



Review

# A systematic review of obstetric complications as risk factors for eating disorder and a meta-analysis of delivery method and prematurity

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HIGHLIGHTS

- ▶ The literature on obstetric complications and eating disorders is contradictory.
- ▶ Vaginal instrumental delivery and prematurity were not related to anorexia nervosa.
- ▶ Upcoming studies should pool datasets together to obtain sufficient power.

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ABSTRACT

**Objective:** The aim of this study was to systematically review the literature on obstetric factors at birth and their role as risk factors for a subsequent eating disorder (ED) and where possible to perform a meta-analysis of case-control studies of EDs and obstetric complications (OCs).

**Method:** Studies were ascertained by computer searches of electronic databases (Medline, PsycINFO, Web of Science and CINAHL), searches of reference lists and from raw data obtained upon request from the authors. A total of 14 studies were identified for the systematic review, of which 6 were eligible for the subsequent meta-analysis. Of the selected 6 studies, 5 reported on the same OCs, namely vaginal instrumental delivery and prematurity. Accordingly, meta-analyses were run on these two variables. Both analyses were conducted on anorexia nervosa (AN) patients.

**Results:** Findings from the systematic review were conflicting, with some studies reporting a significant relationship between OCs and ED diagnoses and/or ED symptomatology and others refuting it. A non-significant association of instrumental delivery [pooled odds ratio (OR) 1.06, 95%CI: 0.69, 1.65] and prematurity [pooled OR 1.17, 95%CI: 0.91, 1.52] with AN was revealed in our meta-analysis.

**Conclusion:** The current literature on OCs as risk factors for a later ED is contradictory. The range of different occurrences considered as OCs and methodological limitations hinder ultimate conclusions. Upcoming studies should pool datasets together to obtain sufficient power to assess OCs and EDs in combination.

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## 1. Introduction

The aetiology of eating disorders (EDs) appears to be due to a combination of multiple genetic and environmental factors [1,2]. While genetic factors play a major role, most risk factors are thought to be non-shared environmental risk factors [3]. Obstetric complications (OCs) are possible non-shared causes [4–6], which have been included into developmental etiological models [7,8] of EDs.

Even though there is epidemiological evidence that OCs may be implicated in the aetiology of other psychiatric conditions such as ADHD [9] and autism [10], most research in this field has been conducted on schizophrenia [11]. Currently, there are four published meta-analyses on the association between OCs and schizophrenia [11–14], which indicate that premature rupture of membranes, being born preterm, and resuscitation or incubator utilization are significantly associated with a subsequent schizophrenia diagnosis.

Numerous studies [15] have shown that OCs can translate into lasting alterations in the nervous system and the brain, which in turn can increase the risk for schizophrenia: this is what has become known as the ‘neurodevelopmental theory of schizophrenia’ [16,17]. Within the field of EDs, several researchers [8,18] have also advocated for such a neurodevelopmental model. In EDs such a model emphasizes alterations of the hypothalamic–pituitary–adrenal (HPA) axis [19,20] and appetite control [21] as well as poor stress response regulations [22] and possibly also few social interactions [23,24].

Even though, the number of studies on OCs as risk factors for EDs has recently increased in the literature, to our knowledge, no quantitative assessment has been made of the pooled data from the existing studies on OCs as risk factors for EDs. Such a synthesis might help to disentangle the mechanisms for the association between OCs and EDs.

### 1.1. Aims of the review

The aim of this systematic review was therefore to collate, summarize and perform a meta-analysis, where possible, on the literature related to OCs as risk factors for EDs. We aimed to gather more conclusive evidence regarding the size and direction of the association between OCs and EDs by [1] undertaking a systematic review on the relationship between OCs and ED diagnoses and/or ED symptomatology and by [2] assessing the strength of the association between OCs and EDs through a meta-analysis across all suitable studies. We hypothesized that there would be a significant relationship between a variety of OCs and the development of a later ED.

