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The association between Caesarean Section Delivery and Obesity in Childhood: A Longitudinal Cohort Study

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Abstract

Objectives To investigate the association between Caesarean section (CS) birth and body fat percentage (BF%), body mass index (BMI) and being overweight or obese.

Design Prospective longitudinal cohort study.

Setting Babies After Screening for Pregnancy Endpoints: Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints (BASELINE) cohort.

Participants Infants born to mothers recruited from the Screening for Pregnancy Endpoints (SCOPE) study, Cork University Maternity Hospital between November 2007 and February 2011.

Outcome measure Overweight or obese defined according to the International Obesity Task Force criteria.

Results Of the 1305 infants, 362 (27.8%) were delivered by CS. On regression analysis, BF% at two months did not differ significantly by delivery mode. Infants born by CS had a higher mean BMI at six months compared with those born vaginally (adjusted mean difference=0.24; [95% confidence interval (CI) 0.06-0.41], p-value = 0.009). At two years no difference was seen across the exposure groups in the risk of being overweight or obese. At five years, the association between pre-labour CS and the risk of overweight or obesity was not statistically significant (adjusted relative risk ratio (aRRR) =1.37; [95% CI 0.69-2.69]) and the association remained statistically non-significant when children who were macrosomic at birth were excluded from the model (aRRR=0.86; [95% CI 0.36-2.08]).

Conclusion At six months of age children born by CS had a significantly higher BMI but this did not persist into future childhood. There was no evidence to support an association between mode of delivery and long term risk of obesity in the child.

Key words

Caesarean section; body composition; body fat; obesity; childhood; Ireland

Article summary

Strengths and limitations of this study

- Data was obtained from a well phenotyped contemporary prospective longitudinal cohort study.
- Body fat percentage was measured by air displacement plethysmography which is regarded as the gold standard method.
- A limitation was the unavailability of maternal pre-pregnancy body mass index.
- The number of cases at two and five years of age was limited.

Introduction

Over recent decades Caesarean section (CS) rates have risen considerably worldwide and in some countries rates now exceed 50%.[1] The aetiology of the global CS rate increase is multifactorial and includes a decline in vaginal births after Caesarean (VBAC), physician fear of litigation, maternal request, more multiple pregnancies resulting from greater assisted reproductive technology use and access to private health insurance.[2-7]

Although a timely CS can be both necessary and life-saving, for example, in cases of obstructed labor, transverse lie and fetal distress/compromise, it nevertheless conveys complications. For the mother, these include an increased length of hospital stay, infection and haemorrhage, as well as a higher risk of respiratory complications in the infant and consequent admission to the neonatal intensive care unit.[8]

Birth weight is the most commonly used indicator of *in utero* growth, however, body composition at birth, the relative proportion of fat and fat-free mass, can provide a more accurate picture.[9] We have shown retrospectively that neonatal body fat percentage is more closely linked to risk of CS than birth weight.[10] It has been hypothesized that the described association between abnormal birth weight and future cardio-metabolic disease[11] across the life course, can be more closely attributed to differences in early life body composition than to birth weight differences.[9]

CS itself has been consistently associated with an increased risk of obesity later in life, although studies have been inconclusive.[12-14] It is also unclear whether this increased risk pertains to elective/prelabour CS or emergency CS/CS in labour. Making this distinction is challenging because of limited literature so much so that the latest systematic review and meta-analysis on the topic (2018) performed an analysis including all CS and did not differentiate.[15] Several research papers have been able to distinguish between elective and

emergency CS but these have been limited by small sample sizes.[16-18] With CS in labour, membranes are more likely to have ruptured thereby exposing the infant to vaginal microflora. However lack of exposure to the vaginal microflora among infants born by elective CS, where membranes are more likely to be intact, has been suggested as the main causal mechanism for the increased risk of obesity later in life.[19-21] Some have disputed this,[22] [23] nevertheless robust data from animal experiments demonstrates a potential causal role for CS delivery in the development of childhood obesity.[24]

Given the worldwide increase in non-medically indicated prelabour CS[8], this type of CS represents a potentially modifiable risk factor for childhood obesity. The aim of this study was to investigate the relationship between CS delivery, particularly prelabour CS, and childhood body composition and growth, using a well phenotyped prospective longitudinal birth cohort with detailed clinical phenotyping of both mothers and their children. We wanted, in particular, to examine the potential confounding effect of macrosomia, as this is both a risk factor for CS, and for long term obesity.

Methods

Data source and population sampled

Data was obtained from the Irish cohort of the prospective Screening for Pregnancy Endpoints (SCOPE) study of 'low risk' nulliparous women with singleton pregnancies (ACTRN12607000551493, www.scopestudy.net/) and its follow-up prospective Irish birth cohort, the Babies After SCOPE: Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints (BASELINE) study (NCT01498965, www.baselinestudy.net/).
The SCOPE and BASELINE study methodology are reported in detail elsewhere.[25] [26] Briefly, the aim of the SCOPE study was to develop screening approaches, clinical and molecular, to

predict fetal growth restriction, pre-eclampsia, and spontaneous preterm birth in healthy nulliparous women during early gestation. Exclusion criteria included: 1) considered to be at high risk of fetal growth restriction, pre-eclampsia, or spontaneous preterm birth due to underlying medical conditions (chronic hypertension, diabetes, renal disease, systemic lupus erythematosus, anti-phospholipid syndrome, sickle cell disease, HIV), previous cervical knife cone biopsy, ≥ 3 previous terminations or ≥ 3 miscarriages, current ruptured membranes; 2) had a major uterine anomaly, a known major fetal anomaly or abnormal karyotype; or 3) received an intervention that could modify pregnancy outcome (e.g. aspirin therapy, cervical suture).

In brief, the BASELINE cohort participant's mothers were recruited at 15 ±1 weeks of pregnancy from Cork University Maternity Hospital between November 2007 and February 2011. Of the 2579 women approached to participate, 1774 (69%) gave their written informed consent. From those, 1537 (87%) had infants recruited into the BASELINE study. The socio-demographic, lifestyle and physical measurements were collected by trained research midwives. A complete audit trial was available for the data that was entered into a centrally accessed internet database (MedSciNet AB, Stockholm, Sweden).

Exposure and outcome ascertainment

Delivery mode was grouped into four categories, namely unassisted vaginal delivery (VD), operative VD, prelabour lower segment (LS) CS and LSCS in labour. Operative VD constituted delivery by either vacuum extraction or forceps.

Whole body density was calculated from naked weight measured by an electronic scale (seca 384; seca, Birmingham, UK) to the nearest gram divided by body volume estimated by the PEA POD air displacement plethysmography system (COSMED, Concord, California, USA)

within the first four days of life and also at age two months. The PEA POD agrees highly with the gold standard four-compartment model and is non-invasive, fast and safe.[10 27 28] Based on body density and a two-compartment model of body composition (fat and fat-free mass), using values established by Fomon[27], body fat percentage (BF%), the primary outcome, was calculated as [(Fat mass (kg)/body mass (kg))×100].

The child's height and weight were measured by a trained interviewer using standardised protocols and medically approved instruments. At birth, two months, six months, one year, two years and five years of age, body mass index (BMI) in kg/m^2 was calculated for each child. At age two and five years, BMI was classified as thin, normal, overweight or obese, according to the International Obesity Task Force (IOTF) criteria.[29 30] The IOTF classification begins at age two years.

The following potential confounders as reported in the literature[12-14 31 32] were included *a priori*: maternal age, education, ethnicity, marital status, infant sex, maternal smoking before and during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia.

Statistical analysis

Stata version 14SE (StataCorp LP College Station, TX) was used for statistical analysis. Categorical variables were described using frequency (n) and percent (%). Numeric variables were described using the mean (standard deviation-SD) or median (interquartile range-IQR). Crude and adjusted linear regression models were used to examine the association between mode of delivery and BF%. Linear regression models were also used to evaluate the association between delivery mode and BMI as a continuous measure.

Crude and adjusted multinomial logistic regression models were used to examine the association between mode of delivery and the risk of being overweight or obese. Adjusted mean differences and adjusted relative risk ratios (aRRR), for the linear and multinomial logistic regression models respectively, were calculated with 95% confidence intervals (CIs). Unassisted VD was the reference category and normal BMI was the base outcome for the multinomial logistic regression models. Models were stratified by whether infants were macrosomic or not which was defined as a birth weight > 4000g or ≤ 4000g respectively. We also explored interaction by infant sex. Statistical significance was defined as a p-value < 0.05.

Patient involvement

Participants were not involved in establishing the research question, outcome measures including the study design and interpretation or writing of this paper. The results will be disseminated via the study website, social media, information evenings and by newsletter.

Results

Of the 1305 infants, 943 (72.3%) were delivered vaginally. The remainder of the deliveries (27.8%) were by CS; prelabour LSCS (12.0%) and LSCS in labour (15.8%) respectively (Table 1). At birth, 13.0% of infants were macrosomic (> 4000g); 11.0% were large for gestational age (> 90th percentile for customised birth weight centiles). At two years of age, 116 (10.9%) children were overweight or obese (using IOTF cut-offs). At age five, the respective number was 118 (14.5%). At age two months, the mean (SD) BF% was calculated at 21.8% (±4.3%). BF% approximated to the normal distribution.

The average BMI, by the four birth modes, at each of the six time points is depicted by Figure 1 and for all vaginal and CS births by Figure 2. The maximum divergence in BMI by delivery mode occurred at six months of age. At six months, the mean BMI of infants delivered vaginally and those born by CS was 17.3 kg/m^2 and 17.6 kg/m^2 respectively.

