Obese mothers stratified by glucometabolic status during pregnancy (GDM testing) and at delivery (HbA_{1c})			
		GDM−, normal HbA_{1c}	GDM−, high HbA_{1c}	GDM+, normal HbA_{1c}	GDM+, high HbA_{1c}
Maternal characteristics during pregnancy					
N	149	313	135	165	136
Age at conception, years	32.9 (4.8)	30.8 (5.1)	31.2 (5.9)	**32.6 (4.9)**	**32.8 (5.0)**
Pre-conception BMI, kg/m^2	21.9 (1.6)	36.2 (5.1)	36.8 (5.4)	36.3 (5.2)	**38.5 (5.5)**
Fasting glucose at GDM testing, mmol/l[a]	4.36 (0.44)	4.41 (0.40)	**4.52 (0.33)**	**5.30 (0.71)**	**5.65 (0.89)**
Smoking at any time during pregnancy	20 (13.4%)	84 (26.8%)	34 (25.2%)	42 (25.5%)	47 (34.6%)
GDM treatment					
Diet only	0 (0.0%)	0 (0.0%)	0 (0.0%)	**90 (54.6%)**	**63 (46.3%)**
Insulin and diet	0 (0.0%)	0 (0.0%)	0 (0.0%)	**54 (32.7%)**	**38 (27.9%)**
Insulin only	0 (0.0%)	0 (0.0%)	0 (0.0%)	**21 (12.7%)**	**35 (25.8%)**
Maternal characteristics at delivery					
Excessive total GWG	51 (34.2%)	209 (66.8%)	**104 (77.0%)**	**93 (56.4%)**	**75 (55.1%)**
Total GWG, kg	14.8 (4.9)	12.7 (7.5)	**14.9 (7.6)**	**9.8 (7.7)**	**10.8 (7.8)**
Excessive third-trimester GWG	75 (50.3%)	233 (74.4%)	**115 (85.8%)**	**78 (47.3%)**	**90 (66.7%)**
Third-trimester GWG, kg	5.0 (2.5)	5.2 (3.4)	**6.0 (3.5)**	**2.8 (3.6)**	**4.2 (3.8)**
HbA_{1c} at delivery, percent[b]	5.3 (0.2)	5.3 (0.2)	**5.9 (0.2)**	5.3 (0.3)	**6.0 (0.4)**
Child characteristics at birth					
Sex: female	77 (51.7%)	148 (47.3%)	60 (44.4%)	85 (51.5%)	65 (47.8%)
Gestational age, weeks	40.4 (1.2)	39.9 (1.5)	40.0 (1.4)	39.7 (1.3)	**39.5 (1.4)**
Birth weight, g	3,456 (438)	3,454 (450)	**3,676 (480)**	3,440 (468)	**3,569 (484)**
Birth weight: LGA	8 (5.4%)	21 (6.7%)	**23 (17.0%)**	15 (9.1%)	**24 (17.7%)**
Cord-blood C-peptide, ng/ml[c]	0.48 (0.36)	0.51 (0.34)	**0.60 (0.40)**	0.57 (0.41)	**0.63 (0.49)**
Breastfeeding (exclusive), ≥1 month	117 (78.5%)	166 (53.0%)	67 (49.6%)	83 (50.3%)	59 (43.4%)
Maternal characteristics postpartum					
N	47	86	37	52	46
Time after index pregnancy, years	4.4 (0.7)	3.9 (0.9)	**3.1 (0.9)**	3.6 (0.9)	**3.4 (0.8)**
BMI, kg/m^2	22.8 (1.9)	38.8 (6.7)	39.4 (6.8)	38.1 (5.6)	40.5 (7.3)
Waist-to-hip ratio	0.80 (0.05)	0.84 (0.06)	**0.87 (0.06)**	**0.87 (0.05)**	**0.88 (0.07)**
Percentage body fat by BIA, percent	29.5 (5.3)	46.3 (4.8)	46.4 (4.6)	45.4 (3.9)	46.6 (5.2)
Child age (months) at follow-up					
At 2-year follow-up	24.5 (1.3)	24.2 (1.1)	24.3 (1.2)	24.1 (1.3)	24.3 (1.2)
At 3-year follow-up	36.9 (1.1)	36.6 (1.0)	36.6 (1.0)	36.6 (1.3)	36.8 (1.3)
At 4-year follow-up	48.7 (1.5)	48.8 (1.0)	49.0 (1.3)	49.0 (1.0)	48.7 (0.9)

Data are mean (SD) or *n* (%) and tested with regard to the obese, GDM−, normal HbA_{1c} group using Student's *t* test for continuous and χ^2 test for categorical variables. High HbA_{1c} is $HbA_{1c} \geq 5.7\%$ (39 mmol/mol)]; normal HbA_{1c} is $HbA_{1c} < 5.7\%$. Bold font indicates $p < 0.05$. Participants with any missing information for baseline characteristics were excluded.

[a]GDM testing was performed at median 25 weeks and 3 days of gestation (interquartile range 3 weeks and 4 days). To convert glucose mmol/l to mg/dl, multiply by 18.018.

[b]To convert HbA_{1c} percent to mmol/mol: IFCC HbA_{1c} unit (mmol/mol) = [10.93 × DCCT/NGSP unit (%)] − 23.50.

[c]To convert C-peptide ng/ml to nmol/l, multiply by 0.331.

BIA, bioelectrical impedance analysis; BMI, body mass index; DCCT/NGSP, Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HbA_{1c}, glycated hemoglobin; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; LGA, large-for-gestational-age; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening; SD, standard deviation.

https://doi.org/10.1371/journal.pmed.1002681.t001

concentrations were associated with a 2-fold (RR 2.01, 95% CI 1.07–3.78) increase in the risk of LGA birth weight in these babies. At age 4 years, these children had higher mean BMI *z*-score than all other groups except for obese, GDM-positive women with high HbA_{1c} levels at delivery (S2 Fig). The slope of the BMI *z*-score curve between the ages of 2 and 4 years among children of

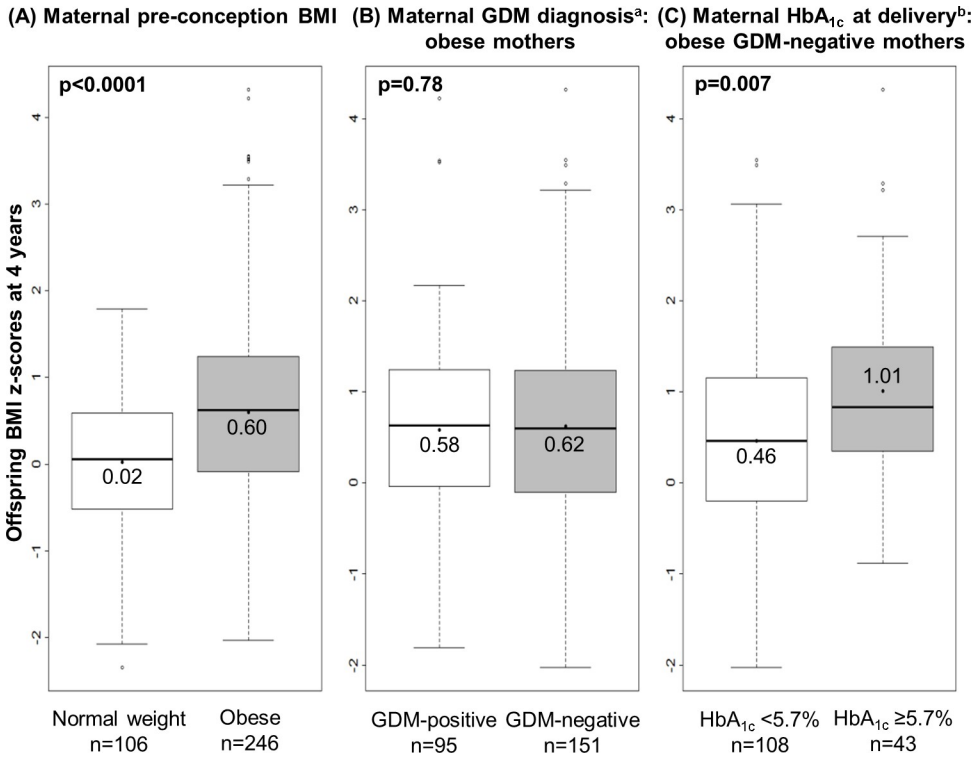

Fig 2. Offspring 4-year BMI *z*-score by maternal pre-conception weight status and glucometabolic status in pregnancy and at delivery. Stratification of maternal groups was performed in enrolled mother–child pairs with offspring 4-year BMI *z*-scores according to the (A) pre-conception BMI group of 352 mothers, (B) positive or negative testing for GDM in 246 obese women, and (C) HbA_{1c} at delivery in 151 obese, GDM-negative women. Data are shown as median (horizontal lines within the boxes), 25th and 75th centile (lower and upper boundaries of the boxes), 1.5 times the interquartile range (whisker ends), and outliers (circles). Numerical values and dots within the boxes represent unadjusted mean 4-year BMI *z*-score of offspring. Differences between groups were tested using Student's *t* test. [a]According to the International Association of Diabetes and Pregnancy Study Groups criteria [18]. [b]Dichotomized based on a predefined cutoff value of ≥5.7% (39 mmol/mol) [17]. BMI, body mass index; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin.

https://doi.org/10.1371/journal.pmed.1002681.g002

obese, GDM-negative mothers with high HbA_{1c} at delivery was positive (0.08), while it was negative (−0.10) among offspring of the respective mothers with normal HbA_{1c} at delivery, for a net difference in slope of 0.18 (95% CI 0.06–0.30) (Table 2). In contrast, birth outcomes, offspring BMI *z*-score slope, and 4-year BMI *z*-score were not different between obese, GDM-positive mothers with high versus normal maternal HbA_{1c} levels at delivery (S5 Table).

To quantify the contribution of late-pregnancy dysglycemia to increased BMI *z*-scores in children of obese, GDM-negative women, we conducted mediation analysis (Fig 3). Compared to offspring of normal weight women ($n = 106$), offspring of mothers with pre-conception obesity ($n = 151$) had 0.59 (95% CI 0.31–0.86) units higher BMI *z*-scores at age 4 years; following adjustment for HbA_{1c} at delivery (high versus normal), offspring of mothers with pre-conception obesity had 0.42 (95% CI 0.13–0.70) units higher BMI *z*-scores at 4 years. Consequently, the proportion of the effect of maternal obesity on offspring BMI *z*-score that is contributed by late-pregnancy dysglycemia was (0.59 − 0.42)/0.59 = 29%.

Excessive weight gain and deterioration of glucometabolic control in the last trimester following negative GDM testing

Next, we investigated whether weight gain has a role in triggering dysglycemia in the last trimester. Children of obese mothers with GDM who received treatment and weight monitoring

Table 2. Late-pregnancy dysglycemia in obese, GDM-negative mothers and offspring outcomes.

Child outcome	Control group (obese, GDM−, normal HbA_{1c})		Maternal late-pregnancy dysglycemia (obese, GDM−, high HbA_{1c})	
	N	Mean (95% CI)	*N*	Mean increment Δ (95% CI) with respect to control group
At delivery[a]				
Birth weight, g	313	3,454 (3,404 to 3,504)	135	**192 (100 to 284)**
Cord-blood C-peptide, ng/ml[b]	296	0.51 (0.47 to 0.55)	130	**0.10 (0.02 to 0.17)**
Long-term follow-up[c]				
BMI *z*-score change per year[d]	595	−0.10 (−0.17 to −0.03)	262	**0.18 (0.06 to 0.30)**
BMI *z*-score at 4 years[e]	108	0.46 (0.24 to 0.68)	43	**0.58 (0.18 to 0.99)**

Mean increments in offspring outcomes by high maternal HbA_{1c} (≥5.7% [39 mmol/mol]) at delivery are shown relative to the obese, GDM−, normal HbA_{1c} group. Bold font indicates $p < 0.05$.

[a]Based on linear regression models, adjusted for maternal pre-conception BMI, total gestational weight gain, maternal smoking at any time during pregnancy, and sex of the child.

[b]To convert C-peptide ng/ml to nmol/l, multiply by 0.331.

[c]Adjusted for maternal pre-conception BMI, total gestational weight gain, maternal smoking at any time during pregnancy, and exclusive breastfeeding ≥1 month.

[d]Based on linear mixed-effects model.

[e]Based on linear regression model.

BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin.

https://doi.org/10.1371/journal.pmed.1002681.t002

because of their diagnosis appeared to have better short- and long-term BMI outcomes than children of obese mothers who remained untreated following negative GDM testing and developed dysglycemia later on (Tables 2, S5 and 3). In offspring of obese, GDM-negative mothers (untreated) with late-pregnancy dysglycemia, the BMI *z*-score slope during the early childhood years was marginally increased (0.13, 95% CI −0.02 to 0.27) compared to that in offspring of obese, GDM-positive mothers (treated) (Table 3). We further found that obese, GDM-negative

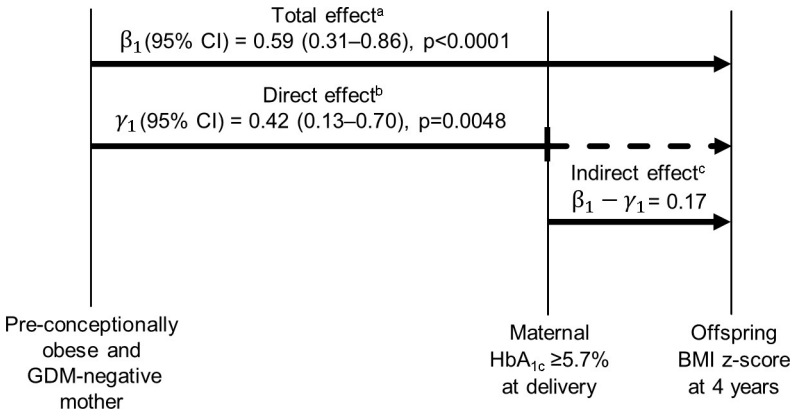

Fig 3. Contribution of late-pregnancy dysglycemia to the effect of maternal obesity on increased weight status in 4-year-old children. Mediation analysis was performed to study the total effect of pre-conception obesity in GDM-negative mothers on offspring BMI *z*-score at age 4 years, comprising the direct effect of maternal obesity and the indirect effect of late-pregnancy dysglycemia (as indicated by a high maternal HbA_{1c} [≥5.7%] at delivery). Data are coefficients derived from linear regression models, adjusted for maternal smoking at any time during pregnancy, total GWG, and exclusive breastfeeding ≥1 month. [a]Estimated as β_1 from: $BMIz_{4\ years} = \beta_0 + \beta_1 * \text{maternal obesity}_{yes/no} + \beta_2 * \text{maternal smoking}_{yes/no} + \beta_3 * \text{total GWG} + \beta_4 * \text{breastfeeding}_{yes/no}$ [b]Estimated as γ_1 from: $BMIz_{4\ years} = \gamma_0 + \gamma_1 * \text{maternal obesity}_{yes/no} + \gamma_2 * \text{maternal smoking}_{yes/no} + \gamma_3 * \text{total GWG} + \gamma_4 * \text{breastfeeding}_{yes/no} + \gamma_5 * HbA_{1c \geq 5.7\% \text{ or } <5.7\%}$. [c]Calculated as $\beta_1 - \gamma_1$ BMI, body mass index; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HbA_{1c}, glycated hemoglobin.

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Table 3. GDM status and late-pregnancy dysglycemia in obese mothers and offspring outcomes.

Child outcome	Control group (obese, GDM+, treated)		Obese, GDM−, high HbA_{1c} (untreated)	
	N	Mean (95% CI)	*N*	Mean increment Δ (95% CI) with respect to control group
At delivery[a]				
Birth weight, g	301	3,498 (3,444 to 3,552)	135	**134 (28 to 239)**
Cord-blood C-peptide, ng/ml[b]	286	0.60 (0.54 to 0.66)	130	−0.04 (−0.14 to 0.07)
Long-term follow-up[c]				
BMI *z*-score change per year[d]	576	−0.05 (−0.11 to 0.03)	262	0.13 (−0.02 to 0.27)
BMI *z*-score at 4 years[e]	95	0.58 (0.36 to 0.79)	43	**0.52 (0.07 to 0.97)**

Mean increments in offspring outcomes in obese, GDM−, high HbA_{1c} mothers are shown relative to the entire obese, GDM-positive group (regardless of HbA_{1c} level at delivery). Bold font indicates $p < 0.05$.

[a]Based on linear regression models, adjusted for maternal pre-conception BMI, total gestational weight gain, maternal smoking at any time during pregnancy, and sex of the child.

[b]To convert C-peptide ng/ml to nmol/l, multiply by 0.331.

[c]Adjusted for maternal pre-conception BMI, total gestational weight gain, maternal smoking at any time during pregnancy, and exclusive breastfeeding ≥1 month.

[d]Based on linear mixed-effects model.

[e]Based on linear regression model.

BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin.

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women with excessive GWG in the third trimester were more likely to have a high HbA_{1c} at delivery compared to those without excessive third-trimester GWG (RR 1.72, 95% CI 1.12–2.65).

Late-pregnancy dysglycemia in obese, GDM-negative women and their future diabetes risk

The relevance of late-pregnancy glucometabolic control in obese, GDM-negative women for their own metabolic health years after delivery (median 3.5 years [IQR 1.2]) was substantiated by follow-up data of the maternal PEACHES population (Tables 4 and S6; $n = 123$). At 3.5 years postpartum, HbA_{1c} and fasting and 1-h post-load glucose concentrations in obese, GDM-negative women with late-pregnancy dysglycemia were elevated, contributing to a 4-fold (RR 4.01, 95% CI 1.97–8.17) increased risk of developing T2DM or prediabetes, as compared to those with normal HbA_{1c} levels at delivery (absolute risk: 43.2% versus 10.5%).

Discussion

Identifying crucial periods of developmental programming is important for designing effective interventions [14], considering that obesity and diabetes in pregnancy are the major transgenerational health burden to date [35,36]. As yet, to our knowledge, the occurrence of dysglycemia in the last trimester of pregnancy despite prior negative testing for GDM has not been considered a problem for long-term health outcomes of obese pregnancies and thus has not been included in respective clinical care guidelines as part of routine monitoring [19]. Our data suggest that late-pregnancy dysglycemia predisposes the offspring of obese, GDM-negative mothers to alterations in weight development during early childhood. Moreover, offspring of obese mothers treated and monitored because of a diagnosis of GDM appeared to have a better BMI outcome in childhood than those of obese mothers who—following negative GDM testing—remained untreated in the last trimester and developed an abnormal glucose metabolism.

Table 4. Late-pregnancy dysglycemia in obese, GDM-negative mothers and glucose metabolism and T2DM/prediabetes risk 3.5 years postpartum[a].

Maternal outcome 3.5 years postpartum	Control group (obese, GDM−, normal HbA_{1c})		Maternal late-pregnancy dysglycemia (obese, GDM−, high HbA_{1c})	
	N	Mean (95% CI)	*N*	Mean increment Δ (95% CI) with respect to control group
HbA_{1c}, percent	86	5.19 (5.13 to 5.25)	37	**0.36 (0.25 to 0.46)**
Fasting glucose, mmol/l	86	4.77 (4.69 to 4.85)	37	**0.19 (0.05 to 0.33)**
1-h post-load glucose, mmol/l	84	7.06 (6.73 to 7.39)	37	**0.76 (0.13 to 1.38)**
2-h post-load glucose, mmol/l	84	5.68 (5.43 to 5.93)	37	0.21 (−0.28 to 0.69)
RR for T2DM/prediabetes[b]	86	1.00 (Ref.)	37	**4.01 (1.97 to 8.17)**

Mean increments in maternal postpartum parameters by high maternal HbA_{1c} (≥5.7% [39 mmol/mol]) at delivery are shown relative to the obese, GDM−, normal HbA_{1c} group. Data are based on linear regression models, adjusted for maternal body fat percentage 3.5 years postpartum. Bold font indicates $p < 0.05$.

[a]Maternal postpartum follow-up data not available in 325 obese, GDM-negative mothers due to loss to follow-up or withdrawal from participation (8.9%), consecutive pregnancy (10.8%), follow-up period too short (31.1%), or being currently in the time window for the follow-up visit (49.2%).

[b]Log-binomial regression model, adjusted for maternal body fat percentage 3.5 years postpartum. Presence of T2DM (fasting glucose ≥ 7.0 mmol/l or 2-h post-load glucose in 75-g OGTT ≥ 11.1 mmol/l or HbA_{1c} ≥ 6.5% [48 mmol/mol]) or prediabetes (fasting glucose 5.6 mmol/l to 6.9 mmol/l or 2-h post-load glucose in 75-g OGTT 7.8 mmol/l to 11.0 mmol/l or HbA_{1c} 5.7% to 6.4% [39 to 47 mmol/mol]) [22].

CI, confidence interval; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin; OGTT, oral glucose tolerance test; Ref., reference; RR, relative risk; T2DM, type 2 diabetes mellitus.

https://doi.org/10.1371/journal.pmed.1002681.t004

Our hypothesis of a possible relevance of dysglycemia in the last trimester for longitudinal offspring outcomes was based on data from mothers with pregestational diabetes. Several studies in non-obese women with T1DM or T2DM have shown an association of elevated third-trimester HbA_{1c} with a 2- to 5-fold increased risk of LGA birth weight [37,38]. Even among the offspring of GDM-negative mothers in our obese cohort, a high HbA_{1c} at delivery was associated with a similarly increased risk of LGA birth weight (RR 2.03, 95% CI 1.17–3.53). The apparent "vulnerability" during this time window goes along with intense differentiation of the fetal pancreatic islet cells that are adaptive to glucose supply. The resulting hyperinsulinemia and increased offspring growth may lead to an insulin secretory defect, contributing to a lifelong higher risk of developing overweight and T2DM, as shown in animal studies [39]. However, information on the possible long-term impact of a dysglycemic intrauterine milieu in the last trimester on the next generation's health in humans is scarce. Adult offspring of normal weight Danish mothers with T1DM and elevated blood glucose during late gestation presented with an increased risk of T2DM or prediabetes at age 22 years [40]. Earlier data from Pima Indians, among whom the prevalence of T2DM is extremely high, further suggest that offspring, as a result of their mothers' third-trimester glucose tolerance, may develop adverse outcomes over time [41]: their risk of obesity was most pronounced by the age of 10 to 14 years, in addition to abnormal glucose metabolism emerging several years later. However, maternal pre-conception BMI was not considered. Our data from obese pregnancies with negative GDM testing suggest that disturbances in maternal glucose homeostasis in the last gestational weeks play a role in faster weight gain and early manifestation of an increased weight status in offspring at preschool age. Glucometabolic control in the last trimester seems critical for future BMI development, considering that children of obese mothers diagnosed with GDM and treated in the last trimester appear to have more favorable outcomes.

We found that an increased HbA_{1c} at delivery indeed reflects late-pregnancy dysglycemia based on our finding of higher glucose concentrations in the 75-g OGTT at GDM testing during pregnancy, albeit below diagnostic cutoffs, in obese, GDM-negative women with high versus normal HbA_{1c} values at delivery, similar to our previous findings [17]. The increased cord-blood C-peptide concentrations in the offspring of obese women with high HbA_{1c} values at

delivery further suggest an exaggerated fetal response initiated by dysglycemic states in late pregnancy leading to macrosomia. These data are in keeping with the results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study showing associations between maternal glucose concentrations in a 75-g OGTT, even below diagnostic thresholds, and adverse pregnancy outcomes [21].

We hypothesized that dysglycemia at the end of such pregnancies might be among the factors that contribute to the association between maternal obesity at conception and later childhood overweight. The results of the mediation analysis suggested that reduction of dysglycemia by efficacious interventions in the third trimester could possibly ameliorate the weight gain of preschool children that is related to maternal pre-conception obesity by 29%. Modifying this and other early-life metabolic risks appears to be a promising target in the development of concepts for the prevention of offspring overweight.

A higher BMI in offspring of mothers with abnormal glucose regulation in pregnancy appears to take time to emerge. Follow-up studies in children up to age 2.5 years did not find a substantial impact of impaired maternal glucose metabolism in pregnancy on offspring obesity [42], and several studies have reported higher BMI *z*-scores beyond preschool age [43,44]. The emergence of an upward shift in BMI *z*-score slope and a higher weight status at a somewhat earlier age (4 years) in the offspring of obese, GDM-negative mothers with high HbA_{1c} in our study might be due to fetal exposure to an additionally obesogenic milieu in utero and an altered "glycemic threshold" in the last trimester. By contrast, the negative slope for BMI *z*-score in offspring of obese, GDM-negative mothers with normal HbA_{1c} at delivery is comparable to the BMI decline that precedes the adiposity rebound at 6 years in the general population [45] and at around 5 years in children of mothers with pre-conception obesity [46].

Since mechanisms underlying the decompensation of glucose homeostasis in late pregnancy in obese women are largely unknown, we speculated that influences associated with excessive GWG in the third trimester could play a role. Indeed, we found that obese, GDM-negative women with excessive GWG in the third trimester were at a considerably higher risk of developing dysglycemia in late pregnancy than those without excessive third-trimester GWG. Interestingly, the proportion of obese women with excessive GWG was higher in the GDM-negative than in the GDM-positive group (77.9%, 95% CI 74.0%–81.7%, versus 56.0%, 95% CI 50.3%–61.5%). Prior negative testing for GDM in obese women might have lowered their risk awareness relating to weight gain control, subsequently leading to excessive GWG in late pregnancy. In contrast to recent data suggesting that intervening at 28 weeks may be too late to improve short- and long-term outcomes [47], our findings suggest that monitoring late gestation in obese women may play a relevant role for childhood outcomes.

In extension of our previous findings on the relevance of late-pregnancy dysglycemia for later maternal health [17], we analyzed the risk of developing T2DM or prediabetes in obese women with a high HbA_{1c} at delivery despite negative GDM testing earlier in pregnancy. Based on cumulative prospective 3.5-year follow-up data from our maternal population, their prediabetes/T2DM risk was increased by 4-fold compared to those with normal glucose homeostasis throughout pregnancy. Interestingly, this risk was even higher than that reported in a meta-analysis of more than 4,000 obese, GDM-positive women (RR 2.85, 95% CI 2.21–3.69) [7]. Whether GDM treatment may have led to a lowered risk in these women is yet to be established, since evidence on the benefits of treatment for long-term maternal health is still limited to date [48].

The strengths of our study relate to the large contemporary mother–child PEACHES cohort, which is unique in the size of the population of obese mothers and the availability of trimester-specific data including HbA_{1c} at delivery as a marker of glycemic control in late pregnancy. Results are based on prospectively collected data, thus avoiding recall bias, and

included a variety of confounding and exposure data from medical documents, in particular on GCTs and OGTTs during pregnancy. Outcome data were ascertained by trained medical staff. There were no relevant differences between offspring and mothers with available and missing follow-up data, suggesting negligible selection bias. A follow-up time of 4 years in offspring appeared to be sufficient to identify relevant BMI increments for prediction of overweight later on, since an increased preschool BMI is known to be highly predictive for overweight and obesity in adolescence [49]. Besides the impact of late-pregnancy dysglycemia on childhood outcomes, we were also able to demonstrate the relevance of late pregnancy as a susceptible time window for later glucometabolic health in the maternal population.

