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# Elective cesarean delivery at term and the long-term risk for endocrine and metabolic morbidity of the offspring*

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## Abstract

Other than obesity, no definitive insights have been gained regarding the apparent association between mode of delivery and long-term endocrine and metabolic outcomes in the offspring. We aimed to determine whether elective cesarean delivery (CD) impacts on long-term endocrine and metabolic morbidity of the offspring. A population-based cohort analysis was performed including all singleton-term deliveries occurring between 1991 and 2014 at a single tertiary medical center. A comparison was performed between children delivered via a non-emergent CD and those delivered vaginally (VD). Hospitalizations of the offspring up to the age of 18 years involving endocrine morbidity were evaluated. A Kaplan–Meier survival curve was used to compare cumulative morbidity incidence. Cox and a Weibull regression models were used to control for confounders. During the study period 131,880 term deliveries met the inclusion criteria; 8.9% were elective non-urgent CDs ($n = 11{,}768$) and 91.1% ($n = 120{,}112$) were VDs. The survival curve demonstrated a significantly higher cumulative incidence of endo-metabolic morbidity in offspring born via CD ($P = 0.010$). In the regression models, adjusted for maternal obesity, CD was not noted as an independent risk factor for long-term pediatric endocrine and metabolic morbidity of the offspring while maternal obesity emerged as a strong predictor. We therefore conclude that CD per-se does not appear to increase the risk for long-term pediatric endo-metabolic morbidity of the offspring.

## Introduction

Cesarean delivery (CD) has become the most common major surgical procedure undertaken worldwide.[1] In the United States alone, CD rates have risen from less than 5% of total deliveries during the 1960's to 32% in the year 2013, and remained steady since.[2] In most organisation for economic co-operation and development countries, average rates of CD have risen from 20% of total deliveries in the year 2000 to 28% in 2013. A minority of countries including Israel, Finland and Sweden, have demonstrated a slight decline in CD rates (15.4, 15.8, 16.4%, respectively) since 2006.[3]

It is now well established, that CD carries a risk of morbidity not only for the mother but also for the offspring[4] which is subjected to immediate respiratory complications inclining with earlier gestational age.[5] In the long run, a correlation was suggested between CD and obesity in childhood [odds ratio (OR 1.32)] and adulthood (OR 1.24) for the offspring.[6,7] A recently published extensive prospective cohort study discovered a 15% increase in the risk for obesity among offspring born via CD as compared with offspring delivered via vaginal delivery (VD).[1] These findings were shown in sibling analyses as well.[1] Another study, demonstrated an association between CD and higher frequency of obesity and dysmetabolic traits such as higher total cholesterol, low-density lipoprotein cholesterol, leptin and apolipoprotein B levels in the offspring.[8] The consistency of these findings, throughout diverse comparison strategies, strongly supports the notion that mode of delivery has a true biological effect upon future obesity risk, unsubverted to variable confounders.

The exact mechanism for the apparent association between CD and offspring obesity remains unknown. Gut microbiota is involved in the development of low-grade inflammation and metabolic disorders and is considered as one environmental factor influencing host energy homeostasis and adiposity.[9] By impacting on gut hormones, gut microbiome can modify appetite and satiety, regulate energy harvest, insulin action and fat storage.[10] The lack of a direct transmission of vaginal microbiota among offspring born via CD, results in a delayed *Bifidobacterium* and *Bacteroides* colonization[11,12] that may modulate chronic inflammation

processes, insulin resistance and obesity.[13] Other studies describe risks to offspring from not experiencing perinatal events such as labor-related stress and immune activation (type 1 and type 2 T-helper cytokines stimulation by bacteria found in the maternal birth canal and rectum) resulting in reduced cytokine levels at birth which is associated with late development of allergy and atopic predisposition,[14] higher incidence of neonatal respiratory infections, asthma and obesity.[15]

Our current study objective is to further investigate the impact of mode of delivery on offspring obesity, by addressing the wide spectrum of endocrine and metabolic morbidities in both mother and offspring, which could mediate (or rather confound) the pathway between mode of delivery and offspring obesity.

## Methods

A population-based retrospective cohort analysis was performed including all singleton-term deliveries occurring between 1991 and 2014 at the Soroka University Medical Center (SUMC).

SUMC is the largest birth center in Israel, and is the sole tertiary hospital, including the single pediatric unit, in Israel's southern region (The Negev). In Israel, all hospitalizations are fully covered by a national health law allowing free access of all citizens to medical treatments. These facts make our cohort representative of all deliveries in the region.

This study was approved by the institutional review board (SUMC IRB committee) in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (revision 2013).