Across delivery mode missing data was distributed equally for the primary and secondary outcomes, BF% and BMI respectively.

Mode of delivery and body fat percentage at age two months

At two months' age there was no association between prelabour CS and BF% (adjusted BF% mean difference=0.46; [95% CI -0.46-1.40]) and LSCS in labour (adjusted BF% mean difference=0.07; [95% CI -0.88-0.73]) in comparison to the reference group of children delivered by unassisted VD (Table 2).

Mode of delivery and body mass index at age six months, two years and five years

Infants born by CS had a significantly higher mean BMI at six months compared with those born vaginally, adjusted BMI mean difference=0.24; [95% CI 0.06-0.41], p-value = 0.009. Limiting analysis to non macrosomic infants resulted in an adjusted BMI mean difference=0.26; [95% CI 0.07-0.45], p-value = 0.008.

There was, however, no statistically significant differential effect by sex (p-value for the interaction term was 0.70) – Supplementary Figure 1).

There was no statistically significant association between prelabour CS (aRRR=1.38; [95% CI 0.73-2.62]) or LSCS in labour (aRRR=0.88; [95% CI 0.48-1.61]) and the risk of being overweight or obese at age two years, as compared to the reference group (Table 3). Limiting

analysis to non-macrosomic infants at age two resulted in the association between prelabour CS and the risk of overweight and obesity being (aRRR=0.95; [95% CI 0.44-2.05]) and for LSCS in labour (aRRR=0.89; [95% CI 0.44-1.82]) (Supplementary Table 1).

At age five years, there was no association between prelabour CS and the risk of being overweight or obese (aRRR=1.37; [95% CI 0.69-2.69]) (Table 4). There was also no association between LSCS in labour and the risk of being overweight or obese (aRRR=1.69; [95% CI 0.92-3.08]). Limiting analysis to non-macrosomic infants at age five resulted in the association between prelabour CS and the risk of overweight and obesity being (aRRR=0.86; [95% CI 0.36-2.08]) and for LSCS in labour (aRRR=2.37; [95% CI 1.19-4.68]) (Supplementary Table 2).

Discussion

Main findings

There was no significant difference in BF% at age two months between modes of delivery. A statistically significant difference in BMI at age six months was observed between infants born by CS and VD. There was no evidence to support a link between prelabour CS and our secondary outcome, being overweight or obese, at two and five years of age.

Strengths and limitations

A major strength was the availability of data from a well phenotyped prospective longitudinal cohort that is among those with the most data available for BF%. This allowed us to investigate the role of factors such as cigarette smoking prior to conception, which is often

not available from prior or extant cohorts. In addition, we used robust measures of body composition obtained by air displacement plethysmography, which is regarded as the gold standard method.

A homogenous sample where 98% of the cohort's participants were Caucasian, primiparous and 'low risk'[26] could limit the generalizability of these findings to heterogeneous populations. However, the cohort reflected the Republic of Ireland's demographics of reproductive age women (15-49 years), where 93% are Caucasian women.[33] The variable pre-pregnancy BMI was unavailable; this variable attenuated effect size estimates towards the null[12] in previous studies. Body mass index at 15 weeks' gestation, a good proxy for pre-pregnancy BMI, was used because 15 weeks is prior to the occurrence of most weight gain in pregnancy. The major limitation was the low number of cases at two and five years of age.

Interpretation

The relationship between CS delivery and offspring being overweight or obese has been explored by several systematic reviews and meta-analyses.[12 14 15 34] A positive association was the most common finding. Our findings are similar to those of infants, born in 2010, from a Danish prospective cohort study which found that the largest BMI difference by delivery mode, from birth to five years of age, occurred at six months' age and that this difference did not track into later childhood at age five.[35] In addition, similar to this study, no significant difference in BF% by delivery mode, was found. Furthermore this Danish study, like ours and also as reported by the systematic reviews and meta-analyses[13 31], did not find a sex-specific growth pattern by mode of birth. This suggests that in humans CS birth might not influence sex-specific growth patterns as has been observed in mouse studies. [24]

Childhood fat mass index data from a Brazilian longitudinal cohort also showed no significant difference between children born by CS and VD at six years of age.[36] The declining influence of CS birth on the risk of obesity as children grow older has been attributed to the increasing influence of other risk factors for obesity like physical inactivity, family dietary habits, watching television (and the use of other electronic devices).[37] Indeed a study which utilized a sibling-pair design attributed the observed association between CS birth and childhood obesity to unmeasured confounding.[38]

Our results are dissimilar to those of children from a Boston, US cohort study which found a positive association between delivery mode and being overweight or obese at age five.[39] The Boston study, unlike ours, did not sub classify CS births into elective and emergency for example, and unusually there were more girls delivered by CS,[40] this might indicate reduced external validity for the US study.

A few studies have been able to differentiate between elective/prelabour CS and emergency/ LSCS in labour and they have been limited by small sample sizes.[16 17] However a higher risk of childhood obesity for infants born by emergency CS than elective CS was reported.[17] Us finding an association at age five between LSCS in labour, when membranes are more likely to have ruptured, and being overweight or obese, but not with prelabour CS suggests no causal role for vaginal flora in the genesis of children being overweight or obese. A possible explanation for the LSCS in labour association is confounding by the indications for CS. However, a divergent BMI trajectory in mid-infancy which then converges by age five between VD and CS babies may suggest a transient role for the vaginal microflora. Further exploration, around mid-infancy, of the association between CS birth and BMI is required.

The CS rate of 27.8% in this cohort, is consistent with published national estimates of 27.1% to 28.6% that prevailed during the study's recruitment period from 2007 to 2011.[41] This suggests the generalizability of findings to the Irish population. A macrosomia (> 4000g) prevalence of 13.0% is almost double that of another high income country, the US at 7.5% during a similar time period, and suggests high baseline Irish rates of excess adiposity.[42] The general Irish population had at age three and five years a prevalence of 24% and 20% respectively for obesity and being overweight[43] which is higher than that observed in this cohort. This cohort's low risk population likely explains its lower prevalence of being overweight or obese compared to the general Irish population.

Conclusion

We have found no evidence to support a relationship between prelabour CS and offspring being overweight or obese in early childhood. No significant differences in outcome at two months and two years, and an increased risk of being overweight or obese in children born by CS in labour, but not prelabour CS at five years, suggests that the previously hypothesized causal effects due to vaginal microflora are also unlikely at least in the long term.

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Author contributions

GM, FPM, PNB, LCK, SMBM, DMM, JOBH, ASK conceived and designed the study. GM and ASK analysed the data and all authors interpreted the results. GM wrote the first draft of

the article and FPM, PNB, LCK, SMBM, DMM, JOBH, ASK revised it critically for important intellectual content. All authors approved the final version and agree to be accountable for all aspects of the work.

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Competing interests

No, there are no competing interests for any author.

Participant consent

Obtained.

Ethics approval

Clinical Research Ethics Committee of the Cork Teaching Hospitals (Ref: ECM5 (9) 01/07/2008.

Data sharing statement

No additional data are available.

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Table 1. Characteristics of the study population at two months.

Characteristic	Overall n (%)	Unassisted vaginal n (%)	Operative vaginal [a] n (%)	Prelabour LSCS n (%)	LSCS in labour n (%)
N	1305 (100)	470 (36.0)	473 (36.2)	156 (12.0)	206 (15.8)
Age (years), median IQR	30 (28-33)	30 (27-32)	30 (28-33)	32 (29.5-34)	31 (29-33)
< 20	19 (1.5)	9 (1.9)	9 (1.9)	1 (0.6)	0 (0.0)
20-24	111 (8.5)	57 (12.1)	38 (8.0)	4 (2.6)	12 (5.8)
25-29	388 (29.7)	157 (33.4)	139 (29.4)	34 (21.8)	58 (28.2)
30-34	615 (47.1)	215 (45.7)	214 (45.2)	85 (54.5)	101 (49.0)
35-39	155 (11.9)	31 (6.6)	66 (14.0)	28 (17.9)	30 (14.6)
≥40	17 (1.3)	1 (0.2)	7 (1.5)	4 (2.6)	5 (2.4)
Ethnicity					
Caucasian	1,287 (98.6)	463 (98.1)	466 (98.5)	155 (99.4)	203 (98.5)
Other	18 (1.4)	7 (1.5)	7 (1.5)	1 (0.6)	3 (1.5)
Schooling (years primary and secondary), median IQR*	13 (13-14)	13 (13-14)	13 (13-14)	13 (13-14)	13 (13-14)
Marital status					
Single	123 (9.4)	52 (11.1)	49 (10.4)	11 (7.1)	11 (5.3)
Married	920 (70.5)	321 (68.3)	330 (69.8)	115 (73.7)	154 (74.8)
Stable relationship not married	261 (20.0)	97 (20.6)	94 (19.9)	29 (18.6)	41 (19.9)
Sex					
Male	666 (51.0)	221 (47.0)	252 (53.3)	81 (51.9)	112 (54.4)
Female	639 (49.0)	249 (53.0)	221 (46.7)	75 (48.1)	94 (45.6)
Pre-eclampsia	48 (3.7)	17 (3.6)	7 (1.5)	16 (10.3)	9 (4.4)
Maternal BMI at 15 weeks (kg/m^2), median IQR	24.0 (22.1-26.9)	23.9 (21.5-26.4)	23.7 (22.1-26.7)	24.9 (22.3-28.7)	24.7 (23.0-27.9)
Gestational age (weeks), median IQR	40.3 (39.3-41.0)	40.3 (39.3-41.0)	40.6 (39.6-41.1)	39.3 (38.6-40.1)	40.6 (39.6-41.3)
Number of cigarettes per day at 15 weeks SCOPE visit, mean (±SD)	0.5 (±2.1)	0.7 (±2.4)	0.4 (±2.1)	0.5 (±2.3)	0.3 (±1.4)
Birth weight (g), median IQR	3460 (3160-3770)	3400 (3120-3690)	3510 (3200-3800)	3345 (2915-3670)	3650 (3300-4000)
Macrosomia (> 4000g)	169 (13.0)	32 (6.8)	65 (13.7)	21 (13.5)	51 (24.8)
Baby size according to customized centile					
SGA < 10th centile	135 (10.3)	59 (12.6)	40 (8.5)	22 (14.1)	14 (6.8)
AGA ≥ 10th centile ≤ 90th centile	1,027 (78.7)	383 (81.5)	374 (79.1)	110 (70.5)	160 (77.7)