A limitation could be that high maternal HbA_{1c} at delivery only reflects late-pregnancy dysglycemia: obese, GDM-negative mothers with a high HbA_{1c} at delivery also had higher glucose concentrations—although below diagnostic cutoffs—at the time of GDM testing in the second trimester than those with a normal HbA_{1c}. Therefore, we cannot rule out earlier priming effects on high offspring BMI *z*-scores at age 4 years, which might have already occurred in the second trimester. Additionally, a false-negative rate for detecting GDM of approximately one-third (18% to 40%) might be expected using the 50-g GCT (2-step procedure), due to its limited sensitivity [50–52]. However, among the obese, GDM-negative mothers, the proportion of high HbA_{1c} was similar irrespective of whether the 1-step or 2-step procedure was used, indicating that exposure group membership was not affected by the GDM test type. An analysis that excluded obese, GDM-negative mothers who underwent the 50-g GCT and developed late-pregnancy dysglycemia showed only a slightly lower difference in BMI *z*-score at age 4 years compared to the original analysis. Even though the rate of 1-step procedures across the participating recruitment departments ranged from 53% to 90%, this did not have an influence on the late-pregnancy dysglycemia in our study. There was also a change in the proportion of 1-step procedures performed over time (from initially more than 80% to about 30% at the end of recruitment) as a result of a change in coverage by the public health insurance system from the 1-step to the 2-step procedure in 2013 [53], which may have introduced misclassification bias. However, since maternal and child characteristics such as pre-conception BMI, total excessive GWG, and birth weight were not statistically noticeably different before and after the policy change, we do not anticipate that this change in practice influenced the associations found in the current study. Further, besides indicating glycemic status, HbA_{1c} variation may be prone to influences by non-glycemic factors such as ethnicity, age, and some diseases that may result in states of high or low glycation [23]. However, we obtained detailed information on factors that account for the biological variation in HbA_{1c}, in particular iron deficiency anemia [54], and analytical and pre-analytical variation in HbA_{1c} measurements was low. The PEACHES cohort is a convenience sample, and we excluded women due to missing data, both of which factors may limit the generalizability of our findings. The overarching study hypotheses are outlined in the study protocol, and our results confirm these hypotheses in general. However, the specific modeling is hypothesis-generating, and its adequacy needs to be validated with more data from the PEACHES cohort. The effect found in the current study is the result of an unplanned interim analysis, and, therefore, alpha error inflation may have resulted in a higher type I error compared to the standard of 5%. However, this issue will be settled after analysis of the full dataset. The results of the interim analysis will have no influence on the further conduct of the study (such as changing follow-up or procedures); recruitment of pregnant women was completed before starting to work on this paper. Also, validation of our findings in other studies and settings is required to improve our understanding of late-pregnancy dysglycemia and its potential implications for the long-term health of the obese mother and her child.

Together, our data point to the necessity of guidelines for identifying and managing late-pregnancy complications in obese pregnancies with negative GDM testing. Screening and diagnosis of GDM is highly valuable, but dysglycemia may still arise in the last trimester, particularly in obese women. Our findings suggest that negative GDM testing at the end of the second trimester in obese pregnancies cannot be considered an "all-clear signal" and should not lead to reduced physician attention, care, and advice. Further, a false sense of security in obese, GDM-negative mothers who consider themselves unexposed to late-pregnancy dysglycemia may result in uncontrolled excessive weight gain due to unfavorable lifestyle behaviors in the last trimester. Therefore, obese women, specifically those with a negative GDM test result, require counseling on their persisting late-pregnancy risks. Tailored BMI-dependent advice including dietary therapy for late-pregnancy glycemic and weight gain control appears to be a suitable intervention. In addition, we suggest monitoring fasting glucose and HbA_{1c} at least once during the third trimester in obese women who were negative for GDM. Retesting these markers at delivery might help to identify "at risk" mother–child pairs for closer preventive health follow-ups.

Supporting information

S1 STROBE Checklist.
(DOC)

S1 Fig. Graph showing linear relationship between maternal HbA_{1c} at delivery and BMI *z*-score in 4-year-old offspring of obese, GDM-negative mothers. Adjusted for maternal preconception BMI, total gestational weight gain, maternal smoking at any time during pregnancy, and exclusive breastfeeding ≥1 month. BMI, body mass index; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin.
(TIF)

S2 Fig. Offspring 4-year BMI *z*-score according to maternal groups defined by pre-conception BMI, GDM status, and HbA_{1c} value at delivery. The group of GDM–, HbA_{1c}+ mothers was compared with all other maternal groups using 1-way analysis of variance (ANOVA) and post hoc testing. Data are shown as median (horizontal lines within the boxes), 25th and 75th centile (lower and upper boundaries of the boxes), 1.5 times the interquartile range (whisker ends), and outliers (circles). Numerical values and dots within the boxes represent unadjusted mean 4-year BMI *z*-score of offspring. GDM status is according to the International Association of Diabetes and Pregnancy Study Groups criteria [18]. HbA_{1c} dichotomized based on a predefined cutoff value of ≥5.7% (39 mmol/mol) [17]. BMI, body mass index; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin; HbA_{1c}–, $HbA_{1c} < 5.7\%$ (39 mmol/mol); HbA_{1c}+, $HbA_{1c} \geq 5.7\%$.
(TIF)

S1 Study Protocol.
(DOCX)

S1 Table. Comparison of relevant characteristics of the study participants included and excluded from analysis due to missing data.
(DOCX)

S2 Table. Glucose concentrations of a 75-g OGTT at GDM testing among obese, GDM-negative mothers stratified according to their HbA_{1c} at delivery.
(DOCX)

S3 Table. Offspring follow-up rates at different ages in women included in the present analysis.
(DOCX)

S4 Table. Comparison of relevant characteristics in normal weight and obese mothers with available and missing offspring follow-up at 4 years of age.
(DOCX)

S5 Table. Late-pregnancy dysglycemia in obese, GDM-positive mothers and offspring outcomes.
(DOCX)

S6 Table. Comparison of relevant characteristics in obese, GDM-negative women with available and missing maternal follow-up visit 3.5 years postpartum.
(DOCX)

Acknowledgments

We are grateful to all participants, physicians, and midwives involved in the PEACHES study, including Rainer Pankau, Finkelstein-Klinik für Kinder- und Jugendmedizin, Heidekreis-Klinikum, Walsrode (northern Germany). We thank Susanne Wullinger, Department of Pediatrics, University Hospital, Ludwig-Maximilians-Universität München, for excellent technical assistance. We also thank Sarah Perschbacher, Institute of Social Paediatrics and Adolescent Medicine, Division of Epidemiology, Faculty of Medicine, Ludwig-Maximilians-Universität München, and Beate Landsberg, Department of General Pediatrics, Neonatology and Pediatric Cardiology, Division of Experimental Pediatrics and Metabolism, University Children's Hospital, Faculty of Medicine, Heinrich Heine University Düsseldorf, for helpful discussions.

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S1 STROBE Checklist.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Author's Response
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and Abstract, "Methods and findings".
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, "Background" and "Methods and findings".
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction, paragraphs 1 to 4.
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, paragraph 4.
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, "Study design and participants".
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, "Study design and participants", "Procedures". Fig 1. S3 Table.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods, "Study design and participants", "Inclusion criteria for analysis", "Outcome variables". S1 Table.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not available
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, "Procedures".
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, "Procedures".
Bias	9	Describe any efforts to address potential sources of bias	Methods, "Exposure variables" and "Statistical analysis". Discussion, paragraph 8-9. S1 Table, S4 Table, S6 Table.

Study size	10	Explain how the study size was arrived at	Results, “Study population”. Fig 1, Table 1, S1 Table, S3 Table, S4 Table, S6 Table.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods, “Procedures”. Results, “Study population”. Table 1.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods, “Statistical analysis”.
		(*b*) Describe any methods used to examine subgroups and interactions	Methods, “Statistical analysis”.
		(*c*) Explain how missing data were addressed	Methods, “Inclusion criteria for analysis”, “Statistical analysis”. Results, “Study population”. Discussion, paragraph 8/9. Table 1, footnote. Table 4, footnote. Fig 1, S1 Table, S3 Table, S4 Table, S6 Table.
		(*d*) If applicable, explain how loss to follow-up was addressed	Any losses to follow-up were excluded from analysis. Methods, “Statistical analysis”. Figure 1, footnote. Table 4, footnote. S3 Table, S4 Table, S6 Table.
		(*e*) Describe any sensitivity analyses	We conducted different subgroup analyses to study the robustness of our results. Confirmatory analysis: Results, “Late-pregnancy dysglycemia in obese, GDM-negative women and their future diabetes risk”. Table 4. Discussion, paragraph 7 and 9.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, “Study population” and “Late-pregnancy dysglycemia and longitudinal offspring outcomes in early childhood”. Fig 1, Fig 2. Tables 1 to 4. S1 to S6 Tables. S2 Fig.
		(b) Give reasons for non-participation at each stage	Fig 1, Table 4, footnote.

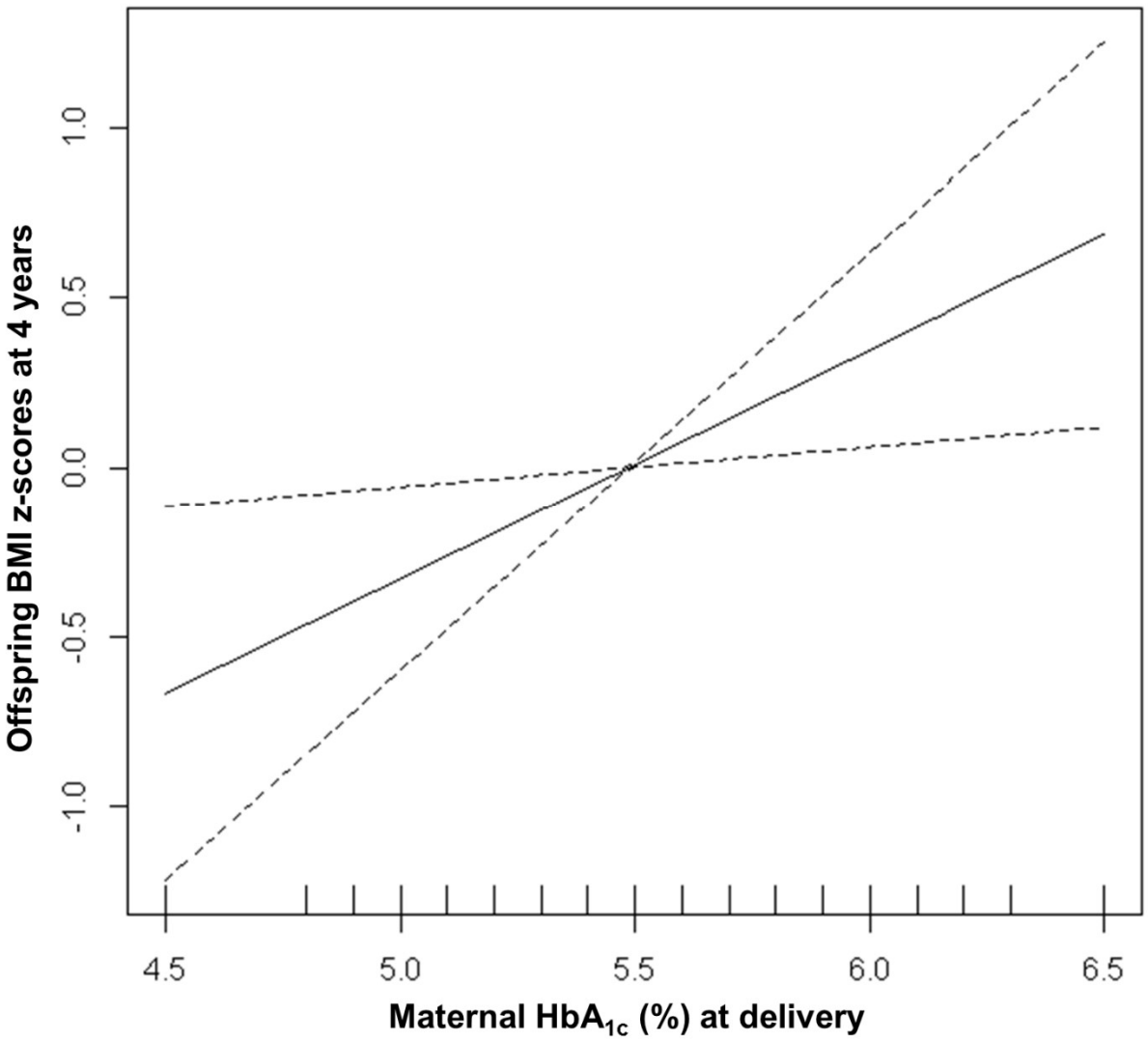
			S1 Table, S3 Table, S4 Table, S6 Table.
		(c) Consider use of a flow diagram	Fig 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results, “Study population”, Table 1, S1 Table, S4 Table, S6 Table.
		(b) Indicate number of participants with missing data for each variable of interest	Number of participants with complete data are given in the following figures and tables: Fig 1, Fig 2. Tables 1 to 4. S2 Fig. S1 to S6 Tables. Participants with any missing data were excluded from analysis.
		(c) Summarise follow-up time (eg, average and total amount)	Methods, “Offspring weight and metabolic outcomes”. Results, “Prenatal risk factors for increased childhood weight status”, “Late-pregnancy dysglycemia in obese, GDM-negative women and their future diabetes risk”. Tables 1 to 4, Fig 1, S3 Table. S5 Table.
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results, “Prenatal risk factors for increased childhood weight status”. Tables 2 to 4. Fig 2 and Fig 3. S1 and S5 Table. S2 Fig.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Methods, “Statistical analysis”. Results, “Prenatal risk factors for increased childhood weight status”, “Late-pregnancy dysglycemia and longitudinal offspring outcomes in early childhood”, “Excessive weight gain and deterioration of glucometabolic control in the last trimester following negative GDM testing”,

			"Late-pregnancy dysglycemia in obese, GDM-negative women and their future diabetes risk". Table 2 (footnote), Table 3 (footnote), Table 4 (footnote), Fig 3 (footnote), S1 Fig (footnote), S5 Table (footnote).
		(*b*) Report category boundaries when continuous variables were categorized	Methods, "Exposure variables" and "Offspring weight and metabolic outcomes".
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results, "Late-pregnancy dysglycemia in obese, GDM-negative women and their future diabetes risk"
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	We conducted different subgroup analyses to study the robustness of our results. Mediation analysis: Results, "Late-pregnancy dysglycemia and longitudinal offspring outcomes in early childhood", Fig 3. Confirmatory analysis: Results, "Late-pregnancy dysglycemia in obese, GDM-negative women and their future diabetes risk", Table 4. Discussion, paragraph 7 and 9.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion, paragraph 1.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, paragraph 9.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, paragraphs 2 to 3, 5 to 7, 9.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, paragraph 9.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original	Submission form, information in "Financial Disclosure" field.

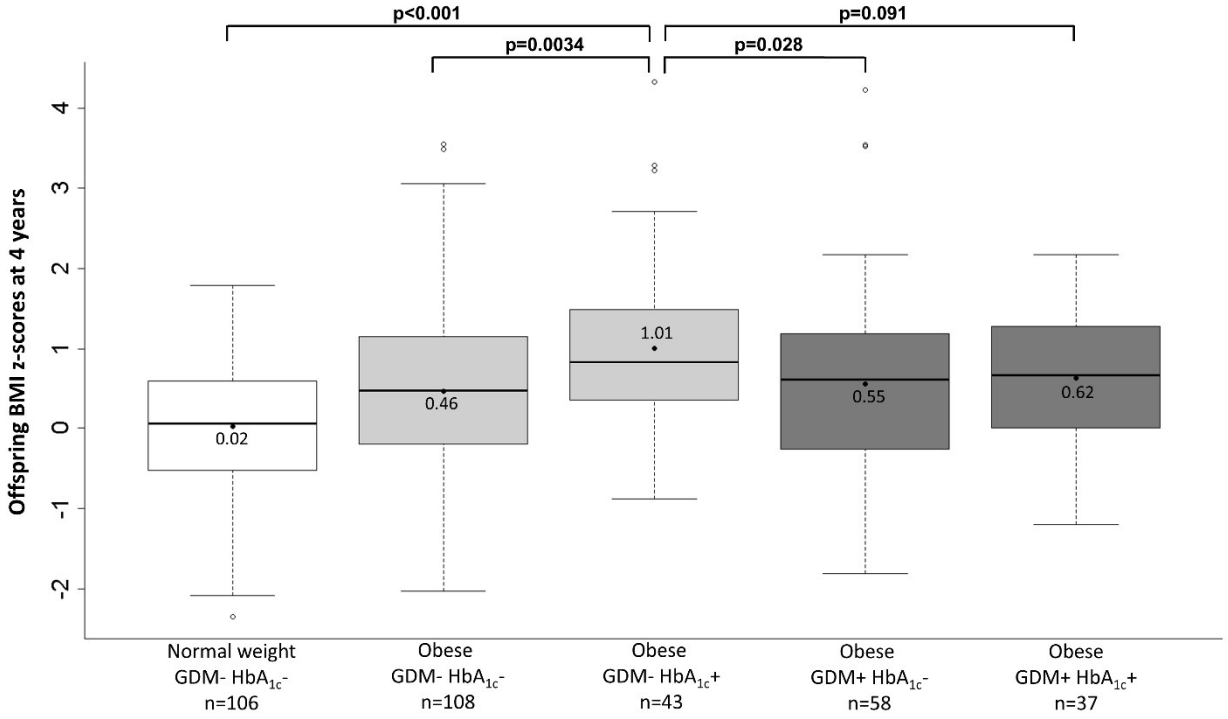
		study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.



S1 Fig. Graph showing linear relationship between maternal HbA_{1c} at delivery and BMI z-score in 4-year-old offspring of obese, GDM-negative mothers. Adjusted for maternal pre-conception BMI, total gestational weight gain, maternal smoking at any time during pregnancy, and exclusive breastfeeding ≥1 month. BMI, body mass index; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin.



S2 Fig. Offspring 4-year BMI z-score according to maternal groups defined by pre-conception BMI, GDM status, and HbA1c value at delivery. The group of GDM−, HbA_{1c}+ mothers was compared with all other maternal groups using 1-way analysis of variance (ANOVA) and post hoc testing. Data are shown as median (horizontal lines within the boxes), 25th and 75th centile (lower and upper boundaries of the boxes), 1.5 times the interquartile range (whisker ends), and outliers (circles). Numerical values and dots within the boxes represent unadjusted mean 4-year BMI z-score of offspring. GDM status is according to the International Association of Diabetes and Pregnancy Study Groups criteria [18]. HbA_{1c} dichotomized based on a predefined cutoff value of ≥5.7% (39 mmol/mol) [17]. BMI, body mass index; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin; HbA_{1c} −, HbA_{1c} < 5.7% (39 mmol/mol); HbA_{1c} +, HbA_{1c} ≥ 5.7%.

S1 Study Protocol.

Study protocol: Does childhood overweight start *in utero*?
Prospective study on “at risk” children of obese mothers to evaluate candidate markers for adiposity risk

PEACHES: Programming of **E**nhanced **A**diposity Risk in **CH**ildhood – **E**arly **S**creening

Project lead: Regina Ensenauer

Background

The prevalence of overweight and obesity among children and adolescents has increased over the last two decades and has become a major public health problem (174, 175)]. According to the results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS), 15% of children and adolescents in Germany are overweight and 6.3% are obese (176)]. Current treatment methods to reduce obesity and to mitigate complications such as insulin resistance and dyslipidemia are not considered to be successful (177)], which emphasizes the importance of the development of obesity prevention concepts.

Evidence for new approaches for primary prevention has emerged from epidemiological and animal studies, suggesting that certain environmental factors during early childhood and the maternal milieu *in utero* during fetal development may have long-term consequences for human health throughout the life span. A multitude of studies have found relationships between fetal development and later risk for diseases such as diabetes or cardiovascular problems in adulthood (178-183)]. In addition, there is evidence for an association between the development of overweight/obesity and metabolic influences on fetal development via poorly defined mechanisms called "fetal programming" (184, 185)]. Scientific data suggest that an increased pre-pregnancy maternal body mass index (BMI) is a risk factor for later childhood overweight. Additionally, gestational diabetes mellitus (GDM), which occurs more often in obese pregnant women, increases the child’s risk of becoming overweight and developing diabetes later in life. Recent data also suggest a potential “programming” effect of maternal weight gain during pregnancy on the fetal metabolic environment. Moreover, maternal obesity and GDM place the mother at a higher risk for adverse health outcomes such as type 2 diabetes or metabolic syndrome (abdominal obesity, elevated triglyceride levels, decreased HDL cholesterol levels, increased blood pressure, elevated fasting glucose levels) (186)].

A number of biomarkers are already established for the biochemical characterization of overt obesity (187)]. However, these do not permit any or only very limited conclusions regarding obesity risk. Such new "risk" biomarkers (e.g. metabolites) are currently not available but are essential for the safe management of early-onset nutritional prevention strategies in future clinical trials. In the prospective mother-child cohort study PEACHES, biomarker candidates for the early detection of obesity risk will be evaluated in "high-risk" newborns of obese mothers, who will have longitudinal follow-up throughout early childhood until the age of 5 years. Further, as a subproject of the PEACHES study, mothers with an increased “gestational risk profile” such as obesity will be evaluated for cardiometabolic dysfunction several years postpartum.

Hypotheses and Aims

Hypotheses:

1. Overt obesity is defined by systemic-metabolic dysregulation in the intermediary metabolism.

2. The effects of metabolic dysregulation before and/or during pregnancy are associated with the risk of subsequent overweight/obesity in the child.

3. The metabolic dysregulation that is associated with the risk of offspring overweight/obesity cannot be detected clinically at birth or in early life.

4. Changes in biomarker profiles in the child’s cells represent this systemic dysregulation of the intermediary metabolism at birth or in early life as an indicator for the risk of obesity.

Aim:
The aim is to derive early prognostic biomarker(s) for childhood obesity risk.

Study population

PEACHES is a prospective cohort study with two different study groups and two control groups. Study group 1 consists of obese women (pre-pregnancy BMI ≥ 30 kg/m²) without GDM and study group 2 consists of obese women with GDM. Accordingly, control group 1 consists of normal weight women (pre-pregnancy BMI ≥ 18.5 ≤ 24.9 kg/m²) without GDM, while control group 2 consists of normal weight women with GDM.

Sample size

The sample size for the PEACHES study was calculated by Prof. Dr. Ulrich Mansmann, Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Faculty of Medicine, Ludwig-Maximilians-Universität München, Munich, Germany.

Assumptions for the calculation:

- The prevalence of obesity in pre-school children of obese mothers (BMI at conception ≥ 30 kg/m²) is 23% (117, 188)].
- The odds ratio for the offspring to be obese (versus not obese) is 3. This strong effect was based on previous findings from various studies.
- The significance level was set at 5% and the power at 80%.

Assuming that 20% of children of obese mothers with a dysregulated biomarker profile and 20% of children of obese mothers with a non-dysregulated biomarker profile are at risk of developing obesity, *n*=184 obese pregnant women should be included in the study. Assuming that 40% of children of obese mothers with a dysregulated biomarker profile and 15% of children of obese mothers with a non-dysregulated biomarker profile are at risk of developing obesity, *n*=157 obese women should be included in the study. Assuming a 30 to 40% drop-out rate up to the examination time point at age 5 years, 300 obese pregnant women (study group 1) should be recruited. In addition, 30 normal weight healthy controls (control group 1) will also be recruited. This will facilitate the assessment of the prenatal influence of maternal obesity on a possible dysregulation of the biomarker panel at birth.

For the calculation of the study group of obese mothers with GDM, the same assumptions are made. It is therefore necessary to recruit an additional 300 obese mothers with GDM (study group 2) and 30 normal weight women with GDM (control group 2).

Examination schedule

Children will be examined at birth, at 3 to 4 months and 5 years of age. A study questionnaire will be mailed to the families 6 to 8 weeks after birth and then annually thereafter until age 5 years. Mothers will be examined 3 years postpartum.

Variables

Exposure variables. Maternal pre-pregnancy obesity, GDM status, and metabolic risk markers such as maternal HbA_{1c} at delivery and offspring metabolites in cord blood.

Outcome variables. Offspring outcomes at birth: Birth weight, large-for-gestational-age (LGA) birth weight, cord-blood C-peptide concentration.

Offspring longitudinal weight status: Offspring age- and sex-specific BMI *z*-score at follow-up visits and well-child visits, as well as waist circumference at 5 years.

Maternal postpartum follow-up: Development of prediabetic/diabetic conditions based on maternal HbA_{1c} and glucose concentrations following an oral glucose tolerance test, body weight, height, fat mass, waist and hip circumferences, blood pressure, intima media thickness, pulse wave analysis, and genetic markers.

Other variables. Other maternal and child information that is collected includes socioeconomic status, maternal health and risk factors during pregnancy (such as smoking, pregnancy weight gain, hypertension), maternal health behaviors postpartum, breastfeeding, and the child's health behaviors including nutritional status.

Statistical analysis

- Descriptive analysis of baseline characteristics relating to maternal and offspring factors will be conducted using Student's *t* test for continuous and chi-square test for categorical variables.

- Univariable and multivariable linear and logistic regression models will be used to estimate the associations between risk markers and continuous and categorical outcomes such as BMI, LGA birth weights, childhood overweight, and maternal prediabetic/diabetic conditions postpartum.

- Multivariable logistic regression models will be used to predict the categorical outcomes from candidate markers such as maternal HbA_{1c} at delivery; variable selection will be done using shrinkage methods. Diagnostic properties of the models for the prediction of the outcomes from candidate markers and other variables will be assessed using receiver operating characteristic (ROC) analysis with k-fold cross validation.

All analyses will be conducted in the statistical software package R.

Sources of funding

The study is supported by the German Federal Ministry of Education and Research grant 01EA1307 to Regina Ensenauer and the Foundation for Cardiovascular Prevention in Childhood, Ludwig-Maximilians-Universität München, Munich, Germany.

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S1 Table: Comparison of relevant characteristics of the study participants included and excluded from analysis due to missing data.

	Included (n=898)		**Excluded due to missing data[a] (n=259)**		***p*-value**
	N		*N*		
Maternal characteristics during pregnancy					
Pre-conception BMI, kg/m^2 [b]	896	34.3 (7.4)	244	34.3 (7.6)	1
Fasting glucose at GDM testing, mmol/l[c]	630	4.88 (0.80)	117	5.03 (0.83)	0.080
GDM diagnosis: negative	898	**597 (66.5%)**	148	**82 (55.4%)**	**0.012**
Smoking at any time during pregnancy	898	227 (25.3%)	254	63 (24.8%)	0.94
Maternal characteristics at delivery					
Total GWG, kg	898	**12.6 (7.5)**	239	**11.4 (7.1)**	**0.022**
Excessive third-trimester GWG	896	591 (66.0%)	241	153 (63.5%)	0.52
Third-trimester GWG, kg	896	4.7 (3.5)	248	4.7 (3.9)	0.84
HbA_{1c} at delivery, percent[d]	898	5.50 (0.39)	176	5.53 (0.36)	0.41
HbA_{1c} ≥5.7% at delivery	898	271 (30.2%)	176	56 (31.8%)	0.73
Child characteristics at birth					
Sex: female	898	435 (48.4%)	259	125 (48.3%)	1
Birth weight, g	898	3,502 (468)	259	3,499 (505)	0.92
Birth weight: LGA	898	91 (10.1%)	259	22 (8.5%)	0.68
Breastfeeding (exclusive), ≥1 month	898	492 (54.8%)	242	124 (51.2%)	0.36
BMI z-score at 4 years	352	0.43 (1.08)	144	0.49 (1.05)	0.53

Data are mean (SD) or *n* (%), Student's *t* test for continuous and χ^2 test for categorical variables. Bold font indicates $p < 0.05$. Participants with any missing information for baseline characteristics were excluded.

[a]Missing data in at least one of the following variables including pre-conception BMI group (normal weight or obese), GDM status (GDM-negative or GDM-positive), maternal HbA_{1c} at delivery (<5.7% [39 mmol/mol] or ≥5.7%), or confounding variables.

[b]Two women with missing pre-conception BMI (kg/m^2) but available pre-conception BMI group (normal weight or obese) were included in the analyses.

[c]GDM testing was performed at median 25 weeks and 3 days of gestation (interquartile range 3 weeks and 4 days). To convert glucose mmol/l to mg/dl, multiply by 18.018.

