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Do Gestational Obesity and Gestational Diabetes Have an Independent Effect on Neonatal Adiposity? Results of Mediation Analysis from a Cohort Study in South India

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Purpose: Neonates born to mothers with obesity or gestational diabetes mellitus (GDM) have an increased chance of various metabolic disorders later in life. In India, it is unclear whether maternal obesity or GDM is related to offspring adiposity. We aimed to understand the independent effect of maternal obesity and GDM with neonatal adiposity and whether GDM has a mediating effect between maternal obesity and neonatal adiposity.

Methods: We recruited a cohort of 1120 women (between April 2016 and February 2019) from the public hospitals in Bangalore, India, who voluntarily agreed to participate and provided written informed consent. The primary outcome was neonatal adiposity, defined as the sum of skinfold thickness >85th percentile. Exposure included maternal obesity, defined as >90th percentile of skinfold thickness. GDM, the potential mediator, was classified using the World Health Organization criteria by oral glucose tolerance test. Binary logistic regression was applied to test the effect of maternal obesity and GDM on neonatal adiposity, adjusting for potential confounders. We used Paramed command in STATA version 14 for analyzing mediating effects.

Results: We found that maternal obesity (odds ratio (OR)=2.16, 95% CI 1.46, 3.18) and GDM (OR=2.21, 95% CI 1.38, 3.52) have an independent effect on neonatal adiposity. GDM significantly mediates 25.2% of the total effect between maternal obesity and neonatal adiposity, (natural direct effect OR = 1.16 95% CI 1.04, 1.30) with significant direct effect of maternal obesity (natural direct effect OR = 1.90 95% CI 1.16, 3.10) and significant total effect (OR=2.20 95% CI 1.35, 3.58).

Conclusion: We showed that maternal obesity and GDM are independently associated with offspring adiposity. Also, GDM mediates the association of maternal obesity on adiposity in children. Interventions focused on obesity prevention in women, and effective screening and management of GDM may contribute to reducing childhood obesity in India.

Keywords: mediation effects, skinfold thickness, GDM, obesity in pregnancy, childhood obesity

Introduction

Obesity in pregnancy is a significant public health concern as it increases the risk of several complications during pregnancy and the perinatal period.^{1,2} Nearly 4.3 million pregnant women are overweight or obese in India, reflecting the high prevalence of overweight and obesity in low-middle income countries (LMICs).^{3,4} Also, it is known that children are twice as likely to have obesity

if their mothers were obese during the first trimester of pregnancy.⁵ Maternal obesity results in fetal macrosomia.^{6–10} Also, obesity during pregnancy significantly predisposes pregnant women to develop Gestational diabetes mellitus (GDM), defined as hyperglycaemia that first develops during pregnancy or first diagnosed during pregnancy. Several mechanisms suggest higher risk of developing GDM in obese women. These include higher insulin resistance in obese women compared to women of healthy weight, leading to the increased availability of lipids for fetal growth and development.^{11,12} GDM affects more than 17.8 million women worldwide, among whom 28% are in India.¹³

Maternal obesity and Gestational diabetes mellitus (GDM) are associated with several adverse effects in mothers as well as children during pregnancy and beyond. These include higher cesarean section rate, pre-term delivery, fetal macrosomia, and fetal death.^{6,14–20} A recent meta-analysis found that obesity during pregnancy increases the risk of fetal adiposity, with risk rising across the overweight and obese categories proportionately.²¹ Moreover, GDM results in several adverse fetal implications. Babies of women with GDM are prone to develop adiposity, characterized by substantial fat deposition in most skin folds in all areas of the body.²² Adult-onset obesity and related complications such as hypertension, Type 2 diabetes mellitus, Cardiovascular Diseases (CVDs) more likely affect children with adiposity.²³ Several factors, including maternal obesity and GDM, are linked to the increasing burden of fetal adiposity.^{6,24,25} Evidence suggests that obesity during pregnancy is a stronger determinant of fetal adiposity compared to pre-pregnancy BMI.¹¹

Hitherto, the role of maternal obesity and GDM in resulting fetal adiposity is mostly studied in high-income countries.^{26,27} Understanding the putative causal path of maternal obesity and fetal adiposity, including the mediation role of GDM is essential to prioritize policy planning and implementation for limiting the adverse effects of these conditions.²⁸ In the Indian context, it is unclear as to what degree of maternal obesity and GDM contribute, and whether they are related to each other in resulting adiposity in children. Since two-thirds of pregnant women in India use the public hospitals for the antenatal care services,²⁹ we aimed to understand the extent of association of maternal obesity with adiposity in neonates, and the mediating role of this association by GDM using a cohort study of women of public hospitals in India.

Materials and Methods

Study Sample, Data Collection, and Ethics Consideration

We established a pregnancy cohort in April 2016, titled as the “Maternal Antecedents of Adiposity Studying the Transgenerational role of Hyperglycemia and Insulin” (MAASTHI). We have published a detailed protocol earlier.³⁰ In brief, we approached women in the waiting area of public hospitals and explained the study in detail and included them if they voluntarily agreed to participate and provided written informed consent. We included pregnant women aged above 18 years, in their second trimester (within 36 gestational weeks) visiting and planning to deliver in three public hospitals with their residence in the nearby study area. We excluded participants with severe, past, or current illness or their inability to complete the oral glucose tolerance test (OGTT) before 36 weeks of gestation.

