Causes and Consequences of Gestational Diabetes in South Asians living in Canada.

Short Title: Gestational Diabetes in South Asians

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Abstract:

Background: Gestational diabetes (GDM) increases the risk of type 2 diabetes in the mother and offspring. We sought to understand the determinants of GDM, and its impact on newborn health in a birth cohort of South Asian women and their offspring.

Methods: We recruited 1,012 women with singleton pregnancies in the second trimester of pregnancy and collected health information, physical measurements, and an oral glucose tolerance test. Birth weight, skinfold thickness, and cord blood glucose and insulin were obtained from newborns.

Results: The incidence of GDM was 36·3% (95% CI: 33.3-39.3%). Factors associated with increased GDM included maternal age (odds ratio (OR): 1·08; 95% CI: 1·04-1·12; P<0·0001), family history of diabetes (OR: 1·65; 95% CI:1·26-2·17, P=0·0003), pre-pregnancy weight (OR: 1·025; 95% CI: 1·01-1·04; P<·0001), and low quality diet (OR: 1·57; 95% CI: 1·16-2·12; P=0·003). Maternal height was associated with lower GDM (OR: 0·97; 95% CI: 0·95-0·99; P<0·01). The population attributable risk (PAR) of modifiable GDM risk factors pre-pregnancy BMI and low quality diet was 37·3%. Newborns of GDM mothers had a significantly higher birth weight (3267 (SE: 23) vs 3181 (SE:17) grams; P=0·005), higher skinfold thickness (11·7 (SE:0·1) vs 11·2 (SE:0·1); P=0·007, and lower insulin sensitivity (6·42 (SE:0·60) vs 8·96 (SE:0·45) mmol/cIU; P<0·001) compared to non-GDM newborns.

Interpretation: GDM impacts one-third of pregnancies among South Asian women in Canada. Pre-pregnancy weight and low quality diet account for 37% of the PAR of GDM.

Newborns of GDM mothers have increased birthweight, increased body fat and lower insulin sensitivity.

Introduction:

Gestational diabetes (GDM) is increasing world-wide and increases the risk of large for gestational age newborns, delivery complications, and of future type 2 diabetes among both mother and offspring (1-4). South Asian migrants to high income countries including the United Kingdom (UK), United States and Canada have an excess prevalence of abdominal obesity and type 2 diabetes (5–10), and a 2 fold increased risk of GDM when compared to white Caucasians. (11–14) The reasons for South Asians' increased propensity to develop GDM are not well characterized. Prior analyses of multiethnic cohorts identified advanced maternal age, family history of diabetes, non-white ethnicity, maternal overweight or obesity and cigarette smoking as common predictors of GDM (15–17). Among South Asian women living in India increasing age, low adult height, urban living, a family history of diabetes, parity of three or more children, and low maternal vitamin B12 (18–20) are associated with the increased GDM prevalence. In high income countries, South Asian women make up an increasing proportion of the population, and are recognized to have a higher risk of GDM, yet specific prevention strategies for this high risk ethnic group are lacking (21–24).

In this prospective birth cohort study conducted among women of South Asian origin living in Canada, we sought to: 1) determine the maternal factors associated with GDM, and 2) determine the impact of GDM on newborn anthropometric characteristics including birth weight, body fat, and insulin sensitivity.

Methods:

Design: The SouTh Asian biRTh cohort (START) is a prospective birth cohort study in Canada (25). South Asian women with singleton pregnancies were recruited during the second trimester of pregnancy from the communities of Brampton and Mississauga, Ontario. Research Ethics Board approval was received on March 3, 2011 and all participants provided written informed consent. Participants were recruited by referral from primary care physicians and obstetric specialists in Peel Region, Ontario, Canada between July 11, 2011 and November 10, 2015.

