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Report on cardiovascular developmental trajectories during fetal life, infancy and early childhood, and the relationship with early-life exposures and cardiovascular risk factors in childhood

Work package 4 – Task 4.1 – Deliverable 4.1

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Table of contents

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1. Summary

Background: Increasing evidence suggests that fetal life, infancy and early childhood are critical periods for the effects of stressors and for future cardio-metabolic health. Maternal obesity during pregnancy has been identified as an important risk factor that might lead to cardiovascular dysfunction in the offspring.

Aim: Task 4.1 aims to study associations of early-life stressors and the early-life exposome with adiposity and cardio-metabolic developmental trajectories in fetal life, infancy and early childhood and subsequently associations of these trajectories with cardio-metabolic risk factors in childhood. As a proof-of-principle, task 4.1 aims to study the associations of maternal body mass index and gestational weight gain with risks of adverse birth outcomes and childhood overweight.

Methods: For these proof-of principle analyses, we used data from 39 European, North American and Australian cohorts that had information available on maternal prepregnancy/early-pregnancy body mass index, and had at least one offspring measurement (birth weight or childhood body mass index). Individual level data from each cohort was harmonized, assembled in a large dataset and pooled together for analysis. We have successfully generated a unique and completely harmonized dataset with data from 277 042 mother-child pairs. Anonymized datasets were stored on a single central secured data server with access for the main analysts only.

Results: Multiple proof-of-principle studies were conducted. First, we developed gestational weight gain reference charts for different pre-pregnancy body mass index groups for women in Europe, North America, and Oceania. This work allowed the estimation of maternal pre-pregnancy body mass index-specific weight gain for gestational age z-scores that were used in subsequent analyses. Higher maternal pre-pregnancy body mass index and gestational weight gain were, across their full ranges, associated with an increased risk of adverse birth outcomes and offspring overweight/obesity throughout childhood and have a considerable population impact. Finally, we estimated the optimal gestational weight gain ranges across prepregnancy body mass index categories.

Conclusion: Preventive strategies for reducing adverse birth outcomes and childhood obesity should focus on maternal adiposity before pregnancy, rather than during pregnancy. Task 4.1 will leverage work conducted in these proof-of-principle studies to further assess additional important early-life stressors of cardio-metabolic health, strengthen causal inference and develop longitudinal developmental trajectories.

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2. Introduction

Work package 4 of the LifeCycle Project focuses on the early-life stressors during preconception, pregnancy, infancy and early childhood and cardiovascular and metabolic outcomes from fetal life until adulthood. The **specific objective of Task 4.1** is to assess the associations of early-life stressors and the early-life exposome with adiposity and cardio-metabolic developmental trajectories in fetal life, infancy and early childhood and subsequently associations of these trajectories with cardio-metabolic risk factors in childhood.

Obesity at the start of pregnancy and excessive gestational weight gain are among the early-life stressors with more pronounced adverse consequences for childhood cardiometabolic health. However, it remains unknown whether the associations with birth outcomes and childhood obesity are present across the full range of body mass index and gestational weight gain or only restricted to the extremes and what is the additional effect of excessive weight gain among overweight/obese women. Also, it is important to estimate the population disease burden due to excessive adiposity in pregnancy for the development of future population preventive strategies designed to reduce the risks of these adverse outcomes. International gestational weight gain charts and estimation of the optimal gestational weight gain ranges for all pre-pregnancy body mass index groups are also needed to improve clinical monitoring and risk selection of pregnant women.

In this report, we describe results from proof-of-principle analyses on the associations of maternal body mass index and gestational weight gain with adverse birth outcomes and childhood overweight.

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3. Proof-of-principle studies

Inclusion criteria and participating cohorts: Pregnancy and birth cohort studies were eligible for inclusion if they included mothers with singleton live-born children who were born from 1989 onwards, had information available on maternal prepregnancy/early-pregnancy body mass index, and had at least one offspring measurement (birth weight or childhood body mass index). We identified eligible cohorts from existing collaborations on childhood health (EarlyNutrition Project, CHICOS Project, www.birthcohorts.net assessed until July 2014). These existing collaborations enable LifeCycle partners to already collaborate with each other before the EU Child Cohort Network was available. Fifty cohorts from Europe, North America, and Oceania were identified and invited, of which 39 cohorts agreed to participate. The cohorts were approved by their local institutional review boards, and written informed consent from all participants or parents was obtained. All cohorts provided written informed consent for using their data. Anonymized datasets were stored on a single central secured data server with access for the main analysts only.