Primary exposure was defined based on the mode of delivery. Children delivered by a non-emergent ('elective') CD at term, and not while in labor, comprised the 'exposed' study group, whereas children delivered via a spontaneous VD served as the comparison (unexposed) group. Elective CD was defined as non-emergent CD and included cases of CD due to previous cesarean deliveries, mal-presentation and maternal request, performed in an elective setting.

As our work was focused on the possible association between CD as a mode of delivery and long-term endocrine and metabolic outcomes we excluded several entities that otherwise might have served as potential confounders. We therefore excluded parturient with gestational or pre-gestational diabetes, thyroid disease, gestational hypertension or chronic hypertension, premature rupture of membranes and Rh immunization.

Instrumental deliveries, cervical ripening and labor induction (via prostaglandins, oxytocin or Foley catheter) which may be indicative of a complicated pregnancy/delivery (i.e. pre-eclampsia, chorioamnionitis) were excluded from the analysis. Prolapse of cord, placental abruption or previa, non-progressive labor, and maternal history of perinatal deaths were also excluded from the analysis. Moreover, congenital malformations, central nervous system malformations and chromosomal abnormalities in the fetus were excluded.

Outcomes assessed included hospitalizations of the offspring, in both groups, up to the age of 18 years involving endocrine and metabolic morbidities. To better estimate the accompanied endocrine and metabolic morbidity, and since diagnoses such as diabetes mellitus, thyroid diseases or overweight do not usually necessitate hospitalization, we constructed a database that included any endocrine and metabolic morbidity, not necessarily as the primary diagnosis. These were defined according to a pre-prepared international classification of diseases (ICD)-9 list of any of the diagnoses detailed in Supplementary Table S1. Endocrine morbidity included specific diagnoses such as hypothyroidism and diabetes mellitus types I and II. Metabolic morbidity referred to medical conditions characterized by abnormal laboratory values as in the case of hypoglycemia.

The diagnosis of hypoglycemia was only given to newborns who presented with low blood serum glucose values requiring medical intervention. The hypoglycemia group did not include any children being treated for diabetes. Obesity was included in the long-term outcome as it combines both endocrine and metabolic impact.

Specific definitions: Offspring obesity – body mass index (BMI) percentile $\geqslant$97% world health organization (WHO).[16] Hypoglycemia – later hospitalizations of offspring due to hypoglycemia (blood serum glucose $<$ 54 mg/dl[17]) following the initial *postpartum* discharge. Diabetes mellitus – according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997 definitions.[18] Congenital hypothyroidism – total thyroxine below the normal range in the newborn screening program, followed by a later low free thyroxine in a following diagnostic test.[19] Acquired hypothyroidism – free thyroxine below normal range for age.[20]

Follow-up time was defined as time to an event of an endocrine or metabolic-related hospitalization or until censored. Censoring occurred in the case of death (during hospitalization, other than endo-metabolic related) or at age 18 (which was calculated for each child based on the date of birth). Only the first endocrine or metabolically related hospitalization for each child was included in the analysis.

Data were derived from the birth-record (perinatal) computerized database of the department of obstetrics and gynecology, and the pediatric computerized-hospitalization database at SUMC.

The hospital's database ('Demog-ICD9') includes ICD-9 codes for all medical diagnoses made during hospitalizations at SUMC. The computerized perinatal database of the obstetrics and gynecology department at SUMC includes comprehensive maternal data which is determined during the pregnancy such as maternal obesity, demographic characteristics and medical history. Pregnancy characteristics and delivery course and outcomes are recorded immediately following delivery by the obstetrician. Data are then routinely reviewed by experienced medical secretaries to insure its accuracy, before entering it into the database. Both databases (Demog-ICD9 and the perinatal database) were cross-linked and integrated according to maternal and offspring ID numbers.

## Statistical analysis

Background and outcome characteristics were compared between the two groups using a *t*-test and Fisher $\chi^2$ tests, depending on variable type and distribution. Kaplan–Meier survival curves were used to compare the cumulative incidence of endocrine and metabolic related pediatric hospitalizations over the 18 years of follow-up, according to delivery mode. A maximum of one hospitalization was recorded for each child.

To establish an independent association between exposure (mode of delivery) and outcome (endocrine or metabolic morbidity), a Cox proportional hazards model was used to estimate the adjusted hazard ratio (aHR) and its 95% confidence interval (95% CI) which adjusted for maternal age, gestational age, birth weight and maternal group B streptococcus (GBS) ano-rectal colonization status.

