Caesarean section and offspring obesity in young adulthood: update of a systematic review with meta-analysis

MASTERARBEIT

Zur Erlangung des akademischen Grades
Master of Medicine

Vorgelegt von
Yannick Graf

Supervision:
Dr. Stéphane Cullati, PhD,
Population Health Laboratory (#PopHealthLab), University of Fribourg
Dr. Cristian Carmeli, PhD,
Population Health Laboratory (#PopHealthLab), University of Fribourg
Leiter:
Prof. Arnaud Chiolero, MD PhD,
Population Health Laboratory (#PopHealthLab), University of Fribourg
Expertin:
Prof. Marie-Julia Guittier, PhD, Haute Ecole de Santé, HES-SO, Genf

Fribourg, 2021
Mathematisch-Naturwissenschaftliche und Medizinische Fakultät der Universität Fribourg

UNI FR
UNIVERSITÉ DE FRIBOURG
UNIVERSITÄT FREIBURG

Inhalt

Danksagung

Ein herzlicher Dank gilt unseren beiden Supervisoren der Masterarbeit sowie Koautoren des Artikels Dr. Stéphane Cullati, PhD und Dr. Cristian Carmeli, PhD, die uns intensiv betreut und unterstützt haben. Weiter danke ich Herrn Prof. Arnaud Chiolero, MD PhD für das Angebot dieser Masterarbeit an seinem Lehrstuhl. Ebenso danke ich Prof. Marie-Julia Guittier, PhD, für ihre Verfügbarkeit als Expertin, Dr Adina-Mihaela Epure, MD und Prof. Valérie Santschi, PharmD PhD, für ihre Beteiligung als Koautorinnen des Artikels und Frau Nathalie Favre für ihre Unterstützung bei der Literatursuche. Zu guter Letzt bedanke ich mich ganz herzlich bei meiner Kommilitonin, Koautorin und guten Freundin Berenike Quecke für die bereichernde Zusammenarbeit.

Individuelle Kurzfassung

EINFÜHRUNG UND ZIEL

In der Schweiz kommen knapp ein Drittel (2019: 32.0%) der Neugeborenen per Kaiserschnitt zur Welt (1), wobei dieser Anteil 1998 noch bei 22.2% lag (2). Die Schweiz folgt dabei einem globalen Trend (3) und liegt weit über dem von der WHO empfohlenen Grenzwert von 10% (4). Gleichzeitig konnte weltweit seit 1975 eine Verdreifachung von Adipositas in der Bevölkerung beobachtet werden (5). Adipositas ist ein Risikofaktor für verschiedenste Erkrankungen (6) und verursachte alleine in der Schweiz im Jahr 2011 direkte Kosten von 2.2 Milliarden Franken, was 0.38% des damaligen Bruttoinlandproduktes darstellte (7). Nun identifizierten zwei Metaanalysen eine positive Assoziation zwischen den beiden oben genannten Phänomenen (8,9). Es existieren plausible Hypothesen, welche die Auswirkung der Geburt per Kaiserschnitt auf die Entwicklung von Adipositas im Erwachsenenalter erklären könnten (10). Sutharsan et al. (11) ermittelten in der bisher aktuellsten Metaanalyse von 2015 ebenfalls eine moderate Erhöhung des Risikos für Adipositas bei Kaiserschnittgeborenen, kommen aber zum Schluss, dass der gefundene Effekt entweder auf eine Publikationsverzerrung oder auf Störfaktoren zurückzuführen sei. 2019 fand eine schwedische Kohortenstudie (12) keine Evidenz für den Zusammenhang der Geburt von Kaiserschnitt und Adipositas bei Männern im Erwachsenenalter.

Zusammen mit Berenike Quecke nahm ich mir für diese Arbeit deshalb die Aktualisierung der Metaanalyse von Sutharsan et al. (11) zum Ziel. Es sollten die aktuellen Forschungserkenntnisse zusammengefasst und mit den vorherigen Metaanalysen verglichen werden.

RESULTATE

Anhand der systematischen Suche in den Datenbanken PubMed und EMBASE liessen sich 3,774 Arbeiten finden. Nach der Berücksichtigung von Duplikaten, der Vorauswahl, der Volltextprüfung und der Anwendung der Ausschlusskriterien blieben sechs Studien übrig. Zusätzlich konnten wir fünf Artikel aus dem Review von Sutharsan et al. (11) einschliessen. Insgesamt erwiesen sich davon schliesslich neun Arbeiten als passend für die Metaanalyse (n = 143,869), wobei acht davon über adjustierte Werte verfügten (n = 143,416). Details dazu sind in der Tabelle 1 im Artikel (i.A.) ersichtlich. Im Forest-Plot des Gesamt-Risikoverhältnisses der Rohdaten ist ein im Vergleich zu vaginal geborenen jungen Erwachsenen um 1.30 [95% Konfidenzintervall (CI) 1.13 bis 1.50, I^2:49%] erhöhtes Risiko für Adipositas bei per Kaiserschnitt geborenen jungen Erwachsenen ersichtlich (Abbildung S3 im Supplementary (i.S.)). Die Risiko-Verhältnisse aller Studien liegen über eins. Bezieht man mögliche Störfaktoren mit ein, so reduziert sich das Gesamt-Risikoverhältnis auf 1.22 [95% CI 1.02 bis 1.46, I^2:63%] (Abbildung 1 i.A.), wobei ausser der Studie von Mamun et al. (13) alle Risiko-Verhältnisse über eins liegen. Eine Sensitivitätsanalyse, welche die eingeschlossenen Arbeiten danach stratifiziert,

ob der vorgeburtliche mütterlichen Body Mass Index (BMI) als Störfaktor respektiert wird, zeigt eine grosse Abnahme des Gesamt-Risikoverhältnisses von 1.43 zu 1.08 bei genannter Adjustierung. Diese Tatsache deutet auf einen substantiellen Störfaktor-Effekt hin (Abbildung 1 i.A.). Die geringe Heterogenität in den beiden Untergruppen der Analyse eröffnet die Argumentation, dass sich die Heterogenität über alle acht Studien (I^2 = 63%) wahrscheinlich anhand der unterschiedlichen Berücksichtigung von möglichen Störfaktoren erklären lässt. Der Funnel-Plot (Abbildung S5 i.S.) zeigt ein recht symmetrisches Muster, was auf eine geringe Publikationsverzerrungen hinweist, wenn überhaupt eine vorhanden sein sollte. Natürlich kann es immer zu Publikationsverzerrungen durch nicht-publizierte Studien kommen.

LIMITATIONEN

Die hohe Heterogenität zwischen den eingeschlossenen Studien ist sicherlich unter anderem auf das Berücksichtigen unterschiedlicher Faktoren in der Adjustierung zurückzuführen und limitiert die Aussagekraft dieser Arbeit. Interessanterweise fanden die vier Studien mit der höchsten Qualitätsbewertung (12–15), welche wiederum zu einem Grossteil durch eine ausführliche Adjustierung bestimmt wird, die geringsten Effekte. Es ist somit annehmbar, dass die in den anderen Studien gefundenen Assoziationen durch mangelhafte Adjustierung vergrössert wurden. Aber auch in maximal adjustierten Studien können wir das Einwirken von verbleibenden Störfaktoren nicht ausschliessen. Der vorgeburtliche mütterlichen BMI ist sowohl mit erhöhtem Risiko für die Geburt per Kaiserschnitt sowie mit erhöhtem BMI der Nachkommen assoziiert (16,17) und stellt somit vermutlich den wichtigsten Störfaktor dar. Umso erstaunlicher ist es, dass vier Studien diesen Faktor nicht berücksichtigt haben (18–21). Auch für Schwangerschaftsdiabetes (22,23), tiefen sozioökonomischen Status (24,25) und mütterliches Rauchen während der Schwangerschaft (26,27) konnte gezeigt werden, dass sie als mögliche Störfaktoren in Frage kommen, was aber nicht von allen eingeschlossenen Studien berücksichtigt wurde. Weitere Limitationen können durch die Teilnehmenden selber angegebene BMI-Werte (15,28) und retrospektiv erfasste Angaben zur Exposition (15) sein, da sie das das Risiko von Messfehlern in sich bergen. Zudem mussten aufgrund nicht passender Effektgrössen zwei Studien aus der Metaanalyse ausgeschlossen werden (29,30). Des Weiteren soll erwähnt werden, dass sich diese Arbeit auf Daten aus nur sechs Ländern bezieht und zwei Studien nur Männer eingeschlossen haben (12,20). Ausserdem werden verschiedene Arten der Exposition (CS) nicht unterschieden und die Literatursuche begrenzt sich auf publizierte Artikel welche in Englisch, Deutsch, Französisch oder Italienisch verfasst wurden.

