HHS Public Access

Author manuscript

*Metabolism*. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

*Metabolism*. 2017 April ; 69: 112–119. doi:10.1016/j.metabol.2017.01.019.

# First and second trimester gestational weight gains are most strongly associated with cord blood levels of hormones at delivery important for glycemic control and somatic growth

**Sheryl L. Rifas-Shiman**[1], **Abby Fleisch**[2], **Marie-France Hivert**[1], **Christos Mantzoros**[3], **Matthew W. Gillman**[4], and **Emily Oken**[1,5]

[1]Obesity Prevention Program, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

[2]Division of Endocrinology, Boston Children's Hospital, Boston, MA, USA

[3]Department of Medicine, Beth Israel Deaconess Hospital, Boston MA USA

[4]Environmental Influences on Child Health Outcomes (ECHO) Program, Office of the Director, National Institutes of Health

[5]Department of Nutrition, Harvard T.H. Chan School of Public Health; Boston, MA

## Abstract

**Background—**Excessive gestational weight gain (GWG) during pregnancy is associated with adverse outcomes for mothers and offspring. Early, mid, and late pregnancy GWG have different associations with fetal growth and later life adiposity, but associations with cord blood hormones, which might predict later health, are not well studied.

**Methods—**In 978 pregnant women from the pre-birth Project Viva cohort, we calculated trimester-specific GWG using clinically recorded prenatal weights. Outcomes were levels of umbilical cord blood hormones related to fetal and postnatal growth. We used linear regression models adjusted for maternal race/ethnicity, pre-pregnancy BMI, parity, education, pregnancy smoking status and child sex; 2nd and 3rd trimester models were additionally adjusted for GWG in prior trimesters.

Corresponding author: Sheryl L. Rifas-Shiman, MPH, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401, Boston, MA 02215, Boston, MA 02215. Telephone: 617-867-4824. Fax: 617-867-4858. sheryl_rifas@hphc.org.

The views expressed in this article do not necessarily represent the views of the US Government, the Department of Health and Human Services or the National Institutes of Health.

**Conflicts of interest:** None

**Authors' contributions:** SRS, EO, and MWG contributed to the conception and design of the study; SRS, CM, MWG, and EO contributed to the acquisition of the data; SRS, AF, MFH, CM, MWG, and EO and contributed to the interpretation of the data; SRS performed statistical analyses; SRS drafted the manuscript; SRS has primary responsibility for the final content. All authors have read, critically revised, and approved the final manuscript.

**Results—**Mean ± SD pre-pregnancy BMI was 24.9 ± 5.5 kg/m$^2$, 30% were non-white, and 63% were college graduates. Mean ± SD cord blood hormone levels were insulin-like growth factor [IGF]-1 (56.4 ± 24.3 ng/mL), IGF-2 (408.5 ± 92.7 ng/mL), IGFBP-3 (1084 ± 318 ng/mL), insulin (6.5 ± 7.2 uU/mL), C-peptide (1.0 ± 0.6 ng/mL), leptin (9.0 ± 6.6 ng/mL) and adiponectin (28.7 ± 6.8 μg/mL). Mean ± SD 1$^{st}$, 2$^{nd}$ and 3$^{rd}$ trimester GWG rates were 0.22 ± 0.22, 0.49 ± 0.19 and 0.46 ± 0.22 kg/wk. Greater 1$^{st}$ trimester GWG (per 0.2 kg/wk) was associated with higher insulin (0.5 uU/mL; 95% CI 0.1, 0.9) and c-peptide (0.06 ng/mL; 95% CI 0.02, 0.09) and lower adiponectin (−0.4 μg/mL; 95% CI −0.9, 0.0). Greater 2$^{nd}$ trimester GWG (per 0.2 kg/wk) was associated with higher IGF-1 (2.3 ng/mL; 95% CI 0.6, 4.0), IGF-2 (7.9 ng/mL; 95% CI 1.2, 14.6), IGFBP-3 (41.6 ng/mL; 95% CI 19.4, 63.7) and leptin (0.9 ng/mL; 0.4, 1.4). 3$^{rd}$ trimester GWG was not associated with cord blood hormones.

**Conclusion—**1$^{st}$ trimester weight gain appears to matter more for cord blood hormones related to offspring glucose/insulin regulation, whereas 2$^{nd}$ trimester gain matters more for hormones related to growth and adiposity.

### Keywords

pregnancy; gestational weight gain; umbilical cord blood; hormones; insulin- like growth factor (IGF); leptin; c-peptide

## Introduction

Maternal weight gain during pregnancy is an important determinant of birth outcomes. Gestational weight gain (GWG) is directly associated with birth weight for gestation length, a marker of fetal growth, which[1,2] is directly associated with child adiposity and long term risks of cancer and cardiometabolic health.[3–5] By alteration of the intrauterine environment, the amount and the timing of weight gained during pregnancy not only influences fetal growth[6–10] but also may result in persistent programming of child health,[6–8,11] as has been shown previously with other intrauterine exposures such as maternal smoking and gestational diabetes mellitus.[12,13]

Early, mid, and late pregnancy GWG have different associations with fetal growth. Greater GWG in early pregnancy represents mainly maternal fat gain and might influence placental nutrient transfer differently than later GWG, which reflects fetal and placental growth and maternal fluid expansion in addition to maternal fat gain. Late pregnancy GWG has been consistently reported to be associated with birth weight.[7,11] In our cohort, rates of GWG in all 3 trimesters were associated with higher fetal growth, with the greatest effect of 2$^{nd}$ trimester GWG.[6] We have also found that greater early and mid-pregnancy weight gain predicted offspring adiposity in mid-childhood, whereas 3$^{rd}$ trimester GWG did not,[6] similar to results from other cohorts.[8]

One of the pathways by which GWG might influence offspring growth and development is through changes in the regulation of mitogenic hormones and adipokines, including insulin, the insulin-like growth factor (IGF) axis, adiponectin, and leptin. We are not aware of prior studies that examined associations of trimester-specific GWG with multiple cord blood hormones, which might predict later health. Therefore, we conducted the present study to

examine the extent to which trimester-specific rates of GWG are associated with cord blood hormone levels.