## 2. Materials and method

### 2.1. Literature search

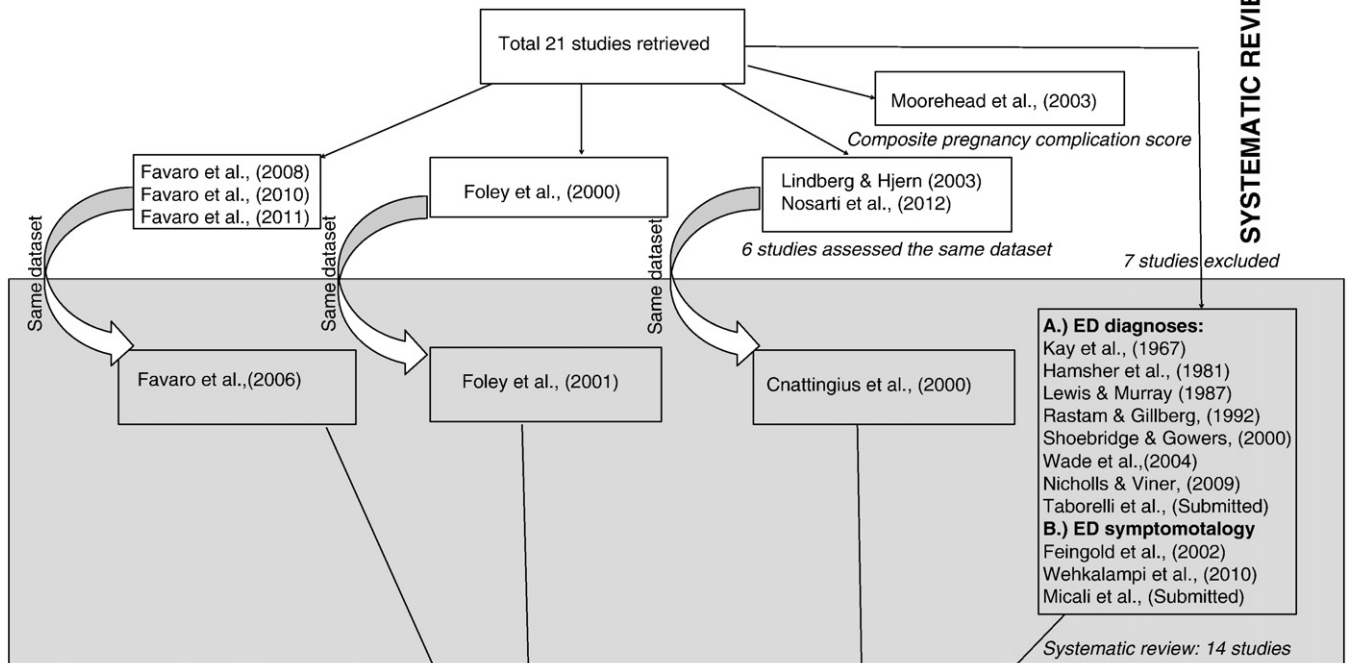
We undertook a systematic literature search by using four international databases: Medline, PsycINFO, Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, and Arts & Humanities Citation Index) and CINAHL. Two researchers (IK, ET) searched all the papers written in English, German, Spanish or Italian, which were published in peer-reviewed journals until June 2012 inclusive. The list of search terms included: “*ED, eating problems, unhealthy eating, anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), binge eating, purging, dieting, dietary restraint, dietary restrictions, weight concerns, body image, and eating attitudes*”. These were linked to search terms for OCs comprising: “*hypertensive disease and diabetes in pregnancy, previous OCs, maternal anaemia, placenta previa, pregnancy bleeding, breech delivery, induced labour, inertia uteri, premature rupture of the membrane, cephalopelvic disruption, forceps, caesarean section, vaginal instrumental delivery, vacuum extraction, cephalhaematoma, umbilical cord wrapped around the neck, placental infarction, meconium staining of the amniotic fluid, cyanosis, jaundice, respiratory and cardiac problems, need for resuscitation, need for oxygen, need for intubation, birth weight, dysmaturity, prematurity, tremors, hypothermia, hypotonia and neuromuscular disturbances*.” We combined each word from the ‘eating’ set with each word from the ‘OCs’ set separately, and all these combinations of words were used combined and not combined with the term ‘risk factor’. We also corresponded with researchers in the field and requested help in identifying draft papers or papers, which were under review. In addition, we performed manual searches of the references cited in the selected papers. Once the abstracts were read, we then obtained the copies of the relevant papers. A total of 21 papers were retrieved [4–6,25–42].