PERSPEKTIVEN

Dieser Systematische Review und die Metaanalyse aktualisieren den Wissensstand zur Assoziation von Kaiserschnitt und Adipositas im Erwachsenenalter. Unsere Resultate zeigen, dass keine solche Assozia-

tion vorhanden ist. Da unsere Sensitivitätsanalyse gezeigt hat, dass die Adjustierung für den vorgeburtlichen mütterlichen BMI zu einer grossen Abnahme des Risiko-Verhältnisses führt, wird davon ausgegangen, dass ebendieser ein Hauptstörfaktor darstellt, welcher möglicherweise zu einem Teil für die beobachteten positiven Assoziationen in früheren Arbeiten verantwortlich sein könnte. Wir ziehen somit den Schluss, dass andere mit dem elterlichen BMI in Beziehung stehende Umweltfaktoren für die Adipositas-Epidemie verantwortlich sein müssen. Das Augenmerk der Forschung um Adipositas soll auf Faktoren wie beispielsweise den Konsum von stark verarbeiteten Nahrungsmitteln oder den Mangel an körperlicher Aktivität gerichtet werden. Klar ist, dass es in Zukunft wichtig sein wird, diese Epidemie genauer zu verstehen, um die damit einhergehenden gesundheitlichen und finanziellen Problematiken angehen zu können.

PERSÖNLICHER BEITRAG ZUR ARBEIT

Zusammen mit SC, CC und BQ habe ich das Design der Studie festgelegt. BQ und ich haben die Literaturrecherche durchgeführt sowie uns unter der Supervision von SC und CC um das Vorauswählen und die Datenextraktion gekümmert. Anschliessend haben BQ und ich das Manuskript entworfen und dabei die Einbringungen der Koautor.innen umgesetzt.

Caesarean section and offspring obesity in young adulthood: update of a systematic review with meta-analysis

Berenike Quecke[1]*, Yannick Graf[1]*, Adina-Mihaela Epure[1], Valérie Santschi[2], Arnaud Chiolero[1,3,4], Cristian Carmeli[1†], Stéphane Cullati[1,5†]

1 Population Health Laboratory (#PopHealthLab), University of Fribourg, Fribourg, Switzerland
2 La Source, School of Nursing Sciences, University of Applied Sciences Western Switzerland, Lausanne, Switzerland
3 Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
4 School of Population and Global Health, McGill University, Montreal, Canada
5 Department of Readaptation and Geriatrics, University of Geneva, Geneva, Switzerland

* equally contributed to the writing of the manuscript

† joint senior authors

CORRESPONDING AUTHOR

Dr. Stéphane Cullati, Population Health Laboratory, University of Fribourg, Route des Arsenaux 41, CH - 1700 Fribourg, Switzerland, phone +41 26 300 94 74, stephane.cullati@unifr.ch

Number of words: abstract 222 (max. 250), manuscript 1535 (max. 1500)

Number of figures: 1

Number of tables: 1

Supplementary file: 1

ABSTRACT

Caesarean section (CS) might be associated with a higher risk of offspring obesity in young adulthood compared to vaginal delivery (VG). We updated a systematic review with meta-analysis of studies evaluating this association. Evidence published since 1st April 2014, namely the end date of searches from the most recent systematic review, was considered. Out of 3,774 abstracts identified on PubMed and Embase, six studies were retained, of which four were included in the meta-analysis. In addition, five studies of the last systematic review regarding the effect on young adulthood were considered in our meta-analysis. The nine studies analysed had a cohort design and included overall 143,869 participants. A higher risk of obesity for young adult born by CS compared to adults born by VD was found using crude estimates (pooled risk ratio (RR): 1.30 [95% confidence interval (CI) 1.13 to 1.50, I^2:49%]) and maximally adjusted estimates (RR: 1.22 [95% CI 1.02 to 1.46, I^2:63%]). Adjustment methods vary across the studies and there was a high between-study heterogeneity. In analyses restrained to the five studies with adjustment for maternal pre-pregnancy body mass index (BMI), considered as a major potential confounding factor, the RR was 1.08 [95% CI 0.92 to 1.27, I^2:23%]. We conclude that the association between CS and obesity in young adulthood is due to confounding notably by maternal pre-pregnancy body weight.

KEY WORDS

Caesarean section; offspring; obesity; young adulthood; meta-analysis.

INTRODUCTION

The prevalence of caesarean sections (CS) as well as of obesity are growing in high-income countries (31,32). Mode of delivery might influence health and the risk of disease in adult life (10), including obesity. The hypothetical mechanisms that might underpin the association remain highly disputed. Few studies have shown that the risk of obesity in adulthood was higher in offspring delivered by CS (18), whereas others have not shown such an association (13). In 2014, a systematic review confirmed the association between CS and offspring adulthood overweight and obesity (9). However, in this review, estimates were not adjusted for possible confounders like maternal pre-pregnancy body mass index (BMI). Another systematic review identified a moderate association but concluded that most of the associations reported could be attributed either to publication bias favouring positive results or to residual confounding (11). Recently, a Swedish national register study found no evidence of an association between CS and obesity in young adult male conscripts (33). We therefore updated the systematic review of Sutharsan et al (11).

METHODS

A systematic review of studies reporting adult measures of obesity by mode of delivery (VD, CS, elective or not) was conducted following PRISMA guidelines for reporting systematic reviews and meta-analyses (34).

Definition of outcomes and exposures

Obesity in humans aged 18 or above is the outcome. We considered any obesity measures, expressed on a metric scale (e.g. kg/m^2) or a standardized scale (e.g. z-score), that are determined anthropometrically. Obesity was classified according to the World Health Organisation's standard (35), namely equal to or greater than $30kg/m^2$. Exposures are either CS, elective or non-elective or VD, natural or operative.

Literature search

A search was conducted using PubMed and EMBASE for any studies published since 1st April 2014, namely the end date of searches of the most recent systematic review (11). Details about the search strategies are described in the supplementary file.

Study selection, data extraction and study quality assessment

Titles and abstracts of identified studies were independently screened by two reviewers [YG and BQ]. Additional details and criteria are described in the supplementary file. Data was extracted using a pre-piloted data collection form [YG and BQ]. When data was not available, the respective authors were contacted to request those. If no response was received, the study was excluded (n = 1). The methodological quality of each study was assessed using the tool of Sutharsan et al. (2015), comprising ten criteria related to bias in observational studies (36) (Figure S1). Each study was assessed by one reviewer [YG or BQ] and each quality assessment was reviewed by a second senior person [CC or SC].

Statistical analysis

We meta-analysed studies reporting associations on the odds ratios or risk ratio scales. Odds ratios were converted to risk ratios. We pooled estimates from each cohort study via the Hartung-Knapp inverse variance random effect meta-analytic mode (37,38). This method provides reliable coverage accuracy in a small number study setting. The inter-study variance was estimated via the DerSimonian-Laird implemented in the meta R package (39). The potential heterogeneity across studies was assessed through the I^2 statistic.

RESULTS

The search revealed 3,774 abstracts (934 PubMed; 2,840 EMBASE). After removing duplicates 3,433 studies remained and were screened for inclusion. Some 17 full texts were assessed for eligibility. Eleven articles were excluded (Figure S2), leaving six studies retained. In addition, five studies included in the review of Sutharsan et al. (2015) which fit our inclusion criteria (13,14,18–20), but were published earlier than 1st April 2014, were identified. In the meta-analysis, we excluded two studies which used continuous BMI (29,30) (Table S1). In total, nine studies with crude estimates (n = 143,689) and eight studies with adjusted estimates (n = 143,416) were included in the meta-analysis. Study characteristics, including quality scores, are shown in Table 1.