[d]To convert HbA_{1c} percent to mmol/mol: IFCC HbA_{1c} unit (mmol/mol) = [10.93 × DCCT/NGSP unit (%)] − 23.50.

BMI, body mass index; DCCT/NGSP, Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HbA_{1c}, glycated hemoglobin; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; LGA, large-for-gestational-age; SD, standard deviation.

S2 Table: Glucose concentrations of a 75-g OGTT at GDM testing among obese, GDM-negative mothers stratified according to their HbA_{1c} at delivery.

Maternal glucose concentrations (mmol/l)[a]	***N***	**Obese, GDM−, normal HbA_{1c}**	***N***	**Obese, GDM−, high HbA1c**
Fasting	186	4.41 (4.35 to 4.47)	80	**4.52 (4.44 to 4.60)**
1-h post-load	185	7.15 (6.95 to 7.35)	81	**7.66 (7.39 to 7.93)**
2-h post-load	177	5.68 (5.52 to 5.84)	75	**6.14 (5.92 to 6.36)**

Data are mean (95% CI), and *p*-values are from Student's *t* test. High HbA_{1c} is $HbA_{1c} \geq 5.7\%$ (39 mmol/mol)]; normal HbA_{1c} is $HbA_{1c} < 5.7\%$. Bold font indicates $p < 0.05$.
[a]GDM testing was performed at median 25 weeks and 3 days of gestation (interquartile range 3 weeks and 4 days). To convert glucose mmol/l to mg/dl, multiply by 18.018.
CI, confidence interval; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin; OGTT, oral glucose tolerance test.

S3 Table: Offspring follow-up rates at different ages in women included in the present analysis.

Offspring age	Follow-up	Normal weight mothers, GDM−, normal HbA_{1c}	Obese mothers stratified by glucometabolic status during pregnancy (GDM testing) and at delivery (HbA_{1c})				Total
			GDM−, normal HbA_{1c}	GDM−, high HbA_{1c}	GDM+, normal HbA_{1c}	GDM+, high HbA_{1c}	
2 years	Missing[a]	5 (3.5%)	13 (4.7%)	2 (1.7%)	5 (3.4%)	9 (7.1%)	34 (4.2%)
	Available	138 (96.5%)	262 (95.3%)	116 (98.3%)	143 (96.6%)	117 (92.9%)	776 (95.8%)
	Total	143 (100%)	275 (100%)	118 (100%)	148 (100%)	126 (100%)	810 (100%)
3 years	Missing[a]	9 (6.5%)	17 (7.0%)	7 (6.4%)	10 (7.6%)	9 (8.0%)	52 (7.1%)
	Available	130 (93.5%)	225 (93.0%)	103 (93.6%)	122 (92.4%)	104 (92.0%)	684 (92.9%)
	Total	139 (100%)	242 (100%)	110 (100%)	132 (100%)	113 (100%)	736 (100%)
4 years	Missing[a]	10 (8.6%)	17 (13.6%)	3 (6.5%)	5 (7.9%)	12 (24.5%)	47 (11.8%)
	Available	106 (91.4%)	108 (86.4%)	43 (93.5%)	58 (92.1%)	37 (75.5%)	352 (88.2%)
	Total	116 (100%)	125 (100%)	46 (100%)	63 (100%)	49 (100%)	399 (100%)

Data are *n* (%). High HbA_{1c} is $HbA_{1c} \geq 5.7\%$ (39 mmol/mol)]; normal HbA_{1c} is $HbA_{1c} < 5.7\%$.
[a]Loss to follow-up or withdrawal from participation.
GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin.

S4 Table: Comparison of relevant characteristics in normal weight and obese mothers with available and missing offspring follow-up at 4 years of age.

Offspring follow-up at 4 years	**Normal weight mothers, GDM−, normal HbA_{1c}**			**Obese mothers stratified by glucometabolic status during pregnancy (GDM testing) and at delivery (HbA_{1c})**											
				GDM−, normal HbA_{1c}			**GDM−, high HbA_{1c}**			**GDM+, normal HbA_{1c}**			**GDM+, high HbA_{1c}**		
	Available	**Missing[a]**	***p*-value**	**Available**	**Missing[a]**	***p*-value**	**Available**	**Missing[a]**	***p*-value**	**Available**	**Missing[a]**	***p*-value**	**Available**	**Missing[a]**	***p*-value**
Maternal characteristics during pregnancy															
N	106	10		108	17		43	3		58	5		37	12	
Pre-conception BMI, kg/m^2	21.9 (1.6)	21.5 (1.4)	0.43	36.7 (4.9)	36.0 (3.3)	0.48	36.7 (5.3)	40.5 (7.6)	0.48	36.7 (4.5)	36.3 (4.1)	0.89	39.1 (5.3)	36.7 (5.2)	0.18
Fasting glucose at GDM testing, mmol/l[b]	4.36 (0.44)	4.29 (0.60)	0.78	4.37 (0.43)	4.58 (0.33)	0.06	4.51 (0.33)	4.66 (0.07)	0.10	5.21 (0.81)	5.07 (0.50)	0.59	5.67 (0.82)	5.77 (1.51)	0.84
Smoking at any time during pregnancy	17 (16.0%)	1 (10.0%)	0.96	**22 (20.4%)**	**9 (52.9%)**	**0.010**	8 (18.6%)	1 (33.3%)	1	17 (29.3%)	3 (60.0%)	0.36	11 (29.7%)	4 (33.3%)	1
Maternal characteristics at delivery															
Total GWG, kg	14.8 (4.4)	15.8 (5.0)	0.55	13.3 (7.5)	14.9 (5.4)	0.29	15.7 (6.2)	11.8 (2.5)	0.09	11.3 (8.6)	12.3 (5.1)	0.70	10.9 (5.7)	10.3 (8.3)	0.83
Excessive third-trimester GWG	55 (51.9%)	7 (70.0%)	0.44	83 (76.9%)	14 (82.4%)	0.85	39 (90.7%)	2 (66.7%)	0.74	33 (57.9%)	4 (80.0%)	0.62	22 (61.1%)	9 (75.0%)	0.60
Third-trimester GWG, kg	5.06 (2.21)	5.55 (2.80)	0.60	5.32 (3.39)	7.29 (4.71)	0.11	6.00 (2.92)	6.37 (4.01)	0.89	3.82 (3.64)	5.24 (2.87)	0.35	3.77 (2.94)	3.52 (4.12)	0.85
HbA_{1c} at delivery, percent[c]	5.25 (0.25)	5.31 (0.25)	0.52	5.32 (0.23)	5.31 (0.22)	0.76	5.89 (0.21)	6.03 (0.35)	0.56	5.32 (0.21)	5.40 (0.17)	0.38	5.96 (0.31)	6.23 (0.96)	0.35

S4 Table (continued): Comparison of relevant characteristics in normal weight and obese mothers with available and missing offspring follow-up at 4 years of age.

Offspring follow-up at 4 years	**Normal weight, GDM−, normal HbA_{1c}**			**Obese mothers stratified by glucometabolic status during pregnancy (GDM testing) and at delivery (HbA_{1c})**											
				GDM−, normal HbA_{1c}			**GDM−, high HbA_{1c}**			**GDM+, normal HbA_{1c}**			**GDM+, high HbA_{1c}**		
	Available	**Missing[a]**	***p*-value**	**Available**	**Missing[a]**	***p*-value**	**Available**	**Missing[a]**	***p*-value**	**Available**	**Missing[a]**	***p*-value**	**Available**	**Missing[a]**	***p*-value**
Child characteristics at birth															
Sex: female	55 (51.9%)	5 (50.0%)	0.58	51 (47.2%)	9 (52.9%)	0.86	16 (37.2%)	3 (100.0%)	0.17	32 (55.2%)	3 (60.0%)	1	16 (43.2%)	5 (41.7%)	1
Birth weight, g	3,465 (421)	3,608 (524)	0.42	3,481 (465)	3,454 (328)	0.77	3,599 (487)	3,620 (334)	0.93	3,450 (486)	3,782 (455)	0.18	3,696 (540)	3,719 (432)	0.88
Birth weight: LGA	4 (3.8%)	2 (9.5%)	0.09	6 (5.6%)	0 (0.0%)	0.56	6 (14.0%)	1 (33.3%)	0.62	5 (8.6%)	2 (40.0%)	0.08	10 (27.0%)	3 (25.0%)	0.69
Cord-blood C-peptide, ng/ml[d]	0.47 (0.31)	0.52 (0.27)	0.61	0.49 (0.29)	0.62 (0.31)	0.13	0.53 (0.33)	0.64 (0.76)	0.82	0.52 (0.33)	0.70 (0.52)	0.47	0.69 (0.42)	0.75 (0.63)	0.78
Breastfeeding (exclusive), ≥1 month	86 (81.1%)	7 (70.0%)	0.65	61 (56.5%)	6 (35.3%)	0.26	20 (46.5%)	1 (33.3%)	0.49	32 (55.2%)	2 (40.0%)	0.38	16 (43.2%)	5 (41.7%)	0.97

Data are mean (SD) or *n* (%), Student's *t* test for continuous and χ^2 test for categorical variables. High HbA_{1c} is $HbA_{1c} \geq 5.7\%$ (39 mmol/mol)]; normal HbA_{1c} is $HbA_{1c} < 5.7\%$. Bold font indicates $p < 0.05$. Participants with any missing information for baseline characteristics were excluded.

[a]Loss to follow-up or withdrawal from participation.

[b]GDM testing was performed at median 25 weeks and 3 days of gestation (interquartile range 3 weeks and 4 days). To convert glucose mmol/l to mg/dl, multiply by 18.018.

[c]To convert HbA_{1c} percent to mmol/mol: IFCC HbA_{1c} unit (mmol/mol) = [10.93 × DCCT/NGSP unit (%)] − 23.50.

[d]To convert C-peptide ng/ml to nmol/l, multiply by 0.331.

BMI, body mass index; DCCT/NGSP, Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HbA_{1c}, glycated hemoglobin; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; LGA, large-for-gestational-age; SD, standard deviation.

S5 Table: Late-pregnancy dysglycemia in obese, GDM-positive mothers and offspring outcomes.

Child outcome	Control group (obese, GDM+, normal HbA_{1c})		Maternal late-pregnancy dysglycemia (obese, GDM+, high HbA_{1c})	
	N	**Mean (95% CI)**	***N***	**Mean increment Δ (95% CI) with respect to control group**
At delivery[a]				
Birth weight, g	165	3,440 (3,368 to 3,511)	136	103 (−4 to 211)
Cord-blood C-peptide, ng/ml[b]	158	0.57 (0.51 to 0.63)	128	0.04 (−0.07 to 0.14)
Long-term follow-up[c]:				
BMI z-score change per year[d]	321	−0.04 (−0.15 to 0.05)	255	−0.003 (−0.14 to 0.15)
BMI z-score at 4 years[e]	58	0.55 (0.24 to 0.86)	37	0.07 (−0.38 to 0.51)

Mean increments in offspring outcomes by high maternal HbA_{1c} (≥5.7% [39 mmol/mol]) at delivery are shown relative to the obese, GDM+, normal HbA_{1c} group.
[a]Based on linear regression models, adjusted for maternal pre-conception BMI, total gestational weight gain, maternal smoking at any time during pregnancy, and sex of the child.
[b]To convert C-peptide ng/ml to nmol/l, multiply by 0.331.
[c]Adjusted for maternal pre-conception BMI, total gestational weight gain, maternal smoking at any time during pregnancy, and exclusive breastfeeding ≥1 month.
[d]Based on linear mixed-effects model.
[e]Based on linear regression model.
BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin.

S6 Table: Comparison of relevant characteristics in obese, GDM-negative women with available and missing maternal follow-up visit 3.5 years postpartum.

Maternal follow-up visit	**Obese, GDM−, normal HbA_{1c}**			**Obese, GDM−, high HbA_{1c}**		
3.5 years postpartum	**Available**	**Missing**[a]	***p*-value**	**Available**	**Missing**[a]	***p*-value**
Maternal characteristics during pregnancy						
N	86	17		37	12	
Pre-conception BMI, kg/m^2	36.6 (4.7)	34.8 (3.7)	0.083	36.4 (5.1)	37.9 (5.5)	0.41
Fasting glucose at GDM testing, mmol/l[b]	4.42 (0.41)	4.48 (0.46)	0.69	4.54 (0.36)	4.47 (0.18)	0.45
Smoking at any time during pregnancy	16 (18.6%)	6 (35.3%)	0.23	11 (29.7%)	4 (33.3%)	1
Maternal characteristics at delivery						
Total GWG, kg	12.1 (7.2)	13.8 (6.4)	0.35	13.6 (6.8)	12.8 (8.3)	0.76
Excessive third-trimester GWG	65 (75.6%)	13 (7.5%)	0.34	32 (86.5%)	10 (83.3%)	0.24
Third-trimester GWG, kg	4.9 (3.1)	6.4 (4.8)	0.24	4.9 (2.3)	6.8 (4.4)	0.18
HbA_{1c} at delivery, percent[c]	5.3 (0.3)	5.3 (0.2)	0.72	5.9 (0.2)	6.0 (0.2)	0.10
Child characteristics at birth						
Sex: female	36 (41.9%)	8 (47.1%)	0.90	15 (40.5%)	7 (58.3%)	0.46
Birth weight, g	3,481 (448)	3,263 (570)	0.15	3,536 (501)	3,678 (440)	0.41
Birth weight: LGA	7 (8.1%)	0 (0%)	0.17	4 (10.8%)	2 (16.7%)	0.54
Cord-blood C-peptide, ng/ml[d]	0.51 (0.32)	0.64 (0.38)	0.22	0.52 (0.36)	0.79 (0.49)	0.10
Breastfeeding (exclusive), ≥1 month	51 (59.3%)	7 (41.2%)	0.35	13 (35.1%)	6 (50.0%)	0.55

Data are mean (SD) or *n* (%), Student's *t* test for continuous and χ^2 test for categorical variables. High HbA_{1c} is HbA_{1c} ≥ 5.7% (39 mmol/mol)]; normal HbA_{1c} is HbA_{1c} < 5.7%. Participants with any missing values for baseline characteristics were excluded.

[a]Loss to follow-up or withdrawal from participation.

[b]GDM testing was performed at median 25 weeks and 3 days of gestation (interquartile range 3 weeks and 4 days). To convert glucose mmol/l to mg/dl, multiply by 18.018.

[c]To convert HbA_{1c} percent to mmol/mol: IFCC HbA_{1c} unit (mmol/mol) = [10.93 × DCCT/NGSP unit (%)] − 23.50.

[d]To convert C-peptide ng/ml to nmol/l, multiply by 0.331.

BMI, body mass index; DCCT/NGSP, Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HbA_{1c}, glycated hemoglobin; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; LGA, large-for-gestational-age; SD, standard deviation.

VI. Paper 2

BMC Medicine

RESEARCH ARTICLE

Open Access

Predicting the earliest deviation in weight gain in the course towards manifest overweight in offspring exposed to obesity in pregnancy: a longitudinal cohort study

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Abstract

Background: Obesity in pregnancy and related early-life factors place the offspring at the highest risk of being overweight. Despite convincing evidence on these associations, there is an unmet public health need to identify "high-risk" offspring by predicting very early deviations in weight gain patterns as a subclinical stage towards overweight. However, data and methods for individual risk prediction are lacking. We aimed to identify those infants exposed to obesity in pregnancy at ages 3 months, 1 year, and 2 years who likely will follow a higher-than-normal body mass index (BMI) growth trajectory towards manifest overweight by developing an early-risk quantification system.

Methods: This study uses data from the prospective mother-child cohort study Programming of Enhanced Adiposity Risk in CHildhood–Early Screening (PEACHES) comprising 1671 mothers with pre-conception obesity and without (controls) and their offspring. Exposures were pre- and postnatal risks documented in patient-held maternal and child health records. The main outcome was a "higher-than-normal BMI growth pattern" preceding overweight, defined as BMI *z*-score >1 SD (i.e., World Health Organization [WHO] cut-off "at risk of overweight") at least twice during consecutive offspring growth periods between age 6 months and 5 years. The independent cohort PErinatal Prevention of Obesity (PEPO) comprising 11,730 mother-child pairs recruited close to school entry (around age 6 years) was available for data validation. Cluster analysis and sequential prediction modelling were performed.

Results: Data of 1557 PEACHES mother-child pairs and the validation cohort were analyzed comprising more than 50,000 offspring BMI measurements. More than 1-in-5 offspring exposed to obesity in pregnancy belonged to an upper BMI *z*-score cluster as a distinct pattern of BMI development (above the cut-off of 1 SD) from the first months of life onwards resulting in preschool overweight/obesity (age 5 years: odds ratio [OR] 16.13; 95% confidence interval [CI] 9.98–26.05). Contributing early-life factors including excessive weight gain (OR 2.08; 95% CI 1.25–3.45) and smoking (OR 1.94; 95% CI 1.27–2.95) in pregnancy were instrumental in predicting a "higher-than-normal BMI growth pattern"

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at age 3 months and re-evaluating the risk at ages 1 year and 2 years (area under the receiver operating characteristic [AUROC] 0.69–0.79, sensitivity 70.7–76.0%, specificity 64.7–78.1%). External validation of prediction models demonstrated adequate predictive performances.

Conclusions: We devised a novel sequential strategy of individual prediction and re-evaluation of a higher-than-normal weight gain in "high-risk" infants well before developing overweight to guide decision-making. The strategy holds promise to elaborate interventions in an early preventive manner for integration in systems of well-child care.

Keywords: Maternal pre-conception obesity, Early weight gain, BMI growth, Infancy, Sequential prediction, Repeated risk assessment, Subclinical stage, Early prevention

Background

Global rates of childhood obesity have increased dramatically [1]. Children with overweight or obesity are at high risk of maintaining overweight or obesity in adulthood and developing morbidities including type 2 diabetes (T2D), hypertension, and cardiovascular disease [2]. Recent evidence supports that the greatest acceleration in the child's body mass index (BMI) growth related to sustained obesity occurs between the age of 2 and 6 years [3], suggesting that this period is critical for establishing long-term growth patterns. Before this period, in the "developmentally plastic" first 2 years of life [4], rapid postnatal weight gain has been shown to be associated with later overweight and obesity [5].

As one of the most important risk factors [6, 7], preconceptional maternal overweight and obesity, which affect up to 70% of pregnant women worldwide [8] and about 40% in Germany (obesity 16.4%) [9], contribute to an average 2- to 6-fold increased risk of overweight or obesity in the offspring. This effect depends on the severity of maternal obesity and the age of the child (ranging from odds ratio [OR] 2.35, 95% confidence interval [CI] 2.14–2.59 at age 2–5 years to OR 5.98, 95% CI 4.50–7.94 at age 10–18 years) [10]. During pregnancy, women with obesity are 2.5 times more likely to experience excessive gestational weight gain (GWG) [11, 12] and have a 3- to 5.5-fold higher chance of developing gestational diabetes (GDM) [13] than women with normal weight. After delivery, more than one third of mothers with overweight/obesity do not initiate breastfeeding [14], all representing specific single risk factors for childhood overweight. Circumstantial observations showed that maternal obesity and the presence of additional prenatal and/or postnatal factors, such as excessive GWG, no or short duration of breastfeeding, and unfavorable childhood eating habits, confer a substantially higher risk of overweight in offspring than maternal obesity alone [15–17]. This suggests that consideration of multiple and cumulative modifiable risk factors emerging across the very early-life span [18, 19] may help to design overweight prevention strategies for offspring of mothers with obesity.

Despite overwhelming evidence for associations of such risk factors with childhood overweight and obesity [20, 21], there is an unmet public health need to identify vulnerable infants who are at highest risk of gaining more weight than expected prior to the manifestation of overweight. Previous studies have focused on the prediction of manifest overweight/obesity in preschool and school-age children, mainly for use at a given age [22]. However, sequential prediction of the earliest deviations in weight gain patterns that precede the manifestation of overweight is not yet achieved on an individual level because of the lack of underpinning data on longitudinal BMI development and contributing predictors to develop such an approach. This would require a dynamic prediction-guided prevention strategy with serial risk assessments for "high-risk" offspring, such as those exposed to obesity in pregnancy.

In this study, we first evaluated longitudinal BMI growth patterns in offspring of mothers with obesity versus those of mothers without obesity. Secondly, a "higher-than-normal BMI growth pattern" was utilized as the endpoint, in order to define a still presymptomatic at-risk status for taking a course towards "manifest overweight." Furthermore, we used well-documented risk associations to analyze potential contributions to the risk of developing this endpoint. The identified contributors were then condensed into a novel risk quantification system to identify those offspring from pregnancies with obesity who are at increased risk of higher-than-normal BMI growth. Finally, we embedded this prediction system into a public health approach utilizing the setting of well-child visits for early preventive interventions. We used a unique and comprehensive set of longitudinal data from the high-risk cohort Programming of Enhanced Adiposity Risk in CHildhood–Early Screening (PEACHES) of mothers with obesity and their offspring and externally validated our findings in the population-based mother-child cohort PErinatal Prevention of Obesity (PEPO).

Methods

Study design and populations

PEACHES is an ongoing prospective mother-child cohort study of 1671 pregnant women, mainly with obesity (n = 949, 56.8%), designed to investigate the long-term consequences of maternal pre-conception obesity on the development of overweight and related metabolic diseases in mothers and their offspring [23, 24]. Pregnant women were prospectively recruited during their first visit to maternity clinics (4–6 weeks before due date) in 23 hospitals mainly in the Munich area, Bavaria (southern Germany), and also in the University Hospital of Düsseldorf (western Germany) and parts of northern Germany between 2010 and 2015 [24]. Inclusion criteria in the PEACHES cohort were maternal age ≥18 years, singleton pregnancy, gestational age at birth ≥37 weeks, pre-conception BMI ≥30 kg/m^2, and absence of preexisting type 1 diabetes (T1D) or T2D [25]. The cohort also includes mothers with normal weight, both with and without GDM, recruited as control groups [24], and a smaller proportion of overweight (and a minor number of underweight) mothers. In case the pregnancy record booklet was not ready to hand at recruitment, the mothers were re-categorized into BMI groups based on measured and recorded weight values as soon as the pregnancy record booklet became available, leading to reclassification of some women into overweight or underweight BMI categories [26], respectively. The study protocol of the PEACHES cohort was published elsewhere [24].

Data from the independent German mother-child cohort PEPO [27, 28] were used for validation. In the PEPO cohort, 11,730 children and their mothers were recruited from October 2009 to June 2011 prior to the mandatory school entry health examinations in 6 widely distributed geographical regions in Bavaria, southern Germany, both urban and rural. Inclusion criterion in the PEPO cohort was age of the child close to school entry (around 6 years). Parents and their children were invited by mail to participate via leaflets.

The local ethics committee of the Ludwig-Maximilians-Universität München, Germany, approved the cohort studies. Written informed consent was provided by all participants. The results from this study were analyzed and reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) [29] and Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) [30] guidelines (Additional file 1: S1 STROBE Checklist, S2 TRIPOD Statement). Data for the analyses were retrieved from the PEACHES and PEPO databases in April 2020.

Procedures

Inclusion criteria for analysis

Mothers included in the analysis were mothers with or without pre-conception obesity, were not diagnosed with T1D/T2D, and had a full-term (≥37 weeks 0 days of gestation) singleton live birth. For all analyses in each of the cohort datasets, we combined mothers with normal weight and overweight into the category "mothers without obesity" (<30 kg/m^2), which served as a control group, as reported by others [31, 32]. Underweight women (PEACHES, n = 17; PEPO, n = 392) were excluded from the analyses.

Potential predictors of higher-than-normal BMI growth

In the PEACHES cohort study, data were obtained mainly from patient-held maternal and child health records (i.e., pregnancy record booklet and well-child booklet) for variables including maternal BMI at conception, total GWG, blood glucose concentrations for diagnosing GDM, parity, offspring sex and birth weight, and child anthropometric data. Data on maternal smoking during pregnancy, parental socioeconomic status (SES), and breastfeeding were gathered through questionnaires using questions from the "German Health Interview and Examination Survey for Children and Adolescents" (KiGGS) cohort study [33]. Information relating to prenatal factors was collected retrospectively shortly after delivery, mainly from documentation in the health records or via questionnaire and/or a standardized physician-administered telephone interview (e.g., smoking during pregnancy) [24]. In the PEPO cohort study, at the time of the health exam prior to primary school entry at around age 6 years, families were requested to fill out a detailed questionnaire, also containing questions from the KiGGS study [33]. In addition, trained study nurses copied all weight-related maternal and offspring data from the pregnancy record and well-child booklets, respectively.

Potential prenatal and postnatal risk predictors of higher-than-normal BMI growth were selected according to their known literature-based associations with offspring growth [34] and/or obesity [21, 35] and the availability of the data in both cohorts: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1, 3, and 6 months, and offspring BMI status at the time of prediction.

Data on maternal pre-conception BMI was obtained at the time of recruitment from the pregnancy record booklet in both the PEACHES and the PEPO cohort studies. The pregnancy record booklet contains detailed

information on ultrasound checkups, laboratory assessments, and weight measurements at multiple times collected by the obstetrician during antenatal care visits [24]. We used the BMI measured at the first antenatal visit as a surrogate for "pre-conception BMI" based on studies showing only a minimal difference between pre-conception weight self-reported and weight measured at the earliest antenatal visit during the first trimester [27, 36] and through own analyses (Additional file 1: Text S2, paragraph 1.1) [37]. In the PEACHES cohort, BMI was based on maternal weight and height measured (in light clothing and without shoes) by trained medical personnel at the first antenatal visit in the physicians' offices, if the visit was before 12 weeks 6 days of gestation (PEACHES 92.4%, mean 9 weeks [SD 2 weeks] of gestation; PEPO 88.5%, mean 8 weeks [SD 2 weeks] of gestation). If the first antenatal visit was later than the 13th week of gestation (PEACHES 7.6%, PEPO 11.5%), pre-conception weight and height data as reported by the woman and documented at the first antenatal visit was abstracted from the pregnancy record booklet to calculate the pre-conception BMI.

Maternal pre-conception BMI groups were defined according to World Health Organization (WHO) categories [26] in both the PEACHES and PEPO cohort studies: normal weight (BMI 18.5 to 24.9 kg/m^2), overweight (BMI 25.0 to 29.9 kg/m^2), or obese (BMI ≥30.0 kg/m^2). Mothers with obesity were further classified according to the severity of obesity, which included class 1 obesity (BMI 30.0 to 34.9 kg/m^2), class 2 obesity (BMI 35.0 to 39.9 kg/m^2), and class 3 obesity (BMI ≥40.0 kg/m^2).

Total GWG was calculated using serial weight measurement data, which were documented in the pregnancy record booklet by the consulted physician throughout pregnancy [27]. Total GWG was defined as the difference between the last measured weight before delivery and pre-conception weight as defined above and was categorized as inadequate, adequate, or excessive according to the 2009 BMI-specific recommendations of the Institute of Medicine (now known as the National Academy of Medicine)/National Research Council [38].

GDM was defined as "diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation" [39]. All women of the PEACHES cohort who met the inclusion criteria for analysis had GDM testing by undergoing a 50-g glucose challenge test (GCT) or a 75-g oral glucose tolerance test (OGTT) during the second or third trimester of pregnancy (median 25 weeks 5 days, interquartile range [IQR] 3 weeks 1 day) [39, 40]. Diagnosis of GDM in the PEACHES cohort was based on blood glucose concentrations obtained either from the pregnancy record booklet or from laboratory test reports provided by the obstetrician. The GDM test was defined as positive when one or more of the three glucose concentrations of a 75-g OGTT met or exceeded the reference values according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (1-step procedure): fasting glucose ≥5.1 mmol/l (92 mg/dl), 1-h post-load glucose ≥10 mmol/l (180 mg/dl), or 2-h post-load glucose ≥8.5 mmol/l (153 mg/dl) [41]. In the 2-step procedure, a positive 50-g GCT (defined as 1-h post-load glucose concentration ≥7.8 mmol/l [140 mg/dl] [39]) was followed by a 75-g OGTT according to the IADPSG diagnostic criteria [41]. In the PEPO cohort, women reported the presence of GDM at the time of the school entry health examinations [42] by answering the question: "Was diabetes newly diagnosed in pregnancy prompting dietary or insulin treatment?". At the time of the mothers' pregnancies, GDM testing was performed between 24 weeks 0 day and 28 weeks 0 day of gestation according to the recommendations of the German Diabetes Association at the time of the study [43], which were comparable to those of the American Diabetes Association at that time [44]. All women with a diagnosis of GDM had received recommendations on treatment with insulin and/or diet, had been advised on weight gain goals, and had been monitored until the end of pregnancy by their treating physicians.