## Methods

Between 1999 and 2002 we recruited pregnant women at 8 obstetric offices of Atrius Harvard Vanguard Medical Associates, a multispecialty group practice in eastern Massachusetts.[14] Exclusion criteria included multiple gestation, inability to answer questions in English, gestational age ≥22 weeks at recruitment, and plans to move away from the study area before delivery. All participating women provided written informed consent, and institutional review boards reviewed and approved the project in line with ethical standards established by the Declaration of Helsinki.

We followed women throughout their pregnancies and obtained clinical data on obstetric and delivery outcomes on 2,128 live singleton births. We collected umbilical cord blood from infants delivered at one hospital that accounted for approximately three-quarters of the cohort births. We obtained cord blood from about two-thirds of deliveries at that hospital, or about one-half of the whole cohort. The midwife or obstetrician obtained umbilical cord blood via syringe and needle from the umbilical vein. Collection of cord blood was challenging given the varied timing of deliveries attended by different clinicians whose primary focus was on clinical care, not research. For this analysis, we excluded 16 mothers with type 1 or type 2 diabetes, 1097 with no cord blood collected, 27 missing cord blood hormone levels, and 10 missing pre-pregnancy BMI or gestational weight gain. Thus the final analysis sample included 978 mother-child pairs with information on gestational weight gain and cord blood hormone levels (Figure 1). Among these 978 vs. the 1150 excluded participants, we found similar mean maternal age (32 years in both groups), pre-pregnancy BMI (24.9 vs. 24.8 kg/m$^2$), total gestational weight gain (15.5 kg in both groups) and rates of smoking during pregnancy (13% in both groups). Women included were less likely to have completed a college degree (63 vs. 66%), more likely to be white (70 v. 63%), and had lower annual household income (60 vs. 62% reported ≥$70,000/year) and had slightly longer gestation length (39.6 vs. 39.2 weeks).

### Measures

**Exposures – definition of total and trimester-specific GWG—**We collected self-reported pre-pregnancy weight at the initial prenatal visit. Among 343 women who had weight recorded in the medical record in the 3 months before their last menstrual period, the association between self-reported and clinically measured weight was linear (r=0.997).[15] We extracted serial prenatal weights from medical records. We obtained a median of 13 (range 5 to 27) clinical weights recorded per woman over the course of the index pregnancy. We calculated total GWG rate as the difference between the last prenatal weight recorded (within 4 weeks of delivery) minus the pre-pregnancy weight, divided by number of gestational weeks at delivery. We defined 1$^{st}$ trimester as the date of last menstrual period to day 91, 2$^{nd}$ trimester as days 91–182, and 3$^{rd}$ trimester as day 182 to the time of the last prenatal weight recorded (within 4 weeks of delivery).

As previously reported,[6,16,17] we performed linear interpolation between the 2 closest weight measures to estimate weights at day 91 and day 182 and calculated GWG rates (kg/wk) for each trimester. We also categorized total gestational weight gain as inadequate, adequate, or excessive according to the 2009 Institute of Medicine (IOM) guidelines, which advise less weight gain for women with higher pre-pregnancy BMI. For an underweight woman (BMI <18.5 kg/m$^2$), the IOM guidelines recommend a total weight gain during pregnancy of 28–40 pounds, for a normal weight woman (BMI 18.5-<25.0 kg/m$^2$) the recommended gain is 25–35 pounds, for an overweight woman (BMI 25.0-<30.0 kg/m$^2$) the recommended gain is 15–25 pounds, and for an obese woman (BMI ≥30.0 kg/m$^2$) the recommended gain is 11–20 pounds.[1]

**Outcomes – umbilical cord hormone levels—**We included as outcomes umbilical cord plasma concentrations of IGF-1, IGF-2, IGFBP-3, insulin, C-peptide, leptin, and adiponectin. We collected cord blood samples from the umbilical vein after delivery of the infant, refrigerated whole blood for <24 hours, then spun and aliquotted plasma samples for storage in liquid nitrogen.[18] We measured hormones using the following commercial assays: adiponectin and leptin (radioimmunoassay, Linco Research Inc., St. Charles, MO);[19] C-peptide and insulin (competitive electrochemiluminescence immunoassay, Roche Diagnostics, Indianapolis, IN), insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein 3 (IGF-BP3; ELISA, R&D Systems, Minneapolis, MN); and insulin-like growth factor-2 (IGF-2; ELISA, Alpco Diagnostics, Salem, NH). Day to day variabilities for each of these assays were below 10%.

**Other variables—**At the initial prenatal visit (median 9.9 weeks gestation), we collected self-reported maternal pre-pregnancy weight, height, education, smoking history, race/ethnicity, and parity.[14] All data collection instruments used in Project Viva are publicly available at https://www.hms.harvard.edu/viva/. We calculated pre-pregnancy body mass index (BMI) in kg/m$^2$. We obtained infant birth date, weight, and sex from the hospital medical record. We calculated gestational age at birth using the date of the last menstrual period, or from a mid-pregnancy ultrasound if the two estimates differed by >10 days. We determined sex-specific birth weight for-gestational-age z scores using US reference data.[20]

