

# Association Between Omentin-1 and Indices of Glucose Metabolism in Early Pregnancy: a Pilot Study

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## Research Article

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# Abstract

**Purpose:** Omentin-1 plays an important role in regulating insulin sensitivity outside pregnancy. We aimed to evaluate whether circulating maternal omentin-1 concentrations are associated with fasting serum glucose, insulin, HOMA-IR and maternal obesity as measured by body mass index (BMI) and subcutaneous and intra-abdominal fat thickness measurements in normoglycemic pregnant participants.

**Methods:** Omentin-1 was measured in a sub-cohort of 50 participants in the Omega study. We examined the cross-sectional association between omentin-1 and fasting glucose, insulin, HOMA-IR, BMI and subcutaneous and intra-abdominal fat thickness. We performed a subgroup analysis by BMI category.

**Results:** Omentin-1 was negatively correlated with HOMA-IR and insulin and inversely associated with serum glucose concentration in the fully adjusted model (  $-47\%$ ; slope per tertile increase in concentration  $-0.19$ ;  $P$ -trend  $0.01$ ). This association was significant in non-overweight/obese ( $<25$  kg/m<sup>2</sup>) but not among overweight/obese ( $\geq 25$  kg/m<sup>2</sup>) participants. The association with serum insulin in the fully adjusted model was not significant.

**Conclusion:** Circulating omentin-1 concentrations are inversely associated with serum glucose concentrations. Although the significance of these findings remains to be elucidated, it may indicate a mechanism for the development of insulin resistance and gestational diabetes. Follow-up studies with larger sample sizes are warranted.

## Introduction

Pregnancy is associated with several biochemical, metabolic, physiological and immunological changes coordinated by placental and non-placental hormones. Glucose metabolism changes throughout pregnancy, which is characterized as a state of physiological insulin resistance state so as the fetus receives adequate amounts of glucose [1–3]. Despite this physiologic insulin resistance, glucose concentrations remain within normal range throughout uncomplicated pregnancies because of compensatory alterations in  $\beta$ -cell function. Abnormal glucose metabolism happens whenever  $\beta$ -cells are unable to adjust to these pregnancy-related changes. Hyperglycemia during pregnancy not only increases the risk of maternal Type 2 Diabetes (T2D), but also predisposes the developing fetus to poor metabolic health later in life [4].

Studies have shown that adipokines, which are primarily secreted from adipose tissue, may play an important role on glucose metabolism during pregnancy [5, 6]. There are several pathways through which adipokines influence metabolic processes like inflammation, appetite control, adipogenesis and altered insulin sensitivity and secretion [7]. Adipokines such as leptin and adiponectin have been extensively studied in association with various cardio-metabolic outcomes [8–14], however, published studies of the role of omentin-1 concentrations on glucose metabolism during pregnancy are sparse and conflicting, with some studies showing an association with glucose and insulin levels, while others were null [12, 15–18].

Omentin-1 an anti-inflammatory adipokine mainly synthesized by visceral adipose tissue and the placenta and to a lesser extent the heart, lung and intestine [19, 20]. Omentin-1 is known to play an important role in regulating insulin sensitivity in men and non-pregnant patients [21, 22]. Furthermore, while omentin-1 is highly expressed in human visceral fat tissue, investigators have reported reduced circulating omentin-1 concentrations in obese individuals [23], as well as inverse associations with BMI, leptin, waist circumference, fasting insulin, and HOMA and positively associated with adiponectin and HDL [23–25]. Although evidence suggests that omentin-1 may be an indicator of insulin resistance [16] and gestational diabetes [12], little is known about the role of omentin-1 in indices of glucose metabolism during pregnancy. Moreover, none of the previously published studies have detailed anthropometric data to characterize maternal visceral and subcutaneous fat and examine the complex interplay between body fatness and omentin-1 regarding glucose metabolism.