## 3. Systematic review

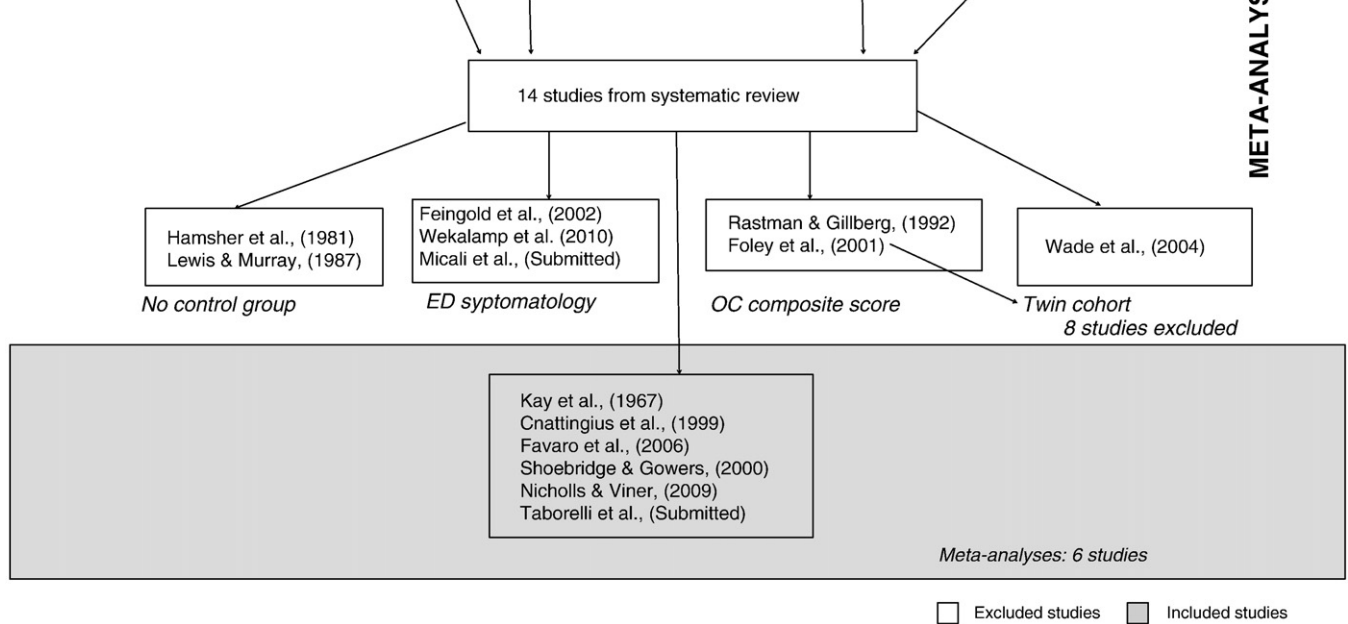
### 3.1. Selection of studies for systematic review

Of the 21 studies retrieved for the present review, four studies by Favaro and colleagues [25–28] and two studies by Foley and colleagues [5,30] assessed the same dataset though with somewhat distinct sampling frames. The same occurred for the following three studies Cnattangius and colleagues [4], Lindberg and Hjern [34] and Nosarti and colleagues [36]. Consequently, when two or more studies examined the same dataset, the study containing more information about OCs was included. In our case these studies were: Favaro and colleagues [26],

**a) Flow diagram for Systematic review**



**b) Flow diagram for Meta-Analysis**



**Fig. 1.** a: Flow diagram for systematic review. b: Flow diagram for meta-analysis.

Foley and colleagues [5] and Cnattingius and colleagues [4]. The study by Moorhead and colleagues [35] was excluded because the authors only included a composite pregnancy complication score and therefore it was impossible to determine whether this study also assessed OCs. Finally a total of 14 papers [4–6,26,29,31–33,35,37–42] were included in the systematic review. Fig. 1a shows the flow diagram of the articles included for the systematic review.

**3.2. Study characteristics**

Table 1 summarizes the 14 studies that fulfilled the inclusion criteria for this study.

The majority of identified studies used a population-based case control design with an assessment at a single time point. In addition cohorts born either preterm [29], very preterm (VPT) [42] or preterm with very low birth weight (VLBW) [51] were also included. Most studies, had a “healthy” comparison group while others included a psychiatric [5,33], a twin [5,40] or a sister [39] comparison group. A few studies did not include a control group [29,31,42].

The majority of studies [6,32,33,38,42] were retrieved from the UK, followed by the United States [5,29,31] and Sweden [4,37]. Individual studies were from Australia [40], Finland [41] and Italy [26]. Taborelli and colleagues (submitted) [39] conducted their study in four different European countries including the UK, Spain, Austria and Slovenia.

