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Personalized prediction models based on early-life stressors to predict development of cardio-metabolic, respiratory and psychiatric disease

LifeCycle report D10.4

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Version 1.0

Delivery date: Month 66

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This project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733206 (LifeCycle).

Document Information

Grant Agreement No.	**733206**
Project Title	Early-life stressors and LifeCycle health (The LifeCycle Project)
Project Start Date	01 January 2017
Work package title	WP10 - Economic, public and individual impact of early-life stressors
Related task(s)	Task 10.4 - Personalized prediction models, based on the early-life stressors, for cardio-metabolic, respiratory and mental risk factors and disease.
Lead Organisation	ERASMUS
Submission date	19 September 2022
Dissemination Level	Public

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List of Abbreviations

AUC: Area Under the Curve
BMI: body mass index
CI: confidence interval
cm: centimeters
IQR: interquartile range
kg: kilograms
m: meters
mm Hg: millimeters mercury
mmol/L: millimoles per liter
n: number
NAM: National Academy of Medicine
OR: odds ratio
P: percentile
ROC: Receiver Operating Characteristics
SD: standard deviation
SDS: standard deviation score
US: United States
WP: work package

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Executive Summary

Task 10.4 aimed to develop personalized prediction models, based on early-life stressors, for cardio-metabolic, respiratory and mental risk factors and disease. We used data from the EU Child Cohort Network to develop models to predict from pregnancy and early childhood stressor data the onset of risk factors for cardio-metabolic, respiratory and mental outcomes throughout the life course. This work follows the knowledge gained about risk factors identified in LifeCycle WP4, WP5 and WP6 and from the literature. This work started with the development of prediction models for gestational weight gain and childhood obesity. Further prediction models for childhood asthma and childhood mental health outcomes have been initiated. The analyses were based on more than 20 European cohorts with more than 100,000 parent-child trios. Results from these prediction models will be used for development of web-based applications. The output of this task will be personalized prediction models based on early-life stressors, to predict the development of cardio-metabolic, respiratory and mental risk factors and disease in later life for use in European populations.

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1. Introduction

European cohort studies and trials have identified a vast amount of knowledge about risk factors for childhood health outcomes. Translation of these findings into effective prediction models has great potential for future prevention strategies. Task 10.4 aimed to develop personalized prediction models, based on early-life stressors, for cardio-metabolic, respiratory and mental risk factors and disease. This work started in the second half of project and was delayed because of the limited availability of the necessary analytical options using federated analytical approaches in DataSHIELD. Therefore, we started individual participant analyses by combining data from different cohorts outside of DataSHIELD. We started with analyses focused on gestational weight gain and childhood obesity. These outcomes were selected based on their importance for public health and on data availability within the collaborating cohorts. Analyses on other outcomes have been initiated and will be continued by the participating cohorts. This report describes the results of the analyses on gestational weight gain and childhood obesity.

2. Gestational weight gain

2.1 Rationale

Gestational weight gain is an important predictor of adverse maternal and child health outcomes. Insufficient weight gain is associated with increased risks of preterm birth and delivering a low birth weight infant, whereas excessive weight gain is associated with increased risks of gestational hypertension, preterm birth, delivering a high birth weight infant, caesarean delivery, and childhood overweight. Appropriate gestational weight gain charts are necessary to monitor the progress of weight gain and to enable risk selection.

2.2 Objectives

We used individual participant data from 218,216 pregnant women from 33 European, North American, and Oceania pregnancy cohort studies to assess the pattern of weight gain and to construct gestational weight gain charts for underweight, normal weight, overweight, and grades 1, 2, and 3 obese women. Second, we examined the associations of ranges of gestational weight gain with risk of adverse maternal and infant outcomes and estimated optimal gestational weight gain ranges across pre-pregnancy body mass index (BMI) categories.

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2.3 Methods

Pregnancy and birth cohort studies participated if they included mothers with singleton live-born children born from 1989 onwards, had information available on maternal pre/early-pregnancy BMI and at least one offspring measurement (birth weight or childhood BMI) and were approved by their local institutional review boards. We identified 50 cohorts from Europe, North America, and Oceania. We invited these cohorts, of which 39 cohorts agreed to participate, providing data of 239,621 singleton births. Detailed information on these cohorts can be found on https://www.birthcohorts.net. We included cohorts with information on pre-pregnancy BMI and weight measurements throughout pregnancy with information on the corresponding gestational age (33 cohorts). Per cohort, women were included if they had information on pre-pregnancy BMI to allow classification into the specific pre-pregnancy BMI groups. Therefore, all women had information on weight at 0 weeks, which refers to pre-pregnancy weight. Since the data were modeled cross-sectionally, no further restriction was applied regarding the weight measurements throughout pregnancy. Our final sample comprised 33 cohorts and 218,216 women who contributed with 679,262 gestational weight measurements, of which 218,216 at 0 weeks and 461,046 throughout pregnancy. Of these women, 9065 (4.2%), 148,697 (68.1%), 42,678 (19.6%), 13,084 (6.0%), 3597 (1.6%), and 1095 (0.5%) were underweight, normal weight, overweight, obese grade 1, obese grade 2, and obese grade 3, respectively, as defined in more detail below. Anonymized datasets were stored on a single central secured data server with access only for the main analysts.