In order to evaluate the role of maternal obesity, which may have served as a potential confounder, a similar Cox proportional

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hazards model was constructed to estimate the aHR and its 95% CI while adjusting for maternal obesity (BMI $\geqslant$ 30 kg/m$^2$), together with maternal age, gestational age, birth weight and maternal GBS ano-rectal colonization status.

Overweight and obesity outcomes, usually listed as comorbid conditions, constituted a large proportion of the pediatric endocrine and metabolic morbidity. To determine whether an independent association between mode of delivery and offspring obesity exist, two separate Cox proportional hazards models were constructed. One model adjusted for maternal age, gestational age and birth weight, and a second model adjusted for maternal obesity (BMI $\geqslant$ 30 kg/m$^2$) as well.

Another Cox proportional hazards model was constructed to evaluate the independent association between mode of delivery and hypoglycemia in offspring, which adjusted for maternal obesity, maternal age, gestational age and low birth weight.

As some parturients appear more than once in the hospital's database and in the offspring cohort (i.e. mothers whom gave birth on several occasions during the study period), a Weibull analysis was used. This analysis uses exposure-discordant sibling pairs from the same mother, in order to control for siblings. The Weibull analysis adjusted for maternal obesity, maternal age, gestational age and low birth weight.

All analyses were two sided, with an $\alpha$ of <0.05 considered statistically significant. All analyses were performed using Stata software version 12 (StataCorp) and SPSS software version 23 (IBM SPSS Statistics).

## Results

During the study period 131,880 term deliveries met the inclusion criteria, of which 8.9% ($n = 11{,}768$) were non-emergent ('elective') CDs and 91.1% ($n = 120{,}112$) were spontaneous VDs.

Maternal and pregnancy characteristics, which were determined during pregnancy, together with delivery course and outcomes in both groups are presented in Table 1. Women who underwent elective CD were older and more likely to be obese. They were also

**Table 1.** Maternal and pregnancy characteristics, delivery course and outcomes

| Characteristics | Elective CD ($n = 11{,}768$) | VD ($n = 120{,}112$) | *P* value |
|---|---|---|---|
| Maternal characteristics | | | |
| Age at delivery (years, mean ± S.D.) | 30.5 ± 5.5 | 27.7 ± 5.6 | <0.001 |
| Age higher than 35 years %(*n*) | 19.4 (2277) | 9.9 (11,828) | <0.001 |
| Age higher than 40 years %(*n*) | 3.6 (417) | 1.5 (1828) | <0.001 |
| GBS carriers %(*n*) | 2.5 (296) | 2.2 (2655) | 0.035 |
| Parity %(*n*) | | | |
| 1 | 17.1 (2010) | 16.2 (19,454) | <0.001 |
| 2–4 | 58.4 (6877) | 55.5 (66,615) | |
| 5 + | 24.5 (2880) | 28.3 (34,016) | |
| Previous CD %(*n*) | 58.9 (6928) | 7.9 (9523) | <0.001 |
| Maternal obesity (BMI $\geqslant$ 30 kg/m$^2$) %(*n*) | 2.6 (305) | 0.7 (782) | <0.001 |
| Pregnancy characteristics | | | |
| Macrosomia (>4000 g) %(*n*) | 8.9 (1050) | 4.0 (4829) | <0.001 |
| Delivery | | | |
| Gestational age upon delivery (weeks, mean ± S.D.) | 38.6 ± 1.3 | 39.5 ± 1.2 | <0.001 |
| Immediate delivery outcomes | | | |
| Birth weight (g, mean ± S.D.) | 3246.5 ± 515 | 3258.5 ± 420 | 0.015 |
| Pathological presentation %(*n*) | 37.0 (4350) | 1.2 (1472) | <0.001 |
| Gender | | | |
| Male %(*n*) | 50.3 (5917) | 49.7 (59,683) | 0.224 |
| Female %(*n*) | 49.7 (5851) | 50.3 (60,429) | |
| Low Apgar 1 min (<7) %(*n*) | 8.5 (1005) | 3.4 (4075) | <0.001 |
| Low Apgar 5 min (<7) %(*n*) | 0.6 (71) | 2.6 (3084) | <0.001 |
| Low birth weight ($\leqslant$2500 g) %(*n*) | 5.0 (590) | 2.7 (3247) | <0.001 |

CD, cesarean delivery; VD, vaginal delivery; GBS, group B streptococcus; BMI, body mass index.

