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Brief Report

Cesarean Delivery and Insulin Sensitivity in the Older Adult: The Microbiome and Insulin Longitudinal Evaluation Study

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Abstract

The present study was designed to evaluate if mode of delivery at birth is associated with body mass index (BMI) and glucose homeostasis traits in later life, controlling for possible confounders, including maternal history of diabetes. Data were obtained through a racially diverse, prospective cohort study of nondiabetic, older adults, the Microbiome and Insulin Longitudinal Evaluation Study (MILES). We used generalized linear models to estimate the association between mode of delivery and glycemic status, BMI (kg/m^2), waist circumference (cm), fasting glucose, fasting insulin, insulin secretion, insulin sensitivity, and insulin clearance. Further, we estimated the direct and indirect effects of cesarean delivery on glucose and insulin-related traits, as mediated by BMI status. Relative to vaginal delivery, cesarean delivery was associated with a significantly higher BMI (adjusted beta [aβ] 3.53 kg/m^2; 95% CI 0.15, 6.91) and fasting glucose (aβ 5.12; 95% CI 0.01, 10.23), a 14% decrease in insulin sensitivity (aβ –0.14; 95% CI –0.28, –0.01), and a 58% increased risk (adjusted relative risk [aRR] 1.58; 95% CI 1.08, 2.31) for prediabetes/diabetes. Associations were mediated in part by BMI, with the strongest evidence observed for glycemic status (proportion mediated 22.6%; $P = .03$), fasting insulin (proportion mediated 58.0%; $P = .05$), and insulin sensitivity index (proportion mediated 45.9%; $P = .05$). Independent of mediation, a significant direct effect of cesarean delivery on glycemic status was observed (aRR 1.88; 95% CI 1.16, 2.60). Cesarean delivery may lead to reduced insulin sensitivity and, ultimately, increased risk for developing prediabetes and diabetes.

Key Words: cesarean delivery, glucose homeostasis, insulin traits, pre-diabetes

Abbreviations: aβ, adjusted beta coefficient;aRR, adjusted relative risk; AUC, area under the curve; BMI, body mass index; MILES, Microbiome and Insulin Longitudinal Evaluation Study; OGTT, oral glucose tolerance test; RR, relative risk.

While the evidence is mixed, a few studies have reported an association between cesarean delivery and increased risk of obesity in children, and a recent report from the Nurses' Health Study indicated an increased risk of obesity and type 2 diabetes for women who were born via cesarean delivery [1, 2]. The pathophysiology underlying any association between cesarean delivery and metabolic derangements is unknown; however, it is hypothesized to be a result of alterations in the gut microbiome in early life that may lead to obesity, metabolic derangement, and, ultimately, impaired glucose homeostasis [3]. One challenge in assessing the association between cesarean delivery and development of diabetes is the potential for confounding from maternal factors. For example, shared familial dietary and physical activity patterns could contribute to both maternal obesity, increased risk of cesarean delivery, and increased risk of obesity and development of diabetes in later life in her offspring. Additionally, maternal history of diabetes could be associated with both an increased risk for cesarean delivery and risk of diabetes in her offspring (through genetic factors) [4]. In the present study we evaluated risk for obesity and diabetes, in relation to having been born through cesarean delivery, accounting for maternal history of diabetes.

Materials and Methods

As a secondary analysis of an existing racially diverse, prospective cohort study of nondiabetic, older adults in the Microbiome and Insulin Longitudinal Evaluation Study (MILES), we evaluated mode of delivery at birth in relation to body mass index (BMI), waist circumference, and glucose homeostasis traits, while controlling for possible confounders, including maternal history of diabetes. MILES has been described elsewhere [5]. Briefly, it is an ongoing longitudinal cohort study (2018 to date) being conducted in the Piedmont region of North Carolina, with adults recruited and enrolled

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through a variety of community outreach approaches, including placement of community flyers, letters to patients meeting study inclusion/exclusion criteria, and through recruitment from community-based events. Individuals either contacted study staff as a result of learning about the study from community fliers, or were contacted by telephone following the patient letters. Individuals were then screened by study staff to ensure eligibility and, when eligible, mailed the study consent and questionnaires and scheduled for an initial in-person, comprehensive clinical assessments. Participants include individuals self-reporting non-Hispanic Black or non-Hispanic White race, and exclude individuals taking proton pump inhibitors or histamine-2 receptor antagonists, with inflammatory bowel disease, ongoing treatment for cancer, and other serious illness. The Wake Forest Baptist Health and Cedars-Sinai Medical Center Institutional Review Boards reviewed and approved the MILES study.