Maternal anthropometrics were measured, derived from clinical records or self-reported. Maternal pre-pregnancy BMI was calculated from information on height and weight before pregnancy and was categorized as underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obesity grade 1 (30.0–34.9 kg/m^2), obesity grade 2 (35.0–39.9 kg/m^2), and obesity grade 3 (≥ 40.0 kg/m^2) according to the World Health Organization criteria (2). Data were obtained on early, mid, and late pregnancy weight as the closest measurement to 13 weeks of gestation (range 6–19.9 weeks of gestation), the closest measurement to 26 weeks of gestation (range 20–31.9 weeks of gestation), and the closest measurement to 40 weeks of gestation (range 32–45 weeks of gestation), respectively.

We modeled gestational weight gain by gestational age separately for each maternal pre-pregnancy BMI group to develop the pre-pregnancy BMI group-specific gestational weight gain charts. Weight measurements at the start of pregnancy and subsequent weights from 8 weeks onwards were available. For

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that reason, we modeled from week 0 onwards. We initially fitted a model in which each woman had a weight gain of 0 kg at the start of pregnancy (0 weeks), but the lack of variation in the outcome caused severe numerical problems. To address this, we imagined a nudge effect equal to the measurement error of body weight. It is known that measurement error of a single dial measurement is about 0.70 kg (3), so the variance of the gain score is equal to $0.70^2 + 0.70^2 = 0.98$ kg. For each woman, the weight gain at the start of pregnancy was taken as a random draw from the Gaussian distribution with mean of 0 and variance of 0.98 kg. The size of the measurement error was used since it is theoretically based but any variance could have been applied. We started the modeling using a Box-Cox Cole and Green distribution (Box-Cox normal), which turned out to be too strict to fit the data. Therefore, we fitted the models, separately for each maternal pre-pregnancy BMI group, by the Box-Cox *t* (BCT) method using the generalized additive model for location, scale, and shape (GAMLSS) package in R version 3.3.1 (4). We used GAMLSS instead of quantile regression since in the latter the centiles are estimated individually and thus may cross, leading to an invalid distribution for the outcome. Additionally, there are no distributional assumptions in quantile regression, which may hamper the estimation of the outer centiles with sufficient precision even when there is enough information at the tails (5). In the BCT method, the default links from the GAMLSS package, namely, an identity link for the mu and nu parts and a log link for the sigma and tau parts of the model, were used. The BCT method summarizes the distribution in four time-dependent smooth curves representing the median (M-curve), the variation (S-curve), the skewness (L-curve), and the kurtosis (T-curve) (6). The smoothing family and the amount of smoothing were determined by visual inspection of the worm plots, the fitted centiles, and the Q statistics (7,8). The worm plots describe salient features of the time-conditional z score distribution and aid in finding proper smoothing values for the model (7). The M-curve of the models for weight gain was fitted using B-splines smoothing on gestational age with specified internal breakpoints to define the splines and three degrees, which is similar to a cubic spline. Cubic splines smoothing on gestational age was also used for the S-curve, L-curve, and T-curve. The models for the different maternal pre-pregnancy BMI groups were fitted with different internal breakpoints and degrees of freedom for the curves.

Optimal gestational weight gain ranges were estimated for each pre-pregnancy BMI category by selecting the range of gestational weight gain that was associated with lower risk for any adverse outcome. The optimal gestational weight gain ranges per clinical BMI group were constructed. The odds ratios (ORs) for any adverse outcome were calculated for each gestational weight gain

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category within the particular clinical BMI group vs all other women within that BMI group. The individual-level data from all cohorts were analyzed simultaneously using multilevel models. The models followed a 2-level hierarchical structure with participants (level 1) nested within cohorts (level 2). We used a generalized linear mixed model with a binominal distribution and logit link.

2.4 Results

Figure 1 shows selected percentiles of weight gain for gestational age (P2.3 (−2 SD), P16 (−1 SD), P50 (0 SD), P84 (1 SD), and P97.7 (2 SD)) for underweight, normal weight, overweight, and grades 1, 2, and 3 obese women. Gestational weight gain strongly differed per maternal pre-pregnancy BMI group and was gradually lower across higher BMI groups. The median (interquartile range) gestational weight gain at 40 weeks was 14.2 kg (11.4–17.4) for underweight women; 14.5 kg (11.5–17.7) for normal weight women; 13.9 kg (10.1–17.9) for overweight women; and 11.2 kg (7.0–15.7), 8.7 kg (4.3–13.4), and 6.3 kg (1.9–11.1) for grades 1, 2, and 3 obese women, respectively.