LGA > 90th centile	143 (11.0)	28 (6.0)	59 (12.5)	24 (15.4)	32 (15.5)
Body composition (at two months)					
Body fat (%), mean SD	21.8 (±4.3)	21.8 (±4.3)	21.6 (±4.4)	22.3 (±4.6)	21.6 (±4.2)
missing	272 (20.8)	98 (20.9)	93 (19.7)	39 (25.0)	42 (20.4)
Body mass index (kg/m^2) at 2 years**					
Thin	77 (5.9)	28 (6.0)	34 (7.2)	6 (3.8)	9 (4.4)
Normal	812 (62.2)	289 (61.5)	286 (60.5)	101 (64.7)	136 (66.0)
Overweight	96 (7.4)	29 (6.2)	39 (8.2)	12 (7.7)	16 (7.8)
Obese	10 (0.8)	4 (0.9)	2 (0.4)	3 (1.9)	1 (0.5)
Missing	310 (23.8)	120 (25.5)	112 (23.7)	34 (21.8)	44 (21.4)
Body mass index (kg/m^2) at 5 years**					
Thin	38 (2.9)	13 (2.8)	17 (3.6)	3 (1.9)	5 (2.4)
Normal	656 (50.3)	236 (50.2)	232 (49.0)	83 (53.2)	105 (51.0)
Overweight	97 (7.4)	22 (4.7)	42 (8.9)	12 (7.7)	21 (10.2)
Obese	21 (1.6)	10 (2.1)	6 (1.3)	3 (1.9)	2 (1.0)
Missing	493 (37.8)	189 (40.2)	176 (37.2)	55 (35.3)	73 (35.4)

LSCS (Lower segment Cesarean section), SD (Standard deviation), IQR (Interquartile range), SGA (Small for gestational age), AGA (Appropriate for gestational age), LGA (Large for gestational age).
[a] Vacuum or forceps
* Total years of schooling (primary and secondary, not pre-school or tertiary)
** International Obesity Task Force age and sex-specific cut-offs

Table 2. Mode of delivery and body fat percent at age two months.

Delivery mode	Cases n	Coef. (95% CI)	p-value	AdjCoef. (95% CI)**	p-value
Unassisted vaginal	372	reference		reference	
Operative vaginal	380	-0.16 (-0.78-0.46)	0.614	-0.10 (-0.72-0.52)	0.743
Prelabour LSCS	117	0.50 (-0.40-1.40)	0.278	0.46 (-0.46-1.40)	0.325
LSCS in labour	164	-0.19 (-0.9-0.61)	0.642	0.07 (-0.88-0.73)	0.864

N for adjusted model = 1,033. Linear regression. BMI – Body mass index, Coef. (β-Coefficient), CI (Confidence intervals), Adj (Adjusted).

**Adjusted for maternal age, education, ethnicity, marital status, infant sex, maternal smoking before and during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia

Table 3. Mode of delivery and body mass index at age two years.

BMI category (normal BMI – base outcome)	Cases n	RRR (95% CI)	p-value	AdjRRR (95% CI)**	p-value
Thin					
Unassisted vaginal	30	reference		reference	
Operative vaginal	37	1.23 (0.74-2.05)	0.417	1.42 (0.83-2.41)	0.199
Prelabour LSCS	6	0.59 (0.24-1.47)	0.259	0.65 (0.26-1.62)	0.352
LSCS in labour	9	0.65 (0.30-1.41)	0.279	0.86 (0.39-1.87)	0.696
Overweight or Obese					
Unassisted vaginal	37	reference		reference	
Operative vaginal	41	1.11 (0.69-1.78)	0.670	0.95 (0.58-1.56)	0.853
Prelabour LSCS	17	1.45 (0.79-2.65)	0.233	1.38 (0.73-2.62)	0.324
LSCS in labour	20	1.18 (0.66-2.10)	0.583	0.88 (0.48-1.61)	0.680

N for adjusted model = 1,062. Multinomial logistic regression. BMI – Body mass index, RRR (Relative Risk Ratio), CI (Confidence intervals), Adj (Adjusted).

**Adjusted for maternal age, education, ethnicity, marital status, infant sex, maternal smoking before and during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia

Table 4. Mode of delivery and body mass index at age five years.

BMI category (normal BMI – base outcome)	Cases n	RRR (95% CI)	p-value	AdjRRR (95% CI)**	p-value
Thin					
Unassisted vaginal	13	reference		reference	
Operative vaginal	18	1.45 (0.69-3.02)	0.324	1.82 (0.84-3.96)	0.294
Prelabour LSCS	3	0.68 (0.19-2.44)	0.553	0.46 (0.16-1.56)	0.279
LSCS in labour	5	0.86 (0.30-2.47)	0.777	1.06 (0.31-3.05)	0.822
Overweight or Obese					
Unassisted vaginal	36	reference		reference	
Operative vaginal	52	1.51 (0.95-2.40)	0.079	1.64 (1.00-2.67)	0.050
Prelabour LSCS	17	1.39 (0.74-2.60)	0.305	1.37 (0.69-2.69)	0.368
LSCS in labour	26	1.61 (0.93-2.80)	0.090	1.69 (0.92-3.08)	0.090

N for adjusted model = 856. Multinomial logistic regression. BMI – Body mass index, RRR (Relative Risk Ratio), CI (Confidence intervals), Adj (Adjusted).

**Adjusted for maternal age, education, ethnicity, marital status, infant sex, maternal smoking before and during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia

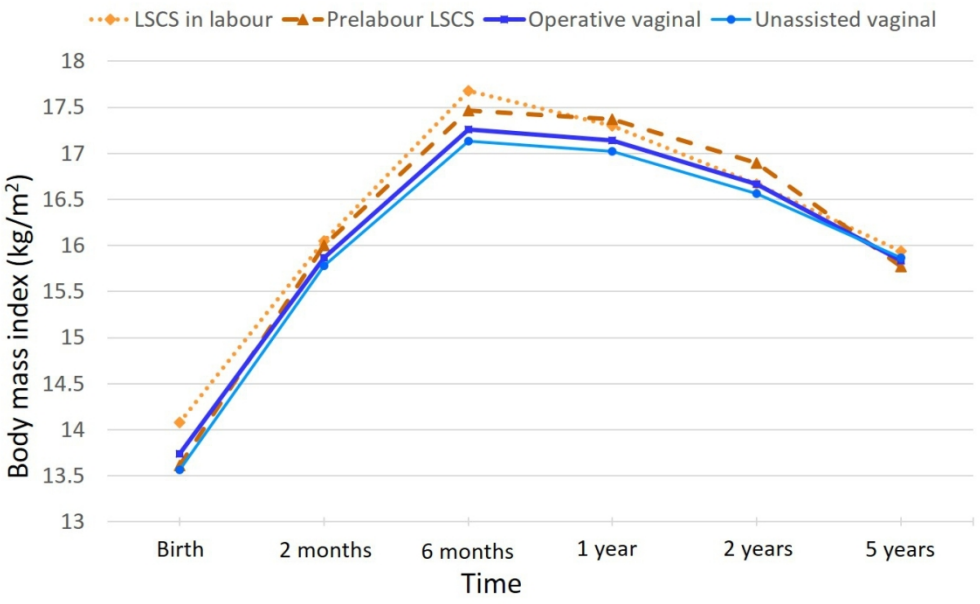

Figure 1. Mean body mass index (BMI) from birth to five years of age. Lower segment Caesarean section (LSCS). Please note that the time axis has been expanded below age one year to permit clearer visualisation.