After obtaining written informed consent, our trained research staff recruited eligible pregnant women and conducted face-to-face interviews by ensuring privacy and confidentiality. Interview details included socio-demographic information, use of tobacco and alcohol, family history of diabetes and cardiovascular diseases (CVD), obstetric history, and assessment of psychosocial environment using a validated version of the Edinburgh Postnatal Depression Scale (EPDS), and social support scale. We measured the physical activity of pregnant mothers using a validated Physical Activity Level (PAL) questionnaire.³¹ The questionnaire had five domains: exercise, hobbies, household chores, sedentary activities, and other common daily activities. These domains include all the activities performed by women in an urban setting. Metabolic Equivalent (MET) values of each activity were then calculated by multiplying three components, namely MET allotted value, duration of activity done, and frequency done in a week. The combined MET value was calculated by adding MET values of individual physical activity. Categorization of the combined score was done, and the level of physical activity was defined as “low” if it was <600 METs, “moderate” when 600–2999 METs, and as “high” when it is ≥ 3000 METs.

For the current analyses, we used data from April 2016 to February 2019. Research assistants entered all data in a validated application on an Android device.

The study protocol was reviewed and approved by the Institutional Ethics Committee of the Indian Institute of

Public Health, Bangalore campus (IEC no: IIPHHB/TRCIEC/091/2015; dated 13/11/2015). The study was conducted in accordance with the Declaration of Helsinki.

Exposure Assessment – Maternal Obesity

Maternal height, weight, and the sum of skinfold thickness (SFT) measurement at three sites (biceps, triceps, and subscapular) was measured during the hospital visit of the participant using a calibrated portable stadiometer (SECA 213), digital weighing scale (Tanita), and Holtain Calipers (Holtain, UK) respectively. Two readings for weight and height and three readings for skinfold thickness measurements were taken. Women were considered obese - if the sum of skinfold thickness was higher than the 90th percentile of the distribution of the sum of skinfold thickness in the study sample. Research assistants were trained and certified in anthropometry at the beginning of the study and then annually to obtain accurate measurements and to avoid inter- and intra-observer variation. All anthropometric equipment were calibrated and validated every month using standardized weights and scales.

GDM Diagnosis

Between 24 to 36 weeks of gestation, we invited the participants to undergo a 2 hr 75 grams oral glucose tolerance test (OGTT) after overnight fasting for at least eight hours.³² We collected 2mL blood in fasting and 2 hr postprandial for glucose analysis. We followed the WHO diagnostic criteria developed by the International Association of Diabetes and Pregnancy Study Group (IADPSG) for the classification of gestational diabetes mellitus (GDM). Accordingly, GDM was diagnosed if the fasting blood sugar (FBS) was equal to or more than 92 mg/dL, and 2 hr postprandial blood sugar (PPBS) equal to or more than 153 mg/dL.³³

Neonatal Adiposity

We collected details at birth through structured interviews and anthropometric measurements within seven days of the birth of the child. Anthropometric measurements included weight, length, crown-rump length (CRL), circumferences – head, chest, waist, hip, middle-upper arm (MUAC), and skinfold thickness. We weighed the neonates on the calibrated digital weighing scale (SECA 354), with two readings taken to the nearest 0.5g. We measured crown-heel and crown-rump length using SECA 417 infantometer to the nearest 0.1 cm. We used the Chasmors body circumference tape to measure circumferences, with two readings taken to the

nearest 0.1 cm. We measured the skinfold thickness in neonates using Holtain Calipers (Holtain, UK) at three sites, namely biceps, triceps, and subscapular areas. The sum of skinfold thickness was calculated (SFT), and centile charts for the sum were determined. A neonate was classified as having excessive fat deposition (adiposity) if SFT was above the 85th percentile for the neonate's gestational age. Indian standard for classification of neonates based on the sex and order of the birth was used for the weight for gestational age.³⁴ The primary information regarding gestational age, parity, and sex from the cohort were used to derive the variable, weight for gestational age. Hence a neonate weighing less than the 10th percentile was classified as small for gestational age (SGA), between 10 to 90th percentile was appropriate for gestational age (AGA) or healthy, and higher than 90th percentile was large for gestational age (LGA).³⁴

Confounders

Confounders were selected based on literature review and included a priori in the analyses. Studies have shown that GDM significantly and progressively increases due to increased age; the other confounders include parity and family history of diabetes.³⁵ We also adjusted for maternal obesity as measured through the sum of skinfold thickness measured during pregnancy, as they are closely correlated.^{36,37} Maternal height is an independent risk factor for GDM.^{37,38} The religion of the respondent, husband's income, and alcohol intake were also adjusted.³⁹ We also adjusted for physical activity (MET values), as increased physical activity is associated with decreased neonatal adiposity,⁴⁰ and reduced rates of GDM.⁴¹

Statistical Analysis

Power analysis was performed for testing mediation effect in multiple logistic regression by a method proposed by Vittinghoff, Sen, and McCulloch's using the "R" package.⁴² The power of the study was 99% considering n=1120, the regression coefficient of GDM (after adjusting for confounders) =1.99, the standard deviation of GDM = 0.370, the prevalence of neonatal obesity =0.146, multiple correlations of GDM with the confounders and neonatal obesity =0.048 and level of significance = 0.05.