For all maternal pre-pregnancy BMI groups, weight gain trajectories throughout pregnancy followed a non-linear shape. The rate of weight gain was lower in the first half than in the second half of pregnancy for all pre-pregnancy BMI groups. Especially in overweight women, we observed a higher rate of weight gain around 22–25 weeks of gestation. An online tool to produce individual *z* scores and percentiles for gestational weight gain in singleton pregnancies based on our international reference charts is available at https://lifecycle-project.eu.

Overall, any adverse outcome occurred in 37.2% (n = 73,161) of women, ranging from 34.7% (2706 of 7809) among women categorized as underweight to 61.1% (592 of 969) among women categorized as obesity grade 3 (**Figure 2**)(9). Optimal gestational weight gain ranges were 14.0 kg to less than 16.0 kg for women categorized as underweight; 10.0 kg to less than 18.0 kg for normal weight; 2.0 kg to less than 16.0 kg for overweight; 2.0 kg to less than 6.0 kg for obesity grade 1; weight loss or gain of 0 kg to less than 4.0 kg for obesity grade 2; and weight gain of 0 kg to less than 6.0 kg for obesity grade 3 (**Figure 3**)(9). These gestational weight gain ranges were associated with low to moderate discrimination between those with and those without adverse outcomes (range for area under the receiver operating characteristic curve, 0.55-0.76).

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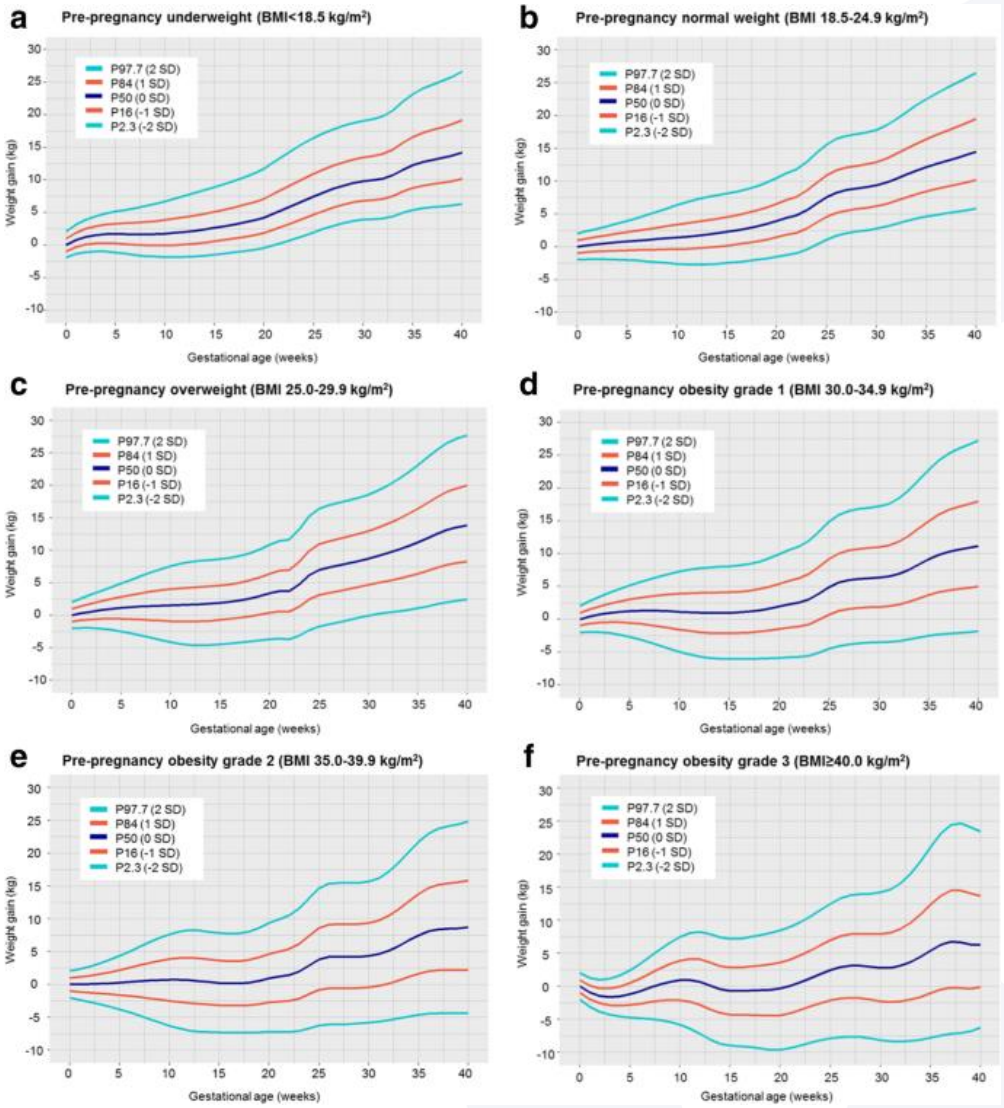

Figure 1. Selected percentiles of weight gain for gestational age for maternal pre-pregnancy BMI. Underweight (a), normal weight (b), overweight (c), obesity grade 1 (d), obesity grade 2 (e) and obesity grade 3 (f).

