

ELECTIVE CAESAREAN SECTION IN LOW-RISK WOMEN AT TERM: CONSEQUENCES FOR MOTHER AND OFFSPRING SUPPLEMENT



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COLOPHON

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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
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- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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■ SUPPLEMENT

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1. CAESAREAN SECTION RATES WORLDWIDE

1.1. Caesarean section rates in 2010 in 31 high-income countries

Table 1 – Caesarean section rates in 2010 in 31 high-income countries

Country	CS %	Mean maternal age	Gender ratio (M/F)	Mult. Pregnancy (/1000)	GDP per capita (US \$)	Gini index *	Preterm birth (%)	Infant mortality (/1000 live births)
Australia	31.5	30.7	1.06	15.6	51746	0.34	7.6	4.2
Austria	28.3	29.8	1.05	17.2	44723	0.26	10.9	3.5
Belgium	19.9	29.8	1.05	20	42960	0.26	7.9	3.5
Canada	27.8	29.6	1.05	16.8	46212	0.32	7.8	4.9
Czech Rep.	24.1	29.6	1.06	21	18867	0.26	7.3	3.4
Denmark	21	30.6	1.06	20.9	56486	0.25	6.7	3.3
Estonia	20.3	29.2	1.06	14.7	14110	0.32	5.7	3.5
Finland	16.1	30.2	1.04	15.3	43846	0.26	5.5	2.6
France	21	30	1.05	17.4	39186	0.29	6.7	3.5
Germany	32.1	30.4	1.06	18.5	40145	0.3	9.2	3.5
Greece	50	30.3	1.07	N/A	25851	0.31	6.6	4
Hungary	32.8	29.3	1.06	N/A	12750	0.27	8.6	5.6
Iceland	16.6	30	1.05	14.3	39507	0.3	6.5	1.9
Ireland	26.3	31.4	1.07	16.8	46492	0.29	6.4	3.5
Israel	19.9	30.1	1.05	N/A	30389	0.37	8	3.6
Italy	38.5	31.3	1.06	15	33761	0.34	6.5	3.4
Japan	23.3	31.2	1.06	N/A	43118	0.33	5.9	2.4
Korea Rep.	35.2	31.26	1.07	27.4	20540	0.32	9.2	3.5
Luxembourg	25.7	30.8	1.05	18.3	102009	0.29	8.1	2
Netherlands	15.6	30.8	1.06	17.7	46468	0.29	8	3.7
New Zealand	23.6	28.8	1.06	17	32796	0.33	7.6	4.9
Norway	17.1	30.1	1.06	16.4	86156	0.25	6	2.5
Poland	33.7	28.8	1.06	13.4	12302	0.31	6.7	5.1
Portugal	35.8	29.8	1.06	15.1	21382	0.35	7.7	3.1
Slovakia	28.7	28.6	1.05	14.5	16036	0.26	6.3	6.8
Slovenia	18.2	30.1	1.05	18.5	22898	0.24	7.5	2.8
Spain	25.3	31.2	1.06	20.2	29863	0.32	7.4	4
Sweden	16.9	30.7	1.06	14	49360	0.26	5.9	2.4
Switzerland	32.8	31.2	1.05	18.4	70370	0.3	7.4	3.8
UK	23.8	29.5	1.05	15.5	36703	0.34	7.8	4.4
United States	32.8	28	1.05	16.5	48358	0.38	12	6.3

Source: Xie et al. (2015).¹ * The Gini index measures the extent to which the distribution of income among individuals or households within an economy deviates from a perfectly equal distribution. Thus a Gini index of 0 represents perfect equality, while an index of 100 implies perfect inequality.



1.2. Caesarean section trend data between 1987 and 2007 worldwide

Table 2 – Trend data for CS rates between 1987 and 2007 (number of CS in percentage of live births)

Country	1987	1992	1997	2002	2007	Change 1992-2007
Australia	—	18.2	20.1	26.8	30.6	68.1
Austria	—	—	14	20.6	27.2	119.4
Belgium	9.6	12	14.5	17.4	17.3	44.2
Canada	19.6	17.7	18.4	23.4	26.6	50.3
Czech Republic	7	8.8	11.8	14.1	19.6	122.7
Denmark	12.9	12.2	13.7	18.3	21.4	75.4
Finland	14.3	14.5	15.5	16.4	16.3	12.4
France	—	14.5	16	18.7	19.9	37.2
Germany	—	15.9	18.1	23.7	28.4	78.6
Hungary	—	—	15.7	23.2	28.1	106.6
Ireland	8.9	12	15.3	22.5	26.6	121.7
Italy	17.5	23.2	27	36.2	39.8	71.6
The Netherlands	—	8.2	10.4	13.5	13.9	69.5
New Zealand	—	12.5	16.5	22.2	22.8	82.4
Norway	12.9	12.6	12.9	16.1	16.9	34.1
Portugal	13.2	21.8	27.4	30.2	—	59.2c
Slovak Republic	7.3	9.9	13	17.7	22.3	125.3
Spain	12.2	16.2	19.8	23.4	25.3	56.2
Sweden	10.8	10.7	12.5	15.6	17.6	64.4

Source: Declercq et al. (2011).²



2. SEARCH STRATEGIES

2.1. MEDLINE(R)

Date	2016-02-02		
Database segments	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Ovid MEDLINE(R) Daily Update <January 29, 2016>		
Search strategy	#	Query	Results
	1	c?esar#?n.ab,ti.	47183
	2	c-section?.ab,ti.	756
	3	abdominal delivery.ab,ti.	366
	4	abdominal deliveries.ab,ti.	79
	5	1 or 2 or 3 or 4	47778
	6	exp cesarean section/	37499
	7	5 or 6	59110
	8	exp elective surgical procedures/	9597
	9	elective.ab,ti.	58454
	10	((maternal or mother or patient?) adj3 request).ab,ti.	1975
	11	((without or non or non-medical or no) adj3 (reason? or indication?)).ab,ti.	19893
	12	(non-indicated or nonindicated).ab,ti.	124
	13	8 or 9 or 10 or 11 or 12	82226
	14	7 and 13	6968
	15	limit 14 to yr="2011 -Current"	1848
	16	remove duplicates from 15	1838
	17	limit 16 to animals	24
	18	limit 16 to humans	1396
	19	16 not (17 not 18)	1827
	20	limit 19 to systematic reviews	77



2.2. Cochrane Database

The Cochrane database has been searched on 2nd February 2016 using the same query as on Medline with adapted syntax to Wiley interface. The retrieved results were 40 for Cochrane database of systematic reviews, 558 for CENTRAL, 5 for Database of Articles of Relative Effectiveness (DARE) and 4 for NHS Economic Evaluations Database.

2.3. Embase

Date	2016-02-01		
Database	Embase		
	#	Query	Results
Search strategy	1	cesarian:ab,ti OR caesarian:ab,ti OR cesarean:ab,ti OR caesarean:ab,ti OR caesaran:ab,ti OR cesaran:ab,ti	64114
	2	'c section':ab,ti	1993
	3	'abdominal delivery':ab,ti	447
	4	'abdominal deliveries':ab,ti	97
	5	#1 OR #2 OR #3 OR #4	65675
	6	'cesarean section'/exp	71547
	7	#5 OR #6	86368
	8	'elective surgical procedures'/exp	23623
	9	elective:ab,ti	82301
	10	((maternal OR mother* OR patient*) NEXT/3 request*):ab,ti	6130
	11	((without OR non OR 'non medical' OR no) NEXT/3 (reason* OR indication*)):ab,ti	22750
	12	'non indicated':ab,ti OR nonindicated:ab,ti	214
	13	#8 OR #9 OR #10 OR #11 OR #12	116414
	14	#7 AND #13	10624
	15	#14 AND [2011-2016]/py	4139
	16	#15 NOT [medline]/lim	2678
	17	#16 AND ('meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review' OR 'guideline' OR 'practice guideline'/exp)	138



3. QUALITY APPRAISALS

3.1. Systematic reviews and meta-analyses

For the quality appraisal of systematic reviews and meta-analyses the AMSTAR instrument was used as described in the report. Studies are described in the alphabetical order of the first author.

Table 3 – Quality appraisal for systematic reviews and meta-analyses using the AMSTAR instrument

Azam 2014 ³	Score	Justification
1. Was an 'a priori' design provided	Yes	Protocol based on contemporary methods and reported in accordance with the PRISMA statement (but not reported in the paper)
2. Was there duplicate study selection and data extraction?	Yes	
3. Was a comprehensive literature search performed?	Yes	• Medline, Embase, PubMed, Cumulative Index to Nursing and Allied Health Literature and the Cochrane Library. • MeSH, keywords and word variants for women, pregnancy, mode of delivery and caesarean
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	No limit of language or publication date
5. Was a list of studies (included and excluded) provided?	No	No clear identification of excluded studies
6. Were the characteristics of the included studies provided?	Yes	Table 1
7. Was the scientific quality of the included studies assessed and documented?	Yes	Based on Newcastle-Ottawa Scale (NOS) for observational studies and the risk of bias tool for RCTs
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Subgroup analysis according to the level of evidence: evidence from RCT was analysed separately from observational evidence
9. Were the methods used to combine the findings of studies appropriate?	Yes	Random effects model was used for meta-analyses when heterogeneity was observed (tested graphically with forest plots and statistically using chi-square test and the I ² value) – these were not reported in the publication
10. Was the likelihood of publication bias assessed?	No	Funnel asymmetry was assessed to examine publication and related biases when there were sufficient studies (ccl: when assessable, funnel asymmetry was not evident.)
11. Was the conflict of interest included?	Yes	No conflict of interests
Total score	9/11	A protocol with a priori design was used but was not reported; no clear identification of excluded studies



Bager 2008 ⁴	Score	Justification
1. Was an 'a priori' design provided	Yes	
2. Was there duplicate study selection and data extraction?	Cannot answer	
3. Was a comprehensive literature search performed?	Yes	Medline through pubmed, Language selection not mentioned
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	
5. Was a list of studies (included and excluded) provided?	No	
6. Were the characteristics of the included studies provided?	Yes	Total of 26 studies: 23 cohort and 3 case control studies.
7. Was the scientific quality of the included studies assessed and documented?	Cannot answer	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Cannot answer	
9. Were the methods used to combine the findings of studies appropriate?	Yes	
10. Was the likelihood of publication bias assessed?	Yes	Through funnel plots
11. Was the conflict of interest included?	Yes	Supported by a grant from the Danish Medical Research Council, Danielsen's Foundation, Dagmar Marshall's Foundation and General Manager Bonnelycke and Wife's Foundation.
Total score	7/11	

Bruce 2014 ⁵	Score	Justification
1. Was an 'a priori' design provided	Yes	
2. Was there duplicate study selection and data extraction?	Yes	Plus confirmation by third author
3. Was a comprehensive literature search performed?	Yes	Embase, CINAHL and Medline from 1948 to present through OVID. No specific end-date mentioned. No date or language limits. Additional search through handsearching of reference lists.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	
5. Was a list of studies (included and excluded) provided?	No	7 included studies, no list of excluded studies;



6. Were the characteristics of the included studies provided?	Yes	Cohort or case-control studies
7. Was the scientific quality of the included studies assessed and documented?	Yes	Risk of bias within each study was assessed by applying the CASP quality assessment tool (Critical Appraisal Skills Program checklist for cohort and case-control studies).
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	
9. Were the methods used to combine the findings of studies appropriate?	Yes	Statistical analysis was carried out to perform a meta-analysis of the results using the software, Review Manager (version 5). For all studies, raw data was used to calculate unadjusted odds ratios and 95% confidence intervals for risk of developing IBD after CS delivery compared with vaginal birth. Sensitivity analyses were performed to assess the effect size and direction specific to individual study designs or method of data collection.
10. Was the likelihood of publication bias assessed?	Yes	A funnel plot (not shown) was created to assess publication bias within this review. The only potential bias identified was the lack of publication of small studies demonstrating a positive association. Because publication bias is more prevalent in studies with negative findings, we do not anticipate that publication bias would undermine our findings.
11. Was the conflict of interest included?	Yes	The authors have no conflicts of interest to disclose.
Total score	10/11	

Cardwell 2008 ⁶	Score	Justification
1. Was an 'a priori' design provided	Yes	
2. Was there duplicate study selection and data extraction?	Yes	
3. Was a comprehensive literature search performed?	Yes	Medline (through OVID), Web of Science and Embase.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	
5. Was a list of studies (included and excluded) provided?	Yes	21 identified articles and finally 16 retained, all referenced. The 16 articles corresponded to 20 independent studies.
6. Were the characteristics of the included studies provided?	Yes	Cohort (many registry studies) and case-control studies. Diagnosis between 0 up to 29 years of age.
7. Was the scientific quality of the included studies assessed and documented?	Yes	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	



9. Were the methods used to combine the findings of studies appropriate?	Yes	ORs and SEs were calculated for the association between diabetes and Caesarean section for each study. Conditional logistic regression was used to calculate the ORs and SEs for the matched case-control studies. In cohort studies with varying duration of participant follow-up, rate ratios and their SEs were used instead of ORs, which were not directly calculable. Poisson regression was used to adjust these rate ratios for differences in the year of birth between cases and controls, a consequence of this study design, by adding a year of birth and age term to the regression model in addition to Caesarean section. Tests for heterogeneity between studies were conducted, and random effects models used to calculate pooled ORs. Random effects models were deemed more appropriate than fixed effects models because it was anticipated that there would be between study heterogeneity due to their observational nature. The I^2 statistic was calculated to quantify the degree of heterogeneity between studies. Seventeen authors provided the raw independent patient data for this analysis.
10. Was the likelihood of publication bias assessed?	Yes	Publication/selection bias was investigated by checking for asymmetry in funnel plots of the study
11. Was the conflict of interest included?	Yes	No conflicts of interest declared.
Total score	11/11	

Carter 2006⁷	Score	Justification
1. Was an 'a priori' design provided	Yes	
2. Was there duplicate study selection and data extraction?	Cannot answer	
3. Was a comprehensive literature search performed?	Yes	Medline and Psychinfo, English only
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	
5. Was a list of studies (included and excluded) provided?	No	
6. Were the characteristics of the included studies provided?	Yes	
7. Was the scientific quality of the included studies assessed and documented?	Cannot answer	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Cannot answer	
9. Were the methods used to combine the findings of studies appropriate?	Yes	Two separate meta-analyses: 1) Studies using the EPDS 2) overall meta-analysis using different outcome measures.
10. Was the likelihood of publication bias assessed?	No	Not formally stated



11. Was the conflict of interest included?	No
Total score	5/11

Cho 2013⁸	Score	Justification
1. Was an 'a priori' design provided?	No	
2. Was there duplicate study selection and data extraction?	Cannot answer	
3. Was a comprehensive literature search performed?	No	MEDLINE with keywords and manual search from the references cited in relevant reviews, letters, and editorials.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	English only
5. Was a list of studies (included and excluded) provided?	No	No clear identification of excluded studies
6. Were the characteristics of the included studies provided?	No	
7. Was the scientific quality of the included studies assessed and documented?	No	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	
9. Were the methods used to combine the findings of studies appropriate?	Cannot answer	
10. Was the likelihood of publication bias assessed?	No	
11. Was the conflict of interest included?	Yes	None declared
Total score	1/11	

Cuppari 2015⁹	Score	Justification
1. Was an 'a priori' design provided	Cannot answer	Little info on methods
2. Was there duplicate study selection and data extraction?	Cannot answer	Little info on methods
3. Was a comprehensive literature search performed?	Yes	PubMed, EMBASE, Medline, and Cochrane Library
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Cannot answer	Little info on methods
5. Was a list of studies (included and excluded) provided?	No	None info about excluded studies



6. Were the characteristics of the included studies provided?	No
7. Was the scientific quality of the included studies assessed and documented?	No
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	NA
9. Were the methods used to combine the findings of studies appropriate?	NA
10. Was the likelihood of publication bias assessed?	No
11. Was the conflict of interest included?	No
Total score	1/11

Darmasseelane 2014 ¹⁰	Score	Justification
1. Was an 'a priori' design provided?	Yes	A priori protocol registered in PROSPERO (p2)
2. Was there duplicate study selection and data extraction?	Yes	
3. Was a comprehensive literature search performed?	Yes	PubMed, Google scholar, Web of Knowledge + Handsearch (p2)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	No limit of language, country, study type or publication period (p2)
5. Was a list of studies (included and excluded) provided?	No	No clear identification of excluded studies
6. Were the characteristics of the included studies provided?	Yes	Table 1
7. Was the scientific quality of the included studies assessed and documented?	Yes	Based on Newcastle-Ottawa Scale (NOS), scores based on population selection, study comparability and outcomes. (Table 1)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Sensitivity analysis of high quality studies (p4)
9. Were the methods used to combine the findings of studies appropriate?	Yes	
10. Was the likelihood of publication bias assessed?	Yes	Funnel plots and Egger's test (p4)
11. Was the conflict of interest included?	Yes	Competing interest: none (p1)
Total score	10/11	



Gurol-Urganci ¹¹	Score	Justification
1. Was an 'a priori' design provided	Yes	(p1944)
2. Was there duplicate study selection and data extraction?	Yes	
3. Was a comprehensive literature search performed?	Yes	Cochrane Library, Medline, Embase, CINAHL+ and Maternity and Infant Care databases
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	No limit of language or publication date
5. Was a list of studies (included and excluded) provided?	No	No clear identification of excluded studies
6. Were the characteristics of the included studies provided?	Yes	Table 1
7. Was the scientific quality of the included studies assessed and documented?	Yes	Based on Newcastle-Ottawa Scale (NOS),
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Subgroup analysis for studies with NOS>6
9. Were the methods used to combine the findings of studies appropriate?	Yes	
10. Was the likelihood of publication bias assessed?	No	
11. Was the conflict of interest included?	Yes	
Total score	9/11	But no clear identification of excluded studies and no assessment of publication bias

Huang 2015 ¹²	Score	Justification
1. Was an 'a priori' design provided?	Cannot answer	
2. Was there duplicate study selection and data extraction?	Yes	
3. Was a comprehensive literature search performed?	Yes	PUBMED, Google Scholar, EMBASE, and MEDLINE (p17)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	English language only
5. Was a list of studies (included and excluded) provided?	No	No clear identification of excluded studies
6. Were the characteristics of the included studies provided?	Yes	Table 1
7. Was the scientific quality of the included studies assessed and documented?	No	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	



Huang 2015 ¹²	Score	Justification
9. Were the methods used to combine the findings of studies appropriate?	Yes	
10. Was the likelihood of publication bias assessed?	Yes	Funnel plots and Begg's test
11. Was the conflict of interest included?	Yes	Source of funding quoted p23 in the subtitle 'declaration of interest'
Total score	6/11	No QA, no identification of excluded studies and inclusion of English language studies

Kuhle 2015 ¹³	Score	Justification
1. Was an 'a priori' design provided?	Cannot answer	
2. Was there duplicate study selection and data extraction?	Yes	
3. Was a comprehensive literature search performed?	Yes	Medline, Embase, Web of Knowledge + Handsearch (p295)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	All human observational studies (p296)
5. Was a list of studies (included and excluded) provided?	No	No clear identification of excluded studies
6. Were the characteristics of the included studies provided?	Yes	Table 1
7. Was the scientific quality of the included studies assessed and documented?	No	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Not applicable	
9. Were the methods used to combine the findings of studies appropriate?	Yes	
10. Was the likelihood of publication bias assessed?	Yes	Funnel plots and Egger's test (p300)
11. Was the conflict of interest included?	Yes	Competing interest: none (p302)
Total score	7/11	No QA and no identification of excluded studies



Lavender 2012 ¹⁴	Score	Justification
1. Was an 'a priori' design provided	No	
2. Was there duplicate study selection and data extraction?	Yes	- Three review authors independently assessed for inclusion all the potential studies. - A form to extract data was designed.
3. Was a comprehensive literature search performed?	Yes	Cochrane Pregnancy and Childbirth Group's Trials Register (CENTRAL, Medline, Embase, handsearches and alerts from BioMed Central) + search for further studies in the reference lists
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	No limit of language or publication date
5. Was a list of studies (included and excluded) provided?	Yes	Two studies were excluded; they were identified and their characteristics were reported. No studies were found for inclusion in this review.
6. Were the characteristics of the included studies provided?	NA	
7. Was the scientific quality of the included studies assessed and documented?	NA	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	NA	
9. Were the methods used to combine the findings of studies appropriate?	NA	
10. Was the likelihood of publication bias assessed?	No	
11. Was the conflict of interest included?	Yes	No conflict of interests
Total score	5/11	No RCTS were found by authors to be included in this review

Li 2013 ¹⁵	Score	Justification
1. Was an 'a priori' design provided	No	
2. Was there duplicate study selection and data extraction?	Yes	- All searches were conducted by one author and double-checked by another one. The two reviewers reached a consensus at each stage before proceeding. - Information on effect estimates and study characteristics was independently extracted by two reviewers using a pretested structured form. Discrepancies were resolved on the basis of a consensus discussion between the two reviewers or with the third reviewer



Li 2013 ¹⁵	Score	Justification
3. Was a comprehensive literature search performed?	Yes	- Pubmed, Embase and Web of Science databases from inception to the end of June 2012 - Authors used different combinations of two groups of free text search terms
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	No additional restrictions on language + hand-search the references of the retrieved articles for additional relevant studies
5. Was a list of studies (included and excluded) provided?	No	The included studies were clearly identified but not the excluded studies.
6. Were the characteristics of the included studies provided?	Yes	Table 1
7. Was the scientific quality of the included studies assessed and documented?	Yes	The quality of each included study was independently assessed by two reviewers according to the Newcastle-Ottawa Scale
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	A sensitivity analysis was performed to compare associations found by control-cases studies and by cohort studies.
9. Were the methods used to combine the findings of studies appropriate?	Yes	A random-effects model meta-analysis based on the generic inverse variance method was done to estimate the pooled ORs for all syntheses.
10. Was the likelihood of publication bias assessed?	Yes	Publication bias was assessed using funnel plot and Begg's rank correlation test
11. Was the conflict of interest included?	Yes	No conflict of interests
Total score	9/11	

Li 2014 ¹⁶	Score	Justification
1. Was an 'a priori' design provided	No	
2. Was there duplicate study selection and data extraction?	Yes	One author performed the initial library search, the results of which were scrutinized by two independent reviewers to identify studies for inclusion; data extraction was performed by 2 authors.
3. Was a comprehensive literature search performed?	Yes	Search in Pubmed, Medline and Embase before September 2013. The following index terms were used in combination: ulcerative colitis, Crohn's disease, inflammatory bowel disease, cesarean section, cesarean, mode of delivery, perinatal, and perinatal risk factors
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	Only English-written epidemiological (case-control or cohort) studies were selected.
5. Was a list of studies (included and excluded) provided?	No	The included studies were clearly identified but not the excluded studies.
6. Were the characteristics of the included studies provided?	Yes	Table 1



Li 2014 ¹⁶	Score	Justification
7. Was the scientific quality of the included studies assessed and documented?	Yes	All included studies were ranked according to the four quality parameters in rating study quality section.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	A sensitivity analysis was performed to compare associations found by control-cases studies and by cohort studies.
9. Were the methods used to combine the findings of studies appropriate?	Yes	A fixed effects model was used for pooling of data when statistical heterogeneity was not present. If statistical heterogeneity was present ($p < 0.05$), a random effects model was used.
10. Was the likelihood of publication bias assessed?	Yes	Data showed that there was no evidence of publication bias (Begg's test p-Value = 0.348; Egger's test p-Value = 0.4).
11. Was the conflict of interest included?	Yes	No conflict of interests
Total score	8/11	

Nelson 2010 ¹⁷	Score	Justification
1. Was an 'a priori' design provided	Yes	At the last page, authors refer to differences between protocol and review, that was first published in 2007 and amended in 2009
2. Was there duplicate study selection and data extraction?	No	The study selection was performed by one researcher (RN) but two review authors (RN and CF) independently extracted the data
3. Was a comprehensive literature search performed?	Yes	- Medline-PubMed was the search engine and the date range from 1966 through July, 2009. Searches were also conducted in Embase and the Cochrane Central Register of Controlled Trials (Central) in the Cochrane Library issue 2 2009. - MeSH and Search terms include: *Caesarean Section; Delivery, Obstetric [adverse effects]; Fecal Incontinence [*prevention & control]; Flatulence [prevention & control]
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	Single institution and single practice publications were included along with cohorts recruited prior to delivery and population based surveys.
5. Was a list of studies (included and excluded) provided?	Yes	
6. Were the characteristics of the included studies provided?	Yes	
7. Was the scientific quality of the included studies assessed and documented?	Yes	Risk of bias measures were included for the following items: prospective cohort study design, adjustment for age and parity, pregnancy and delivery history, analysing emergency and elective CD separately and the timing of the assessment of outcomes after more than 4 months post-partum
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Subgroup analysis according to the level of evidence: evidence from RCT was analysed separately from observational evidence



Nelson 2010 ¹⁷	Score	Justification
9. Were the methods used to combine the findings of studies appropriate?	Yes	No meta-analysis was performed due to the absence of RCTs
10. Was the likelihood of publication bias assessed?	No	
11. Was the conflict of interest included?	Yes	No conflict of interests
Total score	9/11	The study selection was performed by one researcher and there is no assessment of likelihood of publication bias

O'Callaghan 2013 ¹⁸	Score	Justification
1. Was an 'a priori' design provided	Cannot answer	
2. Was there duplicate study selection and data extraction?	Yes	
3. Was a comprehensive literature search performed?	Yes	MEDLINE, Embase, and ClinicalTrials. gov
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	English only
5. Was a list of studies (included and excluded) provided?	No	No clear identification of excluded studies
6. Were the characteristics of the included studies provided?	Yes	Table 1
7. Was the scientific quality of the included studies assessed and documented?	Yes	Based on Newcastle-Ottawa Scale (NOS),
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	No information on the results of the NOS
9. Were the methods used to combine the findings of studies appropriate?	Yes	
10. Was the likelihood of publication bias assessed?	Yes	Funnel plots
11. Was the conflict of interest included?	Yes	None declared
Total score	7/11	No real use of QA, no identification of excluded studies and inclusion of English language studies only



O'Neill 2013 ¹⁹	Score	Justification
1. Was an 'a priori' design provided	Yes	Protocol registered on PROSPERO (unique identification number: CRD42012003166) and is available in full on the National Institute for Health Research (NIHR) website
2. Was there duplicate study selection and data extraction?	Yes	Titles and abstracts of studies retrieved were reviewed independently; data extraction was done independently by two assessors
3. Was a comprehensive literature search performed?	Yes	CINAHL; the Cochrane Library; Embase; Medline; PubMed; SCOPUS and Web of Knowledge (1945 - October 2012)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	No date or language restrictions were imposed. Inclusion of the database 'Web of Knowledge'
5. Was a list of studies (included and excluded) provided?	No	No clear identification of excluded studies
6. Were the characteristics of the included studies provided?	Yes	Table 1
7. Was the scientific quality of the included studies assessed and documented?	Yes	Based on six different types of bias common in observational studies (selection, exposure, outcome, analytic, attrition and confounding)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	No information on the results of the NOS
9. Were the methods used to combine the findings of studies appropriate?	Yes	The generic inverse variance method with a fixed-effect model was used to calculate pooled estimates across the studies
10. Was the likelihood of publication bias assessed?	Yes	Funnel plots using the pooled OR and standard error (SE)
11. Was the conflict of interest included?	Yes	Funded by the National Perinatal Epidemiology Centre (NPEC) in Cork, Ireland.
Total score	9/11	No identification of excluded studies

Prior 2012 ²⁰	Score	Justification
1. Was an 'a priori' design provided?	Yes	A review protocol and a PRISMA guidelines (p1113)
2. Was there duplicate study selection and data extraction?	No	Yes for data extraction but no for selection
3. Was a comprehensive literature search performed?	No	PubMed + handsearch
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	No limit of language
5. Was a list of studies (included and excluded) provided?	Yes	Identification of excluded studies and reason for exclusion (p1115)
6. Were the characteristics of the included studies provided?	Yes	Table 1
7. Was the scientific quality of the included studies assessed and documented?	No	



Prior 2012 ²⁰	Score	Justification
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	
9. Were the methods used to combine the findings of studies appropriate?	Yes	
10. Was the likelihood of publication bias assessed?	Yes	Funnel plots, Egger's test and trim-and-fill analysis (p1115)
11. Was the conflict of interest included?	Yes	Support for educational conference by Pfizer Nutrition for one author and by Danone International for another. Consultancy fees from Ferring Pharmaceuticals for a third.
Total score	7/11	No comprehensive search, no QA, no duplicate study selection

Tähtinen 2016 ²¹	Score	Justification
1. Was an 'a priori' design provided?	Yes	A review protocol was registered in PROSPERO and followed the PRISMA guidelines
2. Was there duplicate study selection and data extraction?	Yes	See protocol: Investigators will screen titles and abstracts to select papers for full-text assessment. All screening will be in duplicate. Then, they will screen full text papers to confirm eligibility of the articles. All data extraction will again be in duplicate. Reviewers will resolve any disagreement through discussions, and any remaining will be discussed with one of two adjudicators.
3. Was a comprehensive literature search performed?	Yes	Medline (1946 to present), Scopus (1995 to present), and CINAHL (1960 to present). Authors also searched abstracts published from the annual meetings of the International Continence Society and the International Uro-gynecological Association (1999–2014).
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	No language restrictions
5. Was a list of studies (included and excluded) provided?	No	Excluded studies were not reported
6. Were the characteristics of the included studies provided?	Yes	Table 1
7. Was the scientific quality of the included studies assessed and documented?	Yes	Each study was assessed according to six criteria: sampling and representativeness of population, assessment of the exposure, assessment of the outcome, presence of the outcome at the start of study, adjustment for confounding, and missing data Results: See Supplement Fig. 3 – Risk of bias in individual studies.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	



Tähtinen 2016 ²¹	Score	Justification
9. Were the methods used to combine the findings of studies appropriate?	Yes	Authors calculated pooled estimates of adjusted estimates using the DerSimonian-Laird random-effects inverse variance method, and the I ² statistic and Cochran's Q as indices of heterogeneity. Random-effects model were chosen.
10. Was the likelihood of publication bias assessed?	Yes	Funnel plot testing the presence of publication bias in studies addressing the risk of stress incontinence between vaginal delivery and cesarean section.
11. Was the conflict of interest included?	Yes	All financial support, sponsorship and professional affiliations are reported
Total score	10/11	Note: despite that the main analyses compared CS (elective or emergency) to vaginal delivery, some sub-analyses cover specifically elective CS

3.2. Randomized clinical trials

For the quality appraisal of RCTs the Cochrane Collaboration's tool for assessing risk of bias instrument was used as described in the report.

Table 4 – Quality appraisal for RCTs using the Cochrane Collaboration's tool for assessing risk of bias

Hannah ²²	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	The original study was conducted in 121 centres in 26 countries. The 2-year follow-up was performed in a subset of 85 centres in 18 countries. Randomisation was centrally controlled at the University of Toronto Maternal Infant and Reproductive Health Research Unit with a computerised randomisation program, accessible by means of a touch-tone telephone.	No selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence was suspected.
Allocation concealment	Randomisation was stratified by parity (0 and ≥1) with block sizes of two. No stratification was done by centre, since researchers would have had to use large block sizes to avoid unmasking of allocation, and large block sizes could have resulted in imbalance since they expected that some centres would enrol only a few women. 1041 were randomised to the planned caesarean section group and 1042 to the planned vaginal birth group. For women randomised to the planned caesarean section group, 941 (90.4%) were delivered by caesarean section. For those randomised to the planned vaginal birth group, 591 (56.7%) were delivered vaginally.	No selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment was suspected.



Performance bias

Blinding of participants and personnel
Assessments should be made for each main outcome (or class of outcomes)

Blinding of participants and personnel is impossible in this study.

Blinding of participants and personnel is impossible in this study. At this step, the risk of bias is low.

Detection bias

Blinding of outcome assessment
Assessments should be made for each main outcome (or class of outcomes)

The primary outcome was perinatal or neonatal mortality at less than 28 days of age; blinding is less important for the interpretation of this outcome.

Other primary outcomes include serious neonatal morbidity: for these ones, blinding of assessors is really needed but not reported in the paper.

Secondary outcome was maternal mortality or serious maternal morbidity during the first 6 weeks post-partum. All other outcomes of maternal morbidity were judged by members of the steering committee, masked to allocation group and if possible to mode of delivery, to determine whether they might be related to the delivery and whether they should be regarded as serious.

In countries with a high perinatal mortality rate a detection bias is suspected in that babies in these countries are less likely to be closely observed by caregivers for evidence of outcomes. Moreover, most babies, particularly if delivered vaginally, are discharged home before these problems can be detected by health-care workers.

Blinding of assessors would be required, at least for primary outcomes that are at risk of interpretation (not for mortality).

There is no indication that primary outcomes were assessed by blinded evaluators. The risk of bias is high.

Attrition bias

Incomplete outcome data
Assessments should be made for each main outcome (or class of outcomes)

Researchers enrolled 2088 women between Jan 9, 1997, and April 21, 2000, at 121 centres in 26 countries. They received entry and outcome data for 2083 (99.8%) women, of whom 1041 were randomised to the planned caesarean section group and 1042 to the planned vaginal birth group.

The results were analysed according to intention to treat, and all women who underwent randomisation and for whom data were available were included in the analysis.

The follow-up rate at 2 years was almost 80% among the selected centres that agreed to undertake this part of the study.

Attrition bias cannot be excluded.

Reporting bias



Selective reporting	No reporting bias identified.	No reporting bias identified.
Other bias		
Other sources of bias	No other bias identified.	No other bias identified.

* *The Term Breech Trial is a multicentre international randomized controlled trial that included countries with low national perinatal mortality rates (Australia, Canada, Chile, Denmark, Germany, Israel, the Netherlands, New Zealand, Poland, Portugal, Romania, Switzerland, the United Kingdom, and the United States) and countries with high national perinatal mortality rates (Argentina, Brazil, Jordan, and Pakistan)*

3.3. Cohort studies

For the quality appraisal of cohort studies the Cochrane Collaboration's risk of bias tool was used as described in the report. Studies are described in the alphabetical order of the first author.

Table 5 – Quality appraisal for cohort studies using the Cochrane Collaboration's tool for assessing risk of bias

Al Khalaf 2015 ²³	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? No	Children who would have been 9 months of age at the time of interview (between September 2008 and end of April 2009) were selected from the Child Benefit Register (CBR) provided by the Department of Social and Family Affairs = population-based study. The CBR was used as a sampling frame because child benefit is a universal welfare entitlement in Ireland and has <i>practically complete coverage of all children born</i> in the Republic of Ireland at the time of the study. The sample was selected on a systematic basis, pre-stratifying by marital status, county of residence, nationality and number of children (i.e. less than 16 years of age) in the household to ensure that <i>households less likely to respond were oversampled</i>, using a random start and constant sampling fraction. The total eligible Register population was <i>all births occurring during the period 1st December 2007 – 30th June 2008</i> which amounted to 41 185 children. 17 264 families were approached to take part in the study representing a sampling fraction of 0.42 (by which procedure?), of which 11 134 families consented to take part in the study representing an overall response rate of 64.5%. This can indeed lead to a differential selection bias
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? No	Data on the following potential confounders were collected at 9 months postpartum and available for analysis: maternal educational level, maternal age, ethnicity, smoking during pregnancy, alcohol consumption during pregnancy, and maternal body mass index (BMI), family social class, hypertension, gestational diabetes, preeclampsia, gestational age, parity, duration of labour, birth weight infant sex, antenatal care and breastfeeding.



Al Khalaf 2015 ²³	Explanation
	Information on social, psychiatric or psychological factors including fear of childbirth for example were not available for the current study. There is no information about the collection of these data, but we can reasonably suppose that the collection was the same for all children. Logistic models were used. The estimates were observed to test whether a specific factor was a confounder or not by comparing the estimates before and after each variable was added in the model. If the estimate did not change by $\geq 10\%$ the variable was dropped from the model and the next factor was tested. Authors cannot rule out the possibility that some of the observed associations were due to chance considering that the statistical analysis was not corrected for multiple testing.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? Yes	The exposure of interest was obtained from the first wave by direct face-to-face interview with the mother by asking "what was the final mode of delivery?" Mode of delivery was then categorized into Spontaneous Vaginal Delivery, Instrumental Vaginal Delivery, elective Caesarean Section and emergency Caesarean Section.
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? No	When children were around 9 months old, the Ages and Stages Questionnaire (ASQ, 2nd Ed.) was used to assess the behavioural, cognitive and motor developmental outcomes. At around age 3 years, parent(s) were asked to complete a modified version of the Strengths and Difficulties Questionnaire (SDQ) for children aged 3–4 years. These validated questionnaires were filled in by the parents and no experienced healthcare professional was involved in the evaluation of the outcomes. The outcome measures of behavioural problems and neurodevelopment disorders were defined based on assessment tools/questionnaires. Parents usually have few opportunities to observe their child's interaction with others as in the classroom environment.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? Yes	Developmental disorders can be present at birth but not possible to diagnose.
6. Is the assessment of outcome made blind to exposure status? - No → Does this have an influence on the assessment of outcome? - No	

**Al Khalaf 2015²³****Explanation**

7. Is the follow-up sufficiently long to measure all relevant outcomes?
- Difficult to evaluate

Data regarding behavioural outcomes were collected prospectively; therefore, recall and measurement bias are less likely to occur.

The ASQ, which was completed by the parents at 3 years, is a validated and reliable instrument to identify emotional/behavioural problems among children and adolescents in the community and clinical settings. Is a follow-up of 3 years sufficiently long to observe dimensions such as communications skills, problem solving, personal social, gross motor and fine motor?