Data on maternal smoking were obtained retrospectively through two independent data sources in the PEACHES cohort (questionnaire sent to each participant and telephone interview, both carried out shortly after delivery) and by questionnaire alone in the PEPO cohort. Reported maternal smoking during pregnancy and/or the postpartum phase were categorized as "any time" versus "no time" [27].

Information on parity was abstracted from the pregnancy record booklet and categorized as primiparous (one child) or multiparous (more than one child) [45].

Data on offspring sex and birth weight were abstracted from the well-child booklets [24]. Birth weight adjusted for gestational age and sex was categorized as large-for-gestational-age (LGA; >90th percentile), average-for-gestational-age (AGA; 10th to 90th percentile), or small-for-gestational-age (SGA; <10th percentile) based on the German reference population [46].

Parental SES at birth was defined using an additive index based on maternal and paternal educational background and current type of maternal and paternal employment [47]. Information on parental education and parental employment was collected using a questionnaire, either sent to each participant in the PEACHES cohort or completed at the school entry health exam in the PEPO cohort. Educational background was categorized as "low" (<10 years of formal education [score: 1]),

"medium" (10 years of formal education [score: 2]), or "high" (>10 years of formal education [score: 3]). Type of employment was categorized as "not employed" (score: 1) or "at least part-time employed" (score: 2). The parental scores of educational background and employment status were added to derive the total parental score or SES, which was categorized as "low/medium" (total parental score ≤8) or "high" (total parental score > 8).

Breastfeeding data at each time point including ages 1 month, 3 months, and 6 months were obtained retrospectively through questionnaires in both the PEACHES (at child's ages 6 weeks and 1 year) and the PEPO cohorts and dichotomized as "not full" or "full." "Full" includes both exclusive and predominant breastfeeding [48], where "predominant" means that the infant's main source of nourishment during that time was breastmilk and that the infant may also have received water, water-based drinks, fruit juice, drops, or syrups [49].

Growth outcomes until age 5 years

In both the PEACHES and the PEPO cohort studies, child anthropometric data were abstracted from records of the regular well-child visits conducted by trained pediatricians and other professionals of the preventive health program offered to all children in Germany. In addition, anthropometric measurements were taken by trained study nurses during the school entry health exam of the PEPO children, including weight, height, and waist circumference, and carried out three times under standardized conditions [27].

In the PEACHES cohort, data from up to 9 consecutive measurements of weight and length/height were available during the first 5 years of life. These 9 measurements were collected at birth, the 1-month visit (ages 4 to 5 weeks), 3-month visit (ages 3 to 4 months), 6-month visit (ages 6 to 7 months), 1-year visit (ages 10 to 12 months), 2-year visit (ages 21 to 24 months), 3-year visit (ages 34 to 36 months), 4-year visit (ages 46 to 48 months), and 5-year visit (ages 60 to 64 months). The PEPO cohort consisted of a maximum of 4 measurements from both the well-child visits (i.e., at birth, 1-year visit, and 2-year visit) and the school entry health examination.

Consecutive age- and sex-specific BMI *z*-scores (WHO Child Growth Standards) [50, 51] were calculated to first identify (i) upper BMI growth clusters and (ii) offspring with overweight/obesity at ages 4 and 5 years, respectively. We defined offspring weight status at each time point using the WHO BMI *z*-score categorizations including >1 to ≤2 SD, >2 to ≤3 SD, >3 SD as "at risk of overweight," "overweight," and "obesity," respectively, for children aged ≤60 months [51]. For children ≥61 months, we defined "overweight" and "obesity" as >1 to ≤2 SD and >2 SD, respectively. The category "BMI *z*-score >1 SD" included offspring "at risk of overweight," with overweight, or with obesity [51]. We assumed that within a normally distributed population of offspring, 15% of offspring will be above the WHO BMI *z*-score cut-off of 1 SD [50].

Next, as the main study outcome, we used "higher-than-normal BMI growth pattern" preceding overweight, which we defined as exceeding the BMI *z*-score cut-off >1 SD at least twice in relevant offspring growth phases between 6 months and 5 years of age. Within this time window, we defined "early phase" and "late phase" as the period between 6 months to 2 years and 3 years to 5 years, respectively. Each growth phase contained three follow-up time points of BMI *z*-score assessments from well-child visits (early phase: 6-month, 1-year, and 2-year follow-ups; late phase: 3-year, 4-year, and 5-year follow-ups).

Statistical analysis

The statistical analysis plan for all analyses can be found in the Text S1 (Additional file 1) [38, 46, 51]. We used the PEACHES cohort to search for structures and develop prediction models and performed sample size calculations to determine the appropriate size of the validation cohort. Internal and external validation was performed. Missing data were handled as missing completely at random since missing data relate to the timing of recruitment into the PEACHES cohort (i.e., offspring were too young to have their well-child follow-up at the time of data retrieval). Follow-up drop-out in offspring mainly occurred because of moving away from the study area (Additional file 1: Table S1). Given the small proportions of missing values in child follow-up data (PEACHES: 7%, PEPO: 4%, Additional file 1: Table S1), we could not identify factors related to the drop-out of participants and hence did not apply missing at random or informative missing principles.

To identify distinct BMI growth patterns from birth to 5 years of age, we performed a *k*-means cluster analysis on the longitudinal data of children of mothers with obesity (target group) and those of mothers without obesity (control group), respectively, as a non-parametric explorative analysis. We explored simultaneous effects of prenatal and postnatal factors on the endpoint "higher-than-normal BMI growth pattern" in offspring from birth to 5 years of age and during the early and late phases separately by logistic regression (including the early-phase BMI growth pattern as a potential factor influencing the late-phase pattern).

The predictive potential of prenatal and postnatal factors on the offspring's "higher-than-normal BMI growth pattern" was examined using penalized logistic regression (least absolute shrinkage and selection operator

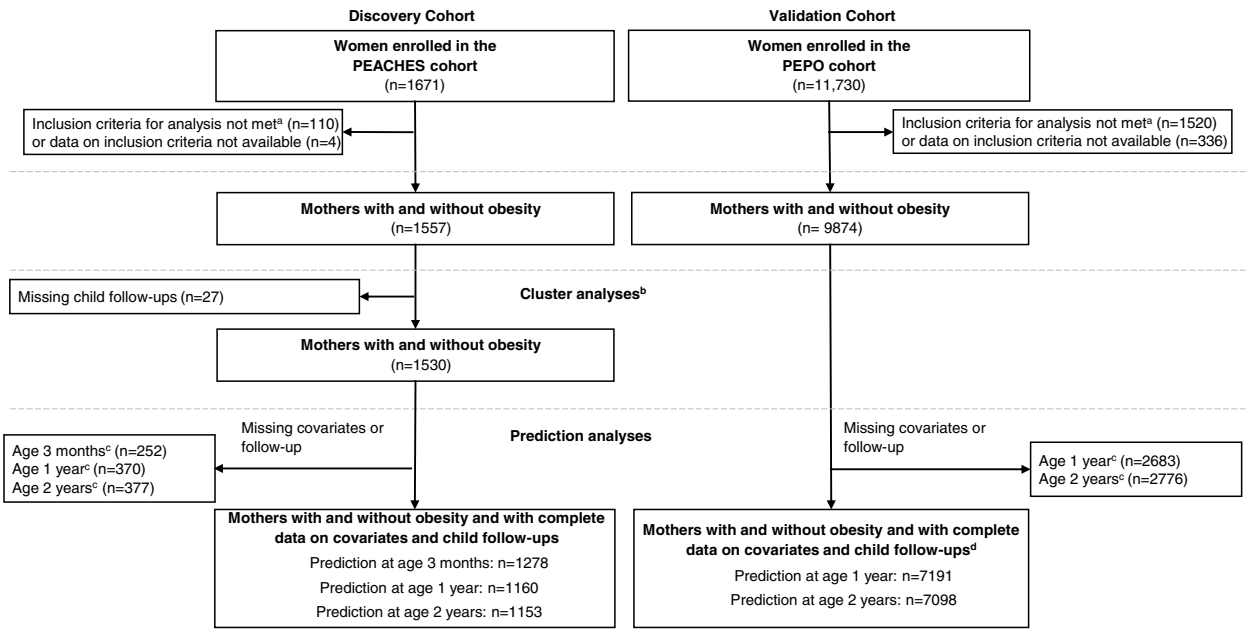

Fig. 1 Flow chart of the study populations. [a]Did not meet inclusion criteria for analysis, i.e., pre-conception obesity, overweight, or normal weight, full-term (≥37 weeks 0 days of gestation) singleton live birth, or absence of T1D/T2D. [b]Identification of BMI growth clusters was not performed in the PEPO cohort due to limited offspring follow-up time points. BMI growth clusters identified in the PEACHES cohort were validated in the PEPO cohort. [c]Missing information on at least one of the potential prenatal and postnatal predictors including maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1, 3, and 6 months, and/or on offspring BMI status at the respective prediction time point. [d]External validation of prediction models at age 3 months was not performed due to unavailability of offspring BMI data at age 3 months in the PEPO cohort. BMI, body mass index; GDM, gestational diabetes; GWG, gestational weight gain; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening; PEPO, PErinatal Prevention of Obesity; SES, socioeconomic status; T1D, type 1 diabetes; T2D, type 2 diabetes

[LASSO]) to develop consecutive prediction models and risk scoring during well-child visits at age 3 months, 1 year, and 2 years. Models were optimized according to their discriminative power (area under the receiver operating characteristic [AUROC]) by internal cross-validation. Risk scores were based on linear predictors from logistic regression. All prediction models were externally validated in the PEPO cohort. Calibration plots were based on Steyerberg et al. [52]. Data were analyzed using R software, version 3.5.1. Additional details on all statistical methods are available in the Text S2 (Additional file 1) [37, 51, 53–65]. Information on the quantification of individual risk including the development of risk scoring and risk probability assessment is provided in the Text S3 (Additional file 1).

Results

Characteristics of study populations

A total of 1557 women ($n = 887$ [57.0%] with obesity and $n = 670$ [43.0%] without obesity) of the PEACHES cohort and 9874 women ($n = 917$ [9.3%] with obesity and $n = 8957$ [90.7%] without obesity) of the PEPO cohort were included in our analyses (Fig. 1, Table 1). The proportion of women excluded from the analyses due to missing data is <1% in the PEACHES cohort and 3.3% in the PEPO cohort (Fig. 1).

Baseline characteristics of mothers with and without obesity and their children are presented in Table 1. Among the mothers without obesity in the PEACHES cohort, 442 (66%) were normal weight and 228 (34%) were overweight, whereas in the PEPO cohort, 6808 (76%) were normal weight and 2149 (24%) were overweight. There was good agreement (98.7%, $n = 1218/1234$) between pre-conception weight self-reported and weight measured at the earliest antenatal visit (mean 9 weeks [SD 2 weeks] of gestation) of the PEACHES women (correlation coefficient 0.988), similar to data of the PEPO cohort [27].

Compared to control mothers without obesity, mothers with obesity in each cohort had higher percentages of LGA birth weight and shorter durations of full breastfeeding. Among women with obesity in each of the cohorts, despite having a lower mean total GWG, there was a higher proportion of excessive GWG according to the BMI-specific cut-offs [38] than among women without obesity. The proportion of GDM among women

Table 1 Characteristics of the study populations

Maternal/child characteristics	Discovery cohort: PEACHES ($n = 1557$)		Validation cohort: PEPO ($n = 9874$)	
	Mothers with obesity ($n = 887$)	Mothers without obesity ($n = 670$)	Mothers with obesity ($n = 917$)	Mothers without obesity ($n = 8957$)
Maternal characteristics				
Age at conception, years	31.3 (5.3)	32.6 (5.3)	29.2 (4.9)	29.0 (5.3)
Pre-conception BMI, mean (SD), kg/m^2	37.0 (5.2)	24.0 (3.1)	34.1 (3.8)	23.1 (2.7)
Pre-conception BMI, median (IQR), kg/m^2	36.1 (7.3)	23.6 (4.8)	33.0 (3.8)	22.6 (4.8)
Pre-conception BMI group				
Normal weight	NA	442 (66.0)	NA	6808 (76.0)
Overweight	NA	228 (34.0)	NA	2149 (24.0)
Obese class I	384 (43.3)	NA	633 (69.0)	NA
Obese class II	278 (31.3)	NA	200 (21.8)	NA
Obese class III	225 (25.4)	NA	84 (9.2)	NA
GDM	321 (40.2)	359 (55.9)[a]	65 (7.2)	213 (2.4)
Smoking at any time during pregnancy	250 (28.4)	110 (16.7)	146 (16.2)	977 (11.1)
Primiparous	444 (50.1)	387 (57.8)	551 (62.3)	5648 (66.3)
Socioeconomic status at birth, high	244 (31.0)	408 (69.6)	125 (14.2)	2519 (29.3)
Total GWG, kg	10.9 (6.9)	13.0 (5.3)	10.3 (6.6)	13.8 (5.0)
Total GWG				
Adequate	218 (24.7)	237 (35.7)	197 (23.1)	3175 (38.4)
Excessive	512 (58.0)	237 (35.7)	486 (57.1)	3171 (38.3)
Inadequate	153 (17.3)	190 (28.6)	168 (19.7)	1925 (23.3)
Child characteristics				
Sex, female	420 (47.4)	351 (52.4)	450 (49.1)	4315 (48.2)
Birth weight category				
Average-for-gestational-age	690 (77.8)	520 (77.6)	684 (76.6)	7070 (81.1)
Large-for-gestational-age	101 (11.4)	45 (6.7)	130 (14.6)	677 (7.8)
Small-for-gestational-age	96 (10.8)	105 (15.7)	79 (8.8)	971 (11.1)
Full breastfeeding, at 1 month	430 (49.2)	470 (71.5)	521 (59.0)	6475 (74.4)
Full breastfeeding, at 3 months	338 (38.9)	431 (66.5)	401 (46.1)	5381 (62.2)
Full breastfeeding, at 6 months	156 (18.0)	185 (28.6)	198 (22.9)	2977 (34.8)
Child age (months) at follow-up[b]				
At 1-month follow-up	1.1 (0.2)	1.1 (0.2)	NA	NA
At 3-month follow-up	3.3 (0.5)	3.3 (0.5)	NA	NA
At 6-month follow-up	6.3 (0.7)	6.3 (0.7)	NA	NA
At 1-year follow-up	11.7 (0.9)	11.8 (0.8)	11.8 (0.8)	11.8 (0.8)
At 2-year follow-up	23.9 (1.2)	24.0 (1.2)	23.8 (1.2)	23.9 (1.1)
At 3-year follow-up	36.1 (1.1)	36.2 (1.1)	NA	NA
At 4-year follow-up	48.2 (1.4)	48.2 (1.3)	NA	NA
At 5-year follow-up	62.3 (2.2)	62.1 (1.7)	69.9 (4.8)[c]	69.7 (4.4)[c]

Values are mean (SD), median (IQR), or *n* (%). Participants with any missing information for baseline characteristics were excluded

BMI, body mass index; *GDM*, gestational diabetes; *GWG*, gestational weight gain; *IQR*, interquartile range; *NA*, not available; *PEACHES*, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening; *PEPO*, PErinatal Prevention of Obesity

[a] The group of mothers without obesity also comprises a group of normal weight mothers with GDM, recruited as one of the control groups, as reported previously [24]

[b] Follow-up anthropometric measurements at the well-child visits

[c] Data collected at the school entry health examination, which is an obligatory check-up for children eligible to enter primary school in the coming year (before turning 6 years old) and generally takes place after the 5-year well-child visit

with obesity in the PEACHES cohort was 40% as in other studies [66], considering the average maternal age of > 30 years as an additional risk factor, whereas in the PEPO cohort this number was only 7.2% resulting from former less stringent criteria for diagnosing GDM [43, 44]. The mean (SD) age at child follow-up in each cohort is provided in Table 1. The median number of available follow-up data from the well-child visits was 9 (IQR 1) in the PEACHES cohort and 4 (IQR 1) in the PEPO cohort.

Data on demographic characteristics of mothers enrolled in the PEACHES and PEPO cohorts (Table 1) are similar to the German estimates, including maternal age (Germany: mean 31.6 years at birth [67]) and proportion of female offspring (Germany 48.6% [9]). The proportion of mothers belonging to a low SES at birth was 18.1% in the PEACHES cohort (Germany 20.1% [68]), whereas more women of the PEPO cohort had a low SES (32.9%). Furthermore, the proportion of children with overweight/obesity was higher in the PEACHES cohort as a total (age 3 years 7.2%) than the German (3.3%) [69] or PEPO (4.5%) estimates, based on the specific recruitment of mothers with obesity, whereas the proportions were similar when compared to only the children of mothers without obesity in the PEACHES cohort (3.2%).

BMI growth patterns in offspring

The overall follow-up rate was 93% in PEACHES children and 96% in PEPO children providing 12,699 and 38,022 consecutive anthropometric measurements, respectively (Additional file 1: Table S1). Individual BMI growth patterns among PEACHES offspring of mothers with obesity (Fig. 2A) and mothers without obesity (controls) (Fig. 2B) allowed identification of two distinct BMI growth patterns from birth to 5 years of age (Fig. 2C, D, Additional file 1: Table S2). Among offspring of mothers with obesity, 21% (185/875) belonged to the upper growth cluster showing steep mean BMI *z*-score increments from birth onwards resulting in an early crossing of the WHO BMI *z*-score cut-off >1 SD at age 6 months and a growth peak at age 2 years (Fig. 2C). Across the subsequent 3 years, the mean BMI *z*-score leveled off (1.79 SD) resulting in overweight and obesity at 4 years (OR 44.56, 95% CI 20.64–96.17) and 5 years of age (OR 16.13, 95% CI 9.98–26.05).

In contrast, among 27.9% (183/655) of offspring of mothers without obesity, the upper-cluster pattern showed crossing of the mean BMI *z*-score >1 SD at 1 year of age, which appeared to decrease after peak growth at age 2 years (1.27 SD) (Fig. 2D) but also contributed to preschool overweight and obesity (age 4 years: OR 31.86, 95% CI 4.08–249.01 and age 5 years: OR 27.55, 95% CI 11.88–63.88).

Among all children belonging to upper clusters (Fig. 2C, D), those exposed to gestational obesity were at much higher risk of having multiple occasions (≥5 times) of BMI *z*-score >1 SD from age 6 months onwards (OR 5.09, 95% CI 2.99–8.68) or developing preschool overweight and obesity (age 4 years: OR 7.38, 95% CI 3.68–14.81 and age 5 years: OR 4.90, 95% CI 2.80–8.59) than offspring of mothers without obesity (Additional file 1: Figure S1) [51].

In contrast to the patterns of upper BMI growth clusters, the clusters of lower BMI growth showed similar dynamics from birth to age 2 years in the offspring of mothers with and without obesity and were below 1 SD throughout the entire period until 5 years of age (Fig. 2C, D, Additional file 1: Table S2). However, the cluster of lower BMI growth in the offspring of mothers without obesity was lower than that observed in the offspring of mothers with obesity. Among all offspring of the clusters of lower BMI growth who were older than 2 years of age, those exposed to maternal obesity in pregnancy showed a plateau in mean BMI *z*-scores, whereas offspring of mothers without obesity showed a constant reduction in mean BMI *z*-scores, i.e., before the onset of adiposity rebound. Adiposity rebound relates to a "period of dynamic changes in body composition" [70] and is equivalent to the age of the nadir of a child's BMI curve when the BMI starts to rise again [71].

Based on the BMI growth cluster group and BMI *z*-score in the 5-year-old PEACHES offspring, we validated BMI growth clusters in the PEPO cohort for the offspring of both mothers with obesity (AUROC 0.72) and without (AUROC 0.69).

Higher-than-normal BMI growth patterns in consecutive early-life phases

Subsequently, we found that the upper BMI growth curves of offspring with LGA (40.2%, $n = 39/97$), AGA (19.6%, $n = 131/669$), and SGA (12.8%, $n = 12/94$) birth weights from mothers with obesity (Additional file 1: Figure S2A) converged at age 3 months and continued all at a similarly high BMI growth level until age 5 years (Additional file 1: Figure S3A, Figure S3B). Comparable dynamics were seen in offspring of mothers without obesity (Additional file 1: Figure S2B, Figure S3C, Figure S3D). Based on these patterns leading to BMI convergence at 3 months and subsequent levelling off after 2 years in offspring of mothers with obesity, we determined the time points age 3 months to predict higher-than-normal BMI growth in the early phase and ages 1 year and 2 years to predict the late phase, respectively.

Maternal pre-conception obesity influenced offspring BMI growth dynamics in the transition from early to late phase, e.g., twice as many offspring of mothers with

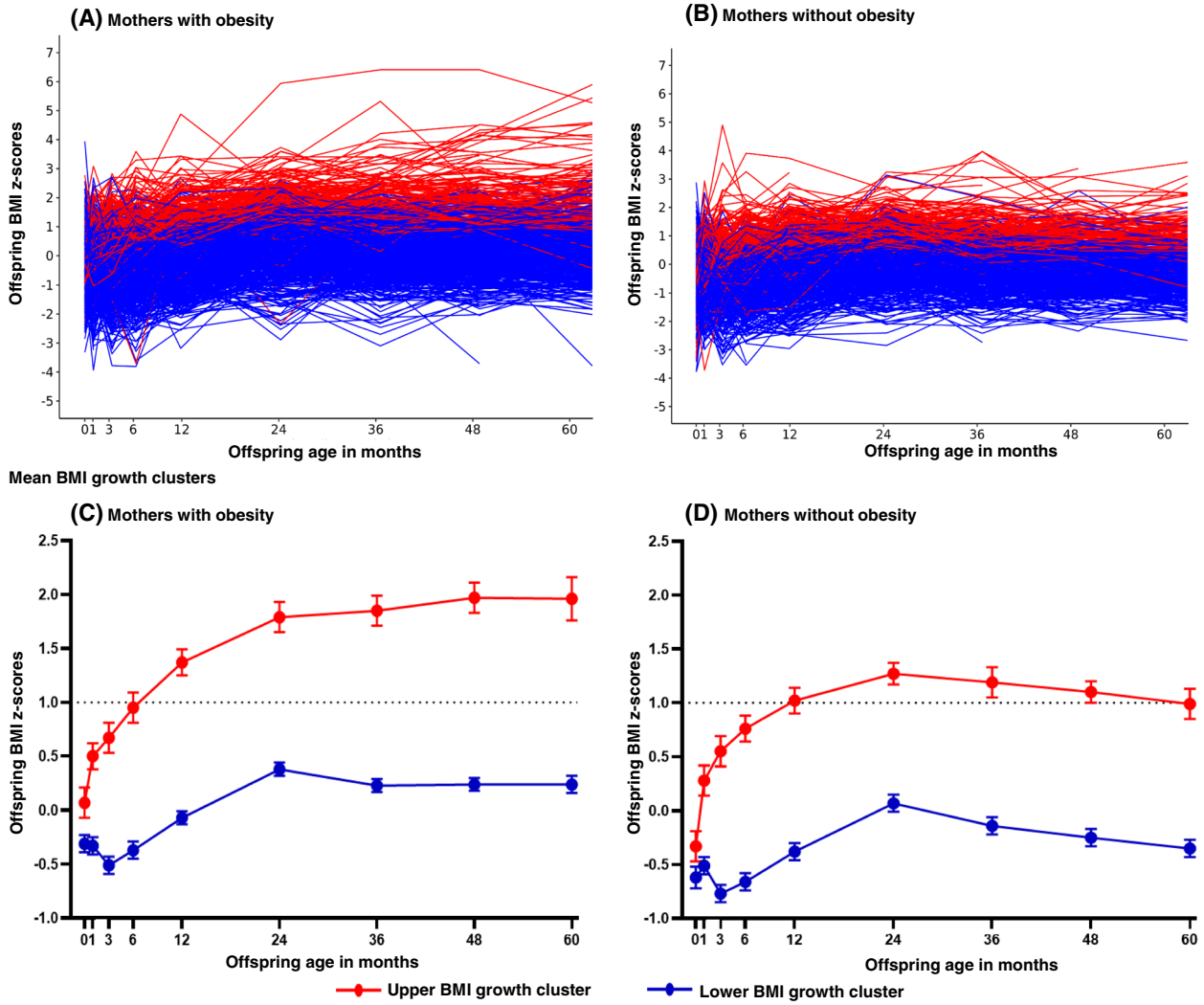

Fig. 2 BMI growth patterns in young offspring of mothers with and without obesity. Shown are individual BMI *z*-score growth curves from birth to age 5 years in offspring of mothers with obesity (panel **A**) and without (panel **B**) enrolled in the PEACHES cohort study. Mean BMI *z*-score growth clusters along with their 95% CI are presented for offspring of mothers with obesity (panel **C**) and without (panel **D**). BMI, body mass index; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening

obesity developed or maintained a "higher-than-normal BMI growth pattern" when they reached the late phase (32.7%, $n = 191/584$) compared to offspring of mothers without obesity (16.8%, $n = 72/428$) (Additional file 1: Table S3) [51, 72].