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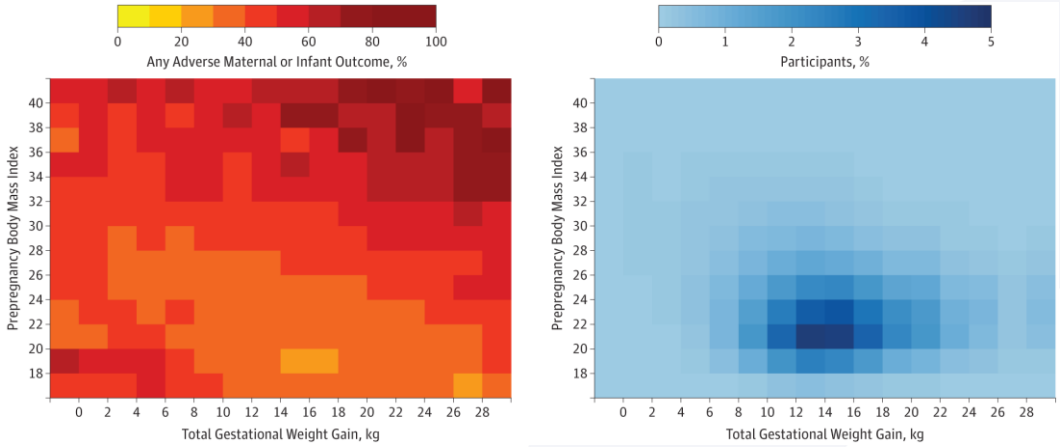

Figure 2. Heatmap of Absolute Risk for Any Adverse Maternal or Infant Outcome. Values represent the absolute risks of any adverse maternal and infant outcome (left panel) and the percentages of participants (right panel) for each combination of body mass index and gestational weight gain. Absolute risk was calculated as No. of participants (any adverse outcome)/No. of participants (body mass index and gestational weight gain category) × 100. The percentages of participants were calculated as the number of participants with each combination of body mass index and gestational weight gain as a percentage of the total study sample. The total study sample size was 196,670. Participants in the extreme categories of pre-pregnancy body mass index (calculated as weight in kilograms divided by height in meters squared) and gestational weight gain had values beyond the most extreme labeled tick marks. Any adverse outcome includes preeclampsia (gestational hypertension plus proteinuria), gestational hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or both after 20 weeks of gestation in previously normotensive women), gestational diabetes (a random glucose level >11.0 mmol/L, a fasting glucose level ≥7.0 mmol/L, or a fasting glucose level between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test [glucose level >7.8 mmol/L after glucose intake]), cesarean delivery, preterm birth (gestational age at birth <37 weeks), and small or large size for gestational age at birth (sex- and gestational age–adjusted birth weight <10th percentile and >90th percentile, respectively).

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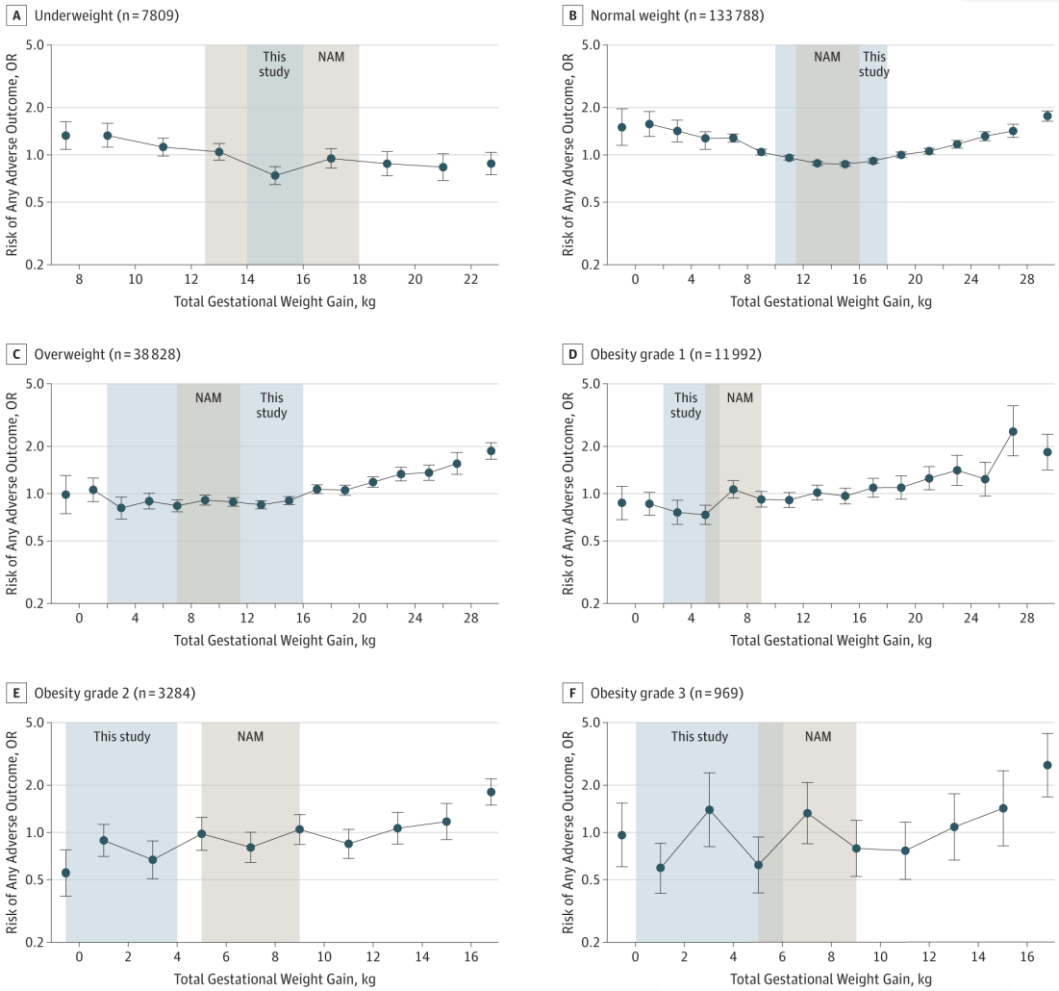