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?
- Yes

Recall bias cannot be ruled out as many lifestyle variables such as smoking and alcohol consumption were collected 9 months post-delivery although the questions referred to the pregnancy period.

Although 65% of the invited families participated at 9 months only 59% (90% of the 65%) of the children had outcome data at three.

The loss to follow-up at 3 years, however, was equally distributed across all modes of delivery and therefore is unlikely to affect the study findings.

Bager 2012²⁴**Explanation****SELECTION BIAS**

1. Can selection bias sufficiently be excluded?
- Yes

The cohort (2.1 million singleton born during the period January 1 1973 through December 31 2008) was established using data from the Civil Registration System (CRS).

The CRS is a continually updated demographic database covering the entire Danish population, which includes information on, e.g., date of birth, vital status, emigration, addresses, and family relations since April 1 1968. The cohort was subsequently linked to the Medical Birth Registry and the National Patient Registry. Accurate linkage between Danish registries is possible because individual data are kept under the unique 10-digit personal identification number assigned to all Danish residents.

2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?
- No

IRRs were adjusted for age (1-year groups), calendar-year (1-year groups), sex, birth weight (≤ 2500 , 2501–3000, 3001–3500, 3501–4000, and ≥ 4001 grams), birth order (1 [for first born], 2, 3, ≥ 4), and county of birth (14 counties).



Bager 2012 ²⁴	Explanation
	Because the likelihood of c-section for pregnant women with IBD might differ from that of other women and because offspring of patients with IBD are known to be at an increased risk of IBD, the measure of the association between mode of delivery and IBD risk was stratified according to parental IBD status (none, one or both parents, father only, and mother only) at the time of birth or at end of follow-up. However, unmeasured confounding factors may have contributed to the observed excess risk of IBD in childhood following c-section. For instance, if mothers of children delivered by c-section are less likely to breastfeed than mothers of children born vaginally this might contribute to the observed moderate increase in IBD risk associated with c-section. A more general health disadvantage of infants born by c-section might also account for the excess risk. For instance, compared with vaginally delivered infants, children delivered by c-section are more often challenged by complications such as cord blood compression, placenta praevia, and respiratory distress syndrome.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? Yes	Since 1973 the Medical Birth Registry has contained computerized information about birth characteristics, which are mandatorily recorded after delivery, including, e.g., mode of delivery, birth weight, county of birth, and maternal age. A distinction between elective and acute c-section has been possible since 1997.
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? Yes	Since 1977 the National Patient Registry has contained information about all non-psychiatric hospital admissions in Denmark. Outpatient hospital contacts have been included since 1995. Information concerning dates of admission and discharge, hospital department, and diagnoses is kept for every hospital contact linked to the patient's unique personal identification number. Diagnoses are coded according to the 8th revision of the International Classification of Diseases (ICD8) from 1977 to 1993 and according to its 10th revision (ICD10) since January 1994. Identification of cases was based on first in- or outpatient hospital contact with UC (ICD8 codes 563.19 and 569.04 and ICD10 group K51) and with CD (ICD8 codes 563.00–563.09 and ICD10 group K50). In a supplementary analysis we obtained information about parental IBD status using the same diagnostic ICD8 and ICD10 codes. In all analyses we defined type (UC or CD) and date of IBD using the first discharge diagnosis, regardless of whether the patient was later admitted again and discharged with a diagnosis of the other IBD.

**Bager 2012²⁴****Explanation**

High levels of completeness (94%) and validity (90%–97%) of IBD diagnosis recorded in the National Patient Registry; for all ages (0–95 years) only 8.6% of patients with UC and 1.0% of patients with CD had been diagnosed outside Danish hospitals.

5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?

- Yes

6. Is the assessment of outcome made blind to exposure status?

- Insufficient information to answer

While the authors cannot entirely exclude the possibility that c-section mothers may be more likely than other women to have their children examined for gastrointestinal symptoms, it seems unlikely that this would explain the findings, because Danish children who develop IBD will eventually be diagnosed and registered in the National Patient Registry with their IBD, regardless of their mode of entering this world.

7. Is the follow-up sufficiently long to measure all relevant outcomes?

- Yes

IBD incidence has been reported to peak at ages 16–25 years
32.6 million person-years of follow-up in the age span 0–35 years: Each person in the cohort was observed from date of birth or January 1 1977, when the National Patient Registry was started, whichever came later, and until end of follow-up.
End of follow-up was on December 31 2008, or date of emigration, death, or first hospital discharge with a code for UC or CD, whichever came first.

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?

- Yes

.

Bager 2010²⁵**Explanation****SELECTION BIAS**

1. Can selection bias sufficiently be excluded?

- Yes

A study cohort of 1.71 million singleton persons born during the period from 1 January 1973 through 4 April 2005 to Danish-born parents was established by linkage between the Medical Birth Registry, the Civil Registration System, the Integrated Database for Labor Market Research, and the Registry of Enteric Pathogens.

The information is kept under the unique Danish personal identification number assigned to all Danish residents since 1 April 1968, thus ensuring precise and secure linkage of person-identifiable information between registers.



Bager 2010 ²⁵	Explanation
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? Insufficient information to answer	IRRs are adjusted for birth weight, gestational age, age, sex, birth order, season of birth, maternal age, average gross annual income, degree of urbanization, and the interaction term calendar-year x county of residence.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? Insufficient information to answer	Since 1973, the Medical Birth Registry has contained computerized information about birth characteristics, including mode of delivery, which are required to be recorded shortly after birth. Information about gestational age has been uniformly registered since 1977, and a distinction between elective and acute c-section has been possible since 1997.
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? Yes	The Registry of Enteric Pathogens contains information on laboratory-confirmed positive intestinal bacterial infections in Denmark since 1991. Cases were laboratory-confirmed non typhoidal <i>Salmonella</i> species, <i>Campylobacter</i> species, <i>Yersinia enterocolitica</i>, <i>Shigella</i> species, and Shiga toxin-producing <i>Escherichia coli</i> from 1991–2005 in the National Registry of Enteric Pathogens.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? Yes	
6. Is the assessment of outcome made blind to exposure status? Insufficient information to answer	
7. Is the follow-up sufficiently long to measure all relevant outcomes? Yes	
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? Yes	

**Black 2015²⁶****SELECTION BIAS**

- | | |
|--|---|
| 1. Can selection bias sufficiently be excluded? <ul style="list-style-type: none">• Yes | Vital statistics data. |
| 2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? <ul style="list-style-type: none">• Yes | Hazard ratios were adjusted for prespecified confounding factors based on experts knowledge and published literature. |

DETECTION BIAS

- | | |
|---|---|
| 3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? <ul style="list-style-type: none">• Yes | Quality assurance of the Scottish Morbidity Record demonstrates accuracy of 97% for caesarean delivery as mode of birth. |
| 4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? <ul style="list-style-type: none">• Yes | For asthma, records at discharge from all acute admissions to Scottish hospitals, with validity checks suggesting 87% accuracy. |
| 5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? <ul style="list-style-type: none">• Yes | |
| 6. Is the assessment of outcome made blind to exposure status? <ul style="list-style-type: none">• Yes | Routine data |
| 7. Is the follow-up sufficiently long to measure all relevant outcomes? <ul style="list-style-type: none">• Yes | |

ATTRITION BIAS

- | | |
|---|--|
| 8. Can selective loss-to-follow-up be sufficiently excluded? <ul style="list-style-type: none">• Insufficient information to answer | Poor impact of emigration according to the authors |
|---|--|



Bråbäck 2013 ²⁷	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? a. Yes	This study population was based on information from the national health databases held by the Swedish National Board of Health and Welfare and Statistics Sweden. The population included all full term (gestational week 37-<42), singleton children born in Sweden between 1/1/1999 and 31/12/2006, according to the Swedish Medical Birth Register. From this population authors selected children who were residents in Sweden on December 2009 (according to the Register of the Total Population), were offspring of two native Swedish parents, had no major malformations reported at birth.
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? a. Yes	Information about parity, maternal age (at childbirth), measured maternal BMI in early pregnancy, mode of delivery, smoking habits in early pregnancy, maternal diseases and pregnancy complications was collected from Swedish Medical Birth Register. Perinatal data about sex, gestational age, birth weight, and low Apgar scores (<7 at five minutes) of the offspring were collected from the same Register. Data on parental education and social welfare benefits were also collected. A county variable with different levels of retrieval of prescribed ICS was created to adjust the analysis to the regional differences. Hierarchical models were tested including socio-demographic confounders (including smoking and maternal age) and parental dispensed ICS. The last Model added perinatal risk factors associated with mode of delivery. In a second analysis, the effect of mode of delivery was assessed within sibling pairs discordant for mode of delivery and asthma medication.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? a. Yes	Mode of delivery was categorised into: non assisted vaginal delivery, emergency caesarean section, elective caesarean section and vacuum extraction. Caesarean section was defined as emergency if the operation was made after the onset of labour and otherwise considered as elective.
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? a. Yes	Asthma was captured based on data of retrieved prescriptions from the Swedish Prescribed Drug Register, which contains all drugs prescribed and dispensed in Swedish pharmacies, excluding drug treatment in hospital care. Three indicators were used as proxys to define the intensity of the asthma based on the frequency of the prescriptions of inhaled steroids or any medication for obstructive lung disease.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	Newborns cannot be diagnosed with asthma before their birth.



Bråbäck 2013 ²⁷		Explanation
a. Yes		
6. Is the assessment of outcome made blind to exposure status?		Investigators used retrospective data from a national registry and they did not assess the exposures or the outcomes themselves.
a. No → Does this has an influence on the assessment of outcome?		
1. No		
7. Is the follow-up sufficiently long to measure all relevant outcomes?		Outcomes were assessed at two age periods: 2-5 years and 6-9 years.
a. Yes		However, a similar Swedish registry-based study did not detect any association between elective caesarean section and asthma in sibling-pairs aged 9 and 12 years (longer follow-up).
ATTRITION BIAS		
8. Can selective loss-to-follow-up be sufficiently excluded?		The number of patients that were loss-to-follow up is not documented.
• Insufficient information to answer		
Curran 2016 ²⁸		Explanation
SELECTION BIAS		
1. Can selection bias sufficiently be excluded?		The Millennium cohort study is a nationally representative UK cohort of children (including 18 827 children born in the UK between 2000 and 2002)
• Yes		13 141 children), There have been five surveys of the MCS participants to date; conducted at 9 months and 3, 5, 7 and 11 years of age. Data on mode of delivery and potential confounders for the present study were obtained from the first survey (conducted at 9 months)
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?		Included confounders were determined a priori based on previous literature: small for gestational age (SGA), gestational age at birth, maternal high blood pressure/pre-eclampsia/eclampsia, mother smoking (>1 cigarette a day while pregnant), being the first born child, bleeding or threatened miscarriage during pregnancy, poverty, white ethnicity, maternal age, maternal education, maternal depression and maternal BMI.
• Yes		Additional variables that were assessed included: infant age when he/she came home from the hospital, infant gender, urbanicity, single parent household at time of first survey, paternal age, paternal education, whether pregnancy was unplanned, and maternal irritable bowel syndrome (IBS).



Maternal attachment was measured using a subset of six questions from the Condon Maternal Attachment Questionnaire. The Condon Maternal Attachment Questionnaire has been previously shown to have acceptably high construct validity and test-retest reliability

DETECTION BIAS

3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?

- Yes

Mode of delivery was categorized into “spontaneous VD,” “assisted VD,” “induced VD,” “emergency CS,” “planned CS” and “induced CS.” The variable was defined this way to assess the effect of any intervention on labour as compared to no intervention (i.e. spontaneous, non-assisted VD).

Clear categories followed in the text.

4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?

- Yes

In surveys 3 and 4, i.e. at age 5 and 7 years respectively, respondents were asked, in two separate questions, if a doctor or health professional had ever told them that their child had ADHD or ASD. The authors considered children of parents that responded “yes” to either question in survey 4 as cases for that particular disorder. A Chi squared test was performed on those that responded “yes” in both surveys 3 (age 5 years) and 4 (age 7 years) as a sub-group of “confirmed cases” to see if it was meaningfully different from the population of all cases reported in survey 4 with regards to mode of delivery.

Behavioural difficulty was measured using the Strengths and Difficulties Questionnaire (SDQ) that was completed by parents in survey 4. The SDQ measures behavioural difficulties in five areas: conduct problems, hyperactivity, emotional symptoms, peer problems and pro-social behaviours. All scores except pro-social can be combined to create a “total difficulties” score. Consistent with the recommended cut-off for parent-scored SDQ in the UK, a total difficulties score of 17 was used to indicate an “abnormal” score. This has previously been found to correspond to the top 10 % of scorers, and is associated with an increased overall risk of being diagnosed with a psychiatric disorder including not only ASD/ADHD, but also anxiety disorders, conduct-oppositional disorders, and obsessive-compulsive disorder, among others.

The validity of ADHD diagnoses can be questionable, especially in younger children, in part because some health professionals diagnose ADHD solely in terms of behavioural difficulties. Therefore, in the posthoc analysis children with ADHD and/or children with abnormal SDQ scores were grouped into one “behavioural difficulties” category.

5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?

- NA



6. Is the assessment of outcome made blind to exposure status?
- No but it is difficult to evaluate the impact on the assessment of the outcome

7. Is the follow-up sufficiently long to measure all relevant outcomes?
- 7 years
- Yes

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?
- Loss to follow-up is a potential limitation of this study although the original weights used at 9 months appeared to be valid at 7 years
- No

Daltveit 2008²⁹

Explanation

SELECTION BIAS

1. Can selection bias sufficiently be excluded?
- Historical cohort design – authors used data on births registered in the Medical Birth Registry of Norway between 1967 and 2003. The registry is based on compulsory notification and comprises data on all live births as well as all stillbirths after 16 weeks of gestation, identified by the national identification number of the mother
- Yes
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?
- Maternal age, year of birth and gestational age at delivery were considered as potential confounders. They were identically recorded irrespective of the group under study (CS or VD).
- Yes

DETECTION BIAS

3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?
- Data on mode of delivery were entered as free text until 1998 and in checkboxes thereafter. No more information was provided by the authors.
- Insufficient information to answer
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?
- Data on complications and maternal disease were entered into the notification form as free text until 1998 and in checkboxes or as free text from 1999 onward. Data on maternal disease are coded according to International Classification of Diseases (ICD) (ICD-8 from 1967 to 1998 and ICD-10 from 1999 onward). From 1967 to 1998, free text on complications was coded according to a system for the registry based on international definitions; it has been coded according to ICD-10 since 1999. No more information was provided by the authors.
- Insufficient information to answer
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?
- The birth notification form contains data on the mother's health before and during pregnancy, pregnancy complications, and data on the delivery and the newborn.



- No

6. Is the assessment of outcome made blind to exposure status?

- No → Does this has an influence on the assessment of outcome?
 - o No

7. Is the follow-up sufficiently long to measure all relevant outcomes?

- Yes

All the outcomes occur during the pregnancy, the birth or early in the postpartum.

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?

- Yes

Emilsson 2015³⁰

Explanation

SELECTION BIAS

1. Can selection bias sufficiently be excluded?

- No

Prospectively collected Norwegian MoBa cohort conducted by the Norwegian Institute of Public Health. Pregnant women were recruited around 18 gestational weeks from all over Norway from 1999 to 2008. The participation rate was 40.6%.

2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?

- Yes

Data on parental smoking, maternal education, maternal CD, and parity were collected from the MoBa follow-up questionnaires.

All analyses were adjusted for attained age, sex, and maternal CD; these data were available for 620 individuals in the CD cohort and 102 218 individuals in the non-CD cohort. Data on gluten introduction and breastfeeding were also obtained from the questionnaires. These variables were added into a second model as adjustment variables; complete data on these variables were available for 523 of 83 610 individuals.

DETECTION BIAS

3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?

- No

Data on mode of delivery and indication for caesarean section were collected from the MoBa follow-up questionnaires.

4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?

Questionnaires were used (around weeks 18 and 30 of pregnancy, at ages 6 and 18 months as well as 7 and 8 years of age. (All of the questionnaires are available at www.fhi.no/moba.)



- Yes

The cohort database is also linked to the Medical Birth Registry of Norway (MBRN) and the National Patient Registry (NPR). The NPR contains information on all diagnoses according to the ICD 10th revision codes, set in all government-owned Norwegian hospitals and outpatient clinics. The information is mandatory and virtually complete. Information in this registry has been available on an individual level since 2008, when the Norwegian 11-digit personal identification number was included. The ICD 10 used to classify CD was K90.0.

CD was defined as being reported in the questionnaires at 7 or 8 years of age or at least 2 different registrations of CD diagnosis in NPR (in absence of being reported in the questionnaires, many participants have not reached the age of 7).

In a validation sample, participants identified with CD through questionnaires or NPR completed a separate questionnaire to provide details about the diagnostic process. Of 468 respondents, 94.2% (277 of 294) of those identified with 2 or more entries in the NPR confirmed the diagnosis, and only 4% and 1.8% had a false-positive or uncertain diagnosis, respectively.

Of those who had reported the CD diagnosis in a previous questionnaire, 92.4% confirmed the diagnosis in the validation study. Diagnosis confirmed by biopsy was reported in 83.0%, 15.7% had been diagnosed through positive antibody tests, and only 1.3% was reported without serology or biopsy.

5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?

- NA

6. Is the assessment of outcome made blind to exposure status?

- Insufficient information to answer

7. Is the follow-up sufficiently long to measure all relevant outcomes?

- No

Many participants did not reach the age of 7 years. The FU is short.

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?

- Yes



Francis 2014 ³¹	Explanation
NOTE	The whole methodology is described in a previous publication (Ma X, Buffler PA, Layefsky M, Does MB, Reynolds P. Control selection strategies in case-control studies of childhood diseases. Am J Epidemiol 2004; 159:915–21).
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? a. Yes	This study is a part of a large study of childhood leukaemia that started in California in 1995. Incident cases of newly diagnosed childhood leukemia (in children aged 0–14 years) are prospectively ascertained (usually within 72 hours after diagnosis) from major pediatric clinical centers in Northern and Central California. The NCCLS protocol successfully identified 88% of all age-eligible, newly diagnosed childhood leukemia cases among residents of the San Francisco–Oakland Metropolitan Statistical Area. The authors selected two controls per case: one from among children identified by using computerized birth records and located successfully, the other from a roster of friends; both were matched on demographic factors.
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? a. No	Logistic regression models were used to examine the relationship between leukemia and CS. Matched pairs were separated to include all controls and increase sample size. Covariates assessed as plausible confounders were identified by obstetrical consultants. Covariate information (breastfeeding, gestational age, income, gender, maternal race, and maternal ethnicity) was recorded during the conduct of the routine CCLS questionnaire either in person or over the phone. Whether the observed differences are the result of some unmeasured confounding or bias cannot be ascertained with these data.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? a. Probably not.	The mode of delivery was reported on California birth certificates. Results were reported by distinguishing vaginal delivery or caesarean section. No more information is reported. Authors did not have data on elective versus emergency CS delivery. Although CS is usually recalled correctly in questionnaires, in this study CS was recorded from birth certificates, in which any potential bias of questionnaire derived exposure histories is deleted.



Francis 2014 ³¹	Explanation
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? a. No	Cases were stratified by major subtype of leukemia; acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), and common ALL (cALL). cALL is defined as ALL with expression of CD10 and CD19 surface antigens (pre-B-cell ALL) and diagnosis occurring between 2 and 5.9. No more information about diagnostic methods used and classification of diseases.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? a. Insufficient information to answer	
6. Is the assessment of outcome made blind to exposure status? a. No → Does this have an influence on the assessment of outcome? 1. No	Investigators start with children diagnosed with leukemia (cases) or without leukemia (controls) and searched the mode of delivery. There is no possible blinding in this type of study.
7. Is the follow-up sufficiently long to measure all relevant outcomes? a. Yes	Incident cases were searched in children aged 0 to 14 years, but mean ages in all leukemia groups were between 3 and 5 years.
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? Insufficient information to answer	



Guibas 2013 ³²	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? a. No	Sampling of schools for the recruitment of children was random, multistage, and stratified by parents' educational level and total student population within municipalities of each county. On the basis of this sampling, 77 primary schools were chosen. Parents, who agreed to participate, signed a consent form; consent forms were signed for 2572 children (response rate 63%). To assess the potential for selection bias they compared available characteristics between the subjects who consented to participate (n = 2572) and those who did not (n = 1529), without stressing any difference. The same comparative analysis was performed between study population (n = 2016) vs. those of the entirety of the subjects that were excluded because of partial information (n = 556). Significant difference was found in maternal education and parity.
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? a. No	Socio-demographic and perinatal data were either reported by the parents or extracted from the children's birth certificates and medical records. If parents were unable to attend the meeting (approximately 5%), data were collected by telephone.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? a. No	All information related to the exposure were collected by interviewing the parents 9-13 years after the birth: type of delivery (normal labour vs. C-section); type of pregnancy (single vs. multiple gestation); maternal smoking during pregnancy; parity; children's feeding practices from birth to 6 months of age (breastfeeding, mixed or exclusive vs. no breastfeeding);
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? a. No	Interviews with parents also included asthma-related questions which were based on the ISAAC core questionnaire (without medical diagnosis). The following self-reported asthma outcomes were studied: (i) Current wheeze (Has your child had wheezing or whistling in the chest in the past 12 months?); (ii) Ever wheeze (Has your child ever had wheezing or whistling in the chest at any point in time?); (iii) Asthma ever (Has your child ever had asthma diagnosed by a doctor?).
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? a. Yes	Newborns cannot be diagnosed with asthma before their birth.
6. Is the assessment of outcome made blind to exposure status? a. Insufficient information to answer	



Guibas 2013 ³²		Explanation
7.	Is the follow-up sufficiently long to measure all relevant outcomes? a. Yes	All information related to the exposure were collected by interviewing the parents 9-13 years after the birth of their child.
ATTRITION BIAS		
8.	Can selective loss-to-follow-up be sufficiently excluded? • Insufficient information to answer	The number of patients that were loss-to-follow up is not documented.
Gurol-Urganci 2014 ³³		Explanation
SELECTION BIAS		
1.	Can selection bias sufficiently be excluded? a. Yes	Authors used the Hospital Episode Statistics (HES) - a data warehouse that includes records of all inpatient admissions and day cases in the English NHS trusts (acute hospital organizations) - to identify all deliveries that took place between April 2000 and March 2012. The analysis was confined to NHS trusts that had parity information recorded in at least half of the deliveries, and had a proportion of primiparous women between 25 and 55% (overall about 40% of women giving birth in England and Wales are primiparous). Authors found comparable distributions of maternal age, pregnancy complications and mode of delivery in NHS trusts with good quality data with those hospitals having poor quality data. A recent study also concluded that birth cohorts from hospitals with high completeness of recording for key fields in HES may be generalizable and representative of all hospitals nationally (Murray et al., 2013).
2.	Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? a. Insufficient information to answer	For maternity episodes, the HES database has supplementary fields known as the 'maternity tail' which capture parity, birthweight, gestational age, method of delivery and pregnancy outcome. The accuracy and completeness of diagnostic and procedures data is high. However, the maternity tail is not compulsory and the level of data completeness varies across NHS Trusts. However, no information was provided on how these factors were measured.
DETECTION BIAS		
3.	Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? a. Yes	Exposures were defined as vaginal delivery, instrumental delivery, elective Caesarean for breech and transverse lie, elective Caesarean for other indications and emergency Caesarean section.



Gurol-Urganci 2014 ³³		Explanation
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? a. Yes		Time to subsequent birth was defined from the start date of index delivery episode to the date of the subsequent birth. Reaching a maternal age of 45 years or the end of study period (31 March 2012), whatever came first, was handled as censoring events.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? a. No		This is sequentially impossible.
6. Is the assessment of outcome made blind to exposure status? a. Not possible in this type of exposure		However, the risk of bias is very low since outcomes is either a dichotomic answer (subsequent birth or not) or a time before the second birth.
7. Is the follow-up sufficiently long to measure all relevant outcomes? a. Yes		The study covered a 12-year period, between 1 April 2000 and 31 March 2012. Follow-ups were done at 3, 5 and 10 years. Complete 10-year follow-up was available for only 2 years of the study cohort, for index deliveries in 2000 and 2001.
ATTRITION BIAS		
8. Can selective loss-to-follow-up be sufficiently excluded? • Yes		See point 7.
Hanlon ³⁴		Explanation
SELECTION BIAS		
1. Can selection bias sufficiently be excluded? • Yes		Retrospective cohort study of term, singleton births from 1st January 2013 to 31st December 2013 at a tertiary obstetric facility (n=5574 in total). Outcomes were compared for 1816 women having vaginal births versus 1205 women having instrumental or caesarean births. Exclusion criteria were the need for an interpreter, multiple births, pre-existing maternal mental health disorder, including history of post-natal depression, Edinburgh Postnatal Depression Score (EPDS) ≥ 12 at the time of booking, preterm birth (<37 weeks 0 days), stillbirth or neonatal death, where the baby had a major congenital or chromosomal abnormality, and where UPNC data were incomplete. The final data set comprised 3021 patient records.



Hanlon ³⁴	Explanation
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? Yes	Baseline maternal characteristics (age, parity, body mass index (BMI), smoking status, illicit drug use in the previous 12 months, education level), risk factors for psychological morbidity (EPDS (Edinburgh Postnatal Depression Score) at booking, recent stressors or relationship concerns at booking, whether pregnancy was planned, whether the partner was supportive of the pregnancy), information about birth (mode of birth, duration of labour, analgesia, estimated blood loss, gender of baby) and postnatal course (feeding method, answers to UPNC (Universal Postnatal Contact) questions).
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? Yes	Outcomes were compared for women who had an operative birth (vacuum, forceps, CS) with those who had an unassisted vaginal birth.
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? Yes	The primary outcome measure was any affirmative answer to the following UPNC questions: difficulty coping; disturbed rest and sleep; altered diet and appetite; and the question 'Do you have any concerns with changes to your relationship with your partner since having your baby?' Relationship discord has been recognised as an adverse consequence of PND, as well as a risk factor for its development⁷, and thus, it was used in this study as another potential symptom of psychological morbidity.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? Yes	History of post-natal depression was one the exclusion criteria.
6. Is the assessment of outcome made blind to exposure status? Not possible in this type of exposure	No
7. Is the follow-up sufficiently long to measure all relevant outcomes? No	7-10 days post-discharge
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? No	As the UNPC is part of the exclusion criteria a selective loss to follow-up cannot be excluded.



Khashan 2014 ³⁵	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? Yes	Population-based cohort study of all singletons live births in Sweden using data from the Swedish Medical Birth Register, between January 1, 1982, and December 31, 2009. This register contains obstetric, maternal, and neonatal data on 99% of births in Sweden.
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? Yes	Sibling analysis Exploration of the confounding effect: - gestational age, large for gestational age, small for gestational age, birth order, preeclampsia, infant gender, maternal age, BMI, pre pregnancy diabetes and gestational diabetes (obtained from the Medical Birth Register) - Maternal education level (from the Education register) - Induction of labour
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? Yes	Data on obstetric complications were retrieved from the Medical Birth Register. Mode of delivery was classified into unassisted vaginal delivery (spontaneous and induced), IVD (forceps or vacuum extraction), emergency CS (after onset of labour), and elective CS (before onset of labour).
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? Yes	T1D diagnoses were identified from the Swedish National Patient Register that contains records of inpatient diagnoses in Sweden since 1964 (full national coverage since 1987) and outpatient diagnoses since 2001. The date of onset of T1D is defined as the date of the first admission to hospital, which led to the diagnosis of T1D. The primary outcome measure in this study was childhood T1D, before 15 years of age, (ICD-8; 250); ICD-9 (250); and ICD-10 (E10). Secondary outcome measures included T1D at any age (maximum age was 27 years in the study cohort) and any diabetes diagnosis defined according to ICD-8 (250), ICD-9 (250), and ICD-10 (E10-14).
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? Yes	
6. Is the assessment of outcome made blind to exposure status? Insufficient information to answer	Suppose yes but not sure
7. Is the follow-up sufficiently long to measure all relevant outcomes?	



Khashan 2014 ³⁵		Explanation
Yes		
ATTRITION BIAS		
8. Can selective loss-to-follow-up be sufficiently excluded?	Yes	The Migration register provided the dates of migration from Sweden, whereas information on date of death was obtained from the Cause of Death register. The number of T1D cases in the current study are comparable to those reported from the Swedish Childhood Diabetes register between 1977 and 2007 (12 842 vs 12 880)
Kristensen 2016 ³⁶		Explanation
SELECTION BIAS		
1. Can selection bias sufficiently be excluded?	Yes	Population-based study (all children born in Denmark from January 1997 through December 2012)
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?	No	Data on maternal age, maternal smoking during pregnancy, complications during pregnancy (preeclampsia, eclampsia, haemorrhage, and hyperemesis), sex, gestational age at birth and birth weight from the Danish National Birth Potential effect of birth season and birth year eliminated by matching on date of birth. However, no data on BF and maternal asthma the risk of delivery by CS in mothers with asthma is only slightly increased and only 6% of pregnant women in Denmark reported asthma)
DETECTION BIAS		
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?	Yes	Records from the Danish National Birth Registry (VD, acute and elective CS according to ICD-10 codes)
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?	Yes	Records from the Danish National Patient Registry: laryngitis (ICD-10 code J05.0), pneumonia and lower respiratory tract infection (ICD-10 codes J12.0-J15.9 and J20.0-J22.9), asthma (ICD-10 codes J45.0-J45.9), gastroenteritis (ICD-10 codes A08.1 and A09.9), Crohn disease (ICD-10 codes K50.0-K50.9), ulcerative colitis (ICD-10 code K51.0-K51.9), celiac disease (ICD-10 code K90.0), juvenile arthritis (ICD-10 codes M08.0-M08.9), diabetes (ICD-10 codes E10.0-E10.9 and E14.0-E14.9), lymphatic leukemia (ICD-10 codes C91.0-C91.9), myeloid leukemia (ICD-10 codes C92.0-C92.9), malignant lymphoma (ICD-10 codes C81.0-C85.9), and non-hematologic cancer (ICD-10 codes C00.0-C80.9).



Kristensen 2016 ³⁶		Explanation
		There was no attempt to validate the diagnostic coding but it improbable that mode of birth should affect diagnostic coding in the offspring, and therefore differential misclassification is unlikely to affect the relative estimates reported. Likewise, the reliability of the Danish hospital registers has been demonstrated in numerous studies.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?		
• Not applicable		
6. Is the assessment of outcome made blind to exposure status?		
• Insufficient information to answer		
7. Is the follow-up sufficiently long to measure all relevant outcomes?		Children were followed from the day of birth to an outcome of diagnosis, emigration, death, or the end of follow-up on December 31, 2012, whichever came first.
• Yes		
ATTRITION BIAS		
8. Can selective loss-to-follow-up be sufficiently excluded?		
• Insufficient information to answer		
Kristensen 2015 ³⁷		Explanation
SELECTION BIAS		
1. Can selection bias sufficiently be excluded?		Population-based study (all children born in Denmark between January, 1997 and June, 2003.
• Yes		
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?		Data on gestational age at birth, asphyxia, birthweight, multiple births, respiratory distress syndrome including transient tachypnea of the newborn (ICD-10) diagnoses codes P22.0-9, single parenthood, maternal smoking during pregnancy, older siblings, asthma diagnoses (ICD-10 diagnoses codes J45.0-9) and chronic diseases were extracted from the Danish National Birth Registry and the Danish National
• No		However, there is a lack of data on atopic disposition, while maternal asthma is associated with both an increased risk of CS and an increased risk of hospitalization for RSV in the offspring. But according to the authors, the risk of delivery by CS in mothers with asthma is only slightly increased, and self-reported asthma is only present in 6% of pregnant women in Denmark, thus maternal asthma cannot explain the findings.

Kristensen 2015³⁷

Explanation

DETECTION BIAS

3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?
- Yes

Records from the Danish National Birth Registry

4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?
- Yes

Data on hospitalizations for RSV were obtained from the Danish National RSV database, which contains the results of all RSV tests obtained in Denmark from January, 1997 through June, 2003. During the study period all RSV diagnoses were confirmed by antigenic testing.

Antigenic testing and not PCR (PCR = the best?)

Compared with the Danish National Patient Registry the database covers 96% of patients discharged with an RSV-specific diagnosis, and the reliability of the Danish Hospital Registers has been demonstrated in several studies.¹⁵ Data on use of Palivizumab was obtained from the Danish Registry of Medicinal Product Statistics.

5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?
- Yes

6. Is the assessment of outcome made blind to exposure status?
- Insufficient information to answer

7. Is the follow-up sufficiently long to measure all relevant outcomes?
- Yes

Children were followed from birth to 23 months of age or to their first RSV hospitalization or to a diagnosis of an acquired chronic disease or to June, 2003

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?
- Insufficient information to answer



Lydon-Rochelle 2001 ³⁸		Explanation
SELECTION BIAS		
1. Can selection bias sufficiently be excluded? • Yes	Data were obtained from the Washington State Birth Events Record Database. This data base links more than 95 percent of birth certificates in Washington State with maternal and infant records from the Comprehensive Hospital Discharge Reporting System for the hospitalization associated with delivery.	
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? • Yes	The following variables, reported at the time of the second delivery, were examined for possible confounding effects in all analyses: maternal age; race or ethnic background; marital status; smoking status during pregnancy; presence or absence of pre-existing diabetes mellitus, chronic hypertension, moderate-to-severe preeclampsia, and genital herpes; interval between the deliveries; payer; hospital level; infant birth weight and estimated gestational age; presence or absence of breech presentation; and presence or absence of placenta praevia. Variables were considered to be confounders if their inclusion changed the model's relative risk for uterine rupture at the second delivery associated with any labour-status category by 10 percent or more.	
DETECTION BIAS		
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? • Yes	A delivery was classified as a repeated cesarean delivery without labour if "repeat cesarean no labor" was checked on the birth certificate and if labour-related procedure or diagnosis codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) were not recorded on hospital-discharge forms. Labour was considered to have been induced if "induction of labour" was checked on the birth certificate or if any ICD-9-CM medical-induction procedure or diagnosis codes were recorded in hospital-discharge data. Induced labour was classified as induction of labour with prostaglandins if ICD-9-CM procedure code 96.49 was recorded on the hospital-discharge form. All other induced labour was classified as induction of labour without prostaglandins.	
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? • Yes	Uterine rupture was considered to have occurred if ICD-9-CM diagnosis code 665.0 or 665.1 was recorded on the hospital-discharge form.	
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? • No		
6. Is the assessment of outcome made blind to exposure status? • Not possible in this type of exposure		



7. Is the follow-up sufficiently long to measure all relevant outcomes?

- Yes

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?

- Yes

MacArthur 2011³⁹

Explanation

SELECTION BIAS

1. Can selection bias sufficiently be excluded?

- Yes

The sample was all women who delivered over a 12-month period (1993/94) in three maternity units, in Aberdeen (UK), Birmingham (UK) and Dunedin (New Zealand), and were followed up 12 years later. They were not allocated to one specific group but their health state, the baby's presentation and the labour progression will determine the mode of delivery. Comparison of baseline characteristics of women who did and did not respond at 12 years was performed.

2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?

- Insufficient information to answer

Adjustment was made for the following factors: maternal age at first birth, total number of births, BMI and ethnic origin. Measurement of these factors was self-reported, or not reported. They were included in a logistic regression model.

DETECTION BIAS

3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?

- Yes

Baseline data on maternal and obstetric characteristics were obtained for all deliveries from routine hospital case-notes. Follow-up questionnaires at 6 and 12 years obtained date and mode of every delivery, which enabled delivery mode history to be determined.

4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?

- Yes

The outcome measure of interest was faecal incontinence (FI) 12 years after the index birth. To assess FI, women were asked, 'do you ever lose control of bowel motions (stool/faeces) from your back passage in between visits to the toilet?' Optional responses were 'never', 'occasionally', 'sometimes', 'most of the time' and 'all of the time'. More severe FI was defined as that occurring more often than 'occasionally'.

The questions were designed by the study team (no suitable validated questionnaires on incontinence)



MacArthur 2011 ³⁹	Explanation
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? Yes	A postal questionnaire was sent at 3 months postpartum to assess prevalence of FI. The aim of the 12-year follow up was to investigate whether incontinence at this time was less common in women who had only ever delivered by caesarean section relative to those who had only ever had spontaneous vaginal births.
6. Is the assessment of outcome made blind to exposure status? - No → Does this has an influence on the assessment of outcome? - No	Not reported; but women completed themselves and returned postal questionnaires (relating to outcomes) 3 months and 12 years after index birth.
7. Is the follow-up sufficiently long to measure all relevant outcomes? Yes	Yes, the mean duration of follow-up was 12.9 years (SD 0.67; range 10.6–14.3).
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? No	Rate of follow up at 12 years might be seen as the main limitation of the study at just under 50% (48.7%) of those initially contacted at 3 months.
Magnus 2011 ⁴⁰	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? No	Population-based study (pregnant women in Norway from 1999 through 2008 but selection of some setting (38/50), poor participation (38,5% among pregnant women and 59,1% for response rate, sampling frame comprising pregnant women who attend routine ultrasound examination (for practical reasons). However, according to Nilsen 2009, prevalence estimates of exposures and outcomes, but not estimates of exposure outcome associations are biased due to self-selection in the Norwegian Mother and Child Cohort Study (MoBa).
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? Yes	Factors that could plausibly influence the associations examined were identified on the basis of I - MBRN literature and preanalytical assumptions. Data on maternal prepregnancy factors: BMI, completed years of education, and atopic status (asthma, hay fever, atopic dermatitis, animal hair allergies, and/or other allergies) (based on questionnaire). Data on maternal chronic condition: cardiovascular heart disease, hypertension, chronic renal disease, and/or diabetes (based on the Medical Birth Registry of Norway).