232x146mm (150 x 150 DPI)

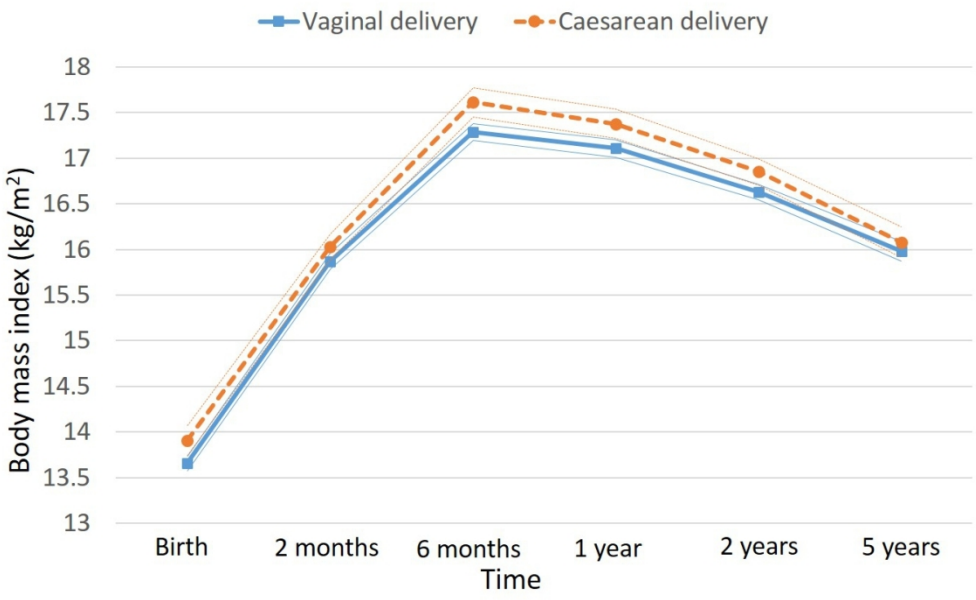

Figure 2. Mean body mass index (BMI) from birth to five years of age with 95% confidence intervals (CIs) around the mean BMI – thin lines. There is no overlap of the 95% CIs at six months of age. Please note that the time axis has been expanded below age one year to allow clearer visualisation.

231x144mm (150 x 150 DPI)

Supplementary information

The association between Caesarean Section Delivery and Obesity in Childhood: A Longitudinal Cohort Study

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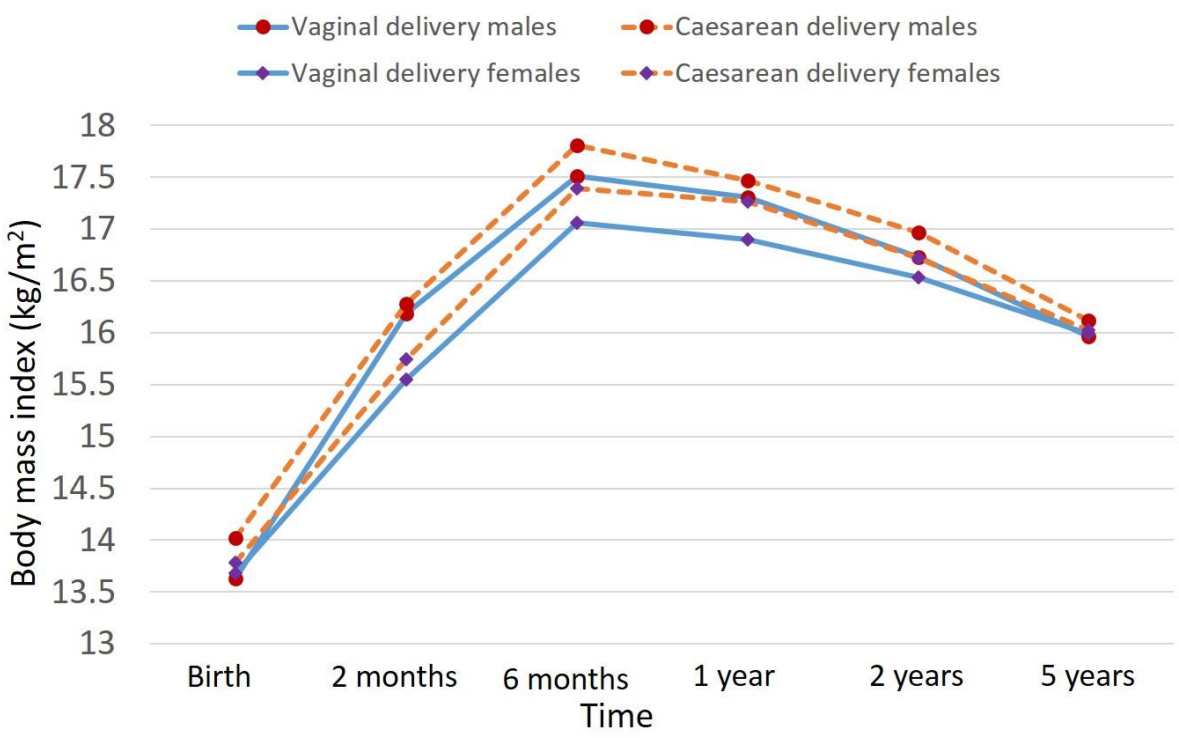

Supplementary Figure 1. Mean body mass index (BMI) from birth to five years of age by delivery mode and sex. Please note that the time axis has been expanded below age one year to allow clearer visualisation.

Supplementary Table 1. Mode of delivery and body mass index at age two years. Non-marosomic.

BMI category (normal BMI – base outcome)	RRR (95% CI)	p-value	AdjRRR (95% CI)**	p-value
Thin				
Unassisted vaginal	reference		reference	
Operative vaginal	1.41 (0.84-2.36)	0.188	1.51 (0.89-2.58)	0.130
Prelabour LSCS	0.26 (0.24-1.62)	0.357	0.67 (0.27-1.68)	0.398
LSCS in labour	0.73 (0.32-1.64)	0.443	0.83 (0.37-1.90)	0.664
Overweight or Obese				
Unassisted vaginal	reference		reference	
Operative vaginal	0.98 (0.58-1.64)	0.929	0.93 (0.54-1.59)	0.789
Prelabour LSCS	0.93 (0.44-1.95)	0.842	0.95 (0.44-2.05)	0.891
LSCS in labour	1.01 (0.51-1.98)	0.982	0.89 (0.44-1.82)	0.747

N for adjusted model = 921. Multinomial logistic regression. BMI – Body mass index, RRR (Relative Risk Ratio), CI (Confidence intervals), Adj (Adjusted).
**Adjusted for maternal age, education, ethnicity, marital status, infant sex, maternal smoking before and during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia

Supplementary Table 2. Mode of delivery and body mass index at age five years. Non-macrosomic.

BMI category (normal BMI – base outcome)	**RRR (95% CI)**	**p-value**	**AdjRRR (95% CI)****	**p-value**
Thin				
Unassisted vaginal	reference		reference	
Operative vaginal	1.59 (0.76-3.32)	0.221	1.85 (0.85-4.04)	0.120
Prelabour LSCS	0.73 (0.20-2.63)	0.629	0.46 (0.14-1.55)	0.209
LSCS in labour	1.09 (0.38-3.14)	0.880	1.14 (0.39-3.34)	0.815
Overweight or Obese				
Unassisted vaginal	reference		reference	
Operative vaginal	1.43 (0.87-2.36)	0.161	1.77 (1.03-3.04)	0.038
Prelabour LSCS	0.89 (0.41-1.95)	0.768	0.86 (0.36-2.08)	0.750
LSCS in labour	1.59 (0.85-2.98)	0.150	2.37 (1.19-4.68)	0.014

N for adjusted model = 741. Multinomial logistic regression. BMI – Body mass index, RRR (Relative Risk Ratio), CI (Confidence intervals), Adj (Adjusted).
**Adjusted for maternal age, education, ethnicity, marital status, infant sex, maternal smoking before and during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5,6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5,6

	#6b	For matched studies, give matching criteria and number of exposed and unexposed	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7,8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6,7,8
Bias	#9	Describe any efforts to address potential sources of bias	9
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6,7,88
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7,8
	#12b	Describe any methods used to examine subgroups and interactions	
	#12c	Explain how missing data were addressed	
	#12d	If applicable, explain how loss to follow-up was addressed	
	#12e	Describe any sensitivity analyses	
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6,7,8
	#13b	Give reasons for non-participation at each stage	
	#13c	Consider use of a flow diagram	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	8,8,10

		confounders. Give information separately for exposed and unexposed groups if applicable.	
	#14b	Indicate number of participants with missing data for each variable of interest	
	#14c	Summarise follow-up time (eg, average and total amount)	
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	8,9,10
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9,10
	#16b	Report category boundaries when continuous variables were categorized	
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	8
Key results	#18	Summarise key results with reference to study objectives	8,9,10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11,12,13
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11,12,13
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

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The association between Caesarean Section Delivery and Obesity in Childhood: A Longitudinal Cohort Study in the Republic of Ireland

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The association between Caesarean Section Delivery and Obesity in Childhood: A Longitudinal Cohort Study in the Republic of Ireland

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Abstract

Objectives To investigate the association between Caesarean section (CS) birth and body fat percentage (BF%), body mass index (BMI) and being overweight or obese in early childhood.

Design Prospective longitudinal cohort study.

Setting Babies After Screening for Pregnancy Endpoints: Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints (BASELINE) cohort.

Participants Infants born to mothers recruited from the Screening for Pregnancy Endpoints (SCOPE) study, Cork University Maternity Hospital between November 2007 and February 2011.

Outcome measure Overweight or obese defined according to the International Obesity Task Force criteria.

Results Of the 1305 infants, 362 (27.8%) were delivered by CS. On regression analysis, BF% at two months did not differ significantly by delivery mode. Infants born by CS had a higher mean BMI at six months compared with those born vaginally (adjusted mean difference=0.24; [95% confidence interval (CI) 0.06-0.41], p-value = 0.009). At two years no difference was seen across the exposure groups in the risk of being overweight or obese. At five years, the association between pre-labour CS and the risk of overweight or obesity was not statistically significant (adjusted relative risk ratio (aRRR) =1.37; [95% CI 0.69-2.69]) and the association remained statistically non-significant when children who were macrosomic at birth were excluded from the model (aRRR=0.86; [95% CI 0.36-2.08]).

Conclusion At six months of age children born by CS had a significantly higher BMI but this did not persist into future childhood. There was no evidence to support an association between mode of delivery and long term risk of obesity in the child.