The primary objective of this pilot study is to examine the cross-sectional association between omentin-1 and indices of glucose metabolism in early pregnancy pointing to the potential of its predictive and clinical value. We examined whether circulating maternal omentin-1 concentrations are associated with fasting serum glucose, insulin, HOMA-IR and maternal body fat composition as measured by body mass index (BMI) and subcutaneous and intra-abdominal fat thickness measurements.

## Methods

### Study population

Data used for this study were collected as part of the Omega study, a prospective pregnancy cohort that was designed to examine risk factors for preeclampsia and other pregnancy complications. Details about the study design and data collection have been published previously [26]. Briefly, pregnant participants were recruited from clinics associated with Swedish Medical Center and Tacoma General Hospital in Washington State from 1996 to 2008. Participants were eligible in the Omega study if they were at least 18 years old, able to speak and read English, initiated prenatal care prior to 16 weeks of pregnancy, and planned to carry the pregnancy to term and deliver at one of the study hospitals. Of 5,063 eligible patients who were approached, 4,602 agreed to participate (91%). Among the study participants, a sub-cohort of 50 randomly selected patients had omentin-1 measurements at the time of the laboratory examination at the  $11.6 \pm 0.8$  week of pregnancy, along with the first trimester biochemical screening. The Omega study was approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants gave written informed consent.

### Data collection

Study participants completed an in-person structured interview after enrollment trained interviewers (45–60 minutes in length) to collect data on expectant mothers' age, height, weight, socioeconomic characteristics, medical history and tobacco consumption. BMI at blood collection was measured as weight in kg divided by height in meters squared. Expectant mothers with  $BMI \geq 25\text{kg/m}^2$  were classified

as overweight/obese and were compared to participants with BMI < 25kg/m<sup>2</sup> in analyses of potential effect modification by overweight/obese status. Maternal race was classified as non-Hispanic white, non-Hispanic black, Asian, Hispanic, or other. Maternal peripheral blood was collected after an overnight fast shortly after enrollment.

## **Blood collection and omentin-1 measurement**

Peripheral fasting blood samples, collected at an average of 11.6 weeks of gestation (range 10–13), were kept at 4°C until processing that occurred within 1 hour of collection. The omentin-1 ELISA kit was obtained from Millipore Sigma (Human omentin-1 ELISA, EZH0MNTN1-29K SDS) and performed according to the manufacturers' instructions). The calculated inter-assay and intra-assay coefficients of variation (CV) were all less than 10%. The limit of detection of the assay was 1.6 pg/ml.

## **Glucose, Insulin, HOMA-IR and maternal obesity**

Blood glucose determination was performed in the hospital's Center for Perinatal Studies using an automated glucose oxidase/oxygen-rate method. Standard ELISA assay kits for insulin (Diagnostic Systems Laboratories, Webster, TX; limit of detection 0.26 IU/ml), leptin (Rocky Hill, NJ; limit of detection 63 pg/ml), and adiponectin (R&D Systems, Minneapolis, MN; limit of detection 32 pg/ml), were used according to the manufacturer's instructions. Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR) method where HOMA-IR = fasting plasma glucose (mmol/l) times fasting plasma insulin (μU/ml) divided by 22.5 [27].

### **Measurements of subcutaneous and intra-abdominal fat thickness in mm by using ultrasonography.**

Subcutaneous fat measurements were obtained using a high frequency 13 MHz linear transducer to maximize resolution of the measured interfaces. The measurements were made 5 cm cephalad to the umbilicus in the midline xipho-umbilical line on the frozen digital image on the scanner screen in a cross-sectional plane. The calipers were positioned at the skin-fat (excluding the skin) and fat-muscle interfaces. The measurements were reported to the nearest mm.

Intra-abdominal fat measurements were made 5 cm cephalad to the umbilicus at the same location as the subcutaneous measurement in the same image plane. The calipers were positioned at the internal abdominal interface (excluding the muscle) and the posterior external wall of the abdominal aorta. The measurements were reported to the nearest mm. The methodology of measurements has been established in the literature [28, 29] and showed good intra and inter-observed variability.