Maternal Measurements: During the second trimester, participants who did not have pre-existing diabetes completed a 75 gram oral glucose tolerance test (OGTT). GDM was classified using the new cut-off values derived from the Born in Bradford (BiB) cohort of South Asian women defined as a fasting glucose ≥ of 5·2 mmol/L or a 2 h post-load level of ≥ 7·2 mmol/L. These cut-offs were recently shown to be associated with a high infant birth weight [>90th percentile for gestational age] and adiposity [sum of skinfolds >90th percentile for gestational age] in 5,408 babies born to South Asian mothers living in the UK (26). All START participants completed detailed health questionnaires including self-reported personal medical and family history, social and cultural questions, and a previously validated ethnic-specific food frequency questionnaires (FFQ) (27). Using the FFQ data, we derived a score to assess maternal diet quality using the following algorithm: 1 point was given if they consumed more than the study population median for (a) green vegetables, (b) raw vegetables, (c) cooked vegetables and (d) fruits; or less than the study population median for (e) fried foods and (f) meat. The score ranged from zero to six; diet

quality was classified as low (zero-one), intermediate (two-three), or high (four-six) (28). Social disadvantage was determined using a previously validated index which includes employment, marital status and income. (29) A standardized protocol was used to measure maternal resting blood pressure using an oscillometric device (OMRON), body weight, height, hip circumference and skinfold thickness. Maternal body fat was estimated by adding the skinfold thickness from triceps and subscapular sites (30). Participants self-reported their pre-pregnancy weight, and gestational weight gain was calculated by subtracting the pre-pregnancy weight from the end pregnancy weight immediately prior to delivery, and expressed both as absolute and percent weight gained from the pre-pregnancy weight. Insulin and metformin use during pregnancy was captured either from the self-reported questionnaire at baseline or from a post-partum chart review. Family history was defined mother or father having a history of type 2 diabetes.

Delivery Information and Newborn Measurements: Type, duration and outcomes of labour were obtained from hospital charts by trained research assistants using a standardized protocol. Placental weight was determined by reducing the untrimmed complete placenta weight, as measured by the delivery nurse, to a trimmed weight (31). Birthweight was taken from the hospital chart. Newborns born 37 weeks or greater were classified as large for gestational age (LGA) or small for gestational age (SGA) by gestational age and sex specific cutpoints of >=90th and <10th respectively (32). Additional measurements of newborns were completed by trained research assistants using a standardized protocol. Specifically, newborn length was collected using the O'LEARY length board. Head circumference was measured using a non-stretchable measuring tape. Waist and hip circumferences were measured using an OHAUS non-stretchable tape with an attached spring balance. Sum of skinfold thickness includes measurements from

triceps and subscapular sites. Skinfold thickness were taken in triplicate and recorded to the nearest mm using the HOLTAIN calipers (0·2 mm). The intraclass correlation (reliability) of the skinfold measurements was calculated and was 0·98 for subscapular skin folds and 0·96 for triceps skinfolds overall (33). Ponderal index (a measure of neonatal leanness) was calculated as birthweight/length^3 (32). These measures were taken within 24 hours in 81·0% percent of newborns and between 24 and 96 hours after delivery in 7·6%. If no measurements were taken before 96 hours, the chart recording of measure was used, if available.

Biospecimens: A cord blood sample from the umbilical vein was taken at birth and was collected in 777/1002 (77·3%) percent of babies using a standardized protocol. Within two hours of collection specimens were centrifuged and sample aliquots frozen at -70 degrees Celsius and shipped for storage in liquid nitrogen at the Clinical Research Laboratory and BioBank, Hamilton Health Sciences. All suitable samples were analyzed for glucose and insulin. Glucose was measured using the Becton Dickenson Unicell DxC 600 Synchron Clinical System using a timed endpoint method to determine glucose. Insulin was measured with Roche Elecsys® 2010 immunoassay analyzer using an electrochemiluminescence immunoassay. The coefficient of variation (CV) for glucose and insulin were 24·4% and 84·6% respectively.

Statistical Considerations: Statistical analyses were performed using SAS, version 9·4 (SAS Institute, Cary, NC, USA). Means (SD) and counts (%) were calculated to summarize continuous variables and categorical data respectively. Means (SE) were calculated for adjusted continuous results. The incidence of GDM was directly age-standardized to the general Canadian population using the 2011 Census population for women aged 20-44 years as the standard population (34).

The univariate associations between maternal factors and GDM were assessed using chi-square tests for categorical variables and t-tests for continuous variables as appropriate. Factors with a univariate p-value of > 0·10 were then considered for a multivariable logistic regression model; for any set of factors which were highly correlated, only one was included. Stepwise selection methods were used to determine the final model. The univariate associations between newborn anthropometric and maternal GDM were assessed using ANCOVA, adjusting for newborn gestational age, sex, and maternal insulin use during pregnancy. Population attributable risk (PAR) estimates and 95% CIs were calculated by the interactive risk-attributable program software (US National Cancer Institute, 2002). (35) The PAR is calculated by considering the frequency of the exposure in the population and the relationship of the risk factor to disease, and quantifies the proportion of GDM that can be prevented if a specific risk or exposure is eliminated from the study population while holding other risks constant.