**Statistical analysis—**We conducted linear regression analyses modeling weekly rate of GWG – per 0.2 kg/week – for the total period of pregnancy and for each trimester, to examine their associations with cord blood hormone levels. We selected 0.2 kg/week as the effect size since this was the approximate standard deviation of GWG rate at each trimester in our cohort. We adjusted models for maternal race/ethnicity, pre-pregnancy BMI, parity, education, and pregnancy smoking status. Since weight gain may track across time, to evaluate the independent contributions of each trimester, we additionally adjusted 2$^{nd}$ trimester models for GWG during the 1st trimester, and 3$^{rd}$ trimester models for 1$^{st}$ and 2$^{nd}$ trimester GWGs. Additional adjustment for maternal lifestyle factors during pregnancy (physical activity, television viewing, and intake of sugar-sweetened beverages and fast food) did not appreciably alter findings, so we did not include these measures in our final models. We did not adjust for birth weight, fetal growth, or gestation length because these factors might be on the causal pathway, and conditioning on factors present at birth is likely

to introduce collider bias.[21,22] All models met standard assumptions for linear regression. Distributions of insulin and C-peptide were somewhat right-skewed, but when we re-ran our analyses using log-transformed results, the directions and significance of estimates were very similar, and therefore we present the untransformed values for ease of interpretation and for comparability across outcomes. We additionally adjusted models with IGF-1 or IGF-2 as the outcome for levels of IGFBP-3, to get an estimate of the effect on IGF-1 or IGF-2 independent of the level of the binding protein. We also conducted linear regression analyses modeling GWG as a categorical variable – inadequate, adequate, or excessive weight according to the 2009 IOM guidelines.[1]

As a secondary analysis, we stratified models by child sex and also examined interaction p-values. As a sensitivity analysis, we repeated our final models after excluding 59 participants with GDM because management of GDM can influence subsequent weight gain, as well as 36 with pre-pregnancy BMI <18.5 kg/m$^2$and 12 with gestation length <34 weeks, given small numbers and likely different weight gain patterns in these categories. We performed all analyses using SAS version 9.3 (SAS Institute, Cary NC).

## Results

Of the 978 women included in this analysis, mean ± SD age at enrollment was 31.8 ± 5.2 years and pre-pregnancy BMI was 24.9 ± 5.5 kg/m$^2$. At enrollment,30% were non-white, 63% were college graduates, 45% were nulliparous, 92% were married or cohabitating, and 60% reported a household income of >$70,000 per year (Table 1). Mean ± SD 1$^{st}$, 2$^{nd}$ and 3$^{rd}$ trimester GWG rates were 0.22 ± 0.22, 0.49 ± 0.19 and 0.46 ± 0.22 kg/wk. Rate of GWG for the whole pregnancy was strongly correlated with rate of GWG in the 1$^{st}$ trimester (Pearson r=0.58), 2$^{nd}$ trimester (r=0.75), and 3$^{rd}$ trimester (r=0.70). The correlation coefficient for 2$^{nd}$ and 3$^{rd}$ trimester GWG was 0.43, 1$^{st}$ and 2$^{nd}$ trimester GWG was 0.15, and 1$^{st}$ and 3$^{rd}$ trimester GWG was −0.01.

According to the 2009 IOM guidelines for total pregnancy weight gain, 57% of women gained excessive weight, 30% gained adequate weight, and 13% gained adequate weight. Proportions were similar for categorical weight gain within 2$^{nd}$ and 3$^{rd}$ trimesters (data not shown).

Mean ± SD cord blood hormone levels were: insulin-like growth factor [IGF]-1 (56.4 ± 24.3 ng/mL), IGF-2 (408.5 ± 92.7 ng/mL), IGFBP-3 (1084 ± 318 ng/mL), insulin (6.5 ± 7.2 uU/mL), C-peptide (1.0 ± 0.6 ng/mL), leptin (9.0 ± 6.6 ng/mL) and adiponectin (28.7 ± 6.8 μg/mL). Cord blood hormone concentrations differed substantially by infant sex, with lower levels of all hormones among boys (data not shown).[23]

Umbilical cord blood hormone concentrations were correlated with each other to varying degrees, with the strongest correlations between C-peptide and insulin (Spearman r=0.80), IGFBP-3 and IGF-1 (r=0.65), and IGFBP-3 and IGF-2 (r=0.65). IGF-1 was modestly correlated with IGF-2 (r=0.26) and also with insulin (r=0.38), C-peptide (r=0.33), and leptin (r=0.24).[23]

Estimates of association were only minimally different unadjusted v. adjusted for maternal race/ethnicity, pre-pregnancy BMI, parity, education, pregnancy smoking status and child sex, and so we report only the adjusted estimates (Table 2). Greater 1st trimester GWG (per each 0.2 kg/wk) was associated with higher insulin (0.5 uU/mL; 95% CI 0.1, 0.9) and c-peptide (0.06 ng/mL; 95% CI 0.02, 0.09) and lower adiponectin (−0.4 μg/mL; 95% CI −0.9, 0.0). 2nd trimester gain was more weakly associated with insulin (0.4; 95% CI: −0.1, 0.9) and c-peptide (0.04; 95% CI: −0.01, 0.08). Additionally, greater 2nd trimester GWG (0.2 kg/wk) was associated with higher IGF-1 (2.3 ng/mL; 95% CI 0.6, 4.0), IGF-2 (7.9 ng/mL; 95% CI 1.2, 14.6), IGFBP-3 (41.6 ng/mL; 95% CI 19.4, 63.7) and leptin (0.9 ng/mL; 0.4, 1.4). 3rd trimester GWG was not associated with cord blood hormones. When we additionally adjusted for IGFBP-3, 2nd trimester GWG was no longer associated IGF-1 (0.2 ng/mL; 95% CI −1.0, 1.5) or IGF-2 (−0.8 ng/mL; 95% CI −5.7, 4.1). Total GWG was directly associated with almost all outcomes (Table 2) with the exception of adiponectin, and was not associated with IGF-1 or IGF-2 after adjustment for IGFBP-3. We observed similar results when we compared excessive v. inadequate total GWG per IOM guidelines.[1] (Table 3)

The association of 1st trimester GWG with IGF-1 differed by infant sex (interaction p-value = 0.01). Among girls, greater 1st trimester GWG (0.2 kg/wk) was associated with lower IGF-1 (−2.3 ng/mL; 95% CI −4.3, −0.2) but not among boys (−1.2 ng/mL; 95% CI −0.5, 2.9). The rest of the associations did not differ by infant sex.