## **Statistical analysis**

Descriptive statistics were reported as means and standard deviations for normally distributed continuous variables or medians and interquartile range (IQR) otherwise and frequencies and percentages for categorical variables. Characteristics of study participants were summarized in the overall population and stratified by tertiles of glucose concentration. When we tested the models using quartiles or quintiles, the inferences were similar. Because omentin-1 values were skewed, we log-

transformed them. We calculated Spearman rank correlation coefficients and constructed linear plots with 95% prediction intervals to represent the univariate association between log-transformed omentin-1 and fasting glucose, insulin, HOMA-IR, BMI and subcutaneous and intra-abdominal fat thickness.

We explored further the association between circulating serum concentration of omentin-1 and fasting serum glucose and serum insulin by using multivariate linear models. Given that insulin may be in the causal pathway of the association between omentin-1 and glucose, we did not include insulin in our models but we evaluated the association between omentin-1 and insulin separately. Two multivariable linear regression models were built. Model 1 was adjusted for maternal age (as a continuous variable) and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic including Mexican American and other). Model 2 also included cigarette smoking status (never, former, current smoker), income and maternal education (as socioeconomic status indicators) and BMI. We also run the models using subcutaneous and intra-abdominal fat to capture residual confounding from body fatness instead of BMI. We calculated the percentage difference in the geometric means of omentin-1 between the third and the first tertile by subtracting the geometric mean of the first tertile from the geometric mean of the third tertile divided by the geometric mean of the first tertile  $((Q3 - Q1)/Q1)$ .

In the light of previous evidence that the association between omentin-1 and glucose is modified by obesity status [30], we performed a subgroup analysis by BMI category. We explored the association separately in normal weight ( $BMI < 25 \text{ kg/m}^2$ ) versus overweight/obese ( $BMI \geq 25 \text{ kg/m}^2$ ) pregnant participants. All tests were two-sided. P values  $< 0.05$  were considered statistically significant, and all analyses were performed using survey data analysis commands in STATA version 15 (College Station, TX).

## Results

Baseline characteristics of the 50 participants included in the analysis are presented in Table 1. The mean age of participants was 34 (SD 4.5) years and most of the participants were white (84 %). The mean BMI was  $24.7 \text{ kg/m}^2$  (4.8) and the prevalence of overweight/obesity based on BMI ( $> 25 \text{ kg/m}^2$ ) was 42%. Ten percent of participants were current and 21% were prior smokers, 94% never consumed alcohol during pregnancy and 35% attended graduate school. The geometric mean of all the laboratory values were within normal range. There were no statistically significant differences in the distribution of participant characteristics according to the tertiles of glucose concentrations. Mean omentin-1 concentrations were 107 (44.6) ng/ml and these concentrations were significantly lower (87.4 (32.3) ng/ml) in the highest glucose tertile (p-value = 0.04).

Table 1  
Characteristics of the study population

		Total population	Glucose Concentration Tertiles			p-value
			71–79	80–87	88–95	
		50	15	17	18	
Maternal Age (years), mean (SD)		34 (4.5)	33.5 (5.2)	34.2 (4.2)	34.3 (4.4)	0.87
<b>Maternal race</b>	White	42 (84%)	14 (93%)	13 (76%)	15 (83%)	0.27
	Black	1 (2%)	1 (7%)	0 (0%)	0 (0%)	
	Asian	4 (8%)	0 (0%)	3 (18%)	1 (6%)	
	Other	3 (6%)	0 (0%)	1 (6%)	2 (11%)	
<b>Educational Status</b>	Some College	5 (10%)	1 (7%)	1 (6%)	3 (17%)	0.48
	College grad	27 (55%)	6 (43%)	10 (59%)	10 (61%)	
	Grad School	17 (35%)	7 (50%)	6 (35%)	4 (22%)	
<b>Parity (0 = nulliparous, 1 = multiparous)</b>	Nulliparity	25 (50%)	9 (60%)	9 (53%)	7 (39%)	0.53
<b>Smoking status</b>	Never	34 (69%)	10 (71%)	12 (71%)	12 (67%)	0.83
	Prior	10 (20%)	2 (14%)	3 (18%)	5 (28%)	
	Current	5 (10%)	2 (14%)	2 (12%)	1 (6%)	
<b>Alcohol consumption during pregnancy</b>	No	47 (94%)	14 (94%)	17(100%)	16 (89%)	0.54
<b>Overweight/Obese (BMI &gt;= 25 kg/m<sup>2</sup>)</b>		21 (42%)	8 (53%)	6 (35%)	7 (39%)	0.56
<b>BMI (kg/m<sup>2</sup>)</b>		24.7 (4.8)	24.2 (3.3)	23.7 (3.4)	26.1 (6.5)	
<b>Fasting plasma Insulin IU/ml mean (SD)</b>		4.3 (4.8)	3.4 (2.6)	3.1 (1.5)	6.2(7.3)	0.11
<b>HOMA insulin resistance, mean (SD)</b>		0.89 (1.1)	0.6 (0.5)	0.6 (0.3)	1.4 (1.7)	0.07