Figure 3. Associations of Gestational Weight Gain Categories With Any Adverse Outcome. OR indicates odds ratio and it reflects the risk for any adverse outcome per gestational weight gain category for women with underweight, normal weight, overweight, obesity grade 1, obesity grade 2, and obesity grade 3, parts A-F, respectively, compared with all other gestational weight gain categories in that specific group for clinical maternal body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). The solid circles represent the OR for all participants in each gestational weight gain category. The error bars indicate 95% CIs. The blue area represents the optimal gestational weight gain range according to the current analysis, the gray area represents the gestational weight gain ranges recommended by the US National Academy of Medicine (NAM; formerly the Institute of Medicine). The gestational weight gain categories were 2 kg each. Participants in the extreme categories of gestational weight gain had values beyond the most extreme labeled tick marks. The maternal BMI categories were underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), obesity grade 1 (30.0-34.9), obesity grade 2 (35.0-39.9), and obesity grade 3 (≥40.0). Any adverse outcome includes preeclampsia (gestational hypertension plus proteinuria), gestational hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or both after 20 weeks of gestation in previously normotensive women), gestational diabetes (a random glucose level >11.0 mmol/L, a fasting glucose level ≥7.0 mmol/L, or a fasting glucose level between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test [glucose level >7.8 mmol/L after glucose intake]), caesarean delivery, preterm birth (gestational age at birth <37 weeks), and small or large size for gestational age at birth (sex- and gestational age–adjusted birth weight <10th percentile and >90th

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percentile, respectively). For the gestational weight gain ranges defined in this study, a statistically significant OR lower than 1 for a gestational weight gain category was considered the optimal weight gain. If a non-significant association (either with an OR >1, <1, or of 1) for a gestational weight gain category was surrounded by 2 significant estimates with an OR below 1, that gestational weight gain category was included in the optimal gestational weight gain range.

2.5 Conclusion

We developed novel gestational weight gain charts for different pre-pregnancy BMI groups for women in Europe, North America, and Oceania. Gestational weight gain strongly differed per maternal pre-pregnancy BMI group and was gradually lower across higher BMI groups. For all maternal BMI groups, weight gain throughout pregnancy followed a non-linear trajectory. The rate of weight gain was greater in the second than in the first half of pregnancy.

Maternal pre-pregnancy BMI, and to a lesser extent gestational weight gain, are associated with risks of adverse maternal and infant adverse outcomes. Gestational weight gain ranges that were associated with lower risks for adverse outcomes were 14.0 kg to less than 16.0 kg for women categorized as being underweight; 10.0 kg to less than 18.0 kg for normal weight; 2.0 kg to less than 16.0 kg for overweight; 2.0 kg to less than 6.0 kg for obesity grade 1; weight loss or gain of 0 kg to less than 4.0 kg for obesity grade 2; and weight gain of 0 kg to less than 6.0 kg for obesity grade 3.

Pre-pregnancy BMI was more strongly associated with adverse maternal and infant outcomes than the amount of gestational weight gain. The estimates of optimal gestational weight gain may inform prenatal counselling; however, the optimal gestational weight gain ranges had limited predictive value for the outcomes assessed.