Magnus 2011 ⁴⁰	Explanation
	Pregnancy-related data: maternal smoking during pregnancy and preference for delivery by caesarean section (questionnaires); Preference for CS included the mother's agreeing to a question asked during pregnancy stating that, if she could choose, she would deliver by a caesarean section. Pregnancy-related data on pregnancy complications preeclampsia/ eclampsia, pregnancy-induced hypertension, and HELLP syndrome (hemolytic anaemia, elevated liver enzymes, and low platelet count), in addition to duration of membrane rupture (based on MBRN). Information at the time of delivery: maternal age, previous delivery by CS, marital status, parity, infant's gender, birth weight in grams and gestational age (MBRN). Information on whether the child was still breastfed at 6 months of age and day care attendance before 18 months (questionnaires).

DETECTION BIAS

3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?	Records from the Medical Birth Registry of Norway
• Yes	
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?	Questionnaires were filled out by the participating mothers at the time of recruitment, in the 22nd gestational week, in the 30th gestational week, and when the child was 6, 18, and 36 months of age
• No	
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	
• Yes	
6. Is the assessment of outcome made blind to exposure status?	
• Insufficient information to answer	
7. Is the follow-up sufficiently long to measure all relevant outcomes?	
• Yes	

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?	
• No	

Mamun 2013⁴¹

Explanation

SELECTION BIAS

1. Can selection bias sufficiently be excluded?
 - No

In total, 8 556 consecutive public women were approached at their first obstetrical clinic visit at Mater Hospital during the baseline survey and were invited to participate in the study. 7 223 women constituted the cohort.

The major losses were women who had their child at another hospital (usually due to change of residence) and miscarriages.

The resulting sample appears to be representative of public obstetrical patients but differs from private obstetrical patients in a number of characteristics. Public patients are predominantly from middle to lower socioeconomic status (SES) groups (lower family income and education levels), they are much more likely to be tobacco smokers, to be unmarried at the time they were recruited and more frequently exhibited a range of risk characteristics generally associated with poorer health outcomes.

Initial attempts to recruit a sub-sample of private patients were of limited success and a decision was, therefore, made to obtain as complete a sample of public patients as possible.

Because of limited funding, at 21 years, physical assessments was conducted in a subsample of nearly 2,664 young adults.

There were 520 mothers who delivered two newborns during 1981–1983 recruitments. However, at 21-year follow-up, of 2 625 adult offspring who provided measured heights and weights and had mode of delivery data at birth, only 185 sibling pairs had provided usable data for the main analysis.

2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?
 - Yes

Available potential confounders were maternal age at birth, offspring sex, race, maternal educational attainment, maternal smoking during pregnancy, gestation, birth weight, maternal pre-pregnancy BMI, gestational weight gain during pregnancy, and hypertensive disorder of pregnancy.

Women characteristics differed between VD and CS (hypertensive disorder of pregnancy, heavy smoking during pregnancy, mother age, gestational age at delivery, birth weight, pre-pregnancy BMI and proportion of obese).

The multivariable model was adjusted for maternal age at delivery, educational attainment, maternal smoking during pregnancy, parental race, gestation, birth weight, gestational weight gain, hypertensive disorder in pregnancy, maternal pre-pregnancy BMI, and duration of breastfeeding.

DETECTION BIAS



Mamun 2013 ⁴¹	Explanation
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? • Yes	Based on records on the obstetric sheet
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? • Yes	Maternal questionnaires when their offspring were 6 months and 5, 14, and 21 years of age. In addition, at 5, 14, and 21 years, detailed physical, cognitive, and developmental examinations of the offspring (with clear definition of how to measure and multiple measures) At 14 and 21 years, health, social, and lifestyle questionnaires completed by the offspring's.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? • Yes	
6. Is the assessment of outcome made blind to exposure status? • Insufficient information to answer	
7. Is the follow-up sufficiently long to measure all relevant outcomes? • Yes	21 years
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? • Yes and No	Analysis concerned a sample of 2382 offspring's from 7223 women included at the beginning of the project. According to the authors, the disproportionate loss to follow-up may have led to underestimates of the strength of associations although they had previously used multiple strategies to assess the effect of attrition on the estimates of association, and they had conclude that substantial variations in loss to follow-up had very little effect on the findings. In Najman 2015, an analysis of the attrition bias of this cohort led the author to notice that "Those disproportionately lost to follow-up are young, economically disadvantaged, of separated/divorced marital status and with higher rates of anxiety, depression and alcohol, tobacco and illicit substance use behaviour. Consequently, it is routine to undertake some forms of adjustment and repeatedly finding that after adjustment for loss to follow-up the results remain unaffected.



Momen 2014 ⁴²	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? • Yes	Based on nationwide data where all live born children are assigned a unique civil register number at birth or immigration. Were included all children with a recorded mode of delivery born in Denmark from 1973 to 2007 and Sweden from 1973 to 2006, and, as a result of national regulation, a random sample of 90% of children born in Finland from 1987 to 2007.
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? • No	Covariates were selected a priori: potential confounders at baseline (birth) included birthweight (<2500, 2500–3999, ≥4000 g), gestational age (<37, ≥37 weeks), multiplicity (single or multiple birth), maternal age (≤26, 27–30, ≥31 years), and parity (1, 2, ≥3). In sub analyses, there was also adjustment for maternal status in the labour market (available from 1981 onwards in Denmark, 1973 onwards in Sweden and 1990 onwards in Finland), maternal smoking status during pregnancy (from 1991 in Denmark, 1983 in Sweden and 1987 in Finland), congenital anomalies (in Denmark from 1977), paternal age group (in Denmark and Sweden), 5-minute Apgar score (from 1978 in Denmark and 1973 in Sweden), 1-minute Apgar score (in Sweden and Finland) and country of birth's CS rate by birth year. However, no all potential confounders were taken into account (e.g. environmental exposure)
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? • Yes	Information on mode of delivery was obtained from the Medical Birth Registers for the entire period for Finland and Sweden. For births in Denmark before 1994, information was obtained from the Medical Birth Register; for births from 1994 onwards, information was obtained from the Danish National Hospitalisation Register, using the ICD-10 codes. In Sweden, information on the type of CS (planned versus unplanned) was available after 1990. Elective caesarean delivery was defined as CS before the onset of labour and unplanned CS was defined as CS where labour started spontaneously or by induction. In Finland, an indicator for elective CS was introduced in October 1990 and, in January 2004, a division for urgent and emergency CS was introduced. In the Danish data, it was possible to distinguish between elective and unplanned CS between 1982 and 1990, and then from 1994 onwards, as some ICD codes for CS indicate the type (elective and emergency CS ICD-10 codes O82.0 and O82.1, respectively).



Momen 2014 ⁴²	Explanation
	Where there was no information on planning, type was classified as unknown.
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? • Yes	Data on cancer diagnoses were extracted from the Danish, Swedish and Finnish Cancer Registers. The main outcomes of interest were all incident cancers (ICD-7 codes 104–205; ICD-10 codes C00–97) diagnosed before the children's 15th birthday. In addition, more specific childhood cancer diagnoses were considered, including leukaemia (ICD-7 204; ICD-10 C91–95; ICD-O C42; and morphology codes 9800–9948), Hodgkin's lymphoma (ICD-7 201; ICD-10 C81; ICD-O C77; and morphology codes 9650–9667), non-Hodgkin's lymphoma (ICD-7 200 and 202; ICD-10 82–85; ICD-O C77; and morphology codes 9590–9599 and 9670–9728), central nervous system and sympathetic nervous system tumours (ICD-7 193; ICD-10 C47 and C70–72), renal tumours (ICD-7 180; ICD-10 C64), hepatic tumours (ICD-7 155; ICD-10 C22) and testis cancer (ICD-7 178; ICD-10 C62). The cancer registries have high levels of completeness in Denmark, Sweden and Finland.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? • Yes	• Children diagnosed with cancer within 6 months of birth were excluded to remove cancers that may have been present at birth (n = 830, 6.9% of those with a childhood cancer diagnosis) • Children who were diagnosed with cancer but did not have a date of cancer diagnosis were also excluded (n = 104, 0.9% of those with a childhood cancer diagnosis).
6. Is the assessment of outcome made blind to exposure status? • Insufficient information to answer	
7. Is the follow-up sufficiently long to measure all relevant outcomes? • Yes	The follow-up started at birth, and ended at the first of the following events: relevant cancer diagnosis, death, emigration, the day before the 15th birthday or end of follow-up (31 December 2006 in Sweden, 31 December 2007 in Denmark and 31 December 2010 in Finland). Follow-up for cancer of the testis was extended beyond 15 years of age because the incidence peaks after childhood (between 25 and 34 years).³³ Data on cancers diagnosed from 15 years of age were available in Denmark and Sweden only.
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? • Insufficient information to answer	



Moore 2012 ⁴³	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? • Yes	A population cohort of singleton live births between 1996 and 2005 was identified from the Midwives' Notification System detailing pregnancy, labour and birth details, the Birth and Death Register and the Hospital Morbidity Database System providing details of all hospitalisations throughout WA. Data were extracted using Western Australian Data Linkage System (WADLS), a record linkage system that brings together data from numerous population-based administrative health datasets
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? • Yes/No	The analysis included: maternal age, number of previous pregnancies, pre-eclampsia, gestational diabetes, breech presentation, maternal smoking during pregnancy, maternal asthma, infant gender, season of birth, gestational age in weeks, birth year and proportion of optimal birth weight (POBW), a measure which takes into account gestational duration, foetal sex, maternal age, maternal height and parity. Socio-economic status was measured using the Socio-Economic Index for Areas for relative disadvantage, derived from low income, low educational attainment, high unemployment and jobs in unskilled occupations. However, there were no data on breastfeeding.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? • Yes	Mode of delivery was obtained from the Midwives' Notification System. As many births had multiple modes of delivery recorded, an algorithm was developed that ranked the different delivery methods in the following order: emergency caesarean, elective caesarean, instrumental (combining vacuum and forceps) and spontaneous vaginal so that a delivery was classified as an elective caesarean if that was one of the modes recorded regardless of other information on the midwives' form unless an emergency caesarean was noted. According to guidelines for completion of the midwife form, an elective caesarean is defined as a planned procedure prior to the onset of labour and before spontaneous rupture of membranes and without any procedure used to induce labour. These guidelines also state that if a woman is scheduled for an elective caesarean and either goes into spontaneous labour or has a spontaneous rupture of membranes and the caesarean section is performed prior to the intended elective caesarean section, then the delivery is recorded as an emergency caesarean. Mode of delivery was available for all births.



Moore 2012 ⁴³	Explanation
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? Yes	Hospitalisations for both bronchiolitis and pneumonia under 24 months of age were identified using one principal and 20 additional International Classification of Diseases (ICD) diagnosis codes (ICD-10 code J21 for bronchiolitis admissions and ICD-10 codes J12–J18, B59, B05.2, B37.1 and B01.2 for pneumonia admissions. Admissions for bronchiolitis or pneumonia within 14 days of a previous admission were classified as a single episode. If an admission had ICD-10 codes for both bronchiolitis and pneumonia, the admission was coded as pneumonia.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? Yes	
6. Is the assessment of outcome made blind to exposure status? Insufficient information to answer	
7. Is the follow-up sufficiently long to measure all relevant outcomes? Insufficient information to answer	The follow-up of participants is 23 months. No argument was provided to justify this duration.
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? Yes	Based on registry

Mueller 2015 ⁴⁴	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? a. No	At the beginning of the cohort (Whyatt 2002), the participation rate was 70% (360 women) and there is a difference between women who refused and the other: women who agreed to participate were somewhat younger (24 ± 4.9 vs. 25.4 ± 5.4 years, $p = 0.06$, t-test), and a higher proportion were African American (44% vs. 39%, $\chi^2 = 1.2$, $p = 0.3$) We have no information on the subsequent recruitment.



Mueller 2015 ⁴⁴	Explanation
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? a. Yes	The questionnaire administered during pregnancy collected information on demographics, history of passive smoke exposure, educational and income levels, receipt of public assistance during pregnancy, maternal height and pre-gravid weight, and number of previous live births. Infant sex, birth weight, and whether the mother was diagnosed with diabetes or hypertension during pregnancy were determined from medical records, and breastfeeding was determined by questionnaire during follow-up. Several adjusted analysis were performed.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? a. Yes	Based on the mothers' and infants' medical records by research staff following delivery
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? a. Yes	At age 7 years, weight (to the nearest 0.1 kg) and body composition were measured using a Tanita scale (model BC-418; Tanita Corporation of America, Arlington Heights, IL, USA) while the child wore light clothes and no shoes. The Tanita scale calculated percentage of body fat (% body fat), fat mass and lean mass using bioimpedance formulas validated in children as young as 7 years. Height (to the nearest 0.1 cm) was obtained using a Detecto Cardinal 750 digital scale/stadiometer (Cardinal Scale Manufacturing Company, Webb City, MO, USA) until January 2010, and thereafter with the Holtain-Harpender Wall Mounted Stadiometer Counter 602VR (Holtain Limited, Crymch, UK). Waist circumference was measured halfway between the iliac crest and the lowest rib to the nearest 0.5 cm using non-stretchable tape.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? a. Yes	
6. Is the assessment of outcome made blind to exposure status? a. Insufficient information to answer	
7. Is the follow-up sufficiently long to measure all relevant outcomes? a. Yes	However obesity at 7 years is not sufficient because some difference could be observable only after puberty.
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? • No	Finding not changed with sensitivity analyses using inverse probability weights for successful follow-up to assess potential bias because of incomplete follow-up on effect estimates

**Mueller 2015⁴⁴****Explanation**

However, the authors mentioned they cannot rule out residual bias from unmeasured factors that influence drop out, and that themselves were associated with exposure and child anthropometric outcomes.

O'Neill 2014⁴⁵**SELECTION BIAS**

1. Can selection bias sufficiently be excluded?
 - Yes

This Danish population register-based cohort study covered all admissions in Danish hospitals between 1982 and 2010. All primiparous live births were eligible for analyses. No exclusion criteria were defined.

2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?
 - Insufficient information to answer

Detailed information on previous recognized pregnancy loss, access to fertility services and underlying medical conditions including diabetes, placenta praevia and pre-eclampsia and key potential confounders such as smoking and BMI, were available for the current analyses.

Important maternal and infant covariates were included.

However, no information was provided on how these confounders were measured.

DETECTION BIAS

3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?
 - Yes

Mode of delivery in the first live birth was classified according to the recorded indication for mode of delivery: (i) SVD, (ii) operative vaginal delivery [assisted forceps or vacuum delivery], (iii) emergency Caesarean section (i.e. unplanned Caesareans due to complications for example, foetal distress), (iv) elective Caesarean section (planned Caesarean section with or without medical indication) and (v) maternally requested Caesarean section (recorded as a tick box option indicating maternal choice to elect a Caesarean). Data for maternally requested Caesarean section were available from 2002 to 2010 only.

4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?
 - Yes

Two outcomes were evaluated: rate of subsequent live birth following the index delivery and median time to next live birth (defined as the time elapsed beginning at the date of birth of the index child until the date of birth of the subsequent live born child).

Diagnostic information is based on the Danish version of the International Classification of Disease 8th revision (ICD) [from 1977 to 1993], and the ICD-10th revision (from 1994 to the present time).

5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?

This is sequentially impossible.



O'Neill 2014⁴⁵

- No

6. Is the assessment of outcome made blind to exposure status?
- Not possible in this type of exposure

However, the risk of bias is very low since outcomes is either a dichotomic answer (subsequent birth or not) or a time before the second birth.

7. Is the follow-up sufficiently long to measure all relevant outcomes?
- Yes

All women with index live births were followed until their subsequent live birth or censored (maternal death, emigration or study end, i.e. December 2010). The Danish Civil Registration System (CRS) data include information on over 830 000 women spanning 28 years of follow-up.

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?
- Yes

See point 7.

O'Neill 2015⁴⁶

Explanation

SELECTION BIAS

1. Can selection bias sufficiently be excluded?
- No

The study population was restricted to include all women with a first live birth in AUH between 25 August 1989 and 31 December 2010. Only women who were recruited into the study were included.

The reasons for which a delivery mode was chose above another are not reported.

Only women who agreed to participate in the ABC study are included in the analyses and therefore non-responders may be different from women who agreed to take part.

2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?
- Insufficient information to answer

Maternal characteristics collected included: age in years; country of origin; pre-pregnancy BMI; smoking status (before and during pregnancy); marital status (data collected from 1998 to 2010); educational attainment (data collected from 1998 to 2010); obstetric history (history of stillbirth, miscarriage or ectopic pregnancy before the first live birth); co-morbidities (including pre-eclampsia, eclampsia, placenta praevia, placental abruption, diabetes and gestational diabetes) and whether the pregnancy was planned (data collected from 1992 to 2010). Infant characteristics included: Apgar score; birthweight, length, sex and gestation.

Important maternal and infant covariates were included.

However, no information was provided on how these confounders were measured.

DETECTION BIAS



O'Neill 2015 ⁴⁶	Explanation
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? Yes	Mode of delivery was recorded by the midwife present at time of delivery as outlined in the birth registration form. Registration forms are manually checked with medical records by a research midwife before data entry to ensure data accuracy and validation. Authors re-classified mode of delivery from 11 categories into six as follows: (1) SVD (reference group), (2) operative vaginal delivery (forceps and vacuum [soft and hard] deliveries), (3) breech vaginal delivery (external cephalic breech, other types of breech deliveries), (4) vaginal delivery complicated by shoulder dystocia (arm dystocia, and shoulder dystocia [McRoberts]), (5) emergency caesarean section (including emergency but planned caesarean) and (6) elective caesarean section (including caesarean on maternal request).
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? Yes	The rate and time to next live birth following the index delivery was the outcome of interest in the current study. Time to next live birth was defined as the time elapsed from the date of birth of the index child to the date of birth of the subsequent live born child with the unit of measurement recorded in days. This information was obtained from the questionnaire completed by mothers and the birth registration form completed by midwives in the ABC cohort.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? No	This is sequentially impossible.
6. Is the assessment of outcome made blind to exposure status? Not possible in this type of exposure	However, the risk of bias is very low since outcomes is a dichotomic answer (subsequent birth or not).
7. Is the follow-up sufficiently long to measure all relevant outcomes? No	Women were recruited from 1989 to 2010. It is impossible to know the length of follow-up for the last years of enrolment. Additional analysis were performed with a minimum of 12 months follow up for each woman (i.e., only women giving birth up until 31 December 2009 were included in this analysis) Authors concluded that 12 months are sufficient for a woman to have a second live birth → doubtful
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? No	Women were followed up from the date of birth of the first child until the subsequent live birth. Women with no subsequent live birth were followed up until the end of the study period (31 December 2010). In this study it was not possible to identify any women who died, emigrated or had a subsequent live birth outside of the AUH municipality since the first live birth.

**O'Neill 2014⁴⁷****SELECTION BIAS**

1. Can selection bias sufficiently be excluded?
 - Yes

This Danish population register-based cohort study covered all admissions in Danish hospitals between 1982 and 2010 (n = 832 996), with follow-up until the next event (stillbirth, miscarriage, or ectopic pregnancy) or censoring by live birth, death, emigration, or study end. All primiparous live births were eligible for analyses (including singleton and multiple gestation (twins or more) deliveries). No exclusion criteria were defined.

2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?
 - Insufficient information to answer

Maternal covariates included maternal age, maternal country of origin, birth type (singleton or multiple delivery), smoking status (data from 1997–2010), maternal body mass index (BMI) (data from 2003–2010), obstetric history, history of fertility treatment (data from 1994–2005), maternal educational attainment, mother's and father's gross income, mother's marital status, and comorbidities in the first live birth. Adjustments were performed for medical complications of the first live birth including delivery type, diabetes, gestational diabetes, placenta praevia, placental abruption, and hypertensive disorders. Infant covariates included birth weight, length, sex, and gestational age. However, no data were available on known risk factors, including the number of previous sexual partners, history of pelvic inflammatory disease, and age at first intercourse.

Unfortunately, no information was provided on how these confounders were measured.

DETECTION BIAS

3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?
 - Yes

Mode of delivery in the first live birth was classified according to the recorded indication for mode of delivery: (i) SVD = reference group, (ii) operative vaginal delivery [assisted forceps or vacuum delivery], (iii) emergency Caesarean section (i.e. unplanned Caesareans due to complications for example, foetal distress), (iv) elective Caesarean section (planned Caesarean section with or without medical indication) and (v) maternally requested Caesarean section (recorded as a tick box option indicating maternal choice to elect a Caesarean). Data for maternally requested Caesarean section were available from 2002 to 2010 only.

4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?
 - Yes

Stillbirth was defined as the death of a foetus at 28 weeks gestation or later until 2004. After this period, the definition was changed to the death of a foetus born after 22 completed weeks' gestation. Stillbirth was recorded according to ICD-8 code 779 and ICD-10 code P95. Data for all stillbirths were available from 1982–2010; however, data on the specific causes of stillbirth were available from 1982–1996 only.

**O'Neill 2014⁴⁷**

Miscarriage was defined as a pregnancy spontaneously ended before 28 weeks gestation until April 2004, and before 22 weeks gestation from 2004 onwards. Miscarriage was recorded according to the ICD-8 codes 634.2 and 643 (643.0, 643.1, 643.2, and 643.9) and ICD-10 codes O02 and O03. Ectopic pregnancy was recorded using the ICD-8 code 631 and ICD-10 code O00.

Diagnostic information is based on the Danish version of the International Classification of Disease 8th revision (ICD) [from 1977 to 1993], and the ICD-10th revision (from 1994 to the present time).

5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?

- Yes

This is possible for stillbirth and miscarriage.

6. Is the assessment of outcome made blind to exposure status?

- Not possible in this type of exposure

However, the risk of bias is very low.

7. Is the follow-up sufficiently long to measure all relevant outcomes?

- Yes

Women were followed up from the date of birth of the first child until the subsequent reproductive event of interest (stillbirth, miscarriage, or ectopic pregnancy) or until censoring due to live birth, death, emigration, or study end (December 31, 2010). The Danish Civil Registration System (CRS) data include information on over 830 000 women spanning 28 years of follow-up.

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?

- Yes

See point 7.



Patel 2005 ⁴⁸	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? Yes	14 663 women recruited antenatally with a due date between 1 April 1991 and 31 December 1992 with a response rate of over 80% in all categories (elective or emergency CS and SVD or IVD)
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? Yes	Several variables were measured in this retrospective cohort. Those were group into 'categories' were created in which similar risk factors were grouped together. These nine categories were: sociodemographic; past medical history; obstetric history; subfertility; pregnancy activity/work since 18 weeks' gestation; antenatal history; diet; infant size and infant characteristics, and a tenth category of labour, used only in the emergency Caesarean section analysis.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? Yes	Exposure was well documented.
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? Yes	Edinburgh postnatal depression scale score ≥ 13 at eight weeks postnatal on self-completed questionnaire.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? No	No
6. Is the assessment of outcome made blind to exposure status? - No → Does this has an influence on the assessment of outcome? - No - Not possible in this type of exposure	No, but inevitable
7. Is the follow-up sufficiently long to measure all relevant outcomes? Yes	13 weeks or more appears to be sufficient for this kind of analysis of immediate post-natal depression.
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? Yes	High response rate across all categories ($> 80\%$) in 14663 women recruited antenatally.

**Ponsonby 2009⁴⁹****Explanation****SELECTION BIAS**

1. Can selection bias sufficiently be excluded?

- Yes

The entire Victorian birth cohort 1983 to 1998 was included.
The CD register included all Victorian IBD cases

2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?

- No

There was adjustment for sex, maternal age, marital status, SES, interventional births, proportion of firstborn children, or congenital abnormality.
No information on maternal and paternal history, on breastfeeding...

DETECTION BIAS

3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?

- Yes

The Victorian Perinatal Data Collection Unit (VPDCU) collects data on every birth of 20 weeks gestation or birth weight over 400 g and the birth record database, which commenced in 1982, is 99% complete. The exposure was classified as elective caesarean section, emergency caesarean section, forceps/vacuum extraction/any interventional delivery and spontaneous delivery.

4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?

- Yes

The CD cases were diagnosed at the Royal Children's Hospital or Monash Medical Centre, Melbourne. Children were identified as having CD if confirmed by histology or radiology

From 1983 to 1998 live births in Victoria, 278 developed paediatric onset CD by age 16 and were successfully linked to the Perinatal Morbidity Statistics database. An additional 7 possibly Victorian-born cases could not be verified or record-linked, and so were not included in this study.

5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?

- Yes

6. Is the assessment of outcome made blind to exposure status?

- Insufficient information to answer

Moreover, the authors mentioned that those women who have an interventional delivery are more likely to present their child for medical specialist care for mild gastrointestinal symptoms than other women.

7. Is the follow-up sufficiently long to measure all relevant outcomes?

- No

15 year maximum is not long for a disease which can be diagnosed during adulthood.

ATTRITION BIAS

8. Can selective loss-to-follow-up be sufficiently excluded?

- No

.



Pyrhönen 2014 ⁵⁰		Explanation
SELECTION BIAS		
1. Can selection bias sufficiently be excluded? a. Yes		This study comprised all children born between April 2001 and March 2005, who lived in the province of South Karelia, and were 1 to 4-year-olds when their parents were invited to take part in the questionnaire-based survey (N = 4779). The study population is a subset of the whole population of the SKARP study (N = 5973), identified from the Finnish Population Register Centre, excluding all children who were newborn at the time of the survey.
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? a. Yes		Main confounders were gender, birth order and weight at birth, duration of pregnancy, parental allergies, total duration of breastfeeding and smoking during pregnancy and were taken into account using a Cox model.
DETECTION BIAS		
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? a. Yes		The mode of the delivery was asked during an interview with parents, choosing between normal birth and caesarean section (without specifying if emergency or elective).
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? a. No		The results of all the allergy tests <i>that had been ordered by a physician for clinical purposes</i> , and performed between April 2001 and September 2006, were collected from all healthcare units in the area. The study subjects were <i>not exposed to any diagnostic procedures</i> because of the study (so children without symptoms were not exposed to an assessment of the outcome). For those who were not tested, information was asked to parents using a questionnaire.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? a. Yes		Newborns cannot be diagnosed with asthma before their birth.
6. Is the assessment of outcome made blind to exposure status? a. Insufficient information to answer		
7. Is the follow-up sufficiently long to measure all relevant outcomes? a. No		All information related to the exposure were collected by interviewing the parents 1-4 years after the birth of their child (there were 835 children aged of 1 year, 819 aged of 2 years, 759 aged of 3 years and 768 aged of 4 years).
ATTRITION BIAS		
8. Can selective loss-to-follow-up be sufficiently excluded? • Insufficient information to answer		The number of patients that were loss-to-follow up is not documented.



Rauh 2012 ⁵¹	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? a. Partly	The study was conducted as part of the Franconian Maternal Health Evaluation Studies (FRAMES) FRAMES is a prospective and longitudinal cohort investigation that included a total of 1,100 pregnant women during the period from July 2005 to February 2007 in one German University hospital. The patients were asked to complete structured questionnaires for psychometric assessments, common medical and obstetrics related history. After the completion of the questionnaire, a structured interview was performed to ensure a high completeness of the answered questions. FRAMES included women aged 18 or over with an intact pregnancy and at least 30 weeks' gestation. The women registered during pregnancy at the outpatient department of our University Perinatal Centre. However, selection bias cannot be completely excluded since it concerns a University hospital with a selected population and women who agreed to participate.
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? a. Unclear	Unclear
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? a. Yes	Mode of delivery is clearly defined.
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? a. Yes	Three questionnaires: after 30 weeks gestations, 48-72 hours after birth and at 6 months after birth (n=865, 81.4%). The first two were by personal interview by trained medically qualified staff while the third was through a telephone interview.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? a. Unclear	Unclear
6. Is the assessment of outcome made blind to exposure status? a. Not possible in this type of exposure	No
7. Is the follow-up sufficiently long to measure all relevant outcomes? a. Yes	Up to 6 months after birth



Rauh 2012 ⁵¹		Explanation
ATTRITION BIAS		
8. Can selective loss-to-follow-up be sufficiently excluded?		High response rate, 81.4% after six months.
• Yes		
Regan 2013⁵²		
SELECTION BIAS		
1. Can selection bias sufficiently be excluded?		Vital statistics data.
• Yes		
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?		Sociodemographic factors, medical risk factors, and pregnancy-related risk factors were also compared to assess influence on breastfeeding initiation rates.
• Yes		
DETECTION BIAS		
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?		
• Yes		
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?	Records	
• Yes		
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?		
• Insufficient information to answer		
6. Is the assessment of outcome made blind to exposure status?		
• Insufficient information to answer		
7. Is the follow-up sufficiently long to measure all relevant outcomes?		
• Yes		
ATTRITION BIAS		
8. Can selective loss-to-follow-up be sufficiently excluded?		
• Not applicable (no follow-up).		



Sevelsted 2015 ⁵³	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? Yes	The registry cohort of live born children in Denmark in the period 1973-2012. Children were followed for hospitalizations from 1977 or from date of birth. Children were followed until January 1 st 2012 or until age 16, emigration or death.
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? Yes	Confounders were chosen a priori as gender, parity, birth weight, gestational age, maternal age, mother smoking during pregnancy, maternal disease, multiple births, mother's use of antibiotics during pregnancy, and maternal employment/education. All confounders were included in the regression models as categorical variables in registry analyses. However, nothing is mentioned concerning paternal smoking and asthma.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? Yes	Yes, adequate birth records.
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? Yes	Yes, hospital records and ICD codes
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? NA	Not applicable
6. Is the assessment of outcome made blind to exposure status? Yes	Registry records
7. Is the follow-up sufficiently long to measure all relevant outcomes? Yes	Up to age 16
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? Yes	Only emigration or death. Other children are in the registry databases.



Sevelsted 2016 ⁵⁴	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? a. Yes	Two cohorts were used: • The COPSAC2000 birth cohort consists of 411 children born 1998-2001 to mothers with a history of asthma, excluding children born before 36 weeks of gestation and anyone suspected of chronic diseases or lung symptoms prior to inclusion. • The registry cohort of live born children in Denmark in the period 1997-2010
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? a. Yes	Confounders were chosen a priori as sex, parity, birth weight, gestational age, maternal age, mother smoking during pregnancy, maternal disease, multiple births, mother's use of antibiotics during pregnancy, and maternal employment/education. All confounders were included in the regression models as categorical variables in registry analyses. However, nothing mentioned concerning paternal smoking and asthma.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? a. Yes	In the COPSAC2000 cohort, caesarean delivery was a dichotomous variable. The National Registry classified caesarean delivery as: (1) elective caesarean performed before delivery; (2) emergency caesarean because of delivery complications performed during delivery; (3) emergency caesarean because of pregnancy complications performed during delivery; and (4) emergency caesarean performed before onset of labour. Children with no registration of caesarean delivery were coded as vaginal delivery. The different classifications were combined to comprise either caesarean delivery performed before rupture of membranes (1 and 4) or caesarean delivery performed after rupture of membranes (2 and 3).
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? a. Yes	In the COPSAC2000 cohort, asthma was diagnosed by trained physicians at the research unit in accordance with strict, standardized criteria. Asthma exacerbations were defined by need for oral prednisolone, high-dose inhaled corticosteroids, or acute hospitalization with asthmatic symptoms In the registry, asthma is defined as long-term recurrent use of inhaled corticosteroids: at least 200 defined daily doses filled at a pharmacy. The child becomes a case at first collection of medication. The Danish National Patient Registry covers all hospital admissions nationwide as well as children attending outpatient clinics. Asthma diagnosis in the National Patient Registry has previously been validated.



Sevelsted 2016 ⁵⁴	Explanation
	In the sensitivity analyses, 2 alternative definitions of childhood asthma was defined, based on asthma hospitalizations: (1) recurrent hospital admissions for asthma: at least 2 inpatient admissions (primary diagnosis of asthma ICD10: J45.x; J46.x) separated by at least 1 month (child is considered case at first admission); or (2) long-term outpatient attendance related to asthma: child followed in outpatient care (primary diagnosis of asthma ICD10: J45.x J46.x) for minimum 1 year (child becomes case at date of outpatient treatment initiation). For each definition, cases were compared with non-cases where non-cases were all children not fulfilling case definitions.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? a. NA	
6. Is the assessment of outcome made blind to exposure status? a. Insufficient information to answer	
7. Is the follow-up sufficiently long to measure all relevant outcomes? a. Yes	Max 14 years
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? Insufficient information to answer	
Silver 2006 ⁵⁵	Explanation
SELECTION BIAS	
1. Can selection bias sufficiently be excluded? Yes	This study consisted of a prospective observational cohort of women undergoing caesarean delivery from 1999 through 2002 at 19 academic medical centres within the National Institute of Child Health and Development Maternal-Foetal Medicine Units Network. Two groups were compared: women undergoing increasing number of caesarean deliveries were compared with those undergoing primary caesarean deliveries.



Silver 2006 ⁵⁵	Explanation
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? • Yes	Multivariable logistic regression analysis was performed to adjust for potential confounding variables contributing to adverse maternal outcome. Potential confounding variables included race, maternal age, insurance status, prenatal care, maternal disease, and gestational age at delivery.
DETECTION BIAS	
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? • Yes	The exposure is 1 CS versus repeat CS.
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? • Insufficient information to answer	Primary outcome variables included the occurrence of placenta accreta, placenta previa, bladder, bowel or ureteral injury, the need for hysterectomy, blood products and admission to the intensive care unit, and ventilator support, and the occurrence of deep venous thrombosis, pulmonary embolism, postpartum endometritis, wound infection, wound dehiscence, ileus, and maternal death. However, no details allow to check the similarity of their definitions in both groups.
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? • Insufficient information to answer	
6. Is the assessment of outcome made blind to exposure status? • No → Does this has an influence on the assessment of outcome? i. Insufficient information to answer	
7. Is the follow-up sufficiently long to measure all relevant outcomes? • Yes	All inpatient medical records were abstracted through 6 weeks postpartum. However, patients were not directly contacted to determine whether they had additional complications that were treated in institutions other than where their caesarean deliveries were performed. Thus, some late-onset complications, such as thrombosis or ureteral injury, may not have been ascertained.
ATTRITION BIAS	
8. Can selective loss-to-follow-up be sufficiently excluded? • Yes	



Van Berkel 2015⁵⁶

SELECTION BIAS

- | | |
|--|--|
| 1. Can selection bias sufficiently be excluded? | Staff recruitment; voluntary based |
| <ul style="list-style-type: none"> No | |
| 2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? | Several confounding factors obtained by questionnaires |
| <ul style="list-style-type: none"> Yes | |

DETECTION BIAS

- | | |
|---|--|
| 3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? | Midwives and hospital registries |
| <ul style="list-style-type: none"> Yes | |
| 4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? | Wheezing and physician-diagnosed asthma were assessed by questionnaire but this method is widely accepted in epidemiological studies according to the authors. |
| <ul style="list-style-type: none"> Yes | |
| 5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? | Newborns cannot be diagnosed with asthma before their birth |
| <ul style="list-style-type: none"> Not applicable | |
| 6. Is the assessment of outcome made blind to exposure status? | |
| <ul style="list-style-type: none"> Insufficient information to answer | |
| 7. Is the follow-up sufficiently long to measure all relevant outcomes? | But asthma is difficult to diagnose in young children |
| <ul style="list-style-type: none"> Yes | |

ATTRITION BIAS

- | | |
|--|--|
| 8. Can selective loss-to-follow-up be sufficiently excluded? | Difference in the characteristics of the non-responders and participants without FU data at age 6 y. |
| <ul style="list-style-type: none"> No | |

Watt 2012⁵⁷**SELECTION BIAS**

1. Can selection bias sufficiently be excluded?
- Yes

A quota (proportionate) sampling strategy was used to determine the number of participants from each hospital site (2 hospitals in each of the five geographic regions of Ontario).

Postpartum unit nurses or site managers attempted to assess all women for eligibility during the recruitment period and to invite all eligible women to participate. The number of women not assessed at each hospital site was documented.

Voluntary participation

2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?
- Insufficient information to answer?

Good description of the characteristics of the population but without clear comparison.

DETECTION BIAS

3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?
- Yes

For mode of delivery: hospital records

4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?
- Yes

For breastfeeding: Questionnaire

5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?
- Not applicable

6. Is the assessment of outcome made blind to exposure status?
- Insufficient information to answer

We have no information on the data known or unknown by the interviewer.

7. Is the follow-up sufficiently long to measure all relevant outcomes?
- Yes

Watt 2012⁵⁷**ATTRITION BIAS**

8. Can selective loss-to-follow-up be sufficiently excluded?
- Yes for data at 6 weeks.

The study sample included data on 2560 women in hospital; data about delivery method, data for breastfeeding in hospital and data for BF at 6-weeks postpartum were available for 97.5%, 99.6% and 90.1% women respectively. Due to financial constraints, questionnaires were collected at 6-month from women from nine hospital sites (n = 1823) and at 12-month from women from eight sites (n = 1310), representing 71% and 51% respectively of the initial sample.

3.4. Case-control studies

For the quality appraisal of cohort studies the Cochrane Collaboration's risk of bias tool was used as described in the report. Studies are described in the alphabetical order of the first author.