In our sensitivity analysis, excluding 107 participants with GDM, BMI <18.5 kg/m$^2$, or gestation length <34 weeks, estimates of association were only minimally different. For example, greater 2nd trimester GWG (per 0.2 kg/wk) was associated with higher IGF-1 (2.5 ng/mL; 95% CI 0.8, 4.4), IGF-2 (8.5 ng/mL; 95% CI 1.5, 16.6), IGFBP-3 (45.5 ng/mL; 95% CI 22.6, 68.3) and leptin (1.0 ng/mL; 0.5, 1.4).

## Discussion

In this prospective study of almost 1000 mother-infant pairs, we found that greater 1st trimester GWG was associated with higher insulin and c-peptide and lower adiponectin, whereas greater 2nd trimester GWG was associated with higher IGF-1, IGF-2, IGFBP-3, and leptin. 3rd trimester GWG was not associated with cord blood hormones. This pattern suggest that 1st trimester weight gain may impact glucose and insulin regulation, whereas 2nd trimester gain may impact fetal and postnatal growth.

Our results are consistent with the existing, limited literature on weight gain during pregnancy and cord blood hormone concentrations. Higher weight gain over the entire pregnancy has been associated with higher cord blood leptin[24,25] and insulin[24] in population-based birth cohorts. Also in line with our findings, the “Rhea” cohort in Crete further subdivided the timing of GWG and demonstrated associations of cord blood leptin with mid-late (2nd/3rd trimester) but not early (1st trimester) weight gain.[8] However, that approach could not distinguish between 2nd and 3rd trimester-specific effects. Our study adds to the existing literature by examining additional cord blood hormones related to

growth and adiposity and by examining pregnancy weight gain separately during each trimester.

Disentangling the influence of GWG during each trimester on the metabolic profile of the fetus provides insight into potential biological pathways through which trimester-specific GWG differentially impacts fetal and child adiposity. For example, in our cohort[6] and others,[7,8,11] early but not late GWG was associated with greater adiposity in offspring during childhood. Here, we found greater GWG during the 1st but not later trimesters to be associated with lower adiponectin and higher c-peptide and insulin in cord blood.

Early GWG represents primarily maternal rather than fetal fat gain, and a resultant metabolically dysregulated intrauterine environment (i.e., lower adiponectin and higher insulin) could predispose offspring to adiposity and insulin resistance. Adiponectin acts on the central nervous system to increase energy expenditure and decrease body weight,[26] and low adiponectin has been specifically associated with central adiposity.[27,28] Thus, low adiponectin *in utero* may be a pathway through which 1st trimester GWG could program increased adiposity, especially central adiposity[6,8,11] in mid-childhood. Adiponectin also acts directly on adipose tissue to increase insulin sensitivity.[29] Our finding of an association between 1st trimester GWG and higher cord blood insulin and c-peptide may reflect low adiponectin leading to impaired insulin action in adipose and other peripheral tissues. Cord blood insulin tracks with insulin levels later in life, suggesting that it may be a marker of later insulin resistance.[30] However, studies have not shown a consistent association between GWG and insulin resistance into adolescence.[11,31,32]

Higher GWG has been consistently reported to be associated with higher birth size, with the strongest associations between mid-late pregnancy GWG and birth size.[6–10] This is in line with the fact that mid-late pregnancy GWG primarily reflects fetal and placental growth rather than maternal fat gain. In Project Viva, we previously found that higher rates of GWG during each trimester were associated with higher birth weight for gestational age z-scores, with the largest effect size for 2nd trimester weight gain.[6] Similarly, in the present study, we found greater GWG specifically during the 2nd trimester to be associated with higher levels of growth-promoting factors IGF-1, IGF-2, IGFBP-3, and leptin in cord blood. This raises the possibility that mid-pregnancy GWG leads to an intrauterine growth-promoting hormonal milieu and thereby increased size at birth.

The 2nd trimester is the most important period for development of adipose tissue and fetal organs, including muscle, heart, liver, and bone.[33] IGF-2 plays a role in organogenesis,[34] and IGF-1 promotes fetal growth in mid-late pregnancy.[35] Cord blood IGF-1[36] and leptin[25,37,38] correlate strongly with size at birth, with weaker associations between IGF-2 and birth size.[39] IGFBP-3 is a major IGF binding protein, with approximately 80% of IGF-I and IGF-2 bound to IGFBP-3 and 1% free.[40] We found that 2nd trimester GWG was no longer associated with IGF-1 and IGF-2 when we additionally adjusted for IGFBP-3. GWG may impact this binding protein rather than directly altering IGF-1 or IGF-2 levels, although these results require replication.

Strengths of this study are its large sample size, inclusion of important covariates including maternal BMI, evaluation of a large array of cord blood hormones, and prospective assessment of trimester-specific GWG. However, generalizability may be limited because women were generally well-educated and all recruited from a single health system. Another limitation was that we were able to evaluate only subset of the Project Viva cohort because we did not collect cord blood on all participants. However, we believe our results are unlikely to be influenced by selection bias, as included versus excluded participants were similar in pre-pregnancy BMI, GWG, and other characteristics.

In summary, we found that 1st trimester weight gain appears to matter more for cord blood hormones related to glucose and insulin regulation, whereas 2nd trimester gain matters more for those related to fetal and postnatal growth. 3rd trimester GWG was not associated with the cord blood hormonal milieu. These findings suggest that the intrauterine metabolic environment may be programmed by GWG during early to mid- rather than late pregnancy. Thus, interventions to limit excessive GWG may benefit by starting in very early pregnancy.

## Acknowledgments

**Funding:** Project Viva is supported by the National Institutes of Health (R01HD034568). Dr. Oken is additionally supported by K24 HD069408 and P30 DK092924. Dr. Fleisch is additionally supported by K23ES024803.