Pre-processing of data: Main efforts have been put in data harmonization, cleaning and assembling into one large dataset. We have developed a list of variables related to lifestyle factors, socio-demographic characteristics and cardiometabolic outcomes of interest for these proof-of-principle analyses. The definitions for each variable were based on scientific literature, expert knowledge, international classification systems and, most importantly, on data available in participating cohorts. WP1 build upon and extended this work. Each cohort harmonized their own data and provided to the leading group. A thorough quality check of data was performed and data was further cleaned if needed. We have successfully generated a unique and completely harmonized dataset with data from 277 042 mother-child pairs.

Results: We first developed gestational weight gain reference charts for different pre-pregnancy body mass index groups for women in Europe, North America, and Oceania (**Paper 1** in Scientific Output). Gestational weight gain strongly differed per maternal pre-pregnancy body mass index group and was gradually lower across higher body mass index groups. **These reference charts can be used to classify weight gain independently of gestational age in etiological research focused on maternal and offspring consequences of weight gain and may be useful in clinical practice to identify women at risk for adverse short- and long-term health outcomes.** This work allowed the estimation of maternal pre-pregnancy body mass index-specific weight gain for gestational age z-scores that were used in the following papers. **Papers 2 and 3** in Scientific Output suggest that higher maternal pre-pregnancy body mass index and gestational weight gain are across their full ranges associated with an increased risk of large size for gestational age at birth and offspring overweight/obesity throughout childhood and have a considerable population impact. Interestingly, the effect of gestational weight gain in addition to the effect of maternal pre-pregnancy body mass index on childhood overweight/obesity was small. To further understand the role of maternal body mass index on childhood cardio-metabolic health, we also explored the influence of maternal obesity on the association between common pregnancy complications and risk of childhood obesity. We observed that the associations of gestational diabetes, gestational hypertension, and pre-eclampsia with childhood obesity are largely explained by maternal prepregnancy and early-pregnancy body mass index (**Paper 4** in Scientific Output). **Our findings provide evidence for advocating a healthy body mass index in women who are planning to become pregnant and an adequate weight gain during pregnancy to reduce the burden of adverse birth outcomes and**

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childhood overweight and obesity. Following these findings, we endeavored in the estimation of optimal gestational weight gain ranges across prepregnancy body mass index categories (**Paper 5** in Scientific Output). **The estimates of optimal gestational weight gain may inform prenatal counseling; however, the optimal gestational weight gain ranges had limited predictive value for the outcomes assessed.** Also, as part of these proof-of-principle analyses, we assessed the associations of parental smoking during pregnancy, specifically of quitting or reducing smoking and maternal and paternal smoking combined, with preterm birth, small size for gestational age, and childhood overweight (**Paper 6** in Scientific Output). We observed that maternal smoking during the first trimester only is not associated with the risks of small size for gestational age and preterm birth but is associated with a higher risk of childhood overweight. Reducing the number of cigarettes during pregnancy without quitting may be beneficial for the risk of small size for gestational age but does not influence the risks of preterm birth and childhood overweight. Paternal smoking seems to be associated, independently of maternal smoking, with the risks of childhood overweight. **Population strategies should focus on parental smoking prevention before or at the start of, rather than during, pregnancy.**

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4. Scientific output

Below, we present a list of summaries of published papers related to this deliverable. Involved partners are ordered according to the partner numbers in the LifeCycle Project.

Paper 1: Gestational weight gain charts for different body mass index groups for women in Europe, North America, and Oceania [1]

Partners involved: ERASMUS, ISGLOBAL, UNITO, UOS, UNIVBRIS, UCPH, UMCG, UOC, NIPH, INSERM, UWA;