Key words

Caesarean section; body composition; body fat; obesity; childhood; Ireland

Article summary

Strengths and limitations of this study

- Data was obtained from a well phenotyped contemporary prospective longitudinal cohort study.
- Body fat percentage was measured by air displacement plethysmography which is regarded as the gold standard method.
- A limitation was the unavailability of maternal pre-pregnancy body mass index.
- The number of overweight and obesity cases at two and five years of age was limited.

Introduction

Over recent decades Caesarean section (CS) rates have risen considerably worldwide and in some countries rates now exceed 50%.[1] The aetiology of the global CS rate increase is multifactorial and includes a decline in vaginal births after Caesarean (VBAC), physician fear of litigation, maternal request, more multiple pregnancies resulting from greater assisted reproductive technology use and access to private health insurance.[2-7]

Although a timely CS can be both necessary and life-saving, for example, in cases of obstructed labor, transverse lie and fetal distress/compromise, it nevertheless conveys complications. For the mother, these include an increased length of hospital stay, infection and haemorrhage, as well as a higher risk of respiratory complications in the infant and consequent admission to the neonatal intensive care unit.[8]

Birth weight is the most commonly used indicator of *in utero* growth, however, body composition at birth, the relative proportion of fat and fat-free mass, can provide a more accurate picture.[9] We have shown retrospectively that neonatal body fat percentage is more closely linked to risk of CS than birth weight.[10] Therefore conversely changes in body fat percentage could be an early and more sensitive indicator of future health. It has been hypothesized that the described association between abnormal birth weight and future cardio-metabolic disease[11] across the life course, can be more closely attributed to differences in early life body composition than to birth weight differences.[9]

CS itself has been consistently associated with an increased risk of obesity later in life, although studies have been inconclusive.[12-14] It is also unclear whether this increased risk pertains to elective/prelabour CS or emergency CS/CS in labour. Making this distinction is challenging because of limited literature so much so that the latest systematic review and meta-analysis on the topic (2018) performed an analysis including all CS and did not

differentiate.[15] Several research papers have been able to distinguish between elective and emergency CS but these have been limited by small sample sizes.[16-18] With CS in labour, membranes are more likely to have ruptured thereby exposing the infant to vaginal microflora.[19] However lack of exposure to the vaginal microflora among infants born by elective CS, where membranes are more likely to be intact, has been suggested as the main causal mechanism for the increased risk of obesity later in life.[20-22] Some have disputed this,[23] [24] nevertheless robust data from animal experiments demonstrates a potential causal role for CS delivery in the development of childhood obesity.[25]

Given the worldwide increase in non-medically indicated prelabour CS[8], this type of CS represents a potentially modifiable risk factor for childhood obesity. The aim of this study was to investigate the relationship between CS delivery, particularly prelabour CS, and childhood body composition and growth, using a well phenotyped prospective longitudinal birth cohort with detailed clinical phenotyping of both mothers and their children. We wanted, in particular, to examine the potential confounding effect of macrosomia, as this is both a risk factor for CS, and for long term obesity.

Methods

Data source and population sampled

Data was obtained from the Irish cohort of the prospective Screening for Pregnancy Endpoints (SCOPE) study of 'low risk' nulliparous women with singleton pregnancies (ACTRN12607000551493, www.scopestudy.net/) and its follow-up prospective Irish birth cohort, the Babies After SCOPE: Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints (BASELINE) study (NCT01498965, www.baselinestudy.net/).

The SCOPE and BASELINE study methodology are reported in detail elsewhere.[26 27] Briefly, the aim of the SCOPE study was to develop screening approaches, clinical and molecular, to predict fetal growth restriction, pre-eclampsia, and spontaneous preterm birth in healthy nulliparous women during early gestation. Exclusion criteria included: 1) considered to be at high risk of fetal growth restriction, pre-eclampsia, or spontaneous preterm birth due to underlying medical conditions (chronic hypertension, diabetes, renal disease, systemic lupus erythematosus, anti-phospholipid syndrome, sickle cell disease, HIV), previous cervical knife cone biopsy, ≥ 3 previous terminations or ≥ 3 miscarriages, current ruptured membranes; 2) had a major uterine anomaly, a known major fetal anomaly or abnormal karyotype; or 3) received an intervention that could modify pregnancy outcome (e.g. aspirin therapy, cervical suture).

In brief, the BASELINE cohort participant's mothers were recruited at 15 ±1 weeks of pregnancy from Cork University Maternity Hospital between November 2007 and February 2011. Of the 2579 women approached to participate, 1774 (69%) gave their written informed consent. From those, 1537 (87%) had infants recruited into the BASELINE study. The socio-demographic, lifestyle and physical measurements were collected by trained research midwives. A complete audit trial was available for the data that was entered into a centrally accessed internet database (MedSciNet AB, Stockholm, Sweden).

Exposure and outcome ascertainment

Delivery mode was grouped into four categories, namely unassisted vaginal delivery (VD), operative VD, prelabour lower segment (LS) CS and LSCS in labour. Operative VD constituted delivery by either vacuum extraction or forceps.

Whole body density was calculated from naked weight measured by an electronic scale (seca 384; seca, Birmingham, UK) to the nearest gram divided by body volume estimated by the

PEA POD air displacement plethysmography system (COSMED, Concord, California, USA) within the first four days of life and also at age two months. The PEA POD agrees highly with the gold standard four-compartment model and is non-invasive, fast and safe.[10 28 29] Based on body density and a two-compartment model of body composition (fat and fat-free mass), using values established by Fomon[28], body fat percentage (BF%), the primary outcome, was calculated as [(Fat mass (kg)/body mass (kg))×100].

The child's height and weight were measured by a trained interviewer using standardised protocols and medically approved instruments. At birth, two months, six months, one year, two years and five years of age, body mass index (BMI) in kg/m^2 was calculated for each child. At age two and five years, BMI was classified as thin, normal, overweight or obese, according to the International Obesity Task Force (IOTF) criteria.[30 31] The IOTF classification begins at age two years.

The following potential confounders as reported in the literature[12-14 32 33] were included *a priori*: maternal age, education, ethnicity, marital status, infant sex, maternal smoking during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia. For instance smoking cigarettes is a potential confounder because it is a risk factor for both CS birth[34] and for childhood obesity.[35]

Statistical analysis

Stata version 14SE (StataCorp LP College Station, TX) was used for statistical analysis. Categorical variables were described using frequency (n) and percent (%). Numeric variables were described using the mean (standard deviation-SD) or median (interquartile range-IQR). Crude and adjusted linear regression models were used to examine the association between mode of delivery and BF%. Linear regression models were also used to evaluate the association between delivery mode and BMI as a continuous measure.

Crude and adjusted multinomial logistic regression models were used to examine the association between mode of delivery and the risk of being overweight or obese. Adjusted mean differences and adjusted relative risk ratios (aRRR), for the linear and multinomial logistic regression models respectively, were calculated with 95% confidence intervals (CIs). Unassisted VD was the reference category and normal BMI was the base outcome for the multinomial logistic regression models. Models were stratified by whether infants were macrosomic or not which was defined as a birth weight > 4000g or ≤ 4000g respectively. We also explored interaction by infant sex. Statistical significance was defined as a p-value < 0.05.

Patient involvement

Participants were not involved in establishing the research question, outcome measures including the study design and interpretation or writing of this paper. The results will be disseminated via the study website, social media, information evenings and by newsletter.

Results

Of the 1305 infants, 943 (72.3%) were delivered vaginally. The remainder of the deliveries (27.8%) were by CS; prelabour LSCS (12.0%) and LSCS in labour (15.8%) respectively (Table 1). At birth, 13.0% of infants were macrosomic (> 4000g); 11.0% were large for gestational age (> 90th percentile for customised birth weight centiles). At two years of age, 116 (10.9%) children were overweight or obese (using IOTF cut-offs). At age five, the respective number was 118 (14.5%). At age two months, the mean (SD) BF% was calculated at 21.8% (±4.3%). BF% approximated to the normal distribution.

The average BMI, by the four birth modes, at each of the six time points is depicted by Figure 1 and for all vaginal and CS births by Figure 2. The maximum divergence in BMI by delivery mode occurred at six months of age. At six months, the mean BMI of infants delivered vaginally and those born by CS was 17.3 kg/m^2 and 17.6 kg/m^2 respectively.

Across delivery mode missing data was distributed equally for the primary and secondary outcomes, BF% and BMI respectively. Thus missing data was unlikely to have affected the results or conclusions (Supplementary Table 1).

Mode of delivery and body fat percentage at age two months

At two months' age there was no association between prelabour CS and BF% (adjusted BF% mean difference=0.46; [95% CI -0.46-1.40]) and LSCS in labour (adjusted BF% mean difference=0.07; [95% CI -0.88-0.73]) in comparison to the reference group of children delivered by unassisted VD (Table 2).

Mode of delivery and body mass index at age six months, two years and five years

Infants born by CS had a significantly higher mean BMI at six months compared with those born vaginally, adjusted BMI mean difference=0.24; [95% CI 0.06-0.41], p-value = 0.009. Limiting analysis to non macrosomic infants resulted in an adjusted BMI mean difference=0.26; [95% CI 0.07-0.45], p-value = 0.008.

There was, however, no statistically significant differential effect by sex (p-value for the interaction term was 0.70) – Supplementary Figure 1).