We cleaned and organized the data ahead of performing analysis using STATA version 14. A total of 1120 observations were considered for the analysis, of which 1091 were included for SFT analysis. Missing data were analyzed using available case analysis. Categorical variables were expressed

as frequency (f) and percentages (%) and normally distributed as mean and standard deviation. Association between various socio-demographic factors to GDM, Obesity, SFT, and weight for gestational age were assessed using the Chi-square test and Fisher's exact test when appropriate.

We used univariate logistic regression to test the independent effect of maternal obesity and GDM on neonatal adiposity. Homogeneity of odds ratio (Breslow-Day test) across the levels of GDM and test of conditional independence was assessed using the Mantel Haenszel test. Multiple logistic regression was adopted to adjust for potential confounders. We evaluated multicollinearity among the confounders using a correlation matrix; no multicollinearity if the correlation was less than 0.90. Multicollinearity between exposure and mediator was assessed using the variance inflation factor (VIF) using linear regression, as suggested by Midi H for logistic regression models.⁴³

Four separate models were performed and compared using different model diagnostics (Likelihood value, Hosmer & Lemeshow test of the goodness of fit, Nagelkerke R Square, and classification accuracy). Model 1 shows the association of maternal obesity on neonatal adiposity adjusting for confounders. Model 2 shows the association of GDM on neonatal adiposity adjusting for confounders. Model 3 shows the association of maternal obesity, GDM on neonatal adiposity adjusting for confounders (with interaction). Model 4 shows the association of maternal obesity, GDM on neonatal adiposity adjusting for confounders (without interaction). We report the odds ratio (OR) with 95% confidence interval (CI) and p values.

The natural direct, natural indirect (mediated by GDM), and the marginal total effects were estimated using mediation analysis using the Logit model. We performed a bootstrapping analysis with 1000 replications. The direct effect= the effect of GDM on the neonatal adiposity without the effect of GDM, and indirect effect= the effect of GDM on the neonatal adiposity mediated via GDM. The product of direct and indirect effects are expressed as the total effect. We estimated the proportion mediated,⁴⁴ using Paramed command,⁴⁵ as per the approach suggested by Baron and Kenny.⁴⁶

Logit {P(neonatal adiposity = 1 | maternal obesity, neonatal adiposity, confounders)} = ($\beta_0 + \beta_1$ maternal obesity + β_2 GDM) + β_3 confounders} — (a)

Logit {P(GDM = 1 | maternal obesity, confounders)} = λ + λ_1 maternal obesity + λ_3 confounders} — (b)

Results

The characteristics of women (N=1020) and neonates enrolled in the MAASTHI cohort from 2016 to 2019 based on neonatal adiposity and large for gestational age (LGA) are presented in Table 1. Among the neonates born during the cohort, 14.6% had SFT >85th percentile and were large for gestational age (n=163/1120). Almost all children born in the group were reportedly healthy during assessment after birth. We found that less than 3.6% reported aspiration of babies while resuscitation was reported in 42% obese babies and 23.6% of babies with LGA. Additionally, 4.3% of neonates with adiposity did not cry soon after delivery compared to less than 2% LGA neonates (Table 1).

The characteristics of pregnant women and neonates based on maternal GDM and obesity status are provided in Table 2. Out of the total participants, 9.7% of the mothers were obese, and 16.4% were diagnosed with GDM. We found that 62.4% (n=109) obese and 52.2% (n=184) with GDM were Muslims. In our study sample, approximately seven out of 10 women with obesity (70.7%) and nearly two-thirds of women with GDM (63.5%) were multiparous. Infertility was reported in women with GDM as well as among women with obesity. Some form of resuscitation was reported in 34.9% of babies born to women with obesity, and 36% of babies born to GDM mothers (Table 2).

As seen in Table 3, women with obesity delivered a higher proportion of babies with large birth weight than mothers without obesity (18.3% vs 9.1%). Similarly, women with GDM also delivered a higher proportion of babies with large birth weight compared to non-GDM women (18.5% vs 8.3%). Further, compared to women without obesity, babies born to women with obesity had higher head (8.9% vs 12.8%), chest (8.3% vs 12.8%), and middle-upper arm circumference (9.0% vs 18.3%); similarly women with GDM delivered higher proportion of babies with larger MUAC than non-GDM mothers (16.8% vs 8.3%). The percentage of babies with adiposity (>85th percentile of the sum of skinfold thickness) was higher among women with obesity (25.7% vs 13.5%) and women with GDM (23.9% vs 12.7%) when compared to their respective control groups. (Table 3)

Table I Descriptive Statistics of Maternal and Neonatal Characteristics in Relation to Neonatal Adiposity and Large for Gestational Age (LGA) in MAASTHI Cohort 2016–19, India