	Total population	Glucose Concentration Tertiles			
Mean subcutaneous fat (mm)	15.4 (5.8)	15.4 (5.8)	19 (8.4)	28.8 (23)	0.07
Mean intra-abdominal fat (mm)	50.5 (19)	50.3 (13.7)	44.2 (13)	52.2 (26.2)	0.62
Omentin 1 (ng/ml)	107 (44.6)	124 (54)	113 (41)	87.4 (32.3)	0.04

We examined univariate associations with Spearman rank correlation coefficients. Omentin-1 was significantly negatively correlated with glucose ( $r=-0.32$ ,  $p$ -value = 0.01), HOMA-IR ( $r=-0.33$ ,  $p$ -value = 0.02) and insulin ( $r=-0.30$ ,  $p$ -value = 0.01). Omentin-1 was also negatively correlated with BMI at blood collection ( $r=-0.26$ ,  $p$  = 0.06), maternal intra-abdominal fat thickness ( $r=-0.21$ ,  $p$  = 0.36) and subcutaneous fat thickness ( $r = 0.22$ ,  $p$  = 0.15) but these associations was not statistically significant. Figure 1 shows the linear prediction and 95% CIs between the log-transformed omentin-1 concentrations and fasting glucose, fasting plasma insulin, HOMA-IR, maternal BMI at blood collection, transabdominal and subcutaneous fat, where there is an inverse association with all the variables.

Geometric means and 95% CIs for omentin-1 concentration by quantiles of glucose from the linear regression analysis are shown in Table 2. On average, serum omentin-1 concentration was strongly inversely associated with serum glucose in Model 1 (% difference (Q3 - Q1)/Q3 geometric means - 43%; slope per tertile increase in concentration - 0.18;  $P$ -trend 0.006) and 2 (% difference - 51 %; slope - 0.21;  $P$ -trend 0.004). The geometric mean of omentin-1 in the glucose lowest was 119 ng/mL, while in the highest tertile it was 81 ng/ml. Table 3 presents the associations between omentin-1 and insulin concentration. Serum omentin-1 concentration was not associated with serum insulin in Model 1 (% difference (Q3 - Q1)/Q3 geometric means - 15%; slope per tertile increase in concentration - 0.08;  $P$ -trend 0.28) and 2 (% difference - 14%; slope - 0.07;  $P$ -trend 0.36) and remained non-significant after additional adjustment for physical activity and BMI (% difference - 4.2 %; slope - 0.04;  $P$ -trend 0.61). When we used the mean subcutaneous and intra-abdominal fat instead of BMI, the results were essentially the same.

Table 2

Geometric means and 95 % confidence intervals of serum omentin-1 (ng/ml) concentrations in the tertiles of fasting glucose concentration (mg/dl).