Table 1: *Characteristics of longitudinal studies included in the meta-analysis*

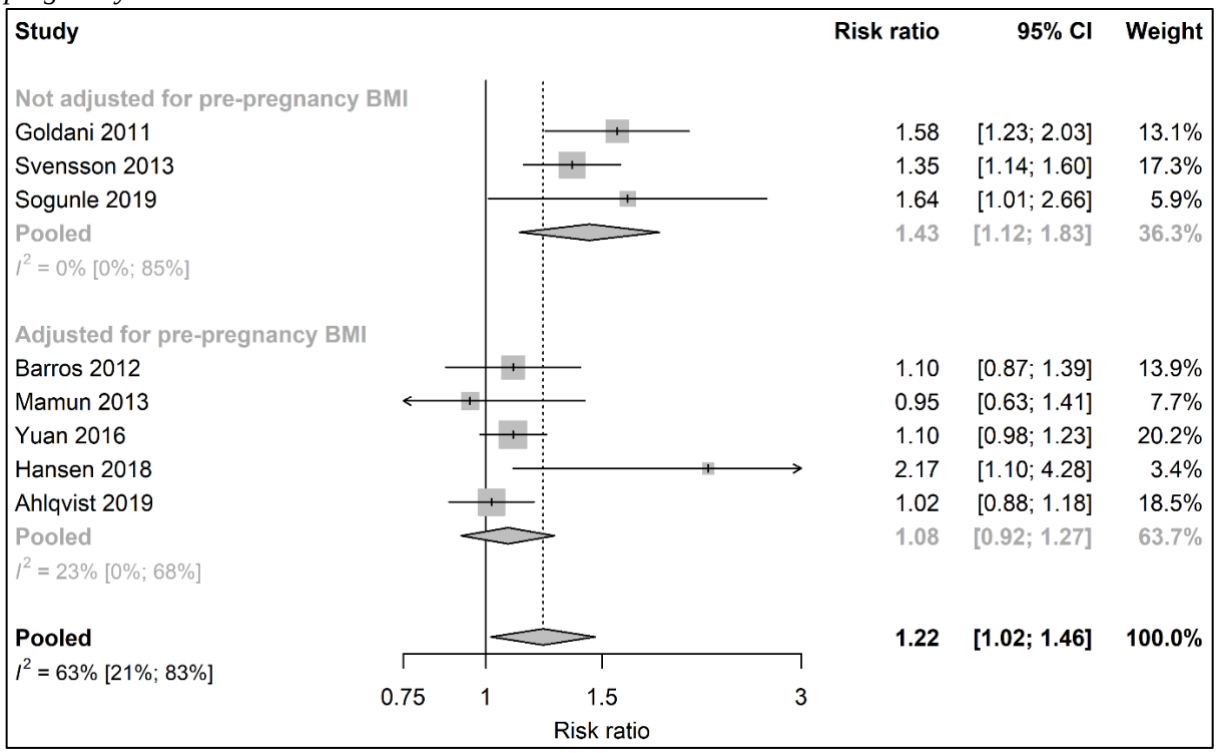
First author, year	Sample, year of exposure, country	Sample size	Mean age or Age range	Out-come	Definition of obesity	Measure of association	Crude estimates	Fully adjusted estimates	Adjusted for maternal pre-pregnancy BMI	Factors adjusted for	Quality Score
Goldani, 2011 (18)	Population based, 1978-1979, Brazil	2,057 M = 992 F = 1,065	23-25 years	BMI	BMI ≥30kg/m^2	PR_{ob}	1.46 (1.15, 1.85) n.a.	1.58 (1.23, 2.02) n.a.	No	Maternal factors: education and smoking Child factors: birth weight, sex, physical activity, smoking, education and income	0.52
Rooney, 2011 (19)	Population based, 1988, USA	453	18-20 years	BMI	BMI ≥30kg/m^2	RR_{ob}	2.78 (1.30, 5.94)	Adolescent and adulthood models were not adjusted.	No	None	0.37
Barros, 2012 (14)	Population based, 1982, Brazil	4,288 n.a. n.a.	23 years	BMI	BMI ≥30kg/m^2	$PR_{ob\ all}$ $PR_{ob\ M}$ $PR_{ob\ F}$	1.10 (0.89, 1.37) 1.13 (0.82, 1.55) 1.08 (0.81, 1.46)	1.10 (0.87, 1.41) 0.94 (0.60, 1.31) 1.33 (0.94,1.89)	Yes Yes Yes	Maternal factors: age, pre-pregnancy, weight and height, skin colour, smoking and education Family factors: family income, type of payment for delivery Child factors: birth order and birth weight, education, physical activity, smoking and alcohol consumption ditto ditto	0.82
Mamun, 2013 (13)	Population based, 1981-1983, Australia	2,382	21 years	BMI	BMI ≥30kg/m^2	OR_{ob}	1.3 (0.9, 1.8)	0.94 (0.63, 1.41)	Yes	Maternal factors: age, pre-pregnancy BMI, smoking, education, gestational weight gain, hypertensive disorder Family factors: parental ethnicity Child factors: gestation, birth weight, breast feeding,	0.86
Svensson, 2013 (20)	Conscription record (all males), 1977-1983, Denmark	21,051	≈18 years	BMI	BMI ≥30kg/m^2	PR_{ob}	1.41 (1.22, 1.63)	1.35 (1.14, 1.59)	No	Maternal factors: age, gestational hypertensive disorder, diabetes, marital status, maternal hospitalization for infection Child factor: birth weight, gestational age. parity	0.74

Yuan, 2016 (15)	Population based, ≈1982-1995, USA	14,763	19-28 years	BMI	BMI ≥30kg/m^2	RR_{ob} (model 1)	1.23 (1.11, 1.37)	1.10 (0.98, 1.24)	Yes	Maternal factors: age, height, pre-pregnancy BMI, pre pregnancy smoking, gestational diabetes, preeclampsia, pregnancy-induced hypertension, previous caesarean delivery Child factors: ethnicity, region, year of birth, gestational age, birth weight, sex, birth order	0.83
						RR_{ob} (model 2)	ditto	1.08 (0.96, 1.21)		Ditto, but modelling pre-pregnancy BMI as a continuous variable.	
Hansen, 2018 (28)	Population based, 1988-1989, Denmark	695	20 years	BMI	BMI ≥25kg/m^2	$OR_{ow\ and\ ob}$ (model 2)	2.02 (1.07, 3.82)	2.17 (1.10, 4.27)	Yes	Maternal factors: pre-pregnancy BMI, age, education, smoking in pregnancy, parity, pre-eclampsia, gestational diabetes Child factors: birth weight, gestational age	0.77
		M = 320 F = 375					n.a.	n.a.			
Sogunle, 2019 (21)	Population based,1990, South Africa	889	21-24 years	BMI	BMI ≥30kg/m^2	$IRR_{ob\ all}$	1.75 (1.05, 2.92)	1.64 (1.01, 2.68)	No	Maternal factors: education, parity Child factors: birth weight, sex,	0.54
		M = 444				$IRR_{ob\ M}$	3.79 (1.07, 13.38)	4.01 (1.14, 14.09)		ditto	
		F = 454				$IRR_{ob\ F}$	1.49 (0.87, 2.54)	1.44 (0.85, 2.44)		ditto	
Ahlqvist, 2019 (33)	Conscription record, 1982-1987, Sweden	Total = 97,291 (all male) eCS = 4,147	18 years	BMI	BMI ≥30kg/m^2	$RRR_{eCS,\ ob}$	1.14 (1.00, 1.13)	1.02 (0.88, 1.18)	Yes	Maternal factors: pre-pregnancy maternal BMI, diabetes at delivery, hypertension at delivery, smoking, age, preeclampsia Child factors: parity, birth weight standardized according to gestational age, gestational age Family factors: parental education	0.89
		n-eCS = 4,120				$RRR_{n\text{-}eCS,\ ob}$	1,18 (1.02, 1.35)	0.96 (0.83, 1.10)	Yes	ditto	

BMI: body mass index, CS: caesarean section, eCS: elective CS, n-eCS: non-elective CS, F: female, IRR: incidence rate ratio, M: male, n.a.: not available, ob: obesity, OR: odds ratio, ow: overweight, PR: prevalence risk, RR: relative risk, RRR: relative risk reduction.