Characteristics	Categories	Sum of Skinfold Thickness			Weight for Gestational Age		
		≤85th Percentile (n=957)	>85th Percentile (n=163)	p value	≤90th Percentile (n=957)	>90th Percentile (n=163)	p value
		f (%)	f (%)		f (%)	f (%)	
Maternal Age ^a		24.24±4.03	24.25±4.03	0.96	24.12±3.99	25.94±4.22	0.02
Religion	Hinduism	458(48%)	78(47.9%)	0.79	427(46.4%)	24(43.6%)	0.08
	Christianity	31(3.2%)	7(4.3%)		30(3.3%)	5(9.1%)	
	Islam	466(48.8%)	78(47.9%)		463(50.3%)	26(47.3%)	
Participant's Education	Primary school and below	68(7.1%)	11(6.7%)	0.86	68(7.4%)	3(5.5%)	0.59
	Middle school and above	887(92.9%)	152(93.3%)		852(92.6%)	52(94.5%)	
Husband's Education	Primary school and below	182(19.1%)	37(22.7%)	0.28	184(20%)	11(20.0%)	1.000
	Middle school and above	773(80.9%)	126(77.3%)		736(80.0%)	44(80.0%)	
Participant's current occupation	Unemployed	894(93.4%)	147(90.2%)	0.17	862(93.7%)	51(92.7%)	0.81 [#]
	Unskilled worker	44(4.6%)	9(5.5%)		39(4.2%)	3(5.5%)	
	Skilled workers	19(2.0%)	7(4.3%)		19(2.1%)	1(1.8%)	
Parity	Nulliparous	417(43.6%)	65(39.9%)	0.37	414(45.0%)	24(43.6%)	0.84
	Multiparous	539(56.4%)	98(60.1%)		506 (55.0%)	31(56.4%)	
Family history of diabetes	None	748(78.4%)	123(75.5%)	0.38	718(78.3%)	41(74.5%)	0.78
	One parent	182(19.1%)	33(20.2%)		175(19.1%)	12(21.8%)	
	Both parent	24(2.5%)	7(4.3%)		24(2.6%)	2(3.6%)	
Participant's history of GDM	Yes	10(1.0%)	3(1.8%)	0.42 [#]	10(1.1%)	1(1.8%)	0.47 [#]
Participant's history of Hypertension	Yes	13(1.4%)	2(1.2%)	1.000 [#]	14(1.5%)	0	1.000 [#]
Participant's history of Anaemia	Yes	418(43.8%)	67(41.1%)	0.53	394(42.9%)	25(45.5%)	0.71
Current GDM status during assessment	Yes	140(14.6%)	44(27.0%)	<0.001	148(16.1%)	20(36.4%)	<0.001
Current Hypertension status during the assessment	Yes	41(4.4%)	14(9.2%)	0.01	47(5.3%)	4(7.4%)	0.53 [#]
Participant's obesity status	Yes	81(8.7%)	28(17.4%)	0.001	91(10.1%)	10(18.9%)	0.05
Husband's alcohol consumption	Yes	130(13.8%)	28(17.5%)	0.208	119(13.1%)	9 (16.4%)	0.5

(Continued)

Table I (Continued).

Characteristics	Categories	Sum of Skinfold Thickness			Weight for Gestational Age		
		≤85th Percentile (n=957)	>85th Percentile (n=163)	p value	≤90th Percentile (n=957)	>90th Percentile (n=163)	p value
		f (%)	f (%)		f (%)	f (%)	
Delivery type	Spontaneous vaginal delivery	506(52.9%)	79(48.5%)	0.54 [#]	484(52.6%)	23(41.8%)	0.34 [#]
	Emergency caesarean	270(28.2%)	55(33.7%)		270(29.3%)	21(38.2%)	
	Elective caesarean	179(18.7%)	29(17.8%)		164(17.8%)	11(2%)	
	Outlet forceps delivery	2(0.2%)	0		2(0.2%)	0	
Health status of the mother	Healthy	818(85.5%)	136(83.4%)	0.5	784(85.2%)	46(83.6%)	0.75
	Illness present	139(14.5%)	27(16.6%)		136(14.8%)	9(16.4%)	
Health status of the baby	Healthy	950(99.3%)	161(98.8%)	0.63 [#]	914(99.3%)	55(100%)	1.000 [#]
	Diseased	7(0.7%)	2(1.2%)		6(0.7%)	0	
Sex	Male	480(50.2%)	87(53.4%)	0.45	455(49.5%)	31(56.4%)	0.32
	Female	477(49.8%)	76(46.6%)		465(50.5%)	24(43.6%)	
Baby cried soon after delivery	Yes	938(98.0%)	156(95.7%)	0.09 [#]	900(97.8%)	54(98.2%)	1.000 [#]
Aspiration	Yes	23(2.4%)	3(1.8%)	1.000 [#]	19(2.1%)	2(3.6%)	0.33 [#]
Resuscitation	Yes	321(34.2%)	47(42.0%)	0.013	309(33.6%)	13(23.6%)	0.13

Notes: ^aMean±standard deviation is mentioned instead of frequency and percentage with an independent sample t-test, p-value. [#]Fishers exact test p-value. Bold indicates statistical significance at 5%.