	<b>Geometric mean</b>	<b>95% confidence interval</b>	<b>Slope, P-value*</b>
Model 1 (age and race adjusted)			-0.19, 0.006
Glucose first tertile (71–79 mg/dl)	118	97–144	
Glucose second tertile (80–86 mg/dl)	105	88–125	
Glucose third tertile (87–95 mg/dl)	82	69–95	
Model 2 (adjusted for maternal age, race, education, smoking status, income, BMI**)			
Glucose first tertile (71–79 mg/dl)	121	99–147	-0.21, 0.004
Glucose second tertile (80–86 mg/dl)	105	88–125	
Glucose third tertile (87–95 mg/dl)	80	68–95	
*Change in Omentin-1 concentration in ng/mL per one quintile change in serum glucose concentration			
**Results remained essentially the same when adjusting for subcutaneous and intra-abdominal fat			

Table 3

Geometric means and 95 % confidence intervals of serum omentin-1 (ng/ml) concentrations in the tertiles of insulin concentration (mg/dl).

	Geometric mean	95% confidence interval	Slope, P-value*
Model 1 (age and race adjusted)			-0.08 0.28
Insulin first tertile (< = 2.0 IU/dl)	102	84–125	
Insulin second tertile (2.1–3.7 IU/dl)	101	82–127	
Insulin third tertile (> = 3.8 IU/dl)	87	72–106	
Model 2 (adjusted for maternal age, race, education, smoking status, income, BMI**)			
Insulin first tertile (< = 2.0 IU/dl)	103	84–126	-0.07, 0.36
Insulin second tertile (2.1–3.7 IU/dl)	104	81–133	
Insulin third tertile (> = 3.8 IU/dl)	88	71–109	
*Change in Omentin-1 concentration in ng/mL per one quintile change in serum glucose concentration			
**Results remained essentially the same when adjusting for subcutaneous and intra-abdominal fat			

The results of the analysis regarding stratification by obesity status are displayed in Table 4 where the inverse association was significant in normal weight participants in the fully adjusted model (slope: -0.33, p-value: 0.03) while it was non-significant among overweight/obese pregnant participants (slope: -0.09, p-value: 0.66).

Table 4

Effect modification of the association between omentin-1 and fasting glucose concentrations and omentin-1 by obesity status

	Non-overweight/obese (n = 29)			Overweight/Obese (N = 21)		
	Geometric mean	95% confidence interval	Slope, P-value*	Geometric mean	95% confidence interval	Slope, P-value*
Model 1 (age and race adjusted)			<b>-0.23, 0.01</b>			-0.14 0.16
Glucose first tertile (71–79 mg/dl)	102	81–130		102	76–137	
Glucose second tertile (80–86 mg/dl)	114	89–145		100	76–132	
Glucose third tertile (87–95 mg/dl)	96	76–120		82	61–109	
Model 2 (adjusted for maternal age, race, education, smoking status, income, BMI**)			<b>-0.30, 0.05</b>			-0.15, 0.19
Glucose first tertile (71–79 mg/dl)	102	83–127		102	76–137	
Glucose second tertile (80–86 mg/dl)	118	97–143		108	74–133	
Glucose third tertile (87–95 mg/dl)	93	75–115		87	60–110	
*Change in Omentin-1 concentration in ng/mL per one quintile change in serum glucose concentration						
**Results remained essentially the same when adjusting for subcutaneous and intra-abdominal fat						

## Discussion

In this pilot cross sectional study, we evaluated the association between omentin-1 and indices of glucose metabolism in early pregnancy pointing to its potential predictive and clinical use. Univariate analysis revealed a significant inverse association between omentin-1 and fasting plasma glucose and insulin and consequently HOMA-IR, and a non-significant inverse association with BMI at blood collection, mean intra-abdominal and subcutaneous fat thickness. When we explored the association between omentin-1 and fasting glucose and insulin further in multivariate models, the inverse association remained statistically significant only for fasting glucose. When we stratified by overweight/obesity status, this association remained significant in normal weight pregnant participants and became non-significant for obese pregnant participants.