Crude risk ratios (RR) from all studies were above one (Figure S3). A higher risk of obesity for young adults born by CS compared to those being born by VD was found using crude estimates (pooled RR of 1.30 [95% confidence interval (CI) 1.13 to 1.50, I^2:49%]) (Figure S3) and maximally adjusted estimates (RR: 1.22 [95% CI 1.02 to 1.46, I^2:63%]) (Figure 1). There was a substantial between-study heterogeneity. In analyses restrained to the five studies with adjustment for maternal pre-pregnancy BMI, the RR was 1.08 [95% CI 0.92 to 1.27, I^2:23%] (Figure 1). The low heterogeneity in the two sub-groups indicates that the heterogeneity in all eight studies could be partly explained by the difference in the adjustment for potential confounders. The funnel plot shows quite a symmetric pattern, indicating a low probability of publication bias (Figure S5).

Figure 1 *Forest plot for maximally adjusted risk ratios with sub-groups defined by adjustment for pre-pregnancy BMI*



Pooled estimates are represented by a diamond. The size of the grey square for each study is related to the amount of variance that a study contributes to the meta-analysis (column "weight").

DISCUSSION

Main findings

Of the eleven studies included in the qualitative synthesis, two were excluded in the analytical phase. The remaining nine studies were considered in the meta-analysis and involved 143,869 participants. In the minimally adjusted model, CS was found to increase the pooled risk of obesity in adult offspring by 30% compared to young adults born by VD. Maximal adjustment reduced the risk to 22%, which opens the argument for a substantive role of potential confounding factors. Adjustment methods varied across the studies, causing a high between-study heterogeneity. It is highly probable that the association of CS with the risk of obesity observed in the current meta-analysis may be driven by confounding in studies unadjusted for maternal pre-pregnancy BMI (the risk reduced from 1.43 in unadjusted to 1.08 in adjusted studies) as well as by other residual confounding factors.

Comparison with other studies

This is the forth meta-analysis assessing the association of CD and obesity in young adulthood (8,9,11). The meta-analysis of Li et al. (8) consists of nine studies, of which only three show estimates for young adulthood (14,18,19). Therefore they did not conduct a formal subgroup analysis for young adulthood. The adjusted pooled OR was significantly high as was the between-study heterogeneity (OR 1.50; 95% CI 1.02, 2.20; $I^2 = 74\%$). Darmasseelane et al. (9) included eleven studies with a combined population of ≈35,000 participants and considered, too, only the effect of CS on adults. Their findings revealed 22% higher odds of obesity in adults born by CS (95% CI 1.05, 1.42; p = 0.01; $I^2 = 22\%$) and the mean BMI difference was 0.44 kg/m^2 (95% CI 0.17, 0.72; p = 0.002; $I^2 = 39\%$). The low heterogeneity may be explained by the fact that they did not use adjusted data but only applied a sensitivity analysis. Sutharsan et al. (11) examined the effect on both childhood and young adulthood. Yet only five studies have taken the latter into account (n = 30,231). Sutharsan et al. used the same appropriate quality assessment instrument as we do and did adjust for confounders. They found a 28% increase in the effect on obesity (95% CI 1.02, 1.56). A clear overview of these comparisons is given in Table S2.

Strengths and limitations

The strength of our systematic review lies primarily in a large population size with participants from four continents. We included five studies (13,14,18–20) of the previous meta-analysis from Sutharsan et al. (11) in our meta-analysis for the purpose of better comparability. Furthermore, we applied a quality assessment instrument to be able to rank studies with regard to their bias adjustment and methodological quality. As we investigated a strict adult population, timing of outcome assessment and duration of follow-up were adequate for the outcome to occur.

Confidence was limited by a high between-study heterogeneity, which could partially be due to differences in the set of factors adjusted for. Interestingly, the four studies with the highest quality score (13–15,33), which is particularly determined by the adjustment for confounders, revealed the lowest adjusted estimates. Thus, it is plausible that a lack of adjustment could partly explain the higher effect sizes of the other studies. Even in maximally adjusted models, we could not exclude residual confounding explaining a part of the observed association. Four studies did not adjust for maternal pre-pregnancy BMI, probably the most significant confounding factor, which is not only associated with increased risk of CS but also with increased BMI in offspring (16,17). There is also evidence for such mechanisms regarding other maternal risk factors as gestational diabetes (22,23), lower socioeconomic status (24,25) and maternal smoking during pregnancy (26,27), which were not part of the adjustment of all included studies. Potential measurement errors were related to two limitations: Firstly, self-reported BMI from included studies (15,28) and secondly whether data about the exposure was collected soon after birth (13,14,18–21,28,33) or retrospectively recalled (15). Due to not fitting effect sizes we had to exclude two studies from the meta-analysis (29,30). It is to be mentioned that this review only included evidence out of six countries and two studies limited to male participants (20,33). In addition, we did not explore the different types of exposure (CS) and our search was limited to published studies whose language was either English, German, French or Italian.

Conclusions and public health implications

This systematic review and meta-analysis update the evidence on the association between CS and obesity in young adulthood. Although there is no doubt that both the prevalence of obesity and the one of CS are increasing in high-income countries, our findings did not support any association between CS and offspring obesity. Based on the significant drop of the risk ratio upon adjustment for pre-pregnancy BMI, we identified the latter as a major confounder and probably responsible for the association seen in previous studies and meta-analyses. We therefore plead for other environmental factors related to parental BMI such as consumption of ultra-processed food or low activity level to be considered as an explanation for the obesity epidemic.

ACKNOWLEDGEMENTS

We thank Mrs. Nathalie Favre for her support in the literature search.

AUTHOR CONTRIBUTIONS

All authors designed the study. BQ and YG made the literature search, screening and data extraction, under the supervision of CC and SC. CC developed the statistical model and analysed the data. All authors reviewed the study findings. BQ and YG drafted the manuscript with contributions of CC and SC. All co-authors revised the first draft of the manuscript. All authors approved the final version of the manuscript before submission.

COMPETING INTERESTS

We declare no competing interests.

FUNDING

This project did not receive any specific funding.

DATA SHARING

Access to data requires contacting the last author.

Supplementary information

Caesarean section and offspring obesity in young adulthood: update of a systematic review with meta-analysis

Berenike Quecke, Yannick Graf, Adina-Mihaela Epure, Valérie Santschi, Arnaud Chiolero, Cristian Carmeli, Stéphane Cullati

Table of content

1 METHODS

Search strategies

The following search strategies were used:

[1] PubMed: (Delivery, obstetric [MeSH] OR Cesarean Section [MeSH] OR Cesarean [TI/AB]) AND (Obesity, Abdominal [MeSH] OR Obesity, Metabolically Benign [MeSH] OR Obesity, Morbid [MeSH] OR Abdominal circumference OR Body Weights and Measures [MeSH] OR Waist Circumference [MeSH] OR Waist-Hip Ratio [MeSH] OR Body Mass Index [MeSH] OR Body Fat Distribution [MeSH] OR Waist-Height Ratio [MeSH] OR Height Weight Ratio [MeSH] OR Abdominal Fat [MeSH] OR Fat Body [MeSH]).

[2] EMBASE: ('Delivery, obstetric'/de OR 'Cesarean Section'/exp OR Cesarean*:ti OR Cesarean:ab) AND ('abdominal obesity'/exp OR 'metabolically benign obesity'/exp OR 'adolescent obesity'/exp OR 'morbid obesity'/exp OR 'abdominal circumference'/exp OR 'body mass'/exp OR 'body weight control'/exp OR 'hip circumference'/exp OR 'waist circumference'/exp OR 'waist hip ratio'/exp OR 'waist to height ratio'/exp OR 'weight'/exp OR 'weight height ratio'/exp OR 'abdominal fat'/exp OR 'body fat'/exp OR 'body fat distribution'/exp).