Table 6 – Quality appraisal for case-control studies using the Cochrane Collaboration's tool for assessing risk of bias

Karlström 2013⁵⁸**Explanation****SELECTION BIAS**

1. Are cases and controls a representative sample of the same source population?
- Yes
2. Are the same exclusion criteria used for both cases and controls?
- Yes
3. Are participants and non-participants compared to establish their similarities and differences?
- Yes

This study used data from the Swedish Medical Birth Register, which covers 97 to 99% of all births. All hospitals in Sweden are obligated to provide copies of their prenatal and delivery records to the register. Both cases and controls came from this registry. For both groups, the time period included was from 1997 to 2006.

Only singleton babies who presented in the vertex position were included in both groups.

Participants and non-participants were compared to establish their similarities and differences.

Women who had an elective caesarean section were older than the women who had a spontaneous onset to labour, and a dose-response effect was observed in the older age group. This group consisted of more multiparous women and more women who were born in Sweden. No differences were observed between the two groups in terms of civil status or smoking habits, but women who had a caesarean section without medical indication were more likely to have a higher Body Mass Index and infertility problems.

→ **Groups are not comparable**



Karlström 2013 ⁵⁸		Explanation
4. Are cases clearly defined and differentiated from controls? • Yes		Full-term caesarean sections where no medical indication was present are registered under a specific code (code O828 in the register). For comparison, two control groups were established from birth records for 13 774 women with full-term, singleton babies who presented in the vertex position with spontaneous onset of labour and the intention of a vaginal birth. The control groups were composed depending on the actual mode of delivery and were divided into those women who actually had a vaginal birth and those who ended up with an emergency caesarean section. Women whose labour was induced were excluded.
5. Is it clearly established that controls are non-cases? • Yes		See point 4.
DETECTION BIAS		
6. Are measures taken to prevent knowledge of primary exposure from influencing case ascertainment? • Insufficient information to answer		
7. Is exposure status measured in a standard, valid and reliable way? • Insufficient information to answer		No information can help us to be certain about the way the classification was done.
CONFOUNDING		
8. Are the main potential confounders identified and taken into account in the design and analysis? • No		No confounders were considered in this study. No details about the outcomes measured are provided (no definition, no indication about how they were evaluated).
DECISION		This study is not included due to high risk of bias

Kelmanson 2013 ⁵⁹		Explanation
SELECTION BIAS		
1. Are cases and controls a representative sample of the same source population? • Insufficient information to answer		Small population (community) based matched 1/1 case control study (40 cases/40 controls). Apparently healthy 5 year old singletons within a community sample identified through healthcare records.



Kelmanson 2013 ⁵⁹	Explanation
	Matching was done as closely as possible to the case children with respect to their age at study, sex, and date of birth. The, selection process is described as a simple random sample. However, the 100% participation rate seems unusual. It is unclear whether for the non-participants replacements were drawn. Moreover, the selection criteria included not only the normal ones but also for example: married couples, appropriate household condition, attending preschool day-care etc. It is unclear how this information was obtained and whether it was before or after patient selection for inclusion. Parents responded themselves using a reportedly validated 99 point questionnaire (CBLC 1.5/5). Another worry is that, although the title mentions CS on maternal request, but it is unclear how this was ascertained.
2. Are the same exclusion criteria used for both cases and controls? • Yes	Control children met the same inclusion criteria as the case children, except that they were born from uncomplicated vaginal deliveries. Required information was drawn from the pre-existing medical records stored at the paediatric out-patient centres.
3. Are participants and non-participants compared to establish their similarities and differences? • No	They were compared, but the study mentions that all parents of the recruited children (80: 40 cases/40 controls) agreed to participate. This is unusual. So is unclear whether those that refused were replaced by others which might introduce a selection bias. Children in the case group had a lower (38 weeks) gestation age than those in the control group (39 weeks). This difference is statistically significant. Children in the case group also have somewhat lower birthweight but this is not statistically significant. Both differences might be due to iatrogenic parameters (the decision for CS in the first place, or to confounding by indication). We found no information on the reason for CS.
4. Are cases clearly defined and differentiated from controls? • Yes	Yes, based on hospital records. However, worries about full participation rate. This might have led to bias. It is unclear how CS on maternal request was ascertained.
5. Is it clearly established that controls are non-cases? • Yes	See 4
DETECTION BIAS	
6. Are measures taken to prevent knowledge of primary exposure from influencing case ascertainment? • No	Although it seems difficult to so with a parental questionnaire who obviously know there exposure status.
7. Is exposure status measured in a standard, valid and reliable way? • Yes	Exposure status (VD or CS) was ascertained through health-care records. So this will influence his/her answers.



Kelmanson 2013 ⁵⁹		Explanation
CONFOUNDING		
8. Are the main potential confounders identified and taken into account in the design and analysis? Insufficient information to answer		The authors mention controlling for confounders although no explicit list of confounders was given. In the discussion it is mentioned that gestational age was used as a confounder to adjust for. It is also unclear where the information on the confounders came from: the authors mention a combination of the questionnaire and health care data. Health care served as the only sources of information 'such as birth weight and level of length of gestation'.

Malmberg 2012 ⁶⁰		Explanation
SELECTION BIAS		
1. Are cases and controls a representative sample of the same source population? Yes		All patients diagnosed with paediatric (<16 years) CD and born between 1973 and 2006 should be included since they were identified through the national Swedish patient Register. Each case was matched with 10 controls identified through the Medical Birth Register, which has recorded information on virtually all births in Sweden since 1973. Controls were selected at random among children born in the same week and at the same delivery unit with the same sex as their matched cases. Where fewer than 10 suitable controls were identified, usually due to a limited number of births in small delivery units, all those available were selected.
2. Are the same exclusion criteria used for both cases and controls? Insufficient information to answer		
3. Are participants and non-participants compared to establish their similarities and differences? Yes		There were no statistically significant associations with CD for gestational age, birth weight, or mother's age. The matching was based on delivery unit in order to ensure other aspects of cases and controls' living conditions and perinatal handling are similar.
4. Are cases clearly defined and differentiated from controls? Yes		Patients diagnosed with paediatric (<16 years) CD and born between 1973 –2006 were identified through the national Swedish patient Register, where the diagnosis associated with any inpatient admission or procedure, including colonoscopy, is recorded.



Malmberg 2012 ⁶⁰	Explanation
	Patients were identified when diagnosed with the codes for CD (ICD 8 (563,00), ICD 9 (K555A, K555B, K555C, K555X), and ICD 10 (K.50.0, K.50.1, K.50.2, K.50.9)). Where patients also received a subsequent diagnosis of ulcerative colitis, only those with a final diagnosis of CD were designated as cases.
5. Is it clearly established that controls are non-cases? • Yes	To be selected as controls, subjects had to be alive and resident in Sweden (defined by the Total Population Register) and without a diagnosis of IBD at the time that their matched case received a diagnosis of CD.
DETECTION BIAS	
6. Are measures taken to prevent knowledge of primary exposure from influencing case ascertainment? • Insufficient information to answer	
7. Is exposure status measured in a standard, valid and reliable way? • Yes	Exposure information was supplied by the same sources for both cases and controls. Information on perinatal exposures, including delivery mode and maternal diagnoses during and immediately after pregnancy, was provided by the Medical Birth Register. Additional information on neonatal infectious exposures for the mother and child was provided by the Inpatient Register. The Medical Birth Register also identified the number of older siblings. The association of CS with paediatric CD was analysed within the subset of term children born after 1981, where it is possible to determine if it was an elective or unplanned caesarean section.
CONFOUNDING	
8. Are the main potential confounders identified and taken into account in the design and analysis? • No	Adjustment was performed for socioeconomic index, maternal infections during pregnancy, number of older siblings, gestational age, and mother's. Males and females were examined together and then the analysis was stratified by sex. Parental socioeconomic index based on occupation for cases and controls was provided by the census that occurred nearest in time to the delivery. After 1981, maternal urinary tract infection during pregnancy was specifically recorded in the Medical Birth Register and this was assessed as a risk for paediatric CD, as well as being included in the adjusted analysis as an additional potential confounding factor signalling infectious events in the mother. However some confounding factors are lacking such as breastfeeding.



Marild 2012 ⁶¹	Explanation
SELECTION BIAS	
1. Are cases and controls a representative sample of the same source population? Insufficient information to answer	Cases were identified in the computerized registers of Sweden's 28 pathology Departments. (But what is its coverage?) The government agency Statistics Sweden then matched each individual with celiac disease with five controls from the general population by age at diagnosis, sex, calendar period, and county. 29 148 individuals with celiac disease were identified from which 11 749 individuals were included in the analysis.
2. Are the same exclusion criteria used for both cases and controls? Yes	
3. Are participants and non-participants compared to establish their similarities and differences? Yes	
4. Are cases clearly defined and differentiated from controls? Yes	Study participants consisted of 11 749 offspring with biopsy-verified celiac disease identified through histopathology reports from Sweden's 28 pathology departments and 53 887 age- and sex matched controls from the general population. The biopsies had been performed between 1969 and 2008. For each biopsy, the authors recorded (a) arrival date of the biopsies, (b) personal identity number, (c) morphology, and (d) topography (duodenum or jejunum). In individuals with more than one biopsy available statistics were based on first positive biopsy showing villous atrophy. More than 95% of Swedish gastroenterologists and paediatricians perform a small intestinal biopsy before celiac disease diagnosis.
5. Is it clearly established that controls are non-cases? Insufficient information to answer	The likelihood of a non-registered celiac disease in the control group is not mentioned.
DETECTION BIAS	
6. Are measures taken to prevent knowledge of primary exposure from influencing case ascertainment? Insufficient information to answer	
7. Is exposure status measured in a standard, valid and reliable way? Yes	The Swedish Medical Birth Register, which is of high quality, encompasses prospectively recorded data on more than 98% of all pregnancies since 1973. The register will only accept gestational age data between 22 and 46 weeks and birth weight data in the range of 300–7000 grams.

**Marild 2012⁶¹****Explanation**

Data on type of caesarean delivery were available in children born 1982-1989 and from 1991 onwards.

Potential misclassification of pregnancy data should not differ by celiac disease status and therefore not bias our results.

CONFOUNDING

8. Are the main potential confounders identified and taken into account in the design and analysis?
- Yes

Adjustment for parity, maternal age at delivery, education level, maternal diabetes mellitus, and maternal celiac disease as potential confounders.

In an additional multivariate analysis (model II), adjustment for smoking (births from 1983 and onwards).

In a separate analysis of caesarean delivery, adjustment for parental cohabitation (registered from 1982/1983 onwards).

In sub analyses, stratification for calendar period of birth and early diagnosed celiac disease (before age 2 years).

Breastfeeding is lacking but the link with celiac disease is not so clear.

Samuelsson 2015⁶²**Explanation****SELECTION BIAS**

1. Are cases and controls a representative sample of the same source population?
- Yes

All children who developed type 1 diabetes during the years 2000–2012 and were registered in SWEDIABKIDS were compared with a control group that consisted of children born in Sweden during the same years.

In Sweden, paediatric clinics treat all children and adolescents aged 0–18/19 years (in some cases up to 20 years of age) with diabetes from defined geographic areas. Thus, the register includes data on almost all (approximately 99%) children and adolescents with diabetes in Sweden.

For the controls, the Medical Birth Register (MBR) includes nearly all pregnancies that have resulted in births in Sweden since 1973 and contains information about the pregnancy, delivery and antenatal health of the child. Only 1–3% of deliveries are missing from the register each year. These cases are missing due to hospital errors in reporting.

2. Are the same exclusion criteria used for both cases and controls?
- Yes

No exclusion criteria



Samuelsson 2015 ⁶²	Explanation
3. Are participants and non-participants compared to establish their similarities and differences? • Yes	All patients (0-18/19 years of age) with type 1 diabetes in Sweden were included (= about 99% of all children with diabetes in Sweden)
4. Are cases clearly defined and differentiated from controls? • Yes	Based on a register concerning all paediatric clinics in Sweden (from 2008)
5. Is it clearly established that controls are non-cases? • Insufficient information to answer	Controls are children without a diagnosis of diabetes. However no search of diabetes was performed in the control group. The likelihood of unknown diabetes among the control group is not mentioned.
DETECTION BIAS	
6. Are measures taken to prevent knowledge of primary exposure from influencing case ascertainment? • Yes	The diagnosis of diabetes is based on clinical and biological symptoms, and not on screening. The mode of delivery should not influence this diagnosis.
7. Is exposure status measured in a standard, valid and reliable way? • Yes	The MBR includes nearly all pregnancies that have resulted in births in Sweden since 1973 and contains information about the pregnancy, delivery and antenatal health of the child. Only 1–3% of deliveries are missing from the register each year. These cases are missing due to hospital errors in reporting. The register is based on the medical charts from antenatal, obstetric as well as neonatal care.
CONFOUNDING	
8. Are the main potential confounders identified and taken into account in the design and analysis? • Yes/No	By use of the personal identification number of the women, information about height and weight in early pregnancy, parity, smoking habits, gestational week at childbirth as well as mode of childbirth was collected in the MBR. In addition, information about maternal diabetes was collected which corresponded to the diagnostic code O24 in ICD-10. In 1997, MBR started to report the different types of diabetes; before that the diagnosis of diabetes was not further specified (i.e. diabetes could be type 1, type 2 or gestational diabetes). In MBR, there are missing data on BMI in early pregnancy (n=12 021), smoking (n=2 703) and Apgar score (n=7 723). The major lacking information concerns the medical history of the fathers (as in most studies).



4. EVIDENCE TABLES

4.1. Systematic reviews and meta-analyses

Table 7 – Evidence tables for systematic reviews and meta-analyses

Azam 2014 ³	
Methods	
• Design	Systematic review and meta-analysis
• Source of funding and competing interest	• Source of funding: not stated. • Declaration of interest: The authors declare no conflicts of interest
• Search date	January 2013 and update in November 2013
• Searched databases	Medline, Embase, PubMed, Cumulative Index to Nursing and Allied Health Literature and the Cochrane Library. Hand searches of bibliographies from retrieved primary articles were also performed.
• Included study designs	Cohort studies
• Number of included studies	7 studies (6 observational studies and 1 RCT included in the review)
• Statistical analysis	• Relative risks (RR) and 95% confidence intervals (CI) for individual studies were plotted. • Heterogeneity was assessed graphically with forest plots and statistically using chi-square test and the I^2 value. • Random effects model was used for meta-analyses when heterogeneity was observed. • Funnel asymmetry was assessed to examine publication and related biases when there were sufficient studies.
Patient characteristics	
• Eligibility criteria	Low-risk women in their first pregnancy, who planned antenatally to deliver by caesarean section or vaginal birth and whose outcomes were grouped by antenatal intention to have caesarean section or vaginal birth (rather than by actual mode of delivery) and whose follow-up ensured removal of the influence of subsequent pregnancies on outcomes.
• Exclusion criteria	Studies that recruited women with caesarean section or vaginal birth and based their results on actual mode of delivery.
• Patient & disease characteristics	• Low risk women who decided before the birth to opt for a VD or a CS.
• Intervention group	Primary elective CS
• Control group	Spontaneous VD
Results	



The results were grouped by intention to give birth by caesarean section or vaginal birth.

• Maternal mortality	- RCT (Breech Trial; n= 2083 women): no difference in risk of maternal mortality between the two groups (RR 1.24, 95% CI 0.79–1.95, P=0.35) - Observational evidence (2 studies; n = 2 340 615 women): combined RR 0.19, 95% CI 0.0013– 27.27, P=0.51
• Postpartum haemorrhage (PPH)	RCT (Breech Trial; n= 2083 women): There was no difference in risk of PPH between the two groups (RR 0.77, 95% CI 0.34–1.75, P=0.53).
• Blood transfusion, as a marker of PPH	- Observational evidence (PPH; 2 studies; n = 4 589 women): combined RR 1.15, 95% CI 0.40–3.31, P=0.79 - Observational evidence (blood transfusion; 1 study; n = 144 705): combined RR 0.91, 95% CI 0.39–2.13, P=0.84)
• Postnatal depression (PND)	RCT (Breech Trial; n= 2083 women): There was no difference in risk of developing postnatal depression symptoms at 6 weeks (RR 6.94, 95% CI 0.36–134.2, P=0.2), 3 months (RR 0.93, 95% CI 0.70–1.24, P=0.68) and 2-year postpartum without any subsequent pregnancies (RR 0.90, 95% CI 0.62–1.30, P=0.60)
• Urinary incontinence	RCT (Breech Trial; n= 2083 women): A reduced risk of developing urinary incontinence symptoms was found at 3-month postpartum in the planned caesarean section group (RR 0.62, 95% CI 0.41–0.93, P=0.02); findings at 2-year postpartum in women with no subsequent pregnancies during this period showed no difference (RR 0.81, 95% CI 0.63–1.06, P=0.14).

Limitations and other comments

• Limitations	- The synthesized data are not applicable to clinical practice; however, they prompt much further investigation into planned delivery and its associated morbidity risk. - A decision analysis model could be helpful to appropriately address the benefits and risks associated with antenatal planned delivery choice.
• CCL	Planned caesarean section is associated with a lower risk of developing urinary incontinence symptoms postpartum or having a blood transfusion yet conversely results showed an increased risk of postpartum haemorrhage.

Bager 2008⁴

Methods

• Design	Systematic review and meta-analysis
• Source of funding and competing interest	This study was supported by a grant from the Danish Medical Research Council (grant no. 271-05-0700), Aase and Ejnar Danielsen's Foundation (grant no. 104988), Dagmar Marshall's Foundation, and General Manager Kurt Bønnelycke and Wife's Foundation.
• Search date	1966 to May 2007
• Searched databases	Medline through Pubmed



• Included study designs	Cohort and case-control
• Number of included studies	26 studies included, 23 cohort and 3 case-control
• Statistical analysis	Meta-analysis for each of six studied outcomes. Summary effect (OR) using fixed- and random-effect models. Two-tailed p-values using a 95% at a 5% level. Publication bias assessed through funnel plots
Patient characteristics	
• Eligibility criteria	Association between CS and specific allergic diseases
• Exclusion criteria	Exclusion of children born <37 weeks of gestation (preterm). Studies on allergy without information on mode of delivery.
• Patient & disease characteristics	At term children: outcome
• Intervention group	All CS
• Control group	All VD
Results	

Outcome	N*	Summary ORs		Heterogeneity statistics	
		Fixed effects model OR, 95% CI	Random effects model OR, 95% CI	Q	P-value
Food allergy/food atopy	6	1.32 (1.12–1.55)	1.45 (1.12–1.86)	8.99	0.11
Inhalant atopy	4	1.06 (0.87–1.28)	1.07 (0.82–1.38)	4.14	0.25
Eczema/atopic dermatitis	8	1.03 (0.98–1.09)	1.03 (0.98–1.09)	1.64	0.98
Allergic rhinitis	7	1.23 (1.12–1.35)	1.24 (1.08–1.43)	10.60	0.10
Asthma	13	1.18 (1.11–1.23)	1.18 (1.05–1.32)	31.38	<0.01
Hospitalization for asthma	7	1.23 (1.18–1.27)	1.21 (1.12–1.31)	18.58	<0.01

*The number of studies included in each meta-analysis of an outcome. The sum of all studies is 45 and exceeds the number of 26 included studies because 11 studies reported on multiple types of allergic outcomes.

CI, confidence interval; c-section, caesarean section; OR, odds ratio.



- For clarity: the p-value in the above table is for the heterogeneity statistic

Limitations and other comments

- **Limitations** Indications from funnel plot that smaller studies were biased towards larger effect estimates. Significant heterogeneity between studies and no information on method nor timing of assessment of outcome.
- **CCL** Large meta-analysis based on 26 studies a moderate risk increase for allergic rhinitis, asthma, hospitalization for asthma, and perhaps food allergy/food atopy, but not with inhalant atopy or atopic dermatitis. According to the authors, the increased use of CS during the last decades is unlikely to have contributed much to the allergy epidemic observed during the same period.

Bruce 2014⁵

Methods

- **Design** Systematic review and meta-analysis
- **Source of funding and competing interest** No conflict of interest disclosed. No funding data provided but originating from the University of Aberdeen Medical School.
- **Search date** From 1948 to present through OVID. 'Present' was not specified. No date or language limits
- **Searched databases** Embase, CINAHL and Medline
- **Included study designs** Cohort, case-control or trial design.
- **Number of included studies** The seven Included studies are five cohort studies and two case control studies.
- **Statistical analysis** Statistical analysis was carried out to perform a meta-analysis of the results using the software, Review Manager (version 5). For all studies, raw data was used to calculate unadjusted odds ratios and 95% confidence intervals for risk of developing IBD after CS delivery compared with vaginal birth. Sensitivity analyses were performed to assess the effect size and direction specific to individual study designs or method of data collection.

Patient characteristics

- **Eligibility criteria** Full manuscript available, cohort, case control or trial design information on mode of delivery and outcome assessment of IBD (either CD or UC) by patient reporting or confirmed diagnosis.
- **Exclusion criteria** Not specifically reported
- **Patient & disease characteristics** CS vs VD delivery, outcome assessment through various methods: hospital records (ICD), histology or radiology, the Vienna classification or self-reported

- **Intervention group** CS

- **Control group** VD

Results



• IBD	Pooled OR for CS delivery for IBD is 1.00 (95% CI 0.75 – 1.33)
• IBD	In population based cohort studies the pooled OR for CS delivery for IBD is 0.83 (95% CI 0.52 – 1.32)
	In case-control studies the pooled OR for CS delivery for IBD is 1.19 (95% CI 0.91 – 1.57)
Limitations and other comments	
• Limitations	A limitation of this study is that it was not possible to aggregate data on confounder status of individuals, such that only unadjusted data were included in the meta-analysis. To perform such an analysis adjusting for important potential confounders, an individual patient data meta-analysis would be required, which was out with the scope of this review. There is a possibility of unmeasured clinical heterogeneity within the studies included in the meta-analysis because of differences in methodology including diagnostic criteria, such as ICD coding or histology reports, to confirm IBD diagnoses. Statistical heterogeneity was less evident with only 1 included study showing outlying results.
• CCL	This analysis observed no significant difference in risk of IBD in offspring delivered by CS compared with those born vaginally.

Cardwell 2008⁶

Methods

• Design	Systematic review and meta-analysis
• Source of funding and competing interest	Support from the Czech Republic Ministry of Education (grant MSM 0021620814), the NHS National Coordinating Centre for Research Capacity Development UK, the Research Council of Norway, Diabetes UK and the Northern Ireland Department of Health and Social Services.
• Search date	Studies published before September 2007
• Searched databases	Medline through OVID, Web of Science and EMBASE
• Included study designs	Cohort and case-control studies
• Number of included studies	16 publications reporting on 20 independent studies (overall =9938 DM type 1 cases).
• Statistical analysis	ORs and SEs were calculated for the association between diabetes and Caesarean section for each study. Conditional logistic regression was used to calculate the ORs and SEs for the matched case-control studies. In cohort studies with varying duration of participant follow-up, rate ratios and their SEs were used instead of ORs, which were not directly calculable. Poisson regression was used to adjust these rate ratios for differences in the year of birth between cases and controls, a consequence of this study design, by adding a year of birth and age term to the regression model in addition to Caesarean section. Tests for heterogeneity between studies were conducted, and random effects models used to calculate pooled ORs. Random effects models were deemed more appropriate than fixed effects models because it was anticipated that there would be between study heterogeneity due to their observational nature. The I^2 statistic was calculated to quantify the degree of heterogeneity between studies. Seventeen authors provided the raw independent patient data for this analysis. There was little evidence for heterogeneity
Patient characteristics	
• Eligibility criteria	Cohort or case-control studies studying the association between DM type 1 and mode of delivery.
• Exclusion criteria	≤ 15 cases of DM type 1.



• Patient & disease characteristics	No further information. Live births either by CS or VD.
• Intervention group	CS
• Control group	VD
Results	
•	Overall OR 1.23 (95% CI 1.15-1.32) random effects model unadjusted..
•	Pooled analysis after adjusting for confounders (GA, birth weight, maternal age, birth order, breast-feeding and maternal diabetes, aOR 1.19 (95% CI 1.04-1.36)
Limitations and other comments	
• Limitations	Very limited heterogeneity
• CCL	This analysis demonstrates a 20% increase in the risk of childhood-onset type 1 diabetes after Caesarean section delivery that cannot be explained by known/measured confounders.

Carter 2006⁷

Methods	
• Design	Systematic review and two separate meta-analyses: 1) Studies using the EPDS 2) overall meta-analysis using different outcome measures.
• Source of funding and competing interest	Unclear, but Australian University Department. No conflicts of interest declared.
• Search date	Medline from 1966 onward and PsychInfo from 1974 onward. No end-date mentioned
• Searched databases	Medline and PsychInfo
• Included study designs	Cohort, case-control studies and case-series.
• Number of included studies	24 studies included
• Statistical analysis	Two separate meta-analyses were conducted. First, a meta-analysis was conducted involving studies with comparable assessments of PPD (Edinburgh Postnatal Depression Scale >12, >12.5, or ≥13) that were conducted at similar times postpartum (6–20 weeks postpartum). Second, another meta-analysis was conducted involving studies that met criteria for inclusion in the first meta-analysis plus had been classified as being “methodologically superior” Overall measures of the effect of CS on PND were calculated using the Mantel-Haenszel odds ratio estimate. Measure of the homogeneity of the association of CS and PND across studies was calculated using the Breslow-Day χ^2 -squared test.
Patient characteristics	
• Eligibility criteria	Studies that specifically focus on post-natal depression. Evaluation of maternal mood between 10 days up to 1 year post-partum.



• Exclusion criteria	Studies evaluation the 'baby blues' rather than PND, heterogeneous outcomes such as psychiatric admission or psychiatric contacts, and other psychological variables than mood.
• Patient & disease characteristics	Mode of delivery, evaluation of mood between 10 days up to 1 year post-partum

• Intervention group	CS
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• Control group	VD
------------------------	----

Results

•	Of the 24 included studies, five found a significant adverse association between CS and PND, 15 found no association and four found mixed results.
•	Overall the meta-analysis of the nine methodologically superior studies, including the only RCT (Breech trial) and assessing PND within a range of 6-20 weeks. Here the common odds ratio for the effect of CS on PND was 1.08 (95% CI 0.95 – 1.24).

Limitations and other comments

• Limitations	Important heterogeneity, mix of cohort, case-control studies and case series.
• CCL	A link between cesarean section and postpartum depression has not been established in this study.

Darmasseelane 2014¹⁰

Methods

• Design	Systematic review and Meta-Analysis
• Source of funding and competing interest	• Source of funding: Imperial College BSc studentship. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. • Declaration of interest (stated but none declared)
• Search date	31st March 2012
• Searched databases	Pubmed, Google Scholar and Web of Science
• Included study designs	Cohorts (retrospective, prospective, population-based)
• Number of included studies	15 studies (163 753 subjects)
• Statistical analysis	• Inverse-variance method for mean BMI difference • Mantel-Haenszel method for overweight and obesity odds ratios (OR) • Differences between groups provided as pooled estimated mean differences with 95% CI or unadjusted OR with 95% CI • Random-effect meta-analysis (with some exception) in RevMan5



	• Chi-squared test for Cochrane's Q statistic and I^2 for Heterogeneity (between study variation) • Funnel plots and Egger's Test in Stata 12 to investigate publication bias and other small-study effects.
Patient characteristics	
• Eligibility criteria	Cohorts reporting birth characteristics and long-term offspring follow-up into adulthood • Outcomes studied: offspring BMI, overweight and obesity in adulthood (>18 years). • Type of exposure: vaginal delivery (VD) (including natural, forceps and vacuum extraction) and CS, with CS groups further categorised as Pre-Labour CS (pre-labour-CS) or In-Labour CS (in-labour-CS).
• Exclusion criteria	Lack of mode of delivery data
• Patient & disease characteristics	No global description of the population but description in sub-group analysis • Sex (data from 12 studies: 40 229 men & 123 069 women) • Mode of delivery (data from 4 studies): 281 In-labour-CS, 261 pre-labour-CS & 17 662 VD
Interventions	
• Intervention group	CS (all types)
• Control group	VD
Results	
• BMI in adulthood	• Mean BMI difference: 0.44 kg/m² (95% CI 0.17, 0.72; p=0.002), comparing all CS to VD in pooled-gender unadjusted analyses. • Mean BMI difference: 0.32 kg/m² (95% CI 0.21, 0.85; p=0.24) in subgroup analysis (4 studies) comparing elective/pre-labour-CS to VD. Heterogeneity was low in all primary analyses. Similar results were found in gender-specific subgroup analyses. Subgroup analyses comparing types of CS to VD showed no significant impact on any outcome.
• Incidence of overweight in adulthood (WHO definition)	• OR: 1.26 (95% CI 1.16, 1.38; p<0.00001), comparing all CS to VD in pooled-gender unadjusted analyses. • OR: 1.20 (95% CI 0.93, 1.55; p=0.15) in subgroup analysis (4 studies) comparing elective/pre-labour-CS to VD.
• Obesity in adulthood (WHO definition)	• OR for incidence of obesity: 1.22 (95% CI 1.05, 1.42; p=0.01), comparing all CS to VD in pooled-gender unadjusted analyses. • OR for incidence of obesity: 1.13 (95% CI 0.80, 1.59; p=0.50) in subgroup analysis (3 studies) comparing elective/pre-labour-CS to VD.
Limitations and other comments	
• Limitations	• Lack of adjustment for confounders (due to a lack of patient level data) • Nb of CS-delivered participants included in subgroup analysis by type of CS = less than 10% of the total nb of CS. • Possible reporting bias • Poor collection of mode of delivery data in cohort studies • Old cohorts (inclusion of older cohorts is likely to attenuate the effect sizes)
• CCL	SR of high quality (Amstar score 10/11)



- No clear identification of CS for non-medical reason.
- Main results: Strong association between CS and increased offspring BMI, overweight and obesity in adulthood not confirmed in subgroup analysis for elective CS (5 studies only and lack of power)
- Hypotheses:
 - o Differences in offspring microbiome leading to increased energy harvesting
 - o Lower rate of breastfeeding
 - o Persistence of fetal gene expression and altered metabolism due to non-exposure to labour.
- But no info of high maternal BMI or gestational diabetes, etc.

Gurol-Urganci 2013¹¹

Methods

- | | |
|---|---|
| • Design | Systematic review and Meta-Analysis |
| • Source of funding and competing interest | <ul style="list-style-type: none"> • Source of funding: Royal College of Obstetricians and Gynecologists • Declaration of interest (stated and none declared) |
| • Search date | 16 December 2011 |
| • Searched databases | Cochrane Library, Medline, Embase, CINAHL+ and Maternity and Infant Care databases |
| • Included study designs | Cohort studies... |
| • Number of included studies | 18 studies (591 850 women in 31 countries) |
| • Statistical analysis | <ul style="list-style-type: none"> • Log risk ratio and SE • Random-effect meta-analysis in RevMan5 • I² for Heterogeneity • Sub-group analysis for maternal age, maternal choice, cohort period (pre or post 1985), total Newcastle Ottawa Scale (NOS) score and size. • No meta-analysis for interval before subsequent pregnancy (few studies and too different methodologies) |

Patient characteristics

- | | |
|--|--|
| • Eligibility criteria | Studies reporting fertility outcomes after a previous CS vs previous VD |
| • Exclusion criteria | Studies in which the calculation of the pregnancy rate was not possible due to the study design (e.g. case-control studies); studies in low-income countries |
| • Patient & disease characteristics | From primiparous women with one live singleton to all inclusive.
None study excluded women with previous fertility problems. |



All reasons for CS included.	
Interventions	
• Intervention group	CS (all types)
• Control group	VD (all types)
Results	
• Rate of subsequent pregnancy or birth	• RR: 0.91 (95% CI 0.87, 0.95) for subsequent pregnancy, comparing all CS to VD. • RR: 0.89 (95% CI 0.87, 0.92) for subsequent birth, comparing all CS to VD. High Heterogeneity (I^2 : 86% for pregnancies and 81% for births) • In subgroup analysis, smaller effect for studies with NOS score >6, maternal age and risk adjustment, • No effect for maternal choice, cohort period, study size and CS for breech presentation.
Inter-pregnancy and inter-birth interval	• Median inter-pregnancy intervals: 2-6 mo longer after CS vs VD. • Stat difference in 2 studies. • Median inter-birth intervals: 3 mo longer after CS than VD. • Stat difference in 1 study.
Limitations and other comments	
• Limitations	• High heterogeneity between studies • No info on publication bias • Few studies with data on the indication of the CS, on maternal age, on obesity, on previous problem of fertility. • No data on spontaneous or induced abortions and on ectopic pregnancies. • Data collection on potential counfounders in few studies
• CCL	• SR of high quality (Amstar 9/11) • No clear identification of CS for elective and mainly non-medical reason. • Main results: Association between all kind of CS and lower subsequent pregnancy or birth rate. Smaller effect with elective CS for breech presentation (2 studies only).

Huang 2015¹²

Methods

- **Design** Systematic review and Meta-Analysis
- **Source of funding and competing interest**
 - Source of funding: National Natural Science Foundation of China, Shanghai Municipal Health Bureau, Doctoral Foundation of Shanghai Jiao Tong University, Xinhua Hospital Foundation and Science and Technology Commission of Shanghai Municipality.
 - Declaration of interest = source of funding
- **Search date** October 2013
- **Searched databases** Pubmed, Google Scholar, EMBASE, and MEDLINE
- **Included study designs** Cohorts (retrospective, prospective)
- **Number of included studies** 26 studies
- **Statistical analysis**
 - Natural log and Standard Error (SE) of the natural log of effect estimates were calculated from the raw data
 - Fixed and Random-effect meta-analysis in Stata9.2
 - I^2 tests for heterogeneity
 - Determinants of the heterogeneity between the study-specific estimates assessed in meta-regression analysis by using the “metareg” module.
 - Funnel plots and Begg's test to investigate publication bias.

Patient characteristics

- **Eligibility criteria**
 - Original study with information that can be used to estimate the relation between mode of delivery and the risk of asthma as an odds ratio, incidence rate ratio, cumulative incidence ratio, hazard ratio, or prevalence ratio
 - Study population should be children, or both children and adults Cohorts reporting birth characteristics and long-term offspring follow-up into adulthood
 - Outcomes studied: prevalence of asthma (definition of asthma was based on physician's diagnosis; hospitalization for asthma; asthma reported by the child/patient, his or her parent, or both; or a history of asthma)
 - Type of exposure: vaginal delivery (VD) (spontaneous or instrumental) and CS (**Elective i.e. a planned CS performed for either maternal or fetal indications** before the onset of labor, and emergency CS defined as CS in an obstetric emergency generally after the onset of labor.)
- **Exclusion criteria**
- **Patient & disease characteristics**
 - No global description of the population
 - The majority of studies (20/26) were carried out in Europe (Denmark, Finland, Germany, Norway, Sweden, and UK).
 - In most of the studies (15/26), the age of asthma diagnosed was <10 years old.

Interventions



• Intervention group	CS (all types)
• Control group	VD
Results	
• Prevalence of asthma in childhood (<18 y)	• OR 1.16 (95% CI 1.14, 1.19) comparing all CS to VD (26 studies). No evidence of heterogeneity: I^2: 24.6% OR 1.21 (95% CI 1.17, 1.25) comparing elective CS to VD (random-effects model with 9 studies): Moderate heterogeneity (I^2: 39.9%) No statistically significant publication bias was found by Begg's test
Limitations and other comments	
• Limitations	• Lack of adjustment for confounders (except low birth weight) • Lack of clear identification of elective CS for non medical reasons • Reliability of the asthma diagnosis in some primary studies (e.g. based on parents questionnaire)
• CCL	• SR of low quality (Score Amstar 6/11) • No clear identification of CS for non-medical reason. • Main results: Elective (and emergency CS) moderately increased the risk of asthma • Hypotheses: - o Earlier delivery in elective CS (<39 weeks) and lung immaturity - o Hygiene hypothesis (intestinal bacterial flora are important to the children's immune system development and they can be different according to the early life exposure of vaginal flora) - o Some indirect factors associated to CS (such as prophylactic antibiotics, less breastfeeding) • But no info on maternal asthma, maternal smoking or other confounders such as less breastfeeding or prematurity(the risk of lower birthweight was adjusted in some primary studies with low influence).
Kuhle 2015¹³	
Methods	
• Design	Systematic review and Meta-Analysis
• Source of funding and competing interest	• Source of funding: ? • Declaration of interest (stated but none declared)
• Search date	July 2014 (+ Pubmed alert during the conduct of the research)
• Searched databases	Medline, Embase and Web of Science



• Included study designs	Cohorts studies (68%), cross-sectional, case control
• Number of included studies	28 studies (? subjects)
• Statistical analysis	• Inverse-variance method • Random-effect meta-analysis to estimate the pooled RR • Adjustment for maternal prepregnancy weight • Subgroup analysis for age of BMI assessment (before 6 years or after), design of the studies, high-income vs middle-income countries and importance of CS rate. • Cochrane's Q statistic and I^2 for Heterogeneity • Funnel plot and Egger's test for publication bias
Patient characteristics	
• Eligibility criteria	Studies reporting mode of delivery and overweight or obesity in children (age range 2-18 years)
• Exclusion criteria	Studies reporting results for children and adults combined
• Patient & disease characteristics	No global description of the population but description in sub-group analysis • Median CS rate: 22% (range 8.2-64.6%) • Median age at BMI assessment: 6 years (range 2-15%) • Median of obesity prevalence: 9.2% (range 2.2-25.2%)
Interventions	
• Intervention group	CS (all types)
• Control group	VD
Results	
• Obesity in childhood (WHO definition)	• RR: 1.34 (95% CI 1.18, 1.51), comparing all CS to VD (19 studies). Moderate Heterogeneity (I^2: 45%) • RR: 1.29 (95% CI 1.16, 1.44) vs RR: 1.55 (95% CI 1.11, 2.17) in pooled studies that adjusted for maternal prepregnancy weight vs that did not adjust. • Studies with CS rates >30% reported slightly lower RRs than studies with rates <30% but subgroups too small to draw any conclusions. • One study (Chinese birth cohort study) performed subgroup analysis by the indication for CS did not observe significant differences between the groups.
• Overweight & obesity combined in childhood	• RR: 1.16 (95% CI 1.05, 1.27), comparing all CS to VD (13 studies). Substantial Heterogeneity (I^2: 57%)
• Overweight in childhood (WHO definition)	• RR: 1.16 (95% CI 1.06, 1.27), comparing all CS to VD (6 studies). No Heterogeneity (I^2: 0%)



Limitations and other comments	
Limitations	- No assessment of the quality of the included primary studies - Moderately high heterogeneity - Possible publication bias
CCL	- SR of moderate quality - No clear identification of CS for non-medical reason. - Main results: All CS increased the risk of developing obesity in childhood and this is not invalidated by the only study considering the indication of CS (Chinese cohort study). - Hypothesis: - Influence on the intestinal microbiome of the infant (The gut flora of infants born by VD resembles the maternal vaginal microbiota while the gut flora of infants delivered by CS resembles that of the mother's skin and is colonized later and less frequently by Bacteroides species and Bifidobacterium species) - Maternal prepregnancy weight in subgroup analysis is not BMI.