There was no statistically significant association between prelabour CS (aRRR=1.38; [95% CI 0.73-2.62]) or LSCS in labour (aRRR=0.88; [95% CI 0.48-1.61]) and the risk of being

overweight or obese at age two years, as compared to the reference group (Table 3). Limiting analysis to non-macrosomic infants at age two resulted in the association between prelabour CS and the risk of overweight and obesity being (aRRR=0.95; [95% CI 0.44-2.05]) and for LSCS in labour (aRRR=0.89; [95% CI 0.44-1.82]) (Supplementary Table 2).

At age five years, there was a non-significant association between prelabour CS and the risk of being overweight or obese (aRRR=1.37; [95% CI 0.69-2.69]) (Table 4). There was also no association between LSCS in labour and the risk of being overweight or obese (aRRR=1.69; [95% CI 0.92-3.08]). Limiting analysis to non-macrosomic infants at age five resulted in the association between prelabour CS and the risk of overweight and obesity being (aRRR=0.86; [95% CI 0.36-2.08]) and for LSCS in labour (aRRR=2.37; [95% CI 1.19-4.68]) (Supplementary Table 3).

Discussion

Main findings

There was no significant difference in BF% at age two months between modes of delivery. A statistically significant difference in BMI at age six months was observed between infants born by CS and VD. Infants born by CS had a higher mean BMI. There was no evidence to support a link between prelabour CS and our secondary outcome, being overweight or obese, at two and five years of age.

Strengths and limitations

A major strength was the availability of data from a well phenotyped prospective longitudinal cohort that is among those with the most data available for BF%. This allowed us to investigate the role of factors such as cigarette smoking prior to conception, which is often not available from prior or extant cohorts. In addition, we used robust measures of body composition obtained by air displacement plethysmography, which is regarded as the gold standard method.

A homogenous sample where 98% of the cohort's participants were Caucasian, primiparous and 'low risk'[27] could limit the generalizability of these findings to heterogeneous populations. However, the cohort reflected the Republic of Ireland's demographics of reproductive age women (15-49 years), where 93% are Caucasian women.[36] The variable pre-pregnancy BMI was unavailable; this variable attenuated effect size estimates towards the null[12] in previous studies. Body mass index at 15 weeks' gestation, a good proxy for pre-pregnancy BMI, was used because 15 weeks is prior to the occurrence of most weight gain in pregnancy. It has been suggested that any association between CS birth and childhood obesity is due to antibiotics administered during CS, with CS delivery serving as a proxy, nonetheless this proposition has not been supported by evidence.[37 38] The major limitation was the low number of cases at two and five years of age.

Interpretation

The relationship between CS delivery and offspring being overweight or obese has been explored by several systematic reviews and meta-analyses.[12 14 15 39] A positive association was the most common finding. Our findings are similar to those of infants, born in 2010, from a Danish prospective cohort study which found that the largest BMI difference by delivery mode, from birth to five years of age, occurred at six months' age and that this difference did

not track into later childhood at age five.[38] In addition, similar to this study, no significant difference in BF% by delivery mode, was found. It is worth highlighting that the first two years of life have been identified as a critical developmental window during which perturbations in growth and development are more likely to result in lifelong sequelae.[40] This Danish study, like ours and also as reported by the systematic reviews and meta-analyses[13 32], did not find a sex-specific growth pattern by mode of birth. This suggests that in humans CS birth might not influence sex-specific growth patterns as has been observed in mouse studies.[25]

Childhood fat mass index data from a Brazilian longitudinal cohort also showed no significant difference between children born by CS and VD at six years of age.[41] The declining influence of CS birth on the risk of obesity as children grow older has been attributed to the increasing influence of other risk factors for obesity like physical inactivity, family dietary habits, watching television (and the use of other electronic devices).[42] Indeed a study which utilized a sibling-pair design attributed the observed association between CS birth and childhood obesity to unmeasured confounding.[43]

Our results are dissimilar to those of children from a Boston, US cohort study which found a positive association between delivery mode and being overweight or obese at age five.[37] The Boston study, unlike ours, did not sub classify CS births into elective and emergency for example, and unusually there were more girls delivered by CS,[44] this might indicate reduced external validity for the US study.

A few studies have been able to differentiate between elective/prelabour CS and emergency/ LSCS in labour and they have been limited by small sample sizes.[16 17] However a higher risk of childhood obesity for infants born by emergency CS than elective CS was reported.[17] Us

finding an association at age five between LSCS in labour, when membranes are more likely to have ruptured, and being overweight or obese, but not with prelabour CS suggests an attenuated role for vaginal flora in the genesis of children being overweight or obese. A possible explanation for the LSCS in labour association is confounding by the indications for CS. The exact indications for CS were not available for this cohort. However, a divergent BMI trajectory in mid-infancy which then converges by age five between VD and CS babies may suggest a transient role for the vaginal microflora. Further exploration, around mid-infancy, of the association between CS birth and BMI is required.

The CS rate of 27.8% in this cohort, is consistent with published national estimates of 27.1% to 28.6% that prevailed during the study's recruitment period from 2007 to 2011.[45] This suggests the generalizability of findings to the Irish population, particularly 'low risk' first time mothers. A macrosomia (> 4000g) prevalence of 13.0% is almost double that of another high income country, the US at 7.5% during a similar time period, and suggests high baseline Irish rates of excess adiposity.[46] The general Irish population had at age three and five years a prevalence of 24% and 20% respectively for obesity and being overweight[47] which is higher than that observed in this cohort. This cohort's low risk population likely explains its lower prevalence of being overweight or obese compared to the general Irish population.

Conclusion

We have found no evidence to support a relationship between prelabour CS and offspring being overweight or obese in early childhood. No significant differences in outcome at two months and two years, and an increased risk of being overweight or obese in children born by

CS in labour, but not prelabour CS at five years, suggests that the previously hypothesized causal effects due to vaginal microflora are also unlikely at least in the long term.

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Author contributions

GM, FPM, PB, LCK, SM, DM, JH, AK conceived and designed the study. GM and ASK analysed the data and all authors interpreted the results. GM wrote the first draft of the article and FPM, FPM, PB, LCK, SM, DM, JH, AK revised it critically for important intellectual content. All authors approved the final version and agree to be accountable for all aspects of the work.

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Competing interests

No, there are no competing interests for any author.

Participant consent

Obtained.

Ethics approval

Clinical Research Ethics Committee of the Cork Teaching Hospitals (Ref: ECM5 (9) 01/07/2008.

Data sharing statement

Data may be accessed by request from the Babies After SCOPE: Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints (BASELINE) study. Contact details are available on the study website http://www.baselinestudy.net/.

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Table 1. Characteristics of the study population at two months.

Characteristic	Overall n (%)	Unassisted vaginal n (%)	Operative vaginal [a] n (%)	Prelabour LSCS n (%)	LSCS in labour n (%)
N	1305 (100)	470 (36.0)	473 (36.2)	156 (12.0)	206 (15.8)
Maternal age (years), median IQR	30 (28-33)	30 (27-32)	30 (28-33)	32 (29.5-34)	31 (29-33)
< 20	19 (1.5)	9 (1.9)	9 (1.9)	1 (0.6)	0 (0.0)
20-24	111 (8.5)	57 (12.1)	38 (8.0)	4 (2.6)	12 (5.8)
25-29	388 (29.7)	157 (33.4)	139 (29.4)	34 (21.8)	58 (28.2)
30-34	615 (47.1)	215 (45.7)	214 (45.2)	85 (54.5)	101 (49.0)
35-39	155 (11.9)	31 (6.6)	66 (14.0)	28 (17.9)	30 (14.6)
≥40	17 (1.3)	1 (0.2)	7 (1.5)	4 (2.6)	5 (2.4)
Ethnicity					
Caucasian	1,287 (98.6)	463 (98.1)	466 (98.5)	155 (99.4)	203 (98.5)
Other	18 (1.4)	7 (1.5)	7 (1.5)	1 (0.6)	3 (1.5)
Schooling (years primary and secondary), median IQR*	13 (13-14)	13 (13-14)	13 (13-14)	13 (13-14)	13 (13-14)
Marital status					
Single	123 (9.4)	52 (11.1)	49 (10.4)	11 (7.1)	11 (5.3)
Married	920 (70.5)	321 (68.3)	330 (69.8)	115 (73.7)	154 (74.8)
Stable relationship not married	261 (20.0)	97 (20.6)	94 (19.9)	29 (18.6)	41 (19.9)
Sex of baby					
Male	666 (51.0)	221 (47.0)	252 (53.3)	81 (51.9)	112 (54.4)
Female	639 (49.0)	249 (53.0)	221 (46.7)	75 (48.1)	94 (45.6)
Pre-eclampsia	48 (3.7)	17 (3.6)	7 (1.5)	16 (10.3)	9 (4.4)
Maternal BMI at 15 weeks (kg/m^2), median IQR	24.0 (22.1-26.9)	23.9 (21.5-26.4)	23.7 (22.1-26.7)	24.9 (22.3-28.7)	24.7 (23.0-27.9)
Gestational age (weeks), median IQR	40.3 (39.3-41.0)	40.3 (39.3-41.0)	40.6 (39.6-41.1)	39.3 (38.6-40.1)	40.6 (39.6-41.3)
Number of cigarettes per day at 15 weeks SCOPE visit, mean (±SD)	0.5 (±2.1)	0.7 (±2.4)	0.4 (±2.1)	0.5 (±2.3)	0.3 (±1.4)
Birth weight (g), median IQR	3460 (3160-3770)	3400 (3120-3690)	3510 (3200-3800)	3345 (2915-3670)	3650 (3300-4000)
Macrosomia (> 4000g)	169 (13.0)	32 (6.8)	65 (13.7)	21 (13.5)	51 (24.8)
Baby size according to customized centile					
SGA < 10th centile	135 (10.3)	59 (12.6)	40 (8.5)	22 (14.1)	14 (6.8)
AGA ≥ 10th centile ≤ 90th centile	1,027 (78.7)	383 (81.5)	374 (79.1)	110 (70.5)	160 (77.7)