**Table 1**  
Summary of studies included in the systematic review.

Reference	Sample	ED diagnosis/ED symptomatology	Obstetric complication-source	Obstetric complication-assessment	Main findings
<i>ED diagnoses</i>					
Kay et al. [32]	- 16 AN - 8 other neurotic disorder - 8 healthy controls	-	- Semi-structured interview conducted with mothers	- OCs (forceps including breech delivery and induced labour, placenta previa) and birth weight	- OCs: AN > controls - 5 AN with OCs; 3 forceps (including 1 breech delivery and 2 with induced labour) - 1 control with placenta previa - 16 AN had one or more OCs
Hamsher et al. [31]	- 20 AN	-	- An amnesic fashion provided by parents	- Prenatal and postnatal birth complications	- 16 AN had one or more OCs
Lewis and Murray [33]	- 76 AN - 869 other psychiatric disorders	-	- Medical records (blind to diagnosis)	- Recorded notes of OC	- AN > neurotic patients
Råstam and Gillberg [37]	- 51 AN - 51 controls	- DSM-III-R	- Medical records (blind to diagnosis)	- Pre-, peri- and neonatal periods - The Gillberg and Gillberg [69] method was used for scoring	- General OC frequency: AN = controls
Cnattinguis et al. [4]	- 781 AN - 3905 controls	- ICD-9	- Medical records	- Hypertensive diseases during pregnancy, diabetes, pregnancy bleeding, inertia uteri, premature rupture of the membranes, vaginal instrumental delivery, caesarean section, multiple birth - Cephalhaematoma, other head or neck injuries or traumas, neonatal jaundice, gestational age, birth weight, and birth weight for gestational age	- Vaginal instrumental delivery and multiple births: AN > controls - Girls with a cephalhaematoma and with very preterm birth had an increased risk for AN
Shoebridge and Gowers [38]	- 40 AN - 40 controls	- DSM-III-R - Control group: EAT-40	- Structured interview conducted with mothers - Medical records (blind to diagnosis)	- Toxaemia, antepartum haemorrhage, previous OCs, gestation, forceps deliveries, caesarean sections, mean birth weight, Apgar scores	- General OC frequency: AN = controls
Foley et al. [5]	Twin cohort: - 7 AN - 71 broad AN - 42 BN - 100 broad BN - 1524 other psychiatric disorders	- Lifetime DSM-III diagnosis	- Retrospective assessment provided by parents - For some twins, birth certificates were also obtained	- Birth weight, gestational age - Composite index for prenatal and postnatal complications	- Gestational age was associated with a significantly increased risk for AN - Pregnancy complications (prenatal) were related with a significantly increased risk for AN, AN broad, BN and broad BN.
Wade et al. [40]	- 9 AN twin - 9 non-AN co-twin	- DSM-III-R	- Mailed questionnaire	Birth weight	AN twin > co-twin
Favaro et al. [26]	- 114 AN (61 AN-R and 53 AN-BP) - 73 BN - 554 controls	- DSM-IV	- Medical records (blind to diagnosis)	- Mother's information: age at birth, outcomes of previous pregnancies, pregnancy-related diseases (e.g., bleeding, preeclampsia, diabetes, threatened miscarriages and anaemia) - Infant's information: gestational age, birth weight, birth length, head circumference, delivery complications (inertia uteri, premature rupture of the membranes, breech delivery, placental infarction or abruption, placenta previa, meconium staining of the amniotic fluid, caesarean delivery, forceps, or vacuum extraction, umbilical cord	- Maternal anaemia, diabetes mellitus, preeclampsia, umbilical cord wrapped around the neck, placental infarction, neonatal cardiac problems, hypothermia, tremors, hyporeactivity, hypotonia, early cardiac problems and oxygen administration reactivity: AN > controls - Total number of OCs increased the risk for AN - Age of onset of AN was associated with increasing number of OCs - AN-R = AN-BP