Independent Effect

Univariate logistic regression was performed to determine the independent effects of GDM and maternal obesity with neonatal adiposity. We found that both GDM and maternal obesity have an independent impact on neonatal adiposity, maternal obesity OR=2.16 (95% CI 1.46, 3.18), and GDM OR=2.21(95% CI 1.38, 3.52) respectively (Table 4). The homogeneity of odds ratio across the levels of GDM using the Breslow-Day test was insignificant ($\chi^2=0.14$, p-value =0.71), indicating that the association between GDM and neonatal adiposity did not differ significantly between women with and without GDM. The test of conditional independence using Mantel Haenszel indicated that maternal obesity and neonatal adiposity are conditionally independent, given the status of maternal obesity (p-value =0.008) and also vice versa (p-value =0.002) (data not present in the table).

Adjusted Effect

The results of the multiple Binary logistic regressions for four models are also shown in Table 4. Due to multicollinearity among gravida and parity, we performed separate multiple regression models to choose the best model. Based on the Likelihood ratio test, parity was better than gravida in model fitting. The final model included GDM, maternal obesity, religion, MET values, participant's history of diabetes, parity, family history of diabetes, husband's alcohol consumption status, maternal age, husband's income, and participant's height. Four separate models were performed and compared using different model diagnostics. We observed no significant multiplicative interaction between maternal obesity and GDM (p value=0.78). The likelihood value, Hosmer & Lemeshow test of the goodness of fit, Nagelkerke R Square, and

Table 2 Descriptive Statistics of Maternal and Neonatal Characteristics in Relation to Maternal Obesity and Gestational Diabetes Mellitus (GDM) in MAASTHI Cohort 2016–19, India

Characteristics		Maternal Obesity Status ^b			GDM Status ^c		
		Yes (n=109)	No (n=982)	p value	Yes (n=184)	No (n=936)	p value
		f (%)	f (%)		f (%)	f (%)	
Maternal Age ^a		25.14±4.23	24.16±4.0	0.02	25.37±4.25	24.01±3.95	<0.001
Religion	Hinduism	37(33.9%)	482(49.1%)	0.01	83(45.1%)	453(48.5%)	0.54
	Christianity	4(3.7%)	34(3.5%)		5(2.7%)	33(3.5%)	
	Islam	68(62.4%)	466(47.5%)		96(52.2%)	448(48.0%)	
Participant's Education	Primary school and below	4(3.7%)	73(7.4%)	0.15	14(7.6%)	65(7.0%)	0.75
	Middle school and above	105(96.3%)	909(92.6%)		170(92.4%)	869(93.0%)	
Parity	Nulliparous	32(29.4%)	436(44.4%)	0.003	67(36.4%)	415(44.4%)	0.05
	Multiparous	77(70.7%)	546(55.6%)		117(63.5%)	520 (55.7%)	
Family history of diabetes	None	74(67.9%)	771(78.8%)	0.03	749(80.3%)	122(66.3%)	<0.001
	One parent	30(27.5%)	182(18.6%)		162(17.4%)	53(28.8%)	
	Both parent	5(4.6%)	26(2.7%)		22(2.4%)	9(4.9%)	
Participant's history of Infertility treatment	Yes	4(3.7%)	9(0.9%)	0.03[#]	6(3.3%)	7(0.8%)	0.004
Participant's history of GDM	Yes	3(2.8%)	9(0.9%)	0.11 [#]	1(0.5%)	12(1.3%)	0.71 [#]
Participant's history of Hypertension	Yes	3(2.8%)	12(1.2%)	0.19 [#]	14(1.5%)	1(1.0%)	0.49 [#]
Metabolic Equivalent (MET) value	Low	1(0.9%)	21(2.2%)	0.72 [#]	3(1.7%)	19(2.1%)	1.000 [#]
	Moderate	107(99.1%)	950(97.8%)		177(98.3%)	904(97.9%)	
EPDS score ^{**}	≤13	101(92.7%)	897(91.3%)	0.64	856(91.6%)	168(91.3%)	0.91
	> 13	8(7.3%)	85(8.7%)		79(8.4%)	16(8.7%)	
Husband's tobacco use	Yes	51(46.8%)	397(41.0%)	0.25	83(45.4%)	378(41%)	0.28
Delivery type	Spontaneous vaginal delivery	52(47.7%)	516(52.5%)	0.45 [#]	78(42%)	507(54.2%)	0.024[#]
	Emergency caesarean section	31(28.4%)	288(29.3%)		66(36%)	259(27.7%)	
	Elective caesarean section	26(23.9%)	176(17.9%)		40(22%)	168(17.9%)	
	Vacuum extraction	0	2(0.2%)		0	2(0.2%)	
Health status of the baby	Healthy	108(99.1%)	974(99.2%)	1.000 [#]	183(100%)	928(99.1%)	1.000 [#]
	Diseased	1(0.9%)	8(0.8%)		1(1.0%)	8(0.8%)	

(Continued)

Table 2 (Continued).