LGA > 90th centile	143 (11.0)	28 (6.0)	59 (12.5)	24 (15.4)	32 (15.5)
Body composition (at two months)					
Body fat (%), mean SD	21.8 (±4.3)	21.8 (±4.3)	21.6 (±4.4)	22.3 (±4.6)	21.6 (±4.2)
missing	272 (20.8)	98 (20.9)	93 (19.7)	39 (25.0)	42 (20.4)
Body mass index (kg/m^2) at 2 years**					
Thin	77 (5.9)	28 (6.0)	34 (7.2)	6 (3.8)	9 (4.4)
Normal	812 (62.2)	289 (61.5)	286 (60.5)	101 (64.7)	136 (66.0)
Overweight	96 (7.4)	29 (6.2)	39 (8.2)	12 (7.7)	16 (7.8)
Obese	10 (0.8)	4 (0.9)	2 (0.4)	3 (1.9)	1 (0.5)
Missing	310 (23.8)	120 (25.5)	112 (23.7)	34 (21.8)	44 (21.4)
Body mass index (kg/m^2) at 5 years**					
Thin	38 (2.9)	13 (2.8)	17 (3.6)	3 (1.9)	5 (2.4)
Normal	656 (50.3)	236 (50.2)	232 (49.0)	83 (53.2)	105 (51.0)
Overweight	97 (7.4)	22 (4.7)	42 (8.9)	12 (7.7)	21 (10.2)
Obese	21 (1.6)	10 (2.1)	6 (1.3)	3 (1.9)	2 (1.0)
Missing	493 (37.8)	189 (40.2)	176 (37.2)	55 (35.3)	73 (35.4)

LSCS (Lower segment Cesarean section), SD (Standard deviation), IQR (Interquartile range), SGA (Small for gestational age), AGA (Appropriate for gestational age), LGA (Large for gestational age).

[a] Vacuum or forceps

* Total years of schooling (primary and secondary, not pre-school or tertiary)

** International Obesity Task Force age and sex-specific cut-offs

Table 2. Mode of delivery and body fat percent at age two months.

Delivery mode	Cases n	Coef. (95% CI)	p-value	AdjCoef. (95% CI)**	p-value
Unassisted vaginal	372	reference		reference	
Operative vaginal	380	-0.16 (-0.78-0.46)	0.614	-0.10 (-0.72-0.52)	0.743
Prelabour LSCS	117	0.50 (-0.40-1.40)	0.278	0.46 (-0.46-1.40)	0.325
LSCS in labour	164	-0.19 (-0.9-0.61)	0.642	0.07 (-0.88-0.73)	0.864

N for adjusted model = 1,033. Linear regression. BMI – Body mass index, Coef. (β-Coefficient), CI (Confidence intervals), Adj (Adjusted).

**Adjusted for maternal age, education, ethnicity, marital status, infant sex, maternal smoking during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia

Table 3. Mode of delivery and body mass index at age two years.

BMI category (normal BMI – base outcome)	Cases n	RRR (95% CI)	p-value	AdjRRR (95% CI)**	p-value
Thin					
Unassisted vaginal	30	reference		reference	
Operative vaginal	37	1.23 (0.74-2.05)	0.417	1.42 (0.83-2.41)	0.199
Prelabour LSCS	6	0.59 (0.24-1.47)	0.259	0.65 (0.26-1.62)	0.352
LSCS in labour	9	0.65 (0.30-1.41)	0.279	0.86 (0.39-1.87)	0.696
Overweight or Obese					
Unassisted vaginal	37	reference		reference	
Operative vaginal	41	1.11 (0.69-1.78)	0.670	0.95 (0.58-1.56)	0.853
Prelabour LSCS	17	1.45 (0.79-2.65)	0.233	1.38 (0.73-2.62)	0.324
LSCS in labour	20	1.18 (0.66-2.10)	0.583	0.88 (0.48-1.61)	0.680

N for adjusted model = 1,062. Multinomial logistic regression. BMI – Body mass index, RRR (Relative Risk Ratio), CI (Confidence intervals), Adj (Adjusted).

**Adjusted for maternal age, education, ethnicity, marital status, infant sex, maternal smoking during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia

Table 4. Mode of delivery and body mass index at age five years.

BMI category (normal BMI – base outcome)	Cases n	RRR (95% CI)	p-value	AdjRRR (95% CI)**	p-value
Thin					
Unassisted vaginal	13	reference		reference	
Operative vaginal	18	1.45 (0.69-3.02)	0.324	1.82 (0.84-3.96)	0.131
Prelabour LSCS	3	0.68 (0.19-2.44)	0.553	0.46 (0.14-1.56)	0.212
LSCS in labour	5	0.86 (0.30-2.47)	0.777	1.06 (0.36-3.09)	0.915
Overweight or Obese					
Unassisted vaginal	36	reference		reference	
Operative vaginal	52	1.51 (0.95-2.40)	0.079	1.64 (1.00-2.67)	0.050
Prelabour LSCS	17	1.39 (0.74-2.60)	0.305	1.37 (0.69-2.69)	0.368
LSCS in labour	26	1.61 (0.93-2.80)	0.090	1.69 (0.92-3.08)	0.090

N for adjusted model = 856. Multinomial logistic regression. BMI – Body mass index, RRR (Relative Risk Ratio), CI (Confidence intervals), Adj (Adjusted).

**Adjusted for maternal age, education, ethnicity, marital status, infant sex, maternal smoking during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia

Figure 1. Mean body mass index (BMI) from birth to five years of age. Lower segment Caesarean section (LSCS). Please note that the time axis has been expanded below age one year to permit clearer visualisation.

Figure 2. Mean body mass index (BMI) from birth to five years of age with 95% confidence intervals (CIs) around the mean BMI – thin lines. There is no overlap of the 95% CIs at six months of age. Please note that the time axis has been expanded below age one year to allow clearer visualisation.

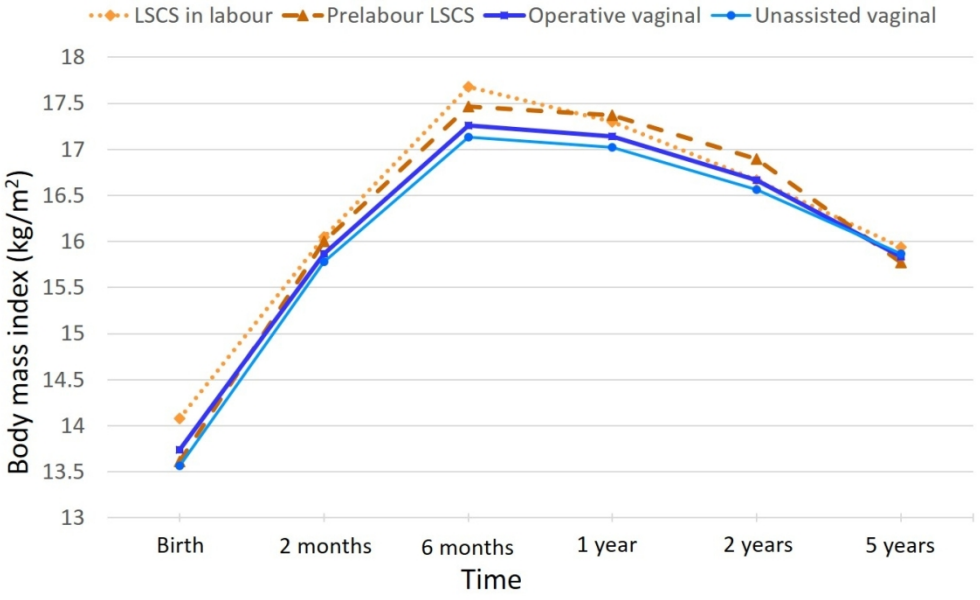

Figure 1. Mean body mass index (BMI) from birth to five years of age. Lower segment Caesarean section (LSCS). Please note that the time axis has been expanded below age one year to permit clearer visualisation.

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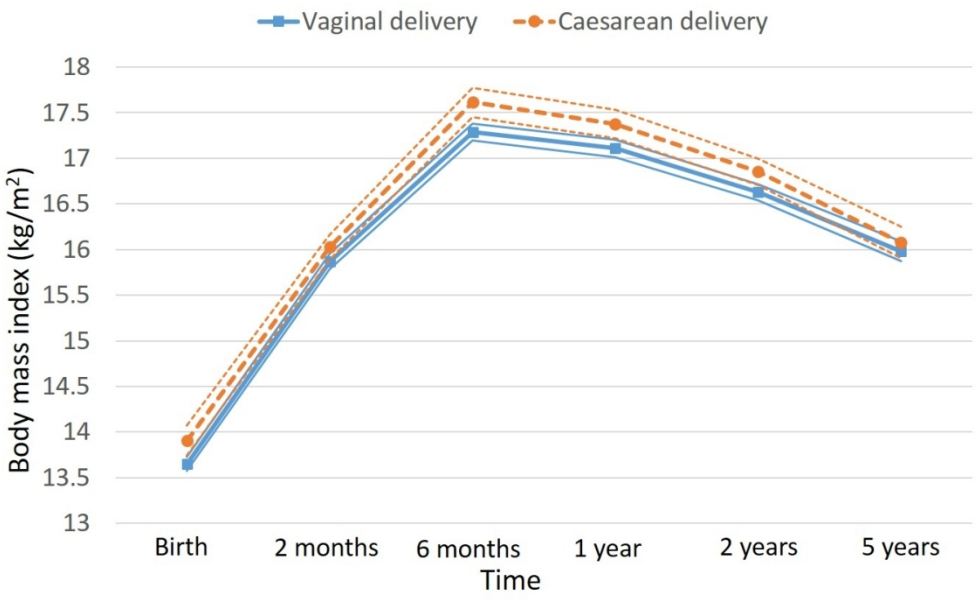

Figure 2. Mean body mass index (BMI) from birth to five years of age with 95% confidence intervals (CIs) around the mean BMI – thin lines. There is no overlap of the 95% CIs at six months of age. Please note that the time axis has been expanded below age one year to allow clearer visualisation.