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more likely to have had a previous CD. Pregnancies in the elective CD group were characterized by higher rates of macrosomia (8.9 *v.* 4%, $P < 0.001$). Low Apgar scores (<7) at 1 min were more prevalent among the elective CD group (8.5 *v.* 3.4%, $P < 0.001$), whereas low Apgar scores at 5 min were more common among the VD group (2.6 *v.* 0.6%, $P < 0.001$). Low birth weight (⩽2500 g) was more common in the elective CD group (5.0 *v.* 2.7%, $P < 0.001$), while mean birth weight was higher among the VD group (3258.5 ± 420 g *v.* 3246.5 ± 515 g, $P = 0.015$). Gestational age at delivery was more advanced in the VD group (39.5 ± 1.2 weeks *v.* 38.6 ± 1.3 weeks, $P < 0.001$).

Selected pediatric endocrine and metabolic morbidities of the offspring according to mode of delivery are presented in Table 2. Crude hospitalization rate due to hypoglycemia was significantly higher in the elective CD group (0.2 *v.* 0.1%, $P = 0.023$). Total endocrine and metabolic hospitalization incidence per follow-up years was higher as well (HR = 1.51, 95% CI 1.13–2.03). Moreover, the Kaplan–Meier survival curve demonstrated a significantly higher cumulative incidence of endocrine and metabolic hospitalizations in the elective CD group (Fig. 1, log rank $P = 0.010$).

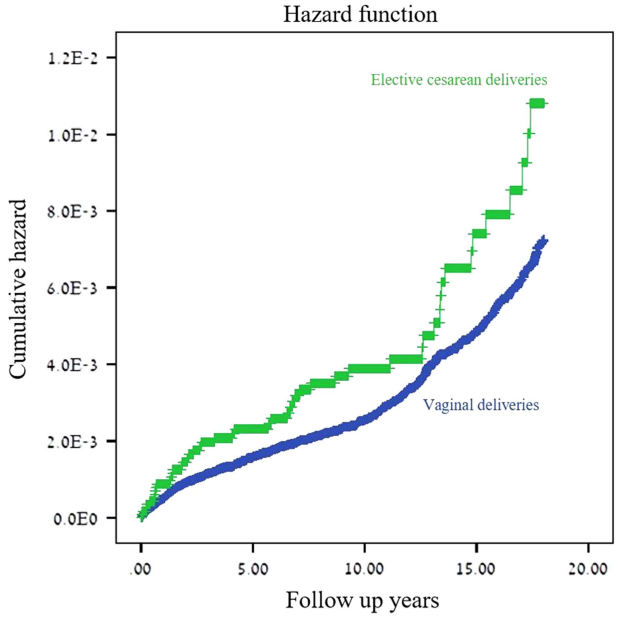


**Fig. 1.** Kaplan–Meier survival curve demonstrating the cumulative incidence of endocrine and metabolic morbidity in children delivered by elective cesarean deliveries and vaginal deliveries.

Table 3 presents the Cox proportional hazards model of the association between mode of delivery and long-term pediatric endocrine and metabolic morbidity in offspring. While the model adjusted for maternal age, gestational age, birth weight and maternal GBS ano-rectal colonization status, elective CD was noted as an independent risk factor for long-term pediatric endocrine and metabolic morbidity of the offspring (aHR = 1.37, 95% CI 1.01–1.86, $P = 0.041$).

However, when the model additionally adjusted for maternal obesity (BMI ⩾ 30 kg/m$^2$), elective CD was not noted as an independent risk factor (aHR = 1.32, 95% CI 0.97–1.79, $P = 0.077$). Instead, maternal obesity emerged as an independent predictor (aHR = 2.75, 95% CI 1.63–4.62, $P < 0.001$).

In the Cox proportional hazards models evaluating the association between mode of delivery and offspring obesity specifically, elective CD was not noted as an independent risk factor for offspring obesity whether adjusted for maternal obesity (aHR = 1.35, 95% CI 0.78–2.34, $P = 0.282$) or not (aHR = 1.58, 95% CI 0.92–2.72, $P = 0.097$).

In the Cox proportional hazards model of the association between mode of delivery and hypoglycemia in offspring, elective CD was noted as an independent risk factor for hospitalization due to hypoglycemia in offspring (aHR = 1.67, 95% CI 1.01–2.75, $P = 0.044$).

Lastly presented, is the Weibull analysis evaluating the association between mode of delivery and long-term pediatric endocrine and metabolic morbidity in offspring, while controlling for siblings. The analysis adjusted for maternal obesity, maternal age, gestational age and low birth weight. In this analysis, elective CD was not noted as an independent risk factor for long-term pediatric endocrine and metabolic morbidity of the offspring (aHR = 0.91, 95% CI 0.67–1.24, $P = 0.573$) while maternal obesity emerged, again, as a strong and independent predictor (HR = 2.21, 95% CI 1.21–4.04, $P = 0.009$).