				knotted or wrapped tightly around the neck, and cephalopelvic disproportion) and any neonatal complications (cyanosis, respiratory and cardiac problems, cephalhaematoma, jaundice, neuromuscular disturbances such as hyporeactivity, hypotonia and tremors, hypothermia, need for resuscitation, need for oxygen and need for intubation difficulties)	- Placental infarction, neonatal hyporeactivity and low birth weight for gestational age: were significantly related to BN - Being shorter for gestational age significantly differentiated BN from AN patients
Nicholls and Viner [6]	- 101 AN - 10 906 controls	- Self-report lifetime AN	- Medical records	- The McNeil-Sjoestroem Scale was used for the definition of OC - Birth weight, prematurity, maternal anaemia, maternal antenatal admissions, gestational diabetes, oxygen required at birth, ventilation required at birth	- Perinatal events, gestational age/birth weight: AN = controls -No dose-response relation with risk of AN - OC: AN = unaffected AN sister; BN = unaffected BN sister - Anxiety during pregnancy: AN > unaffected AN sisters
Taborelli et al. [39]	- 94 AN - 94 unaffected AN sister - 63 BN - 63 unaffected BN sisters	- Lifetime AN and BN according to DSM-IV diagnoses - A diagnostic algorithm was used following the semi-structured EATATE interview	- Retrospective questionnaire provided by the mothers	Pregnancy factors: conception problems, investigation during pregnancy, hospital admissions, bleeding, preeclampsia, infections, Birth-baby: weight, prematurity, rupture of membranes, breech, forceps, ventouse, meconium, induced caesarium, multiple	
<i>ED symptomatology</i> Feingold et al., [29]	- 53 individuals born preterm	- EDI-2 - EAT	- Medical records of OCs	- Composite variable was created by adding the number of pregnancy and perinatal complications - Gestational age, birth weight, preeclampsia	- No statistical significant association between OCs and ED symptomatology  - EDI-2 total scores: VLBW < controls - Body dissatisfaction: VLBW < controls - Drive for thinness and bulimia: VLBW = controls - Preeclampsia: unrelated to EDI total scores in VLBW ED diagnosis: - AN: 1VLBW; 5 controls (born at term) - Broad AN: 9 VLBW and 10 controls - 2 BN: 2 VLBW and 7 controls - Broad BN: 6 VLBW and 11 controls - VPT individuals: >ED psychopathology - None of the perinatal predictors investigated were predictive of ED symptomatology or bingeing behaviours. - Caesarean delivery predicted engaging in compensatory behaviours
Wehlikalampi et al. [41] <sup>a</sup>	- 163 VLBW born preterm - 189 controls born at term	- Self-report lifetime AN and BN - EDI-2 (drive for thinness, body dissatisfaction and bulimia subscales)	- Questionnaires on medical history		
Micali et al., (submitted) [42]	- 143 individuals born VPT (at <33 weeks of gestation)	- EDE-Q	- Clinical records	- Birth weight, gestational age, type of delivery (caesarean section or vaginal delivery), ventricular dilatation (on ultrasound performed at birth), neonatal complication (including any of the following: jaundice, pneumothorax, convulsions, apnoeic attacks, endotracheal mechanic ventilation, patent ductusarteriosis) and Apgar score at 5 min	

AN: anorexia nervosa; AN-R: anorexia nervosa restrictive; AN-BP: anorexia nervosa binge-purging; BN: bulimia nervosa; OCs: obstetric complications; VLBW: very low birth weight; VPT: very preterm.

<sup>a</sup> This study was included in the ED symptomatology group because it mainly assessed ED symptomatology not ED diagnoses.

The ethnicity of included participants was predominantly Caucasian [6,26,31,38]. The mean age of the participants studied ranged from [32,33,37] to 37 years [40]. Only the study by Micali and colleagues (submitted) [42] conducted separate analyses for males and females.

### 3.3. Eating disorder diagnoses and symptomatology assessment

The Diagnostic Statistical Manual (DSM) version III or IV, [43–45] was used in most instances to derive ED diagnoses such as AN and BN. Only the study by Cnattingius and colleagues [4] used the International Classification of Disease criteria (ICD) version 9 [ICD-9, [46]] to classify AN diagnosis. In the large population-based studies [e.g., 4,37] a specialist physician reliably performed the registered diagnosis of EDs. Therefore individuals assessed in these studies represent a subset of ED patients, who were ill enough to receive inpatient treatment during the timeframe studied. The older studies [32,33] did not report details on how diagnoses were made. All of the clinical studies [4–6,26,31–33,37–40] assessed AN. However, in two of these studies [26,40], the criteria for cessation of menses was not required for the diagnosis of AN. Favaro and colleagues [26,40] were the sole researchers who assessed AN restrictive and binge-purging subtypes separately. A few studies [5,26,39,41] also included BN in their analyses and two studies [5,41] examined both narrow and broad definitions of AN and BN. While most studies described people with current ED diagnoses, only a few studies [5,6,39,41] referred to a lifetime ED history.

The method of ED symptomatology assessment was not detailed in numerous studies. The few studies that provided details on ED symptomatology either employed self-report questionnaires [e.g., the EDI-2 [29,41], the EAT [29] and the EDE-Q [42]] or clinical interviews [e.g., the EATATE {designed to assess ED symptomatology and to derive ED diagnoses [39]}].

### 3.4. Obstetric complication assessment

The assessment of OCs varied noticeably across studies, with some studies [29,33,37,42] employing only birth records and others [31,32,39] relying solely on either the parental or the participants' recall [40,41]. Only a handful of studies combined different sources of information [4–6,26,38]. In a few studies [26,33,37,38] the evaluation of OCs was conducted blind to the diagnosis. Structured OC assessment, namely the McNeil–Sjostrom Scale [26,37] and/or the Gillberg and Gillberg [69] method [37] were rarely used. Finally it is important to note that several studies [5,31–33,35,37] reported a composite OC score, which made comparisons across studies impossible, since individual OC factors could not be determined.