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Supplementary information

The association between Caesarean Section Delivery and Obesity in Childhood: A Longitudinal Cohort Study in the Republic of Ireland

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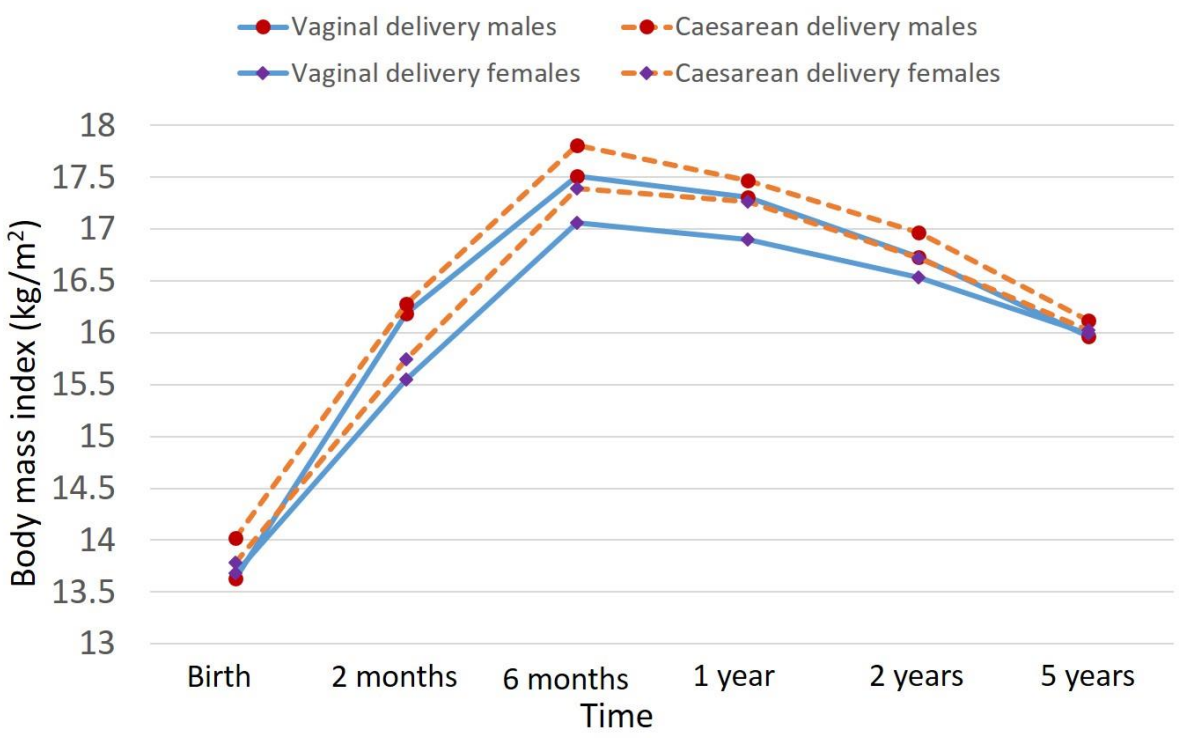

Supplementary Figure 1. Mean body mass index (BMI) from birth to five years of age by delivery mode and sex. Please note that the time axis has been expanded below age one year to allow clearer visualisation.

Supplementary Table 1. Missing data for body fat % at age two months.

Characteristic	Body fat % data available at age two months (n %) n=1033	Body fat % data missing at two age months (n %) n=272	p-value[a]
Maternal age (years), median IQR	31 (28-33)	30 (28-33)	0.6021
Ethnicity[b]			0.558
Caucasian	1018 (98.5)	269 (98.9)	
Other	15 (1.5)	3 (1.1)	
Schooling (years primary and secondary), median IQR	13 (13-14)	13 (13-14)	0.5227
Marital status[b]			0.879
Single	100 (9.7)	23 (8.5)	
Married	725 (70.2)	195 (71.7)	
Stable relationship not married	207 (20.0)	54 (19.9)	
Sex of baby[b]			0.081
Male	540 (52.3)	126 (46.3)	
Female	493 (47.7)	146 (53.7)	
Pre-eclampsia[b]	40 (3.9)	9 (3.3)	0.664
Maternal BMI at 15 weeks (kg/m^2), median IQR	24.1 (22.1-26.9)	23.7 (22.0-26.7)	0.2455
Gestational age (weeks), median IQR	40 (39-41)	40 (39-41)	0.4624
Number of cigarettes per day at 15 weeks SCOPE visit, mean (±SD)[c]	0.5 (±2.2)	0.4 (±2.0)	0.2517
Birth weight (g), median IQR	3460 (3150-3770)	3475 (3160-3750)	0.9099

IQR – Interquartile range, BMI – Body mass index, SD – standard deviation, SCOPE – Screening for pregnancy endpoints.

[a] Mann-Whitney test

[b] Pearson's χ^2 test or Fisher's exact

[c] Two-sample t test

Supplementary Table 2. Mode of delivery and body mass index at age two years. Non-marosomic.

BMI category (normal BMI – base outcome)	**RRR (95% CI)**	**p-value**	**AdjRRR (95% CI)****	**p-value**
Thin				
Unassisted vaginal	reference		reference	
Operative vaginal	1.41 (0.84-2.36)	0.188	1.51 (0.89-2.58)	0.130
Prelabour LSCS	0.26 (0.24-1.62)	0.357	0.67 (0.27-1.68)	0.398
LSCS in labour	0.73 (0.32-1.64)	0.443	0.83 (0.37-1.90)	0.664
Overweight or Obese				
Unassisted vaginal	reference		reference	
Operative vaginal	0.98 (0.58-1.64)	0.929	0.93 (0.54-1.59)	0.789
Prelabour LSCS	0.93 (0.44-1.95)	0.842	0.95 (0.44-2.05)	0.891
LSCS in labour	1.01 (0.51-1.98)	0.982	0.89 (0.44-1.82)	0.747

N for adjusted model = 921. Multinomial logistic regression. BMI – Body mass index, RRR (Relative Risk Ratio), CI (Confidence intervals), Adj (Adjusted).
**Adjusted for maternal age, education, ethnicity, marital status, infant sex, maternal smoking during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia

Supplementary Table 3. Mode of delivery and body mass index at age five years. Non-macrosomic.

BMI category (normal BMI – base outcome)	**RRR (95% CI)**	**p-value**	**AdjRRR (95% CI)****	**p-value**
Thin				
Unassisted vaginal	reference		reference	
Operative vaginal	1.59 (0.76-3.32)	0.221	1.85 (0.85-4.04)	0.120
Prelabour LSCS	0.73 (0.20-2.63)	0.629	0.46 (0.14-1.55)	0.209
LSCS in labour	1.09 (0.38-3.14)	0.880	1.14 (0.39-3.34)	0.815
Overweight or Obese				
Unassisted vaginal	reference		reference	
Operative vaginal	1.43 (0.87-2.36)	0.161	1.77 (1.03-3.04)	0.038
Prelabour LSCS	0.89 (0.41-1.95)	0.768	0.86 (0.36-2.08)	0.750
LSCS in labour	1.59 (0.85-2.98)	0.150	2.37 (1.19-4.68)	0.014

N for adjusted model = 741. Multinomial logistic regression. BMI – Body mass index, RRR (Relative Risk Ratio), CI (Confidence intervals), Adj (Adjusted).
**Adjusted for maternal age, education, ethnicity, marital status, infant sex, maternal smoking during pregnancy, maternal BMI at the first antenatal visit, gestational age (at delivery), birth weight and pre-eclampsia

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5,6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5,6

	#6b	For matched studies, give matching criteria and number of exposed and unexposed	
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7,8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6,7,8
Bias	#9	Describe any efforts to address potential sources of bias	9
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6,7,88
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7,8
	#12b	Describe any methods used to examine subgroups and interactions	
	#12c	Explain how missing data were addressed	
	#12d	If applicable, explain how loss to follow-up was addressed	
	#12e	Describe any sensitivity analyses	
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6,7,8
	#13b	Give reasons for non-participation at each stage	
	#13c	Consider use of a flow diagram	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	8,8,10

		confounders. Give information separately for exposed and unexposed groups if applicable.	
	#14b	Indicate number of participants with missing data for each variable of interest	
	#14c	Summarise follow-up time (eg, average and total amount)	
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	8,9,10
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9,10
	#16b	Report category boundaries when continuous variables were categorized	
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	8
Key results	#18	Summarise key results with reference to study objectives	8,9,10
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11,12,13
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11,12,13
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14