Li 2013 ¹⁵

Methods

Design	Systematic review and meta-analysis
Source of funding and competing interest	- Source of funding: not stated. - Declaration of interest: The authors declare no conflict of interest
Search date	June 2012
Searched databases	Pubmed, Embase and Web of Science databases
Included study designs	Cohort (historical or prospective) or case-control design
Number of included studies	7 cohort studies and 2 case-control studies
Statistical analysis	A random-effects model meta-analysis based on the generic inverse variance method was done to estimate the pooled ORs for all syntheses. Statistical heterogeneity across estimates was assessed by I^2 statistics, and the values of 25%, 50% and 75% indicated low, medium and high heterogeneity, respectively.

Patient characteristics

Eligibility criteria	Offspring in whom overweight and/or obesity were measured in childhood (3–8 years), adolescence (9–18 years) and/or adult (419 years).
Exclusion criteria	None reported



• Patient & disease characteristics	• Overweight and obesity were defined using different definitions and cut-offs (BMI ≥ 30 kg/m², IOTF cut-offs)
• Intervention group	CS
• Control group	Spontaneous VD
Results	
• Overweight/obesity for offspring	• The overall pooled odds ratio (OR) was: • 1.33 (95% CI 1.19, 1.48; I²=63%) for all studies • 1.18 (1.09, 1.27; I²=29%) for high-quality studies • 1.78 (1.43, 2.22; I²=24%) for medium-quality studies
• Overweight/obesity for children	OR = 1.32 (95% CI: 1.15, 1.51) • Overweight: pooled OR 1.22 (95% CI 0.99, 1.50; I²=64%) • Obesity: pooled OR 1.40 (95% CI 1.17, 1.67; I²=50%) For childhood estimates, the funnel plot indicated a publication bias, and the Begg's test was significant (P=0.009). However, the trim-and-fill analysis still showed a significant effect (OR=1.20, 95% CI 1.00, 1.44; P=0.048), indicating that the publication bias was not likely to substantially affect the results.
• Overweight/obesity for adolescents	OR = 1.24 (95% CI: 1.00, 1.54) • Obesity: pooled OR 1.24 (95% CI 1.00, 1.54; I²=0%)
• Overweight/obesity for adults	OR = 1.50 (95% CI: 1.02, 2.20) • Obesity: pooled OR 1.50 (95% CI 1.02, 2.20; I²=74%)
Limitations and other comments	
• Limitations	• Some nonindependent longitudinal results were included in calculating childhood, adolescence and adulthood pooled effect sizes, which may lead to biased subgroup estimates. • Residual confounding effects cannot be totally excluded.
• CCL	• SR of high quality • No clear identification of CS for non-medical reason. • Main results: cesarean section was associated with a 33% increased risk of subsequent overweight and obesity • Hypotheses: - o the hygiene hypothesis provides one possible mechanism (fewer intestinal Bifidobacteria and Bacteroides after CS, both of which were reported to be protective factors against later obesity) - o Potential reduced rate of breastfeeding



Li 2014¹⁶

Methods

- **Design** Systematic review and meta-analysis
- **Source of funding and competing interest** This study was supported in part by funding from National Ministry of Health for the Digestive Disease (Grant 201002020) and National Natural Science Foundation of China (Grant 81200263, 30972881 and 81170365). The authors report no conflicts of interest.
- **Search date** English language epidemiological papers (cohort or case-control) before September 2013.
- **Searched databases** PubMed, MEDLINE, and EMBASE
- **Included study designs** Cohort and case-control studies
- **Number of included studies** Nine studies: six studies investigated CD, four UC and three investigate IBD in general. Of the total nine studies included in the analysis, four were case-control studies whereas the remaining five reports were cohort studies [
- **Statistical analysis** A meta-analysis was performed using Review Manager (Version 5.0.18.0, Cochrane Collaboration, Oxford, UK) when needed. Statistical analysis of dichotomous variables was carried out using odds ratio (OR) as the summary statistic, which was reported with 95% confidence interval (CI). Heterogeneity was evaluated by the Cochrane Q-test among the studies. A fixed effects model was used for pooling of data when statistical heterogeneity was not present. If statistical heterogeneity was present ($p < 0.05$), a random effects model was used. A fixed-effects model using the Mantel-Haenszel method or a random-effects model using the DerSimonian and Laird method were used to pool the results. The significance of the pooled OR was determined by the Z-test, a p-Value < 0.05 was considered significant. All p-Values are two-sided. Begg's and Egger's tests were also performed to evaluate the presence of publication bias. Publication bias analysis was conducted by using Stata 11.

Patient characteristics

- **Eligibility criteria** Primary prerequisite for the inclusion of studies in the meta-analysis was the presence of a control group, which could be formed by population controls, by hospital inpatients, or by outpatients who did not suffer from IBD or other chronic diseases that might be related to mode of delivery.
- **Exclusion criteria** Not formally mentioned
- **Patient & disease characteristics**

- **Intervention group** CS

- **Control group** VD

Results

OR for CD: 1.38 (95% CI 1.12-1.70)

OR for UC: 1.07 (95% CI 0.87-1.32)

OR for paediatric CD 1.20 (95% CI: 1.06–1.35), however, paediatric CD is not really defined.



Limitations and other comments

- Limitations**

Limitations of this study include the relatively small number of studies available for pooling, especially in the case of paediatric CD and UC. Also, the pooled analyses were hindered by significant heterogeneity between studies, both in study design and in study population characteristics.

In addition, the major weakness of this study relates to the lack of control for confounders and to the disregard of the major issue of selection bias which were due to the nature of original articles. Confounding was not treated statistically in four of the nine studies included. Generally, confounding factors may potentially bias the results as several perinatal

Caesarean delivery and IBD characteristics are believed to be associated with higher CD risk. Although adjustment for potential confounders such as age, previous pregnancies families residing in an urban location, a residential area of higher socioeconomic status, births to married mothers and births with a congenital abnormality showed little difference between the adjusted OR that controls and the crude OR. Factors such as parental IBD predisposition was indicated to be the significant risk of CD, whereas breastfeeding was associated with lower risks of IBD. Therefore, the lack of adjustment to confounders in some studies probably results in some potential limitations of the pooled data. However, our subgroup analysis with high-quality studies including those confounding controlled studies also confirmed the positive association between caesarean delivery and CD. Selection bias and confounding are serious potential biases in this study because IBD is associated with genetic and ethnicity factors as well as with behavioural factors and environmental factors.
- CCL**

Results of this meta-analysis support the hypothesis that caesarean delivery was associated with the risk of CD but not of UC. The total rate of caesarean delivery of IBD patients was similar with that of control subjects.

Nelson 2010¹⁷

Methods

- Design**

Systematic review (Cochrane review)
- Source of funding and competing interest**
 - Source of funding: ?
 - Declaration of interest: no interest known
- Search date**

July, 2009
- Searched databases**

Medline-PubMed, Embase and the Cochrane Central Register of Controlled Trials (Central) in the Cochrane Library issue 2 2009.
- Included study designs**

RCT and studies which compare in cohorts or in cross sectional surveys women having either CS or VD
- Number of included studies**

21 studies
- Statistical analysis**

Crude incidence data of anal incontinence were determined as well as odds ratios and 95% CI for individual studies.

Numbers needed to treat (NNT) are presented, that is, the number of CDs needed to be performed to prevent a single case of fecal or flatus incontinence, for each individual study.

Patient characteristics

- Eligibility criteria**

Women with a history of pregnancy and delivery of a live infant, including breech presentations and twin pregnancies.
- Exclusion criteria**

Vaginal delivery patients were excluded if they had an instrumented delivery (by suction or forceps).



• Patient & disease characteristics	• 31 698 deliveries, 6028 being CS and 25 170 being VD- one study is awaiting classification
• Intervention group	Elective or emergency CS
• Control group	Spontaneous VD
Results	
• Fecal incontinence (elective CS versus VD)	Four studies presented analyses that compare elective CS versus VD (Abramov 2005; Lal 2003; MacArthur 1997; MacArthur 2001). There was no significant advantage of elective CS over VD in any of these four studies
• Fecal incontinence (all CS versus VD – highest quality studies)	Seven studies adjusted for age, avoided misclassification or overlap of delivery mode, and assessed incontinence at an appropriate time (Abramov 2005; Altman 2007; Goldberg 2003; MacArthur 2005; MacLennan 2000; Varma 2006; Melville 2005). A validated instrument for the detection of anal incontinence was used in four of these studies (Abramov 2005; Altman 2007; Goldberg 2003; Melville 2005). None of these studies showed a significant benefit of CS over VD and aside from (Abramov 2005), the odds ratios are closely clustered around 1.0.
Limitations and other comments	
• Limitations	• Ascertainment of incontinence: A variety of methods were used and included maternal self reporting to mailed questionnaires. Only five studies used an instrument specifically validated for anal continence assessment. Two studies failed to separate anal incontinence, i.e. presented a combined flatus/fecal outcome. • A number of studies made their only assessment within four months of the baby being born: too soon for vaginal/rectal healing
• CCL	• SR of high quality • Main results: No benefit for CS over VD can be demonstrated in this review of 21 non-randomized studies. Elective primary CD in average risk women when done for the preservation of anal continence cannot be recommended. • Hypotheses: Average risk is the key factor.

O'Callaghan 2013¹⁸**Methods**

• Design	Systematic review and Meta-Analysis
• Source of funding and competing interest	• Source of funding: Supported by the Australian National Health and Medical Research Council and CP Alliance Research Foundation. • Declaration of interest (stated and none declared)
• Search date	December 2012
• Searched databases	MEDLINE, Embase, and ClinicalTrials.gov
• Included study designs	Nine case-control and four cohort studies



• Number of included studies	13 studies (3810 cerebral palsy case group & 1.7 million control group)
• Statistical analysis	• Fixed-effect meta-analysis in RevMan5 when there was no evidence for heterogeneity and • Random-effect analysis when heterogeneity was significant ($I^2 > 30\%$) • I^2 for heterogeneity • Subgroup analysis for CS either elective or emergency, gestational age subgroups, and cephalic or breech presentation. • Funnel plot for publication bias
Patient characteristics	
• Eligibility criteria	Studies reporting an intervention or risk of caesarean delivery and endpoint of cerebral palsy, writing in English, and giving sufficient details to perform meta-analysis.
• Exclusion criteria	Cases in which a confirmed neurologic diagnosis of cerebral palsy was absent
• Patient & disease characteristics	No global description of the included population (a total of 3 810 cerebral palsy case group participants and 1.7 million control group participants)
Interventions	
• Intervention group	CS (all types): elective and emergency; preterm or term
• Control group	Non CS
Results	
• Cerebral palsy	• OR 1.29 (95% CI 0.92, 1.79) comparing all CS to no CS. High Heterogeneity (I^2: 86%) • OR 2.17 (95% CI 1.58, 2.98) comparing emergency cesarean delivery to no CS. High heterogeneity (I^2: 42%) • OR 0.81 (95% CI 0.41, 1.58; comparing elective cesarean delivery to no CS (764 case group participants and 1,928 control group participants). High Heterogeneity (I^2: 86%)
Limitations and other comments	
• Limitations	• High heterogeneity (different cerebral palsy diagnoses criteria, different selection strategies for control group participants in case-control studies, insufficient reporting of CS type, different indication for CS, or different criteria defining emergency, elective, term, preterm... • Possible publication bias (except for elective CS) • Data collection on potential confounders in few studies • None of the study provided details about the indication for CS
• CCL	• SR of moderate quality (Amstar 7/11) • No clear identification of CS for non-medical reason.



- Main results: no association between CS delivery (all kind and elective CS) and cerebral palsy; increased risk for cerebral palsy outcome in association with emergency CS, but with the likely confounding that acute or chronic fetal compromise will often precipitate this intervention.
- Hypothesis:
 - CS delivery may protect against cerebral palsy (because in the very preterm neonate a common pathway to the neuropathology that later causes cerebral palsy is early neonatal intraventricular hemorrhage)

O'Neill 2013¹⁹**Methods**

- | | |
|---|--|
| • Design | Systematic review |
| • Source of funding and competing interest | <ul style="list-style-type: none"> • Source of funding: National Perinatal Epidemiology Centre (NPEC) in Cork University Maternity Hospital, Wilton, Cork, Ireland. • Declaration of interest: authors declare that they have no competing interests |
| • Search date | 17 October 2012 |
| • Searched databases | CINAHL; the Cochrane Library; Embase; Medline; PubMed; SCOPUS and Web of Knowledge (1945 - October 2012) |
| • Included study designs | Cohort, cross-sectional or case-control studies |
| • Number of included studies | <ul style="list-style-type: none"> • 11 studies included in the systematic review (10 cohort studies and 1 case-control study) • 5 studies that adjusted for a minimum of three confounders including maternal age confounders were included in the meta-analysis |
| • Statistical analysis | <ul style="list-style-type: none"> • The generic inverse variance method with a fixed-effect model was used to calculate pooled estimates across the studies. • A funnel plot was produced to estimate the likelihood of publication bias using the pooled OR and standard error (SE). • Heterogeneity between the included studies was assessed using the I^2 statistic • Subgroup analyses: estimations of <ul style="list-style-type: none"> ◦ Separate ORs by parity (primiparous versus not limited to primiparous women), to assess the degree of confounding by number of previous deliveries. ◦ Pooled OR by publication date (pre-2000, post 2000). ◦ Analysis by length of follow-up (<10 years, >10 years) ◦ Analysis based on whether an indication for mode of delivery was available or not (yes, not specified). ◦ Analysis by cohort size (<35,000, >35,000) ◦ Analysis by definition of sub-fertility used: (a) BI versus IPI and (b) categorical measures (e.g. <1 year, >3 years) vs. continuous measures |



Patient characteristics

- **Eligibility criteria** Studies in which mode of delivery and the subsequent Inter-pregnancy interval (IPI) or birth interval (BI) were reported. Women can be primiparous or multiparous. No more criteria were specified.
- **Exclusion criteria** Lack of data on the exposure (mode of delivery) or the outcome of interest (sub-fertility defined as time to next pregnancy/birth)
- **Patient & disease characteristics**
 - Eight studies included primiparous women only (i.e. those women with only one previous pregnancy) and three were not limited to primiparous women
 - Indication for mode of delivery was reported in four studies
 - Length of follow-up ranged from a minimum of one year to a maximum of 34 years

- **Intervention group** CS (breech Caesarean delivery, elective Caesarean delivery, and emergency Caesarean delivery...)
- **Control group** VD

Results (Caesarean section and subsequent sub-fertility; meta-analysis of 5 studies)

- **Inter-pregnancy interval and Birth Interval (data on 750,407 women)** Pooled adjusted OR of subfertility is 0.90 (95% CI 0.86, 0.93)

•

Results (individual studies without meta-analysis)

- **Inter-pregnancy interval (2 studies; no meta-analysis):** One study (547 primiparous women with breech emergency or elective CS) reported a longer IPI following Caesarean delivery (elective Caesarean delivery 22 months versus vaginal delivery 16 months; a difference of six months). The second study (5 513 primiparous women without indication for the CS) reported that a Caesarean delivery was not associated with any delay in subsequent IPI. Median IPI in the overall cohort was reported as 21.8 months.
- **Birth interval (3 studies)** One study (570 primiparous women without indication for the CS) reported a longer BI among women with a Caesarean delivery (5.5% of women with a Caesarean delivery compared to 1.4% of women with a vaginal delivery took greater than two years to conceive). Two studies (respectively 812 and 12 918 primiparous women without indication for the CS) reported no delay in time to next birth among women with a Caesarean delivery
- **Inter-pregnancy interval and Birth Interval (1 study)** No evidence existed to show that a Caesarean delivery was associated with a longer time to next pregnancy or birth (1 study including 1 152 primiparous women for which a CS was underwent for failure to progress/foetal distress).

Limitations and other comments

- **Limitations**
 - Only five out of the 11 included studies adjusted for potential confounders, and the other six studies used matching to reduce the likelihood of bias
 - It was not possible to meta-analyse the six studies which only presented crude estimates as each reported pregnancy interval
 - Sample sizes were quite small in three of the studies that reported an association and thus the findings may be due to chance.



	• The indication for mode of delivery (instrumental vaginal, vaginal breech, elective caesarean section, emergency caesarean section, etc.) was available in only two of the meta-analysed studies and so confounding by indication may also exist in some of the included studies. • Two major confounders were not investigated: whether women were deliberately delaying pregnancy, and whether any fertility treatment was used by the study populations.
• CCL	• SR of high quality (Amstar 9/11) • No clear identification of CS for non-medical reason. • Main results: Caesarean delivery is associated with an increase in subsequent sub-fertility (i.e. a delay in time to next pregnancy or birth) compared to vaginal delivery by as much as 14%. Underlying mechanisms for an association between caesarean delivery and subsequent sub-fertility remains unclear • Even if an increased waiting time to next pregnancy or birth is reported, it could be due to biological or psychological factors and therefore, the woman's opinion about the length of acceptable pregnancy interval is perhaps the most important predicting factor and should be incorporated into future research where possible.

Prior 2012²⁰**Methods**

• Design	Systematic review and Meta-Analysis
• Source of funding and competing interest	• Source of funding: ? • Declaration of interest (stated and declared)
• Search date	31 January 2011
• Searched databases	PubMed
• Included study designs	Cohorts, cross-sectional, random selection...
• Number of included studies	48 studies (>500 000 women in 31 countries)
• Statistical analysis	• Multivariable logistic regression (use of log OR & its SE for the meta-analysis) • Inverse variance method • Fixed-effect meta-analysis in RevMan5 • Cochrane's Q statistic and I² for Heterogeneity • Random-effect meta-analysis when heterogeneity • Sub-group analysis in meta-regression • Funnelt plot and Egger's test for publication bias

Patient characteristics



• Eligibility criteria	Studies reporting mode of delivery and any breastfeeding outcome
• Exclusion criteria	Multiple reports of the same study population, selective study population, only qualitative data reported or no suitable data on breastfeeding reported.
• Patient & disease characteristics	No global description of the included population
Interventions	
• Intervention group	CS (all types): elective/scheduled/prelabour and emergency/after labour onset.
• Control group	VD (all types)
Results	
• Early Breastfeeding (BF) at discharge from hospital postpartum or any report of breastfeeding initiation	• OR: 0.78 (95% CI 0.76, 0.79; $p < 0.00001$), comparing all CS to VD (42 studies; 556 363 subjects). High Heterogeneity (I^2: 96%) • OR (fixed-effects for factors associated to early BF in 14 studies): 0.74 (95% CI 0.72, 0.77; $p < 0.00001$) High Heterogeneity (I^2: 93%) • OR: 0.83 (95% CI 0.80, 0.86; $p < 0.00001$), comparing ELECTIVE CS to VD (8 studies; 145 184 subjects). • OR: 1.00 (95% CI 0.97, 1.04; $p = 0.86$), comparing EMERGENCY CS to VD (8 studies).
• Breastfeeding at 6 mo (exclusive or partial according to the WHO definition)	• OR: 0.86 (0.82, 0.91; $p < 0.00001$), comparing all CS to VD (15 studies; 84 518 subjects). Moderate Heterogeneity (I^2: 38%) - No significant difference for BF at 6 months between CD and VD if the analysis is restricted to women initiating breastfeeding.
Limitations and other comments	
• Limitations	• No assessment of the quality of the included primary studies • Moderately high heterogeneity • Possible publication bias (overestimation?) according to the funnel plot but as the relation between breastfeeding and mode of delivery was not the primary outcome in 74% of the included studies, the likelihood of true publication bias is reduce and the trim-and-fill analysis did not alter the conclusion. • Data collection on potential counfonders in few studies
• CCL	• SR of moderate quality (Amstar 7/11 but large population in 31 countries, subgroup analysis for examining recall bias, non standard definition of breastfeeding, potential effect of confounders. • No clear identification of CS for non-medical reason. • Main results: Negative association between elective CS and early breastfeeding. If breastfeeding is initiated, mode of delivery has no apparent effect on the number of mothers still breastfeeding at 6 mo. • Hypothesis: - o Processes that delay the onset of lactation, disrupt mother-infant interaction, or inhibit infant suckling (e.g. post-operative care).



- o Metabolic or endocrine milieu of labor can be different (e.g. magnitude of oxytocin and prolactin responses, blood concentrations of appetite-regulating hormones in infants...)

Tähtinen 2016²¹

Methods

- **Design** Systematic review and meta-analysis
- **Source of funding and competing interest**
 - Source of funding: Academy of Finland (276046), Competitive Research Funding of different Finnish hospitals and foundations as well as by the UK Medical Research Council.
 - Declaration of interest: All financial support, sponsorship and professional affiliations are reported
- **Search date** October 31, 2014
- **Searched databases** Medline (1946 to present), Scopus (1995 to present), and CINAHL (1960 to present). Authors also searched abstracts published from the annual meetings of the International Continence Society and the International Uro-gynecological Association (1999–2014).
- **Included study designs** Randomized trials, cross-sectional, or cohort studies that recorded the delivery mode as well as Stress urinary incontinence (SUI) and/or Urgency urinary incontinence (UUI) outcome beyond 1 yr after delivery among primi- and multiparous women and provided an analysis comparing at least two delivery modes with SUI and/or UUI.
Cross-sectional and cohort studies were included if they adjusted/ matched for at least one of the following: age, BMI, or parity.
Studies with <100 participants were excluded.
- **Number of included studies** 16 studies
- **Statistical analysis** Authors calculated pooled estimates of adjusted estimates using the DerSimonian-Laird random-effects inverse variance method, and the I^2 statistic and Cochran's Q as indices of heterogeneity. Random-effects model were chosen.

Patient characteristics

- **Eligibility criteria** Delivery modes including caesarean section (pre-labour, early labour or late labour), spontaneous vaginal delivery, and instrumental vaginal delivery (vacuum or forceps).
No other eligibility criteria mentioned (see also included study designs)
- **Exclusion criteria** Women with foetuses with breech presentations
- **Patient & disease characteristics** Women from different age categories, primiparous or not who were delivered by caesarean section or vaginally.

- **Intervention group** Elective CS

- **Control group** VD

Results



• Stress incontinence (SUI)	urinary	When comparing elective caesarean with the decision made before the onset of labour only, two (both high risk of bias) studies reported a risk of SUI over three times higher with vaginal delivery (aOR: 3.53; 95% CI, 2.55–4.90; heterogeneity: $p = 0.84$; $I^2 = 0\%$; risk difference: 10.7%).
• Urgency incontinence (UUI)	urinary	The pooled analysis (eight studies, three low and five high risk of bias) demonstrated that the risk of UUI was modestly increased after vaginal delivery when compared with caesarean delivery (aOR: 1.30; 95% CI, 1.02–1.65; heterogeneity: $p = 0.14$; $I^2 = 37\%$; risk difference: 2.6%). No study reported the impact of elective caesarean only versus vaginal delivery on UUI.
• SUI and UUI		One high risk of bias study reported no significant differences between caesarean in the first stage of labour versus elective caesarean (aOR: 0.88; 95% CI, 0.40–1.91) or caesarean in the second stage of labour versus elective caesarean (aOR: 1.30; 95% CI, 0.57–2.95) but had more than a fourfold risk of SUI (aOR: 4.45; 95% CI, 2.14–9.27) in instrumental vaginal delivery versus elective caesarean.

Limitations and other comments

• Limitations	• Mean age and parity of study populations, case definition of SUI and UUI, definition of vaginal delivery groups, risk of bias, and survey methods varied across studies. • Most primary studies combined all cesarean sections, irrespective of timing. • The effect estimates in the analysis comparing elective cesarean and vaginal delivery were imprecise due to a lack of statistical power.
• CCL	• SR of very high quality • Authors have separately quantified the larger benefit associated with elective prelabor cesarean, compared with any cesarean section (either before or during labor). • The results demonstrate that vaginal delivery is associated with almost double the odds of long-term SUI, an absolute increase of approximately 8% when compared with caesarean section. The odds of UUI is also increased after vaginal delivery, but the pooled absolute difference is sufficiently small (3%) that caesarean section rates have only a small impact on UUI at a population level.

4.2. Primary studies

Table 8 – Evidence tables for primary studies

Al Khalaf 2015²³

Methods

• Design	Families with infants born between December 2007 and May 2008 (N = 11 134) were randomly selected and recruited to the Growing Up in Ireland (GUI) study. Mode of delivery was classified into spontaneous vaginal delivery; instrumental vaginal delivery; emergency Caesarean section (CS); and elective CS. The 'Ages and Stages Questionnaire' was completed at age 9-months and the 'Strengths and Difficulties Questionnaire' at 3 years. Data were weighted to represent the Irish national sample (N = 73 662) Questionnaires with trained interviewers through face-face interviewers at 9 months.
• Source of funding and competing interest	The Growing Up in Ireland data have been funded by the Government of Ireland through the Department of Children and Youth Affairs and have been collected under the Statistics Act, 1993 of the Central Statistics Office. The project has been designed and implemented by the joint Economic and Social Research Institute (ERSI) and Trinity College Dublin (TCD) Growing Up in Ireland Study Team. This work was supported by the Masters in Public Health Programme Team, University College Cork, Cork, Ireland.



	The authors declared no conflict of interest.
• Setting	Ireland. Study within a subset in the nationally representative longitudinal study of infants born in Ireland. It involves interviewing children and their families on various occasions over a number of years]. The first wave of data collection was conducted when the infants were 9 months and the second wave at 3 years of age.
• Sample size	Give the number of patients needed (= the calculated before protocol) as cited (described) by the author(s) (should clearly report if it is numbers by group or not) and the number of patients actually included
• Duration and follow-up	December 2007 and May 2008 (N = 11,134) Duration of follow-up 9 months and 3 years.
• Statistical analysis	Multivariate logistic regression was used for the statistical analyses.
Patient characteristics	
• Eligibility criteria	Children born between December 2007 and May 2008, randomly chosen from the GUI study.
• Exclusion criteria	Children were excluded from this study if the primary caregivers were not their mothers (n = 38), because most of the potential confounders were related to the mother such as maternal age, educational level, and health status.
• Patient & disease characteristics	58.4% SVD, 14.8% IVD, 12.9% Elective CS, 13.8% Emergency CS. Those numbers are from the total GUI study, but in this subsample characteristics were matched to represent this sample.
Exposures	
• Exposure group	IVD, Elective CS, Emergency CS
• Control group	SVD
Results	
• Outcome 1	At age 9 months, elective CS was associated with a delay in personal social skills [adjusted odds ratio, aOR 1.24; (95 % confidence interval, CI 1.04, 1.48)] and gross motor function [aOR 1.62, (95 % CI 1.34, 1.96)], whereas emergency CS was associated with delayed gross motor function [aOR 1.30, (95 % CI 1.06, 1.59)]. At age 3 years there was no significantly increased risk of an abnormal total SDQ score across all modes of delivery.
Limitations and other comments	
• Limitations	Several limitations were noted, including the difficulty in assessing behaviour in young children. The outcome measures of behavioural problems and neurodevelopment disorders were defined based on assessment tools/questionnaires rather than clinical diagnoses such as autism and ADHD. Also, to calculate parity we the number of children in the household was counted, which may not necessarily be the number of the study member's siblings. Data on mode of delivery were collected 9 months postpartum.
• CCL	Children born by elective CS may face a delay in cognitive and motor development at age 9 months. No increase in total SDQ score was found across all modes of delivery. Further investigation is needed to replicate these findings in other populations and explore the potential biological mechanisms.

Bager 2012²⁴

Methods

- **Design** Register-based national cohort study of 2.1 million Danes born 1973–2008
- **Source of funding and competing interest**
 - Source of funding: grant from the Danish Medical Research Council, Aase and Ejnar Danielsen's Foundation, Dagmar Marshall's Foundation, and General Manager Kurt Bønnelycke and Wife's Foundation.
 - Conflict of interest: not stated
- **Setting** Denmark, hospitals
- **Sample size** 2 098 039 singleton persons born during the period January 1 1973 through December 31 2008
- **Duration and follow-up** 32.6 million person-years of follow-up in the age span 0–35 years: Each person in the cohort was observed from date of birth or January 1 1977, when the National Patient Registry was started, whichever came later, and until end of follow-up. End of follow-up was on December 31 2008, or date of emigration, death, or first hospital discharge with a code for UC or CD, whichever came first.
- **Statistical analysis**
 - Log-linear Poisson regression models.
 - Separate IRRs for UC and CD in a competing risk model, as a nontrivial proportion of IBD patients, were first recorded with one IBD disease and later diagnosed with the other.
 - Age-specific IRRs were calculated in 5-year age groups in the age interval 0–35 years. Because IBD incidence has been reported to peak at ages 16–25 years, the 5-year groups before and after the age of 15 years were combined and IRRs for the two new age-groups were calculated to obtain more robust numbers (i.e., 0–14 vs. 15–35 years).
 - Population attributable risk percent (PAR%) were estimated as $PAR\% = \frac{1}{4} 100[p(RR-1)/(p(RR_1)+1)]$, where p is the proportion of newborns delivered by c-section and RR is our IRR estimate of the relative risk of IBD with onset in childhood associated with delivery by c-section.

Patient characteristics

- **Eligibility criteria** All singleton born in Denmark between 1973 and 2008
- **Exclusion criteria** Not singleton
- **Patient & disease characteristics** VD (86.6%) and CS (13.4%)
During the FU, there were 8142 recorded cases of IBD, including 4318 cases of UC, 2858 cases of CD, and 966 cases of IBD that were initially recorded as one of the two diseases but were later recorded as the other.

Exposures

- **Exposure group** C-Section (elective or acute since 1997)
- **Control group** VD

Results



• IBD (combined IBD outcome comprising patients with UC, patients with CD, and those with ambiguous IBD diagnoses)	• RR 1.14 (95% CI 1.06;1.22) for persons delivered by c-section compared with persons born vaginally. • Restricting analyses to children in the age-group 0–14 years, the overall IRR associated with c-section was 1.29 (95% CI 1.11;1.49), while among older children and young adults (age 15–35 years) the overall IRR was 1.10 (95% CI 1.01;1.20). However, the two age-specific IRRs were not statistically significantly different ($P_{\text{interaction}} = 0.22$). • The effect of mode of delivery on IBD risk at age 0–14 years was higher for acute c-section (IRR 1.51, 95% CI 1.01;2.27) than for elective c-section (IRR 0.72, 95% CI 0.33;1.53), although this difference was not statistically significant ($P_{\text{homogeneity}} = 0.06$).
• Crohn disease (CD)	• In the competing risk model, IRRs for CD: 1.26 (95% CI 1.01;1.58) at age 0–14 years and 1.06 (95% CI 0.92;1.23) at age 15–35 years.
• Ulcerative colitis (UC)	• In the competing risk model, IRRs for UC: 1.30 (95% CI 1.05–1.62) at age 0–14 years and 1.11 (95% CI 0.99;1.24) at age 15–35 years.
Limitations and other comments	
• Limitations	• Lack of some confounders (such as breastfeeding) • Some IBD diagnosis can be identified outside hospital. However, for all ages (0–95 years) only 8.6% of patients with UC and 1.0% of patients with CD had been diagnosed outside Danish hospitals. • Those born 1973–1976 could not be followed for IBD during their entire 0–4 year age interval because the National Patient Registry only started in 1977. However, because IBD cases in infancy are likely to be hospitalized again at a later point and probably before the age of 14 years, this limitation is unlikely to have affected the overall result. • No distinction of elective CS for non medical reason.
• CCL	• Cohort study of moderate risk of bias. • Main results: Moderately increased rates of IBD in childhood, adolescence, and young adulthood after CS (all kind and acute) vs VD, most notably in the age span 0–14 years. However, even if the association is causal, the possible impact of increasing cesarean section practices on the overall burden of IBD in childhood is small. • Hypothesis: underlying mechanisms remain unclear.

Bager 2010²⁵

Methods

• Design	Register-based national cohort study of 1.7 million Danes born 1973–2005
• Source of funding and competing interest	• Source of funding: grant from the Danish Medical Research Council, Aase and Ejnar Danielsen's Foundation, Dagmar Marshall's Foundation, and General Manager Kurt Bønnelycke and Wife's Foundation. • Conflict of interest: stated and none declared
• Setting	Denmark
• Sample size	1.71 million singleton persons born during the period January 1 1973 through April 4 2005 22 486 individuals were diagnosed with ≥ 1 intestinal bacterial infection
• Duration and follow-up	14.0 million person-years of follow-up



Each person was observed from 1 January 1991 or date of birth, whichever came later, until 5 April 2005, emigration, death, or registered date of intestinal bacterial infection, whichever came first.	
Statistical analysis	- Log-linear Poisson regression models. - Adjustment for adjusted for age, sex, birth order, season of birth, maternal age, average gross annual income, degree of urbanization, birth weight, and gestational age. - An interaction term for calendar-year and county of residence was included to account for diagnostic and reporting differences between regional laboratories. - Assessment of the potential association between gestational age and birth weight on one side and risk of intestinal bacterial infections on the other with adjustment for mode of delivery and all other variables. - To evaluate the impact of c-section on the burden of intestinal bacterial diseases at the population level, the population attributable risk percent (PAR%) was calculated as follows: $PAR\% = 100 \times [px(RR-1)/(px(RR-1) + 1)]$, where p is the proportion of newborns in the population who are delivered by c-section, and RR is the relative risk of intestinal bacterial infection associated with c-section. The PAR% can be considered as the proportion of all intestinal bacterial infections in the population that is theoretically preventable if all children were born by vaginal delivery.
Patient characteristics	
Eligibility criteria	All persons born in Denmark between 1973 and 2005
Exclusion criteria	None reported
Patient & disease characteristics	VD (87.4%) and CS (12.6%)
Exposures	
Exposure group	C-Section (elective or acute since 1997)
Control group	VD
Results	
Intestinal bacterial infections (laboratory-confirmed non typhoidal Salmonella species, Campylobacter species, Yersinia enterocolitica, Shigella species, and Shiga toxin-producing Escherichia coli from 1991–2005 in the National Registry of Enteric Pathogens.)	IRR 1.05 (95% CI 1.01;1.09) for all intestinal bacterial infections in persons delivered by c-section compared with persons born vaginally. - For specific infections, the IRR was significantly increased for Y. enterocolitica only (IRR 1.13; 95% CI 1.01;1.25). - Overall, CS was associated with a small, but statistically significant increase in risk for intestinal bacterial infection at ages 1 to <2 years (IRR 1.09; 95% CI 1.00;1.18) and 2 to <5 years (IRR, 1.08; 95% CI 1.00; 0.17). - The age-specific IRR was not significantly increased for any specific infection, except for infections at age 1 to <2 years with Shigella species or Shiga toxin-producing E. coli (IRR 1.33; 95% CI 1.06;1.66). - In an additional analysis restricted to subjects born since 1997, the age-specific IRRs for infections with Salmonella or Campylobacter species were not significantly different between those born after acute and planned c-sections - for Salmonella infection, p=0.47 for age 0 to <5 years and p= 0.19 for age >5 years; - for Campylobacter infection, p=0.26 for age 0 to <5 years and p=0.64 for age >5 years) - The proportion of all intestinal bacterial infections in Denmark during the study period that were theoretically attributable to c-section was <1% (PAR%= 0.62%)



Limitations and other comments

- **Limitations**
 - Lack of some confounders (such as breastfeeding)
 - No distinction of elective CS for non medical reason.
- **CCL**
 - Cohort study of moderate risk of bias.
 - Main results: Individuals delivered by c-section were at an overall 5% increased risk of intestinal bacterial infections compared with vaginally delivered peers, a finding that was restricted to infections in children aged <5 years. Mode of delivery appears thus not to be a clinically relevant determinant of risk for intestinal bacterial infections. The possible impact of increasing frequencies of c-section on the overall burden of intestinal bacterial infections appears negligible.
 - Hypothesis: an altered intestinal microflora following delivery by c-section might compromise the defense against intestinal pathogens.