### 3.5. Obstetric complications in anorexia nervosa

The majority of studies assessed OCs in relation to a later AN diagnosis. Older studies [31–33] simply reported the prevalence of OCs in participants, without conducting any comparisons with a control group. Therefore, it is difficult to draw any inferences from these studies. Of the remaining nine studies, about half of the studies [4,5,26,40] found a statistically significant association between OCs and AN. However, it should be noted that for a few studies (e.g., [40]) the sample size of ED individuals was too small to make meaningful comparisons.

Specific associations identified include preterm birth [4,5], birth weight [40] cephalhaematoma (mediated through forceps delivery and vacuum extraction) [4], maternal anaemia, diabetes mellitus, preeclampsia, placental infarction and wrapping of the umbilical cord around the neck, neonatal cardiac problems, hypothermia, tremors, hyporeactivity, hypotonia and demand for oxygen [26]. Prematurity was associated with AN in two studies [5,26], despite differences in the populations studied [twins were studied in the latter study [5]].

As regards to birth weight, most studies revealed no significant association with AN with the exception of one study [40], which suggested (in contrast to what would be expected) that a higher birth weight was related to AN. Most probably the sample studied (twins) and the small sample size (only 9 AN-twins and 9 healthy co-twins), might have affected the results.

Finally a more thorough investigation of the association of age of onset and OCs revealed a “dose–response” effect in Favaro and colleagues' [26] study, a finding, which was however not replicated by Nicholls and colleagues [6].

As regards to the AN subtypes no significant differences between restrictive and binge-purging subtypes could be identified in Favaro and colleagues' [26] study. Similarly, Foley and colleagues [5] found that prenatal complications predicted both threshold and broadly defined AN. However, as regards to gestational age, the same study found a significant relationship only for full AN but not broadly defined AN, suggesting that gestational age may differ as a result of the seriousness of the disorder or the diagnostic threshold.

### 3.6. Obstetric complications in bulimia nervosa

A few studies analysed OCs in BN [5,26,39]. In the study by Favaro and colleagues (2006) placental infarction, hyporeactivity, small head circumference, low birth weight, shorter birth length and small head circumference were associated with a subsequent BN. The same authors also found that BN patients had been born at a significantly shorter gestational age than AN individuals. Conversely, Foley and colleagues [5] found that unspecified OCs were related to both full and broadly defined BN. Finally, the study by Taborelli and colleagues (submitted) [39] revealed no significant associations between BN and OCs.

### 3.7. Eating disorder symptomatology in populations ascertained through prematurity and low birth weight

Only 3 studies [29,41,42] have followed-up longitudinally samples of individuals with prematurity or low birth weight and assessed their risk for subsequent ED symptomatology. While the study by Feingold and colleagues [29] revealed no significant association between individuals born preterm and later ED symptomatology, Micali and colleagues (submitted) [42] reported that individuals born VPT had higher levels of ED psychopathology (body dissatisfaction and compensatory behaviours) than individuals born at term. Conversely, the study by Wehkalampi and colleagues [41] revealed that individuals born preterm with VLBW had lower EDI-2 total scores than the control group. This study also looked at ED diagnoses, even though sample sizes were extremely small for this assessment, and found no differences between both threshold and broadly defined AN and BN individuals born preterm with VLBW and those born at term.

## 4. Meta-analysis

### 4.1. Inclusion criteria for meta-analysis

Studies were eligible for inclusion in the meta-analysis if they fulfilled the following criteria: a.) they investigated the effect of OC on ED and a healthy comparison group; b.) the presentation of OC data, allowed for comparisons between studies. Papers were excluded, if they: a.) did not report data on a healthy control group; b.) did not assess OCs in relation to ED diagnoses; c.) the OC data was presented as a composite score; and d.) employed a twin study design, because twins have higher rates of perinatal mortality, prematurity and low birth weight [47]. The criteria for excluded and included articles were checked by the other reviewer (IK or ET, respectively) and a third reviewer (NM). After retrieving the studies for the meta-analysis, all the

necessary data were taken from each paper for both the ED and control groups.

#### 4.2. Selection of studies for meta-analysis

Out of the 14 studies included in the systematic review, only a total of 6 papers [4,6,26,32,38,39] fulfilled all the previously specified inclusion criteria and were entered in the meta-analysis. Two studies [31,33] had to be excluded because they did not include a comparison group. A further three studies [29,41,42] were not included because their main focus was on ED symptomatology and not on ED diagnoses. Two studies [5,37] were excluded because they included a composite OC score. Finally, two studies [5,40] had to be excluded because they assessed a twin cohort. Fig. 1b shows the flow diagram of the articles included for the meta-analysis.