The present analysis is based on data obtained at the baseline visit. At this visit, participants underwent an oral glucose tolerance test (with glucose, insulin, and C-peptide measures obtained at 0, 30, 120 minutes) and completed detailed health and demographic questionnaires, from which self-reported mode of delivery at the time of their birth was recorded. Using generalized linear models (linear model for continuous outcome measures; robust [modified] Poisson model to estimate relative risk for dichotomous outcome measures) [6], we estimated the crude and adjusted association between mode of delivery (cesarean vs vaginal [referent]) and glycemic status (prediabetes/diabetes vs normal glucose), BMI (kg/m^2), waist circumference (cm), fasting glucose, fasting insulin, insulin secretion, insulin sensitivity, and insulin clearance. A sensitivity analysis was performed to evaluate potential for unbalanced covariate distribution for age and gender; specifically matching those with a cesarean delivery on those with a vaginal delivery at ratio of 1:4 for age (±5 years of age for those with cesarean delivery) and gender. A secondary analysis was performed to estimate the direct and indirect effects (PROC CAUSAL MED) of cesarean delivery on glucose and insulin-related traits, as mediated by BMI status, as well as quantify the proportion of effect mediated by BMI. Glucose values at 0 and 120 minutes were used to categorize participants as normal, prediabetes, or diabetes per American Diabetes Association guidelines. Insulin secretion was calculated as the area under the curve (AUC) for insulin from baseline to 30 min over the corresponding AUC for glucose ($AUC\text{-}Insulin_{30}/AUC\text{-}Glucose_{30}$) [7]. Insulin sensitivity index was calculated using the Matsuda index [8]. Insulin clearance was calculated as AUC-C-peptide/AUC-Insulin from 0 to 120 minutes of the OGTT [9]. Insulin-related traits were log transformed after visualization of departure from normality and to improve model fit. Multivariable models included adjustment for participant-reported maternal history of hypertension or diabetes, gender, race, and age at baseline visit, with selection of possible confounders determined a priori through development of a directed acyclic graph. All analyses were conducted using SAS v9.4 (Cary, NC).

Results

A total of 353 participants were enrolled in MILES, with a mean (SD) age of 59 (9.0) years, 61.8% female, 36.5% non-Hispanic Black, and 63.5% non-Hispanic White (Table 1). Of

Table 1. Demographic attributes of study participants, by mode of delivery (n = 338)

Demographic attribute	All n = 353, n (%) or median (IQR)	Vaginal delivery n = 321, n (%) or median (IQR)	Cesarean delivery n = 17, n (%) or median (IQR)
Age at baseline visit, median (IQR)	59 (52, 66)	60 (53, 67)	55 (49, 58)
Self-reported race			
Black	129 (36.5)	116 (36.1)	7 (41.2)
White	224 (63.5)	205 (63.9)	10 (58.8)
Gender			
Female	218 (61.8)	201 (62.6)	4 (64.7)
Male	135 (38.2)	120 (37.4)	13 (35.3)
Maternal high blood pressure			
No	265 (75.1)	241 (75.1)	10 (58.8)
Yes	88 (24.9)	80 (24.9)	7 (41.2)
Maternal diabetes			
No	314 (89.0)	285 (88.8)	15 (88.2)
Yes	39 (11.1)	36 (11.2)	2 (11.8)