Risk factors of higher-than-normal BMI growth

Next, we assessed prenatal and postnatal factors triggering higher-than-normal BMI growth from birth until age 5 years and during early and late phases (Fig. 3, Additional file 1: Figure S4) [51]. Offspring exposed to the highest maternal pre-conception BMI in each of the groups of mothers with and without obesity were more likely to belong to the upper BMI growth cluster (Fig. 3A, Additional file 1: Figure S4A). Further, an LGA birth weight in offspring of mothers with obesity was a risk factor for a "higher-than-normal BMI growth pattern" in all growth phases studied between birth and age 5 years including both the early and late phases (Fig. 3A–C). In contrast, in offspring from pregnancies without obesity, an LGA birth weight influenced higher-than-normal BMI growth only in the early phase, not later on (Additional file 1: Figure S4B). An SGA birth weight was related to a lower BMI growth cluster in offspring of women without

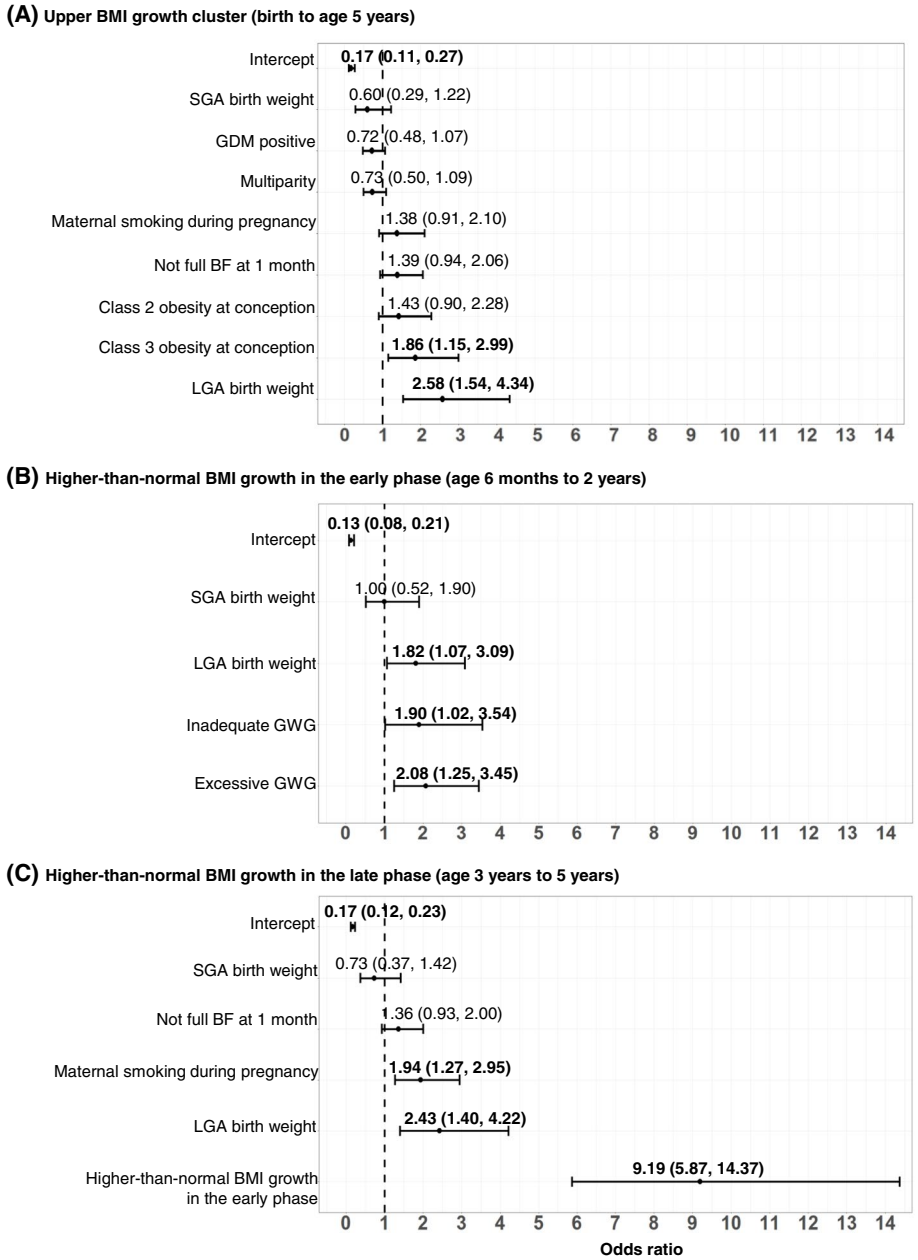

Fig. 3 Effects of prenatal and postnatal factors on BMI growth outcomes in offspring of mothers with obesity. Shown are ORs and 95% CI of the influence of prenatal and postnatal factors on the development of an upper cluster of BMI growth (birth to age 5 years, panel **A**) and a "higher-than-normal BMI growth pattern," defined as BMI *z*-score >1 SD [51] at least twice, during early phase (6 months to 2 years, panel **B**) and late phase (3 to 5 years, panel **C**) in offspring of mothers with obesity enrolled in the PEACHES cohort study. Values were derived from multivariable logistic regression with stepwise backward selection. Only final models based on the lowest Akaike information criterion are presented. Included variables in all initial models were maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month. Additionally, for associations shown in panel **C**, "higher-than-normal BMI growth pattern" in the early phase was also included as an explanatory variable in the initial model. BMI, body mass index; BF, breastfeeding; CI, confidence interval; GDM, gestational diabetes; GWG, gestational weight gain; LGA, large-for-gestational-age; OR, odds ratio; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening; SES, socioeconomic status; SGA, small-for-gestational-age

Table 2 Predictive performance of a sequential algorithm to identify higher-than-normal BMI growth in offspring of mothers with obesity

Predictive parameter	Prediction at age 3 months[a]	Prediction at age 1 year[b]		Prediction at age 2 years[c]	
	Higher-than-normal BMI growth in early phase (6 months–2 years)	Higher-than-normal BMI growth in late phase (3 years–5 years)		Higher-than-normal BMI growth in late phase (3 years–5 years)	
	Discovery cohort	Discovery cohort	Validation cohort	Discovery cohort	Validation cohort
N	711	645	670	640	666
AUROC	0.69 (0.66, 0.72)	0.73 (0.70, 0.75)	0.61	0.79 (0.76, 0.81)	0.71
Cut-off score value[d]	− 1.689	− 1.135	NA	− 1.133	NA
Prevalence, *n* (%)	140 (20.0)	194 (30.8)	221 (33.0)	192 (30.0)	223 (33.5)
Sensitivity, %	70.7 (55.5, 82.3)	73.7 (67.6, 79.0)	68.1 (62.5, 73.2)	76.0 (70.0, 81.1)	61.0 (55.3, 66.5)
Specificity, %	74.1 (61.6, 83.6)	64.7 (58.2, 70.7)	58.2 (52.5, 63.7)	78.1 (72.9, 82.5)	68.0 (63.3, 72.4)
Positive predictive value, %	40.5 (26.5, 55.6)	48.2 (41.9, 54.5)	45.3 (40.1, 50.6)	60.7 (53.5, 67.4)	49.5 (43.6, 55.3)
Negative predictive value, %	91.0 (84.7, 95.0)	84.7 (80.2, 88.3)	78.2 (73.4, 82.4)	88.0 (84.5, 90.7)	77.2 (73.3, 80.8)
Positive likelihood ratio	2.73 (1.44, 5.03)	2.09 (1.62, 2.69)	1.63 (1.32, 2.02)	3.47 (2.58, 4.64)	1.91 (1.50, 2.41)
Negative likelihood ratio	0.40 (0.21, 0.72)	0.41 (0.30, 0.56)	0.55 (0.42, 0.71)	0.31 (0.23, 0.41)	0.57 (0.46, 0.71)

We used the PEACHES cohort study as the discovery cohort and the PEPO cohort study as the external validation cohort for calculation of the individual child's risk of a "higher-than-normal BMI growth pattern" (BMI *z*-score >1 SD [51] at least twice). Values are predictive parameters and their 95% CI

AUROC, area under the receiver operating characteristic; *BMI*, body mass index; *CI*, confidence interval; *GDM*, gestational diabetes; *GWG*, gestational weight gain; *NA*, not applicable; *PEACHES*, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening; *PEPO*, PErinatal Prevention of Obesity; SES, socioeconomic status

[a] Potential predictors included: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, and BMI *z*-score >1 SD at age 3 months. External validation of models at age 3 months could not be performed due to the lack of follow-up data at age 3 months in the validation cohort PEPO

[b] Potential predictors included: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, breastfeeding status at 6 months, and BMI *z*-score >1 SD at age 1 year. External validation of models at age 1 year was performed in the validation cohort PEPO

[c] Potential predictors included: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, breastfeeding status at 6 months, and BMI *z*-score >1 SD at age 2 years. External validation of models at age 2 years was performed in the validation cohort PEPO

[d] Offspring with a risk score above or equal to the respective cut-off score value are considered to be at risk of developing a "higher-than-normal BMI growth pattern." The cut-off value of the score was optimized to avoid false-negative findings (sensitivity), which resulted in negative cut-off score values

obesity (Additional file 1: Figure S4A). Offspring of mothers with obesity who were exposed to either excessive or inadequate GWG or smoking during pregnancy were likely to develop higher-than-normal BMI growth in the early phase or late phase, respectively (Fig. 3B, C). Lastly, regardless of maternal pre-conception obesity, higher-than-normal BMI growth in the early phase strongly triggered higher-than-normal BMI growth in the late phase (Fig. 3C, Additional file 1: Figure S4C).

Sequential prediction of higher-than-normal BMI growth

Using these risk factors showing differential effects on BMI growth in consecutive life phases after birth, we explored and externally validated their potential to predict early-phase and late-phase "higher-than-normal BMI growth patterns" at ages 3 months, 1 year, and 2 years (Table 2, Additional file 1: Table S4) [51]. Based on these findings, we provide a workable approach for individual risk score calculations and risk probability assessment (Additional file 1: Text S3, Table S5) [51]. Risk scores above or equal to the respective cut-offs indicate risk for higher-than-normal BMI growth.

The score based on the first risk quantification model applicable at age 3 months allowed a good prognosis of early-phase growth, and the cut-off value was optimized to avoid false-negative findings: 70.7% of offspring of mothers with obesity with scores ≥ -1.689 will develop higher-than-normal BMI growth in the early phase (sensitivity) and 74.1% with scores < -1.689 will not (specificity) (Table 2). The positive predictive value indicates that 40.5% of all offspring of mothers with obesity identified as "at risk" at age 3 months will certainly develop a "higher-than-normal BMI growth pattern" in the early phase, and the negative predictive value indicates that 91.0% of all offspring of mothers with obesity classified as being "not at risk" will indeed not develop a "higher-than-normal BMI growth pattern." Furthermore, the positive likelihood ratio value of 2.73 indicates an increase (15%) [57] in the likelihood of developing a "higher-than-normal BMI growth pattern" in offspring identified as "at risk" by the prediction model at age 3 months. The negative likelihood ratio value of 0.40 indicates a decrease (20%) [57] in the likelihood of developing a "higher-than-normal BMI growth pattern" in

offspring identified as "not at risk" by the same prediction model at 3 months of age.

The subsequent prediction models at ages 1 year and 2 years developed for risk re-assessments for the late phase showed even higher predictive performance (Table 2). While the negative predictive values were similarly high for all models, the predictive model at age 2 years had the highest sensitivity, specificity, positive predictive value, and positive likelihood ratio and the lowest negative likelihood ratio. Similarly good parameters were observed in offspring of mothers without obesity (Additional file 1: Table S4).

In the independent validation cohort PEPO, prediction models using available data at ages 1 year and 2 years showed fair predictive performances in offspring of both mothers with and without obesity (Table 2, Additional file 1: Table S4). Furthermore, prediction models at age 1 year and 2 years for offspring of mothers with obesity and at age 1 year for offspring of mothers without obesity showed good and very good calibration (i.e., agreement between observed and predicted risks), respectively, using the external cohort PEPO (Additional file 1: Figure S5) [51]. Details on use of individual risk score calculations, risk probability assessment, and clinical case scenarios are provided in Table S5 and the Text S3 (Additional file 1).

Discussion

Longitudinal data from two large mother-child cohorts led to the identification of a "high-risk" subpopulation of offspring susceptible to early upper deviations from healthy weight gain trajectories and novel risk stratification in the very first "plastic phase" of life. Such a strategy could allow cost-effective and personalized advice and measures to slow down or prevent otherwise ongoing increases in BMI growth. Several modifiable influences associated with gestational overnutrition, such as grade of maternal obesity at conception, excessive GWG, and LGA birth weight, contributed sequentially during consecutive early phases to the offspring's susceptibility to gain more weight than expected. Here, these already well-documented risk associations were translated and condensed into a novel serial prediction strategy for primary prevention of a "higher-than-normal BMI growth pattern" as a subclinical stage preceding overweight in clinical settings. The system of well-child visits is ideal for identifying risks by the pediatricians and providing targeted supportive measures to guide offspring BMI growth from early life onwards.

The 2- to 3-fold increased risk of overweight/obesity even in young children from pregnancies with obesity below age 5 years [10] prompted us to study the type and potential predictors of very early growth patterns towards overweight. Unlike previous studies [31, 73], we focused on identifying such growth patterns among offspring exposed to an adipogenic intrauterine milieu. The identified BMI growth pattern showing recurrent crossing of BMI *z*-scores >1 SD—the WHO cut-off for "at risk of overweight"—from an early age of 6 months is highly likely to set the stage for developing overweight at preschool age, which is critical to sustained obesity [3]. The upper BMI growth cluster in obesity-exposed offspring plateaued at high levels after age 2 years. This levelling off is in contrast to the typical BMI decline [71] preceding the adiposity rebound at around 6 years [74]. Our findings suggest that obesity in pregnancy could potentially "hit" cellular processes in the fetus, which may influence offspring outcomes such as postnatal appetite regulation and fat accretion before overweight manifestation [75].

Besides maternal pre-conception obesity [34, 76], offspring weight development can be shaped by additional influences highly associated with an obesogenic environment during prenatal and postnatal life [77, 78]. We found that among such obesity-associated factors, those relating to intrauterine overnutrition including excessive GWG contributed strongly to higher-than-normal BMI growth during the "plastic phase" of the first 2 years. Indeed, there is a need for women with obesity to be provided with more customized advice on dietary intake and physical activity to optimize gestational weight management [24, 79]. For the subsequent time period of the preschool years, gestational smoking emerged as a relevant modulator of growth in offspring exposed to obesity in pregnancy in our study. This association may take time to appear since mothers who smoke at the beginning and/or later during pregnancy are likely to resume smoking postnatally and therefore refrain from breastfeeding more frequently [80, 81], predisposing offspring to develop overweight [82]. In mothers with obesity of the PEACHES cohort study who had smoked during pregnancy, any smoking (versus no smoking) within the first weeks postpartum was related to higher odds of stopping full breastfeeding by the end of the first month (OR 1.97, 95% CI 1.10–3.53). Irrespective of smoking, mothers with obesity have been recognized to experience major difficulties with initiating and continuing breastfeeding resulting in lower breastfeeding rates in these women [83]. Supporting previous evidence [75], our data also show the relevance of an LGA birth weight for overweight development, irrespective of maternal pre-conception BMI, albeit it seemed to have adverse longer-term consequences only in children of mothers with obesity. Our data point to the differential contribution of "obesogenic influences" arising from the pre-gestational, gestational, and perinatal periods, such as grade of maternal obesity at conception, excessive weight gain and smoking during

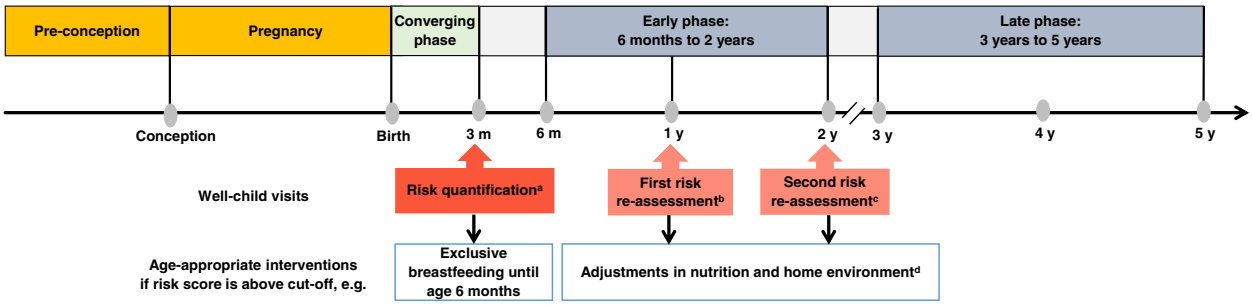

Fig. 4 Prediction-guided prevention strategy for the risk of developing a "higher-than-normal BMI growth pattern" preceding overweight. "Higher-than-normal BMI growth pattern" defined as BMI *z*-score >1 SD [51] at least twice in relevant growth phases from 6 months to 5 years. [a]Initial risk quantification is performed at the 3-month well-child visit for "higher-than-normal BMI growth pattern" during the early phase (6 months to 2 years). [b]First risk re-assessment is performed at the 1-year visit for "higher-than-normal BMI growth pattern" during the late phase (3 to 5 years). [c]Second risk re-assessment is performed at the 2-year visit for "higher-than-normal BMI growth pattern" during the late phase (3 to 5 years). [d]Overweight-preventive measures such as healthier complementary and family food choices, reduced screen time, increased physical activity, and a sleep duration of 10 to 14 h per day. If a risk score is above or equal to the respective cut-off score value (Table 2, Additional file 1: Table S4), the child is at risk of developing a "higher-than-normal BMI growth pattern," and age-appropriate obesity-preventive measures should be initiated by the pediatrician. BMI, body mass index; h, hours; m, months; y, year(s)

pregnancy, as well as LGA birth weight on higher-than-normal BMI growth during successive early-life phases after birth.

Using these modifiable factors [84], we developed a novel strategy to identify infants likely to deviate from the normal BMI growth pattern as a subclinical stage before establishing preschool overweight. Unlike previous methods that offered prediction of manifest overweight [56, 85] and/or were applicable at a certain age only [22] and were developed for offspring born to women of heterogeneous BMI [22], we propose a novel sequential strategy of prediction and re-evaluation of higher-than-normal weight gain in "high-risk" offspring of mothers with obesity at ages 3 months, 1 year, and 2 years to guide pediatric decision-making (Fig. 4). Owing to these differences in the outcome ("higher-than-normal BMI growth pattern"), population (offspring of mothers with obesity), and prediction time points (sequential prediction) between our and previous work, prediction models cannot be directly compared. Integrating such a novel dynamic element in the existing health care system of well-child visits could help to quantify and confine risk to subpopulations and individuals at high necessity to intervene. These preventive visits have a high participation rate [86], even up to 99% of children in Germany, and take place seven times during the first 2 years of life [87]. Interventions to optimize BMI development during the first 1000 days are more beneficial than during preschool ages [88], as an "adaptive phase" when offspring have a chance of returning to their "genetic growth potential" [89].

Thus, following risk stratification by individual risk score and probability calculation at the 3-month well-child visit, breastfeeding continuation can be reinforced by the pediatrician, given the protective role of breastfeeding, e.g., in overweight prevention [82]. Considering the generally low exclusive breastfeeding rates at 6 months (Europe 25% [90]; Germany 12.5% [91]) and the lack of effective intervention strategies to increase the rate and duration of breastfeeding particularly in mothers with obesity [92], prediction-guided "individualized" breastfeeding support by prescribing extra lactation counselling beyond standard care seems promising. Following risk prediction at the 1-year and 2-year visits, mothers with obesity and "high-risk" children may benefit from specific dietary counselling by nutritionists to encourage healthy complementary and family food choices, since early eating patterns determine future eating habits and the development of childhood overweight/obesity [93].

Typical for a screening setting, our prediction models show high sensitivity to avoid false-negative cases and high negative predictive values to avoid misclassification as being "not at risk" in offspring with higher-than-normal BMI growth. Furthermore, even a high false-positive rate, i.e., identifying offspring with normal BMI development as being "at risk," can be considered acceptable since obesity-preventive interventions including exclusive breastfeeding [82] and improved nutrition (such as healthier complementary and family food choices) as well as supportive environments (such as reducing screen time, increasing physical activity, maintaining a sleep duration of 10 to 14 h per day) [94–96] (Fig. 4) are beneficial and safe for young children's growth in general. However, targeting such interventions to a defined subpopulation of offspring at need will direct resources, i.e.,

costs for personal counselling, to those at the highest risk of excessive BMI growth and help minimizing health care costs.

The strength of our study is the large contemporary prospective mother-child cohort PEACHES of 1671 mothers and children providing a unique longitudinal dataset with wide-ranging pre-, peri-, and postnatal variables from mothers with obesity, and thus, it was used as the discovery cohort. Multiple anthropometric measurements improved precision to identify minor deviations in BMI growth especially in the sensitive first months of life. Based on the time structure of the data and use of robust machine learning techniques [97, 98], our proposed strategy provides multiple prediction occasions within an early window of opportunity for prevention of higher-than-normal BMI growth, utilizing routinely available data and making it easy-to-use in clinical settings [99]. Internal (cross-validation) and external (PEPO cohort) validation showed good discrimination between higher-than-normal and normal BMI growth in offspring of mothers either with or without obesity. Attrition bias is unlikely as the follow-up rates in offspring were around 95% in both the PEACHES and PEPO cohorts. The prediction models performed sufficiently well and showed good to very good calibration for early-risk stratification and identification of "high-risk" offspring.

Minor differences between the two cohorts relating to the recruitment strategy, the proportion of mothers with pre-conception obesity, and offspring follow-up time points could influence the lower predictive potential of models in the PEPO cohort. However, despite the differences, external validation showed adequate predictive performance and indicates robustness of our results. Furthermore, we aimed at developing discriminative models for offspring of mothers with and without obesity separately and did not recalibrate the models when applied to the external cohort PEPO. Nevertheless, the predictive models require recalibration when applied to other populations. For prediction models relating to offspring of mothers without obesity, results may not be comparable to other studies with a different composition in the proportions of mothers with normal weight and overweight. Still, we were able to confirm our findings in the PEPO cohort. Regarding the association analyses, we used literature-based risk associations for manifest overweight and applied them to the endpoint "higher-than-normal BMI growth pattern" to test whether there is evidence for an association based on a qualitative approach. Therefore, we did not correct model coefficients by specific shrinking techniques. However, for the development of our prediction score, this was accounted for using penalized regression strategies.

Future studies should develop a user-friendly tool for risk score calculations and evaluate prospectively whether the proposed prediction strategy is effective in guiding favorable BMI growth in early childhood. Such a tool should be easy-to-use in clinical practice, and results should be communicated in an informative manner [100, 101], e.g., a web-based Shiny application developed using the Shiny R package for building easy and interactive web apps in R [102]. Implementing such an instrument and designing a prospective validation study are plans for our future research.

Conclusion

In conclusion, based on a unique set of validated longitudinal data on BMI outcomes in offspring exposed to obesity in pregnancy, we identified a population of offspring at highest risk of an early-starting higher-than-normal BMI growth trajectory inevitably followed by overweight. For individual risk quantification, we devised a novel sequential prediction system to allow early-risk stratification and re-evaluation for prevention of a "higher-than-normal BMI growth pattern" as a subclinical stage preceding overweight. Our proposed prediction strategy could stimulate the use of cost-effective and personalized advice and measures counteracting the risk of very early excess weight gain. Integrating such a procedure in the existing health care systems of well-child visits could help to quantify and confine risk to subpopulations and individuals at high necessity to intervene.

Abbreviations

AGA: Average-for-gestational-age; AUROC: Area under the receiver operating characteristic; BMI: Body mass index; CI: Confidence interval; GCT: Glucose challenge test; GDM: Gestational diabetes; GWG: Gestational weight gain; IADPSG: International Association of Diabetes and Pregnancy Study Groups; IQR: Interquartile range; KiGGS: German Health Interview and Examination Survey for Children and Adolescents; LASSO: Least absolute shrinkage and selection operator; LGA: Large-for-gestational-age; OGTT: Oral glucose tolerance test; OR: Odds ratio; PEACHES: Programming of Enhanced Adiposity Risk in CHildhood–Early Screening; PEPO: PErinatal Prevention of Obesity; SES: Socioeconomic status; SGA: Small-for-gestational-age; T1D: Type 1 diabetes; T2D: Type 2 diabetes; WHO: World Health Organization.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-022-02318-z.

Additional file 1: S1 STROBE Checklist. **S2** TRIPOD Statement. **Text S1.** Statistical analysis plan. **Text S2.** Statistical methods. **Text S3.** Quantification of individual risk. **Figure S1.** Influence of maternal obesity on offspring BMI growth outcomes. Shown are ORs and 95% CIs of the influence of maternal pre-conception obesity on BMI growth outcomes up to age 5 years in all offspring belonging to upper BMI growth clusters from the PEACHES cohort study. Values were derived from univariate logistic regression. [a]The term "multiple occasions" was defined as having BMI z-scores >1 SD [51] at least 5 out of 6 times at the well-child visits at age 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years. BMI, body mass index; CI, confidence interval; OR, odds ratio; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening. **Figure S2.** Proportion of offspring in upper and lower BMI growth clusters according to birth weight category. Shown are percentages in offspring of mothers

with obesity (panel A) and without (panel B) enrolled in the PEACHES cohort study, according to their birth weight category for gestational age and sex. AGA, average-for-gestational-age; BMI, body mass index; LGA, large-for-gestational-age; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening; SGA, small-for-gestational-age. **Figure S3.** Mean BMI growth clusters by birth weight category in offspring of mothers with and without obesity. Shown are mean BMI z-score growth clusters from birth to age 6 months (panel A, C) and birth to age 5 years (panel B, D) by birth weight category for gestational age and sex in offspring of mothers with and without obesity enrolled in the PEACHES cohort study. AGA, average-for-gestational-age; BMI, body mass index; LGA, large-for-gestational-age; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening; SGA, small-for-gestational-age. **Figure S4.** Effects of prenatal and postnatal factors on BMI growth outcomes in offspring of mothers without obesity. Shown are ORs and 95% CI of the influence of prenatal and postnatal factors on the development of an upper cluster of BMI growth (birth to age 5 years, panel A) and a "higher-than-normal BMI growth pattern," defined as BMI z-score >1 SD [51] at least twice, during early phase (6 months to 2 years, panel B) and late phase (3 years to 5 years, panel C) in offspring of mothers without obesity enrolled in the PEACHES cohort study. Values were derived from multivariable logistic regression with stepwise backward selection. Only final models based on the lowest Akaike information criterion are presented. Included variables in all initial models were maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month. Additionally, for associations shown in panel C, "higher-than-normal BMI growth pattern" in the early phase was also included as an explanatory variable in the initial model. BMI, body mass index; CI, confidence interval; GDM, gestational diabetes; GWG, gestational weight gain; LGA, large-for-gestational-age; OR, odds ratio; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening; SES, socioeconomic status; SGA, small-for-gestational-age. **Figure S5.** Calibration plots of prediction models for identifying a "higher-than-normal BMI growth pattern" in the validation cohort. Shown are calibration curves (blue lines) and calibration slopes and intercepts for offspring of mothers with obesity (panel A, B) and without obesity (panel C, D) by the prediction models at age 1 year and 2 years. The diagonal gray lines represent the optimal prediction; the closer the model curve is to the diagonal line, the more accurate is the prediction. At the top of each graph, dots indicate presence of the outcome "higher-than-normal BMI growth pattern," defined as BMI z-score >1 SD [51] at least twice, in the late phase (3 years to 5 years). At the bottom of each graph, dots indicate absence of the outcome "higher-than-normal BMI growth pattern" in the late phase. Calibration of models at age 3 months for "higher-than-normal BMI growth pattern" in the early phase (6 months to 2 years) could not be performed due to the lack of follow-up data at age 3 months in the validation cohort PEPO. BMI, body mass index; PEPO, PErinatal Prevention of Obesity. **Table S1.** Offspring follow-up rates in the study populations. Values are n (%). [a]Missing data in the PEACHES cohort were due to loss to follow-up. Missing data in the PEPO cohort were due to lack of availability of data in the records of the regular well-child visits at the time of school entry health examination. [b]A total of 13 and 297 children enrolled in the PEACHES cohort were too young for the follow-up visit at age 4 and 5 years, respectively, and therefore were not included in the "total" category. Missing data were considered missing completely at random. NA, not available; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening; PEPO, PErinatal Prevention of Obesity. **Table S2.** Mean BMI z-scores by BMI growth cluster in offspring of mothers with and without obesity. Values are mean and 95% CI in offspring of mothers with and without obesity enrolled in the PEACHES cohort study. [a]Of a total of 887 children included for cluster analysis, 875 children could be categorized into longitudinal BMI growth clusters based on an adequate number of data points. [b]Of a total of 670 children included for cluster analysis, 655 children could be categorized into clusters based on an adequate number of data points. [c]A total of 276 and 549 children enrolled in the PEACHES cohort were not included in the cluster analysis at age 4 and 5 years, respectively, because of follow-up not yet due (age 4 years: n=13, age 5 years: n=297) or missing data due to loss to follow-up (age 4 years: n=263, age 5 years: n=252). Missing data were considered missing completely at random. BMI, body mass index; CI, confidence interval; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening. **Table S3.** Offspring BMI growth dynamics in consecutive life phases after birth following exposure to gestational obesity. Values are n (%) in offspring enrolled in the PEACHES cohort study. Only children with complete data on BMI z-scores in both the early and late phase are presented. [a]Includes values for categories "normal range" (≥-2 to ≤1 SD) and a minor proportion of children with <-2 SD [72]. [b]BMI z-score >1 SD defined as occurring once. Includes values for categories "at risk of overweight" (>1 to ≤2 SD), overweight (>2 to ≤3 SD), and obesity (>3 SD) [51]. [c]"Higher-than-normal BMI growth pattern" defined as BMI z-score >1 SD [51] at least twice. BMI, body mass index; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening. **Table S4.** Predictive performance of a sequential algorithm to identify higher-than-normal BMI growth in offspring of mothers without obesity. We used the PEACHES cohort study as the discovery cohort and the PEPO cohort study as the external validation cohort for calculation of the individual child's risk of a "higher-than-normal BMI growth pattern" (BMI z-score >1 SD [51] at least twice). Values are predictive parameters and their 95% CI. [a]Potential predictors included: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, and BMI z-score >1 SD at age 3 months. External validation of models at age 3 months could not be performed due to the lack of follow-up data at age 3 months in the validation cohort PEPO. [b]Potential predictors included: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, breastfeeding status at 6 months, and BMI z-score >1 SD at age 1 year. External validation of models at age 1 year was performed in the validation cohort PEPO. [c]Potential predictors included: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, breastfeeding status at 6 months, and BMI z-score >1 SD at age 2 years. External validation of models at age 2 years was performed in the validation cohort PEPO. [d]Offspring with a risk score above or equal to the respective cut-off score value are considered to be at risk of developing a "higher-than-normal BMI growth pattern." The cut-off value of the score was optimized to avoid false-negative findings (sensitivity), which resulted in negative cut-off score values. AUROC, area under the receiver operating characteristic; BMI, body mass index; CI, confidence interval; GDM, gestational diabetes; GWG, gestational weight gain; NA, not applicable; PEACHES, Programming of Enhanced Adiposity Risk in CHildhood–Early Screening; PEPO, PErinatal Prevention of Obesity; SES, socioeconomic status. **Table S5.** Scoring system for quantification of risk of higher-than-normal BMI growth in young offspring. [a]The equations can be used for sequential individual risk quantification of a "higher-than-normal BMI growth pattern" (BMI z-score >1 SD [51] at least twice) in offspring of mothers with or without pre-conception obesity separately. The prenatal and postnatal variables in the risk quantification equations should be replaced by pre-defined values (0 or 1) depending on whether the condition stated is fulfilled (1) or not (0). The calculated risk score should be compared to the respective cut-off score value (Table 2, Additional file 1: Table S4) . Offspring with a risk score above or equal to the respective cut-off are considered to be at risk of developing a "higher-than-normal BMI growth pattern." Details on calculating individual risk probabilities and use of individual risk score calculations along with clinical case scenarios are provided in the Text S3 (Additional file 1). BMI, body mass index; BF, breastfeeding; GDM, gestational diabetes; GWG, gestational weight gain; m, month(s); LGA, large-for-gestational-age; SES, socioeconomic status; SGA, small-for-gestational-age; y, year(s).