## Discussion

In this large retrospective cohort analysis of term infants, an association was detected between elective CD and long-term pediatric endocrine and metabolic morbidity in the offspring. Consecutive regression models, adjusted for maternal obesity and sibling, confirmed the association to be primarily with maternal

**Table 2.** Selected pediatric endocrine and metabolic morbidity of the offspring according to mode of delivery group

| Morbidity | Elective CD $n = 11{,}768$ %($n$) | VD $n = 120{,}112$ %($n$) | $P$ value | Elective CD $n = 11{,}768$ $n$ (rate per 100,000-person years) | VD $n = 120{,}112$ $n$ (rate per 100,000-person years) | HR (95% CI) |
|---|---|---|---|---|---|---|
| Thyroid disease | 0.04 (5) | 0.03 (40) | 0.596 | 5 (0.01) | 40 (0.01) | 1.59; 0.63–4.05 |
| Parathyroid disease | 0.0 (0) | 0.01 (22) | 0.255 | 0 (–) | 22 (<0.01) | – |
| Diabetes mellitus | 0.1 (8) | 0.1 (95) | 0.862 | 8 (0.02) | 95 (0.02) | 1.18; 0.58–2.43 |
| Hypoglycemia | 0.2 (20) | 0.1 (116) | 0.023 | 20 (0.06) | 116 (0.02) | 1.86; 1.16–1.99 |
| Obesity | 0.1 (15) | 0.1 (149) | 0.906 | 15 (0.04) | 149 (0.03) | 1.73; 1.03–2.91 |
| Other | 0.0 (0) | 0.002 (3) | 1 | 0 (–) | 3 (<0.01) | – |
| Total endo-metabolic hospitalization | 0.4 (49) | 0.4 (442) | 0.43 | 49 (0.16) | 442 (0.10) | 1.51; 1.13–2.03 |

CD, cesarean delivery; VD, vaginal delivery; HR, hazard ratio; CI, confidence interval.

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**Table 3.** Mode of delivery and long-term endocrine and metabolic outcome of the offspring, Cox proportional hazards model

| Outcome studied | Adjusted HR | CI 95% | *P* value |
|---|---|---|---|
| [a]Total endo-metabolic hospitalization Elective cesarean delivery (*v.* vaginal delivery) | 1.37 | 1.01–1.86 | 0.041 |
| [b]Total endo-metabolic hospitalization Elective cesarean delivery (*v.* vaginal delivery) | 1.32 | 0.97–1.79 | 0.077 |
| [c]Offspring obesity Elective cesarean delivery (*v.* vaginal delivery) | 1.58 | 0.92–2.72 | 0.097 |
| [d]Offspring obesity Elective cesarean delivery (*v.* vaginal delivery) | 1.35 | 0.78–2.34 | 0.282 |
| [e]Hypoglycemia in offspring Elective cesarean delivery (*v.* vaginal delivery) | 1.67 | 1.01–2.75 | 0.044 |
| [f]Elective cesarean delivery (*v.* vaginal delivery) | 0.91 | 0.67–1.24 | 0.573 |

HR, hazard ratio; CI, confidence interval.
[a]This model adjusted for maternal age, gestational age, birth weight and maternal group B streptococcus (GBS) colonization status.
[b]This model adjusted for maternal obesity [body mass index (BMI) $\geqslant 30\,kg/m^2$], maternal age, gestational age, birth weight and maternal GBS colonization status.
[c]This model adjusted for maternal age, gestational age and birth weight.
[d]This model adjusted for maternal obesity (BMI $\geqslant 30\,kg/m^2$), maternal age, gestational age and birth weight.
[e]This model adjusted for maternal obesity (BMI $\geqslant 30\,kg/m^2$), maternal age, gestational age and low birth weight.
[f]A Weibull analysis was used in order to control for siblings. This model adjusted for maternal obesity (BMI $\geqslant 30\,kg/m^2$), maternal age, gestational age and low birth weight.

obesity, and not with CD. In addition, crude hospitalization rate due to hypoglycemia in the offspring was found to be significantly higher in the elective CD group, which emerged as an independent risk factor for hypoglycemia in the regression analysis (Table 3).