Black 2015²⁶

Methods

- **Design** Population-based retrospective cohort study in Scotland (1993–2007); data-linkage study.
- **Source of funding and competing interest**
 - Source of funding: Wellcome Trust (as part of a personal research training fellowship)
 - Declaration of interest: stated and none declared
- **Setting**
 - All births in Scotland identified from the Scottish Morbidity Record database (1993-2007) and linked with 6 other databases.
- **Sample size**
 - The study sample included data on 321 287 term first-born singletons.
 - Designed to provide 95% power to detect a clinically and statistically significant difference of 1% in incidence of asthma requiring hospital admission (population incidence, 3.5%) following planned cesarean delivery, compared with vaginal birth at a significance level of 5%.
- **Duration and follow-up**
 - FU until February 2015
 - Mean duration: 14.8 years (SD 4.4)
- **Statistical analysis**
 - Mean and standard deviation for normally distributed data or median and interquartile range for skewed data for continuous variables.
 - For comparison, t test or the Mann-Whitney U test.
 - Hazard ratios(HRs) with Cox proportional hazards models. For outcomes for which time at risk was the same for all offspring, and for consistent estimation purposes, the relevant duration was included in the Cox model.
 - Test of the proportional hazards assumption of the Cox model using plots of the log of the negative log of the survival function against log of time for each comparison group.
 - Hazard ratios adjusted for prespecified confounding factors.
 - To assess the effects of multiple imputation on the main study findings, sensitivity analysis that involved complete case analyses for each outcome studied.
 -



Patient characteristics		
• Eligibility criteria	• All term (≥37 completed weeks of gestation) singleton live births in first-time mothers between January 1, 1993, and December 31, 2007, in Scotland, United Kingdom.	
• Exclusion criteria	• Offspring with missing or implausible data on date and mode of delivery, gestation, birthweight, or sex (less than 0.1% of cases for each variable)	
• Patient & disease characteristics	Mode of delivery: • Scheduled CS: 3.8% • Unscheduled CS: 17.4% • VD: 78.7% More details in Table 1.	
Exposure		
• Exposure group	Scheduled caesarean (performed during the day, with both staff and patient fully prepared).	
• Control group 1	VD	
• Control group 2	Unscheduled CS	
Results		
• Asthma requiring hospital admission	• Adjusted HR 1.22 (95% CI 1.11, 1.34) comparing planned CS and VD. • Adjusted HR 1.00 (95% CI 0.90, 1.12) comparing planned CS and unscheduled CS.	
• Salbutamol inhaler prescription at age 5 years	• Adjusted HR 1.13 (95% CI 1.01, 1.26) comparing planned CS and VD. • Adjusted HR 1.01 (95% CI 0.90, 1.15) comparing planned CS and unscheduled CS.	
• Obesity at age 5 years	• Adjusted HR 1.12 (95% CI 0.99, 1.26) comparing planned CS and VD. • Adjusted HR 0.93 (95% CI 0.82, 1.06) comparing planned CS and unscheduled CS.	
• Inflammatory bowel disease	• Adjusted HR 0.86 (95% CI 0.50, 1.49) comparing planned CS and VD. • Adjusted HR 1.01 (95% CI 0.97, 1.05) comparing planned CS and unscheduled CS.	
• Type 1 diabetes	• Adjusted HR 1.20 (95% CI 0.95, 1.52) comparing planned CS and VD. • Adjusted HR 1.35 (95% CI 1.05, 1.75) comparing planned CS and unscheduled CS.(may be attributable to type I error)	
• Cancer	• Adjusted HR 1.05 (95% CI 0.72, 1.55) comparing planned CS and VD. • Adjusted HR 1.02 (95% CI 0.98, 1.05) comparing planned CS and unscheduled CS.	
• Death up to age 21 years	• Adjusted HR 1.41 (95% CI 1.05, 1.90) comparing planned CS and VD. • Adjusted HR 0.98 (95% CI 0.96, 1.00) comparing planned CS and unscheduled CS.	



- **Sensitivity analyses**
 - Complete-cases analysis revealed a significantly increased risk of offspring obesity at age 5 years following planned cesarean delivery compared with vaginal birth, but no significant differences in risk of salbutamol inhaler prescription at age 5 years, asthma requiring hospital admission, inflammatory bowel disease, cancer, or death up to age 21 years.

Limitations and other comments

- **Limitations**
 - Misclassification of cesarean delivery type, missing data, risk of type 1 error and unmeasured confounding.
 - For some outcomes, knowledge of mode of birth can influence surveillance of offspring health (and further diagnosis).
- **CCL**
 - Population-based retrospective cohort study with low risk of bias.
 - Main results: Small increase in risk of offspring asthma and death in childhood after a planned CS in a first pregnancy compared to VD (but not compared to unscheduled CS). However, for asthma, the absolute increase in risk to individuals is low. Concerning mortality, until indications for cesarean delivery can be fully accounted for and cause of mortality measured, it would be premature to assume that planned cesarean delivery increases the risk of death in childhood (but given the consistency of findings from published studies, it is important to investigate this further).
 - Hypothesis: For asthma, avoidance of exposure to maternal bowel flora may affect development of T-cell-mediated asthma

Curran 2012²⁸

Methods

- **Design** The Millennium cohort study, a nationally representative UK cohort of children
- **Source of funding and competing interest**
 - Source of funding: The Irish Centre for Fetal and Neonatal Translational Research (INFANT) (Science Foundation Ireland funded centre)
 - Conflict of interest: stated; none declared
- **Setting** UK, Sampling was stratified by region, electoral ward, ethnic composition of the ward, and social disadvantage
- **Sample size** The Millennium Cohort Study (MCS) is a nationally representative sample of 18 827 children born in the UK between 2000 and 2002. Among them, 13 141 singletons participated in both the 2001 and the 2008 survey with data on mode of delivery. Of these, 13 049 answered the question on ASD (99.3 %), 13 038 answered the question on ADHD (99.2 %) and 12 683 had complete data for SDQ scores (96.5 %).
- **Duration and follow-up** 7 years
- **Statistical analysis**
 - Logistic regression
 - Survey commands were used and estimates were weighted to account for complex survey design
 - Sensitivity analyses were performed excluding babies who were SGA, pre-term, female, or in a breech presentation, as well as babies with mothers over the age of 40 and mothers who reported gestational hypertension
 - Though analyses were originally performed comparing children with ASD to the entire cohort of children without ASD, a sensitivity analysis was conducted excluding children with ADHD and behavioral difficulties from the control group.
 - Similar sensitivity analyses were performed for ADHD and behavioral difficulties.



	- As maternal depression, maternal IBS and gestational age may have played a mediating role in this association, these variables were not only included in the main analysis, but also tested separately to examine their effect on the association between mode of delivery and the outcome measures. - Likewise, breastfeeding was included in a separate analysis to assess a potential mediating effect.
Patient characteristics	
• Eligibility criteria	Singleton birth
• Exclusion criteria	No singleton birth
• Patient & disease characteristics	Spontaneous VD (48%), Assisted VD (10%), Induced VD (20%), Planned CS (8%), Emergency CS (7%), Induced CS (6.5%) There were 209 (1.5 %) reported cases of ASD and 173 (1.3 %) reported cases of ADHD. Abnormal SDQ scores were present in 951 (8 %) children, 338 of whom were girls and 613 of which were boys.
Exposures	
• Exposure group	"assisted VD," "induced VD," "emergency CS," "planned CS" and "induced CS."
• Control group	Spontaneous, non-assisted VD
Results	
• Autism spectrum disorders (ASD),	• Adjusted OR 0.58 (95% CI 0.19; 1.79) for planned CS compared with VD
• Attention-deficit/hyperactivity disorder (ADHD)	• Adjusted OR 0.54 (95% CI 0.18; 1.64) for planned CS compared with VD
• Behavioral difficulties	• Adjusted OR 0.73 (95% CI 0.43; 1.24) for planned CS compared with VD
Limitations and other comments	
• Limitations	- All variables, including exposures and outcomes, were self-reported, and as external validation of responses through medical records was not possible, these may be subject to recall bias, or social desirability bias. However, mode of delivery has been shown to be accurately reported in this dataset compared to medical records. - Some potential confounders were not measured in this cohort, for example parental history of ASD/ADHD, or behavioral difficulties (although maternal depression and depression treatment were included in the full model). Similarly, there was no measure for IQ, and thus it was not possible to stratify cases of ASD by intellectual disability.
• CCL	- Cohort study of moderate risk of bias - Main results: No association found between CS (planned or not) and ASD, ADHD or behaviour.



Daltveit 2008²⁹

Methods

• Design	Historical cohort design
• Source of funding and competing interest	- Source of funding: Funded by the Research Council of Norway. - Conflict of interest: The authors have no potential conflicts of interest to disclose.
• Setting	Norway, births registered in the Medical Birth Registry of Norway between 1967 and 2003.
• Sample size	N = 637 497 women with one previous birth N = 242 812 women with two previous births
• Duration and follow-up	Data were the first two or the first three births of women who gave birth for the first time in 1967 or later.
• Statistical analysis	All analyses were based on sibships with only single births. Data were analyzed in cross-tables with Pearson χ^2 statistics. For outcomes with a cell frequency less than 5, observed odds ratios (ORs) and Fisher's exact P value were calculated. Maternal age and year of birth were considered as potential confounders and were included in an unconditional logistic regression analysis as categorical variables. Effects are presented as adjusted ORs with 95% confidence intervals (CIs)

Patient characteristics

• Eligibility criteria	Women with more than 1 birth
• Exclusion criteria	Women who had experienced the same outcome in any of their previous pregnancies. Sibships with birth weights below 500 g or below 20 weeks of gestation
• Patient & disease characteristics	Among women with one previous birth, the caesarean delivery rate at second birth was 41.3 per 1,000 after a first vaginal delivery and 508.0 per 1,000 after a first caesarean delivery. Among women with two previous births, the caesarean delivery rate at third birth was 46.8 per 1,000 after a first and second vaginal delivery, 280.2 per 1,000 after a vaginal first delivery and a caesarean second delivery, and 974.0 per 1,000 after repeated caesarean delivery.

Exposures

• Exposure group	Women with a first caesarean delivery
• Control group	Women with a first vaginal delivery



Results

Complications in second pregnancy

Table 2. Adverse Outcomes in Second Pregnancy According to Mode of Delivery at First Birth Among Women With Two or More Single Births—Norway, 1967–2003

Outcome 2nd Pregnancy	Mode of 1st Delivery		OR* (95% CI)	P
	Vaginal per 1,000	Cesarean per 1,000		
All women (N=637,497)				
Bleeding in pregnancy	27.5	28.3	1.1 (1.0–1.1)	.002
Preeclampsia	16.0	50.4	2.9 (2.8–3.1)	<.001
SGA	74.6	93.1	1.5 (1.4–1.5)	<.001
Placenta previa	2.2	3.6	1.5 (1.3–1.8)	<.001
Placenta accreta	0.3	0.7	1.9 (1.3–2.8)	.002
Placental abruption	4.8	9.7	2.0 (1.8–2.2)	<.001
Uterine rupture	0.06	2.0	37.4 (24.9–56.2)	<.001
Selected women†				
Bleeding in pregnancy	26.4	26.5	1.1 (1.0–1.1)	.04
Preeclampsia	12.8	24.3	1.7 (1.6–1.8)	<.001
SGA	64.7	76.3	1.3 (1.3–1.4)	<.001
Placenta previa	2.2	3.3	1.4 (1.2–1.7)	<.001
Placenta accreta	0.3	0.6	1.9 (1.3–2.8)	.001
Placental abruption	4.8	8.4	1.7 (1.6–1.9)	<.001
Uterine rupture	0.06	2.0	37.2 (24.7–55.9)	<.001

OR, odds ratio; CI, confidence interval; SGA, small for gestational age.

* Adjusted for maternal age and year of birth.

† Women without actual outcome at first birth.

Complications in third pregnancy



Complications per 1,000 Births at Third Birth According to Mode of First and Second Delivery				
	Vaginal-Vaginal	Vaginal-Cesarean	Cesarean-Vaginal	Cesarean-Cesarean
All women (N=242,812)				
Bleeding in pregnancy	29.1	34.8	31.6	27.3
Preeclampsia	17.2	39.3	38.0	39.1
SGA	65.6	83.7	77.5	86.1
Placenta previa	2.8	5.0	2.5	4.1
Placenta accreta	0.3	0.7	0.1	0.4
Placental abruption	6.2	14.3	8.4	8.1
Uterine rupture	0.1	1.4	1.0	0.7
Selected women†				
Bleeding in pregnancy	27.3	30.0	29.0	25.1
Preeclampsia	13.8	22.1	16.9	18.0
SGA	47.2	53.8	50.6	54.1
Placenta previa	2.8	4.2	2.4	4.0
Placenta accreta	0.3	0.7	0.1	0.4
Placental abruption	6.0	10.1	7.1	5.7
Uterine rupture	0.1	1.4	1.0	0.7

OR, odds ratio; CI, confidence interval; SGA, small for gestational age.

* Adjusted for maternal age and year of birth.

† Women without actual outcome at first birth.

‡ Observed odds ratio and Fischer exact *P* value.

Vaginal First, Cesarean Second		Cesarean First, Vaginal Second		Cesarean First and Second	
OR* (95% CI)	<i>P</i>	OR* (95% CI)	<i>P</i>	OR* (95% CI)	<i>P</i>
1.3 (1.2–1.5)	<.001	1.2 (1.1–1.4)	.001	1.1 (0.9–1.2)	.5
2.3 (2.0–2.6)	<.001	2.2 (2.0–2.5)	<.001	2.2 (2.0–2.5)	<.001
1.5 (1.3–1.6)	<.001	1.4 (1.3–1.5)	<.001	1.5 (1.4–1.7)	<.001
1.8 (1.3–2.5)	.002	1.0 (0.6–1.5)	.8	1.5 (1.0–2.1)	.03
2.6 (1.0–6.5)	.04	0.4 (0.05–2.8)	.5*	1.4 (0.4–4.4)	.5*
2.4 (2.0–3.0)	<.001	1.5 (1.2–1.9)	<.001	1.4 (1.1–1.8)	.01
24.2 (10.7–54.5)	<.001	20.3 (8.6–47.9)	<.001	13.1 (4.6–36.9)	<.001
1.2 (1.0–1.4)	.002	1.2 (1.1–1.4)	.008	1.0 (0.9–1.2)	.7
1.6 (1.3–1.9)	<.001	1.2 (1.0–1.5)	.02	1.3 (1.1–1.5)	.01
1.3 (1.1–1.5)	.003	1.2 (1.1–1.4)	.002	1.3 (1.1–1.5)	<.001
1.5 (1.0–2.2)	.04	0.9 (0.6–1.4)	.7	1.4 (1.0–2.1)	.05
2.6 (1.0–6.5)	.04	0.4 (0.05–2.8)	.5*	1.4 (0.4–4.4)	.5*
1.8 (1.4–2.3)	<.001	1.3 (1.0–1.7)	.03	1.0 (0.7–1.4)	.9
24.2 (10.8–54.6)	<.001	20.3 (8.6–48.0)	<.001	13.1 (4.6–37.2)	<.001



Limitations and other comments

- **Limitations** /
- **CCL** This study suggests a moderately increased risk of placenta previa, placenta accreta, and placental abruption and a highly increased risk of uterine rupture after a caesarean delivery. Excess risks were reduced after excluding women with the actual complication in any of their previous births.

Emilsson 2015³⁰

Methods

- **Design** Prospective Norwegian MoBa cohort of pregnant women of 18 gestational weeks from all over Norway from 1999 to 2008.
- **Source of funding and competing interest**
 - Source of funding: Ketil Stordal is funded by an unrestricted grant from Oak Foundation, Geneva, Switzerland.
 - Conflict of interest: Stated and none declared
- **Setting** Norway
- **Sample size** 114 285 children
- **Duration and follow-up** Max 8 years
- **Statistical analysis**
 - Adjusted logistic regression (for child's attained age, maternal CD, and sex - referred to as model 1) and (for gluten introduction and breastfeeding (referred to as model 2)
 - Sensitivity analysis restricted to singletons concerning birth weight and length (z scores)

Patient characteristics

- **Eligibility criteria** Pregnant women of 18 gestational weeks
- **Exclusion criteria** Children participating in MoBa without data from MBRN available (n = 5689) or uncertain diagnosis of CD (e.g., recorded only once in the NPR, n = 118)
- **Patient & disease characteristics**
 - CD reported in the questionnaires at 7 or 8 years of age (n = 159)
 - CD reported in at least 2 different registrations in NPR (in absence of being reported in the questionnaires, n = 491, because many participants have not reached the age of 7).
 - CS = 12.8% in the CD group and 15.0% in the control group
 - Elective CS = 4.8% in the CD group and 6.8% in the control group

Exposures

- **Exposure group** CS (whether it was due to elective, breech, child growth, maternal indication, or overall)
- **Control group** VD



Results

- **Celiac disease (questionnaire at 7 or 8 years old or registry)**
 - Adjusted OR 0.83 (95% CI 0.63;1.09) after CS (independent of indication and electivity) compared to VD
 - Adjusted OR 0.93 (95% CI 0.34;2.49) after elective CS compared to VD

Limitations and other comments

- **Limitations**
 - Norway cohort but with 41% participation rate
 - Mode of delivery and indication for CS based on maternal questionnaire
 - Short FU for this kind of pathology
 - However, inclusion of several confounding factors in the analysis
- **CCL**
 - Cohort study with moderate risk of bias
 - Main results: no association of mode of delivery, intrauterine growth, or factors pertaining to intrauterine fetal growth on future development of CD. CD was significantly associated to female sex, maternal CD, and maternal type I diabetes mellitus.

Gurol-Urgancı 2014³³

Methods

- **Design** Retrospective cohort study (between 1 April 2000 and 31 March 2012)
- **Source of funding and competing interest**
 - IG-U is supported by the Lindsay Stewart R&D Centre, Royal College of Obstetricians and Gynaecologists, UK.
 - The authors have no conflicts of interest to declare.
- **Setting** English maternity units (NHS trusts)
- **Sample size** 1 047 644 primiparous women
- **Duration and follow-up** The study covered a 12-year period, between 1 April 2000 and 31 March 2012. Follow-ups were done at 3, 5 and 10 years. Complete 10-year follow-up was available for only 2 years of the study cohort, for index deliveries in 2000 and 2001.
- **Statistical analysis** Kaplan–Meier analyses and Cox proportional hazard models were used to assess the effect of mode of delivery on time to subsequent birth, adjusted for age, ethnicity, socio-economic deprivation and year of index delivery. To account for a lack of independence in the data of women treated in the same NHS trust, the standard errors of the model coefficients were calculated using a clustered sandwich estimator.

Patient characteristics

- **Eligibility criteria** Low-risk primiparous women aged 15–40 years who had a singleton, term, live birth in the English National Health Service.
- **Exclusion criteria** All women who had inpatient fertility treatments before the index delivery, and those reported to have had a history of infertility. Women with high-risk pregnancies involving placenta praevia, pre-eclampsia, eclampsia (gestational or pre-existing), hypertension or diabetes were analysed separately.



Patient & disease characteristics	Over two-thirds of the women were <30 years of age when they gave birth. The overall Caesarean section rate for the cohort was 21.4%, with <4% of women having an elective Caesarean section (3% in 15-29 years and 7.7% in 35-40 years). Women with standard VD represent 57% of the cohort (62.7% in 15-29 years and 38.9% in 35-40 years).
Exposures	
Exposure group	Instrumental delivery, elective Caesarean for breech and transverse lie, elective Caesarean for other indications and emergency Caesarean section.
Control group	Vaginal delivery
Results	
Subsequent birth rate	The unadjusted Kaplan–Meier estimate of the subsequent birth rate at 10 years for the cohort was 74.7%. Women aged 30–34 years, on average, had their second baby earlier than women younger than 30 (at 3 years, 41.8% vs 32.5%; at 5 years, 63% vs. 45.9%). Women who had an elective Caesarean section for an indication other than a breech baby were least likely to have a subsequent birth (64.4% vs. 76% for vaginal delivery, 74.8% for instrumental VD, 73.5% for elective CS due to breech presentation and 71.3% for emergency CS). Association between the risk of a subsequent pregnancy and characteristics of index deliver (VD= index delivery) - Instrumental delivery: Adjusted HR 1.00 (0.99,1.01) - Elective CS for breech: Adjusted HR 0.96 (0.94,0.98) - Elective CS other indication: Adjusted HR 0.81 (0.78,0.83) - Emergency CS: Adjusted HR 0.91 (0.90,0.93) Results from a Cox regression model with age category and mode of delivery interaction terms demonstrated that subsequent fertility declines with age, regardless of mode of delivery ($P < 0.001$ for each pairwise comparison, data not shown).
Limitations and other comments	
Limitations	There may be residual bias in the adjusted results due to the impossibility to adjust for maternal factors such as obesity and voluntary absence of conception or completely account for history of infertility. Subsequent fertility outcomes should ideally be measured as the next pregnancy following the index delivery, but HES data do not capture spontaneous or induced abortions or ectopic pregnancies
CCL	Results provide strong evidence that there is no or only a slight effect of Caesarean section on future fertility. The medical and social circumstances leading to the decision to carry out a Caesarean section may contribute more to the observed reduction in fertility than the Caesarean section itself.



Hanlon ³⁴	
Methods	
• Design	Retrospective cohort study of term, singleton births from 1 st January 2013 to 31 st December 2013 at a tertiary obstetric facility. Outcomes were compared for 1816 women having vaginal births versus 1205 women having instrumental or caesarean births.
• Source of funding and competing interest	Not explicitly stated but University of Brisbane, Queensland, Australia setting.
• Setting	A tertiary obstetric facility
• Sample size	3021 births, 1816 SVD and 1205 IVD or CS
• Duration and follow-up	7-10 days post discharge
• Statistical analysis	Multivariate logistic regression.
Patient characteristics	
• Eligibility criteria	Term, singleton births from 1st January 2013 to 31st December 2013 at one tertiary obstetric facility
• Exclusion criteria	Exclusion criteria were the need for an interpreter, multiple births, pre-existing maternal mental health disorder, including history of post-natal depression, Edinburgh Postnatal Depression Score (EPDS) ≥ 12 at the time of booking, preterm birth (<37 weeks 0 days), stillbirth or neonatal death, where the baby had a major congenital or chromosomal abnormality, and where UPNC data were incomplete. The final data set comprised 3021 patient records.
• Patient & disease characteristics	Average age for SVD 29.8 years and for IVD and SR 30.6 years. Longer labour in IVD and SC group compared to SVD. More nulliparity in IVD and SR group.
Exposures	
• Exposure group	SVD
• Control group	IVD and CC
Results	
• Postnatal symptoms of psychological morbidity	aOR for VD vs. IVD and CS: 1.23 (95% CI 0.75-2.04)
• Postnatal symptoms of psychological morbidity	Nulliparity vs. multiparity: aOR 1.69 (95% CI 1.09-2.63)
Limitations and other comments	
• Limitations	Tertiary hospital setting
• CCL	Population based cohort but with stringent exclusion criteria in a tertiary hospital setting. So possibly a selected population. No indications for an association between mode of delivery and postnatal depression.

Khashan 2014³⁵

Methods

• Design	Population-based cohort study of all singletons live births in Sweden between 1982 and 2009
• Source of funding and competing interest	• Source of funding: in part by Science Foundation Ireland. Financial support was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, the Swedish Research Council, and through the Swedish Initiative for research on Microdata in the Social and Medical Sciences (SIMSAM) framework, the Swedish Heart-Lung foundation, and the Strategic Research Program in Epidemiology at Karolinska Institutet. • Conflict of interest: stated and none declared
• Setting	All settings in Sweden
• Sample size	2 638 083 included (among 2 838 056 births) 2200 siblings discordant on mode of delivery and diabetes type 1 diabetes diagnosis
• Duration and follow-up	From the date of birth until the onset of the outcome measure, 15th birthday (for the primary outcome only), death, migration, or December 31, 2009 (end of the study period).
• Statistical analysis	• Log-linear Poisson regression with aggregated person years by using the full cohort; Poisson model adjusted for several confoundants. (Table 1) • Conditional logistic regression for sibling-control analyses with the mother as the grouping variable. The sibling analysis included siblings who were discordant for both mode of delivery and T1D. The conditional logistic regression was adjusted for the same variables as in the Poisson model apart from the maternal country of birth, which was the same for both siblings. • Sensitivity analyses were performed by excluding children who were SGA, LGA, preterm birth, and those of women with preeclampsia. • Analyses for the primary outcome were restricted to births from 1990 onwards when the coverage of the national registers was complete and the recording variable for mode of delivery was changed including information on induction of labor.

Patient characteristics

• Eligibility criteria	All birth live
• Exclusion criteria	Multiple births, stillbirths, unknown mode of delivery
• Patient & disease characteristics	Unassisted VD (79.4%); IVD (7.3%); emergency CS (7.1%) and elective CS (6.1%). Women who had elective CS were more likely to be older, have higher education level attainment, and higher BMI compared with women who had unassisted vaginal birth. Both emergency and elective CS were more common in women who had SGA, LGA, preterm birth, or prepregnancy diabetes. Any diabetes mellitus (0.51%) from which 77.7% T1D; Median age at diagnosis: 9.8 years (interquartile range 5.7-14.0)

Exposures

• Exposure groups	Instrumental vaginal delivery (IVD); Emergency CS; Elective CS.
• Control group	Unassisted vaginal delivery

**Results**

- **Type 1 Diabetes (T1D), before 15 years of age**
 - Adjusted **RR 1.15 (95% CI 1.06, 1.25)** comparing children born by elective CS and unassisted VD.
 - Adjusted **RR 1.14 (95% CI 1.06, 1.23)** comparing children born by IVD and unassisted VD.
 - Adjusted RR 1.02 (95% CI 0.95, 1.11) comparing children born by emergency CS and unassisted VD.

However, the effect of elective CS and IVD on childhood T1D almost disappeared and became nonsignificant in the sibling-control analyses

 - Adjusted RR 1.06 (95% CI 0.85, 1.31) comparing children born by elective CS and unassisted VD.
- **Type 1 Diabetes (T1D), at any age (max 27 years old)**
 - Adjusted **RR 1.15 (95% CI 1.07, 1.24)** comparing children born by elective CS and unassisted VD.
 - Adjusted **RR 1.13 (95% CI 1.06, 1.21)** comparing children born by IVD and unassisted VD.
 - Adjusted RR 1.03 (95% CI 0.96, 1.11) comparing children born by emergency CS and unassisted VD.

However, the effect of elective CS and IVD on childhood T1D almost disappeared and became nonsignificant in the sibling-control analyses

Adjusted RR 1.06 (95% CI 0.85, 1.31) comparing children born by elective CS and unassisted VD.

Limitations and other comments

- **Limitations**
 - This analysis included the first 2 children of the mother, and therefore some of these siblings may have had different fathers, who were discordant for mode of delivery and T1D diagnosis.
 - Wide Cis in the sibling analysis
 - Lack of some confounders (e.g. maternal lifestyle during pregnancy such as physical activity, diet, and weight gain or family lifestyle) but impact reduced with the sibling control analysis
- **CCL**
 - Population-based cohort study with low risk of bias
 - Main results: The small association between elective CS and IVD and T1D was not confirmed after the sibling-control analysis, suggesting that these findings are not consistent with causal effects of mode of delivery on T1D and may be due to familial confounders such as genetic susceptibility and environmental factors.
 - Hypothesis: the positive association between the mode of delivery and T1D may reflect the lack of information, and hence lack of adjustment, on genetics and the lifestyle of the children.



Kristensen 2016 (immune disorders)³⁶

Methods

• Design	Population-based national register-based cohort study (1997-2012)
• Source of funding and competing interest	• Source of funding: Edith og Henrik Henriksens Mindelegat • Conflict of interest: stated: L. H. participated in an AbbVie safety study on palivizumab.
• Setting	Denmark
• Sample size	790 569 children aged 0 to 14 years included among the 1 031 424 children born during the period.
• Duration and follow-up	Children were followed from the day of birth to an outcome of diagnosis, emigration, death, or the end of follow-up on December 31, 2012.
• Statistical analysis	• Cox proportional hazards model stratified by exact date of birth with vaginal delivery as the reference. Results are reported as hazard ratios with 95% CIs. • To avoid children being censored at an outcome of diagnosis, a separate analysis performed for each of these. • Multivariate analysis with prespecified covariates: gestational age at birth, sex, birth weight, maternal age, maternal smoking during pregnancy, and complications during pregnancy (preeclampsia, eclampsia, hemorrhage and hyperemesis).

Patient characteristics

• Eligibility criteria	All children born in Denmark between 1997 and 2012.
• Exclusion criteria	• Children born at gestational ages of less than 37 weeks and those born as part of multiple births. • Children with congenital chronic conditions, including all with congenital malformations (Q-diagnoses). • Children with missing information on gestational age at birth, • Children whose gestational ages were recorded as 44 or 45 weeks, Children with recorded birth weight was less than or greater than 2 SDs from the mean birth weight for all gestational ages included
• Patient & disease characteristics	63 811 born by elective CS (8.1%); 60 319 by acute CS (7.6%) Children 0-14 years

Exposure

• Exposure group	CS (acute or elective)
• Control group	VD

Results

• Asthma	• Adjusted hazard ratio 1.24 (95% CI 1.20, 1.28) comparing elective CS to VD • Adjusted hazard ratio 1.06 (95% CI 1.02, 1.10) comparing acute CS to VD
• Laryngitis	• Adjusted hazard ratio 1.19 (95% CI 1.14, 1.25) comparing elective CS to VD • Adjusted hazard ratio 1.14 (95% CI 1.09, 1.20) comparing acute CS to VD



• Pneumonia and Low respiratory infection	• Adjusted hazard ratio 1.20 (95% CI 1.16, 1.24) comparing elective CS to VD
	• Adjusted hazard ratio 1.01 (95% CI 0.97, 1.04) comparing acute CS to VD
• Gastro-enteritis	• Adjusted hazard ratio 1.18 (95% CI 1.13-1.23) comparing elective CS to VD
	• Adjusted hazard ratio 1.22 (95% CI 1.17, 1.27) comparing acute CS to VD
• Ulcerative colitis	• Adjusted hazard ratio 0.74 (95% CI 0.45-1.23) comparing elective CS to VD
	• Adjusted hazard ratio 1.47 (95% CI 1.02, 2.12) comparing acute CS to VD
• Celiac disease	• Adjusted hazard ratio 0.69 (95% CI 0.43-1.12) comparing elective CS to VD
	• Adjusted hazard ratio 1.52 (95% CI 1.06, 2.20) comparing acute CS to VD
• Crohn	• No association comparing elective or acute CS to VD
• Juvenile idiopathic arthritis	• Adjusted hazard ratio 1.25 (95% CI 1.04, 1.51) comparing elective CS to VD
	• Adjusted hazard ratio 0.99 (95% CI 0.82, 1.20) comparing acute CS to VD
• Cancers (Lymphatic leukemia, myeloid leukemia, lymphoma, malignant non-hematologic cancer)	• No association comparing elective or acute CS to VD
• Diabetes	• No association comparing elective or acute CS to VD
Limitations and other comments	
• Limitations	• Lack of data on BF and maternal asthma • Very large sample size with a statistical power that could detect very small effects, which might not be of clinical significance. • Associations found do not necessarily imply causality. • Children for all age without description of characteristics
• CCL	• Population-based cohort study with moderate risk of bias • Main results: Children delivered by both acute and elective CS had an increased risk of asthma, laryngitis, and gastroenteritis. For asthma, the effect of elective CS was higher than the effect of acute CS. Moreover, children delivered by elective CS had an increased risk of lower respiratory tract infection and juvenile idiopathic arthritis. Children delivered by acute CS had an increased risk of ulcerative colitis and celiac disease. • Hypothesis: Disturbed immune function induced by the aberrant microbial colonization present in children delivered by CS (mainly in elective CS because of intact membranes (see Kristensen 2015)



Kristensen 2015^{36, 37}

Methods

• Design	Population-based national register-based cohort study (1997-2003)
• Source of funding and competing interest	• Source of funding:? • Conflict of interest: stated and none declared
• Setting	Denmark
• Sample size	399 175 children with 10 758 hospitalizations for RSV illness
• Duration and follow-up	
• Statistical analysis	• Cox regression model stratified by exact date of birth and sex with adjustment for prematurity, asphyxia, birthweight, multiple births, single parenthood, maternal smoking during pregnancy, older siblings and asthma diagnoses up to 2 weeks before hospitalization for RSV infection. • Test for homogeneity to assess effect over time (between the first and second years of life) • Linear regression after logarithmic transformation due to nonnormality used to analyse the association between CS and duration in days of hospitalization for RSV (reported as geometric mean ratios (GMR))

Patient characteristics

• Eligibility criteria	All children born in Denmark and all hospitalizations for RSV disease from 0-23 months of age.
• Exclusion criteria	All children with congenital chronic conditions including all with Q-diagnoses (congenital malformations).
• Patient & disease characteristics	30 965 born by elective CS (7.6%) 31 715 by acute CS (7.9%)

Exposures

• Exposure group	CS (acute or elective)
• Control group	VD

Results

• Hospitalization for RSV infection= first positive RSV test in the RSV database during the first 2 years of living	• Adjusted hazard ratio: 1.27 (95% CI 1.19,1.36; p<0.001) comparing elective CS to VD. • Adjusted hazard ratio: 1.09 (95% CI 1.01,1.27; p=0.035) comparing acute CS to VD. • The effect of elective CS remained unchanged throughout the first 2 years of life (p=0.53), whereas the effect of acute CS was only present in the second year of life (p=0.001).
• Duration of RSV hospitalization	• Adjusted GMRs: 1.08 (95% CI: 1.03, 1.14; p=0.018) for elective CS • Adjusted GMRs: 1.02 (95% CI: 0.95, 1.08; p=0.91) for acute CS • The effect of acute and elective CS on duration of RSV hospitalization was not statistically different in the first and in the second years of life (p=0.61 and p=0.19 respectively).



Limitations and other comments

- **Limitations**
 - Lack of data on atopic disposition, although maternal asthma is associated with both an increased risk of CS and an increased risk of hospitalization for RSV in the offspring
 - RSV diagnoses based on antigenic testings and not PCR.
- **CCL**
 - Population-based cohort study with moderate risk of bias
 - Main results: Delivery by CS is associated with an increased risk of hospitalization for RSV infection. This effect continues at least throughout the first 2 years of life.
 - Hypothesis: Elective CS in contrast to acute CS is usually performed with intact membranes which leads the newborn born by elective CS to be not exposed to the mother's vaginal microflora.

Lydon-Rochelle 2001³⁸

Methods

- **Design** Population-based, retrospective cohort analysis using data from all primiparous women who gave birth to live singleton infants by caesarean section and who delivered a second singleton child during the same period.
- **Source of funding and competing interest**
 - Source of funding: grants from the Agency for Healthcare Research and Quality (5 T32 HS00034) and from the National Institutes of Health– National Institute of Nursing Research (T32 NR07039).
 - Conflict of interest: not stated
- **Setting** Civilian hospitals in Washington State
- **Sample size** All primiparous women who gave birth to live singleton infants by caesarean section in civilian hospitals in Washington from January 1, 1987, through December 31, 1996, and who delivered a second singleton child in Washington during the same period were included (a total of 20 525 women). Of these, 430 women who had a second delivery before 1989 were excluded.
The final sample included 20 095 women.
- **Duration and follow-up** Study period: From 1987 through 1996
- **Statistical analysis**
 - Mantel–Haenszel rate ratios and 95% CI were used to estimate the relative risks.
 - Interactions between the mother's labor status at the second delivery and the type of uterine incision at the first delivery and the year of the second delivery were assessed by the likelihood-ratio test, with P values below 0.05 denoting statistical significance.

Patient characteristics

- **Eligibility criteria** Primiparous women who gave birth to live singleton infants by caesarean section and who delivered a second singleton child during the same period.
- **Exclusion criteria** None reported.
- **Patient & disease characteristics** There were 6980 women who had repeated caesarean delivery without labour (34.7%), 1960 women who had induction of labour without prostaglandins (9.8%), 366 women who had induction of labour with prostaglandins (1.8%), and 10 789 women who had spontaneous onset of labour (53.7%) available for analysis.



Demographic and perinatal characteristics at the time of the second delivery were similar among women with spontaneous onset of labour and women with no trial of labour.

Exposures

- **Exposure group**
 1. Women who had spontaneous onset of labour
 2. Women who had induction of labour without prostaglandins
 3. Women who had induction of labour with prostaglandins
- **Control group** Women who had repeated caesarean delivery without labour

Results

- **Uterine rupture: incidence**
 - 1.6 per 1000 among women with repeated cesarean delivery without labor (11 women)
 - 5.2 per 1000 among women with spontaneous onset of labor (56 women)
 - 7.7 per 1000 among women whose labor was induced without prostaglandins (15 women)
 - 24.5 per 1000 among women with prostaglandin-induced labor (9 women).
- **Uterine rupture: comparison 1** RR = 3.3; 95% CI (1.8 to 6.0)
- **Uterine rupture: comparison 2** RR = 4.9; 95% CI (2.4 to 9.7)
- **Uterine rupture: comparison 3** RR = 15.6; 95% CI (8.1 to 30.0)

Limitations and other comments

- **Limitations** -
- **CCL** For women with one prior caesarean delivery, the risk of uterine rupture is higher among those whose labour is induced than among those with repeated caesarean delivery without labour. Labour induced with a prostaglandin confers the highest risk.