Summary: Gestational weight gain differs according to pre-pregnancy body mass index and is related to the risks of adverse maternal and child health outcomes. Gestational weight gain charts for women in different pre-pregnancy body mass index groups enable identification of women and offspring at risk for adverse health outcomes. We aimed to construct gestational weight gain reference charts for underweight, normal weight, overweight, and grade 1, 2 and 3 obese women and compare these charts with those obtained in women with uncomplicated term pregnancies. We used individual participant data from 218,216 pregnant women participating in 33 cohorts from Europe, North America and Oceania. Of these women, 9,065 (4.2%), 148,697 (68.1%), 42,678 (19.6%), 13,084 (6.0%), 3,597 (1.6%), and 1,095 (0.5%) were underweight, normal weight, overweight, and grade 1, 2 and 3 obese women, respectively. A total of 138, 517 women from 26 cohorts had pregnancies with no hypertensive or diabetic disorders and with term deliveries of appropriate for gestational age at birth infants. Gestational weight gain charts for underweight, normal weight, overweight, and grade 1, 2 and 3 obese women were derived by the Box-Cox *t* method using the generalized additive model for location, scale and shape (**Figure 1**). We observed that gestational weight gain strongly differed per maternal pre-pregnancy body mass index group. 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 grade 1, 2 and 3 obese women, respectively. The rate of weight gain was lower in the first half than in the second half of pregnancy. No differences in the patterns of weight gain were observed between cohorts or countries. Similar weight gain patterns were observed in mothers without pregnancy complications. **Conclusion: Gestational weight gain patterns are strongly related to pre-pregnancy body mass index. The derived charts can be used to assess gestational weight gain in etiological research and as a monitoring tool for weight gain during pregnancy in clinical practice.**

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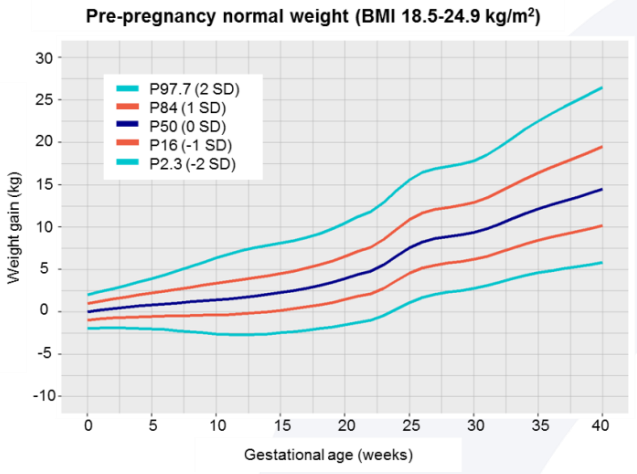
Figure 1. Selected percentiles of weight gain for gestational age for maternal pre-pregnancy normal weight.



Paper 2. Impact of maternal body mass index and gestational weight gain on pregnancy complications: An individual participant data meta-analysis of European, North American and Australian cohorts [2]

Partners involved: ERASMUS, ISGLOBAL, UNITO, UOS, UNIVBRIS, UCPH, BTHFT, UMCG, UOC, NIPH, INSERM, LMU, UWA;

Summary: Both maternal obesity and excessive gestational weight gain are associated with increased risks of short- and long-term adverse health consequences for mother and child. We aimed to assess the separate and combined associations of maternal pre-pregnancy body mass index and gestational weight gain with the risks of pregnancy complications and their population impact. We conducted an individual participant data meta-analysis among 265,270 births from 39 European, North American and Oceania cohorts. Information on maternal pre-pregnancy body mass index, gestational weight gain, gestational hypertension, pre-eclampsia, gestational diabetes, preterm birth, small and large size for gestational age at birth was obtained. Multilevel binary logistic regression models were used. Higher maternal pre-pregnancy body mass index and gestational weight gain were, across their full ranges, associated with higher risks of gestational hypertensive disorders, gestational diabetes and large size for gestational age at birth (**Figure 2**). Preterm birth risk was higher at lower and higher body mass index and weight gain. Compared with normal weight mothers with medium gestational weight gain, obese mothers with high gestational weight gain had the highest risk of any pregnancy complication (odds ratio 2.51, 95% CI 2.31-2.74). We estimated that 23.9% of any pregnancy complication was attributable to maternal overweight/obesity and 31.6% of large size for gestational age infants was attributable to excessive gestational weight gain.

Conclusion: Maternal pre-pregnancy body mass index and gestational weight gain are, across their full ranges, associated with risks of pregnancy complications. Obese mothers with high gestational weight gain are at the highest risk of pregnancy complications. Promoting a healthy pre-pregnancy body mass index and gestational weight gain may reduce the burden of pregnancy complications and ultimately the risk of maternal and neonatal morbidity.