#### 4.3. Quantitative data synthesis for meta-analysis

Meta-analyses were performed in Stata 11 [48], by using the user-contributed commands *metan* [49], *metainf* [50] and *metabias* [51]. The *metan* command was used to calculate odds ratios (OR) and corresponding standard errors for each study, by using the number of participants in the ED group with and without OCs, and the number of healthy controls with and without OCs. An OR greater than 1 corresponds to the occurrence of the OC being associated with an increased risk of EDs.

These ORs were then pooled by using a random effects model through the *metan* command. A random effects model assumes that each study estimates a different effect size, but that each of these is drawn from a common distribution. This means that along with a random sampling error, differences will also be due to differences in the study population and study designs (between-study heterogeneity). Although random effects models are more conservative, and result in wider confidence intervals, they are generally regarded as more realistic due to the variety of case loads and study settings [52]. Cochran's *Q* test for homogeneity was used to evaluate the assumption of the homogeneity of effect sizes. However, since this test lacks power with small sample sizes,  $I^2$  ( $(Q - df)/Q$ ) was also calculated. This statistic is a sample size independent and measures inconsistency of effect sizes [53]. The sensitivity of the pooled effect estimate was examined by using the *metainf* command, which recalculates the pooled effect, excluding one study at a time. The pooled estimate from a meta-analysis will vary depending on the studies included in

the analysis. With a small number of studies the resulting effect size can be unstable, and there may be little power to detect an effect.

Studies with a non-significant or negative result are less likely to be published, and as a result may be underrepresented in the analysis, leading to an overestimation of the treatment effect. The presence of a publication bias was assessed through the visual inspection of funnel plots and formal statistical testing by using Begg's adjusted rank test [54], implemented in *metabias*. A funnel plot is a plot of the sample size (or an expression of sampling uncertainty such as standard error) against the effect size of each study (Fig. 2). These plots can also be used to look for evidence of 'poor trial quality bias', which causes exaggerated effect sizes. In this analysis, evidence for this type of bias will be shown if low precision studies tend to show the largest ORs.

#### 4.4. Results of meta-analysis

A total of 6 studies [4,6,26,32,38,39], all looking at OCs as risk factors for AN, were eligible for our meta-analysis. A meta-analysis of studies examining BN was not possible due to the insufficient number of studies assessing this ED diagnosis. Table 2 outlines all the OC variables for the 6 AN studies where at least two or more studies reported on the same OC. Where possible, the ORs and confidence intervals (CIs) were extracted from the papers; otherwise, these were calculated from the data reported in the paper. The majority of effect sizes for the relationship between obstetric risk factors and AN are non-significant at the 5% level, with very wide CIs. In some instances, the ORs reported are unrealistically large, however the sample sizes of these studies, as well as the frequency of OCs, are generally very small. This will affect the reliability of the measured effect size.

Of the selected 6 studies, 5 reported on the same OCs, namely vaginal instrumental delivery [4,26,32,38,39] and prematurity [4,6,26,38,39]. Accordingly, the meta-analyses were run looking only at these two variables.

##### 4.4.1. Instrumental delivery

The meta-analysis showed no evidence of an association between instrumental delivery and AN (OR 1.06, 95%CI: 0.69–1.65). This result did not change when individual studies were removed. The estimates in the different studies were not found to be substantially inconsistent ( $I^2$  27.2%).

The funnel plot in Fig. 2a is suggestive of a potential bias among the included studies. The smallest study [32] showed the biggest OR (4.41, 95% CI: 0.20–96.38). This effect size is much larger than any