Study selection

Discrepancies in the screening were resolved by consensus with a third person [CC or SC]. The full texts of relevant abstracts were appraised for inclusion [YG and BQ]. Any disagreement over eligibility of a study was referred to a meeting with a third person [CC or SC]. Studies were included if they were (i) observational studies, either cross-sectional or longitudinal (ii) written in English, French, German or Italian and (iii) published from 1st April 2014 until 25 February 2020, and (iv) if participants had at least one measurement of their weight status at age 18 years or older. In addition to the selection criteria already mentioned in the main article, the studies also had to meet the following criteria: (v) determination of obesity in humans anthropometrically and (vi) expression of the measurements on the metric scale (e.g. kg/m^2) or a standardized scale (e.g. z-score), (vii) reporting the association between caesarean section and offspring overweight or obesity. We did not consider studies where (i) full text was not available and authors were not contactable (n = 1), (ii) the full article was not yet published (n = 3), (iii) BMI was not studied as outcome (n = 3), (iv) caesarean section was not studied as exposure (n = 1), (v) population age fell below the limit (n = 2), (vi) the format did not correspond to a research article (n = 1). All searches were limited to human studies. There was no limitation concerning the country or the sex of the participants.

Statistical analysis

We chose to report risk ratios as a common measure of the association. To harmonize the measure across cohort studies, we transformed the odds ratio into relative risk when obesity was common. This happened to be the case for the study of Mamun et al. 2013 (13) where the prevalence of obesity was 12.5%, but not for the study of Hansen et al. 2018 (28) where it was 8%. Furthermore, we interpreted the pre-valence ratios reported in Goldani et al. 2011 (18), Barros et al. 2012 (14), and Svensson et al. 2013 (20) as risk ratios since the recalled or self-reported exposure happened at birth for all participants. Finally, we approximated the rate ratio reported in Sogunle et al. 2019 (21) as a risk ratio, by assuming a similar length of follow-up for exposed and non-exposed participants as the outcome was measured in a narrow window of ages (21-24 years).

Quality assessment

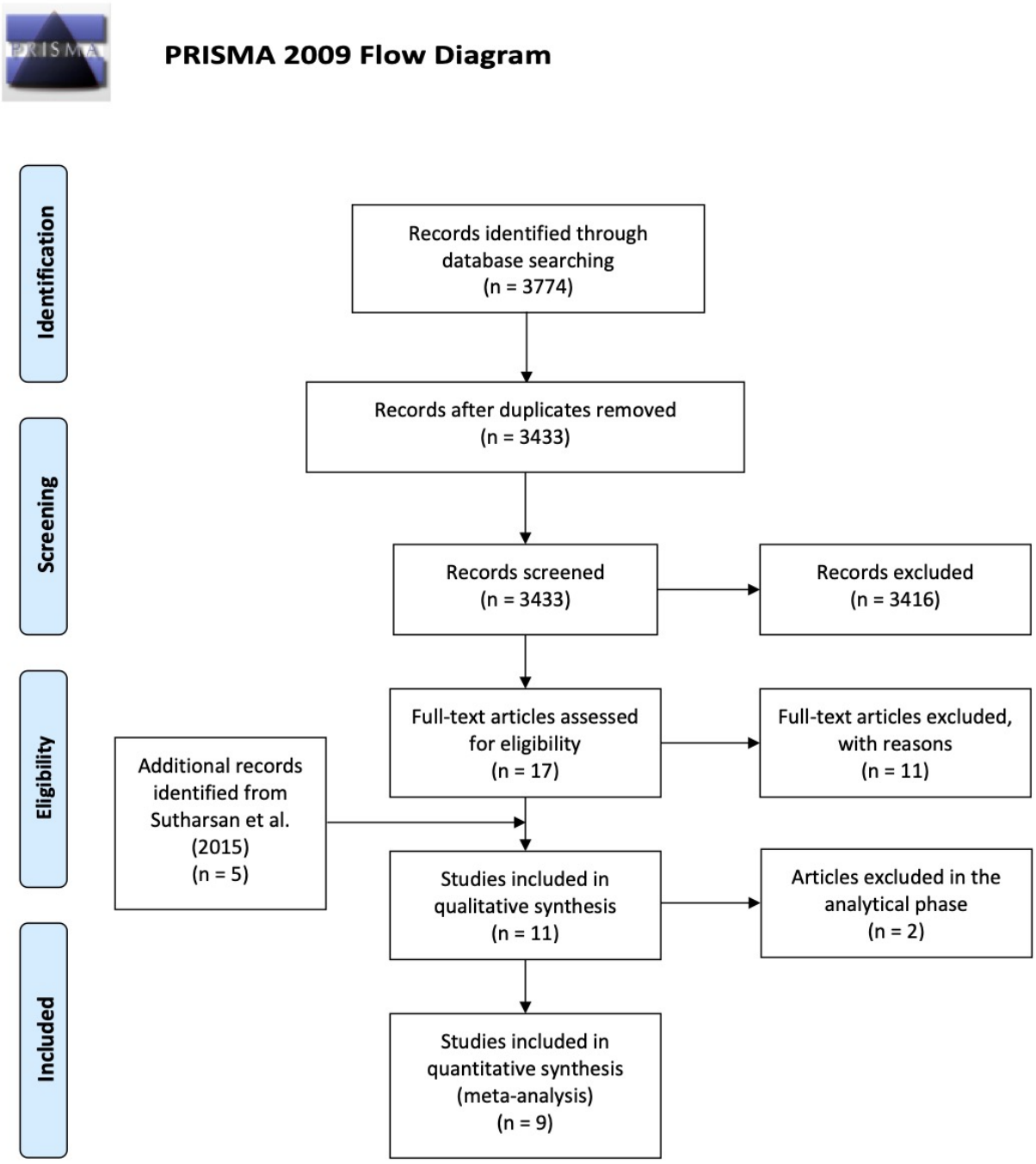
In order to adjust for bias, we applied a quality assessment instrument (Table S1) which was created by Sutharsan et al. (11) based on bias criteria for observational studies (36). Quality score was calculated by dividing the total points received by the maximum number of 18 points.

Figure S1: Sutharsan Quality assessment instrument (11)

A. Design-specific bias		
Q1	*Was the data completely prospectively collected?*	0 = No/others; 1 = Yes
B. Selection Bias		
Q2	*Were consecutive subjects recruited into the study?*	0 = No /others 1= Yes
Q3	*Were the number of participants lost at each stage or protocol deviations, acceptable (based on reason for dropout) or <20%? (justify definition of "acceptable dropouts")*	0 = No or not reported 1 = Yes
Q4	*Were the non-exposed cohort drawn from the same population and in the same way as the exposed cohort?*	0 = No or no description 1 = Drawn from a different source 2 = Yes
Q5	*Were the eligibility criteria clearly specified and applied in the same way in the exposed and unexposed?*	0 = No or no description 0.5 = In part 1 = Yes
C. Confounding		
Q6a	*Was any attempt made to adjust for potential confounders ?* (Birth weight, Maternal pre-preg. BMI, Gestational weight gain, Maternal complications, Gestation, SES, parity, age, race)	0=None 1 = 2-4 confounders 2 = ≥5 confounders
Q6b	If adjusted for maternal pre-preg. BMI	4 = Yes
Q6c	If adjusted for maternal complications or gestational weight gain	2 = Yes
D. Information Bias		
Q7	*Was timing of outcome assessment and duration of follow-up adequate for outcomes to occur?*	No - 0 = <1 year Yes - 1 ≥ 1 year
Q8	*How accurately was outcome measured?*	0 = self-reported 0.5 =reported in chart/Recorded 0.75 = single (one time point) measured by investigators 1 = multiple measured (child/adolescent/adult) by investigators
E. Statistical methods		
Q9	*Was the analysis reported on the entire data?*	0 = Not clearly documented 1 = Yes
Q10	*Was missing data analysed using imputation methods?*	0 = no 1 = yes or missing data < 20%