Results:

The mean time of gestation that the OGTT was performed was 26·5 weeks (SD=1·6). Of the 1,012 women with singleton pregnancies enrolled in the study, four with a history of diabetes and two who withdrew early, were excluded from this analysis. In the remaining 1006, GDM status was classified in 945 using their OGTT results and the remaining 61 as reported on the birth chart. In these 1,006 mothers, birthweight, gestational age and sex information was available for 989 newborns. (sFigure1)

Gestational diabetes: Overall 36·3% (365/1006) (95% CI: 33.3-39.3%) of women were classified with GDM using the Bib criteria which is 40·7% when age-standardized in 20-44 year old women living in Canada.

Baseline characteristics of women with and without GDM: Women with GDM were older age (31·2 vs 29·7 years, P<0·0001), more likely to have a family history of diabetes (52·5% vs 35·7%, P<0·0001), multiparous (65·7 % vs 54·8%; P<0·001), have higher pre-pregnancy weight (64·9 (12·2) vs 61·3 (11·8) kg, P< 0·0001), lower maternal height (161·6 (6·2) vs 162·5 (6·3) cm, P=0·02), higher pre-pregnancy BMI (24·9 (4·6) vs 23·2 (4·3) kg/m^3, P<0·0001), body fat (sum of skin fold thickness: 52·3 (12·3) vs 47·9 (12·4) mm; P=0·0001), and were more likely to consume a low quality diet characterized by about half as many vegetables and twice as many meat and fried food servings daily (33·4% vs 22·9%, P<0·001) compared to women without GDM. Vegetarianism self-reported physical activity in pregnancy, and socioeconomic status were not different between the groups. (Table 1)

Multivariable predictors of GDM: Factors that were independently associated with an increased risk of GDM included maternal age, (per 1 year increase; OR = 1·08 (1·04-1·12), P<0·0001), family history of DM: (OR: 1·65 (1·26-2·17); P=0·0003); pre-pregnancy weight (per 1 kg increase) (OR: 1·025; (1·01-1·04), P<0·0001); and low diet quality (OR: 1·57; (1·16-2·12); P=0·003), and the only protective factor identified was maternal height (per 1 cm increase); (OR: 0·97 (0·95-0·99) P=0·007). The prevalence and odds ratios of these independent factors were used to calculate the PAR. All factors measured in our study accounted for 65·3% (95% CI: 55·6 – 75·1) of the GDM, and the modifiable risk factors of low quality diet and pre-pregnancy BMI>23 accounted for 37·3% of PAR (95% CI: 25·9, 48·7). (Figure 1)

Newborn anthropometrics: 5·8% of newborns were delivered before 37 weeks (pre-term). The mean birthweight was 3,211 grams (95%CI: 3181-3242). Newborns of mothers classified as having GDM had higher birthweight 3267 (SE:23) vs 3181 (SE:17) g, P=0·005); and ponderal index (24·8 (SE:0·2) vs 24·0 (SE:0·1), P=0·002), and an increased skinfold thickness (11·7 (SE:0·1) vs 11·2 (SE:0·1); P=0·007) compared to those without GDM, adjusting for newborn gestational age, sex and mothers use of insulin. (Table 2) Comparing newborns from GDM mothers to those without GDM, a higher percentage of newborns were classified as LGA (13·8% vs 9·0%, P=0·02), and the placental weight was higher in (500·6 (SE: 8·1) vs 475·1 (SE: 5·8), P=0·007). Notably women with GDM were more likely to undergo C-Section delivery compared to those without GDM (35·2% vs 27·9%, P=0·02). In addition, although no difference in newborn cord blood glucose was observed (4·1 (SE: 0·1) vs 4·1 (SE: 0·0) mmol/L), insulin (log) was increased 76·3 (SE:3·8) vs 61·6 (SE:2·8) pmol/L, p<0·002), and the glucose/insulin ratio, a marker of insulin sensitivity was significantly lower (6·42 (0·6) vs 8·96 (0·45) mmol/cIU; p<0·001) signifying reduced insulin sensitivity in the offspring of GDM mothers. (Table 2)

Interpretation:

South Asians living in high income countries like Canada have a high burden of GDM affecting upwards of one-third of the population. The major determinants of GDM accounted for 65·3% of the PAR of GDM, and included non-modifiable factors such as age, family history of type 2 diabetes, and maternal height, as well as modifiable factors such as pre-pregnancy weight, and low diet quality. Furthermore newborns of dysglycemic mothers had increased birthweight, body fat, and reduced insulin sensitivity which may be implicated in their future risk of excess adiposity and type 2 diabetes.