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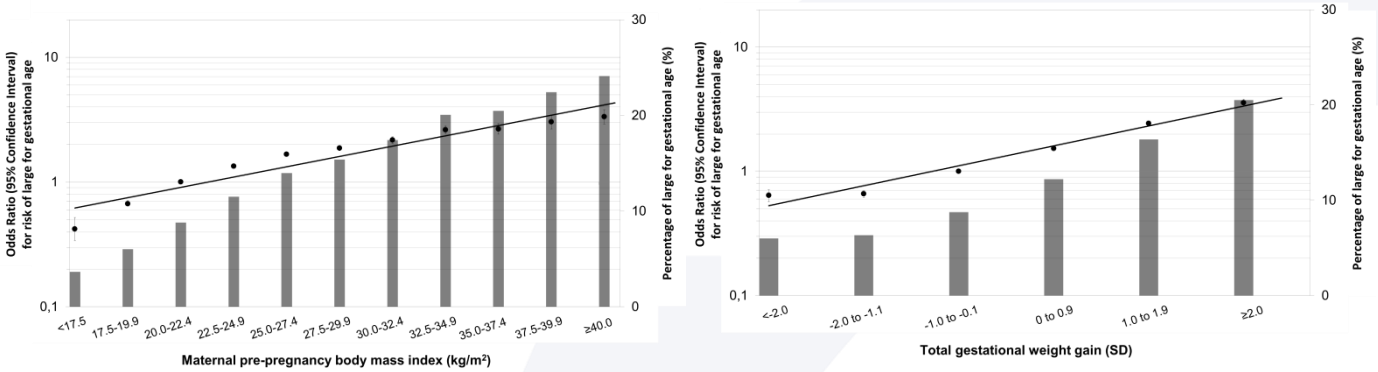
Figure 2. Maternal pre-pregnancy body mass index, gestational weight gain and the risks of large for gestational age.



Paper 3. Maternal body mass index, gestational weight gain and the risk of overweight and obesity across childhood: An individual participant data meta-analysis [3]

Partners involved: ERASMUS, ISGLOBAL, UNITO, UOS, UNIVBRIS, UCPH, BTHFT, UMCG, UOC, NIPH, INSERM, LMU, UWA;

Summary: Maternal obesity and excessive gestational weight gain may have persistent effects on offspring fat development. However, it remains unclear whether these effects differ by severity of obesity, and whether these effects are restricted to the extremes of maternal body mass index and gestational weight gain. We aimed to assess the separate and combined associations of maternal body mass index and gestational weight gain with the risk of overweight/obesity throughout childhood, and their population impact. We conducted an individual participant data meta-analysis of data from 162,129 mothers and their children from 37 pregnancy and birth cohort studies from Europe, North America and Australia. We assessed the individual and combined associations of maternal pre-pregnancy body mass index and gestational weight gain, both in clinical categories and across their full ranges, with the risks of overweight/obesity in early (2.0–5.0 years), mid (5.0–10.0 years) and late childhood (10.0–18.0 years), using multilevel binary logistic regression models with a random intercept at cohort level adjusted for maternal sociodemographic and lifestyle-related characteristics. We observed that higher maternal pre-pregnancy body mass index and gestational weight gain both in clinical categories and across their full ranges were associated with higher risks of childhood overweight/obesity, with the strongest effects in late childhood (odds ratios [ORs] for overweight/obesity in early, mid, and late childhood, respectively: OR 1.66 [95% CI: 1.56, 1.78], OR 1.91 [95% CI: 1.85, 1.98], and OR 2.28 [95% CI: 2.08, 2.50] for maternal overweight; OR 2.43 [95% CI: 2.24, 2.64], OR 3.12 [95% CI: 2.98, 3.27], and OR 4.47 [95% CI: 3.99, 5.23] for maternal obesity; and OR 1.39 [95% CI: 1.30, 1.49], OR 1.55 [95% CI: 1.49, 1.60], and OR 1.72 [95% CI: 1.56, 1.91] for excessive gestational weight gain) (**Figure 3**). The proportions of childhood overweight/obesity prevalence attributable to maternal overweight, maternal obesity and excessive gestational weight gain ranged from 10.2 to 21.6%. Relative to the effect of maternal body mass index, excessive gestational weight gain only slightly increased the risk of childhood overweight/obesity within each clinical body mass index category (*p*-values for interactions of maternal body mass index with