2 RESULTS

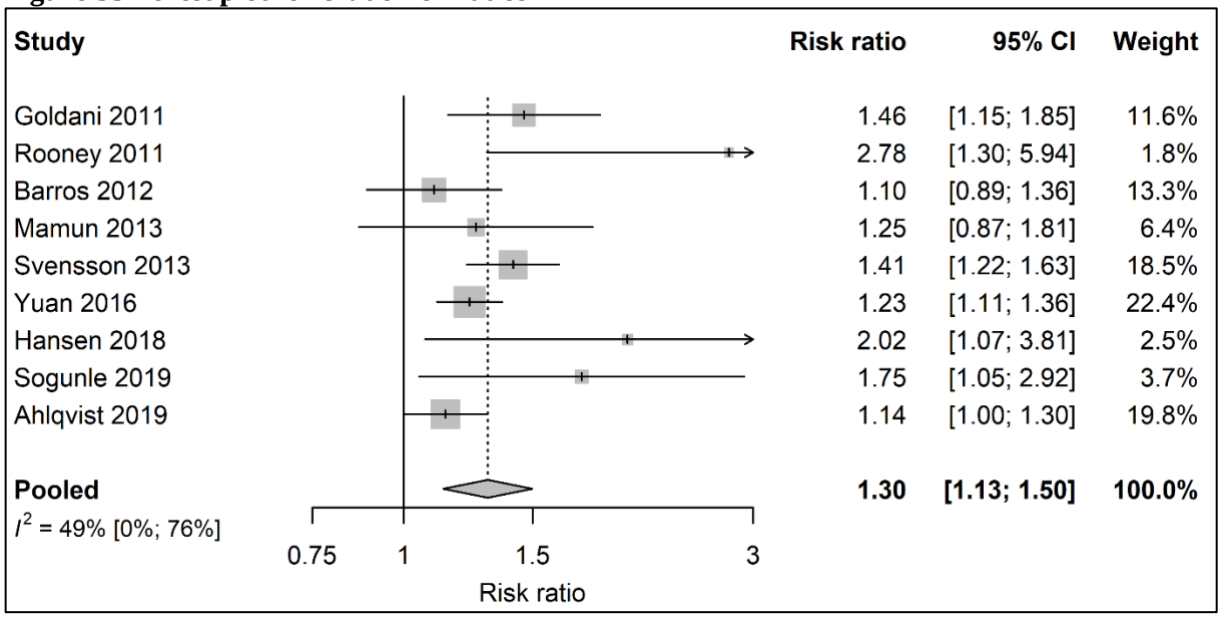
Figure S2: Flow diagram of the systematic selection of articles for the meta-analysis



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

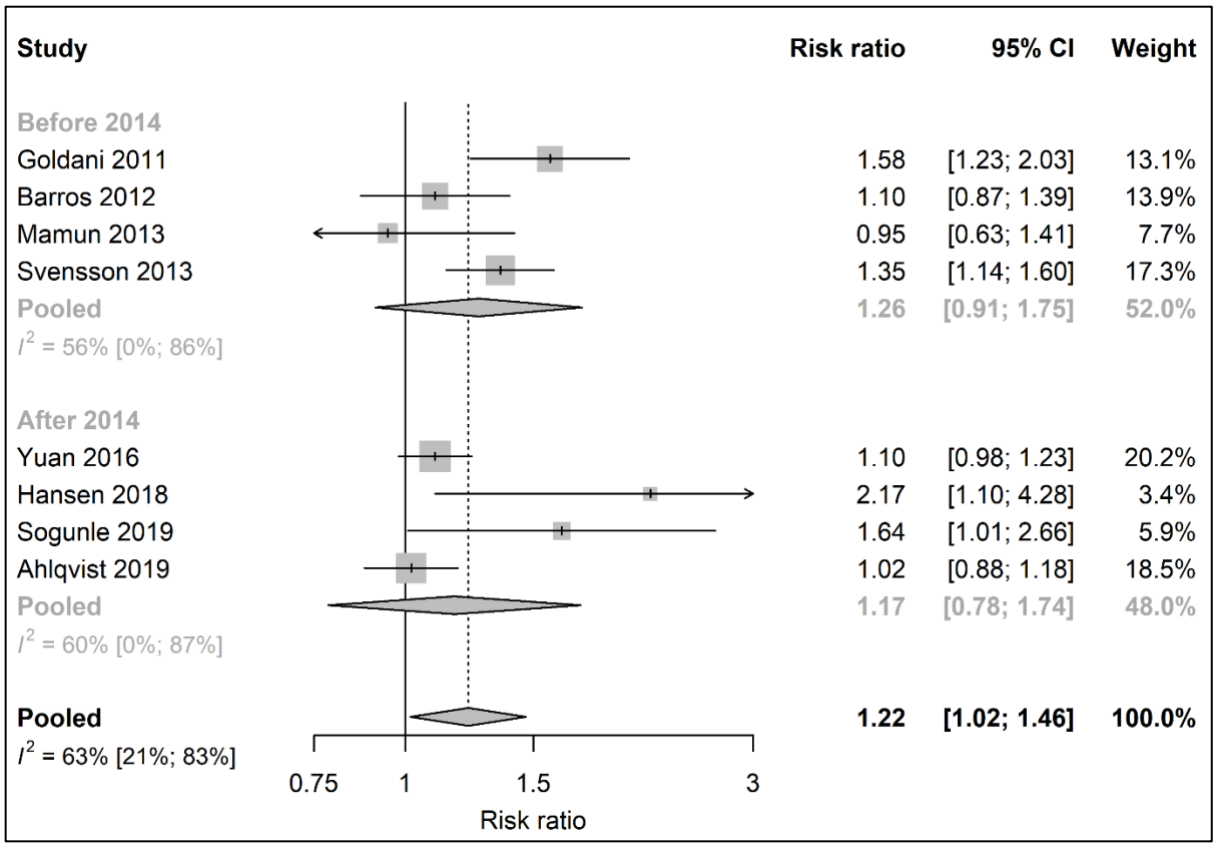
For more information, visit www.prisma-statement.org.

Figure S3 Forest plot for crude risk ratios



Pooled estimates are represented by a diamond. The size of the grey square for each study is related to the amount of variance that a study contributes to the meta-analysis (column "weight").

Figure S4 Forest plot for maximally adjusted risk ratios with sub-groups defined by publication date



Pooled estimates are represented by a diamond. The size of the grey square for each study is related to the amount of variance that a study contributes to the meta-analysis (column "weight").