Our findings are consistent with the results of some previous studies examining the association between serum omentin-1 and glucose metabolism. Decreased omentin-1 has been observed in type 2 diabetes and impaired glucose tolerance [21, 25, 31–33] while evidence for association between omentin-1 and type 1 diabetes are inconsistent [34–37]. This can be explained based on the association between accumulating risk factors such as obesity and central fat distribution with cardio-metabolic diseases, while type 1 diabetes has mainly a genetic etiology.

Our findings are also in agreement with previous studies examining the association between omentin-1 and glucose concentrations in pregnancy [13, 16, 38–40], reporting similar observations regarding glucose concentrations while circulating omentin-1 concentrations were negatively correlated with BMI, insulin, and homeostasis model assessment [21, 23, 41]. We also detected suggestive evidence of effect modification of the omentin-1 glucose association by overweight/obesity status which is in alignment with the results from a previous study [38]. This may be partly explained by the fact that circulating serum omentin-1 reflects its expression in visceral adipose tissue, which decreases in parallel with the increase of visceral obesity [20, 22, 40, 42]. Another possible explanation of our results could be the lack of power due to the small sample size in the overweight/obese category. However, the proportion of overweight/obese participants was large (42%), similar to the proportion of non-overweight-obese, which provides some confidence that the differences in the observed associations are not attributed to differences in the sample size.

The biological functions of omentin-1 in human pregnancy are not well understood. However, omentin-1 is known to enhance insulin-stimulated glucose uptake in human subcutaneous and visceral adipocytes [20] while the chromosomal region of the human omentin-1 gene has previously been reported to be linked to type 2 diabetes in several populations [23]. Omentin-1 has been previously found to be associated with metabolic morbidities, including obesity, diabetes mellitus, metabolic syndrome and polycystic ovary syndrome in non-pregnant populations [43].

The strengths of this study include careful adjustment for demographic characteristics, lifestyle and health factors, and other maternal subcutaneous and visceral fat that were not consistently adjusted for in the prior studies. Using the early pregnancy omentin-1 values as possible predictor of glucose levels and subsequently gestational diabetes provides the opportunity to use it in early predictive models, leaving room for early interventions. The main limitation of our study is the limited sample size, which cannot eliminate the role of chance in our findings. However, our results are consistent with the majority of the literature after careful consideration of anthropometric variables that have not been explored in previous studies. Our analysis suggested possible effect modification by obesity status, therefore further exploration and verification is warranted in larger studies. Finally, our results are based in cross-sectional data and we cannot be certain whether changes in omentin-1 happen before changes in glucose and vice versa.

In conclusion, we found that circulating omentin-1 concentrations are inversely associated with indices of glucose metabolism. Although the physiologic and pathologic significance of these findings remain to be

elucidated, it may indicate a mechanism for the development of insulin resistance in normal weight pregnant participants. Given that prediction models for abnormal glucose metabolism and GDM in pregnancy have modest performance [44], it is important to identify biomarkers and parameters that can be used in early risk stratification and might offer opportunities to improve care for participants at high risk of developing impaired glucose tolerance or GDM. Longitudinal pregnancy cohort studies with larger sample size and serial measurements of omentin-1 and other promising biomarkers are warranted to confirm and expand upon the findings reported here.

## **Declarations**

### **Compliance with Ethical Standards:**

### **Funding:**

No funding was obtained for this study.

### **Conflict of Interest:**

All authors declare that they have no conflict of interest.

### **Ethical approval:**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### **Informed consent:**

Informed consent was obtained from all individual participants included in the study.