Characteristics		Maternal Obesity Status ^b			GDM Status ^c		
		Yes (n=109)	No (n=982)	p value	Yes (n=184)	No (n=936)	p value
		f (%)	f (%)		f (%)	f (%)	
Sex	Male	69(63.3%)	486(49.5%)	0.006	106(58%)	461(49.3%)	0.04
	Female	40(36.7%)	496(50.5%)		78(42%)	475(50.7%)	
Baby cried soon after delivery	Yes	106(97.2%)	960(97.8%)	0.73 [#]	180(98%)	914(97.6%)	1.00 [#]
Aspiration	Yes	2(1.8%)	22(2.2%)	0.60 [#]	2(1.1%)	24(2.6%)	0.29 [#]
Resuscitation	Yes	38(34.9%)	354(36.0%)	0.81	67(36%)	325(34.7%)	0.66

Notes: ^aMean±standard deviation is mentioned instead of frequency and percentage with an independent sample t-test, p value. ^bMore than 90th percentile of sum of skinfold thickness as the obese category. ^cFasting blood sugar (FBS) equal to or more than 92 mg/dL or 2 hr postprandial blood sugar (PPBS) equal to or more than 152 mg/dL(32) as GDM. Bold indicates statistical significance at 5%. [#]Fishers exact test p value. ^{**}Scores range from 0 to 30.

Abbreviation: EPDS, Edinburgh Postnatal Depression Scale to screen for depression.

classification accuracy suggested that model 4 is a better fit to the data than models 1, 2, and 3. Our results indicated that the odds of having adiposity in babies were 1.90 times higher for women with obesity (95% CI: 1.16, 3.12) and 1.99 times higher for women with GDM (95% CI: 1.31, 3.02) adjusting for other confounders.

Mediation Analysis (Table 5)

Model (a) and (b) from the equations were fitted for mediation analysis. These models were fitted with no interaction and no multicollinearity (VIF=1.03) between exposure and mediator but adjusted for potential confounders. GDM significantly mediates the relationship between maternal obesity and neonatal adiposity, (natural direct effect OR = 1.16 95% CI 1.04, 1.30) with significant direct effect of maternal obesity (natural direct effect OR = 1.90 95% CI 1.16, 3.10) and significant total effect (OR=2.20 95% CI 1.35, 3.58). The results indicate that GDM mediates 25.2% of the total effect of maternal obesity and neonatal adiposity. With 1000 replications, there were no significant differences in the confidence intervals (Table 5).

Discussion

We aimed to understand how maternal obesity and GDM during pregnancy are associated with adiposity in the offspring. Our results suggest that both maternal obesity and GDM are independently associated with adiposity in neonates. While neonates born to women with GDM show association with most of the anthropometric markers of adiposity, such association was seen only for birth weight

and middle-upper arm circumference in neonates borne to with women with obesity. This finding is corroborated by other studies demonstrating that obesity in offspring is associated with maternal GDM and obesity.^{47–52} Further, results from the regression models showed that GDM is a stronger determinant of adiposity in neonates and mediates the effect of maternal obesity on neonatal adiposity. These results suggest that the risk factors for adiposity in neonates are to be addressed by using a life course perspective.

India is undergoing a rapid epidemiological and demographical transition.⁵³ Since GDM affects nearly one in five Indian pregnant women, our current study suggests that it is essential to prioritize GDM screening and management by the policymakers. The Indian national guidelines (2014) recommend GDM screening for all pregnant women during pregnancy.⁵⁴ However, only 44% of pregnant mothers in public health facilities underwent OGTT as a screening test for GDM.⁵⁵ Besides, the proportion of women who complete the test is also low. The results from public hospitals suggest that women from lower socio-economic status are equally affected. Therefore, universal screening might be useful in the timely management of GDM and in preventing adverse consequences.^{56,57}

Additionally, we also reported that obesity in women is associated with adiposity in neonates. This suggests that early intervention preventing or controlling obesity in young women can end the vicious cycle of obesity across generations.⁵⁸ Interventions aimed at addressing nutritional intake, healthy weight, and physical activity directed at parents can reduce obesity-related health consequences.

Table 3 Distribution of Neonatal Anthropometric Characteristics Over Obese and GDM Categories