In an ethnic population with such high rates of gestational dysglycemia, modifiable risk factors for GDM are important to identify in order to design intervention studies aimed at preventing GDM. The PAR the modifiable risk factors for GDM including low quality diet and pre-pregnancy BMI alone was 37·3%. This suggests that if South Asian women could achieve an optimal pre-pregnancy weight i.e. BMI < 23, and improve their diet quality, approximately one-third of GDM in South Asian women living in high income countries could be prevented.

We observed that pre-pregnancy BMI was a significant predictor of GDM. Furthermore, a BMI of 23-25 is often classified as "normal pre-pregnancy weight" in white Caucasian women yet likely represents "overweight and excess adiposity" in South Asian women (36,37). Women who developed GDM had a higher pre-pregnancy weight by three kg, were shorter by one cm, and had significantly greater body fat as represented by their higher skinfold thickness. In our multivariate regression pre-pregnancy BMI was the dominant predictor of GDM more so than gestational weight gain, which as expected, was 1 kg lower in GDM mothers, than among those without GDM. This highlights the importance of public health messaging to South Asian women who are contemplating pregnancy to aim for an optimal pre-pregnancy weight *before* pregnancy as a prevention strategy against GDM. Our data would suggest that in Canada if South Asian women who become pregnant have a BMI < 23, 28% of GDM observed in the population would be avoided. To our knowledge such messaging is not routinely provided by primary care physicians or public health specialists.

The low quality diet in START was characterized by higher consumption of meat (red, chicken, and processed), rice, fried foods, and was lower in raw or cooked vegetables, whereas a high

quality diet was associated with higher consumption of vegetables, legumes, and whole grain breads. (Table 4) It would be reasonable to presume that a modified South Asian diet which replaced fried foods and meat with more vegetable protein, and raw and cooked vegetables, and replaced refined grains with whole grains, may reduce GDM in this population by 12%. A prior Cochrane review suggested that diet interventions are more effective than either exercise alone or mixed interventions in preventing GDM (38). We identified no randomized trials which aimed to reduce pre-pregnancy BMI or alter diet quality in pregnancy as a method to prevent GDM in South Asian women living in high income countries. Such interventions should be developed and tested.

Our observation that a family history of type 2 diabetes is a strong risk factor for GDM is consistent with prior studies. This association likely represents a crude marker of a women's genetic risk of type 2 diabetes indicating that women who develop GDM may carry a greater genetic load of variants associated with beta cell dysfunction and insulin resistance, which in turn increases her offspring's genetic load for these conditions (39,40). We also observed that maternal hyperglycemia is associated with increased newborn birthweight, more LGA, more adipose tissue, and greater placental size. Furthermore offspring of mothers with GDM are larger and have reduced insulin sensitivity. Chronic exposure of the growing fetus to hyperglycemia leads to oxidative stress and inflammation, which may in turn induce changes in the regulation of gene expression resulting in reduced insulin secretion or action (41). Future studies are needed which characterize the genetic load and DNA expression/methylation patterns associated with fetal hyperglycemia and relate these profiles to birth and early childhood metabolic profile.

Our study has a number of strengths being a large prospective birth cohort with direct measurement of glycemic status using the 75 gram OGTT with direct measurement of adiposity of mother and newborn. Limitations of our analyses include the fact that our cohort was not a random sample of the population which may overestimate the burden of dysglycemia, although we recruited participants from primary care settings and those attending specialist obstetrical clinics. The lack of random sampling does not affect our association analyses, which remain internally valid. Women's knowledge of a GDM diagnosis leading to change in modifiable factors (such as diet) likely had minimal to no impact on our findings of low diet quality as a predictor of GDM, as only 9·5% (96/1006) of women knew their GDM status when completing the dietary questionnaire.