MacArthur 2001³⁹

Methods

- **Design** Twelve-year longitudinal cohort study
- **Source of funding and competing interest**
 - Source of funding: Grants were obtained from Wellbeing of Women/Royal College of Obstetricians and Gynaecologists for the UK follow up and from the Health Research Council of New Zealand for follow up in New Zealand.
 - All authors declare that they have no interests to declare
- **Setting** This study was conducted in three maternity units, in Aberdeen (UK), Birmingham (UK) and Dunedin (New Zealand).
- **Sample size**
 - 10 989 women were sent a questionnaire at 3 months post-partum; 7879 replied (71.7%)
 - 7725 follow-up questionnaires were sent at 12 years; 3763 were returned completed (48.7%)



• Duration and follow-up	Index births: 1993/1994 – follow-up: 12 years later
• Statistical analysis	Logistic regression was used to assess the independent effects of delivery mode history on symptom outcome and to adjust for and report on other independent predictors.
Patient characteristics	
• Eligibility criteria	All women who delivered over a 12-month period (1993/94) in three maternity units (UK and New-Zealand)
• Exclusion criteria	Women who requested no further contact or had died
• Patient & disease characteristics	The mean age of the women at 12 years was 42.4 years (SD 4.9) Comparison of baseline characteristics of women who did and did not respond at 12 years showed some differences: Parity, delivery mode (CS 16.3% vs 15.9%; SVD 68.0% vs 70.6%), onset of labour and length of second stage of index birth were similar. The prevalence of FI at 3 months was a little lower among respondents (8.2% vs. 9.5%), which is likely to underestimate the prevalence of symptoms at 12 years.
Exposures	
• Exposure group	Caesarean section only
• Control group	Spontaneous vaginal delivery only
Results	
• Faecal incontinence	FI symptoms • SVD: n=213 (11.5%) • Only CS: n=47 (11.7%); OR 0.94 (95% CI 0.66; 1.33) More severe FI symptoms • SVD: n=43 (2.3%) • Only CS: n=9 (2.2%); OR 1.07 (95% CI 0.51; 2.27)
Limitations and other comments	
• Limitations	• There are insufficient numbers of women delivering exclusively by caesarean section to be able to make comparisons with adequate precision • Low rate of follow up at 12 years (48.7%) • No validated questionnaire existed to measure outcomes
• CCL	Caesarean section does not protect from subsequent FI.



Magnus 2011⁴⁰

Methods

- **Design** Prospective cohort study of Norwegian pregnant women (1999-2008)
- **Source of funding and competing interest**
 - Source of funding: public research funds, government, not governmental organization, healthcare industry or other (give name of organization or corporation) and the presence of
 - Conflict of interest: (stated/not stated and specify if any)
- **Setting** 39 out of the 50 maternity units that recorded more than 100 births annually in Norway
- **Sample size**

Among the all pregnant women, participation: 38.5%.
 Among the 84 932 participants who so far have received the 36-months questionnaire, response rate: 59.1%.
 The sample for the current study included the 37 171 children for whom information was available from the questionnaires administered at the 18th and 30th gestational weeks and when the child was 6, 18, and 36 months of age.
- **Duration and follow-up**
- **Statistical analysis**
 - Chi-squared tests.
 - Generalized linear models with the log-link function to report relative risks and 95% confidence intervals.
 - Separate models fitted for wheezing, asthma, and recurrent LRTIs.
 - Multivariable models were adjusted for all covariates identified.
 - Robust variance estimations with cluster adjustments used to account for siblings.
 - A total of 10 imputed data sets were generated through multivariate normal regression, a Markov chain Monte Carlo method using data augmentation.
 - Wald tests used to examine the statistical significance of several coefficients in the multivariable models at the same time and to examine the differences between groups.

Patient characteristics

- **Eligibility criteria** Pregnant women at approximately 18 weeks of gestation
- **Exclusion criteria** Children from multiple births
- **Patient & disease characteristics**

Children born between 2001 and 2007.
 Children delivered by elective CS: 4.7%; by acute CS: 7.7% and unspecified CS: 1.0%
 Children delivered by CS were more likely than children delivered vaginally to have mothers who were older, single, and primiparous; had a preference for delivery by caesarean section; were classified as overweight or obese before pregnancy; had a lower educational level, chronic or atopic disorders, pregnancy complications, and longer duration of membrane rupture; and had delivered previously by CS.
 Furthermore, children delivered by CS were more likely to be male, to have been exposed to smoking during pregnancy, and to have a lower birth weight and shorter gestational age, whereas they were less likely to still be breastfed at 6 months of age.

Exposure

- **Exposure group** CS (acute, elective, or unspecified caesarean section)
- **Control group** VD (all kind)



Results

- Recurrent respiratory infections = 3 or more episodes of RSV, pneumonia, or bronchitis, before 36 months of age**
Low tract
No association between CS and VD and similar finding among those delivered by elective and acute CS
- Wheezing symptoms = maternal report of the child's experiencing at least 1 episode with wheezing, whistling, or chest congestion between 6 and 18 months age.**
No association between CS and VD and similar finding among those delivered by elective and acute CS
- Asthma**

Included in Huang 2015 (Adjusted RR: 1.17 (95% CI: 1.03, 1.32)
Higher risk among children of non atopic mothers than among children of atopic mothers.

Limitations and other comments

- Limitations**
 - Possible selection bias (poor participation rate)
 - Possible misclassification of outcomes (maternal-reported)
 - Lower proportion of CS between respondents
- CCL**
 - Cohort study with high risk of bias but inclusion of very interesting confounding factors.
 - Main results: higher risk of asthma at 36 months among children born by CS compared to VD but no difference for wheezing and LRTIs.

Malmberg 2012⁶⁰

Methods

- Design**

Matched case-control design.
- Source of funding and competing interest**

Supported in part by the Broad Foundation's Broad Medical Research Program and Stiftelsen Samariten
Conflict of interest: Not stated
- Setting**
- Sample size**

1536 patients with a diagnosis of paediatric CD and 15 439 controls.
- Duration and follow-up**



- **Statistical analysis**
 - Conditional logistic regression
 - Adjustment for socioeconomic index, maternal infections during pregnancy, number of older siblings, gestational age, and mother's age (in separate models). Males and females were examined together and then the analysis was stratified by sex.

Patient characteristics

- **Eligibility criteria** State the inclusion criteria cited in the paper
- **Exclusion criteria**
 - Subjects with mothers who had a diagnosis of IBD were exclude from the analysis
 - Subjects born premature
- **Patient & disease characteristics** Describe baseline characteristics cited in the paper (precise if it is on involved and/or analysed numbers). Highlight discrepancies between groups (i.e. involved and analysed)

Exposures

- **Exposure group** Elective (= performed before onset of labour contractions) and acute CS
- **Control group** VD

Results

- **Pediatric Crohn disease**
 - Adjusted OR 1.14 (95%CI 0.97;1.34) comparing all CS vs VD
 - o **1.25 (95% CI 1.01;1.54) in male**
 - o 0.99 (95% CI 0.76;1.29) in female
 - **Adjusted OR 1.36 (95%CI 1.02;1.80) comparing elective CS vs VD**
 - o 1.43 (95% CI 0.98;2.09) in male
 - o 1.28 (95% CI 0.82;2.00) in female
 - Adjusted OR 0.85 (95%CI .60;1.18) comparing acute CS vs VD
 - o 0.91 (95% CI 0.59;1.40) in male
 - o 0.74 (95% CI 0.43;1.28) in female

Limitations and other comments

- **Limitations**
 - Lack of some confounding factors such as breastfeeding.
 - It is possible that the association of CS with pediatric CD in males is a chance finding, as the difference between males and females is not of sufficient magnitude to demonstrate statistically significant effect modification. However, boys may be more susceptible than girls to some exposures that increase the risk of the disease.
 - No information about the reason for a CS.
- **CCL**
 - Case-control study with moderate risk of bias
 - There is a modestly increased CD risk for boys delivered by cesarean section (all kind) compared with VD. Elective procedures were associated with a raised pediatric CD risk in the entire population (without difference according to the sex).



- Hypothesis: an atypical pattern of initial bowel colonization may result in a failure of the immune system to develop appropriate tolerance to normal bowel flora among susceptible individuals. (less likelihood of initial colonization in elective than in acute CS).

Mamun 2013⁴¹**Methods**

- **Design** Prospective cohort study recruited between 1981 and 1983 (MUSP).
- **Source of funding and competing interest**
 - Source of funding: National Health and Medical Research Council of Australia. A.A.M. is supported by a Career Development Awards from the NHMRC. For the work in this article, A.A.M. received a grant from the National Heart Foundation of Australia
 - Conflict of interest: stated and none declared
- **Setting** One major public hospital in Brisbane, Australia
- **Sample size** 7223 (60% among the eligible) women and their offspring recruited. Because of limited funding, at 21 years, physical assessments for a subsample of nearly 2664 young adults of which 2382 provided measured heights and weights and had mode of delivery data at birth and data on potential confounding factors. Only 185 sibling pairs;
- **Duration and follow-up** 21 years
- **Statistical analysis**
 - Chi² for categorical characteristics and F test for continuous characteristics.
 - Multiple logistic regression analysis (odds ratio (OR) with 95% confidence interval (CI)) to examine independent association of maternal and birth characteristics with mode of delivery
 - Likelihood ratio test of the interaction with sex.
 - Multinomial logistic regression to estimate the unadjusted and adjusted ORs of overweight and obesity by 21 years.
 - Multiple regression model to estimate unadjusted and adjusted mean differences of BMI and waist circumference scores at 21 years by mode of delivery.

Patient characteristics

- **Eligibility criteria** Women who delivered at Mater Hospital during the baseline survey
- **Exclusion criteria**
- **Patient & disease characteristics** CS: 12.1% (similar to the original cohort of 7223 women)
At 21 years old, based on BMI: Overweight: 21.5%; obese: 12.4%

Women characteristics differed between VD and CS (hypertensive disorder of pregnancy, smoking during pregnancy, mother age, gestational age at delivery, birth weight, prepregnancy BMI and proportion of obese).



Exposures	
• Exposure group	CS (elective if the decision for CS made before labour; emergency if decision during labour); results presented for all CS "because no difference was found in the association between caesarean elective delivery and caesarean emergency delivery regarding our outcome of interest"
• Control group	VD
Results	
• Overweight based on BMI	Adjusted OR 0.9 (95% CI 0.6, 1.2) comparing all CS to VD.
• Overweight based on Waist circumference	Adjusted OR 0.9 (95% CI 0.6, 1.4) comparing all CS to VD.
• Obesity based on BMI	Adjusted OR 0.9 (95% CI 0.6, 1.4) comparing all CS to VD.
• Obesity based on Waist circumference	Adjusted OR 1.0 (95% CI 0.6, 1.4) comparing all CS to VD.
• Outcome 5	
Limitations and other comments	
• Limitations	• Selection bias due to the voluntary basis and attrition bias linked to the loss of follow-up but very important confounding factors taken into account. • No father data.
• CCL	• Cohort study with moderate risk of bias • Main results: At 21 years old, offspring overweight and obesity status, as well as BMI and waist circumference, were not associated with the mode of delivery. • Hypothesis: Mode of delivery (or cesarean) appears to be a confounder, rather than a causal factor, in the development of overweight and obesity in (young) adulthood of offspring.



Marild 2012⁶¹

Methods

• Design	Prospective population-based case control study between 1973 and 2008
• Source of funding and competing interest	- Source of funding: KM: the Swedish Society of Medicine; OS: the Swedish Society of Medicine; JAM: the National Institutes of Health; JFL: the Swedish Society of Medicine, the Swedish Research Council, the Sven Jerring Foundation, the Örebro Society of Medicine, the Karolinska Institutet, the Clas Groschinsky Foundation, the Juhlin Foundation, the Majblomman Foundation, Uppsala-Örebro Regional Research Council, and the Swedish Celiac Society. - Conflict of interest: Stated and none declared
• Setting	Sweden, 28 pathology departments and population
• Sample size	Study participants consisted of 11 749 offspring with biopsy-verified celiac disease identified through histopathology reports from Sweden's 28 pathology departments and 53 887 age- and sex matched controls from the general population.
• Duration and follow-up	Max 2 years
• Statistical analysis	- Logistic regression analysis conditioned on age at first biopsy (and corresponding date in controls), calendar period, sex, and county. - Adjustment for parity, maternal age at delivery, education level, maternal diabetes mellitus, and maternal celiac disease as potential confounders. - In an additional multivariate analysis (model II), adjustment for smoking (births from 1983 and onward). - In a separate analysis of cesarean delivery, adjustment for parental cohabitation (registered from 1982/1983 onwards). - In subanalyses, stratification for calendar period of birth and early diagnosed celiac disease (before age 2 years). - Data on emergency versus elective cesarean delivery are restricted to children born between 1982 and 1989 and after 1991 because data on type of cesarean delivery have only been specified during that time.

Patient characteristics

• Eligibility criteria	- Individuals born in Sweden after 1973 - Individuals with villous atrophy biopsy-diagnosed and 5 controls - Individuals with complete pregnancy and birth data and so individuals with missing data were censored.
• Exclusion criteria	- Individuals with a small-intestinal biopsy that could potentially originate from the ileum, - those with no matched controls, - other data irregularities
• Patient & disease characteristics	Table I

Exposures

• Exposure group	CS (elective or emergency)
• Control group	VD



Results

- **Celiac disease (=small intestinal villous atrophy)**
 - Adjusted OR 1.06 (95%CI 0.9;1.13; p = 0.074) for any CS compared with VD.
 - **Adjusted OR 1.15 (95%CI 1.04;1.26; p = 0.005) for elective CS** compared with VD.
 - Adjusted OR 1.02 (95%CI 0.92;1.13; p = 0.749) for emergency CS compared VD.

Limitations and other comments

- **Limitations**
 - Only 11% of births were CS (5 or 6% elective and 5% emergency)
 - Many cases excluded
 - Lack of breastfeeding as confounders but appears to be not so important in celiac disease
- **CCL**
 - Case-control study with moderate risk of bias
 - Main results: positive association for celiac disease with elective, but not emergency, cesarean delivery
 - This result is consistent with the hypothesis that the bacterial flora of the newborn plays a role in the development of celiac disease

Momen 2014⁴²

Methods

- **Design** Population based, prospective cohort study between 1973 and 2007
- **Source of funding and competing interest**
 - Source of funding: European Research Council, the European Commission's Seventh Framework Programme (FP7)], the Nordic Cancer Union and NordForsk, the Danish Medical Research Council and the Swedish Council for Working Life and Social Research.
 - Conflict of interest: stated and none declared
- **Setting** Three countries: Denmark, Sweden and Finland
- **Sample size** 7 029 843 children:
Denmark 2 364 160 children born between 1973-2007
Sweden 3 394 981 children born between 1973-2006
Finland 1 270 702 children born between 1987-2007
- **Duration and follow-up** The follow-up started at birth, and ended at the first of the following events: relevant cancer diagnosis, death, emigration, the day before the 15th birthday or end of follow-up (31 December 2006 in Sweden, 31 December 2007 in Denmark and 31 December 2010 in Finland).
The total follow-up time was 79 571 514 person years.
- **Statistical analysis**
 - Hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox regression for children whose mode of delivery was known.
 - The proportional hazards assumption was evaluated using the estat phtest function, which tests the assumption on the basis of Schoenfeld residuals.
 - The analyses were stratified by the type of CS (elective, unplanned, unknown).
 - Covariates were selected a priori: potential confounders at baseline (birth) included birthweight; gestational age, multiplicity, maternal age (≤ 26 , 27–30, ≥ 31 years), and parity.



		- In subanalyses, adjustment for maternal status in the labour market, maternal smoking status during pregnancy, congenital anomalies, paternal age group, 5-minute Apgar, 1-minute Apgar score and country of birth's CS rate by birth year. - Analyses repeated, splitting the follow-up time into two periods (0–4 and 5–14 years), to determine whether the risks were greater in the period closer to exposure and because the assumption of proportional hazards was not met for some of the models.
Patient characteristics		
• Eligibility criteria		All children with a recorded mode of delivery born in Denmark from 1973 to 2007 and Sweden from 1973 to 2006, and, as a result of national regulation, a random sample of 90% of children born in Finland from 1987 to 2007.
• Exclusion criteria		- Children diagnosed with cancer within 6 months of birth to remove cancers that may have been present at birth (n = 830, 6.9% of those with a childhood cancer diagnosis) - Children who were diagnosed with cancer but did not have a date of cancer diagnosis (n = 104, 0.9% of those with a childhood cancer diagnosis).
• Patient & disease characteristics		CS 12.6% (elective 30.3%; unplanned 35.9%; no info on planning 33.8%) CS was more frequent in those with low birthweight, born before 37 weeks, born in multiple births, born to older mothers and of low birth order Incidence rate of cancer: 13.77 per 100 000 person years, the most common being leukaemias.
Exposures		
• Exposure group		CS (elective/unplanned/no info on planning)
• Control group		VD
Results		
• Childhood diagnosis	cancer	- Hazard ratio 1.05 (95% confidence interval 0.99, 1.11) comparing CS and VD. - No substantial differences were seen when stratifying results by type of CS. - The results obtained when splitting the exposure by CS type suggested that no particular type of CS led to an increased childhood cancer risk. Although elevated risks were seen for some cancer subtypes, statistical significance was not present.
Limitations and other comments		
• Limitations		- Unknown kind of CS in 34% which reflects different registration systems over time - For some types of cancer, numbers of cases were small and the lack of statistical significance may be a consequence of a lack of power. - Important confounder (such as environmental exposure) not taken into account
• CCL		- Population-based prospective cohort study with moderate risk of bias. - Main results: No evidence of an increased risk of childhood cancer was found for children born by caesarean section

Moore 2012⁴³

Methods

- **Design** Retrospective population-based data linkage cohort study of singleton births between 1996-2005
- **Source of funding and competing interest**
 - Source of funding: National Health and Medical Research Council Project Grant
 - Conflict of interest: stated and none declared
- **Setting** Australia
- **Sample size** 212 068 non-Aboriginal singleton births of 37–42 weeks gestation
- **Duration and follow-up** 23 months
- **Statistical analysis**
 - Negative binomial regression
 - Adjustment for obstetric and known risk factors

Patient characteristics

- **Eligibility criteria** Non-Aboriginal singleton births of 37–42 weeks gestation
- **Exclusion criteria** Aboriginal
- **Patient & disease characteristics**
 - Elective caesarean section 15.8%
 - Emergency CS: 10.4%
 - Spontaneous VD: 59.9%
 - Instrumental VD: 13.9%

Exposures

- **Exposure group** Elective CS
- **Control group** Spontaneous VD

Results

- **Hospitalisation for Bronchiolitis at age <12 months**
 - **Adjusted incidence rate ratio (IRR) 1.11** (95% CI 1.01; 1.23) for children born by elective CS compared with spontaneous vaginal delivery
- **Hospitalisation for Bronchiolitis at 12–23 months**
 - Adjusted incidence rate ratio (IRR) 1.20 (95% CI 0.94; 1.53) for children born by elective CS compared with spontaneous vaginal delivery
- **Hospitalisation for Pneumonia at age <12 months**
 - Adjusted incidence rate ratio (IRR) 1.03 (95% CI 0.80; 1.33) for children born by elective CS compared with spontaneous vaginal delivery,
- **Hospitalisation for Pneumonia at 12–23 months**
 - Adjusted incidence rate ratio (IRR) 1.09 (95% CI 0.88; 1.34) for children born by elective CS compared with spontaneous vaginal delivery,

**Limitations and other comments**

- | | |
|--|---|
| <ul style="list-style-type: none">• Limitations | <ul style="list-style-type: none">• No distinction of elective CS for non medical reason• Breastfeeding not taken into account |
| <ul style="list-style-type: none">• CCL | <ul style="list-style-type: none">• Population-based prospective cohort study with moderate risk of bias.• Main results: Increased risk of admission for bronchiolitis at age <12 months was found for children born by elective caesarean section compared with VD. However, this increased risk is not significant after 12 months. |

Mueller 2015 (obesity)⁴⁴**Methods**

- | | |
|---|---|
| <ul style="list-style-type: none">• Design | Longitudinal birth cohort study (1998-2006), developed to evaluate the effects of prenatal exposures to ambient and indoor pollutants on birth outcomes, neurocognitive development, and procarcinogenic damage among a cohort of mothers and newborns from minority communities in New York City. |
| <ul style="list-style-type: none">• Source of funding and competing interest | <ul style="list-style-type: none">• Source of funding: US Environmental Protection Agency, National Institute for Environmental Health Sciences, Irving General Clinical Research Center, Educational Foundation of America, John and Wendy Neu Family Foundation, New York Community Trust, and Trustees of the Blanchette Hooker Rockefeller Fund.• Conflict of interest: NTM and EMW received fellowships from the National Institute of Diabetes and Digestive and Kidney Diseases. |
| <ul style="list-style-type: none">• Setting | 2 US hospitals (New-York Presbyterian Hospital and Harlem Hospital Center). |
| <ul style="list-style-type: none">• Sample size | 727 women enrolled; 611 analyzed; 436 children (71.4%) at 7 years of age followed-up with measured BMI. |
| <ul style="list-style-type: none">• Duration and follow-up | 1998-2006 |
| <ul style="list-style-type: none">• Statistical analysis | <ul style="list-style-type: none">• Children's BMI z-scores and percentiles were calculated using the SAS Macro provided by the Centers for Disease Control and Prevention.• Binomial regression models with robust variance to determine if relative risks (RRs) of obesity were higher for children whose mothers had CS (vs VD), or for those whose mothers used antibiotics (vs not having used antibiotics) in second or third trimester.• General linear regression models to examine mode of delivery and gestational antibiotics in relation to continuous BMI z-score units, % body fat and waist circumference at 7 years of age.• A separate linear regression analysis to examine whether first trimester antibiotics were associated with BMI z-score units.• To determine whether gestational antibiotics and CS had compounding impacts, compared multivariable adjusted means for BMI z-score units across four groups: VD+no second or third trimester antibiotics (referent), VD+second or third trimester antibiotics, CS+no second or third trimester antibiotics and CS+second or third trimester antibiotics.• Multivariable model included adjustment• Sensitivity analyses using inverse probability weights for successful follow-up to assess potential bias because of incomplete follow-up on effect estimates. |

Patient characteristics



• Eligibility criteria	Healthy, non-smoking pregnant women aged 18–35 years who self-identified as either African-American or Dominican and had resided in the study area for at least 1 year.
• Exclusion criteria	If first prenatal visit after 20 weeks gestation or if self-reported diabetes, hypertension, known HIV or use of illicit drugs or cigarettes during pregnancy if missing info for delivery mode, maternal receipt of public assistance, maternal pregravid BMI, birth weight and gestational age if premature delivery (<37 weeks)
• Patient & disease characteristics	Healthy, non-smoking, pregnant women At the beginning of the cohort (Whyatt 2002), on 360 women, there is a difference between women who refused and the other: women who agreed to participate were somewhat younger (24 ± 4.9 vs. 25.4 ± 5.4 years, $p = 0.06$, t-test), and a higher proportion were African American (44% vs. 39%, $\chi^2 = 1.2$, $p = 0.3$)
Exposures	
• Exposure group	Caesarean section (elective and emergency)
• Control group	Vaginal delivery
Results	
• Obesity in children at 7 years = BMI percentile $\geq$ the 95% percentile	• RR 1.41 (95% CI 1.01, 1.96) comparing CS and VD, and adjusted for sex, ethnicity, offspring birth weight, maternal age, maternal pre-gravid BMI, receipt of public assistance during pregnancy, prenatal antibiotic use or delivery mode, having breastfed in first year and after exclusion of mothers diagnosed with gestational diabetes and preeclampsia during pregnancy (N=411) • The association was not significantly different for elective (RR 1.53; 95% CI 1.04, 2.25) vs non-elective CS (RR 1.41; 95% CI 0.97, 2.05) compared with VDs. • RR 1.77 (95% CI 1.25, 2.51) comparing 2nd and 3rd trimesters antibiotics vs no antibiotics, and adjusted for same items than above.
Limitations and other comments	
• Limitations	• Selection bias and attrition bias • Obesity not defined according to the WHO criteria but to the percentile.
• CCL	• Population-based prospective cohort study with moderate risk of bias. • Main results: Children born by CS had 46% higher obesity risk at 7 years than VD children. This results are similar for elective and emergency CS and they persist after adjustment notably for maternal pre-gravid BMI. • Hypothesis: bypass of the bacterial inoculum of the vaginal canal at birth.

O'Neill 2014⁴⁵

Methods

- **Design** This Danish population register-based cohort study covered the period from 1982 to 2010.
- **Source of funding and competing interest** Funding was provided by the National Perinatal Epidemiology Centre, Cork, Ireland and conducted as part of the Health Research Board PhD Scholars programme in Health Services Research (Grant No. PHD/2007/16).
The authors have no competing interests to declare
- **Setting** All admissions in a Danish hospital
- **Sample size** 832 996 primiparous women with an index live birth
- **Duration and follow-up** Women were followed until the subsequent live birth or until censoring due to maternal death, emigration or study end (31 December 2010).
- **Statistical analysis** The rate of subsequent live birth was compared among the different modes of delivery using time-to-event analyses including Cox proportional hazards modelling to estimate the hazard ratio (HR) and corresponding 95% confidence intervals (CI).
The gestational age at birth is taken into account (i.e. gestational age varies according to each woman's pregnancy) as well as the fact that some women will have no further pregnancies.
The median time to next live birth with corresponding 95% confidence intervals was calculated according to mode of delivery using the proc univariate command in SAS and crude estimates.

Patient characteristics

- **Eligibility criteria** All primiparous women with an index live birth during the study period (between 1 January 1982 and 31 December 2010; N= 832 996).
- **Exclusion criteria** No exclusion criteria were mentioned.
- **Patient & disease characteristics** There were 832 996 first live births in the cohort. Of these, 607 252 (73%) were by SVD; 79 827 (9.6%) were by operative vaginal delivery; 104 091 (12.5%) were by emergency Caesarean section and 38 950 (4.7%) were by elective Caesarean section. From 2002 to 2010 there were 2876 (1.1%) maternal-requested Caesarean sections.
The Caesarean section rate for the entire study population over the 28-year follow-up was 17.6%.
Overall, there was a trend of increasing Caesarean section rates, with a rate of 12.8% in 1982 rising to 22.8% in 2010. For maternally requested Caesarean section, a similar increasing trend was found, with a rate of 2% in 2002 and over 14% in 2010.

Exposures

- **Exposure group** Caesarean delivery
1. emergency Caesarean section (i.e. unplanned Caesareans due to complications for example, foetal distress) (n= 104 091; 95.08% singleton)
2. elective Caesarean section (planned Caesarean section with or without medical indication) (n= 38 950; 91.04% singleton)
3. maternally requested Caesarean section (data were available from 2002 to 2010) (n= 2876; 93.88% singleton)
- Operative vaginal delivery [assisted forceps or vacuum delivery] (n= 79 827; 99.53% singleton)
- **Control group** SVD (n= 607 252; 98.99% singleton)

**Results**

- **Rate of subsequent live birth following the index delivery**

In all 577 830 (69%) women had a subsequent live birth. Women with any type of Caesarean had a reduced rate of subsequent live birth (hazard ratio [HR] 0.86, 95% confidence intervals [CI] 0.85, 0.87) compared with spontaneous vaginal delivery.

This effect was consistent when analyses were stratified by type of Caesarean: emergency (HR 0.87, 95% CI 0.86, 0.88), elective (HR 0.83, 95% CI 0.82, 0.84) and maternal-requested (HR 0.61, 95% CI 0.57, 0.66).

When smoking, BMI, prior fertility treatment and history of psychiatric illness were adjusted for in the models, the overall results were unchanged.

When a time-dependent covariate analysis based on infant death within 1 year was performed, the hazard rate of a subsequent live birth among women with a maternal-requested Caesarean section increased from 62 to 84% (HR 0.84, 95% CI 0.79, 0.89).
- **Median time to next live birth**

Women with an emergency Caesarean (median 1101 days, 95% CI 1097, 1106) or elective Caesarean (median 1097 days, 95% CI 1088, 1105) section had a slightly longer median time to next birth compared with women with an operative vaginal delivery (median 1043 days, 95% CI 1038, 1047) or SVD (median 1083 days, 95% CI 1081, 1085).

When the cohort was restricted to 2002–2010, women with maternal-requested Caesarean had a median time to second birth of 914 days (95% CI 883, 949) compared with a median of 907 (95% CI 904, 910) among women with a SVD during this time period.

Limitations and other comments

- **Limitations**

Lack of data on personal and social choices

 - did these women plan to have any further pregnancies and were they actively trying to get pregnant again?
 - Knowledge about the physical and mental status of the first baby which may impact on a couple's decision to have a subsequent child
 - Did a change in marital status occur?
- **CCL**

The findings of the current study indicate that a prior Caesarean section is associated with a reduction in subsequent births in the population-based CRS cohort.

The findings may be due to women intentionally delaying or avoiding a subsequent birth, consistent with previous studies, and this may be for a multitude of reasons (financial, social or cultural).

O'Neill 2015⁴⁶**Methods**

- **Design**

Hospital-based cohort study
- **Source of funding and competing interest**
 - Source of funding: the National Perinatal Epidemiology Centre, Cork, Ireland, and conducted as part of the Health Research Board PhD Scholars programme in Health Services Research, Grant No. PHD/2007/16. Over the years the ABC study has been supported by the Aarhus University Research Fund, the Danish Council for Independent Research and the Lundbeck Foundation.
 - Conflict of interest: The authors have no conflicts of interest to declare.
- **Setting**

One hospital: Aarhus University Hospital (AUH), Denmark
- **Sample size**

46 162 index live births were identified



• Duration and follow-up	Women were followed from their first live birth until the subsequent live birth or until censoring due to study end (from September 1989 to December 2010) allowing a 21 years of follow-up. It is impossible to know the length of follow-up for the last years of enrollment. Additional analysis were performed with a minimum of 12 months follow up for each woman (i.e., only women giving birth up until 31 December 2009 were included in this analysis).
• Statistical analysis	The rate and time to next live birth was compared among the different modes of delivery using time-to-event analyses including Cox proportional hazards modelling to estimate the hazard ratio (HR) and corresponding 95% confidence intervals (CI). Analyses of interest were those analyses performed for elective caesarean comparing the results with those from the reference group of women who had a first SVD. Subgroup analyses by planned pregnancy (first births reported as planned), prior fertility treatment, term delivery (>37 weeks), smokers only, advanced maternal age (35+), low birthweight (<2500 g) and by time period (1989–1999, 2000–2010) to assess temporal changes were conducted. Sensitivity analyses excluding women with pregnancy complications (pre-eclampsia, bleeding before and after 28 weeks, diabetes, hypertension, intra-uterine growth restriction [IUGR] and gestational diabetes); delivery complications (shoulder dystocia, having an episiotomy, infection, re-suturing, hematoma, endometritis, suction evacuation of products of conception and rupture of the labia or perineum [data for uterine and vaginal ruptures were limited and not included]) and neonatal complications (admission to the neonatal intensive care unit [NICU], antibiotic treatment, other neonatal problems) were performed.
Patient characteristics	
• Eligibility criteria	All pregnant women attending AUH were invited to enrol in the Aarhus Birth Cohort (ABC) study between 1989 and 2010 (n = 91 625).
• Exclusion criteria	No exclusion criteria were reported
• Patient & disease characteristics	46 162 index live births were identified; 22 462 (49%) had a subsequent live birth during the study period. • Spontaneous vaginal (n = 17 217) • Operative vaginal (n = 1993) • Breech vaginal (n = 176) • Shoulder dystocia vaginal (n = 167) • Emergency caesarean (n = 1784) • Elective caesarean (n = 1125)
Exposures	
• Exposure group	Elective caesarean section (including caesarean on maternal request). N.B. 4 other groups were also analyzed but they are not in the scope of this report
• Control group	Standard vaginal delivery (SVD)
Results	
• Rate of subsequent live birth	Adjusted for maternal age, maternal origin, previous stillbirth, miscarriage or ectopic pregnancy, maternal BMI, fertility treatment in the first birth, smoking (pre- and during pregnancy), birth year, gestational age, birthweight, infant sex, infant length, education and marital status (n = 26 949) • Any type of CS (emergency, elective): HR 0.94, 95% CI 0.89, 0.98 • Elective CS: HR 0.91, 95% CI 0.85, 0.98 Adjustment for a history of macrosomia in the first birth • Elective CS: HR 0.92, 95% CI 0.86, 0.99)



When the model was adjusted for women who reported planning their first pregnancy

- Elective CS: HR 0.86, 95% CI 0.74, 0.99

Adjustment for prior fertility treatment showed a reduced rate of subsequent live birth, although this was not statistically significant across all modes of delivery.

Sensitivity analyses:

Women with a prior elective caesarean (HR 0.89, 95% CI 0.82, 0.96)

had a significant reduction in the rate of subsequent live birth in a sensitivity analysis excluding women with complications of pregnancy with/without neonatal complications, compared with women with a prior SVD

- | | |
|---|---|
| <ul style="list-style-type: none">• Median time to subsequent live birth | <ul style="list-style-type: none">• emergency caesarean (994 days, 95% CI 973, 1026),• elective caesarean (1055 days, 95% CI 1025, 1091),• operative vaginal delivery (1032 days, 95% CI 1011, 1052),• breech vaginal delivery (1038 days, 95% CI 923, 1106),• vaginal delivery complicated by shoulder dystocia (1065 days, 95% CI 994, 1191);• SVD (1009 days, 95% CI 1002, 1016). |
|---|---|

Limitations and other comments

- | | |
|--|---|
| <ul style="list-style-type: none">• Limitations | <p>In this study it was not possible to identify any women who died, emigrated or had a subsequent live birth outside of the AUH municipality since the first live birth.</p> <p>As the questionnaires were completed by mothers (self-reported), under-reporting of sensitive items such as smoking may be a problem. There may be reporting bias in the group of women who testified to 'planning' their pregnancy, and this may be over-reported ('wantedness bias', where couples say that a pregnancy was planned when it was not, for fear of appearing to not want the child).</p> |
| <ul style="list-style-type: none">• CCL | <p>A small reduction in the subsequent birth rate was found among women delivered by caesarean section (6%) and operative vaginal delivery (8%) compared with women who had a SVD. A causal association cannot be ruled out, although the effects of mode of delivery on the rate of subsequent live birth were minimal in this study.</p> |
| <ul style="list-style-type: none">• | |

O'Neill 2014⁴⁷

Methods

- | | |
|---|--|
| <ul style="list-style-type: none">• Design | <p>A Danish Registry Based Cohort Study linking various registries.</p> |
| <ul style="list-style-type: none">• Source of funding and competing interest | <p>Funding: This work was funded by the National Perinatal Epidemiology Centre, Cork, Ireland and conducted as part of the Health Research Board PhD Scholars programme in Health Services Research, Grant No. PHD/2007/16. LCK is a Science Foundation Ireland Principal Investigator (08/IN.1/B2083) and the Director of the SFI funded Centre, INFANT (12/RC/2272). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.</p> <p>The authors have declared that no competing interests exist.</p> |



• Setting	The cohort included primiparous women with a live birth between January 1, 1982, and December 31, 2010 (n = 832 996), with follow-up until the next event (stillbirth, miscarriage, or ectopic pregnancy) or censoring by live birth, death, emigration, or study end. Cox regression models for all types of caesarean sections, sub-group analyses by type of caesarean, and competing risks analyses for the causes of stillbirth were performed. An increased rate of stillbirth (hazard ratio [HR] 1.14, 95% CI 1.01, 1.28) was found in women with primary caesarean section compared to spontaneous vaginal delivery, giving a theoretical absolute risk increase (ARI) of 0.03% for stillbirth, and a number needed to harm (NNH) of 3,333 women. Analyses by type of caesarean section showed similarly increased rates for emergency (HR 1.15, 95% CI 1.01, 1.31) and elective caesarean (HR 1.11, 95% CI 0.91, 1.35), although not statistically significant in the latter case. An increased rate of ectopic pregnancy was found among women with primary caesarean overall (HR 1.09, 95% CI 1.04, 1.15) and by type (emergency caesarean, HR 1.09, 95% CI 1.03, 1.15, and elective caesarean, HR 1.12, 95% CI 1.03, 1.21), yielding an ARI of 0.1% and a NNH of 1,000 women for ectopic pregnancy. No increased rate of miscarriage was found among women with primary caesarean, with maternally requested caesarean section associated with a decreased rate of miscarriage (HR 0.72, 95% CI 0.60, 0.85). Limitations include incomplete data on maternal body mass index, maternal smoking, fertility treatment, causes of stillbirth, and maternally requested caesarean section, as well as lack of data on antepartum/intrapartum stillbirth and gestational age for stillbirth and miscarriage. This study found that caesarean section is associated with a small increased rate of subsequent stillbirth and ectopic pregnancy. Underlying medical conditions, however, and confounding by indication for the primary caesarean delivery account for at least part of this increased rate. These findings will assist women and health-care providers to reach more informed decisions regarding mode of delivery.
• Sample size	832 996 live births from Danish birth registries)
• Duration and follow-up	January 1, 1982, and December 31, 2010
• Statistical analysis	The rate of subsequent stillbirth, miscarriage, or ectopic pregnancy was compared by mode of delivery using time-to-event analyses including Cox proportional hazards modelling to estimate the HR and corresponding 95% CIs. In this study, women were followed up from the date of birth of the first child until the subsequent reproductive event of interest (stillbirth, miscarriage, or ectopic pregnancy) or until censoring due to live birth, death, emigration, or study end (December 31, 2010). Separate models were generated for each outcome. For example, when looking at the rate of stillbirth, censoring occurred for live birth, death, emigration, or study end. This was similarly the case for miscarriage and ectopic pregnancy.
Patient characteristics	
• Eligibility criteria	Children born in primiparous women in Denmark between January 1, 1982, and December 31, 2010
• Exclusion criteria	Not explicitly stated
• Patient & disease characteristics	Describe baseline characteristics cited in the paper (precise if it is on involved and/or analysed numbers). Highlight discrepancies between groups (i.e. involved and analysed)
Exposures	
• Exposure group	Precise details of the Exposures for each group (including dose, length, regimen and timing when relevant)
• Control group	Precise details of the Exposures for each group (including dose, length, regimen and timing when relevant)

**Results**

- **Outcome 1**

Cox regression models for all types of caesarean sections, sub-group analyses by type of caesarean, and competing risks analyses for the causes of stillbirth were performed. An increased rate of stillbirth (hazard ratio [HR] 1.14, 95% CI 1.01, 1.28) was found in women with primary caesarean section compared to spontaneous vaginal delivery, giving a theoretical absolute risk increase (ARI) of 0.03% for stillbirth, and a number needed to harm (NNH) of 3333 women. Analyses by type of caesarean section showed similarly increased rates for emergency (HR 1.15, 95% CI 1.01, 1.31) and elective caesarean (HR 1.11, 95% CI 0.91, 1.35), although not statistically significant in the latter case.