A recently published study suggested mode of delivery to serve as a mediator between maternal obesity and future offspring obesity by shaping early-life gut microbial colonization. In the study, *Firmicutes* species abundance, namely of the family *Lachnospiraceae*, was significantly higher in offspring born by elective CD to obese mothers. On the other hand, offspring born vaginally to obese mothers, presented higher abundance of the *Bacteroides* species and yielded a lower risk for offspring obesity compared with elective CD at ages 1 and 3 years.[21]

Previously published literature demonstrated higher rates of adverse health outcomes associated with CD such as overweight and obesity.[1,6,7,22,23] This association was suggested to be a consequence of differences in gastrointestinal microbiota colonization at birth.[24,25] Gut microbiota can modulate host energy homeostasis and adiposity through regulation of energy harvest and fat storage, initiation of inflammatory state of obesity and insulin resistance.[13]

This settles with the proposed linkage between obesity and increased capacity to harvest energy from short-chain fatty acids. Short-chain fatty acids are produced when the gut microbiota is enriched with the *Firmicutes* species over *Bacteroides* phylum.[26]Adiposity, body fat inflammation and diabetes development are promoted as well by the family *Lachnospiraceae*.[27,28]

Mode of delivery entitles additional components which may affect newborn development and health. Birth setting around CD differs from VD with respect to hormonal events around birth. Stress hormone induction is lower in offspring born via CD[29] which may affect immune maturation. This is supported by lower number of leukocytes, neutrophils, monocytes and natural killer cells detected by blood biomarkers during early life.[30] Other stressful perinatal events such as pre-eclampsia and low gestational age have also been linked to type 1 diabetes.[31]

In our study, however, mode of delivery did not appear to play a significant role in the interaction between maternal obesity and the risk of future endocrine and metabolic morbidity of the offspring.

In the year 2015, reported obesity rates (BMI $\geqslant 30\,kg/m^2$) among female adults in Israel reached 24.6%.[32] Maternal obesity rates in our study population were 2.6% in the elective CD group and 0.7% in the VD group ($P<0.001$). These lower than expected rates of maternal obesity may be due to several reasons. First, only severe cases (i.e. morbid obesity) are noted in the database and thus there is probably under documentation of this disorder. Second, one should consider the association between obesity and subfertility.[33] In obese women, high levels of circulating free-estrogen can hamper follicular recruitment and ovulation.[34] Increased level of leptin can dysregulate gonadotrophin-releasing hormone levels.[35] Even when receiving oocytes from normal-weight donors, obese women are less likely to conceive compared to normal-weight recipients, suggesting a potential role of the endometrium.[36] As our cohort included only women with singleton-term deliveries, obese women, whom are less likely to conceive in the first place, might have been represented to an even lesser proportion in our study population as compared with the general population.

As mentioned earlier, we found a higher hospitalization rate due to hypoglycemia in the elective CD group. During the first 8–12 h of life, plasma glucose concentrations are maintained by the breakdown of hepatic glycogen in response to increased plasma epinephrine and glucagon concentrations.[37] This shift might be spared in the absence of *peripartum* stress, as in elective CD. Developmental immaturity of liver mechanisms that protect against hypoglycemia during fasting, namely gluconeogenesis and ketogenesis,[38] might be further compromised in the setting of elective CD. These processes, however, are insufficient to explain later hospitalizations of offspring due to hypoglycemia following the initial *postpartum* discharge.

Our study possesses multiple strengths that could address various limitations carried by previous similar studies concerning cohort sizes and population characteristics. Differences in neonatal microbiota at time of birth associated with CD happens to be most prominent in unlabored cesarean-delivered neonates (in which the fetus has not yet descended into the vaginal canal before delivery), rather than in neonates who were delivered by a labored cesarean surgery (in which the fetus has already descended into the vaginal canal).[39] By defining elective CD as a non-emergency procedure, we avoided parturitions in which the fetus might have already descended into the vaginal canal (labored CD), emphasizing the effect of the cesarean procedure itself, a nuance overlooked in previous studies.[25,40] Large sample size and a long-term retrospective follow-up are additional strengths of this study.

Nonetheless, the study possesses several inherent weaknesses. First, morbidity cases under ambulatory care were not accounted for, as we included only hospital visits at SUMC. Moreover, we could not differentiate between non-visits due to moving out of the region *v.* being healthy. However, SUMC is the sole tertiary hospital in Israel's southern region (The Negev), and by having the

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single pediatric unit in the entire area, it provides both inpatient and outpatient care for the entire population of this region. Hence, we believe that our population morbidity rates and admission frequencies are adequately represented by the hospital's database. We acknowledge the possibility of negative migration (although the Negev region is experiencing positive immigration in the last decade), nevertheless, it is just as likely in both the study and comparison groups, and its extent cannot be measured.

Second, the use of a Weibull analysis to control for siblings has its limitations. Mothers who have undergone a previous CD have the option of proceeding with a trial of labor after cesarean (TOLAC) delivery or planned repeat cesarean delivery (PRCD). This variation between the two groups might play a residual confounder in terms of neonatal outcomes. TOLAC is associated with higher rates of neonatal sepsis and neonatal mortality as compared with PRCD, while PRCD is associated with higher rates of respiratory complications.[41] Whether the choice of mode of delivery after a prior CD might potentially affect neonatal endocrine and metabolic outcomes should be taken into consideration.

Third, we did not address the role of maternal diet. Diet is known to be a potent modifier of the microbiota in both adults and children.[42,43] Forth, each CD conducted in SUMC is preceded by administration of preoperative antibiotics, which is known to shape gut microbiota patterns. Antibiotic enhanced growth used in livestock farming, is known to improve animal weight gain, and in mice it has been shown to increase total body fat mass.[27,44] Since antibiotic-enhanced growth is absent in microbiota-free animals, it is thought to be mediated by the gut microbiota.[45] A recent study showed that infants exposed to antibiotics early in life, were significantly more likely to become overweight later in childhood compared with those who were unexposed.[10] In an effort to minimize its potential effect, the regression analyses also adjusted for maternal GBS colonization status. Lastly, we lacked data on breastfeeding history, also known to modify infant microbiota.[46]

The process in which a healthy gastrointestinal microbiota is established in the offspring is pending further research. Future studies should be focused on the role of delivery mode as a mediator pathway between maternal obesity and future offspring obesity and investigate whether it holds effect on other endocrine and metabolic morbidities as well. This information could be used in the future for counseling patients who consider CD with no conventional medical indication and by doing so, lessen unnecessary CD rates together with the possible accompanying long-term endocrine and metabolic adverse outcomes mediated by it.

**Supplementary materials.** To view supplementary material for this article, please visit https://doi.org/10.1017/S2040174418001022

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**Conflicts of Interest.** None.

## References

1. Yuan C, Gaskins AJ, Blaine AI, *et al.* Association between cesarean birth and risk of obesity in offspring in childhood, adolescence, and early adulthood. *JAMA Pediatr.* 2016; e162385–e162385.
2. Martin JA, Hamilton BE, Osterman MJ. Births in the United States, 2013. *NCHS Data Brief.* 2014; 175, 1–8.
3. Indicators O. Health at a glance 2011. OECD Indicators; 2015. OECD Publishing: Paris. Retrieved 15 February 2016 from https://doi.org/10.1787/health_glance-2015-en
4. Liu S, Liston RM, Joseph KS, *et al.* Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term. *CMAJ.* 2007; 176, 455–460.
5. Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Risk of respiratory morbidity in term infants delivered by elective caesarean section: Cohort study. *BMJ.* 2008; 336, 85–87.
6. Li H, Zhou Y, Liu J. The impact of cesarean section on offspring overweight and obesity: a systematic review and meta-analysis. *Int J Obes.* 2013; 37, 893–899.
7. Darmasseelane K, Hyde MJ, Santhakumaran S, Gale C, Modi N. Mode of delivery and offspring body mass index, overweight and obesity in adult life: a systematic review and meta-analysis. *PLoS One.* 2014; 9, e87896.
8. Hansen S, Halldorsson T, Olsen S, *et al.* Birth by cesarean section in relation to adult offspring overweight and biomarkers of cardiometabolic risk. *Int J Obes.* 2018; 42, 15–19.
9. Cani PD. Crosstalk between the gut microbiota and the endocannabinoid system: impact on the gut barrier function and the adipose tissue. *Clin Microbiol Infect.* 2012; 18, 50–53.
10. Azad M, Konya T, Persaud R, *et al.* Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG.* 2016; 123, 983–993.
11. Adlerberth I, Lindberg E, Åberg N, *et al.* Reduced enterobacterial and increased staphylococcal colonization of the infantile bowel: an effect of hygienic lifestyle? *Pediatr Res.* 2006; 59, 96–101.
12. Dominguez-Bello MG, Costello EK, Contreras M, *et al.* Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A.* 2010; 107, 11971–11975.
13. Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? *Diabetes Care.* 2010; 33, 2277–2284.
14. Sevelsted A, Stokholm J, Bonnelykke K, Bisgaard H. Cesarean section and chronic immune disorders. *Pediatrics.* 2015; 135, e92–e98.
15. Kulas T, Bursac D, Zegarac Z, Planinic-Rados G, Hrgovic Z. New views on cesarean section, its possible complications and long-term consequences for children's health. *Med Arch.* 2013; 67, 460–463.
16. WHO multicentre growth reference study group. *WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development.* 2006. pp. 312. World Health Organization: Geneva.
17. Achoki R, Opiyo N, English M. Mini-review: management of hypoglycaemia in children aged 0–59 months. *J Trop Pediatr.* 2009; 56, 227–234.
18. Gavin JR III, Alberti K, Davidson MB, DeFronzo RA. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care.* 1997; 20, 1183–1197.
19. American Academy of Pediatrics, Rose SR, Section on Endocrinology and Committee on Genetics, American Thyroid Association, *et al.* Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics.* 2006; 117, 2290–2303.
20. Lem AJ, de Rijke YB, van Toor H, *et al.* Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age. *J Clin Endocrinol Metabol.* 2012; 97, 3170–3178.
21. Tun HM, Bridgman SL, Chari R, *et al.* Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring. *JAMA Pediatri.* 2018; 172, 368–377.
22. Li HT, Zhou YB, Liu JM. Cesarean section might moderately increase offspring obesity risk. *Am J Clin Nutr.* 2012; 96, 215–216, author reply 216.
23. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. *N Engl J Med.* 2016; 375, 2369–2379.
24. Musso G, Gambino R, Cassader M. Statements obesity, diabetes, and gut microbiota the hygiene hypothesis expanded? *Diabetes Care.* 2010; 33, 2277–2284.
25. Neu J, Rushing J. Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. *Clin Perinatol.* 2011; 38, 321–331.
26. Kumari M, Kozyrskyj A. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. *Obes Rev.* 2017; 18, 18–31.