Acknowledgements
We are grateful to all participants, physicians, midwives, and study nurses involved in the PEACHES and PEPO cohorts. We thank the staff members of the obstetric and pediatric departments for their constant support in the

PEACHES cohort study. We also thank Susanne Wullinger, Research Center, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-Universität München for excellent technical assistance.

Authors' contributions
RE conceptualized the study. DG, LL, RE, and UM were involved in the study analysis plan. SP, UH, MD, KL, UN, NAH, HN, AAR, and RE contributed to the acquisition of the data and/or interpretation of the data. DG, LL, and UM carried out the analyses. DG, UM, AAR, and RE prepared the original manuscript. DG and RE contributed to the composition and editing of the final manuscript. All authors read and approved the final manuscript.

Funding
This work was supported by the German Federal Ministry of Education and Research (grants 01EA1307, 01GI0820), Bavarian State Ministry of the Environment and Public Health (grant LP00124), and the Foundation for Cardiovascular Prevention in Childhood, Ludwig-Maximilians-Universität München, Munich, Germany. The funding sources had no role in the study design, data collection, analysis and interpretation of the data, writing of the report, nor in the decision to submit the paper for publication. Open Access funding enabled and organized by Projekt DEAL.

Availability of data and materials
The datasets analyzed during the current study are not publicly available because participants did not explicitly consent to the sharing of their data as per European Union's General Data Protection Regulation and the corresponding German privacy laws. However, data are available from the corresponding author (Regina Ensenauer, principal investigator) on reasonable request for researchers who meet the criteria for access to confidential data.

Declarations

Ethics approval and consent to participate
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects were approved for both the PEACHES (protocol no. 165-10) and the PEPO (protocol no. 271-09) cohort studies by the Research Ethics Committee of the Ludwig-Maximilians-Universität München, Germany. Written informed consent was obtained from all subjects of each cohort study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 22 August 2021 Accepted: 28 February 2022
Published online: 14 April 2022

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Publisher's Note

Additional file 1.

Gomes D, Le L, Perschbacher S, et al. Predicting the earliest deviation in weight gain in the course towards manifest overweight in offspring exposed to obesity in pregnancy: a longitudinal cohort study

Table of Contents

Abbreviations: AGA, average-for-gestational-age; AUROC, area under the receiver operating characteristic; BF, breastfeeding; BMI, body mass index; CI, confidence interval; exp, exponential function; GDM, gestational diabetes; GWG, gestational weight gain; LASSO, least absolute shrinkage and selection operator; LGA, large-for-gestational-age; OR, odds ratio; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening; PEPO, PErinatal Prevention of Obesity; ROC, receiver operating characteristic; SES, socioeconomic status; SGA, small-for-gestational-age; T1D, type 1 diabetes; T2D, type 2 diabetes; WHO, World Health Organization.

S1 STROBE Checklist.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Author's Response
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Pages 1 and 3 to 4, Title; Abstract, "Methods".
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 3 to 4, Abstract, "Background", "Methods", and "Results".
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 5 to 6, Introduction, paragraphs 1 to 3.
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6, Introduction, paragraph 4.
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7, Methods, "Study design and populations".
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 7 to 13, Methods, "Study design and populations", "Procedures"; Fig 1.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pages 7 to 8, Methods, "Study design and populations" and "Procedures": "Inclusion criteria for analysis", Pages 12 to 13, "Growth outcomes until age 5 years"; Fig 1; Additional file 1, Table S1.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 8 to 13, Methods, "Potential predictors of higher-than-normal BMI growth", "Growth outcomes until age 5 years".
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 8 to 13, Methods, "Potential predictors of higher-than-normal BMI growth", "Growth outcomes until age 5 years".
Bias	9	Describe any efforts to address potential sources of bias	Pages 7 to 8, Methods, "Study design and populations"; Pages 8 to 9, "Potential predictors of higher-than-normal BMI growth", Page 14, "Statistical analysis"; Page 34,

			Discussion, paragraph 7; Additional file 1, Table S1.
Study size	10	Explain how the study size was arrived at	Page 8, Methods, “Inclusion criteria for analysis”, Page 14, “Statistical analysis”; Fig 1; Additional file 1, Text S2. “Statistical methods.” (Page 13), Table S1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 8 to 13, Methods, “Inclusion criteria for analysis”, “Potential predictors of higher-than-normal BMI growth”, “Growth outcomes until age 5 years”; Page 19 to 21, Results, “BMI growth patterns in offspring”.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 14 to 15, Methods, “Statistical analysis”. Additional file 1, Text S1. “Statistical analysis plan.”, Text S2. “Statistical methods.”, Text S3. “Quantification of individual risk.”
		(*b*) Describe any methods used to examine subgroups and interactions	Page 14, Methods, “Statistical analysis”; Additional file 1, Text S1. “Statistical analysis plan.”, Text S2. “Statistical methods.”
		(*c*) Explain how missing data were addressed	Page 14, Methods, “Statistical analysis”; Table 1 (footnote); Fig 1; Additional file 1, Text S2. “Statistical methods.”, paragraph 1.6 (Page 14), Table S1 and Table S2.
		(*d*) If applicable, explain how loss to follow-up was addressed	Any losses to follow-up were excluded from analysis. Page 14, Methods, “Statistical analysis”; Table 1 (footnote); Fig 1; Additional file 1, Table S1 and Table S2.
		(*e*) Describe any sensitivity analyses	We used an independent cohort PEPO for validation purposes and to assess the robustness of our results using data-driven approaches. We conducted analyses in two different groups: offspring of mothers with obesity and offspring of mothers without obesity. Page 7, Methods, “Study design and populations”, Pages 14 to 15, “Statistical analysis”; Results, “BMI growth patterns in offspring”, “Sequential prediction of higher-than-normal BMI growth”; Table 2; Additional file 1, Text S1. “Statistical analysis

			plan.", Text S2. "Statistical methods.", Fig S1, Table S4.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pages 15 to 17, Results, "Characteristics of study populations", Page 19, "BMI growth patterns in offspring"; Table 1; Fig 1; Additional file 1, Tables S1 to S4, Fig. S2.
		(b) Give reasons for non-participation at each stage	Page 14, Methods, "Statistical analysis"; Pages 15 to 16, Results, "Characteristics of study populations"; Fig 1; Additional file 1, Tables S1 and S2.
		(c) Consider use of a flow diagram	Fig 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pages 15 to 17, Results, "Characteristics of study populations"; Table 1.
		(b) Indicate number of participants with missing data for each variable of interest	Number of participants with complete data are given in the following figures and tables: Fig 1; Tables 1 and 2; Additional file 1, Tables S1 to S4, Fig. S2. Participants with any missing data were excluded from analysis.
		(c) Summarise follow-up time (eg, average and total amount)	Pages 12 to 13, Methods, "Growth outcomes until age 5 years"; Table 1; Additional file 1, Tables S1 and S2.
Outcome data	15*	Report numbers of outcome events or summary measures over time	Pages 19 to 22, Results, "BMI growth patterns in offspring", "Higher-than-normal BMI growth patterns in consecutive early-life phases"; Figs 1 and 2; Table 2; Additional file 1, Tables S1 to S4.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included.	Page 9, Methods, "Potential predictors of higher-than-normal BMI growth"; Pages 22 to 27, Results, "Risk factors of higher-than-normal BMI growth", "Sequential prediction of higher-than-normal BMI growth"; Fig 3 (including legend); Table 2; Additional file 1, Fig S4 (including legend), Table S4.
		(*b*) Report category boundaries when continuous variables were categorized	Pages 10 to 13, Methods, "Potential predictors of higher-than-normal BMI growth", "Growth outcomes until age 5 years"; Pages 19 to 22, Results, "BMI growth patterns in offspring", "Higher-than-normal BMI growth patterns in consecutive early-life phases";

			Additional file 1, Fig S1, Table S3.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 28, Discussion, paragraph 1.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 34 to 35, Discussion, paragraph 8.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 28 to 35, Discussion, paragraphs 2 to 8.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 34, Discussion, paragraphs 7 and 8.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Pages 36 to 37.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

S2 TRIPOD Statement.

TRIPOD Checklist: Prediction Model Development and Validation				
Section/Topic	**Item***		**Checklist Item**	**Page**
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Page 1, Title.
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Pages 3 to 4, Abstract.
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Pages 5 to 6, Background, paragraphs 1 to 3.
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Page 6, Background, paragraph 4.
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation datasets, if applicable.	Page 7, Methods, “Study design and populations”.
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Page 7, Methods, “Study design and populations”, Pages 12 to 13, “Growth outcomes until age 5 years”.
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Page 7, Methods, “Study design and populations”.
	5b	D;V	Describe eligibility criteria for participants.	Page 7, Methods, “Study design and populations”, Page 8, “Inclusion criteria for analysis”.
	5c	D;V	Give details of treatments received, if relevant.	Not applicable.
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Page 13, Methods, “Growth outcomes until age 5 years” (paragraph 4).
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	Not applicable.
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Pages 8 to 12, Methods, “Potential predictors of higher-than-normal BMI growth”.
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	Not applicable.
Sample size	8	D;V	Explain how the study size was arrived at.	Page 8, Methods, “Inclusion criteria for analysis”, Page 14 “Statistical analysis”; Fig

				1; Additional file 1, Text S2. “Statistical methods.” (Page 13), Table S1.
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Page 14, Methods, “Statistical analysis”; Table 1 (footnote); Fig 1; Additional file 1, Text S2. “Statistical methods.”, paragraph 1.6 (Page 14), Table S1 and Table S2.
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Page 14, Methods, “Statistical analysis”; Additional file 1, Text S1. “Statistical analysis plan.”, Text S2. “Statistical methods.”.
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Page 14, Methods, “Statistical analysis”; Additional file 1, Text S1. “Statistical analysis plan.”, Text S2. “Statistical methods.”.
	10c	V	For validation, describe how the predictions were calculated.	Additional file 1, Text S1. “Statistical analysis plan.”, Text S2. “Statistical methods.”, Table S4; Table 2.
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Table 2; Additional file 1, Text S2. “Statistical methods.”, Table S4.
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Not applicable.
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Page 14, Methods, “Statistical analysis”.
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Pages 7 to 15, Methods, “Study design and populations”, “Procedures”, “Statistical analysis”; Pages 15 to 17, Results, “Characteristics of study populations”; Table 1; Additional file 1, Table S1.
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Fig. 1. Additional file 1, Table S3.
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Pages 15 to 17, Results, “Characteristics of study populations”; Tables 1 and 2; Additional file 1, Tables S1 to S4.
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Pages 15 to 17, Results, “Characteristics of study populations”; Table 1.
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Number of participants with complete data are

				given in the following figures and tables: Fig 1; Tables 1 and 2; Additional file 1, Tables S1 to S4.
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Not applicable.
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Additional file 1, Table S5.
	15b	D	Explain how to use the prediction model.	Additional file 1, Text S3. "Quantification of individual risk.".
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Table 2; Additional file 1, Table S4.
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	Not applicable.
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Pages 34 to 35, Discussion.
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Page 34, Discussion.
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Pages 28 to 35, Discussion.
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Page 35, Discussion.
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and datasets.	Additional file 1, Text S1. "Statistical analysis plan.", Text S3. "Quantification of individual risk.", Table S5.
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Pages 36 to 37.

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Text S1. Statistical analysis plan.

Manuscript: Predicting the earliest deviation in weight gain in the course towards manifest overweight in offspring exposed to obesity in pregnancy: a longitudinal cohort study

Ulrich Mansmann, Delphina Gomes, Regina Ensenauer, and Lien Le

Munich, 2020-01-13

Contents

1 Study population

The following inclusion and exclusion criteria will be applied for the analyses in the children enrolled in the Programming of Enhanced Adiposity Risk in Childhood–Early Screening (PEACHES) cohort and the PErinatal Prevention of Obesity (PEPO) cohort (validation):

Inclusion criteria:

1. Mothers with or without pre-conception obesity
2. Singleton pregnancy
3. Absence of type 1 diabetes (T1D) or type 2 diabetes (T2D) in mothers
4. Full-term (≥37 weeks 0 days of gestation) live birth

Exclusion criteria:

1. Underweight mothers
2. Twin/multiple pregnancy
3. Presence of T1D or T2D in mothers
4. Preterm children (gestational age ≤36 weeks 6 days of gestation)

2 Calculation of specific predictors of higher-than-normal BMI growth in offspring

The majority of predictors including maternal pre-conception body mass index (BMI), gestational diabetes (GDM), parity, smoking during pregnancy, sex, socioeconomic status (SES), and breastfeeding status at 1, 3, and 6 months will be extracted from the PEACHES and PEPO databases. Gestational weight gain (GWG) and birth weight categories will be calculated.

2.1 Calculation of total GWG

Total GWG in kilograms will be calculated as the difference between the last measured weight before delivery and pre-conception weight and will be classified as inadequate, adequate, or excessive according to the BMI-specific recommendations of the Institute of Medicine (now known as the National Academy of Medicine)/National Research Council [38]. Pre-conception weight will be based on data measured at the first antenatal visit if the visit was before 12 weeks 6 days of gestation or on reported and documented data abstracted from the pregnancy record booklet if the first visit was later than the 13th week of gestation.

2.2 Calculation of birth weight categories for gestational age and sex

We will group offspring according to their birth weight adjusted for gestational age and sex into large-for-gestational-age (LGA, >90th percentile), average-for-gestational-age (AGA, 10th to 90th percentile), or small-for-gestational-age (SGA, <10th percentile) categories. These cut-offs were based on the German reference population [46].

2.3 Calculation of offspring BMI z-scores

Offspring BMI z-scores will be calculated according to World Health Organization (WHO) age- and sex-specific growth standards [51].

2.4 Calculation of frequencies of BMI z-score >1 SD

“Early phase” and “late phase” of offspring BMI growth will be defined as the period between 6 months to 2 years and 3 years to 5 years, respectively. Children will be classified as having a “higher-than-normal BMI growth pattern” (BMI z-score >1 SD [51] at least twice) within each growth phase.

Among all children belonging to the group of high BMI growth, we will also categorize offspring with repeated occasions of BMI z-score >1 SD at the 6-month, 1-year, 2-year, 3-year, 4-year, and 5-year follow-up visits to identify offspring with the highest risk of developing preschool overweight.

3 Statistical analyses

3.1 Longitudinal cluster analysis

Analysis with k-means clustering will aim to divide children into BMI growth clusters, which will be characterized by distinct BMI development patterns from birth to 5 years of age. The cluster analysis will be done for children of mothers with and without pre-conception obesity, respectively.

3.2 Validation analysis of cluster findings

The BMI growth clusters that will be identified in offspring enrolled in the PEACHES cohort will be externally validated in the PEPO cohort. The validation procedure will first classify offspring into different clusters using random forests. Next, we will apply this cluster-derived classification rule to the children in the PEPO cohort: offspring will be categorized into one of the different cluster-derived classes. Next, we will quantify whether different cluster classes can discriminate the BMI z-scores at age 5 years of the PEPO children. To this end, the receiver operating characteristic (ROC) will be determined and the area under the ROC (AUROC) will be calculated to quantify the discriminatory ability of the cluster-derived classification rule.

3.3 Analysis of risks of adverse BMI growth outcomes

Using logistic regression analyses, we will calculate odds ratios for the following:

1) Outcome = child overweight (including obesity), predictor = BMI growth cluster, subgroups = mothers with and without obesity. To evaluate the influence of upper cluster BMI growth on the manifestation of childhood overweight/obesity, we will perform regression analysis with offspring overweight/obesity (yes versus no) as outcome and cluster of BMI growth (upper versus lower) as influencing factor in offspring subgroups of mothers with and without obesity. This analysis will be performed for both offspring age 4 and 5 years, respectively.

2) Outcome = child overweight (including obesity), predictor = maternal pre-conception obesity, subgroup = all offspring in upper BMI growth clusters. To evaluate the influence of maternal pre-conception obesity on overweight/obesity risk in all offspring with an upper BMI growth trajectory, we will conduct regression analysis with offspring overweight/obesity (yes versus no) as outcome and maternal pre-conception BMI group (with obesity versus without) as influencing factor in the population of offspring growing in the upper BMI growth clusters (of both mothers with and without obesity). This analysis will be performed for both offspring age 4 and 5 years, respectively.

3) Outcome = at least 5 out of 6 occurrences of having a BMI z-score >1 SD, predictor = maternal pre-conception obesity, subgroup = all offspring in upper BMI growth clusters. Within the offspring population growing in the upper BMI clusters, we will calculate the odds for at least 5 out of 6 occurrences of having a BMI z-score >1 SD with number of occurrences (≥5 versus ≤4) as outcome and maternal pre-conception BMI group (with obesity versus without) as influencing factor.

3.4 Analysis of the influence of pre- and postnatal factors on higher-than-normal BMI growth

We will explore the simultaneous effects of prenatal and postnatal factors on upper BMI growth clusters and “higher-than-normal BMI growth pattern” during the early phase and the late phase in offspring by logistic regression using backward selection. These analyses will be conducted separately for offspring of mothers with and without obesity. The following prenatal and postnatal predictors will be included:

1) Outcome = upper BMI growth cluster, potential predictors = maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight categories for gestational age and sex, SES, and breastfeeding status at 1 month.

2) Outcome = “higher-than-normal BMI growth pattern” in early phase, potential predictors = maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight categories for gestational age and sex, SES, and breastfeeding status at 1 month.

3) Outcome = “higher-than-normal BMI growth pattern” in late phase, potential predictors = maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight categories for gestational age and sex, SES, breastfeeding status at 1 month, and “higher-than-normal BMI growth pattern” in early phase.

3.5 Prediction analysis

Using penalized least absolute shrinkage and selection operator (LASSO) regression analysis, we will explore the predictive power of prenatal and postnatal factors including current child BMI status to predict "higher-than-normal BMI growth pattern" in early and late phases of growth at ages 3 months, 1 year, and 2 years in offspring. LASSO regression analysis will be conducted for early phase and late phase separately in offspring groups of mothers with and without obesity.

All prediction models will include the following prenatal and postnatal factors and their two-fold interactions. Prenatal/postnatal factors included in prediction models are as follows:

1) Prediction at age 3 months = maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight categories for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, and BMI z-score >1 SD at age 3 months.

2) Prediction at age 1 year = maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight categories for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, breastfeeding status at 6 months, and BMI z-score >1 SD at age 1 year.

3) Prediction at age 2 years = maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight categories for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, breastfeeding status at 6 months, and BMI z-score >1 SD at age 2 years.

Internal validation will be performed with the whole PEACHES dataset. AUROC will be calculated to assess the internal prediction performance of the selected model from the LASSO regression analysis. Prediction models at ages 1 year and 2 years will be validated using available data of the PEPO cohort to assess the external prediction performance.

We will calculate different cut-offs and determine cut-off points that are:

1) closest to the upper left corner of the ROC curve, where equal weight is given to false negative and false positive predictions,

2) closest to the upper left corner of the ROC curve, where double weight is given to false positive predictions,

3) closest to the upper left corner of the ROC curve, where double weight is given to false negative predictions,

4) 90th percentile of the linear predictors of children without "higher-than-normal BMI growth pattern".

Text S2. Statistical methods.

The current analysis is exploratory and hypothesis-generating (discovery) on the data of the Programming of Enhanced Adiposity Risk in Childhood–Early Screening (PEACHES) cohort. No formal sample size calculation was done, and no primary hypothesis was formulated. Independent external validation of analyses was performed on the data of the PErinatal Prevention of Obesity (PEPO) cohort. The sample size calculation for the validation was based on example 8.3 (page 226) of Pepe (2003) [53]. A total of 500 children (assuming a 20% prevalence of children with higher-than-normal body mass index [BMI] growth) were needed to reject the null hypothesis (area under the receiver operating characteristic [AUROC] ≤0.55) given the alternative (AUROC=0.70) on a 5% level with a power of at least 90%.

1.1. Assessment of the agreement between self-reported pre-conception weight and weight measured at the first antenatal visit

We assessed the agreement between maternal pre-conception weight self-reported and weight measured at the first antenatal visit in the PEACHES data using the principles of the Bland-Altman method [37]. We further estimated the correlation between the two maternal weight measurements using the Pearson product-moment correlation.

1.2. Cluster analysis and assessment of adequate BMI growth clusters

Cluster analysis was performed using the k-means technique in children of the PEACHES cohort. K-means clustering is a non-parametric approach aimed to group children's growth trajectories into clusters characterized by distinct weight development patterns from birth to 5 years of age. The best number of clusters was chosen by applying the Calinski & Harabasz criterion, where maximum variances between clusters and minimum variances within clusters are reached [54]. The criterion gave two options: setting the number of clusters to two or three.

For the analyses, we used the three-cluster option. The two lower clusters were combined and compared to the upper cluster. We applied the least absolute shrinkage and selection operator (LASSO) logistic regression and 10-fold cross validation to identify models that can best divide the offspring into separate BMI growth clusters.

1.3. Validation of BMI growth clusters

Since the number of offspring BMI z-score measurements differed between the PEACHES (maximum of 9) and the PEPO (maximum of 4) cohorts, clusters of BMI growth were validated in the PEPO cohort based on random forests. The BMI growth clusters obtained from offspring enrolled in the PEACHES cohort were validated by the following steps.

In the first step, using PEACHES data from birth to age 3 months, offspring were classified into upper or lower BMI growth clusters. In the second step, the children of the PEPO cohort were stratified into two groups (i.e. into a potential lower versus a potential upper BMI growth cluster) according to the classification rule of step one. In the third step, within the PEPO cohort, the AUROC was calculated based on the BMI growth cluster membership determined in step two and the BMI z-scores at age 5 years. These steps allowed assessing, within the PEPO cohort, whether the BMI growth cluster membership discriminated children based on their BMI z-score value at age 5 years, in the respective groups of children of mothers with and without obesity.

1.4. Risks of adverse BMI growth outcomes

Based on univariate logistic regression analysis, we calculated the risks of several adverse BMI growth outcomes including i) multiple occasions (≥5 occurrences) of offspring BMI z-score >1 SD between age 6 months to 5 years and ii) child overweight (including obesity) at both age 4 and 5 years, respectively.

Firstly, we evaluated the influence of growing in the upper cluster of BMI growth on the manifestation of childhood overweight/obesity in the offspring populations of mothers with or without obesity. We used the presence of childhood overweight/obesity (yes versus no) as outcome and cluster membership of BMI growth (upper versus lower) as influencing factor.

Next, we studied the influence of maternal pre-conception obesity on the manifestation of childhood overweight/obesity in all offspring with upper BMI growth trajectory (Figure S1). We used the presence of childhood overweight/obesity (yes versus no) as outcome and the maternal pre-conception BMI group (mothers with obesity versus without) as influencing factor.

Among all children belonging to the upper clusters of BMI growth, we classified offspring BMI z-score as below, equal or above 1 SD [51] at each of the well-child visits at age 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years. To identify offspring with the highest risk of developing preschool overweight, we calculated the odds for having a BMI z-score >1 SD on at least 5 out of 6 occasions in offspring growing in the upper BMI growth clusters (Figure S1). We used the number of occurrences (≥5 versus ≤4) as outcome and the maternal pre-conception BMI group (mothers with obesity versus without) as influencing factor.

1.5. Identification of prenatal and postnatal risk factors of higher-than-normal BMI growth

Using log-linear models, we compared the structural differences related to a "higher-than-normal BMI growth pattern" during the early phase and the late phase in offspring of mothers with obesity versus without.

A series of multivariable logistic regression analyses were performed to identify risk factors related to i) the cluster of upper BMI growth membership from birth to 5 years and ii) the main outcome of a "higher-than-normal BMI growth pattern" during the early phase and the late phase of growth, respectively, in offspring of mothers with or without obesity. For models assessing the effect of prenatal and postnatal factors on higher-than-normal BMI growth in the late phase, we used "higher-than-normal BMI growth pattern" in the early phase as an additional potentially influencing variable.

After starting with a comprehensive model that included all potential prenatal and postnatal factors, use of a backward selection method resulted in combinations of factors influencing higher-than-normal BMI growth of offspring during the entire first 5 years after birth and during the early phase and the late phase within this period, respectively. A prenatal or postnatal risk factor was considered relevant if the 95% confidence interval (CI) of its odds ratio did not contain 1.

1.6. Development and validation of risk prediction models

Using the dataset of the PEACHES cohort, we developed several risk models to predict a "higher-than-normal BMI growth pattern" in offspring during their early and late phases of growth, respectively. For the prediction analyses, we only included children with complete data on prenatal and postnatal factors and longitudinal anthropometric measurements. Missing values were not imputed since existing proposals for multiple imputation in penalized logistic regression models (see e.g. R-package MAMI [55] [http://mami.r-forge.r-project.org/]) have not been validated up to now.

Consecutive prediction models were developed using robust techniques such as LASSO, which enabled both individual risk scoring and risk probability assessment at the well-child visits at ages 3 months, 1 year, and 2 years. For each prediction model, we calculated several cut-off score values, because there are no standard criteria for the identification of risk thresholds to predict childhood excess BMI growth [56]. We calculated the sensitivity, specificity, positive and negative predictive values, and likelihood ratios, with corresponding 95% CIs for the prediction models in both the discovery and validation cohorts. Positive likelihood ratio values of 2, 3, and 4 indicate an increase in the likelihood of a "higher-than-normal BMI growth pattern" in offspring identified as "at risk" with a probability of 15%, 20%, and 25%, respectively [57]. Negative likelihood ratio values of 0.5, 0.4, and 0.3 indicate a decrease in the likelihood of a "higher-than-normal BMI growth pattern" in offspring identified as "not at risk" with a probability of 15%, 20%, and 25%, respectively [57].