An increased rate of ectopic pregnancy was found among women with primary caesarean overall (HR 1.09, 95% CI 1.04, 1.15) and by type (emergency caesarean, HR 1.09, 95% CI 1.03, 1.15, and elective caesarean, HR 1.12, 95% CI 1.03, 1.21), yielding an ARI of 0.1% and a NNH of 1,000 women for ectopic pregnancy. No increased rate of miscarriage was found among women with primary caesarean, with maternally requested caesarean section associated with a decreased rate of miscarriage (HR 0.72, 95% CI 0.60, 0.85). Limitations include incomplete data on maternal body mass index, maternal smoking, fertility treatment, causes of stillbirth, and maternally requested caesarean section, as well as lack of data on antepartum/intrapartum stillbirth and gestational age for stillbirth and miscarriage. This study found that caesarean section is associated with a small increased rate of subsequent stillbirth and ectopic pregnancy.

Limitations and other comments

- **Limitations**

Underlying medical conditions, and confounding by indication for the primary caesarean delivery may account for at least part of this increased rate. These findings will assist women and health-care providers to reach more informed decisions regarding mode of delivery.
- **CCL**

This study found that caesarean section is associated with a small increased rate of subsequent stillbirth and ectopic pregnancy. Underlying medical conditions, however, and confounding by indication for the primary caesarean delivery account for at least part of this increased rate. These findings will assist women and health-care providers to reach more informed decisions regarding mode of delivery.

Patel 2005⁴⁸**Methods**

- **Design**

ALSPAC (the Avon longitudinal study of parents and children).

Participants 14 663 women recruited antenatally with a due date between 1 April 1991 and 31 December 1992. Of those recruited participant 10 934 (84%) completed the questionnaire at 8 weeks postnatally.

Main outcome measure Edinburgh postnatal depression scale score at eight weeks postnatal on self-completed questionnaire.
- **Source of funding and competing interest**

Welcome Trust, Medical Research Council, University of Bristol, Department of Health, and Department of Environment. The ALSPAC study is part of the WHO initiated European Longitudinal Study of Pregnancy and Childhood. RP received a clinical academic training fellowship from NHS South West research and development.

Competing interests: None declared.

Ethical approval: The research programme is governed by the four local research ethics committees. The ALSPAC ethics committee approved this project.
- **Setting**

Population based study within the [Avon Longitudinal Study of Parents and Children](#)
- **Sample size**

14 663 pregnant women with due date between April 1st 1991 and December 31st 1992. No sample size calculated a priori.



• Duration and follow-up	14 663 pregnant women with due date between April 1 st 1991 and December 31 st 1992. Follow-up at 8 weeks on self-completed questionnaire.
• Statistical analysis	The calculated the mean (SD) depression score was calculated and the proportion of Edinburgh postnatal depression scale score ≥ 13 for each mode of delivery. Univariable analyses were used to calculate crude odds ratios, 95% confidence intervals, and likelihood ratio P values for the association between mode of delivery and postnatal depression using logistic regression. Adjusted odds ratios were calculated by the addition of confounders associated with mode of delivery into the statistical model. Continuous variables (maternal age, gestational age at delivery, parity, neonatal head circumference, and birth weight), binary (yes/no) variables (previous caesarean section, epidural in labour, previous miscarriage/termination, antenatal class attendance), and categorical variables (diabetes mellitus, foetal presentation, outcome of last pregnancy, preferred labour position, perceived loss of control in labour. History of depression (yes/no) was considered and also additional variables that were identified by a literature search as being associated with postnatal depression in other populations—namely, housing status (categorical) and antenatal depression score at 18 and 32 weeks (< 13 or ≥ 13). Stata 8.0 software was used for all analyses
Patient characteristics	
• Eligibility criteria	All women with singleton, live born infants and term pregnancies (37 to 44 weeks) who completed the eight week postnatal questionnaire. Elective caesarean sections were those with prior planning, and emergency caesarean sections were those without prior planning or that took place after labour started. Assisted vaginal delivery comprised both forceps deliveries and vacuum extraction.
• Exclusion criteria	No exclusion criteria were reported
• Patient & disease characteristics	12 944 women meeting inclusion criteria, 389 with elective CS, 572 with emergency CS, 2353 with IVD and 8731 with SVD that filled in the depression questionnaire at 8 weeks postpartum
Exposures	
• Exposure group	Elective CS
• Control group	Planned VD
Results	
• Postnatal depression	Albeit with wide confidence intervals, there was no evidence that elective caesarean section altered the odds of postnatal depression compared with planned vaginal delivery (adjusted odds ratio 1.06, 95% confidence interval 0.66 to 1.70, $P = 0.80$). Among planned vaginal deliveries there was similarly little evidence of a difference between women who have emergency caesarean section or assisted vaginal delivery and those who have spontaneous vaginal delivery (1.17, 0.77 to 1.79, $P = 0.46$, and 0.89, 0.68 to 1.18, $P = 0.42$, respectively).
Limitations and other comments	
• Limitations	These analyses are based on observational data and are therefore potentially subject to bias. There was a high follow up rate (85%), though one concern is that women with postnatal depression were less likely to complete the questionnaire. This may be particularly relevant to women suffering from severe depression, especially if they were resident in a psychiatric unit.
• CCL	Cohort study of moderate risk of bias. Main results: No reason for women at risk of postnatal depression to be managed differently with regard to mode of delivery. Elective caesarean section does not protect against postnatal depression. Women who plan vaginal delivery and require emergency caesarean section or assisted vaginal delivery can be reassured that there is no reason to believe that they are at increased risk of a postnatal depression.



Ponsonby 2009⁴⁹

Methods

- **Design** Register-based national cohort study of 1 million live births from 1983 to 1998.
- **Source of funding and competing interest**
 - Source of funding: Murdoch Childrens Research Institute internal grant
 - Conflict of interest: not stated
- **Setting** Victoria, Australia
- **Sample size** 1 005 054 live births in Victoria, Australia, from 1983 to 1998.
Of the 278 children with CD in this birth cohort, only those who remained in Victoria 6 years after the child's birth were selected (n = 240). For 238 of these cases, each case was matched to 2 controls that were randomly selected from all live births without CD and matched by year of birth.
- **Duration and follow-up** 15 years for the first included birth.
- **Statistical analysis**
 - The annual CD incidence was calculated
 - A proportional hazards model with censoring at the end of the 15th year or age as of 30 June 2006 was used to take into account that children born in the more recent years (eg, 1998) had a shorter follow-up period than children born in earlier years (eg, 1983).
 - Potential confounders were included in the proportional hazards models as covariates to provide adjusted hazard ratios (HRs).
 - For the matched case– control study investigating sibling exposure, conditional logistic regression was used to provide matched odds ratios as risk estimates.
 - Sensitivity analyses were conducted on relevant restricted groups within the birth cohort

Patient characteristics

- **Eligibility criteria** All birth in Victoria between 1983 and 1998
Children with CD who remained in Victoria 6 years after the child's birth
- **Exclusion criteria**
- **Patient & disease characteristics** Vaginal cephalic: 67.1% (period 1983-91); 66.4% (period 1992-98)
Elective CS: 8.9% (period 1983-91); 11.2% (period 1992-98)
Emergency CS: 7.4% (period 1983-91); 8.5% (period 1992-98)
Vaginal breech: 1.5% (period 1983-91); 1.1% (period 1992-98)
Forceps/vacuum: 15.2% (period 1983-91); 12.8% (period 1992-98)

Exposures

- **Exposure group** Elective caesarean section, emergency caesarean section, or forceps/vacuum extraction, any interventional delivery
- **Control group** Spontaneous VD



Results

- **Crohn Disease (CD)**
 - **Adjusted HR 1.75 (95% CI 1.38; 2.21)** for children delivered by intervention (all kind) compared with those born by spontaneous vaginal delivery.
 - **Adjusted HR 1.67 (95% CI 1.17; 2.39)** for children delivered by elective c-section compared with those born by spontaneous vaginal delivery.
 - Adjusted HR 1.50 (95% CI 0.99; 2.28) for children delivered by emergency c-section compared with those born by spontaneous vaginal delivery.
 - **Adjusted HR 1.95 (95% CI 1.45; 2.62)** for children delivered by forceps/Vacuum compared with those born by spontaneous vaginal delivery.

Limitations and other comments

- **Limitations**
 - Lack of some confounders (such as maternal history or breastfeeding)
 - Short FU for a disease which can be diagnosed during adulthood.
 - Risk of early diagnosis in children born by intervention because their mothers are maybe more likely to present their child for medical specialist care for mild gastrointestinal symptoms than other women.
 - No distinction of elective CS for non medical reason.
- **CCL**
 - Cohort study of high risk of bias.
 - Main results: older maternal age, higher SES, metropolitan residence, interventional delivery, and congenital abnormality were associated with higher CD risk, but the causal significance of these remains unclear.
 - Hypothesis: cesarean section leads to delayed gut colonization with commensal species such as Bifidobacterium and Lactobacillus.

Rauh⁵¹

Methods

- **Design** Longitudinal prospective cohort study
- **Source of funding and competing interest** University sponsored and no conflicts of interest reported
- **Setting** Single University hospital in Germany
- **Sample size** 1100 women of whom 865 completed all three questionnaires
- **Duration and follow-up** After 30 weeks gestation and up to six months post-partum
- **Statistical analysis** Several statistical techniques depending on questionnaire

Patient characteristics

- **Eligibility criteria** Unclear, not explicitly mentioned.



• Exclusion criteria	Unclear, not explicitly mentioned.
• Patient & disease characteristics	Unclear
Exposures	
• Exposure group	SVD
• Control group	Elective CS
Results	
• EPDS score after 30 weeks gestation (planned SVD vs. elective CS)	5.1 vs. 6.9 (p=0.04)
• EPDS score 48-72 hours post-partum weeks gestation (planned SVD vs. elective CS)	SVD 3.8 (3.3-4.3), Elective CS 4.0 (3.3-4.6), Emergency CS 5.6 (4.9-6.3) IVD 4.2 (3.2-5.2) Statistically significant differences p<0.0001
• At 6 months	SVD 5.0 (4.5-5.5), Elective CS 4.8 (4.2-5.5), Emergency CS 4.6 (3.9-5.3) IVD 5.3 (4.3-6.3) No statistically significant differences:
Limitations and other comments	
• Limitations	Unclear methods and poor reporting
• CCL	Conclusions in-line with other studies.

Regan 2013⁵²

Methods	
• Design	Population-based retrospective cohort study of Ohio births (2006–2007); data-linkage study
• Source of funding and competing interest	• Source of funding: ? • Declaration of interest: stated and none declared
• Setting	• All births in Ohio (2006-2007)
• Sample size	• The study sample included data on 280 882 live-born singletons from which 31,511 (11.2% of total) births concerned women who had had a previous cesarean delivery.
• Duration and follow-up	Not applicable
• Statistical analysis	• Unpaired Student's t tests for continuous variables and v2 tests for categorical variables. • Multivariable logistic regression for the association between BF initiation and mode of delivery after cesarean section after accounting for influential coexisting risk factors.



- Univariate techniques to identify factors significantly associated with the outcome of interest ($p < 0.05$) and inclusion of these potential confounding factors in the logistic regression model.
- Final regression model by sequentially removing covariates and testing for differences. Covariates with a value of $p > 0.05$ were removed from the model.
- Adjusted relative risk (RRadj) values and 95% confidence intervals (CIs) for each of the primary outcomes.

Patient characteristics

- **Eligibility criteria**
 - Live births to women with a previous cesarean delivery.
- **Exclusion criteria**
 - Births complicated by major congenital malformations, delivery < 20 weeks or > 42 weeks, or multifetal gestation.
- **Patient & disease characteristics**

Mode of delivery:

 - Scheduled repeat cesarean section: 82.2%
 - Successful VBAC: 12.8%
 - Failed trial of labor with repeat cesarean delivery: 5.0%
 - Missing information on mode of delivery for 320 (0.1%) birth records.

Breastfeeding initiation: 59.8% of women with a prior cesarean section initiated breastfeeding.
More details in Tables 1, 2 and 3

Exposures

- **Exposure group** *Vaginal birth after caesarean (VBAC)*
- **Control group 1** Scheduled repeat CS.
- **Control group 2** CS after an unsuccessful trial of labour

Results

- **Breastfeeding initiation**
 - Adjusted RR 1.47 (95% CI 1.35, 1.60) comparing women delivered by **successful VBAC** and women delivered by scheduled repeat cesarean.
 - Adjusted RR 1.17 (95% CI 1.04, 1.33) comparing women who ultimately delivered by CS after an unsuccessful trial of labor and women with a scheduled repeat cesarean section.
- **Influence of sociodemographic factors, medical risk factors, and pregnancy-related risk factors**
 - Certain demographic characteristics are associated with decreased BF initiation rates in patients who had a cesarean: younger maternal age, increased BMI, lower parity, tobacco usage, and number of prior cesarean sections.
 - Medical risks and pregnancy-related risks are also associated with decreased BF initiation rates in patients who had a cesarean: no prenatal care, chronic hypertension, gestational hypertension, gestational diabetes

Limitations and other comments

- **Limitations**
 - Misclassification and underreporting of certain outcomes such as pre-eclampsia, diabetes, or other co-morbidities. However the selected exposure (mode of delivery) and outcome (breastfeeding) variables had minimal missing data and frequencies equivalent to that in the published literature.



- **CCL**
 - Lack of ascertain information about breastfeeding intent and how mode of delivery after cesarean section affected the success of breastfeeding initiation in women who intended to breastfeed prior to delivery.
 - Population-based retrospective cohort study with low risk of bias.
 - Main results: Women who undergo a scheduled repeat cesarean delivery are less likely to initiate BF than women who attempt and succeed in achieving vaginal birth after a previous cesarean section and also than women who ultimately deliver by cesarean section after an unsuccessful trial of labor. "This suggests there are influences on patient choice for delivery that also may influence the patient's decision to breastfeed."
 - Hypothesis: Women with failed VBAC are "possibly more educated about their experience regarding mode of delivery and more confident and committed to the act of breastfeeding through the entire birth experience."

Samuelsson 2015⁶²

Methods

- **Design** Case-control study with all children diagnosed with type 1 diabetes from 2000 to 2012 matched with four controls from the Swedish Medical Birth Register.
- **Source of funding and competing interest**

Source of funding: Association of Local Authorities and Regions, SALAR; and Futurum, the academy for health care, Jönköping county council

Conflict of interest: stated and none declared
- **Setting** All 43 paediatric clinics in Sweden
- **Sample size** All children diagnosed with type 1 diabetes (n=9,376) matched with four controls with the same year and day of birth, same sex and who were born in the same region of Sweden (n=37 504)
- **Duration and follow-up** NA
- **Statistical analysis**
 - Pearson's χ^2 test was used to analyse the univariate relationship between mode of delivery and maternal as well as obstetric characteristics such as smoking, sex of the child, size for gestational age, birth order and proportion of children who developed type 1 diabetes.
 - The student's t test was used to assess differences between mode of delivery and continuous variables such as maternal age when giving birth, BMI in early pregnancy, birthweight and Apgar score at 5 and 10 min.
 - Multivariate analyses included multiple logistic regression in which the dependent variable was set to type 1 diabetes in the child and independent variables were mode of delivery, maternal diabetes, maternal age when giving birth and BMI in early pregnancy (Table 4).
 - In addition, a separate multiple logistic regression model was performed in which delivery by CS was set as the dependent variable and maternal age when giving birth, BMI in early pregnancy, sex of the child and age at onset of type 1 diabetes (Table 5) were all included as independent variables. Missing data were excluded in the regression analyses.

Patient characteristics

- **Eligibility criteria**

All children (0-18/19 years of age) diagnosed with type 1 diabetes diagnosed between January 2000 and October 2012 and included in the register

All birth from the Swedish Medical Birth Register.



• Exclusion criteria	None
• Patient & disease characteristics	Overall, 13.5% of deliveries were by CS: Vaginal (86.5%), Elective CS (9.9%), Acute CS (3.6%) Among diabetic children, 55.2% boys and 44.8% girls. The age at diagnosis varied from under 1 year of age up to 17 years of age. Higher maternal age and BMI in both the elective and acute CS groups, compared with the VD group ($p < 0.001$).
Exposures	
• Exposure subgroup	Elective and acute CS
• Control subgroup	VD
Results	
• Type 1 Diabetes in children (0-18/19 years of age)	14.7% of children who developed type 1 diabetes were delivered by CS compared with 13.3% of control children ($p < 0.001$). 9.9% born by elective both in children with and without Type 1 diabetes. Maternal diabetes was the strongest predictor of childhood diabetes (OR 3.4), especially if the mother had type 1 diabetes (OR 7.54).
Limitations and other comments	
• Limitations	No data on father history (in particular diabetes) No real comparison between elective CS and VD
• CCL	Case-control study of moderate quality Main results: CS had no influence on the risk of type 1 diabetes during childhood or adolescence. However, maternal diabetes itself strongly increased the risk of offspring developing type 1 diabetes.

Sevelsted 2015⁵³

Methods	
• Design	Longitudinal retrospective registry bases cohort of children born in Denmark between 1973 and 2012
• Source of funding and competing interest	Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) is funded by private and public research funds. COPSAC receives no funding from commercial companies. The Danish Council for Strategic Research, The Lundbeck Foundation, The Pharmacy Foundation of 1991, The Augustinus Foundation, and the Danish Medical Research Council and National Finance Act provided the core support for the COPSAC research. No potential conflicts of interest declared
• Setting	Denmark
• Sample size	1.9 million term children
• Duration and follow-up	Max 16 years
• Statistical analysis	The overall effects of caesarean delivery on the number of cases in each separate disease category in the complete time period and across the entire age span were estimated with log-linear Poisson regression models offset by the log of person time (years of observation), where any underlying age and calendar time variations for the various disease groups can be taken into account by adjusting for the attained age



and calendar year as confounders (3-year intervals were chosen). Further, the chosen confounders were added to obtain the fully adjusted estimates for the effect of caesarean delivery. All confounders were included as categorical variables. The incidence rate ratio (IRR) with 95% confidence interval was calculated to show the effect of caesarean delivery.

Patient characteristics

- **Eligibility criteria** Children born 1973-2012 in the registry cohort
- **Exclusion criteria** Children born before 36 weeks of gestation and anyone suspected of chronic diseases or lung symptoms prior to inclusion. Also children with missing data were excluded.
- **Patient & disease characteristics** Not reported

Exposures

- **Exposure group** CS
- **Control group** VD

Results

- **CS rate** 14% of the study population was delivered by CS but during the observation period the incidence of CS increased markedly from 5% to around 20%



- Immune disorders in period 1977-2011

TABLE 1 IRRs by Cesarean Delivery in the 35-Year Period 1977–2011 Following 1.9 Million Term Children in the Age Span 0 to 15 Years

	Cases	aIRR (95% Confidence Interval); <i>P</i>	PARF (Cases)
Asthma ^a	103 822	1.23 (1.21–1.25); <i>P</i> < .0001	3.07 (3187)
Asthma >5 y ^b	48 858	1.16 (1.13–1.19); <i>P</i> < .0001	2.19 (1070)
Systemic connective tissue disorders	7498	1.11 (1.04–1.19); <i>P</i> = .0021	1.53 (115)
Juvenile arthritis	6946	1.10 (1.02–1.18); <i>P</i> = .0117	1.34 (93)
Diabetes type 1	6136	1.01 (0.93–1.10); <i>P</i> = .82	— ^d
Inflammatory bowel diseases	2697	1.20 (1.06–1.36); <i>P</i> = .004	2.70 (73)
Immune deficiencies	2589	1.46 (1.32–1.62); <i>P</i> < .0001	6.09 (158)
Celiac disease	1944	0.99 (0.87–1.14); <i>P</i> = .89	— ^d
Leukemia	1631	1.17 (1.00–1.36); <i>P</i> = .048	2.31 (38)
Psoriasis	1306	0.98 (0.81–1.18); <i>P</i> = .81	— ^d
Arm fracture ^{a,c}	77 490	0.99 (0.96–1.01); <i>P</i> = .19	— ^d

Cases are defined by first in- or outpatient admission to a hospital in Denmark. IRRs are adjusted for age, calendar year, birth weight, parity, gender, season of birth, maternal age, and maternal illness. The PARF is calculated based on an overall prevalence of 14% cesarean deliveries for diseases with significant association to cesarean delivery.

^a Attained age and calendar year included in 1-y categories.

^b Attained calendar year included in 3-y and age in 6-y categories.

^c Not adjusted for maternal disease.

^d PARF is not calculated for insignificant associations.

Limitations and other comments

- Limitations** Registry data with limited additional information
- CCL** Very large retrospective cohort study with moderate risk of bias but with limited information on mothers and children.

Sevelsted 2016⁵⁴

Methods

- **Design** Two cohort studies:
 - 1) based on the COPSAC2000 birth cohort which consist of 411 children born 1998-2001 to mothers with a history of asthma
 - 2) on a registry cohort of children born 1997-2010 in Denmark
- **Source of funding and competing interest**
 - Source of funding: public COPSAC is funded by the Lundbeck Foundation, The Danish Ministry of Health, Danish Council for Strategic Research, and The Capital Region Research Foundation.
 - Conflict of interest: H.B. has acted as consultant for Chiesi and Boehringer-Ingelheim..
- **Setting**
- **Sample size**
 - 1) High risk group with 411 children from the greater Copenhagen area born to a mother with a history of asthma
 - 2) 864 049 with data on all confounders. (95% of 910 301 children born in Denmark)
- **Duration and follow-up** Max 14 years
- **Statistical analysis**
 - Time to first asthma diagnosis before the age of 7 years illustrated with Kaplan Meier plots.
 - For clinical cohort data, confounder adjusted hazard ratios (HRs) were calculated with Cox regression.
 - All confounders were investigated for proportionality, and nonproportional variables (sex and parity) were added as stratifying variables to get adjusted estimates of cesarean delivery.
 - The number of asthma cases by cesarean delivery was investigated with log-linear Poisson regression models offset by the logtransformed person years of observation adjusted for attained age (1-year group) and attained calendar year (1-year group) (Model 1).
 - In 2 additional models, we included stepwise the a priori chosen confounders.
 - The offset of log-transformed person-years models the rate of diseases, and with the categorical adjustment for timing variable (attained age and calendar year), the resulting incidence rate ratios (IRRs) with 95% CIs can be interpreted as HRs from Cox regression.

Patient characteristics

- **Eligibility criteria**
 - 1) Children born 1998-2001 to mothers with a history of asthma in the COPSAC₂₀₀₀ cohort
 - 2) Children born 1997-2010 in the registry cohort
- **Exclusion criteria** Children born before 36 weeks of gestation and anyone suspected of chronic diseases or lung symptoms prior to inclusion.
- **Patient & disease characteristics**
 - CS: 22% in the COPSAC₂₀₀₀ cohort and 19% in the registry cohort,
 - In the COPSAC₂₀₀₀ cohort delivery definition was dichotomous (CS or VD)
 - In the registry 4 categories were defined:
 - o 10% (87 559) of the children were born by cesarean delivery performed before rupture of membranes (71% elective and 29% emergency before delivery),
 - o 9% (75 863) of the children were born by cesarean delivery performed after rupture of membranes (88% emergency because of delivery complications, 12% emergency because of pregnancy complications).



- In the high-risk COPSAC₂₀₀₀ birth cohort, 18% (72 children) developed asthma before the age of 7 years.
- In the registry cohort 4.4% (38 085) had filled at least 200 defined daily doses of anti-asthmatic steroids.

Exposures

- **Exposure group**
 - All CS in the COPSAC₂₀₀₀ cohort vs VD; 4 categories in the registry cohort
 - Two combined categories for the analysis
 - o CS performed before rupture of membranes (elective CS performed before delivery and emergency cesarean performed before onset of labor)
 - o CS performed after rupture of membranes (emergency cesarean because of delivery complications performed during delivery and emergency cesarean because of pregnancy complications performed during delivery).

- **Control group** VD

Results

- **Development of asthma (= diagnosis by physician) in high risk group**
 - **Adjusted HR 2.18 (95% CI 1.27;3.73)** for CS compared with VD in the COPSAC₂₀₀₀ cohort;
- **Exacerbation of asthma in high risk group**
 - **Adjusted HR 2.48 (95% CI 1.37;4.49)** after CS compared with VD in the COPSAC₂₀₀₀ cohort;
- **Asthma (=200 defined daily dose collected anti-asthmatic steroids) in Register study**
 - **IRR 1.16 (95% CI 1.13;1.19)** for CS compared with VD in the registry cohort;
 - **IRR 1.20 (95% CI 1.16;1.23)** for CS before rupture of membranes compared with VD in the registry cohort;
 - **IRR 1.12 (95% CI 1.09;1.16)** for CS after rupture of membranes compared with VD in the registry cohort;

Limitations and other comments

- **Limitations**
 - Use of two cohorts which is sometimes complex
 - Mixed of emergency and elective CS in the category "CS before rupture of membrane"
 - Possible lack of some confounding factors (paternal smoking or asthma?)
- **CCL**
 - Cohort study with moderate risk of bias
 - Main results: Higher asthma risk among children born by CS compared to VD; more pronounced effect for caesarean delivery performed before rupture of membranes.
 - Hypothesis: Caesarean delivery performed before rupture of membranes could exaggerate the differences in microbiota, as the child in this setting is born without vertical microbial transmission from the mother



Silver 2006 (maternal morbidity)⁵⁵

Methods

- **Design** Prospective observational cohort of 30,132 women who had caesarean delivery without labour in 19 academic centers over 4 years (1999 –2002).
- **Source of funding and competing interest**
 - Source of funding: Supported by grants from the National Institute of Child Health and Human Development
 - Conflict of interest: not stated
- **Setting** 19 academic centers within the National Institute of Child Health and Development Maternal-Fetal Medicine Units Network (USA)
- **Sample size** 30,132 CS occurred without labour and had data on previous pregnancies and detailed outcome data for this pregnancy
- **Duration and follow-up** The study consisted of a prospective observational cohort of women undergoing caesarean delivery from 1999 through 2002. All inpatient medical records were abstracted through 6 weeks postpartum.
- **Statistical analysis**
 - To test for trend among women with increasing number of cesarean deliveries, the Cochran-Armitage trend test was used for binomial outcomes and the Jonckheere-Terpstra test was used for continuous outcomes.
 - To test for any baseline differences among the groups, the χ^2 test was used for categorical outcomes, and the Kruskal-Wallis test was used for continuous outcomes.
 - Odds ratios and 95% confidence intervals were calculated for the risk of adverse outcomes for each successive cesarean delivery compared with the risk for a primary cesarean delivery.
 - The risk of comorbidities by placenta accreta or hysterectomy status was compared by using the χ^2 or Fisher exact test, as appropriate.
 - Multivariable logistic regression analysis was performed to adjust for potential confounding variables contributing to adverse maternal outcome.

Patient characteristics

- **Eligibility criteria** Women undergoing caesarean delivery without labour
- **Exclusion criteria** None reported
- **Patient & disease characteristics** There were 6,201 first (primary), 15,808 second, 6,324 third, 1,452 fourth, 258 fifth, and 89 sixth or more caesarean deliveries.

Exposures

- **Exposure group** Repeat CS
- **Control group** One CS

Results

- **Placenta accreta**
 - Placenta accreta was present in 15 (0.24%), 49 (0.31%), 36 (0.57%), 31 (2.13%), 6 (2.33%), and 6 (6.74%) women undergoing their first, second, third, fourth, fifth, and sixth or more caesarean deliveries, respectively
 - Adjusted OR is 1.75 (95% CI 1.53–1.99)
- **Hysterectomy**
 - Hysterectomy was required in 40 (0.65%) first, 67 (0.42%) second, 57 (0.90%) third, 35 (2.41%) fourth, 9 (3.49%) fifth, and 8 (8.99%) sixth or more caesarean deliveries.



- Adjusted OR is 1.59 (95% CI 1.41 –1.79).

Placenta accreta and hysterectomy by number of CS

Table 3. Odds Ratios With 95% Confidence Intervals for Placenta Accreta and Hysterectomy by Number of Cesarean Deliveries Compared With First Cesarean Delivery

Cesarean Delivery	Accreta [n (%)]	OR (95% CI)	Hysterectomy [n (%)]	OR (95% CI)
First*	15 (0.2)	–	40 (0.7)	–
Second	49 (0.3)	1.3 (0.7–2.3)	67 (0.4)	0.7 (0.4–0.97)
Third	36 (0.6)	2.4 (1.3–4.3)	57 (0.9)	1.4 (0.9–2.1)
Fourth	31 (2.1)	9.0 (4.8–16.7)	35 (2.4)	3.8 (2.4–6.0)
Fifth	6 (2.3)	9.8 (3.8–25.5)	9 (3.5)	5.6 (2.7–11.6)
≥ 6	6 (6.7)	29.8 (11.3–78.7)	8 (9.0)	15.2 (6.9–33.5)

OR, odds ratio; CI, confidence interval.

* Primary cesarean delivery.

Limitations and other comments

- Limitations**
 - Results may not be generalizable to smaller rural hospitals, and these data likely underestimate the actual risk in smaller hospitals without special services.
 - The use of a clinical definition for placenta accreta instead of histologic diagnosis (not always possible because not all women given the diagnosis of placenta accreta underwent hysterectomy).
- CCL**
 - Repeat caesarean delivery was associated with increased maternal morbidity; however, outcomes were good in most women undergoing these procedures

Van Berkel 2015 (asthma)⁵⁶

Methods

- Design**
 - Population-based retrospective cohort study (Generation R Study)
- Source of funding and competing interest**
 - Source of funding: the Erasmus Medical Centre, Rotterdam, the Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development.
 - Declaration of interest: stated and declared (grant from the Netherlands Organization for Health Research and Development and funding from the Lung Foundation Netherlands)
- Setting**
 - Two well-equipped research centers in the study area, with a close collaboration with midwives and hospitals in the Netherlands.
- Sample size**
 - Response rate was based on the number of children at birth: 61%



	9749 live births were included. - At age 6 yr, 8305 children participated in the follow-up study. - The final study sample included data on 6128 children (because of missing data).
• Duration and follow-up	FU until February 2015 Mean duration: 14.8 years (SD 4.4)
• Statistical analysis	- Polynomial, logistic and linear regression models. - Adjustment for confounders and inclusion of covariates using multiple measures. - Missing data in the covariates using Markov chain Monte Carlo methods to select the most likely value for a missing response.
Patient characteristics	
• Eligibility criteria	Mothers with an expected delivery date between April 2002 and January 2006 and are resident in the study area (Rotterdam)
• Exclusion criteria	Children with missing data
• Patient & disease characteristics	Mode of delivery: - Elective CS: 5.2% - Emergency CS: 7.8% - Forceps- or vacuum-assisted delivery: 14.2% - VD: 72.9% More details in Table 1.
Exposures	
• Exposure group 1	All kind of caesarean (distinction between elective and emergency)
• Exposure group 2	Vacuum and forceps assisted VD (not reported below)
• Control group 2	VD
Results	
• Early wheezing = at least 1 wheezing episode during the first 3 yr of life, but no wheezing episode at 4 and 6 yr of age;	OR 1.36 (95% CI 1.06, 1.75) comparing all kind of CS and VD. - Similar effect for elective and emergency CS. - OR 1.43 (95% CI 0.99, 2.05) comparing elective CS to VD - OR 1.31 (95% CI 0.95, 1.80) comparing emergency CS to VD
• Late wheezing = no wheezing episode during the first 3 yr of life, but at least 1 wheezing episode at 4 or 6 yr of age	- OR 1.06 (95% CI 0.59, 1.90) comparing all kind of CS and VD. - OR 0.81 (95% CI 0.31, 2.11) comparing elective CS to VD - OR 1.08 (95% CI 0.55, 2.09) comparing emergency CS to VD



Persistent wheezing = at least 1 wheezing episode in the first 3 yr of life and 1 wheezing episode at 4 or 6 yr of age.	OR 1.73 (95% CI 1.24, 2.40) comparing all kind of CS and VD. - Similar effect for elective and emergency - OR 1.56 (95% CI 0.99, 2.46) comparing elective CS to VD OR 1.56 (95% CI 1.05, 2.31) comparing emergency CS to VD
Physician-diagnosed asthma at 6 years	- OR 1.09 (95% CI 0.76, 1.55) comparing all kind of CS and VD. - OR 0.89 (95% CI 0.52, 1.52) comparing elective CS to VD - OR 1.56 (95% CI 0.81, 1.95) comparing emergency CS to VD
Limitations and other comments	
Limitations	- Potential selection bias (different population between participants and non-responders or lost of FU) - Lack of power due to the low number of cases in several dichotomized outcomes. - Missing confounders such as maternal use of antibiotics during pregnancy or influence of genetic variance. - Arbitrary definition of wheezing categories. - Self-reported outcomes. - The lack of difference could be explained because the diagnosis of asthma is difficult in young children and mainly based on symptoms.
CCL	- Population-based retrospective cohort study with lack of power and moderate risk of bias. - Main results: Small increase in early and persistent wheezing but not in late wheezing and asthma at 6 years after CS (elective and emergency) compared to VD.

Watt 2012⁵⁷

Methods

Design	Prospective cohort panel study according to the authors
Source of funding and competing interest	- Source of funding: Canadian Institute for Health Research - Declaration of interest: stated and none declared
Setting	2 hospitals in each of the five geographic regions of Ontario
Sample size	- A sample size of 690 per group (i.e., 1380 in both groups) was aimed with a target sample of 3774 women. - The study sample included data on 2560 women (68% of the target sample of 3774)
Duration and follow-up	12 months after delivery
Statistical analysis	- Single and multiple predictor generalized estimating equations (GEE) analysis assuming an exchangeable correlation structure - Odds ratios (OR), corresponding two-sided 95% confidence intervals and associated p values.



Patient characteristics	
• Eligibility criteria	• Woman of ≥ 16 years of age; • Delivery of a live singleton infant; • Gestational age ≥ 37 weeks; • Mother assuming care of infant when discharged; • Mother competent to give consent; • Mother can be contacted by telephone.
• Exclusion criteria	• Women with infant requiring admission to a neonatal intensive care or special care nursery for more than 24 hours • Women unable to communicate in one of the four study languages (English, French, Chinese, Spanish).
• Patient & disease characteristics	Mode of delivery: • Planned CS: 17.1% • Unplanned CS: 16% • Unassisted VD: , 57.7% • Forceps or vacuum-assisted VD: 9.2% Breastfeeding initiation: 92.3% More details in Table 1
Exposures	
• Exposure group	Planned and unplanned caesarean delivery
• Control group	Vaginal delivery
Results	
• Breastfeeding initiation (at hospital)*	• OR 0.78 (95% CI 0.59, 1.02; $p=0.0660$) comparing planned CS to vaginal unassisted delivery. • OR 1.48 (95% CI 1.10, 1.99; $p=0.0087$) comparing unplanned CS to vaginal unassisted delivery. • OR 1.42 (95% CI 0.93, 2.18; $p=0.1075$) comparing vaginal assisted to vaginal unassisted delivery.
• Breastfeeding at 6 weeks	• OR 1.09 (95% CI 0.88, 1.35; $p=0.4493$) comparing planned CS to vaginal unassisted delivery. • OR 0.86 (95% CI 0.67, 1.11; $p=0.2505$) comparing unplanned CS to vaginal unassisted delivery. • OR 1.35 (95% CI 0.97, 1.89; $p=0.0729$) comparing vaginal assisted to vaginal unassisted delivery.
Limitations and other comments	
• Limitations	• The study did not focus specifically on breastfeeding. • Lack of external verification of women`s selfreported BF behavior (mainly for the BF at 6 weeks) • High level of breastfeeding initiation (92.3%) in the sample and in Ontario (87.7%) • High level of CS delivery (33.1%) in the sample and in Ontario (28.4%)
• CCL	Cohort study with moderate risk of bias.



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- Main results: no difference in BF initiation between all kind of CD vs VD but women who had an unanticipated type of delivery (assisted VD or unplanned CS) were more likely to breastfeed than women who had an anticipated delivery method (unassisted VD or planned CS).
 - Hypothesis: Having an unanticipated type of delivery can be viewed as a disruption in a woman's vision of a planned sequence of events leading to a safe delivery. These circumstances generate stress which may be appraised as a threat not only to the woman but also, by extension, to her infant. BF initiation becomes a coping strategy. It is a behavior that serves to normalize an abnormal experience and allows the mother to resume control in her own life.
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**Not a primary outcome of the study*



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