## Abbreviations

| | |
|---|---|
| **BMI** | body mass index |
| **CI** | confidence interval |
| **GWG** | gestational weight gain |
| **IGF** | insulin-like growth factor |
| **SD** | standard deviation |

## References

1. Institute of Medicine National Research Council Committee to Reexamine I. O. M. Pregnancy Weight Guidelines. The National Academies Collection: Reports funded by National Institutes of Health. In: Rasmussen, KM., Yaktine, AL., editors. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington (DC): National Academies Press (US) National Academy of Sciences; 2009.
2. Luke B, Hediger ML, Scholl TO. Point of diminishing returns: When does gestational weight gain cease benefiting birthweight and begin adding to maternal obesity? J Matern Fetal Med. 1996; 5:168–73. [PubMed: 8796789]
3. Whitaker RC, Dietz WH. Role of the prenatal environment in the development of obesity. J Pediatr. 1998; 132:768–76. [PubMed: 9602184]
4. Oken E, Gillman MW. Fetal origins of obesity. Obes Res. 2003; 11:496–506. [PubMed: 12690076]
5. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. Am J Obstet Gynecol. 2007; 196:322, e321–e328. [PubMed: 17403405]
6. Hivert MF, Rifas-Shiman SL, Gillman MW, Oken E. Greater early and mid-pregnancy gestational weight gains are associated with excess adiposity in mid-childhood. Obesity (Silver Spring). 2016 Jul; 24(7):1546–53. [PubMed: 27345963]

7. Margerison-Zilko CE, Shrimali BP, Eskenazi B, Lahiff M, Lindquist AR, Abrams BF. Trimester of maternal gestational weight gain and offspring body weight at birth and age five. Matern Child Health J. 2012; 16(6):1215–23. [PubMed: 21735140]
8. Karachaliou M, Georgiou V, Roumeliotaki T, Chalkiadaki G, Daraki V, Koinaki S, Dermitzaki E, Sarri K, Vassilaki M, Kogevinas M, Oken E, Chatzi L. Association of trimester-specific gestational weight gain with fetal growth, offspring obesity, and cardiometabolic traits in early childhood. American Journal of Obstetrics & Gynecology. 212(4):502.e1–502.e14.
9. Ruchat S, Allard C, Doyon M, et al. Timing of excessive weight gain during pregnancy modulates newborn anthropometry. J Obstet Gynaecol Can. 2016; 38:108–117. [PubMed: 27032734]
10. Sridhar SB, Xu F, Hedderson MM. Trimester-Specific Gestational Weight Gain and Infant Size for Gestational Age. PLoS One. 2016; 11:e0159500. [PubMed: 27442137]
11. Gaillard R, Welten M, Oddy WH, Beilin LJ, Mori TA, Jaddoe VW, et al. Associations of maternal prepregnancy body mass index and gestational weight gain with cardio-metabolic risk factors in adolescent offspring: a prospective cohort study. BJOG. 2016; 123:207–16. [PubMed: 26525168]
12. Oken E, Huh SY, Taveras EM, Rich-Edwards JW, Gillman MW. Associations of maternal prenatal smoking with child adiposity and blood pressure. Obes Res. 2005; 13:2021–8. [PubMed: 16339135]
13. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes. 2000; 49:2208–11. [PubMed: 11118027]
14. Oken E, Baccarelli AA, Gold DR, et al. Cohort profile: Project Viva. Int J Epidemiol. Feb; 2015 44(1):37–48. [PubMed: 24639442]
15. Provenzano AM, Rifas-Shiman SL, Herring SJ, Rich-Edwards JW, Oken E. Associations of maternal material hardships during childhood and adulthood with prepregnancy weight, gestational weight gain, and postpartum weight retention. J Womens Health(Larchmt). 2015; 24(7):563–71. [PubMed: 25902486]
16. Kleinman KP, Oken E, Radesky JS, Rich-Edwards JW, Peterson KE, Gillman MW. How should gestational weight gain be assessed? A comparison of existing methods and a novel method, area under the weight gain curve. Int J Epidemiol. Dec; 2007 36(6):1275–1282. [PubMed: 17715174]
17. Walter JR, Perng W, Kleinman KP, Rifas-Shiman SL, Rich-Edwards JW, Oken E. Associations of trimester-specific gestational weight gain with maternal adiposity and systolic blood pressure at 3 and 7 years postpartum. Am J Obstet Gynecol. 2014 Nov 13.
18. Parker M, Rifas-Shiman SL, Belfort MB, et al. Gestational glucose tolerance and cord blood leptin levels predict slower weight gain in early infancy. J Pediatr. 2011; 158(2):227–233. [PubMed: 20855080]
19. Mantzoros CS, Rifas-Shiman SL, Williams CJ, Fargnoli JL, Kelesidis T, Gillman MW. Cord blood leptin and adiponectin as predictors of adiposity in children at 3 years of age: a prospective cohort study. Pediatrics. 2009; 123(2):682–689. [PubMed: 19171638]
20. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatr. 2003; 3(1):6. [PubMed: 12848901]
21. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. Epidemiology. Jan; 2012 23(1):1–9. [PubMed: 22157298]
22. Tu YK, West R, Ellison GT, Gilthorpe MS. Why evidence for the fetal origins of adult disease might be a statistical artifact: the "reversal paradox" for the relation between birth weight and blood pressure in later life. Am J Epidemiol. Jan 1; 2005 161(1):27–32. [PubMed: 15615910]
23. Oken E, Eggleston EM, Rifas-Shiman SL, Switkowski K, Hivert M-F, Mantzoros C, Gillman MW. Sex-specific associations of maternal gestational glycemia with hormones in umbilical cord blood at delivery. American Journal of Perinatology. 2016 in press.
24. Lemas DJ, Brinton JT, Shapiro AL, Glueck DH, Friedman JE, Dabelea D. Associations of maternal weight status prior and during pregnancy with neonatal cardiometabolic markers at birth: the Healthy Start study. Int J Obes (Lond). 2015; 39:1437–42. [PubMed: 26055075]