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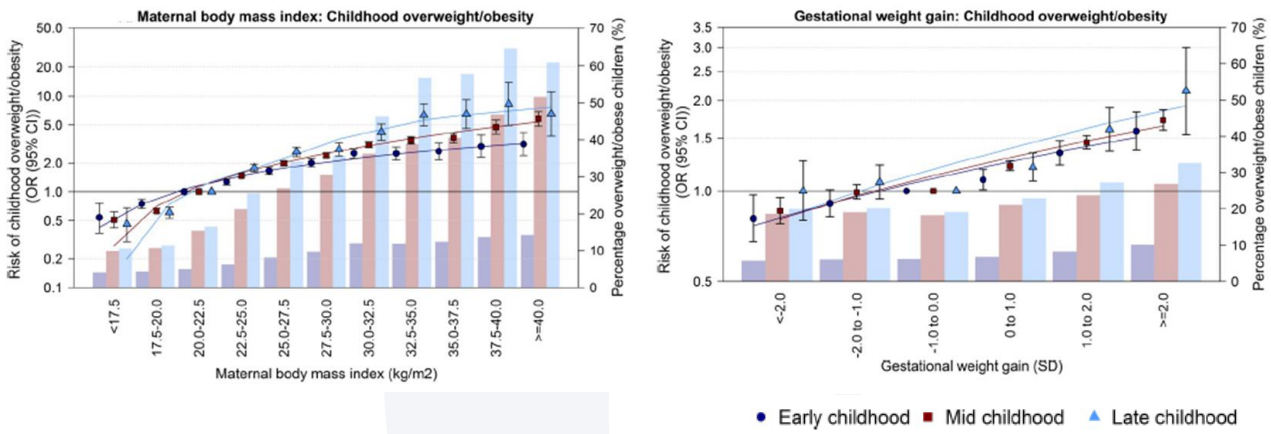
gestational weight gain: $p = 0.038$, $p < 0.001$, and $p = 0.637$ in early, mid, and late childhood, respectively). Limitations of this study include the self-report of maternal body mass index and gestational weight gain for some of the cohorts, and the potential of residual confounding. Also, as this study only included participants from Europe, North America, and Australia, results need to be interpreted with caution with respect to other populations.

Conclusion: In this study, higher maternal pre-pregnancy body mass index and gestational weight gain were associated with an increased risk of childhood overweight/obesity, with the strongest effects at later ages. The additional effect of gestational weight gain in women who are overweight or obese before pregnancy is small. Given the large population impact, future intervention trials aiming to reduce the prevalence of childhood overweight and obesity should focus on maternal weight status before pregnancy, in addition to weight gain during pregnancy.

Figure 3. Associations of maternal pre-pregnancy body mass index and gestational weight gain with the risk of childhood overweight.



Paper 4. Influence of maternal obesity on the association between common pregnancy complications and risk of childhood obesity: An individual participant data meta-analysis [4]

Partners involved: ERASMUS, ISGLOBAL, UNITO, UOS, UNIVBRIS, UCPH, BTHFT, UMCG, UOC, NIPH, INSERM;

Summary: Gestational diabetes and gestational hypertensive disorders are associated with offspring obesity, but the role of maternal adiposity in these associations remains unclear. We aimed to investigate whether these pregnancy complications affect the odds of offspring obesity independently of maternal obesity. We did an individual participant data meta-analysis of mother–offspring pairs from prospective birth cohort studies that had individual participant data on mothers with singleton liveborn children born from 1989 onwards and had information available about maternal gestational diabetes, gestational hypertension or pre-eclampsia, and childhood body mass index. We applied multilevel mixed-effects models to assess associations of gestational diabetes, gestational hypertension, and pre-eclampsia with body mass index SD scores and the odds of overweight and obesity throughout childhood, adjusting for lifestyle characteristics (offspring's sex, maternal age, educational level, ethnicity, parity, and smoking during pregnancy). We then explored the extent to which any association was explained by maternal pre-pregnancy or early-pregnancy