3. Childhood obesity

3.1 Rationale

Childhood obesity is a major global public health concern. Childhood overweight and obesity are known to have major consequences for short- and long-term cardiovascular, metabolic, cancer and mental health outcomes. Consequently, childhood obesity has major individual, societal and economic consequences. An accumulating body of evidence suggests that the first 1000 days of life, covering the period from preconception until the age of 2 years, lay the foundation for the individual risk of childhood obesity. Previous studies have identified various risk factors such as parental socio-economic background, ethnicity, body mass index and smoking, mode of delivery, birth weight, and infant feeding and growth. Risk

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factors in this period tend to cluster within families and are more prevalent among families with a low socio-economic status or from ethnic minority groups. This knowledge urgently needs to be translated into prediction tools. These tools would enable early identification of individuals at high risk of childhood obesity who are likely to benefit from prevention strategies from the earliest phases of life onwards in order to optimize body weight in childhood and health across the life course. Previous studies have developed prediction models for childhood obesity. These prediction models have not yet been widely implemented, because of the limited sample size, selected populations and lack of replication of model performance. An easy-to-use prediction model would enable primary prevention targeted at future parents and infants. A dynamic prediction model covering the first 1000 days of life would enable identification of future parents and young offspring at increased risk for childhood obesity by updating risk factors in the preconception period, fetal life and infancy.

We aimed to develop and validate a dynamic prediction model using risk factors in the preconception period, fetal period, and infancy period, together covering the first 1000 days of life, to predict childhood obesity. This study pooled individual participant data from pregnancy and birth cohorts from Europe, Australia and North America working together in the LifeCycle Project – Maternal Obesity and Childhood Outcomes Consortium.

3.2 Objective

The main objective was to develop a population-based prediction model for childhood obesity based on preconception, pregnancy and infancy factors (family-based socio-demographic, lifestyle, medical and physical factors) using an individual-participant data meta-analysis approach. The main exposures of interest were maternal, paternal and offspring socio-demographic, lifestyle, medical and physical factors in the preconception period, fetal period and infancy; the main outcome of interest was childhood obesity in three distinct age periods (age 2 - 5 years; >5 - 10 years; and >10 years).

3.3 Methods

This study was embedded in the international LifeCycle Project. A pregnancy or birth cohort study was eligible for inclusion if it included mothers with singleton live-born children who were born between 1989 and 2015, had information on maternal pre-pregnancy or early-pregnancy BMI, and had at least 1 offspring outcome measurement (birth weight or childhood BMI). The final date of follow-up was December 2015. No exclusions were made based on previous pregnancy or birth complications. We included 36 cohorts. All had received institutional review board approval and written informed consent had been obtained.

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Women could be included more than once in the analyses if they had multiple singleton pregnancies during the study period. We used the population-based cohorts as the main study sample. The remaining hospital-based cohorts were included as an external validation sample.

For the models, we used an additive approach using candidate predictors clustered based on timing of measurement: preconception, pregnancy/birth and infant candidate predictors. We first selected predictors from the maternal preconception model and further extended this model by including clusters of candidate predictors from pregnancy and infancy respectively. We selected predictors from these predefined models using a backward selection approach. Based on the log-likelihood ratio, we evaluated whether the cluster of variables significantly improved the model. Next, if this cluster of candidate predictors improved the model, candidate predictors from this cluster were stepwise eliminated based on the chi-square statistic. After predictor selection from a cluster of candidate predictors, we fixed the effect estimates before extending the model with predictors from the next clusters. This resulted in three models: 1) the preconception model, including predictors selected from the preconception cluster; 2) the pregnancy/birth model, including the fixed effect estimates from the preconception model and predictors selected from the pregnancy/birth cluster; and 3) the infant model, including fixed effect estimates of the preconception and pregnancy/birth model and predictors selected from the infant cluster. This approach enabled us to use the model in clinical practice during different time periods and to assess the additional predictive value of predictors from different clusters. The individual-level data from all cohorts were analyzed simultaneously by using multilevel models. The models followed a 2-level hierarchical structure with participants (level 1) nested within cohorts (level 2). We used generalized linear mixed models with a binominal distribution and logit link. A random intercept at the cohort level was included to allow heterogeneity between cohorts. Model assumptions regarding linearity were addressed if needed. After model estimation, we assessed model performance on discriminative ability within the development dataset, using Receiver Operating Characteristics (ROC) curve and calculation of the pooled Area Under the Curve (AUC) for mid-childhood obesity. To calculate the pooled AUC, we estimated the AUC within each cohort separately and pooled by the inverse of the sum of the cluster specific sampling variance estimate and the between cluster variance estimate, as described previously (10). Pooled calibration intercepts and slopes were estimated similarly. The intercept should ideally be equal to zero and the calibration slope should ideally be equal to one. To assess direction of potential miscalibration, we used calibration plots within cohorts,

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which compare the mean of all predicted risks with the mean actual risks. We quantified potential miscalibration using an intercept (calibration-in-the-large). The models were externally validated in our validation dataset including four hospital/maternity ward-based cohort studies. Within this dataset, we assessed discrimination and calibration of the final model based on linear prediction obtained in the validation set for the mid-childhood obesity model on cohort level. Again, we assessed the ROC curve and calculation of the AUC on cohort level and pooled these measures. For early-, and late-childhood obesity, we developed prediction models similarly to those for mid-childhood obesity and assessed predictive performance of these outcomes in the training dataset. As sensitivity analyses, we 1) assessed model performance of the mid-childhood obesity models for the prediction of childhood overweight/obesity, 2) assessed model performance of the mid-childhood obesity models without including paternal characteristics to assess applicability in clinical practice when the biological partner is not present.