Figure S5 Funnel plot

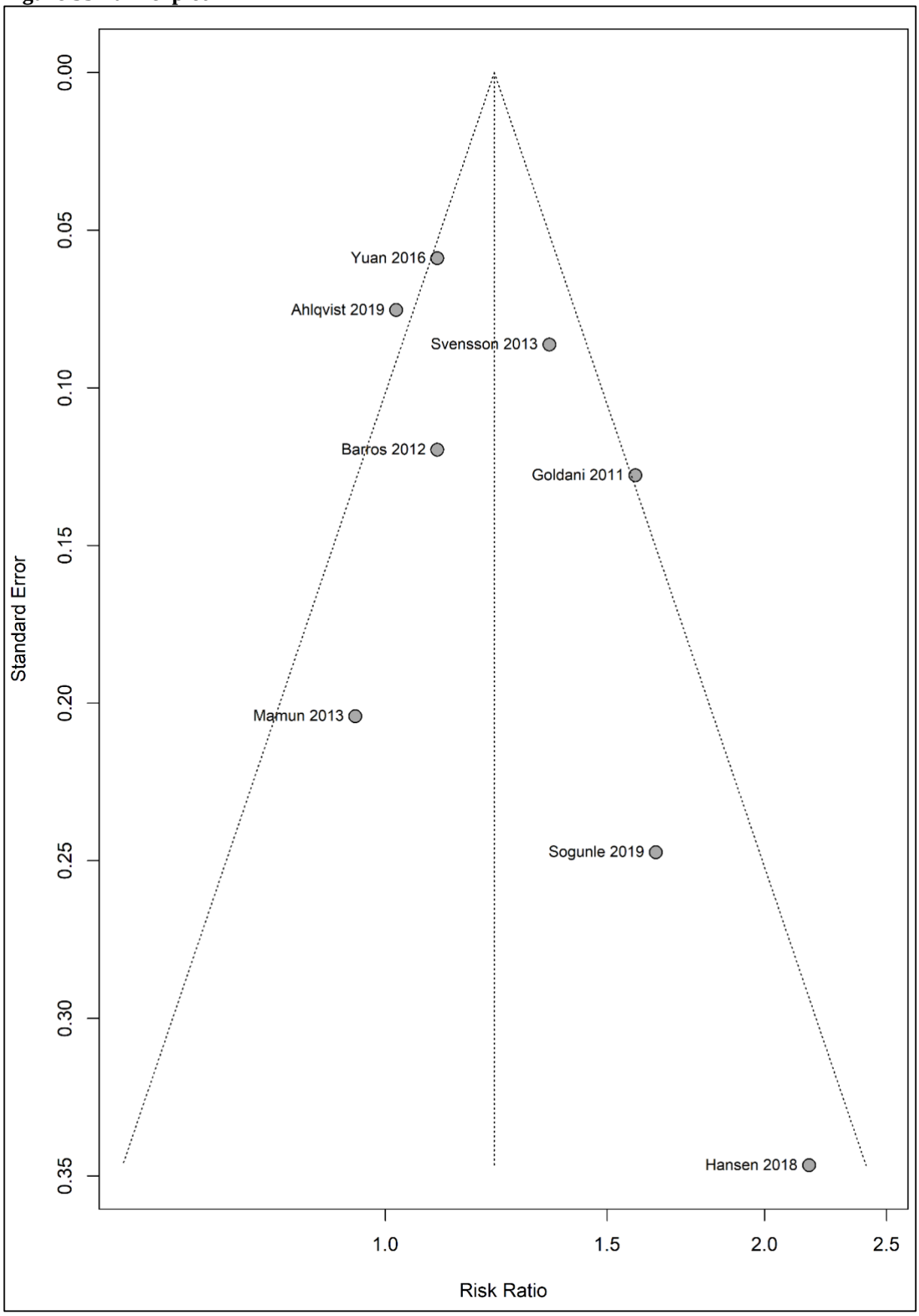


Table S1: Characteristics of longitudinal studies not included in the meta-analysis

First author, year	Sample, year of exposure, country	Sample size	Mean age or Age range	Out-come	Definition of obesity	Measure of association	Crude estimates	Fully adjusted estimates	Adjusted for maternal pre-pregnancy BMI	Factors adjusted for	Quality Score
Bernardi, 2015 (29)	Population based, 1978–1979, Brazil	2,063 M = 995 F = 1,068	23 ± 0.7 years	BMI	not dichoto-mized	B	0.018 (0.010, 0.025) n.a.	0.020 (0.013, 0.028) n.a.	No	Maternal factors: schooling at birth, age, smoking during pregnancy Child factors: birth weight, sex, parity	0.54
Barros, 2017 (30)	Population based, 1982-2013, Brazil 1982 cohort	3,607 M = 1,754 F = 1,853	30 years	BMI z-score	not dichoto-mized	B	0.13 (0.06, 0.21) 0.12 (0.03, 0.21) 0.14 (0.03, 0.26)	0.09 (0.01, 0.17) 0.04 (-0.06, 0.14) 0.15 (0.03, 0.28)	Yes	Maternal factors: education, skin colour, pre-gestational BMI, parity, age at birth and smoking during pregnancy. Family factors: SEP (socioeconomic position), financing of delivery Child factors: birth weight ditto ditto	0.72
	1993 cohort	3,961 M = 1,965 F = 1,996	18 years	BMI z-score	not dichoto-mized	B	0.17 (0.09, 0.25) 0.27 (0.15, 0.38) 0.07 (−0.04, 0.19)	0.06 (-0.02, 0.14) 0.11 (-0.01, 0.23) 0.01 (-0.11, 0.13)	Yes	Maternal factors: education, skin colour, pre-gestational BMI, parity, age at birth and smoking during pregnancy. Family factors: SEP (socioeconomic position), financing of delivery Child factors: birth weight and length ditto ditto	

B: Beta (multiple linear regression), BMI: body mass index, CS: caesarean section, F: female, M: male, n.a.: not available, ob: obesity, RR: relative risk

3 DISCUSSION

Table S2: Comparison with three previous meta-analyses

	Li et al. 2013 (8)	**Darmasseelane et al. 2014 (9)**	**Sutharsan et al. 2015 (11)**	**Present study (Update of Sutharsan 2015)**
Type of studies included	Longitudinal studies Case-control studies	Long term follow-up studies	Longitudinal studies	Longitudinal studies
Number of studies included in analysis (regarding effect on young adulthood)	3	11	5	4 plus 5 (crude analysis) respectively 4 (adjusted analysis) from Sutharsan
Age cut-off for young adulthood	≥19 years	≥18	≥18	≥18
Number of participants	6,807	≈35,000	30,231	143,869 (crude) 143,416 (adjusted)
Consideration for quality of studies	- Newcastle-Ottawa scale - Subgroup analysis not conducted for adulthood	- Newcastle-Ottawa scale - Subgroup analysis by high-, medium- and low-quality studies	Assessment instrument developed by Sutharsan et al., based on bias criteria for observational studies	Studies assessed with the Sutharsan quality score
Effects estimate (RR/OR)	OR	OR	Relative risks (OR transformed in relative risks)	Risk ratios (OR transformed in relative risk; PR and rate ratio interpreted as risk ratios)
Type of model applied	Random-effects model MA, with inverse variance method	Fixed and random-effects model MA, with Mantel-Haenszel method	Meta-regression of relative risks adjusted for synthetic bias variance using on a ranking based on studies' quality score	Random-effects model MA, with DerSimonian-Laird method and Hartung-Knapp adjustment
Results				
Unadjusted estimates for adulthood obesity	(no)	1.22 (95% CI 1.05-1.42); $I^2 = 22\%$	(no)	1.30 (95% CI 1.13-1.50); $I^2 = 49.0\%$
Adjusted estimates for adulthood obesity	1.50 (95% CI 1.02-2.20); $I^2 = 74\%$	(no)	1.28 (95% CI 1.02-1.34)	1.22 (95% CI 1.02-1.46); $I^2 = 63.0\%$

Consideration for confounders	Estimation of adjusted risk ratios	Not performed	Confounding can count up to half the score points	- Estimation of adjusted risk ratios - Sub-group analysis by confounding factor
Publication bias	Methods: Funnel plot with Egger's test Results: analysis not conducted (not enough studies)	Methods: Funnel plot with Egger's test Results: Asymmetry of funnel plot, Egger's test NS	Methods: DOI and funnel plots with Egger's test Results: analysis not conducted (not enough studies)	Methods: Funnel plot Results: no asymmetry pattern

CI: confidence intervals, MA: Meta-analysis, NS: Not significant, OR: odds ratio, PR: prevalence ratios

Referenzen

1. Statistik B für. Reproduktive Gesundheit [Internet]. [zitiert 17. Februar 2021]. Verfügbar unter: https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit/gesundheitszustand/reproduktive.html

2. Hanselmann V, von Greyerz S, Züllig M. Kaiserschnittgeburten in der Schweiz: Grundlagenbericht zur Beantwortung des Postulates Maury Pasquier (08.3935) [Internet]. Bundesamt für Gesundheit (BAG); 2013 [zitiert 17. Februar 2021]. Verfügbar unter: https://www.bag.admin.ch/dam/bag/de/dokumente/cc/bundesratsberichte/2013/kaiserschnittgeburten.pdf.download.pdf/.pdf

3. Boerma T, Ronsmans C, Melesse DY, Barros AJD, Barros FC, Juan L, u. a. Global epidemiology of use of and disparities in caesarean sections. Lancet. 13. Oktober 2018;392(10155):1341–8.

4. WHO statement on caesarean section rates [Internet]. World Health Organization, Department of Reproductive Health and Research; 2015. Verfügbar unter: https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/cs-statement/en/

5. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. The Lancet. 2. April 2016;387(10026):1377–96.

6. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health. 25. März 2009;9(1):88.