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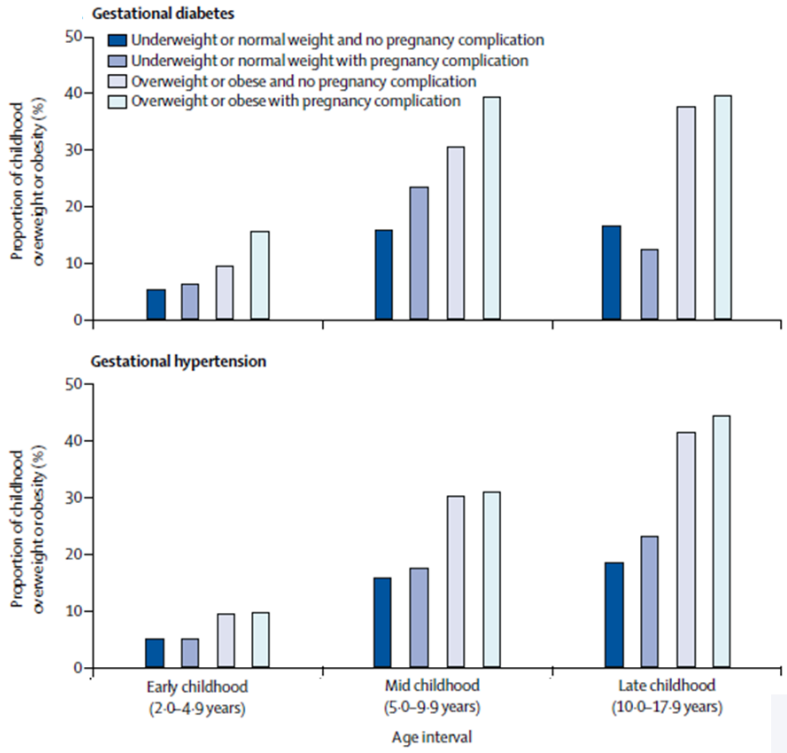
body mass index. 160 757 mother–offspring pairs from 34 European or North American cohorts were analysed. Compared with uncomplicated pregnancies, gestational diabetes was associated with increased odds of overweight or obesity throughout childhood (odds ratio [OR] 1·59 [95% CI 1·36 to 1·86] for early childhood [age 2·0–4·9 years], 1·41 [1·26 to 1·57] for mid childhood [5·0–9·9 years], and 1·32 [0·97 to 1·78] for late childhood [10·0–17·9 years]); however, these associations attenuated towards the null following adjustment for maternal body mass index (OR 1·35 [95% CI 1·15 to 1·58] for early childhood, 1·12 [1·00 to 1·25] for mid childhood, and 0·96 [0·71 to 1·31] for late childhood). Likewise, gestational hypertension was associated with increased odds of overweight throughout childhood (OR 1·19 [95% CI 1·01 to 1·39] for early childhood, 1·23 [1·15 to 1·32] for mid childhood, and 1·49 [1·30 to 1·70] for late childhood), but additional adjustment for maternal body mass index largely explained these associations (1·01 [95% CI 0·86 to 1·19] for early childhood, 1·02 [0·95 to 1·10] for mid childhood, and 1·18 [1·03 to 1·36] for late childhood) (**Figure 4**). Pre-eclampsia was associated with decreased body mass index in early childhood only (difference in body mass index SD score –0·05 SD score [95% CI –0·09 to –0·01]), and this association strengthened following additional adjustment for maternal body mass index.

Conclusion: Although lowering maternal risk of gestational diabetes, gestational hypertension, and pre-eclampsia is important in relation to maternal and fetal pregnancy outcomes, such interventions are unlikely to have a direct impact on childhood obesity. Preventive strategies for reducing childhood obesity should focus on maternal body mass index rather than on pregnancy complications.

Figure 4. Proportions of childhood overweight according to maternal pre-pregnancy body mass index category and presence or absence of gestational diabetes and gestational hypertension.



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Paper 5. Association of gestational weight gain with adverse maternal and infant outcomes [5]

Partners involved: ERASMUS, ISGLOBAL, UNITO, UOS, UNIVBRIS, UCPH, UMCG, UOC, NIPH, INSERM;

Summary: Both low and high gestational weight gain have been associated with adverse maternal and infant outcomes, but optimal gestational weight gain remains uncertain and not well defined for all prepregnancy weight ranges. We aimed to examine the association of ranges of gestational weight gain with risk of adverse maternal and infant outcomes and estimate optimal gestational weight gain ranges across prepregnancy body mass index categories. Individual participant-level meta-analysis using data from 196 670 participants within 25 cohort studies from Europe and North America (main study sample). Optimal gestational weight gain ranges were estimated for each prepregnancy body mass index category by selecting the range of gestational weight gain that was associated with lower risk for any adverse outcome. The main outcome termed *any adverse outcome* was defined as the presence of 1 or more of the following outcomes: preeclampsia, gestational hypertension, gestational diabetes, cesarean delivery, preterm birth, and small or large size for gestational age at birth. Individual participant-level data from 3505 participants within 4 separate hospital-based cohorts were used as a validation sample. Data were collected between 1989 and 2015. The final date of follow-up was December 2015. Of the 196 670 women (median age, 30.0 years [quartile 1 and 3, 27.0 and 33.0 years] and 40 937 were white) included in the main sample, 7809 (4.0%) were categorized at baseline as underweight (body mass index <18.5); 133 788 (68.0%), normal weight (body mass index, 18.5-24.9); 38 828 (19.7%), overweight (body mass index, 25.0-29.9); 11 992 (6.1%), obesity grade 1 (body mass index, 30.0-34.9); 3284 (1.7%), obesity grade 2 (body mass index, 35.0-39.9); and 969 (0.5%), obesity grade 3 (body mass index,≥40.0). 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. 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 5**). 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). Results for discriminative performance in the validation sample were similar to the corresponding results in the main study sample (range for area under the receiver operating characteristic curve, 0.51-0.79).