### **Conflict of Interest statement/Financial Disclosure:**

The authors do not have conflicts of interest or financial disclosures

### **Author Contributions:**

Stefania Papatheodorou: Project development, Data analysis, Manuscript writing

Bizu Gelaye: Project development, Data collection, Manuscript writing

Michelle Williams: Project development, Data collection, Manuscript writing

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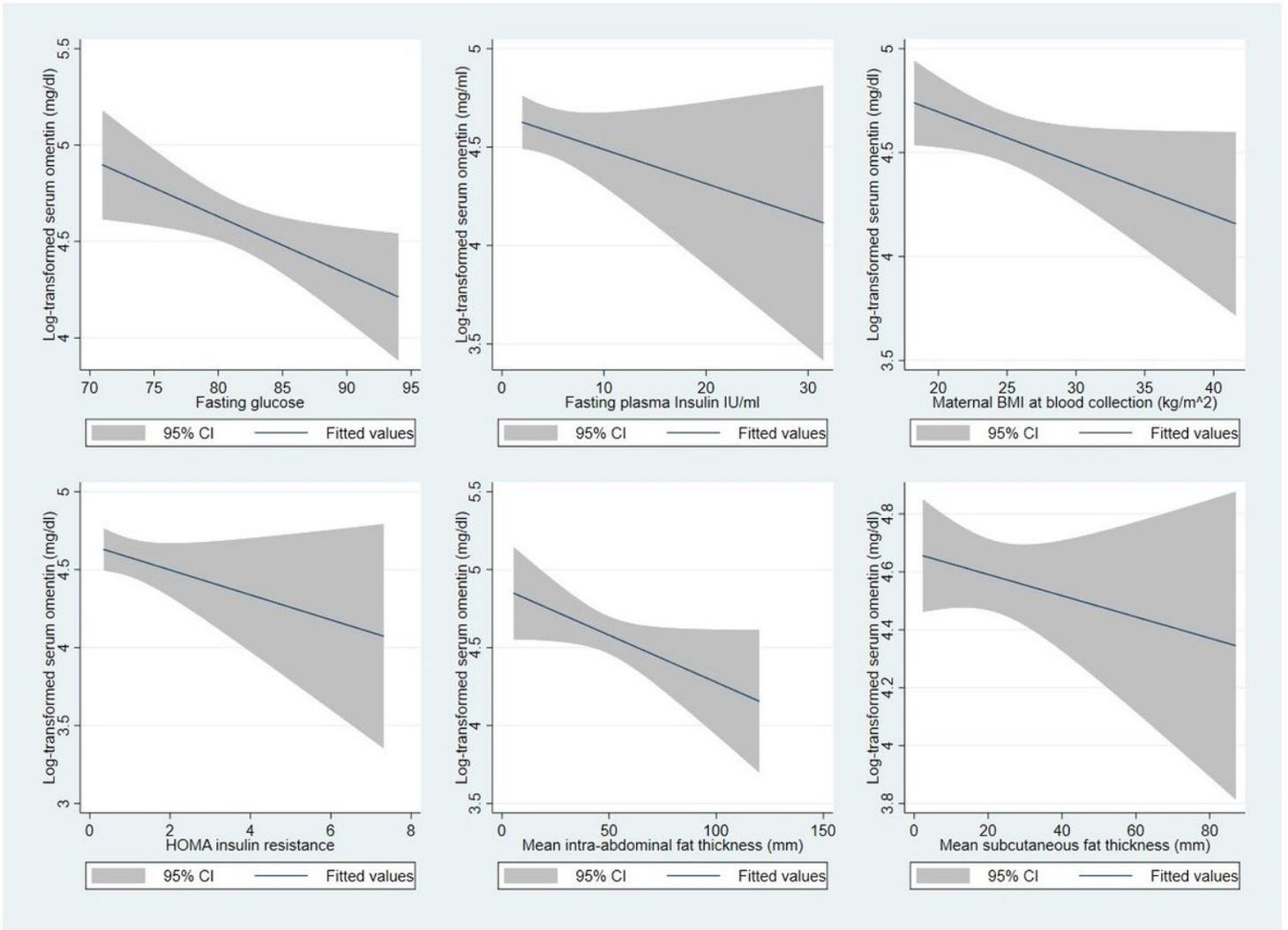
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## Figures



**Figure 1**

Univariate linear prediction of log-transformed omentin concentrations and fasting glucose, fasting insulin, maternal BMI at the time of blood draw and HOMA-IR.