Conclusion*:* GDM affects up to one-third of South Asian women living in Canada. Modifiable risk factors for GDM include pre-pregnancy weight and low quality diet. Newborns exposed to the highest maternal gestational glucose, have increased birthweight, increased body fat and lower insulin sensitivity, the long-term consequences of which require ongoing prospective follow-up.

Author contributions:

SSA, MG, KKT, HG, and KMS had, substantial contributions to the interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately

investigated and resolved. DD, MZ, RdS, GW, MS, JB, NA, EdV had substantial contributions to the interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published and KM had revising the work critically for important intellectual content; final approval of the version to be published.

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There are no relevant conflicts of interest to disclose.

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Table 1: Maternal Characteristics in women with and without GDM

	GDM*	Non GDM	P-value
N	365	641	
Maternal Age (years)	31·2 (4·0)	29·7 (3·8)	<·0001
Years in Canada (years)	8·8 (7·5)	8·2 (7·9)	0·22
Gestational age at study enrolment (weeks)	26·8 (2·1)	26·6 (1·6)	0·10
Parity: Primiparous (%) Multiparous (%)	 123 (34·3%) 236 (65·7%)	 283 (45·2%) 343 (54·8%)	<0·001
Smoked during Pregnancy (%)	0 (0·0%)	2 (0·3%)	0·54
Vegetarian (%)	125 (34·5%)	243 (38·1%)	0·25
Diet Quality score	2·2 (1·4)	2·5 (1·3)	0·002
Low Diet Quality (%)	121 (33·4%)	145 (22·9%)	<0·001
Hours of active sport/week (hours)	1·4 (2·2)	1·6 (2·5)	0·38
Physical Activity in Pregnancy: Sedentary (%) Mild Exercise (%) Moderate Exercise (%)	 97 (26·7%) 202 (55·6%) 64 (17·6%)	 139 (21·7%) 373 (58·3%) 128 (20·0%)	0·18
Family history of Diabetes (%)	191 (52·5%)	228 (35·7%)	<·0001
Social Disadvantage Index: High (%) Moderate (%) Low (%)	 47 (15·2%) 118 (38·1%) 145 (46·8%)	 90 (16·2%) 213 (38·4%) 251 (45·3%)	0·88
Currently Employed (%)	196 (54·0%)	349 (54·5%)	0·87
Annual household income =>50K (%)	143 (46·0%)	242 (43·6%)	0·50
High school education (%)	361 (99·4%)	638 (99·5%)	0·86
Pre-pregnancy weight (kg)	64·9 (12·2)	61·3 (11·8)	<·0001
Height (cm)	161·6 (6·2)	162·5 (6·3)	0·02
Pre-pregnancy BMI (kg/m^2)	24·9 (4.6)	23·2 (4·3)	<·0001
Sum of skinfolds at enrolment (mm)	52·3 (12·3)	47·9 (12·4)	<·0001
Tricep skinfolds at enrolment (mm)	28·5 (6·7)	26·5 (6·8)	<·0001
Subscapular skinfolds at enrolment (mm)	24·1 (6·6)	21·5 (6·5)	<·0001
Area under the curve glucose (mmol.min)	966·8 (164·0)	722·4 (102·5)	<·0001

Gestational weight gain (kg)	13·5 (7·5)	14·7 (7·9)	0·02
GWG/Pre-pregnancy weight	0·22 (0·13)	0·25 (0·15)	<0·001
C-Section (%)	127 (35·2%)	177 (27·9%)	0·02

*GDM by Born in Bradford definition. Mothers with history of DM excluded.
Legend: BMI: Body Mass Index, GWG: Gestational Weight Gain

Table 2: Newborn Characteristics by Maternal GDM Status

	GDM*	Non-GDM	P-value
N	359	630	
Male (%)	188 (52·4%)	304 (48·3%)	
Gestational age at birth (weeks, SD)	38·8 (1·6)	39·3 (1·4)	
Size for gestational age LGA (%) AGA (%) SGA (%)	 48 (13·8%) 277 (79·4%) 24 (6·9%)	 55 (9·0%) 493 (80·6%) 64 (10·5%)	0·02
Birth weight (g)	3267 (23)	3181 (17)	0·005
Length (cm)	51·0 (0·1)	51·1 (0·1)	0·68
Waist circumference (cm)	30·8 (0·1)	30·3 (0·1)	0·009
Head circumference (cm)	34·1 (0·1)	34·0 (0·1)	0·43
Sum of skinfolds (mm)	11·7 (0·1)	11·2 (0·1)	0·007
Tricep skinfolds (mm)	6·1 (0·1)	5·9 (0·1)	0·05
Subscapular skinfolds (mm)	5·5 (0·1)	5·2 (0·1)	0·002
Ponderal index (kg/m^3)	24·8 (0·2)	24·0 (0·1)	0·002
Placental weight (g)	503·2 (8·1)	474·9 (5·8)	0·007
Cord blood glucose (mmol/L)	4·1 (0·1)	4·1 (0·0)	0·88
Cord blood insulin (pmol/L)	76·3 (3·8)	61·6 (2·8)	0·002
Glucose/insulin ratio *(mmol/cIU)	6·42 (0·60)	8·96 (0·45)	0·001