7. Schneider H, Venetz W. Cost of Obesity in Switzerland in 2012 [Internet]. Datagen AG, on behalf of the Bundesamt für Gesundheit; 2014. Verfügbar unter: https://www.bag.admin.ch/bag/de/home/das-bag/publikationen/forschungsberichte/forschungsberichte-ernaehrung-bewegung.html

8. Li H -t, Zhou Y -b, Liu J -m. The impact of cesarean section on offspring overweight and obesity: a systematic review and meta-analysis. Int J Obes (Lond). Juli 2013;37(7):893–9.

9. Darmasseelane K, Hyde MJ, Santhakumaran S, Gale C, Modi N. Mode of delivery and offspring body mass index, overweight and obesity in adult life: a systematic review and meta-analysis. PLoS One. 2014;9(2):e87896.

10. Hyde MJ, Mostyn A, Modi N, Kemp PR. The health implications of birth by Caesarean section. Biological Reviews. 2012;87(1):229–43.

11. Sutharsan R, Mannan M, Doi SA, Mamun AA. Caesarean delivery and the risk of offspring overweight and obesity over the life course: a systematic review and bias-adjusted meta-analysis. Clinical Obesity. 2015;5(6):293–301.

12. Ahlqvist VH, Persson M, Magnusson C, Berglind D. Elective and nonelective cesarean section and obesity among young adult male offspring: A Swedish population-based cohort study. PLoS Med. Dezember 2019;16(12):e1002996.

13. Mamun AA, Sutharsan R, O'Callaghan M, Williams G, Najman J, McIntyre HD, u. a. Cesarean Delivery and the Long-Term Risk of Offspring Obesity. Obstetrics & Gynecology. Dezember 2013;122(6):1176–83.

14. Barros FC, Matijasevich A, Hallal PC, Horta BL, Barros AJ, Menezes AB, u. a. Cesarean section and risk of obesity in childhood, adolescence, and early adulthood: evidence from 3 Brazilian birth cohorts123. Am J Clin Nutr. Februar 2012;95(2):465–70.

15. Yuan C, Gaskins AJ, Blaine AI, Zhang C, Gillman MW, Missmer SA, u. a. Cesarean birth and risk of offspring obesity in childhood, adolescence and early adulthood. JAMA Pediatr. 7. November 2016;170(11):e162385.

16. Chu SY, Kim SY, Schmid CH, Dietz PM, Callaghan WM, Lau J, u. a. Maternal obesity and risk of cesarean delivery: a meta-analysis. Obesity Reviews. 2007;8(5):385–94.

17. Eshriqui I, Valente AMM, Folchetti LD, Almeida-Pititto B de, Ferreira SRG. Pre-pregnancy BMI is associated with offspring body composition in adulthood before adiposity-related disorders: a retrospective cohort. Public Health Nutrition. 28. Dezember 2020;1–8.

18. Goldani HA, Bettiol H, Barbieri MA, Silva AA, Agranonik M, Morais MB, u. a. Cesarean delivery is associated with an increased risk of obesity in adulthood in a Brazilian birth cohort study. The American Journal of Clinical Nutrition. 1. Juni 2011;93(6):1344–7.

19. Rooney BL, Mathiason MA, Schauberger CW. Predictors of Obesity in Childhood, Adolescence, and Adulthood in a Birth Cohort. Matern Child Health J. 1. November 2011;15(8):1166–75.

20. Svensson E, Hyde M, Modi N, Ehrenstein V. Caesarean section and body mass index among danish men. Obesity. 2013;21(3):429–33.

21. Sogunle E, Masukume G, Nelson G. The association between caesarean section delivery and later life obesity in 21-24 year olds in an Urban South African birth cohort. PLoS One. 14. November 2019;14(11).

22. Gorgal R, Gonçalves E, Barros M, Namora G, Magalhães Â, Rodrigues T, u. a. Gestational diabetes mellitus: A risk factor for non-elective cesarean section. Journal of Obstetrics and Gynaecology Research. 2012;38(1):154–9.

23. Kawasaki M, Arata N, Miyazaki C, Mori R, Kikuchi T, Ogawa Y, u. a. Obesity and abnormal glucose tolerance in offspring of diabetic mothers: A systematic review and meta-analysis. PLoS One. 12. Januar 2018;13(1).

24. McLaren L. Socioeconomic Status and Obesity. Epidemiologic Reviews. 1. Januar 2007;29(1):29–48.

25. Miani C, Ludwig A, Breckenkamp J, Sauzet O, Doyle I-M, Hoeller-Holtrichter C, u. a. Socioeconomic and migration status as predictors of emergency caesarean section: a birth cohort study. BMC Pregnancy Childbirth. 13. Januar 2020;20.

26. Lurie S, Ribenzaft S, Boaz M, Golan A, Sadan O. The effect of cigarette smoking during pregnancy on mode of delivery in uncomplicated term singleton pregnancies. J Matern Fetal Neonatal Med. Mai 2014;27(8):812–5.

27. Ino T. Maternal smoking during pregnancy and offspring obesity: Meta-analysis. Pediatrics International. 2010;52(1):94–9.

28. Hansen S, Halldorsson TI, Olsen SF, Rytter D, Bech BH, Granström C, u. a. Birth by cesarean section in relation to adult offspring overweight and biomarkers of cardiometabolic risk. International Journal of Obesity. Januar 2018;42(1):15–9.

29. Bernardi JR, Pinheiro TV, Mueller NT, Goldani HAS, Gutierrez MRP, Bettiol H, u. a. Cesarean delivery and metabolic risk factors in young adults: a Brazilian birth cohort study. Am J Clin Nutr. August 2015;102(2):295–301.

30. Barros AJD, Santos LP, Wehrmeister F, Motta JV dos S, Matijasevich A, Santos IS, u. a. Caesarean section and adiposity at 6, 18 and 30 years of age: results from three Pelotas (Brazil) birth cohorts. BMC Public Health. 14. März 2017;17.

31. Vogel JP, Betrán AP, Vindevoghel N, Souza JP, Torloni MR, Zhang J, u. a. Use of the Robson classification to assess caesarean section trends in 21 countries: a secondary analysis of two WHO multicountry surveys. The Lancet Global Health. 1. Mai 2015;3(5):e260–70.

32. Jaacks LM, Vandevijvere S, Pan A, McGowan CJ, Wallace C, Imamura F, u. a. The Obesity Transition: Stages of the global epidemic. Lancet Diabetes Endocrinol. 1. März 2019;7(3):231–40.

33. Ahlqvist VH, Persson M, Magnusson C, Berglind D. Elective and nonelective cesarean section and obesity among young adult male offspring: A Swedish population-based cohort study. PLoS Med. Dezember 2019;16(12):e1002996.

34. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine. 21. Juli 2009;6(7):e1000097.

35. Puska P, Nishida C, Porter D. Obesity and overweight [Internet]. World Health Organisation; 2003 [zitiert 19. Februar 2021]. Verfügbar unter: https://www.who.int/dietphysicalactivity/media/en/gsfs_obesity.pdf

36. Shamliyan T, Kane RL, Dickinson S. A systematic review of tools used to assess the quality of observational studies that examine incidence or prevalence and risk factors for diseases. Journal of Clinical Epidemiology. 1. Oktober 2010;63(10):1061–70.

37. Guolo A, Varin C. Random-effects meta-analysis: the number of studies matters. Stat Methods Med Res. Juni 2017;26(3):1500–18.

38. Hartung J, Knapp G. On tests of the overall treatment effect in meta-analysis with normally distributed responses. Stat Med. 30. Juni 2001;20(12):1771–82.

39. Schwarzer G, Carpenter JR, Rücker G. Meta-Analysis with R [Internet]. Springer International Publishing; 2015 [zitiert 26. Februar 2021]. (Use R!). Verfügbar unter: https://www.springer.com/gp/book/9783319214153

UNI
FR

UNIVERSITÉ DE FRIBOURG
UNIVERSITÄT FREIBURG

Statement of Independent Work

I hereby declare that I have written this Master Thesis without any help from others and without the use of documents and aids other than those specified. I have mentioned all used sources and cited them correctly according to established academic citation rules.
I am aware that otherwise the Faculty of Science and Medicine, in accordance with the regulation of September 24, 2018, Art. 15, is entitled to revoke the degree awarded on the basis of this Master Thesis.

Place, date: Aarau, 15.3.2021

Signature: