Title

Elective and non-elective cesarean section and the risk for obesity among young adult males: a population-based cohort.

Protocol information

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Summary

Previous research has suggested that cesarean section may be associated with an increased risk of developing obesity in childhood, adolescence and adulthood. Yet, previous studies have been small or unable to differentiate between elective and non-elective cesarean section. Therefore, using a population-based cohort the purpose is to examine the associations between vaginal delivery, elective and non-elective cesarean section on the risk of developing obesity in young adulthood among Swedish young singleton males. Using the Swedish medical birth registry, the recorded mode of delivery and indication of delivery which will be matched to those males who perform military conscription, where their body mass index is recorded. The investigators hypothesize that there will be an elevated risk of obesity in those born with non-elective cesarean section, as a function of confounding, while those born with elective cesarean section will not have a higher risk of obesity than those born with vaginal delivery.

Introduction

Background/rationale
A recent systematic review has suggested that there may be long-term risks for obesity in offspring's following cesarean delivery (1). However, as noted by Rifas-Shiman et al. (2), there is a possibility that the association observed is driven mainly by unmeasured confounding. Yuan et al. (3) conducted an extensive investigation into various confounders that could explain this association, but still observed an association between cesarean section and offspring obesity. Unfortunately, only a few studies (4, 5) and none of the aforementioned (2, 3) have been able to distinguish between elective and non-elective (acute) cesarean section. One of the likely candidates for unmeasured confounding is confounding by indication, which could inflate the risk for obesity in the non-elective cesarean section, as described by Masukume et al. (4). Despite this, at 12-months (5), and at 3 and 5 years (4), there have been reported elevated risks of obesity in elective deliveries with cesarean section. Which, if true, may rule out the potential of confounding by indication. However, large-scale longitudinal studies are warranted and there is a necessity to examine if this indicated association persist into young adulthood.

Objectives
The objective of the study is to examine if there is an association between being born with an elective cesarean section or non-elective cesarean section and developing obesity in young adulthood.

Hypothesis
The hypothesis is that there will be an elevated risk of obesity in those born with non-elective cesarean section, as a function of confounding, while those born with elective cesarean section will not have a higher risk of obesity than those born with vaginal delivery. The hypothesis is rooted in the assumption that the association between non-elective cesarean section and obesity may be subject to greater confounding by indication, while the association between elective cesarean section and obesity may be less confounded. Thus, in the presence of a higher risk of obesity associated with non-elective cesarean section it will interpreted as confounded, while a higher risk of obesity associated with elective cesarean section will be interpreted as a less confounded and a possible causal association.

Methods

Study type
Population-based cohort.

Study design
We will construct a whole population-based cohort using the following Swedish population registries: (i) the Swedish Military Service Conscription Registry, (ii) the Swedish Medical Birth Register, (iii) the Multigenerational Register and (iv) the Population and Housing Censuses from 1970 and 1990. Additionally, we will match full brothers to create a within-families cohort that will be used to identify discordant full brothers which will contribute to the matched-sibling analysis (See *Analytic Methods* & Appendix Figure 1).

For the purpose of this study, we have defined the following inclusion and exclusion criteria's:

Inclusion Criteria:
- Singleton birth
- Retrievable from the medical birth registry

Exclusion Criteria:
- No available information on mode of delivery
- Not conscripted[a]
- Extreme values at conscription[b]

[a] During the period of study period, conscription was mandatory by law in Sweden for all male citizens up to the age of 47 (6). Males could be exempt from conscriptions (requiring state approval) if any of the following conditions applied: i) Physical or mental impairment limiting the possibility to complete military training, ii) at risk of developing physical or mental impairment if conscripted, iii) became Swedish citizen after the age of 28, iv) has performed equivalent military training in foreign country, v) residing abroad for a longer period and returning after the age of 28 and vi) able to demonstrate extensive reasons to be exempt (6). As a previous study has described (7), only 2-3% of all Swedish men were exempt from conscription.
[b] We will exclude conscripts with extreme values of height (≤150 or ≥210 cm), weight (≤40 or ≥150 kg) or BMI (≤15 or ≥60 kg/m^2), in accordance with previous studies on the Swedish Military conscription register (8). In the sensitivity analysis we will examine the impact of this exclusion (see *Analytic Methods*).

Variables
The exposure is the mode of delivery trichotomized as: 1) vaginal birth, 2) birth by elective cesarean section and 3) birth by non-elective cesarean section. To facilitate comparison with previous studies, we will report the association between any form of cesarean section and obesity. However, this will not be the focus on the study nor be included in results and conclusions.

The primary outcome is body mass index (BMI) categorized according to the World Health Organization's (9) standard: underweight BMI<18.5, normal weight BMI 18.5-24.9, overweight BMI 25-29.9 and obese BMI>30. As a secondary outcome, we will model the difference between mode of deliveries in continuous BMI. BMI is derived by weight in kilograms/height in meters squared. Height and weight are measured using a standardized protocol with stadiometer and scale respectively. The reason for choosing to categorize BMI according to the World Health Organization's standard is because they are clinically relevant and because they facilitate comparison with previous and future studies.

The following confounders will be adjusted for in multivariate analysis: Pre-pregnancy maternal BMI, maternal diabetes at delivery, maternal hypertension at delivery, maternal smoking, parity, maternal and paternal education, maternal age at delivery, birth weight standardized according to gestational age, pre-eclampsia and gestational age. For a more detailed description on each included confounder see Appendix Table 1.

Data sources
Using the Medical Birth Registry, which contains validated data on approximately 99% of the Swedish population (10), we will sample all singleton born individuals born between 1982 and 1987 that are available in the Medical Birth Registry. Using the Swedish Military Service Conscription Registry we will retrieve outcome data for all of the singletons participating in conscription (which was mandatory by law). The Multigenerational register will facilitate linkage of parents and offspring's and be used to retrieve information on maternal age. Finally, the Population and Housing Censuses of 1970 and 1990 were used to retrieve information on the highest parental education. Linking of data sources was enabled through the use of a personal identification number, a unique id-code assigned to each Swedish resident at birth. For a more detailed description on each included variable see Appendix Table 1.

Study size
We intend to sample all eligible participants.

Analytic methods
First, we will present descriptive characteristics of our cohort and the within-families cohort with appropriate measures of dispersion and central tendency for each given variable. We do not intend to present any p-values for descriptive characteristics, hence no statistical tests will be performed. Second, we will model the association between mode of delivery (trichotomized variable) and BMI categories using multinomial logistic regression, using the vaginal delivery and normal weight BMI (BMI 18.5-24.9) as reference exposure/outcome. For all multinomial logistic regression, we will present crude and multivariate adjusted estimates for the exposure and their corresponding 95% confidence interval. All confounders will be adjusted for in their modified way (see Appendix Table 1), except for parity which will be treated as a categorical variable to account for non-linearity with the outcome. All analysis will be estimated using robust (sandwich) standard errors to account for correlation between brothers.

A series of sensitivity analysis will be conducted. First, we will employ multinomial logistic regression with fixed effects, to account for factors shared between full-brothers (genetic and environmental). All discordant full brothers with available measures will be able to contribute to fixed-effects analysis. Second, we will present the original adjusted models but allow for nonlinearity of maternal BMI and maternal age using a cubic transformation. Third, we will present a model further adjusted for weight gain during pregnancy, standardized by gestational age and BMI category using Sweden specific growth curves (11), and a model adjusted for previous cesarean delivery. However, we expect the power in this analysis to be compromised by missing data, as validation reviews have indicated that recording of this information varies in the Medical Birth Registry (12). Third, we will include those excluded because of extreme values at conscription to assess the impact of this exclusion on our findings. Finally, to quantify the required magnitude of a residual confounder to fully explain away any observed association, condition on the observed confounders, we will compute the E-value (13). All analysis will be conducted using Stata 14.1 (Stata Corp, College Station, TX, USA).

Missing data
We expect there to be a proportion of missing data. The primary source of data will likely be those individuals participating in conscription but not having measures of BMI. Further, governmental validation reports have noted that 20% of the cesarean deliveries were not coded by indication (15), which makes these individuals ineligible in our main analysis. However, we will in accordance with best practice attempt to describe the characteristics of the participants with specific missing data and describe the implications of missing data for our findings. All analysis will be conducted as complete cases analysis, as we hypothesize there to be missing completely at random and potentially missing not at random in a few cases.

Other information

Preferred reporting

The study will be reported in coherence with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

Funding

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Ethical considerations

The study was approved by the Regional Ethical Review Board, Stockholm (Dnr: 2016/1445-31/1). The authors declare no conflicts of interest.

Existing data

At the time of protocol submission, VHA and DB had not yet received the required data. Yet, they have previously conducted studies in the registries and had access to other aspects of the data sources. However, this access could not facilitate any analysis relevant to this project.

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Appendix:

Table 1. Source, description, original value and the applied manipulation of each included variable.

Source	Variable	Description	Original value	Manipulation
Swedish Medical birth registry	Vaginal birth	Recorded delivery by vaginal birth.	Yes/no	Trichotomized as: 1) vaginal birth, 2) birth by elective cesarean section and 3) birth by non-elective cesarean section
Swedish Medical birth registry	Cesarean birth	Recorded delivery by cesarean section.	Yes/no	
Swedish Medical birth registry	Indication for Cesarean delivery	Recorded reason for cesarean section.	Categorical: 1) Elective or 2) Non-elective	
Swedish Medical birth registry	Pre-pregnancy maternal BMI	BMI at first visit of maternal health clinic (kg/m2), using a standardized scale and self-reported height.	Continuous	No manipulation (see sensitivity analysis)
Swedish Medical birth registry	Maternal diabetes at delivery	Self-reported maternal diabetes mellitus status.	Yes/no	No manipulation
Swedish Medical birth registry	Maternal hypertension at delivery	Self-reported maternal hypertension status.	Yes/no	No manipulation
Swedish Medical birth registry	Maternal smoking	Self-reported smoking habits of the mother at the first visit of the maternal health clinic.	Categorical: 1) Does not smoke 2) 1-9 cigarettes per day & 3) ≥10 cigarettes per day	No manipulation
Swedish Medical birth registry	Parity	Number of children born, after 28 weeks of gestation.	Continuous	No manipulation
Swedish Medical birth registry	Gestational weight gain	Difference in measured weight between first visit and visit at delivery.	Continuous	Standardized according to the week of gestation and pre-pregnancy BMI category
Swedish Medical birth registry	Birth weight	Birth weight in grams (increments of 10).	Continuous	Standardized according to the week of gestation
Swedish Medical birth registry	Pre-eclampsia	As recorded by ICD-8 code: 63703-63710 and with ICD-9 code: 642E-642G in the medical birth registry.	Yes/no	No manipulation
Swedish Medical birth registry	Previous cesarean delivery	Maternal history of cesarean delivery.	Yes/no	No manipulation
Swedish Medical birth registry	Gestational age	Gestational age in completed weeks.	Continuous	No manipulation
Swedish Military Service Conscription Registry	Offspring BMI at conscription	Measured BMI at conscription (kg/m2), measured using a standardized scale and stadiometer.	Continuous	Categorized into: underweight BMI<18.5, normal weight BMI 18.5-24.9, overweight BMI 25-29.9 or obese BMI>30

Source	Variable	Description	Original value	Manipulation
Population and Housing Censuses	Maternal education	Highest attainted education.	Categorical: 1) Primary education (<9 years), 2) Primary education (9-10 years), 3) Secondary education (<=2-years), 4) Secondary education (>2 years), 5) University (< 3-years), 6) University (> 3-years) or 7) Research degree	Highest educational attainment by any of the parents
Population and Housing Censuses	Paternal education	Highest attainted education.	Same as above	
Multigenerational Register	Maternal age at delivery	Maternal age at the date of delivery.	Continuous	No manipulation (see sensitivity analysis)

Figure 1. Flowchart of derivation of analytic sample and matched-sibling sample.