25. Karakosta P, Georgiou V, Fthenou E, Papadopoulou E, Roumeliotaki T, Margioris A, et al. Maternal weight status, cord blood leptin and fetal growth: a prospective mother-child cohort study (Rhea study). Paediatr Perinat Epidemiol. 2013; 27:461–71. [PubMed: 23930782]
26. Qi Y, Takahashi N, Hileman SM, et al. Adiponectin acts in the brain to decrease body weight. Nature medicine. 2004; 10:524–9.
27. Rasmussen-Torvik LJ, Pankow JS, Jacobs DR Jr, Steinberger J, Moran A, Sinaiko AR. Development of associations among central adiposity, adiponectin and insulin sensitivity from adolescence to young adulthood. Diabet Med. 2012; 29:1153–8. [PubMed: 22672197]
28. Steffes MW, Gross MD, Schreiner PJ, Yu X, Hilner JE, Gingerich R, et al. Serum adiponectin in young adults--interactions with central adiposity, circulating levels of glucose, and insulin resistance: the CARDIA study. Ann Epidemiol. 2004; 14:492–8. [PubMed: 15301786]
29. Turer AT, Scherer PE. Adiponectin: mechanistic insights and clinical implications. Diabetologia. 2012; 55:2319–26. [PubMed: 22688349]
30. Wang G, Divall S, Radovick S, Paige D, Ning Y, Chen Z, et al. Preterm birth and random plasma insulin levels at birth and in early childhood. JAMA. 2014; 311:587–96. [PubMed: 24519298]
31. Hrolfsdottir L, Rytter D, Olsen SF, Bech BH, Maslova E, Henriksen TB, et al. Gestational weight gain in normal weight women and offspring cardio-metabolic risk factors at 20 years of age. Int J Obes (Lond). 2015; 39:671–6. [PubMed: 25298277]
32. Perng W, Gillman MW, Mantzoros CS, Oken E. A prospective study of maternal prenatal weight and offspring cardiometabolic health in mid-childhood. Ann Epidemiol. 2014 Nov; 24(11):793–800.e1. [PubMed: 25263237]
33. Poissonnet CM, Burdi AR, Bookstein FL. Growth and development of human adipose tissue during early gestation. Early Hum Dev. 1983; 8(1):1–11. [PubMed: 6851910]
34. Chao W, D'Amore PA. IGF2: epigenetic regulation and role in development and disease. Cytokine & growth factor reviews. Apr; 2008 19(2):111–120. [PubMed: 18308616]
35. Bloomfield FH, Spiroski AM, Harding JE. Fetal growth factors and fetal nutrition. Seminars in fetal & neonatal medicine. Apr 30.2013
36. Wiley AS, Lubree HG, Joshi SM, Bhat DS, Ramdas LV, Rao AS, et al. Cord IGF-I concentrations in Indian newborns: associations with neonatal body composition and maternal determinants. Pediatr Obes. 2016; 11:151–7. [PubMed: 25955285]
37. Donnelly JM, Lindsay KL, Walsh JM, Horan M, Molloy EJ, McAuliffe FM. Fetal metabolic influences of neonatal anthropometry and adiposity. BMC Pediatr. 2015; 15:175. [PubMed: 26555879]
38. Inoue M, Itabashi K, Nakano Y, Tobe T. High-molecular-weight adiponectin and leptin levels in cord blood are associated with anthropometric measurements at birth. Horm Res. 2008; 70:268–72. [PubMed: 18824864]
39. Ong K, Kratzsch J, Kiess W, Costello M, Scott C, Dunger D. Size at birth and cord blood levels of insulin, insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-1 (IGFBP-1), IGFBP-3, and the soluble IGF-II/mannose-6-phosphate receptor in term human infants. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. J Clin Endocrinol Metab. Nov; 2000 85(11):4266–4269. [PubMed: 11095465]
40. Rutanen EM. Insulin-like growth factors in obstetrics. Curr Opin Obstet Gynecol. Jun; 2000 12(3): 163–168. [PubMed: 10873115]

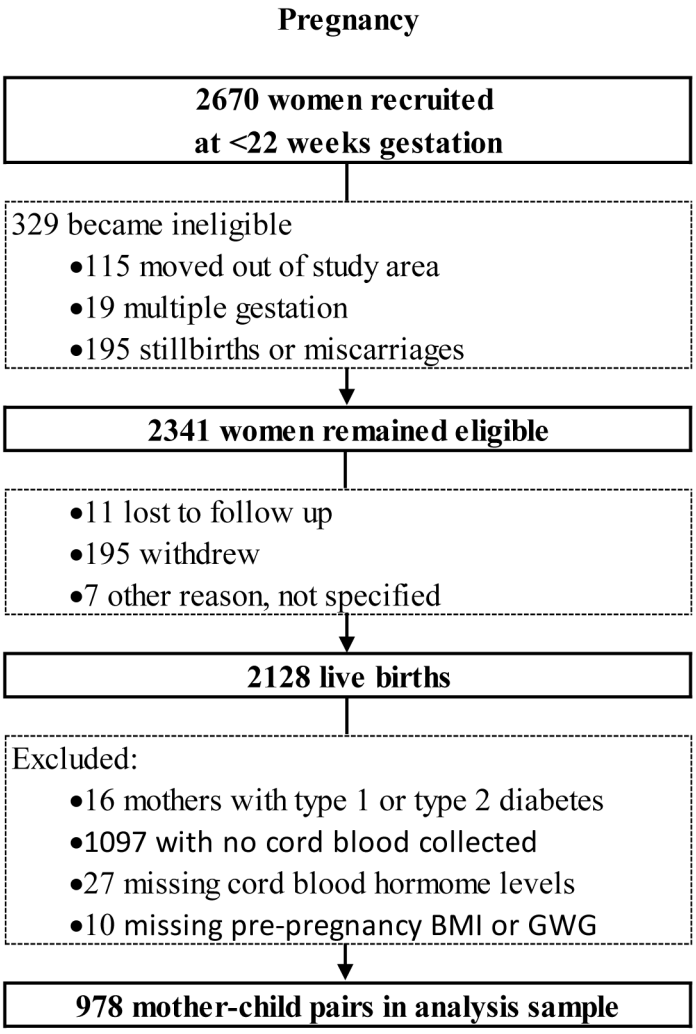


**Figure 1.**
Participant flow from recruitment through analysis sample in the Project Viva cohort

## Table 1

Characteristics of 978 pregnant women and their infants in Project Viva, overall and according to total GWG per 2009 Institute of Medicine (IOM) guidelines[1]