Conclusion: In this meta-analysis of pooled individual participant data from 25 cohort studies, the risk for adverse maternal and infant outcomes varied by gestational weight gain and across the range of prepregnancy weights. The estimates of optimal gestational weight gain may inform prenatal counseling; however, the optimal gestational weight gain ranges had limited predictive value for the outcomes assessed.

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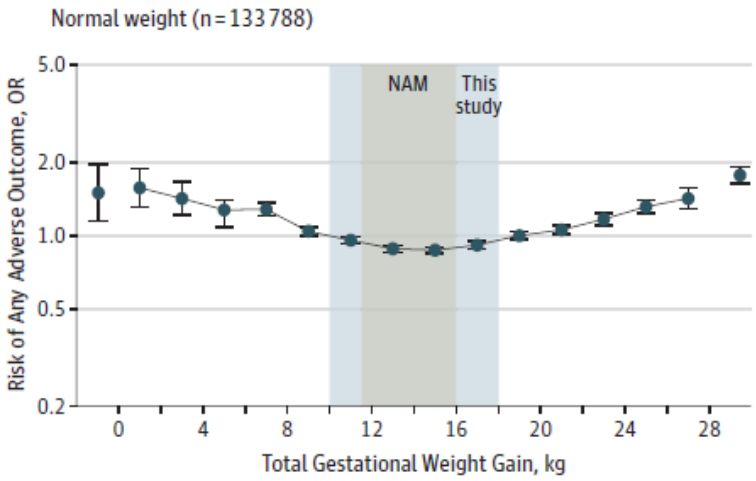
Figure 5. Associations of gestational weight gain categories with any adverse outcome for maternal normal weight, used to determine optimal weight gain ranges.



Paper 6. Changes in parental smoking during pregnancy and risks of adverse birth outcomes and childhood overweight in Europe and North America: An individual participant data meta-analysis of 229,000 singleton births [6]

Partners involved: ERASMUS, ISGLOBAL, UNITO, UOS, UNIVBRIS, UCPH, BTHFT, UOC, NIPH, INSERM;

Summary: Fetal smoke exposure is a common and key avoidable risk factor for birth complications and seems to influence later risk of overweight. It is unclear whether this increased risk is also present if mothers smoke during the first trimester only or reduce the number of cigarettes during pregnancy, or when only fathers smoke. We aimed to assess the associations of parental smoking during pregnancy, specifically of quitting or reducing smoking and maternal and paternal smoking combined, with preterm birth, small size for gestational age, and childhood overweight. We performed an individual participant data meta-analysis among 229,158 families from 28 pregnancy/birth cohorts from Europe and North America. All 28 cohorts had information on maternal smoking, and 16 also had information on paternal smoking. In total, 22 cohorts were population-based, with birth years ranging from 1991 to 2015. The mothers' median age was 30.0 years, and most mothers were medium or highly educated. We used multilevel binary logistic regression models adjusted for maternal and paternal sociodemographic and lifestyle-related characteristics. Compared with nonsmoking mothers, maternal first trimester smoking only was not associated with adverse birth outcomes but was associated with a higher risk of childhood overweight (odds ratio [OR] 1.17 [95% CI 1.02–1.35], *P* value = 0.030). Children from mothers who continued smoking during pregnancy had higher risks of preterm birth (OR 1.08 [95% CI 1.02–1.15], *P* value = 0.012), small size for gestational age (OR 2.15 [95% CI 2.07–2.23], *P* value < 0.001), and childhood overweight (OR 1.42 [95% CI 1.35–1.48], *P* value < 0.001) (**Figure 6**). Mothers who reduced the number of cigarettes between the first and third trimester, without quitting, still had a higher risk of small size for gestational age. However, the corresponding risk estimates were smaller than for women who continued the same amount of cigarettes throughout pregnancy (OR 1.89 [95%