these, 15 (4.2%) were missing delivery status at birth. As expected for this older cohort, cesarean delivery was relatively uncommon (5.0%) [10]. Still, relative to vaginal delivery, cesarean delivery was associated with a significantly higher BMI (adjusted beta [aβ] 3.53 kg/m^2; 95% CI 0.15, 6.91) and fasting glucose (aβ 5.12; 95% CI 0.01, 10.23), a 14% decrease in insulin sensitivity (aβ –0.14; 95% CI –0.28, –0.01), and a 58% increased risk (adjusted relative risk [aRR] 1.58; 95% CI 1.08, 2.31) for prediabetes/diabetes (Table 2). No association was observed between mode of delivery and waist circumference, fasting insulin, insulin secretion, or insulin clearance, although CIs were wide and imprecise given the relatively small number of participants reporting having been born by cesarean delivery (Table 2). Matched analyses yielded similar adjusted estimates as observed in the full sample, but with crude (matched) results more similar to the adjusted results [11]. Causal mediation analysis indicated that the observed associations between cesarean delivery, glucose, and insulin-related traits were mediated in part by BMI, with the strongest evidence observed for glycemic status (proportion mediated by BMI 22.6%; $P = .03$), fasting insulin (proportion mediated by BMI 58.0%; $P = .05$), and insulin sensitivity index (proportion mediated by BMI 45.9%; $P = .05$) (Table 3). Independent of the mediated indirect effect, a significant direct effect of cesarean delivery on glycemic status was observed (aRR 1.88; 95% CI 1.16, 2.60) (Table 3).

Discussion

Cesarean delivery may increase risk of impaired glucose homeostasis later in life. While previous studies have reported associations between cesarean delivery and BMI and type 2 diabetes, here we provide additional context for these observations, with indication that cesarean delivery may lead to reduced insulin sensitivity and, ultimately, increased risk for developing prediabetes and diabetes. The observed relationship between cesarean delivery and glycemic status and insulin-related traits was mediated, in part, by BMI, with statistically significant direct effects of cesarean delivery observed for glycemic status only. For glucose and insulin-related traits, after accounting for the mediating effect of BMI, associations were no longer statistically significant. This suggests that cesarean delivery more directly influences increased BMI, with decreased insulin sensitivity as a resulting manifestation. Cesarean delivery also appears to influence glycemia by pathways independent of BMI.

A limitation of our study is the self-reported assessment of mode of delivery and maternal history of diabetes, such that there is a potential for misclassification, with perhaps underreporting of both cesarean delivery and maternal history of diabetes. With underreporting of cesarean delivery, we would expect this could bias results toward the null, although with underreporting of maternal history of diabetes, this could perhaps lead to residual confounding due to genetic

Table 2. Cesarean delivery in relation to body mass index, glucose and insulin-related traits in older adults (n = 338)

Outcome	Crude, RR (95% CI)	Adjusted[b], aRR (95% CI)
Glycemic status[a]		
Normal	Referent	Referent
Abnormal	1.42 (0.98, 2.06)	1.58 (1.08, 2.31)
Outcome	Crude, β (95% CI)	Adjusted,[b] aβ (95% CI)
Body mass index (kg/m^2)	4.08 (0.49, 7.67)	3.53 (0.15, 6.91)
Waist circumference (cm)	5.38 (–2.93, 13.71)	5.73 (–2.22, 13.68)
Glucose, fasting (baseline)	3.79 (–1.58, 9.15)	5.12 (0.01, 10.23)
Insulin, fasting (baseline)(log)	0.11 (–0.03, 0.24)	0.12 (–0.01, 0.25)
Insulin secretion (log)	0.06 (–0.07, 0.19)	0.05 (–0.08, 0.17)
Insulin sensitivity index (log)	–0.11 (–0.25, 0.03)	–0.14 (–0.28, -0.01)
Insulin clearance (log)	–0.07 (–0.15, 0.01)	–0.07 (–0.14, 0.01)

[a]Abnormal = prediabetes or diabetes.
[b]Adjusted models include adjustment for maternal history of hypertension or diabetes, age at baseline visit, gender and race.