| | | Total GWG per IOM guidelines* | | |
|---|---|---|---|---|
| | Overall | Inadequate | Adequate | Excessive |
| | n=978 | n=122 | n=289 | n=554 |
| | N (%) or Mean (SD) | | | |
| **Maternal Characteristics** | | | | |
| Age, years | 31.8 (5.2) | 31.4 (5.9) | 32.1 (4.9) | 31.9 (5.1) |
| Pre-pregnancy BMI, kg/m$^2$ | 24.9 (5.5) | 24.8 (5.9) | 23.8 (5.5) | 25.6 (5.3) |
| Pre-pregnancy BMI category | | | | |
| 18.5 – <25.0 kg/m$^2$ | 616 (63.0) | 87 (71.3) | 225 (77.9) | 295 (53.2) |
| 25.0 – <30.0 kg/m$^2$ | 207 (21.2) | 14 (11.5) | 37 (12.8) | 154 (27.8) |
| >=30.0 kg/m$^2$ | 155 (15.8) | 21 (17.2) | 27 (9.3) | 105 (19.0) |
| Race/ethnicity, % | | | | |
| Black | 142 (14.6) | 19 (15.6) | 47 (16.3) | 74 (13.4) |
| Hispanic | 65 (6.7) | 17 (13.9) | 22 (7.6) | 26 (4.7) |
| White | 683 (70.1) | 75 (61.5) | 191 (66.3) | 412 (74.5) |
| Other | 85 (8.7) | 11 (9.0) | 28 (9.7) | 41 (7.4) |
| College graduate, % | | | | |
| No | 358 (36.7) | 51 (41.8) | 101 (35.1) | 201 (36.3) |
| Yes | 617 (63.3) | 71 (58.2) | 187 (64.9) | 352 (63.7) |
| Nulliparous, % | | | | |
| No | 533 (54.5) | 79 (64.8) | 164 (56.7) | 282 (50.9) |
| Yes | 445 (45.5) | 43 (35.2) | 125 (43.3) | 272 (49.1) |
| Married or cohabitating, % | | | | |
| No | 82 (8.4) | 12 (9.8) | 23 (8.0) | 47 (8.5) |
| Yes | 892 (91.6) | 110 (90.2) | 264 (92.0) | 506 (91.5) |
| Household income % | | | | |
| <=$70,000/yr | 349 (39.9) | 50 (46.7) | 107 (40.5) | 188 (37.8) |
| >$70,000/yr | 526 (60.1) | 57 (53.3) | 157 (59.5) | 309 (62.2) |
| Smoking status | | | | |
| Never | 654 (67.6) | 90 (73.8) | 206 (71.5) | 351 (63.9) |
| Former | 191 (19.7) | 22 (18.0) | 49 (17.0) | 119 (21.7) |
| During pregnancy | 123 (12.7) | 10 (8.2) | 33 (11.5) | 79 (14.4) |
| Prenatal glycemic status, % | | | | |
| Normal glycemia | 792 (82.0) | 94 (77.7) | 242 (83.7) | 453 (81.9) |
| IH | 85 (8.8) | 11 (9.1) | 22 (7.6) | 52 (9.4) |
| IGT | 30 (3.1) | 2 (1.7) | 8 (2.8) | 20 (3.6) |

| | | Total GWG per IOM guidelines* | | |
|---|---|---|---|---|
| | **Overall** | **Inadequate** | **Adequate** | **Excessive** |
| | **n=978** | **n=122** | **n=289** | **n=554** |
| Gestational diabetes mellitus | 59 (6.1) | 14 (11.6) | 17 (5.9) | 28 (5.1) |
| Total GWG, kg | 15.5 (5.8) | 7.5 (4.2) | 12.8 (2.7) | 18.8 (4.6) |
| 1st trimester GWG, kg/wk | 0.22 (0.22) | 0.02 (0.20) | 0.17 (0.16) | 0.30 (0.22) |
| 2nd trimester GWG, kg/wk | 0.49 (0.19) | 0.29 (0.19) | 0.43 (0.15) | 0.55 (0.18) |
| 3rd trimester GWG, kg/wk | 0.46 (0.22) | 0.27 (0.20) | 0.37 (0.15) | 0.56 (0.20) |
| **Child Characteristics** | | | | |
| Sex, % | | | | |
| Male | 510 (52.1) | 58 (47.5) | 142 (49.1) | 304 (54.9) |
| Female | 468 (47.9) | 64 (52.5) | 147 (50.9) | 250 (45.1) |
| Birth weight, g | 3523 (534) | 3296 (595) | 3436 (510) | 3617 (514) |
| Gestation length, wk | 39.6 (1.6) | 39.1 (2.2) | 39.5 (1.6) | 39.8 (1.5) |
| Birth weight for gestational age, z-score | 0.24 (0.95) | −0.07 (0.96) | 0.07 (0.94) | 0.40 (0.93) |
| Cesarean delivery, % | | | | |
| No | 797 (82.3) | 100 (82.0) | 244 (84.4) | 450 (81.2) |
| Yes | 171 (17.7) | 22 (18.0) | 45 (15.6) | 104 (18.8) |
| ***Cord blood hormones*** | | | | |
| IGF-1, ng/mL | 56.4 (24.3) | 57.6 (25.5) | 55.7 (22.7) | 56.5 (24.7) |
| IGF-2, ng/mL | 409 (93) | 391 (82) | 403 (92) | 416 (95) |
| IGFBP-3, ng/mL | 1084 (318) | 1032 (289) | 1070 (305) | 1100 (328) |
| Insulin, uU/mL | 6.5 (7.2) | 5.6 (5.2) | 5.9 (5.1) | 7.1 (8.4) |
| C-peptide, ng/mL | 1.0 (0.6) | 0.9 (0.5) | 1.0 (0.5) | 1.1 (0.7) |
| Leptin, ng/mL | 9.0 (6.6) | 7.9 (6.0) | 8.5 (6.6) | 9.5 (6.7) |
| Adiponectin, µg/mL | 28.7 (6.8) | 27.7 (7.1) | 29.0 (6.7) | 28.7 (6.8) |