Neonatal Anthropometric Characteristics	Categories	Maternal Obesity Status		p value	GDM Status		p value
		Yes (n=109)	No (n=982)		Yes (n=184)	No (n=936)	
		f (%)	f (%)		f (%)	f (%)	
Birth weight (kg)	<10th 10th - 90th >90th	10(9.2%) 79(72.5%) 20(18.3%)	96(9.8%) 797(81.2%) 89(9.1%)	0.0001	11(6.0%) 139(75.5%) 34(18.5%)	97(10.4%) 761(81.3%) 78(8.3%)	0.01
Crown rump length (cm)	<10th 10th - 90th >90th	10(9.2%) 88(80.7%) 11(10.1%)	99(10.2%) 779(80.1%) 95(9.8%)	0.17	14(7.7%) 139(76.8%) 28(15.5%)	97(10.4%) 751(80.8%) 82(8.8%)	0.14
Length (cm)	<10th 10th - 90th >90th	12(11.0%) 81(74.3%) 16(14.7%)	88(9.0%) 801(81.7%) 92(9.4%)	0.33	13(7.1%) 149(81.0%) 22(12.0%)	91(9.7%) 756(80.9%) 88(9.4%)	0.25
Head Circumference (cm)	<10th 10th - 90 th >90th	9(8.3%) 86(78.0%) 14(12.8%)	101(10.3%) 794(80.9%) 87(8.9%)	0.01	14(7.6%) 142(77.2%) 28(15.2%)	98(10.5%) 762(81.4%) 76(8.1%)	0.34
Chest circumference (cm)	<10th 10th - 90th >90th	11(10.1%) 84(77.1%) 14(12.8%)	93(9.5%) 807(82.3%) 81(8.3%)	0.0001	12(6.5%) 141(76.6%) 31(16.8%)	99(10.6%) 768(82.1%) 68(7.3%)	0.25
Waist circumference (cm)	<10th 10th - 90 th >90th	11(10.1%) 88(80.7%) 10(9.2%)	98(10.0%) 801(81.6%) 83(8.5%)	0.10	12(6.5%) 151(82.1%) 21(11.4%)	100(10.7%) 760(81.2%) 76(8.1%)	0.91
Hip Circumference (cm)	<10th 10th - 90 th >90th	10(9.2%) 84(77.1%) 15(13.8%)	84(8.6%) 811(82.6%) 87(8.9%)	0.02	8(4.3%) 152(82.6%) 24(13.0%)	89(9.5%) 767(81.9%) 80(8.5%)	0.23
Mid upper arm circumference (cm)	<10th 10th - 90 th >90th	11(10.1%) 78(71.6%) 20(18.3%)	104(10.6%) 790(80.4%) 88(9.0%)	0.0003	11(6%) 142(77.2%) 31(16.8%)	109(11.6%) 749(80.0%) 78(8.3%)	0.01
Sum of skinfold thickness (mm)	<10 th 10th - 85 th >85 th	4(3.7%) 77(70.6%) 28(25.7%)	105(10.7%) 744(75.8%) 133(13.5%)	0.001	15(8.2%) 125(67.9%) 44(23.9%)	97(10.4%) 720(76.9%) 119(12.7%)	<0.001

Note: Bold indicates statistical significance at 5%.

We also reported that instead of birth weight, the skinfold thickness of neonates is a reliable marker of adiposity in identifying adverse consequences in the offspring of women with obesity and GDM. The relatively high cost of the calipers and the need for rigorous training and validation of the measurements by research staff makes it tough for scaling up in public hospitals. Our results indicate that a similar positive association is seen with the middle-upper arm circumference for adiposity in neonates. These indirect methods of measurements can be used for identifying and tracking adiposity in neonates, especially in resource-scarce settings, thus ideal for public hospitals. Previous studies

have shown the measurements of MUAC, and CC as measures of adiposity are not only comparable to dual-energy X-ray (DXA) or underwater weighing but also cost-effective and applicable for larger populations.⁵⁹⁻⁶⁶

Further, we found that GDM mediates 25.2% of the association between obesity in women with neonatal adiposity. Future studies can inform regarding the exact biological nature of this mediation mechanism to uncover the causal path between obesity in mother and neonatal adiposity. Maternal obesity has both a direct and indirect effect on infant adiposity. We show that the clustering of risk factors of obesity and GDM predisposes infants to NCDs

Table 4 Logistic Regression Models: Effect of GDM and Obesity Adjusted for Potential Confounders on Neonatal Adiposity