We further examined the clinical applicability of our developed prediction models as follows: 1) based on our developed prediction models for mid-childhood obesity, we constructed a risk calculator as a screening tool using a point system obtained from nomograms representing the regression fit. Using this risk calculator, we estimated the risks of childhood obesity based on three specific combinations of risk factors; 2) we calculated the number of children with a predicted probability of >6% for childhood obesity, who would have actually had developed mid-childhood obesity. This cut off was based on the mean highest tertile of predicted probabilities within the study population of the preconception, pregnancy/birth and infant models and could potentially serve in clinical settings as a definition of being at increased risk to identify those who may require intervention. All statistical analyses were performed in R.

3.4 Results

The analyses were based on 89,528 individuals. **Table 1** gives an overview of the data used for the analyses. **Table 2** describes the 3 models used to predict mid-childhood obesity, with their respective AUCs and calibration intercepts and slopes. In **Figure 4**, we show predicted risks for children at risk for childhood obesity from the risk calculator.

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Table 1. Descriptives of the study population according to mid-childhood obesity

	Full population	Childhood underweight/normal weight/overweight	Childhood obesity
	N = 89,528	**N= 84,700**	**N= 4,828**
Maternal age, years, median (IQR)	30.3 (27.3, 33.5)	30.3 (27.4, 33.5)	30.0 (26.2, 33.0)
Maternal pre-pregnancy BMI, kg/m^2, median (IQR)	22.5 (20.7, 25.1)	22.4 (20.6, 24.9)	25.2 (22.4, 29.0)
Maternal educational level, n low (%)	15,655 (18)	14,175 (17)	1,480 (32)
Maternal parity, n nulliparous (%)	43,334 (51)	41,066 (51)	2,268 (49)
Maternal smoking, n yes (%)	11,235 (16)	10,239 (15)	996 (26)
Paternal age, years, median (IQR)	32.0 (29.0, 36.0)	32.0 (29.0, 36.0)	31.6 (28.0, 35.7)
Paternal BMI, kg/m^2, median (IQR)	24.8 (23.1, 26.9)	24.7 (23.0, 26.8)	26.6 (24.5, 29.4)
Gestational weight gain, n excessive (%)	25,773 (39)	23,994 (39)	1,779 (51)
Paternal smoking, yes (%)	18,612 (31)	17,533 (30)	1,079 (42)
Sex, n girl (%)	43,867 (49)	41,748 (49)	2,119 (44)
Gestational age at birth, weeks, median (IQR)	40.0 (39.0, 41.0)	40.0 (39.0, 41.0)	40.0 (38.9, 40.7)
Birth weight, grams, mean (SD)	3,505.7 (542.6)	3,504.4 (540.9)	3,527.4 (571.6)
Introduction solid foods <6 months, yes (%)	54,519 (83)	52,056 (83)	2,463 (83)
Breast feeding, >6 months n yes (%)	37,543 (53)	35,913 (53)	1,630 (43)
Television watching >2hours/day	12,870 (82)	11,896 (83)	974 (71)
Sleep, hours/day, median (IQR)	11.0 (10.0, 11.5)	11.0 (10.2, 11.5)	10.5 (10.0, 11.0)
Infant age, months, median (IQR)	22.2 (18.0, 23.7)	22.3 (18.0, 23.7)	19.2 (18.0, 23.6)
Infant weight, kilograms, mean (SD)	12.2 (1.4)	12.1 (1.4)	13.2 (1.8)
Infant length, centimeters, mean (SD)	85.7 (3.9)	85.7 (3.9)	86.2 (4.2)
Age early-childhood, years, median (IQR)	48.4 (46.0, 50.5)	48.3 (46.0, 50.4)	49.0 (46.3, 51.5)
Early-childhood BMI, kg/m^2,median (IQR)	15.8 (15.0, 16.7)	15.7 (14.9, 16.6)	18.2 (17.0, 19.5)
Early-childhood obesity, n yes (%)	392 (1)	111 (0)	281 (14)
Age mid-childhood, years, median (IQR)	85.1 (81.5, 89.2)	85.0 (81.3, 89.0)	86.0 (83.6, 97.0)
Mid-childhood BMI, kg/m^2,median (IQR)	15.7 (14.8, 17.0)	15.6 (14.7, 16.7)	21.2 (20.1, 22.8)
Age late-childhood, years, median (IQR)	167.0 (160.5, 183.0)	167.0 (162.0, 183.0)	165.0 (153.0, 179.0)
Late-childhood BMI, kg/m^2,median (IQR)	19.7 (17.9, 22.0)	19.5 (17.8, 21.5)	26.2 (23.8, 28.9)
Late-childhood obesity, n yes (%)	958 (6)	430 (3)	528 (53)