Table 3. Direct and indirect effects of cesarean delivery on glucose and insulin-related traits in older adults as mediated by BMI (n = 338)

Outcome	Direct effect[b], aRR (95% CI)	Indirect effect[b], aRR (95% CI)	Proportion (%) mediated by BMI[b], *P*
Glycemic status[a]			
Normal	Referent	Referent	Referent
Abnormal	1.88 (1.16, 2.60)	1.14 (0.99, 1.29)	22.6; $P = .03$
Outcome	Crude, β (95% CI)	Adjusted[b], aβ (95% CI)	Proportion mediated[b]
Glucose, fasting (baseline)	3.81 (–1.17, 8.79)	1.31 (–0.07, 2.68)	25.6; $P = .12$
Insulin, fasting (baseline) (log)	0.05 (–0.06, 0.16)	0.07 (0.002, 0.14)	58.0; $P = .05$
Insulin secretion (log)	0.01 (–0.11, 0.13)	0.04 (–0.001, 0.07)	73.8; $P = .43$
Insulin sensitivity index (log)	–0.08 (–0.20, 0.04)	–0.07 (–0.13, –0.00)	45.9; $P = .05$
Insulin clearance (log)	–0.05 (–0.12, 0.03)	–0.02 (–0.04, 0.0005)	32.7; $P = .12$

[a]Abnormal = prediabetes or diabetes.
[b]Includes adjustment for maternal history of hypertension or diabetes, age at baseline visit, gender and race.

factors associated with metabolic derangement in the mother and increased risk for cesarean delivery, as well as increased risk for metabolic derangements to her offspring. Our assessment of the mediating effects of BMI assume we have adjusted for possible confounders in the relationship between both cesarean delivery and each of our outcomes, but also between BMI and our outcomes of interest. Other possible unmeasured confounders could explain the associations observed, including shared familial dietary or behavioral patterns that did not necessarily lead to maternal diabetes but could have increased risk for cesarean delivery. Our sample size precluded investigation of sex differences.

The Developmental Origins of Health and Disease hypothesis posits that the fetal and early life are uniquely vulnerable to exposures that have the potential to fundamentally alter physiologic development, including metabolic dysfunction [12]. One framework advanced from investigators focused on developmental origins of health and disease is the assertion that early-life exposures confer an initial insult that primes the individual for increased risk from future insults: the first-hit, second-hit framework [13]. In this framework, cesarean delivery would lead to dysbiosis, but only through additional future insults would increased risk for metabolic derangements occur.

Cesarean delivery is well documented to lead to altered colonization of the microbiome in offspring, and these changes are hypothesized to alter metabolism for her offspring [14, 15]. In observational studies, cesarean delivery has been associated with increased risk of less favorable cardiometabolic outcomes in children and young adults [16, 17]. Other studies have suggested that any differences in obesity in the offspring are likely explained by or unique to offspring born to mothers with obesity [18, 19].

While it is beyond the scope of the current study to determine whether the metabolic derangements observed in MILES participants are a result, in part, of microbiome alterations in early life attributable to cesarean delivery, these results provide additional support for early-life origins in the development of type 2 diabetes, perhaps mitigatable through improved understanding of the relationship between early-life colonization of the gut microbiome and metabolism and identification of therapeutic strategies to optimize the gut microbiome environment and improve long-term metabolic outcomes. Future investigations are needed to evaluate these associations in the context of the developmental origins of health and disease framework, specifically examining how these early-life exposures may prime the individual for susceptibility for metabolic derangement through additional exposures incurred in life.

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Author Contributions

E.T.J. conceptualized the study question and design, conducted study analyses and drafted the manuscript, OLC contributed to data collection, A.G.B., J.I.R., Y.I.C., A.W., S.S.R., and M.O.G. provided critical revision. All authors reviewed and approved the final manuscript.

Disclosure Summary

None of the authors have any relevant conflicts of interest to disclose.

Data Availability

The data are not publicly available because participants did not give consent for the data to be publicly posted. Interested researchers should contact the corresponding author and submit their credentials to the Cedars-Sinai Institutional Review Board for determination of whether if they are eligible to have access to study data. Upon approval, a limited dataset necessary for replication would be provided to the investigator.

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