Prediction models included the following prenatal and postnatal factors (including child's BMI status at the respective prediction time point) and interactions between factors:

Prediction of higher-than-normal BMI growth in early phase at age 3 months: maternal pre-conception BMI group, total gestational weight gain (GWG), gestational diabetes (GDM), parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, socioeconomic status (SES), breastfeeding status at 1 month, breastfeeding status at 3 months, and BMI z-score >1 SD at age 3 months.

Prediction of higher-than-normal BMI growth in late phase at age 1 year: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, breastfeeding status at 6 months, and BMI z-score >1 SD at age 1 year.

Prediction of higher-than-normal BMI growth in late phase at age 2 years: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, breastfeeding status at 6 months, and BMI z-score >1 SD at age 2 years.

Prediction models at offspring ages 1 and 2 years were externally validated by applying them to corresponding mother-child pairs of the PEPO cohort. We were unable to externally validate the prediction model at age 3 months because the PEPO cohort does not offer data on offspring BMI z-scores at age 3 months. We generated calibration plots and provided calibration slopes and intercepts to assess the agreement between the observed and predicted probabilities of the outcome using the validation cohort PEPO [58, 59]. Calibration was considered as optimal, if the observed and predicted risks were on a 45-degree diagonal line.

All P values presented were two-sided. We used the statistical software package R version 3.5.1 [60] supported by the following version-specific packages: kml [61] for the cluster analysis, MASS [62] for backward selection in association analyses, glmnet [63] for LASSO regression analysis, lme4 [64] for analyses using mixed models, and ROCR [65] for prediction analyses.

Text S3. Quantification of individual risk.

The overall prediction-guided prevention strategy is shown in Fig. 4, and equations for individual risk score calculation in offspring of mothers with and without pre-conception obesity are provided in Table S5. Risk scores for higher-than-normal body mass index (BMI) growth in the early phase or late phase, respectively, can be calculated for each child at age 3 months, 1 year, and 2 years by adding the intercept and coefficients of the model. These parameters represent the adjusted contribution of each risk factor to higher-than-normal BMI growth. The final prediction models retained only those factors which contributed considerably to the risk score quantification (being still relevant after a cross validation-guided shrinkage of the coefficient).

The risk score calculated for an individual child is also called linear predictor in the terminology of logistic regression. It can be used to determine the risk in terms of probability as follows ("exp" being the exponential function):

$$\text{Probability of higher} - \text{than} - \text{normal BMI growth} = \frac{\exp(\text{risk score})}{1 + \exp(\text{risk score})}$$

To calculate individual risk scores, each prenatal and postnatal variable in the risk quantification equations (Table S5) should be replaced by pre-defined values (0 or 1) depending on whether the condition stated is fulfilled (1) or not (0).

1.1. Risk quantification in offspring of mother with obesity at well-child visits

To illustrate how risk for higher-than-normal BMI growth in the early phase (between 6 months and 2 years) can be quantified, consider the following clinical case scenario of an offspring who was exposed to obesity in pregnancy:

Initial risk quantification at age 3 months for developing higher-than-normal BMI growth in the early phase:

A primiparous mother with class 3 obesity at conception, who had excessive gestational weight gain (GWG), developed gestational diabetes (GDM), did not smoke during pregnancy, and belonged to low/medium socioeconomic status (SES), gave birth to a boy with a large-for-gestational-age (LGA) birth weight and a BMI z-score of 1.01 SD at age 3 months. The boy was not fully breastfed (BF) at ages 1 month and 3 months. Note that "SGA" indicates "small-for-gestational-age" birth weight.

"Higher-than-normal BMI growth pattern" during the early phase (6 months to 2 years) = -2.094 + 0.036 * LGA + 0.892 * LGA * inadequate GWG - 0.671 * SGA * male sex + 0.185 * GDM positive * SGA + 0.129 * GDM positive * excessive GWG + 0.013 * GDM positive * maternal class 3 obesity - 0.429 * GDM positive * smoking during pregnancy + 0.204 * GDM positive * full BF at 3m + 0.147 * excessive GWG * male sex + 2.003 * BMI z-score > 1 SD at 3m + 0.246 * BMI z-score > 1 SD at 3m * SGA + 0.837 * BMI z-score > 1 SD at 3m * inadequate GWG + 0.388 * BMI z-score > 1 SD at 3m * primiparity + 0.142 * maternal class 2 obesity * LGA + 0.036 * maternal class 2 obesity * SGA + 0.093 * maternal class 2 obesity * primiparity + 0.195 * maternal class 2 obesity * full BF at 3m + 0.287 * maternal class 2 obesity * LGA + 0.183 * maternal class 3 obesity * excessive GWG - 0.193 * smoking during pregnancy * LGA + 0.222 * smoking during pregnancy * SGA + 0.211 * full BF at 3m * excessive GWG =

-2.094 + 0.036 * 1 + 0.892 * 1 * 0 - 0.671 * 0 * 1 + 0.185 * 1 * 0 + 0.129 * 1 * 1 + 0.013 * 1 * 1 - 0.429 * 1 * 0 + 0.204 * 1 * 0 + 0.147 * 1 * 1 + 2.003 * 1 + 0.246 * 1 * 0 + 0.837 * 1 * 0 + 0.388 * 1 * 1 + 0.142* 0 * 1 + 0.036 * 0 * 0 + 0.093 * 0 * 1 + 0.195 * 0 * 0 + 0.287 * 0 * 1 + 0.183 * 1 * 1 - 0.193 * 0 * 1 + 0.222 * 0 * 0 + 0.211 * 0 * 1 =

-2.094 + 0.036 + 0.129 + 0.013 + 0.147 + 2.003 + 0.388 + 0.183 = 0.805.

Calculating the odds of higher-than-normal BMI growth: exp(risk score) = exp(0.805) = 2.24.

Calculating the probability of higher-than-normal BMI growth: exp(risk score)/(1+exp(risk score) = 2.24/3.24 = 0.69.

We will now compare the calculated individual risk score (0.805) to the respective cut-off score value presented in Table 2 in the main text (-1.689). Since 0.805 is greater than -1.689, the child will be classified as belonging to the "higher-than-normal BMI growth pattern" risk group. The calculated risk probability of

the child to develop “higher-than-normal BMI growth pattern” is 69%. The pediatrician should discuss preventive measures with the mother to reduce the risk score measured during the next assessment.

First risk re-assessment at age 1 year for developing higher-than-normal BMI growth in the late phase:

At the well-child visit at age 1 year, the risk of this offspring can be re-assessed using the respective risk quantification equation. The pediatrician obtains new information (after month 3) and learns that this child was not fully breastfed at age 6 months and has a BMI z-score of 1.50 SD at age 1 year.

“Higher-than-normal BMI growth pattern” during the late phase (3 years to 5 years) = -1.446 + 0.28 * LGA * inadequate GWG - 0.052 * SGA * male sex + 0.053 * GDM positive * low/medium SES + 0.648 * BMI z-score > 1 SD at 1y + 0.46 * BMI z-score > 1 SD at 1y * GDM positive + 0.59 * BMI z-score > 1 SD at 1y * excessive GWG + 0.122 * BMI z-score > 1 SD at 1y * primiparity + 0.352 * BMI z-score > 1 SD at 1y * male sex + 0.057 * BMI z-score > 1 SD at 1y * full BF at 1m + 0.311 * maternal class 3 obesity * full BF at 1m + 0.185 * smoking during pregnancy + 0.084 * smoking during pregnancy * LGA + 0.121 * smoking during pregnancy * low/medium SES + 0.551* full BF at 6m * LGA + 0.026 * full BF at 6m * smoking during pregnancy =

-1.446 + 0.28 * 1 * 0 - 0.052 * 0 * 1 + 0.053 * 1 * 1 + 0.648 * 1 + 0.46 * 1 * 1 + 0.59 * 1 * 1 + 0.122 * 1 * 1 + 0.352 * 1 * 1 + 0.057* 1 * 0 + 0.311 * 1 * 0 + 0.185 * 0 + 0.084 * 0 * 1 + 0.121 * 0 * 1 + 0.551 * 0 * 1 + 0.026 * 0 * 0 =

-1.446 + 0.053 + 0.648 + 0.46 + 0.59 + 0.122 + 0.352 = 0.779

Calculating the odds of higher-than-normal BMI growth: exp(risk score) = exp(0.779) = 2.18.

Calculating the probability of higher-than-normal BMI growth: exp(risk score)/(1+exp(risk score) = 2.18/3.18 = 0.69

We will now compare the calculated individual risk score (0.779) to the respective cut-off score value presented in Table 2 (-1.135). Since 0.779 is greater than -1.135, the child will still be classified as belonging to the “higher-than-normal BMI growth pattern” risk group during the late phase. The individual risk probability of this child to develop a “higher-than-normal BMI growth pattern” remains to be 69%. The pediatrician should continue to discuss preventive measures with the mother to reduce the risk score measured during the next assessment.

Second risk re-assessment at age 2 years for developing higher-than-normal BMI growth in the late phase:

At age 2 years, the risk of this offspring can be further re-assessed using the respective risk quantification equation. This child has a BMI z-score of 1.70 SD at age 2 years.

“Higher-than-normal BMI growth pattern” during the late phase (3 years to 5 years) = -1.995 + 0.112 * GDM positive * excessive GWG + 0.022 * GDM positive * low/medium SES + 0.109* GDM positive * smoking during pregnancy + 0.157 * GDM positive * full BF at 3m + 1.734 * BMI z-score > 1 SD at 2y - 0.097 * BMI z-score > 1 SD at 2y * SGA + 0.419 * BMI z-score > 1 SD at 2y * primiparity + 0.214 * BMI z-score > 1 SD at 2y * maternal class 3 obesity + 0.037 * BMI z-score > 1 SD at 2y * male sex + 0.142 * maternal class 3 obesity * full BF at 3m + 0.036 * smoking during pregnancy + 0.144 * full BF at 3m * LGA + 0.044 * full BF at 3m * excessive GWG + 0.015 * full BF at 3m * male sex + 0.531 * full BF at 6m * LGA + 0.14 * full BF at 6m * male sex =

-1.995 + 0.112 * 1 * 1 + 0.022 * 1 * 1 + 0.109 * 1 * 0 + 0.157 * 1 * 0 + 1.734 * 1 - 0.097 * 1 * 0 + 0.419 * 1 * 1 + 0.214 * 1 * 1 + 0.037 * 1 * 1 + 0.142 * 1 * 0 + 0.036 * 0 + 0.144 * 0 * 1 + 0.044 * 0 * 1 + 0.015 * 0 * 1 + 0.531 * 0 * 1 + 0.14 * 0 * 1 =

-1.995 + 0.112 + 0.022 + 1.734 + 0.419 + 0.214 + 0.037 = 0.543

Calculating the odds of higher-than-normal BMI growth: exp(risk score) = exp(0.543) = 1.72.

Calculating the probability of higher-than-normal BMI growth: exp(risk score)/(1+exp(risk score) = 1.72/2.72 = 0.63

We will now compare the calculated individual risk score (0.543) to the respective cut-off score value presented in Table 2 (-1.133). Since 0.543 is greater than -1.133, the child will continue to have a high risk

of higher-than-normal BMI growth during the late phase and an individual risk probability of 63%. The pediatrician should continue to discuss preventive measures with the mother to reduce the child's risk of overweight.

1.2. Risk quantification in offspring of mother without obesity at well-child visits

To illustrate how risk for higher-than-normal BMI growth in the early phase (between 6 months and 2 years) can be quantified, consider the following clinical case scenario of an offspring whose mother was normal weight in pregnancy:

Initial risk quantification at age 3 months for developing higher-than-normal BMI growth in the early phase:

A primiparous mother with normal weight, who gained adequate GWG, developed GDM, did not smoke during pregnancy, and belonged to a high SES, gave birth to a girl with an average-for-gestational-age (AGA) birth weight and a BMI z-score of 0.82 SD at age 3 months. The girl was fully breastfed at ages 1 month and 3 months.

"Higher-than-normal BMI growth pattern" during the early phase (6 months to 2 years) = -2.065 + 0.113 * LGA * primiparity + 1.717 * BMI z-score > 1 SD at 3m + 0.072 * BMI z-score > 1 SD at 3m * GDM positive + 0.08 * BMI z-score > 1 SD at 3m * inadequate GWG + 0.105 * BMI z-score > 1 SD at 3m * smoking during pregnancy - 0.064 * GDM positive - 0.076 * inadequate GWG * primiparity + 0.139 * maternal overweight + 1.731 * maternal overweight * LGA + 0.057 * maternal overweight * excessive GWG + 0.061 * full BF at 1m * smoking during pregnancy =

-2.065 + 0.113 * 0 * 0 + 1.717 * 0 + 0.072 * 0 * 1 + 0.08 * 0 * 0 + 0.105 * 0 * 0 - 0.064 * 1 - 0.076 * 0 * 0 + 0.139 * 0 + 1.731 * 0 * 0 + 0.057 * 0 * 0 + 0.061 * 0 * 0 =

-2.065 - 0.064 = -2.129

Calculating the odds of higher-than-normal BMI growth: exp(risk score) = exp(-2.129) = 0.12.

Calculating the probability of higher-than-normal BMI growth: exp(risk score)/(1+exp(risk score) = 0.12/1.12 = 0.11

We will now compare the calculated individual risk score (-2.129) to the respective cut-off score value presented in Table S4 (Additional file 1) (-2.065). Since -2.129 is lower than -2.065, the child has a low risk of developing higher-than-normal BMI growth (individual risk probability 11%) and will not be classified as belonging to the "higher-than-normal BMI growth pattern" risk group.

First risk re-assessment at age 1 year for developing higher-than-normal BMI growth in the late phase:

At age 1 year, the risk of this offspring can be re-assessed using the respective risk quantification equation, given that this child was fully breastfed at age 6 months and has a BMI z-score of 0.89 SD at age 1 year.

"Higher-than-normal BMI growth pattern" during late phase (3 years to 5 years) =

-1.874 + 0.22 * BMI z-score > 1 SD at 1y =

-1.874 + 0.22 * 0 = -1.874

Calculating the odds of higher-than-normal BMI growth: exp(risk score) = exp(-1.874) = 0.15.

Calculating the probability of higher-than-normal BMI growth: exp(risk score)/(1+exp(risk score) = 0.15/1.15 = 0.13

We will now compare the calculated individual risk score (-1.874) to the respective cut-off score value presented in Table S4 (Additional file 1) (-1.651). Since -1.874 is lower than -1.651 and the risk probability is 13%, the child will again not be classified as belonging to the "higher-than-normal BMI growth pattern" risk group.

Second risk re-assessment at age 2 years for developing higher-than-normal BMI growth in the late phase:

At age 2 years, the risk of this offspring can be further re-assessed using the respective risk quantification equation. This child has a BMI z-score of 0.92 SD at age 2 years.

“Higher-than-normal BMI growth pattern” during the late phase (3 years to 5 years) =

-1.895 + 0.23 * BMI z-score > 1 SD at 2y =

-1.895 + 0.23 * 0 = -1.895

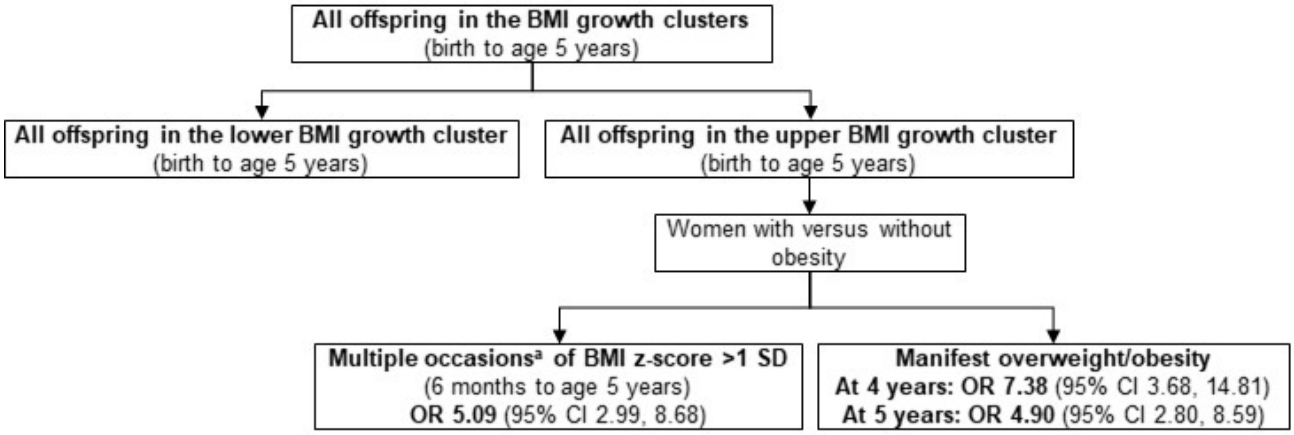
Calculating the odds of higher-than-normal BMI growth: exp(risk score) = exp(-1.895) = 0.15.

Calculating the probability of higher-than-normal BMI growth: exp(risk score)/(1+exp(risk score) = 0.15/1.15 = 0.13

We will now compare the calculated individual risk score (-1.895) to the respective cut-off score value presented in Table S4 (Additional file 1) (-1.665). Since -1.895 is lower than -1.665 and the risk probability remains to be 13%, the child will again not be classified as belonging to the “higher-than-normal BMI growth pattern” risk group.

Supplementary figures

Figure S1. Influence of maternal obesity on offspring BMI growth outcomes.

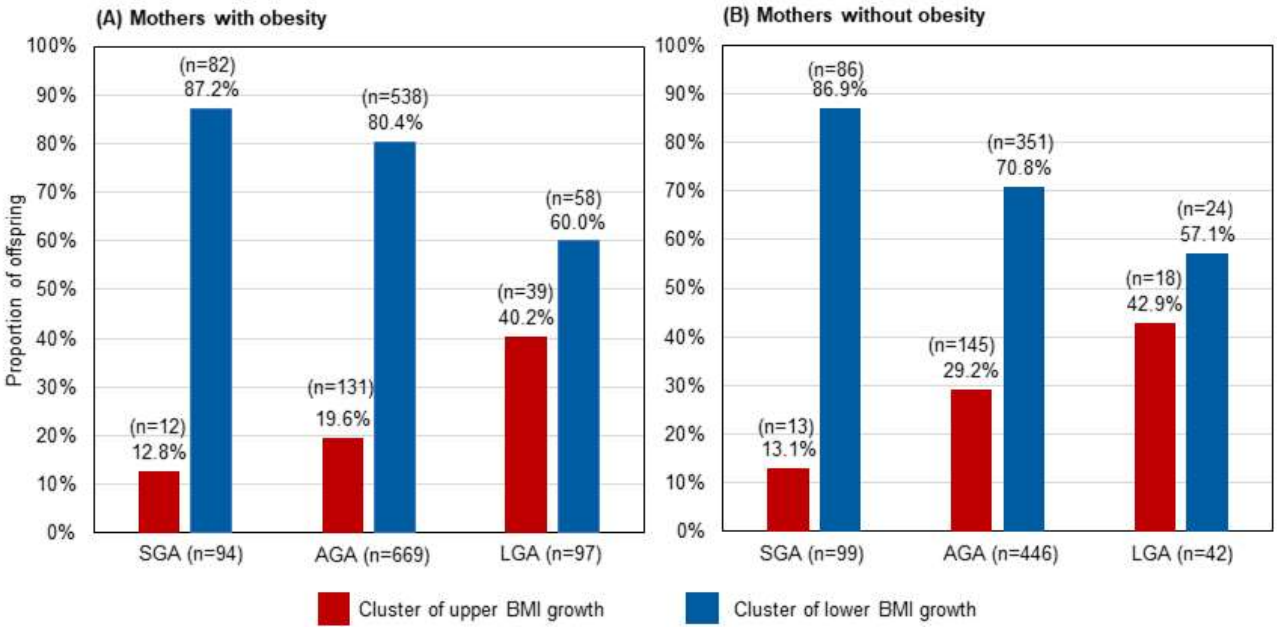


Shown are ORs and 95% CIs of the influence of maternal pre-conception obesity on BMI growth outcomes up to age 5 years in all offspring belonging to upper BMI growth clusters from the PEACHES cohort study. Values were derived from univariate logistic regression.

[a]The term "multiple occasions" was defined as having BMI z-scores >1 SD [51] at least 5 out of 6 times at the well-child visits at age 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years.

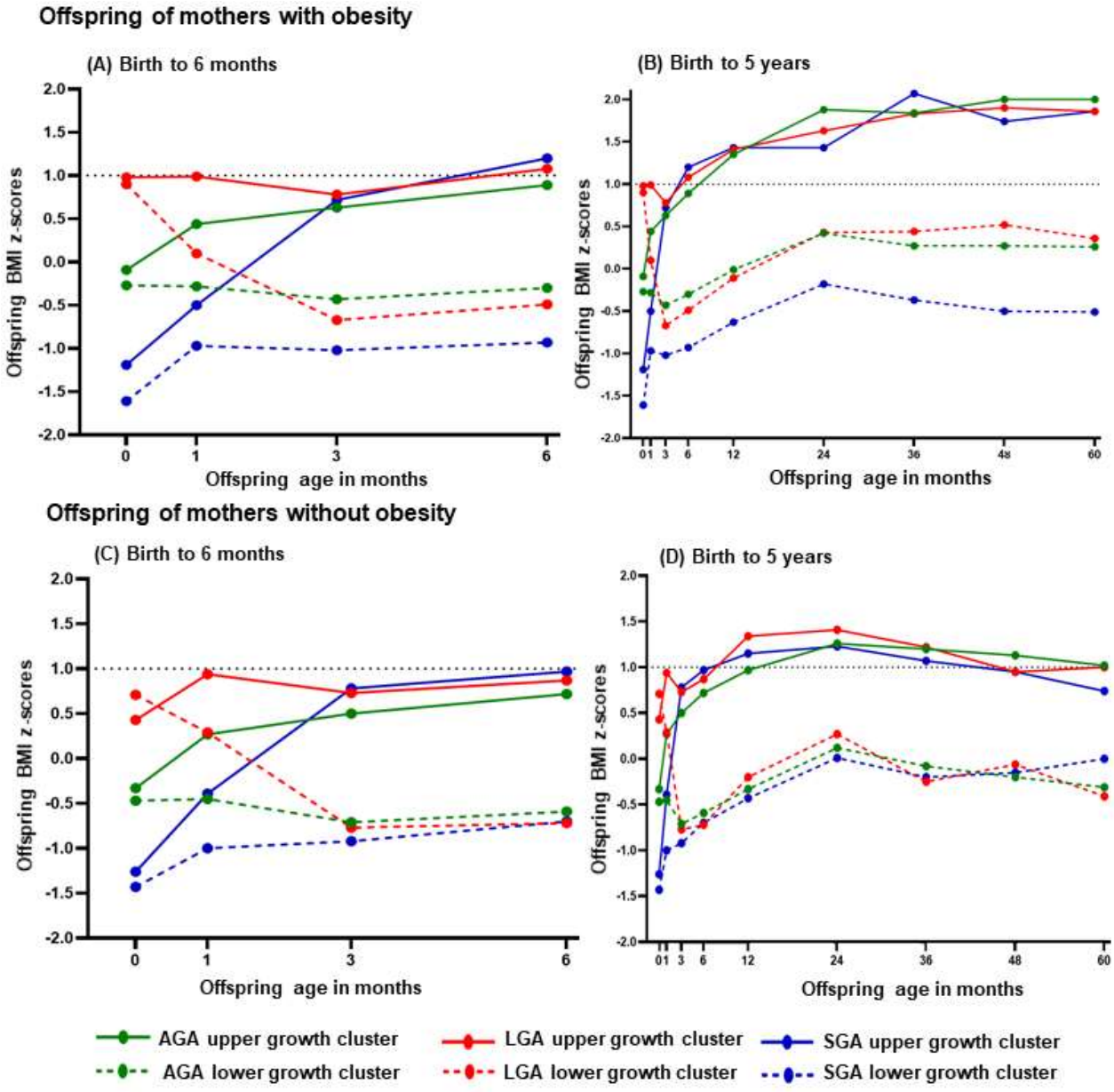
BMI, body mass index; CI, confidence interval; OR, odds ratio; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening.

Figure S2. Proportion of offspring in upper and lower BMI growth clusters according to birth weight category.



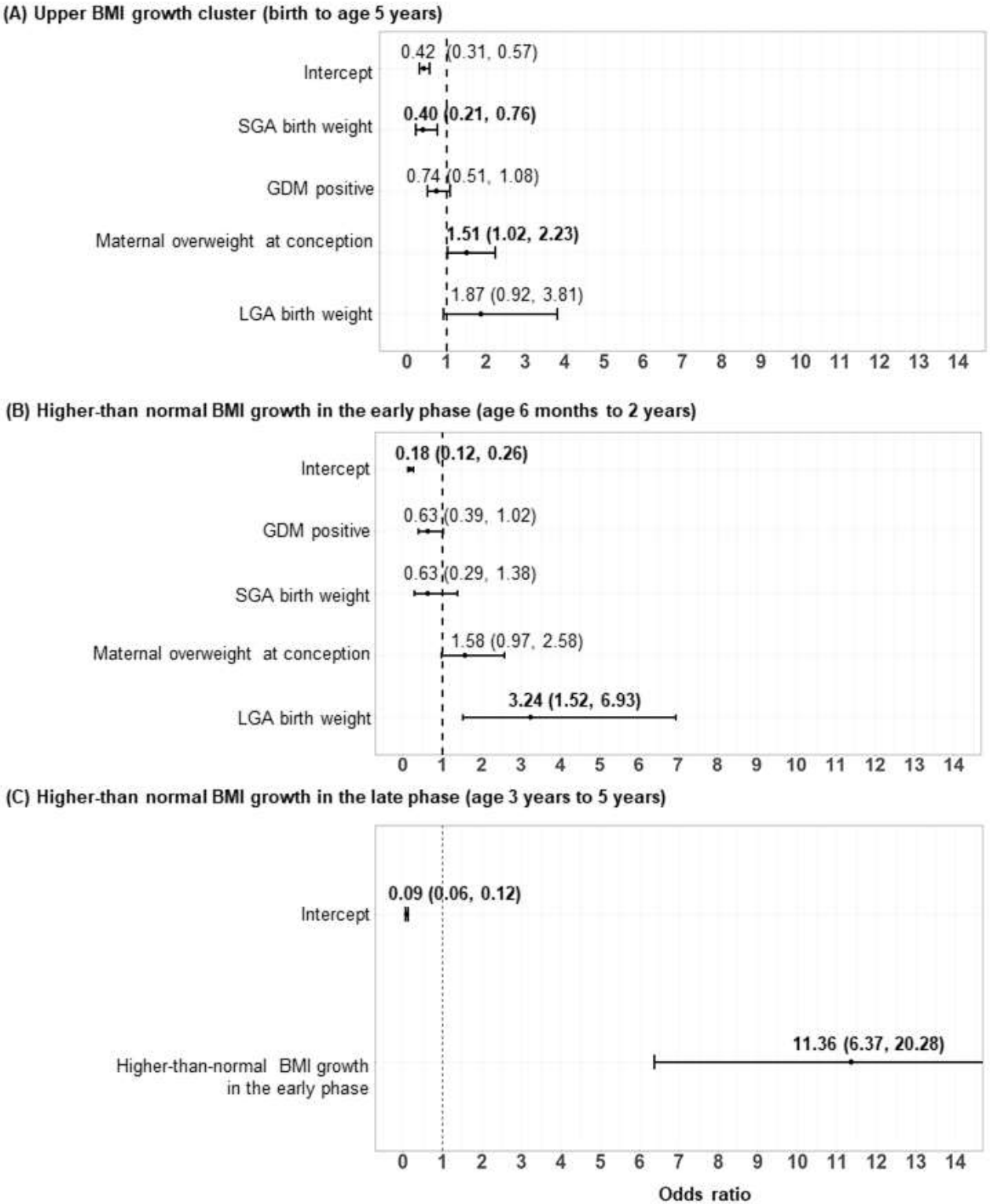
Shown are percentages in offspring of mothers with obesity (panel A) and without (panel B) enrolled in the PEACHES cohort study, according to their birth weight category for gestational age and sex.
AGA, average-for-gestational-age; BMI, body mass index; LGA, large-for-gestational-age; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening; SGA, small-for-gestational-age.