*We categorized total gestational weight gain as inadequate, adequate, or excessive according to the 2009 Institute of Medicine (IOM) guidelines. For an underweight woman (BMI <18.5 kg/m$^2$), the IOM guidelines recommend a total weight gain during pregnancy of 28–40 pounds, for a normal weight woman (BMI 18.5-<25.0 kg/m$^2$) the recommended gain is 25–35 pounds, for an overweight woman (BMI 25.0-<30.0 kg/m$^2$) the recommended gain is 15–25 pounds, and for an obese woman (BMI ≥30.0 kg/m$^2$) the recommended gain is 11–20 pounds.

## Table 2

Multivariable associations of trimester-specific GWG with cord blood hormone concentrations at delivery (N=978)

| | Exposure - GWG (per 0.2 kg/wk) | | | |
|---|---|---|---|---|
| | **1st trim** | **2nd trim** | **3rd trim** | **Total pregnancy** |
| ***Umbilical cord blood hormone*** | **β (95% CI)** | | | |
| IGF-1 ng/mL | −0.4 (−1.7, 0.9) | 2.3 (0.6, 4.0) | 0.5 (−1.0, 2.0) | 1.9 (−0.3, 4.0) |
| IGF-2, ng/mL | 1.1 (−4.2, 6.4) | 7.9 (1.2, 14.6) | 3.6 (−2.4, 9.7) | 10.7 (2.0, 19.4) |
| IGFBP-3 ng/mL | 3.6 (−14.0, 21.1) | 41.6 (19.4, 63.7) | 13.9 (−6.1, 33.9) | 47.6 (19.0, 76.2) |
| IGF-1 ng/mL * | −0.6 (−1.5, 0.4) | 0.2 (−1.0, 1.5) | −0.2 (−1.3, 0.9) | −0.5 (−2.1, 1.1) |
| IGF-2, ng/mL * | 0.3 (−3.5, 4.2) | −0.8 (−5.7, 4.1) | 0.8 (−3.7, 5.2) | 0.8 (−5.5, 7.2) |
| Insulin uU/mL | 0.5 (0.1, 0.9) | 0.4 (−0.1, 0.9) | −0.1 (−0.5, 0.4) | 0.8 (0.1, 1.4) |
| C-peptide ng/mL | 0.06 (0.02, 0.09) | 0.04 (−0.01, 0.08) | −0.01 (−0.05, 0.03) | 0.08 (0.02, 0.14) |
| Leptin, ng/mL | 0.0 (−0.4, 0.4) | 0.9 (0.4, 1.4) | 0.1 (−0.4, 0.5) | 0.8 (0.2, 1.5) |
| Adiponectin, µg/mL | −0.4 (−0.9, 0.0) | 0.4 (−0.1, 1.0) | −0.3 (−0.8, 0.2) | −0.2 (−0.9, 0.5) |

Adjusted for maternal race/ethnicity, pre-pregnancy BMI, parity, education, pregnancy smoking status and child sex.

2nd and 3rd trimester models additionally adjusted for GWG in prior trimesters.

*Additionally adjusted for IGFBP-3.

## Table 3

Multivariable associations of total GWG categories per 2009 Institute of Medicine (IOM) guidelines[1] with cord blood hormone concentrations at delivery (N=978)

| | Total GWG categories per IOM guidelines | | |
|---|---|---|---|
| | **Inadequate** | **Adequate** | **Excessive** |
| ***Umbilical cord blood hormone*** | | **β (95% CI)** | |
| IGF-1 ng/mL | 0.0 (ref) | −0.4 (−5.3, 4.5) | 1.9 (−2.7, 6.5) |
| IGF-2, ng/mL | 0.0 (ref) | 13.0 (−6.8, 32.8) | 25.2 (6.6, 43.7) |
| IGFBP-3 ng/mL | 0.0 (ref) | 46.4 (−19.0,111.8) | 84.4 (23.0,145.7) |
| IGF-1 ng/mL* | 0.0 (ref) | −2.7 (−6.4, 1.0) | −2.3 (−5.8, 1.1) |
| IGF-2, ng/mL* | 0.0 (ref) | 3.4 (−11.0, 17.9) | 7.6 (−5.9, 21.2) |
| Insulin uU/mL | 0.0 (ref) | 0.5 (−1.0, 2.0) | 1.5 (0.0, 2.9) |
| C-peptide ng/mL | 0.0 (ref) | 0.07 (−0.07, 0.20) | 0.15 (0.02, 0.28) |
| Leptin, ng/mL | 0.0 (ref) | 0.6 (−0.9, 2.1) | 1.8 (0.4, 3.2) |
| Adiponectin, μg/mL | 0.0 (ref) | 1.4 (−0.2, 2.9) | 1.2 (−0.2, 2.7) |

Adjusted for maternal race/ethnicity, pre-pregnancy BMI, parity, education, pregnancy smoking status and child sex.

*Additionally adjusted for IGFBP-3.