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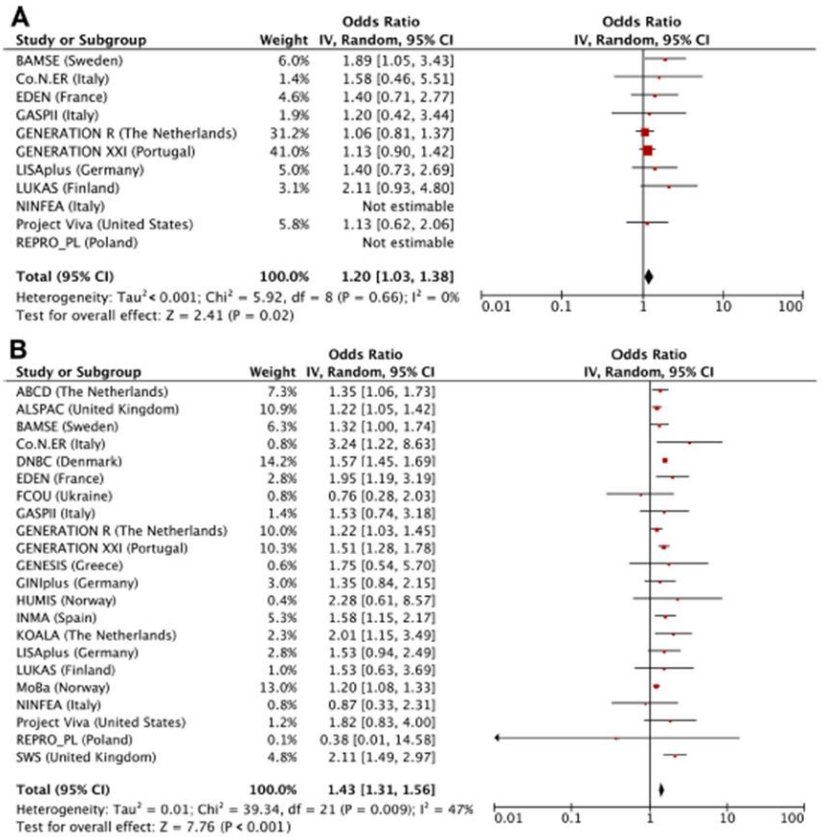
CI 1.52–2.34] instead of OR 2.20 [95% CI 2.02–2.42] when reducing from 5–9 to ≤4 cigarettes/day; OR 2.79 [95% CI 2.39–3.25] and OR 1.93 [95% CI 1.46–2.57] instead of OR 2.95 [95% CI 2.75–3.15] when reducing from ≥10 to 5–9 and ≤4 cigarettes/day, respectively [*P* values < 0.001]). Reducing the number of cigarettes during pregnancy did not affect the risks of preterm birth and childhood overweight. Among nonsmoking mothers, paternal smoking was associated with childhood overweight (OR 1.21 [95% CI 1.16–1.27], *P* value < 0.001) but not with adverse birth outcomes. Limitations of this study include the self-report of parental smoking information and the possibility of residual confounding. As this study only included participants from Europe and North America, results need to be carefully interpreted regarding other populations.

Conclusion: We observed that as compared to nonsmoking during pregnancy, quitting smoking in the first trimester is associated with the same risk of preterm birth and small size for gestational age, but with a higher risk of childhood overweight. Reducing the number of cigarettes, without quitting, has limited beneficial effects. Paternal smoking seems to be associated, independently of maternal smoking, with the risk of childhood overweight. Population strategies should focus on parental smoking prevention before or at the start, rather than during, pregnancy.

Figure 6. Maternal smoking with risks of childhood overweight assessed by two-stage random-effects models. (A) First trimester smoking versus nonsmoking, (B) continued smoking versus nonsmoking.



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5. Further work in Task 4.1

The studies described in this report are part of Task 4.1 and identified maternal adiposity and smoking as important early-life stressors related to cardio-metabolic health in the offspring.

Task 4.1 will leverage work conducted in these proof-of-principle studies to further assess additional important early-life stressors of cardio-metabolic health, strengthen causal inference and develop longitudinal developmental trajectories using data from the EU Child Cohort Network. The final output of this task will provide insight into cardiovascular risk factor development during the earliest phase of life, its main determinants and the long-term consequences of variation. Analyses have overall been performed according to plan.

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