Means (SE) adjusted for newborn gestational age, sex, and insulin use by mothers.

Size for gestational age as determined by gestational age and sex specific percentiles from study data.

Ponderal index defined as birth weight (kg)/birth length (m^3)

* Non log insulin used

Table 3: Population Attributable Risk and GDM

	Odds (95% CI) from Multivariable Model	Prevalence	PAR % (95% CI)[1]
Age 32-43 vs <29	2·10 (1·51, 2·91)	36·4%	24·5 (15·2, 33·7)
Age 29-31 vs <29	1·34 (0·94, 1·90)	28·6%	7·0 (-1·1, 15·0)
Family hx of DM (1/0)	1·70 (1·29, 2·23)	42·1%	21·6 (11·4, 31·8)
Low Diet Quality (1/0)	1·62 (1·20, 2·19)	26·7%	12·8 (5·2, 20·4)
BMI>23 vs lower	1·80 (1·37, 2·37)	51·5%	28·1 (16·6, 39·5)
Low Diet Quality &/or BMI >23		63·5%	37·3 (25·9, 48·7)
All factors			65·3 (55·6, 75·1)

[1]IRAP method: PAR estimates and 95% CIs were calculated by the interactive risk-attributable program software (US National Cancer Institute, 2002) (35); Continuous factors needed to be categorized: Age was divided into tertiles; BMI was split into 3 BMI categories (<18·5, 18·5-23, >23) and highest BMI (>23) was selected as it was significantly different from lower categories.

Table 4: Low quality versus High Quality Diet Foods among South Asians in Pregnancy

Foods which were consumed in greater quantity among those classified as Low Quality Diet	Foods which were consumed in greater quantity in those classified as High Quality Diet
Meat, Meat Dishes, Processed Meats, Organ Meats, Poultry	Vegetable- Raw and Cooked
Fish and Seafood	Legumes -Daals
Rice	Nuts and Seeds
Fried Foods	Low fat Dairy (Low fat and fermented)
Refined Grains- breads and cereals	Whole Grains - Breads and cereals
Fast Foods	Sweets
Eggs	Fruits

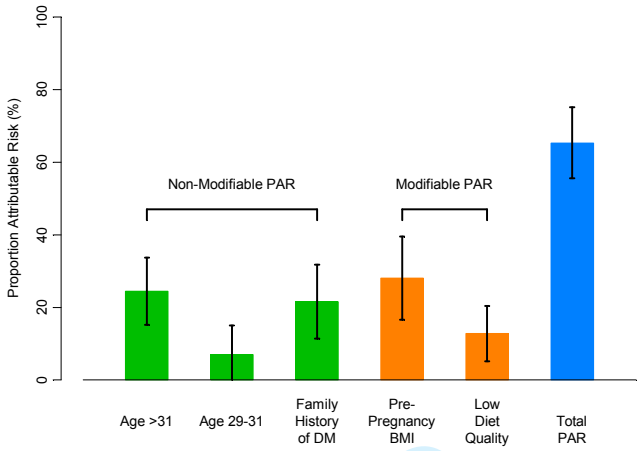

Figure 1 shows the partial proportional attributable risk (PAR) and 95% CI of individual risk factors for South Asian mothers developing GDM. Non-modifiable factors are shown in green; modifiable factors in orange; and the full PAR is shown in blue. PAR estimates and 95% CIs were calculated by the interactive risk-attributable program software (US National Cancer Institute, 2002) (34).

Note to Editor: The information regarding the participants from the cohort included in this analysis may be interest to authors codetermine how subjects were ascertained.

Suppl Figure 1: Study Population