27. Cho I, Yamanishi S, Cox L, *et al*. Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature*. 2012; 488, 621–626.
28. Poroyko VA, Carreras A, Khalyfa A, *et al*. Chronic sleep disruption alters gut microbiota, induces systemic and adipose tissue inflammation and insulin resistance in mice. *Sci Rep*. 2016; 6, 35405.
29. Gitau R, Menson E, Pickles V, *et al*. Umbilical cortisol levels as an indicator of the fetal stress response to assisted vaginal delivery. *Eur J Obstet Gynecol Reprod Biol*. 2001; 98, 14–17.
30. Nikischin W, Peter M, Oldigs HD. The influence of mode of delivery on hematologic values in the umbilical vein. *Gynecol Obstet Invest*. 1997; 43, 104–107.
31. Dahlquist G, Källén B. Maternal-child blood group incompatibility and other perinatal events increase the risk for early-onset type 1 (insulin-dependent) diabetes mellitus. *Diabetologia*. 1992; 35, 671–675.
32. GBD. 2015 obesity collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017; 377, 13–27.
33. Best D, Bhattacharya S. Obesity and fertility. *Horm Mol Biol Clin Investig*. 2015; 24, 5–10.
34. Zain MM, Norman RJ. Impact of obesity on female fertility and fertility treatment. *Women's Health*. 2008; 4, 183–194.
35. Pantasri T, Norman RJ. The effects of being overweight and obese on female reproduction: a review. *Gynecol Endocrinol*. 2014; 30, 90–94.
36. Bellver J, Melo MA, Bosch E, *et al*. Obesity and poor reproductive outcome: the potential role of the endometrium. *Fertil Steril*. 2007; 88, 446–451.
37. Lubchenco LO, Bard H. Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age. *Pediatrics*. 1971; 47, 831–838.
38. Stanley CA, Baker L. The causes of neonatal hypoglycemia. *N Engl J Med*. 1999; 340, 1200–1201.
39. Chu DM, Ma J, Prince AL, *et al*. Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery. *Nat Med*. 2017; 23, 314–326.
40. Azad MB, Konya T, Maughan H, *et al*. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *CMAJ*. 2013; 185, 385–394.
41. Guise J, Denman MA, Emeis C, *et al*. Vaginal birth after cesarean: new insights on maternal and neonatal outcomes. *Obstet Gynecol*. 2010; 115, 1267–1278.
42. Koenig JE, Spor A, Scalfone N, *et al*. Succession of microbial consortia in the developing infant gut microbiome. *Proc Natl Acad Sci U S A*. 2011; 108 (Suppl. 1), 4578–4585.
43. David LA, Maurice CF, Carmody RN, *et al*. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014; 505, 559–563.
44. Jukes TH. Antibiotics in animal feeds and animal production. *Bioscience*. 1972; 22, 526–534.
45. Lin J. Effect of antibiotic growth promoters on intestinal microbiota in food animals: a novel model for studying the relationship between gut microbiota and human obesity? *Front Microbiol*. 2011; 2, 53.
46. Jost T, Lacroix C, Braegger CP, Rochat F, Chassard C. Vertical mother–neonate transfer of maternal gut bacteria via breastfeeding. *Environ Microbiol*. 2014; 16, 2891–2904.

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