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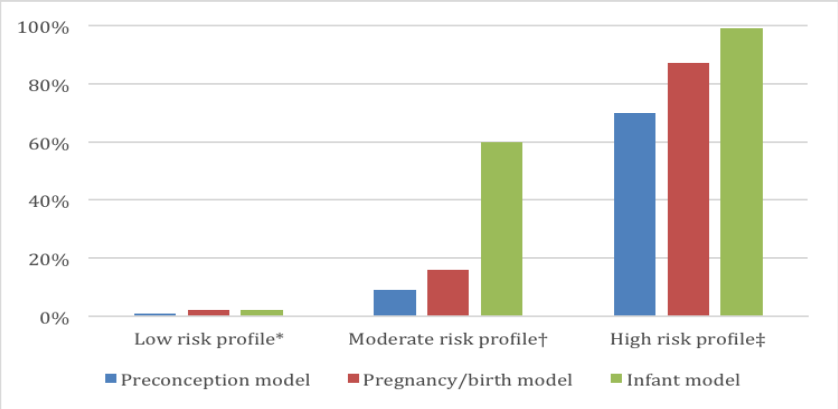
Table 2. Variables included in each model and the corresponding areas under the curve

Models for mid-childhood obesity				
Models	**Variables included per model**	**AUC (95% CI)**	**Calibration intercept (95% CI)**	**Calibration slope (95% CI)**
Preconception model	Maternal age + education level + smoking + BMI +paternal BMI	0.75 (0.73, 0.77)	0.02 (-0.27, 0.30)	0.99 (0.92, 1.06)
Pregnancy/birth model	Preconception model + gestational weight gain + paternal smoking + fetal sex + gestational-age-adjusted birthweight	0.76 (0.74, 0.77)	0.01 (-0.28, 0.31)	0.95 (0.89, 1.01)
Infant model	Pregnancy model + infant sleep + infant television watching + infant length + infant weight	0.81 (0.79, 0.82)	0.01 (-0.31, 0.33)	0.94 (0.89, 0.98)

BMI: Body Mass Index, AUC: Area Under the receiver operating characteristics Curve.

Figure 4. Predicted risks for children at risk for childhood obesity from the risk calculator



*Maternal age: 30, education level is high, does not smoke, pre-pregnancy BMI 20 kg/m^2, paternal BMI 22 kg/m^2, adequate gestational weight gain, fetal sex is female, gestational-age-adjusted birthweight is -1 SDS, no paternal smoking during pregnancy, infant sleep is 11 hours/day, television watching time is less than 2 hours/day, infant length is 80 cm, infant weight is 14 kilogram. †Maternal age: 20, education level is high, mother does not smoke, pre-pregnancy BMI 25 kg/m^2, paternal BMI 28 kg/m^2, excessive gestational weight gain, fetal sex is female, gestational-age-adjusted birthweight is 1 SDS, no paternal smoking during pregnancy, infant sleep is 7 hours/day, television watching time is more than 2 hours/day, infant length is 80 cm, infant weight is 16 kilogram. ‡Maternal age: 20, education level is low, mother smokes, pre-pregnancy BMI 35 kg/m^2, paternal BMI 34 kg/m^2, excessive gestational weight gain, fetal sex is male, gestational-age-adjusted birthweight is 2 SDS, paternal smoking during pregnancy, infant sleep is 5 hours/day, television watching time is more than 2 hours/day, infant length is 85 cm, infant weight is 18 kilograms.

3.5 Conclusion

We have developed European prediction models for childhood obesity based on more than 80,000 mother-father-child trios. The models were based on a limited number of easy-to-use predictors. Results of the models will be used in a web-based application for European children. After peer-reviewed publication, this

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application will be linked to the LifeCycle website, through which it will be easy and free to use.

4. Conclusion

In Task 10.4, we developed novel gestational weight gain charts for different pre-pregnancy BMI groups, as well as a prediction model for childhood obesity using data from more than 200,000 women and more than 80,000 parent-child trios, respectively. An online tool to produce individual *z* scores and percentiles for gestational weight gain in singleton pregnancies based on our international reference charts is available at https://lifecycle-project.eu. The prediction model for childhood obesity will be used in a web-based application for European children and will be accessible to the LifeCycle website after peer review.

Analyses on prediction of respiratory and mental health outcomes have been started and are expected to be completed in 2023. For these analyses, we will use similar approaches for analysis and dissemination.

5. Contribution of partners

- **ERASMUS** has led this task
- **Other beneficiaries** contributed data, did data cleaning, and ran statistical analyses.

6. Deviations from original plan

The analyses are partly finished. Other analyses are expected to be finished in 2023.

7. Dissemination activities

The (preliminary) results gave been presented at several meetings and final results have been published in peer-reviewed journal. The eHealth/web-based applications will be available through the LifeCycle website, with the app for optimal gestational weight gain already on there.

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