Variables		Sum of Skinfold Thickness				
		Univariate	Model 1 Including Obesity	Model 2 Including GDM	Model 3 Obesity with GDM and Interaction	Model 4 Obesity, GDM Without Interaction
		Unadjusted OR (95% CI)	Adjusted OR (95% CI)			
Participant's obesity status	Yes	2.21(1.38, 3.52)	2.18(1.35, 3.54)	–	1.80(0.95, 3.40)	1.90(1.16, 3.12)
	No	1	1	–	1	1
Current GDM status during assessment	Yes	2.16(1.46, 3.18)	–	2.18(1.45, 3.28)	1.93(1.21, 3.10)	1.99(1.31, 3.02)
	No	1	–	1	1	1
Religion	Hinduism	1.02(0.73, 1.43)	1.07(0.73, 1.58)	1.03(0.70, 1.51)	1.07(0.73, 1.58)	1.08(0.73, 1.58)
	Christianity	1.35(0.57, 3.17)	1.45(0.60, 3.52)	1.50(0.62, 3.64)	1.52(0.63, 3.71)	1.52(0.63, 3.70)
	Islam	1	1	1	1	1
MET values	Low	1	1	1	1	1
	Moderate	1.09(0.32, 3.73)	3.01(0.40, 22.87)	3.17(0.41, 24.32)	3.13(0.41, 24.09)	3.10(0.40, 23.88)
Participant's history of diabetes	Yes	1.78(0.48, 6.52)	1.65(0.41, 6.63)	2.07(0.52, 8.26)	1.81(0.44, 7.45)	1.81(0.44, 7.46)
	No	1	1	1	1	1
Parity	Nulliparous	1	1	1	1	1
	Multiparous	1.17(0.83, 1.64)	1.19(0.81, 1.74)	1.22(0.83, 1.78)	1.19(0.81, 1.75)	1.19(0.81, 1.75)
Family history of diabetes	None	1	1	1	1	1
	One parent	1.10(0.73, 1.67)	1.09(0.70, 1.68)	1.04(0.67, 1.61)	1.03(0.66, 1.61)	1.03(0.66, 1.60)
	Both parent	1.77(0.75, 4.20)	1.87(0.77, 4.58)	1.75(0.71, 4.30)	1.68(0.67, 4.18)	1.69(0.68, 4.20)
Husband's alcohol consumption status	Yes	1.33(0.85, 2.08)	1.41(0.87, 2.30)	1.40(0.86, 2.29)	1.43(0.87, 2.33)	1.42(0.87, 2.33)
	No	1	1	1	1	1
Maternal age		1.00(0.96, 1.04)	0.99(0.94, 1.04)	0.98(0.94, 1.03)	0.98(0.93, 1.03)	0.98(0.93, 1.03)
Husband's income		1.00(1.00, 1.00)	1.00(1.00, 1.00)	1.00(1.00, 1.00)	1.00(1.00, 1.00)	1.00(1.00, 1.00)
Participant's height		1.01(0.98, 1.04)	1.02(0.99, 1.05)	1.02(0.99, 1.05)	1.02(0.99, 1.05)	1.02(0.99, 1.05)
Interaction (Obesity × GDM)					p value=0.78	–
2log likelihood			868.65	865.88	859.77	857.77
Nagelkerke R Square			0.032	0.038	0.048	0.048
Hosmer & Lemeshow test			$\chi^2=4.82, p=0.77$	$\chi^2=4.89, p=0.77$	$\chi^2=5.06, p=0.75$	$\chi^2=5.06, p=0.77$
Classification accuracy			85.2%	85.3%	85.3%	85.3%

Notes: Clinically relevant confounders have been included in the model thought the p value is not less than 0.20. Model 1 - Maternal obesity, maternal age, maternal height, Religion, MET values, Husband's income, Diabetes history in family, Parity, Husband's alcohol consumption status. Model 2- GDM, maternal age, maternal height, Religion, MET values, Husband's income, Diabetes history in family, Parity, Husband's alcohol consumption status. Model 3- Maternal obesity, GDM, interaction (Obesity × GDM), Age, Height, Religion, MET values, Husband's income, Diabetes history in family, Parity, Husband's alcohol consumption status. Model 4 –Maternal obesity, GDM, maternal age, maternal height, Religion, MET values, Husband's income, Diabetes history in family, Parity, Husbands alcohol consumption status. Bold indicates statistical significance at 5%.

Abbreviations: OR, Odds ratio; CI, confidence interval.

Table 5 Results of Mediation Analysis Adjusted for Potential Confounders

	OR (95% CI)	p value
Natural direct effect	1.90(1.16, 3.10)	0.011*
Natural Indirect effect	1.16(1.04, 1.30)	0.008*
Marginal total effect	2.20(1.35, 3.58)	0.001*
Proportion mediated	0.252	–

Note: *Indicates statistical significance at 5%.

Abbreviation: CI, confidence interval.

later in life in India. This concurs with earlier studies in the field, showing that maternal obesity is reflective of overall lifestyle and genetics,^{67,68} whereas the effects of GDM might be transient. Our results indicate that children born to mothers who have obesity and GDM as a clustered condition are programmed to a different growth trajectory in early life. Recent evidence suggests that children of obese mothers have increased BMI, blood pressure, and carotid intima-media-adventitia thickness.⁶⁹ Our results indicate that there is a transgenerational effect of maternal obesity and GDM in infants.

The strengths of our study are that it is by far the largest pregnancy cohort in the public-sector health facilities in India to assess the relationship between maternal hyperglycemia and neonatal adiposity as a marker for later chronic conditions. We established the cohort since April 2016, and have included an almost equal proportion of minority groups that mainly belong to the vulnerable sections of the society. Our research staff was well trained, the equipment is well-calibrated, and rigorous quality control measures are strictly followed, complying with the standard operating procedures. Our findings inform policy formulation for scaling up screening for GDM and management in all the public health facilities. The main limitation is the unavailability of the pre-pregnancy BMI of the enrolled participants. This reduced our ability to compare gestational weight gain and its influence on neonatal adiposity. However, since our inclusion criteria include pregnant women that had completed more than 14 weeks of gestational age, the weight before conception was out of the scope of our study. No currently available method to carry out sensitivity analysis was possible since the outcome, exposure, and the mediator variable are dichotomous.

Conclusion

Our study showed that maternal obesity and GDM are independently related to neonatal adiposity in women

belonging to low and middle-income urban India. Also, we found that GDM is a stronger determinant of neonatal adiposity compared to maternal obesity. Since obesity development is influenced in utero, screening, and management of obesity and GDM can limit the future epidemics of childhood obesity.

Data Sharing Statement

To discuss our data sharing policy, please contact Giridhara R. Babu at giridhar@iiph.org.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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