Figure S3. Mean BMI growth clusters by birth weight category in offspring of mothers with and without obesity.



Shown are mean BMI z-score growth clusters from birth to age 6 months (panel A, C) and birth to age 5 years (panel B, D) by birth weight category for gestational age and sex in offspring of mothers with and without obesity enrolled in the PEACHES cohort study.
AGA, average-for-gestational-age; BMI, body mass index; LGA, large-for-gestational-age; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening; SGA, small-for-gestational-age.

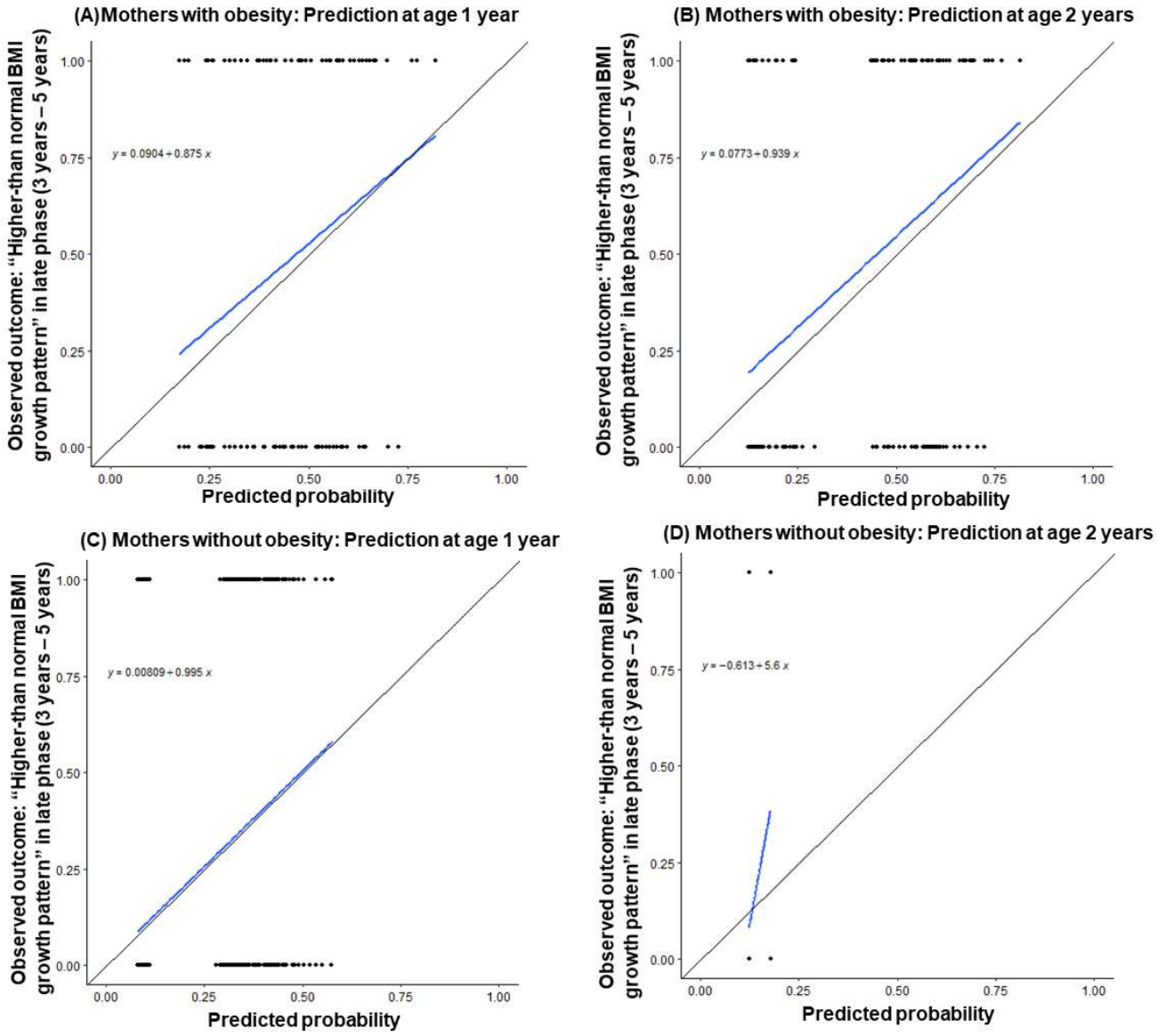
Figure S4. Effects of prenatal and postnatal factors on BMI growth outcomes in offspring of mothers without obesity.



Shown are ORs and 95% CI of the influence of prenatal and postnatal factors on the development of an upper cluster of BMI growth (birth to age 5 years, panel A) and a "higher-than-normal BMI growth pattern", defined as BMI z-score >1 SD [51] at least twice, during early phase (6 months to 2 years, panel B) and late phase (3 years to 5 years, panel C) in offspring of mothers without obesity enrolled in the PEACHES cohort study. Values were derived from multivariable logistic regression with stepwise backward selection. Only final models based on the lowest Akaike information criterion are presented. Included variables in all initial models were maternal pre-conception BMI group, total GWG, GDM, parity, smoking during

pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month. Additionally, for associations shown in panel C, “higher-than-normal BMI growth pattern” in the early phase was also included as an explanatory variable in the initial model.
BMI, body mass index; CI, confidence interval; GDM, gestational diabetes; GWG, gestational weight gain; LGA, large-for-gestational-age; OR, odds ratio; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening; SES, socioeconomic status; SGA, small-for-gestational-age.

Figure S5. Calibration plots of prediction models for identifying a "higher-than-normal BMI growth pattern" in the validation cohort.



Shown are calibration curves (blue lines) and calibration slopes and intercepts for offspring of mothers with obesity (panel A, B) and without obesity (panel C, D) by the prediction models at age 1 year and 2 years. The diagonal grey lines represent the optimal prediction; the closer the model curve is to the diagonal line, the more accurate is the prediction. At the top of each graph, dots indicate presence of the outcome "higher-than-normal BMI growth pattern", defined as BMI z-score >1 SD [51] at least twice, in the late phase (3 years to 5 years). At the bottom of each graph, dots indicate absence of the outcome "higher-than-normal BMI growth pattern" in the late phase. Calibration of models at age 3 months for "higher-than-normal BMI growth pattern" in the early phase (6 months to 2 years) could not be performed due to the lack of follow-up data at age 3 months in the validation cohort PEPO. BMI, body mass index; PEPO, PErinatal Prevention of Obesity.

Supplementary tables

Table S1. Offspring follow-up rates in the study populations.			
Offspring age	**Follow-up anthropometric data**	**Discovery cohort: PEACHES**	**Validation cohort: PEPO**
		All (n=1,557)	**All (n=9,874)**
At birth	Missing[a]	0 (0.0)	38 (0.4)
	Available	1,557 (100.0)	9,836 (99.6)
	Total	1,557 (100.0)	9,874 (100.0)
1 month	Missing[a]	31 (2.0)	NA
	Available	1,526 (97.3)	NA
	Total	1,557 (100.0)	NA
3 months	Missing[a]	42 (2.7)	NA
	Available	1,515 (97.3)	NA
	Total	1,557 (100.0)	NA
6 months	Missing[a]	68 (4.4)	NA
	Available	1,489 (95.6)	NA
	Total	1,557 (100.0)	NA
1 year	Missing[a]	60 (3.9)	502 (5.1)
	Available	1,497 (96.1)	9,372 (94.9)
	Total	1,557 (100.0)	9,874 (100.0)
2 years	Missing[a]	104 (6.7)	627 (6.4)
	Available	1,453 (93.3)	9,247 (93.6)
	Total	1,557 (100.0)	9,874 (100.0)
3 years	Missing[a]	184 (11.8)	NA
	Available	1,373 (88.2)	NA
	Total	1,557 (100.0)	NA
4 years	Missing[a]	263 (17.0)	NA
	Available	1,281 (83.0)	NA
	Total	1,544 (100.0)[b]	NA
5 years	Missing[a]	252 (20.0)	307 (3.1)
	Available	1,008 (80.0)	9,567 (96.9)
	Total	1,260 (100.0)[b]	9,874 (100.0)
Total over all ages	Missing[a]	1,004 (7.3)	1,474 (3.7)
	Available	12,699 (92.7)	38,022 (96.3)
	Total	13,703 (100.0)	39,496 (100.0)

Values are n (%).
[a]Missing data in the PEACHES cohort were due to loss to follow-up. Missing data in the PEPO cohort were due to lack of availability of data in the records of the regular well-child visits at the time of school entry health examination.
[b]A total of 13 and 297 children enrolled in the PEACHES cohort were too young for the follow-up visit at age 4 and 5 years, respectively, and therefore were not included in the "total" category. Missing data were considered missing completely at random.
NA, not available; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening; PEPO, PErinatal Prevention of Obesity.

Table S2. Mean BMI z-scores by BMI growth cluster in offspring of mothers with and without obesity.								
Offspring follow-up	**Upper BMI growth cluster**				**Lower BMI growth cluster**			
	Mothers with obesity[a]		**Mothers without obesity[b]**		**Mothers with obesity[a]**		**Mothers without obesity[b]**	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
At birth	185	0.07 (-0.06, 0.21)	183	-0.33 (-0.47, -0.19)	690	-0.31 (-0.39, -0.24)	472	-0.62 (-0.71, -0.53)
1 month	185	0.50 (0.37, 0.62)	182	0.28 (0.15, 0.42)	687	-0.33 (-0.40, -0.26)	472	-0.51 (-0.58, -0.43)
3 months	184	0.67 (0.54, 0.80)	181	0.55 (0.41, 0.68)	682	-0.51 (-0.58, -0.44)	468	-0.77 (-0.85, -0.70)
6 months	181	0.95 (0.82, 1.08)	176	0.76 (0.64, 0.88)	672	-0.37 (-0.44, -0.29)	460	-0.66 (-0.74, -0.58)
1 year	182	1.37 (1.25, 1.48)	176	1.02 (0.91, 1.14)	677	-0.07 (-0.13, 0.00)	462	-0.38 (-0.46, -0.30)
2 years	174	1.79 (1.66, 1.93)	171	1.27 (1.17, 1.37)	665	0.38 (0.31, 0.44)	443	0.07 (-0.01, 0.15)
3 years	168	1.85 (1.72, 1.99)	165	1.19 (1.05, 1.33)	621	0.23 (0.16, 0.30)	419	-0.14 (-0.21, -0.07)
4 years[c]	155	1.97 (1.83, 2.11)	146	1.10 (1.00, 1.20)	588	0.24 (0.18, 0.31)	392	-0.25 (-0.32, -0.18)
5 years[c]	124	1.96 (1.77, 2.16)	111	0.99 (0.86, 1.13)	461	0.24 (0.16, 0.32)	312	-0.35 (-0.43, -0.28)

Values are mean and 95% CI in offspring of mothers with and without obesity enrolled in the PEACHES cohort study.

[a]Of a total of 887 children included for cluster analysis, 875 children could be categorized into longitudinal BMI growth clusters based on an adequate number of data points.

[b]Of a total of 670 children included for cluster analysis, 655 children could be categorized into clusters based on an adequate number of data points.

[c]A total of 276 and 549 children enrolled in the PEACHES cohort were not included in the cluster analysis at age 4 and 5 years, respectively, because of follow-up not yet due (age 4 years: n=13, age 5 years: n=297) or missing data due to loss to follow-up (age 4 years: n=263, age 5 years: n=252). Missing data were considered missing completely at random.

BMI, body mass index; CI, confidence interval; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening.

Table S3. Offspring BMI growth dynamics in consecutive life phases after birth following exposure to gestational obesity.							
		Late phase: 3 years – 5 years					
		Mothers with obesity (n=584)			**Mothers without obesity (n=428)**		
	BMI z-score category	≤1 SD[a]	>1 SD[b]	"Higher-than-normal BMI growth pattern"[c]	≤1 SD[a]	>1 SD[b]	"Higher-than-normal BMI growth pattern"[c]
Early phase: 6 months – 2 years	≤1 SD[a]	263 (45.0)	39 (6.7)	25 (4.3)	248 (57.9)	17 (4.0)	7 (1.6)
	>1 SD[b]	22 (3.8)	44 (7.5)	70 (12.0)	20 (4.7)	39 (9.1)	28 (6.5)
	"Higher-than-normal BMI growth pattern"[c]	9 (1.5)	16 (2.7)	96 (16.4)	5 (1.2)	27 (6.3)	37 (8.7)
	All patterns	294 (50.3)	99 (16.9)	191 (32.7)	273 (63.8)	83 (19.4)	72 (16.8)

Values are n (%) in offspring enrolled in the PEACHES cohort study. Only children with complete data on BMI z-scores in both the early and late phase are presented.

[a]Includes values for categories "normal range" (≥-2 to ≤1 SD) and a minor proportion of children with <-2 SD [72].

[b]BMI z-score >1 SD defined as occurring once. Includes values for categories "at risk of overweight" (>1 to ≤2 SD), overweight (>2 to ≤3 SD), and obesity (>3 SD) [51].

[c]"Higher-than-normal BMI growth pattern" defined as BMI z-score >1 SD [51] at least twice.

BMI, body mass index; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening.

Table S4. Predictive performance of a sequential algorithm to identify higher-than-normal BMI growth in offspring of mothers without obesity.					
Predictive parameter	**Prediction at age 3 months[a]**	**Prediction at age 1 year[b]**		**Prediction at age 2 years[c]**	
	Higher-than-normal BMI growth in early phase (6 months – 2 years)	**Higher-than-normal BMI growth in late phase (3 years – 5 years)**		**Higher-than-normal BMI growth in late phase (3 years – 5 years)**	
	Discovery cohort	**Discovery cohort**	**Validation cohort**	**Discovery cohort**	**Validation cohort**
N	567	515	6521	513	6432
AUROC	0.68 (0.66, 0.71)	0.69 (0.67, 0.72)	0.65	0.77 (0.75, 0.79)	0.71
Cut-off score value[d]	-2.065	-1.651	NA	-1.665	NA
Prevalence, n (%)	82 (14.5)	71 (13.8)	949 (14.6)	71 (13.8)	924 (14.4)
Sensitivity, %	75.6 (65.7, 83.4)	49.3 (38.3, 60.4)	42.0 (39.3, 44.8)	73.2 (62.2, 81.9)	65.1 (62.4, 67.7)
Specificity, %	59.0 (48.4, 68.9)	88.1 (84.2, 91.1)	75.1 (72.8, 77.3)	80.1 (72.1, 86.3)	72.8 (70.0, 75.4)
Positive predictive value, %	23.3 (17.4, 30.7)	40.2 (28.2, 52.5)	22.6 (20.0, 25.5)	37.5 (26.7, 49.4)	29.0 (26.2, 32.0)
Negative predictive value, %	93.6 (89.5, 96.2)	91.5 (89.4, 93.4)	88.2 (87.4, 89.0)	94.8 (92.1, 96.7)	92.4 (91.6, 93.2)
Positive likelihood ratio	1.84 (1.27, 2.68)	4.14 (2.42, 6.82)	1.69 (1.44, 1.97)	3.68 (2.23, 5.97)	2.39 (2.08, 2.75)
Negative likelihood ratio	0.41 (0.24, 0.71)	0.58 (0.43, 0.73)	0.77 (0.71, 0.83)	0.33 (0.21, 0.52)	0.48 (0.43, 0.54)

We used the PEACHES cohort study as the discovery cohort and the PEPO cohort study as the external validation cohort for calculation of the individual child's risk of a "higher-than-normal BMI growth pattern" (BMI z-score >1 SD [51] at least twice). Values are predictive parameters and their 95% CI.

[a]Potential predictors included: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, and BMI z-score >1 SD at age 3 months. External validation of models at age 3 months could not be performed due to the lack of follow-up data at age 3 months in the validation cohort PEPO.

[b]Potential predictors included: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, breastfeeding status at 6 months, and BMI z-score >1 SD at age 1 year. External validation of models at age 1 year was performed in the validation cohort PEPO.

[c]Potential predictors included: maternal pre-conception BMI group, total GWG, GDM, parity, smoking during pregnancy, sex, birth weight category for gestational age and sex, SES, breastfeeding status at 1 month, breastfeeding status at 3 months, breastfeeding status at 6 months, and BMI z-score >1 SD at age 2 years. External validation of models at age 2 years was performed in the validation cohort PEPO.

[d]Offspring with a risk score above or equal to the respective cut-off score value are considered to be at risk of developing a "higher-than-normal BMI growth pattern". The cut-off value of the score was optimized to avoid false-negative findings (sensitivity), which resulted in negative cut-off score values.

AUROC, area under the receiver operating characteristic; BMI, body mass index; CI, confidence interval; GDM, gestational diabetes; GWG, gestational weight gain; NA, not applicable; PEACHES, Programming of Enhanced Adiposity Risk in Childhood–Early Screening; PEPO, PErinatal Prevention of Obesity; SES, socioeconomic status.

Table S5. Scoring system for quantification of risk of higher-than-normal BMI growth in young offspring.		
Prediction time point and outcome[a]	**Offspring of mothers with obesity**	**Offspring of mothers without obesity**
Prediction at age 3 months: Higher-than-normal BMI growth in early phase (6 months – 2 years)	-2.094 + 0.036 * LGA + 0.892 * LGA * inadequate GWG - 0.671 * SGA * male sex + 0.185 * GDM positive * SGA + 0.129 * GDM positive * excessive GWG + 0.013 * GDM positive * maternal class 3 obesity - 0.429 * GDM positive * smoking during pregnancy + 0.204 * GDM positive * full BF at 3m + 0.147 * excessive GWG * male sex + 2.003 * BMI z-score > 1 SD at 3m + 0.246 * BMI z-score > 1 SD at 3m * SGA + 0.837 * BMI z-score > 1 SD at 3m * inadequate GWG + 0.388 * BMI z-score > 1 SD at 3m * primiparity + 0.142 * maternal class 2 obesity * LGA + 0.036 * maternal class 2 obesity * SGA + 0.093 * maternal class 2 obesity * primiparity + 0.195 * maternal class 2 obesity * full BF at 3m + 0.287 * maternal class 2 obesity * LGA + 0.183 * maternal class 3 obesity * excessive GWG - 0.193 * smoking during pregnancy * LGA + 0.222 * smoking during pregnancy * SGA + 0.211 * full BF at 3m * excessive GWG	-2.065 + 0.113 * LGA * primiparity + 1.717 * BMI z-score > 1 SD at 3m + 0.072 * BMI z-score > 1 SD at 3m * GDM positive + 0.08 * BMI z-score > 1 SD at 3m * inadequate GWG + 0.105 * BMI z-score > 1 SD at 3m * smoking during pregnancy - 0.064 * GDM positive - 0.076 * inadequate GWG * primiparity + 0.139 * maternal overweight + 1.731 * maternal overweight * LGA + 0.057 * maternal overweight * excessive GWG + 0.061 * full BF at 1m * smoking during pregnancy
Prediction at age 1 year: Higher-than-normal BMI growth in late phase (3 years – 5 years)	-1.446 + 0.28 * LGA * inadequate GWG - 0.052 * SGA * male sex + 0.053 * GDM positive * low/medium SES + 0.648 * BMI z-score > 1 SD at 1y + 0.46 * BMI z-score > 1 SD at 1y * GDM positive + 0.59 * BMI z-score > 1 SD at 1y * excessive GWG + 0.122 * BMI z-score > 1 SD at 1y * primiparity + 0.352 * BMI z-score > 1 SD at 1y * male sex + 0.057 * BMI z-score > 1 SD at 1y * full BF at 1m + 0.311 * maternal class 3 obesity * full BF at 1m + 0.185 * smoking during pregnancy + 0.084 * smoking during pregnancy * LGA + 0.121 * smoking during pregnancy * low/medium SES + 0.551* full BF at 6m * LGA + 0.026 * full BF at 6m * smoking during pregnancy	-1.874 + 0.22 * BMI z-score > 1 SD at 1y
Prediction at age 2 years: Higher-than-normal BMI growth in late phase (3 years – 5 years)	-1.995 + 0.112 * GDM positive * excessive GWG + 0.022 * GDM positive * low/medium SES + 0.109* GDM positive * smoking during pregnancy + 0.157 * GDM positive * full BF at 3m + 1.734 * BMI z-score > 1 SD at 2y - 0.097 * BMI z-score > 1 SD at 2y * SGA + 0.419 * BMI z-score > 1 SD at 2y * primiparity + 0.214 * BMI z-score > 1 SD at 2y * maternal class 3 obesity + 0.037 * BMI z-score > 1 SD at 2y * male sex + 0.142 * maternal class 3 obesity * full BF at 3m + 0.036 * smoking during pregnancy + 0.144 * full BF at 3m * LGA + 0.044 * full BF at 3m * excessive GWG + 0.015 * full BF at 3m * male sex + 0.531 * full BF at 6m * LGA + 0.14 * full BF at 6m * male sex	-1.895 + 0.23 * BMI z-score > 1 SD at 2y
[a]The equations can be used for sequential individual risk quantification of a "higher-than-normal BMI growth pattern" (BMI z-score >1 SD [51] at least twice) in offspring of mothers with or without pre-conception obesity separately. The prenatal and postnatal variables in the risk quantification equations should be replaced by pre-defined values (0 or 1) depending on whether the condition stated is fulfilled (1) or not (0). The calculated risk score should be compared to the respective cut-off score value (Table 2). Offspring with a risk score above or equal to the respective cut-off are considered to be at risk of developing a "higher-than-normal BMI growth pattern". Details on calculating individual risk probabilities and use of individual risk score calculations along with clinical case scenarios are provided in the Text S3 (Additional file 1).		

BMI, body mass index; BF, breastfeeding; GDM, gestational diabetes; GWG, gestational weight gain; m, month(s); LGA, large-for-gestational-age; SES, socioeconomic status; SGA, small-for-gestational-age; y, year(s).

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Appendix A: Book chapters

Two book chapters are presented:

1. **Mütterliche Adipositas und langfristige Auswirkungen auf die Nachkommen.** Sarah Perschbacher, Nathalie Eckel, **Delphina Gomes**, Regina Ensenauer (published, DOI: https://doi.org/10.1007/978-3-662-61906-3_15)
2. **Perinatale Determinanten**. S. Perschbacher, N. Eckel, **D. Gomes**, I. Nehring, R. Ensenauer (accepted for publication in 2023)

Sarah Perschbacher, Nathalie Eckel, Delphina Gomes, Regina Ensenauer

15 - Mütterliche Adipositas und langfristige Auswirkungen auf die Nachkommen

Trailer:

Innerhalb der letzten Dekade wurde zunehmend deutlich, dass mütterliche Adipositas sich schon pränatal auf die Entwicklung der Nachkommen auswirken kann und über Mechanismen, die als „fetale Programmierung“ zusammengefasst werden, zu Langzeitfolgen bei den Nachkommen führt. Diverse Studien haben bereits ein erhöhtes Risiko für kindliches Übergewicht nach intrauteriner Exposition gegenüber maternaler Adipositas belegt. Weitere pränatale Risikofaktoren, die häufig mit maternaler Adipositas einhergehen und ein gesundheitliches Risiko bei den Nachkommen von adipösen Müttern noch zu steigern scheinen, sind u.a. die übermäßig hohe (exzessive) Gewichtszunahme während der Schwangerschaft und der Gestationsdiabetes (GDM). Im Folgenden sind Evidenzen für ungünstige Langzeitfolgen bei den Nachkommen nach Exposition gegenüber präkonzeptionell bestehender Adipositas und assoziierten metabolischen Störungen ausgeführt.

Perinatale Determinanten

S. Perschbacher, N. Eckel, D. Gomes, I. Nehring, R. Ensenauer

Hintergrund

Als prä-/perinatale bzw. frühkindliche Determinanten für späteres Übergewicht bei Kindern und Jugendlichen - definiert anhand von alters- und geschlechtsspezifischen Perzentilen oder Z-scores für u.a. den Body Mass Index (BMI) - werden folgende Faktoren mit unterschiedlicher Gewichtung diskutiert: maternaler präkonzeptioneller BMI bzw. maternales präkonzeptionelles Übergewicht und Adipositas (siehe Tab. 3.1), Rauchen und Gewichtszunahme während der Schwangerschaft, Gestationsdiabetes, Gestationshypertonie, Parität, Geburtsmodus, Mikrobiom, Stillen und das Ausmaß der kindlichen Gewichtszunahme in den ersten 1–2 Lebensjahren. Die Evidenz stützt sich dabei auf tierexperimentelle Studien und Beobachtungsstudien beim Menschen, da diese Determinanten nicht in randomisierten Humanstudien getestet werden können.

Eine der ersten tierexperimentellen Arbeiten zum Einfluss der früh-postnatalen Prägung des späteren Gewichts stammt von Widdowson und McCance. In einem Rattenmodell zeigten sie, dass eine unmittelbar postnatale Unterernährung zu späteren Wachstumsverzögerungen führt, während eine Unterernährung nach Ende der Laktation ab der dritten Lebenswoche geringere Auswirkungen auf das spätere Gewicht hat.

Die empirische Evidenz für die Zusammenhänge beim Menschen stammt aus Querschnitts-, Fall-Kontroll- und Kohorten-Studien, deren Ergebnisse oftmals bereits in Metaanalysen zusammengefasst worden sind. Hierbei werden auch additive Effekte der verschiedenen Einflussfaktoren diskutiert. Das wissenschaftliche Interesse an Faktoren der frühen Prägung resultiert aus der möglichen Nutzung dieser Erkenntnisse für die Entwicklung von Präventionsmaßnahmen. Um die Erkenntnisse für die Adipositasprävention zu nutzen, sollten die Zusammenhänge klar belegt sein. Die Evidenz für die einzelnen Risikofaktoren ist bislang unterschiedlich und wird nachfolgend diskutiert.

Acknowledgements

I take this opportunity to express my respectful gratitude to my supervisor Prof. Dr. Regina Ensenauer for her valuable support and guidance throughout this research work. The journey over the last 7 years would not have been possible without your continual encouragement and determination in teaching me how to write and to think critically.

I would like to thank Prof. Ulrich Mansmann who has guided me throughout this research work by providing valuable inputs on statistical procedures. Thank you so much for your constant assistance, advice, performing complicated statistical analysis, and looking at my R scripts.

I express my sincere gratitude to Prof. Dr. Rüdiger von Kries, for his support and advice during my PhD work. I want to express my gratitude to Prof. Adelbert Roscher who has always provided me his valuable feedback on research inquiries and manuscripts. I would like to thank the PEACHES team to always support data acquisition and support me in preparing datasets for analyses. I whole heartedly thank Sarah Perschbacher who was always there to provide me data, listen to my ideas, and give her opinion. I also thank Chunfang Zhang and Dr. Jens Stupin for their valuable feedback on the thesis write-up. Dr. Stupin also corrected the German summary (Zusammenfassung) of the current thesis and I am grateful for his contribution.

I would not have been able to start and complete this research work without the support of my husband, Rachit Kumar. You have provided me a lot of strength and inspiration. Thank you for taking time out on endless occasions so that I could work, for putting up with all my moments of self-doubt, and for helping me in mathematical queries and in coding issues. I dedicate my Ph.D. research work to you. I express my deep gratitude to my mother, Florina Gomes, for her constant encouragement. A special thank you to my girls, Evelyn (4-year-old) and Iris (6-month-old), for understanding that mommy had work to do but kept smiling always!

Delphina Gomes