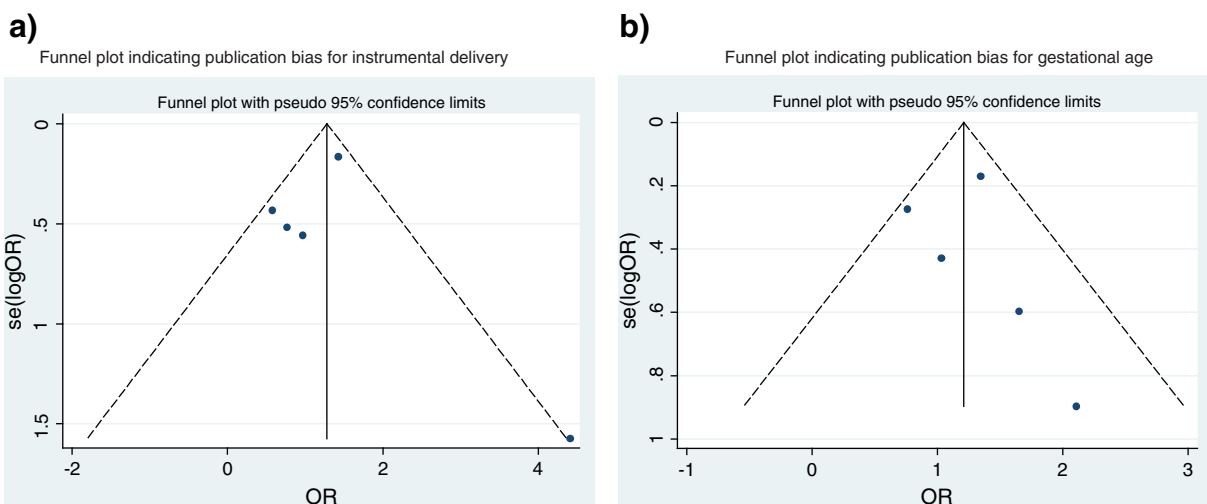


Fig. 2. a: Funnel plot indicating publication bias for instrumental delivery. b: Funnel plot indicating publication bias for gestational age.

**Table 2**  
Case control studies of the association between obstetric complications and eating disorders included in the meta-analysis.

OC	Kaye [32]		OR	95% CI	Cnattingius [4]		OR	95% CI	Shoebridge [38]		OR	95% CI	
	n (%)	AN (n=16)			Controls (n=8)	AN (n=781)			Controls (n=3905)	AN (n=40)			Controls (n=40)
<i>1.) Previous complications</i>													
Previous miscarriages	-	-	-	-	-	-	-	-	-	-	-	-	
Previous OC	-	-	-	-	-	-	-	-	5 (12.5)	1 (2.5)	5.57	0.62–50	
<i>2.) Pregnancy complications</i>													
Diabetes	-	-	-	-	1 (0.1)	18 (0.5)	0.28	0.04–2.07	-	-	-	-	
Pregnancy bleeding	-	-	-	-	24 (3.1)	90 (2.3)	1.34	0.85–2.12	5 (12.5)	2 (5)	2.71	0.49–14.9–0	
Maternal anaemia	-	-	-	-	-	-	-	-	-	-	-	-	
<i>3.) Delivery complications</i>													
Breech delivery	1 (6.25)	0	a	a	-	-	-	-	-	-	-	-	
Induced labour	2 (12.5)	0	a	a	-	-	-	-	-	-	-	-	
Premature rupture of the membrane	-	-	-	-	14 (1.8)	51 (1.3)	1.38	0.76–2.50	-	-	-	-	
Vaginal instrumental delivery	3 (18.97)	0	a	a	50 (6.4)	181 (4.6)	1.41	1.02–1.94	9 (22.5)	11 (27.5)	0.77	0.28–2.11	
Caesarean section	-	-	-	-	65 (8.3)	322 (8.2)	1.01	0.76–1.33	4 (10)	1 (2.5)	4.33	0.46–40.61	
Cephalhaematoma	-	-	-	-	19 (2.4)	41 (1.1)	2.35	1.36–4.07	-	-	-	-	
<i>4.) Abnormal foetal growth and development</i>													
Apgar score at 5 min (score <7)	-	-	-	-	15 (2)	63 (1.7)	0.22	0.13–0.39	0	0	a	a	
Jaundice	-	-	-	-	3 (0.4)	19 (0.5)	0.79	0.23–2.67	-	-	-	-	
Need for oxygen	-	-	-	-	-	-	-	-	-	-	-	-	
Birth weight (<2500 g)	-	-	-	-	52 (6.7)	166 (4.3)	1.61	1.17–2.21	-	-	-	-	
Gestational age (<37 weeks)	-	-	-	-	46 (5.9)	733 (18.8)	0.27	0.20–0.36	4 (10)	2 (5)	2.11	0.36–12.24	
OC	Favaro [26]		OR	95% CI	Taborelli (submitted) [39]		OR	95% CI	Nicholls [6]		OR	95% CI	
	n (%)	AN (n=114)			Controls (n=554)	AN (n=94)			AN sister (n=94)	n			AN
<i>1.) Previous complications</i>													
Previous miscarriages	28 (23)	106 (18)	1.38	0.85–2.21	14 (18)	14 (18)	a	a	-	-	-	-	
Previous OC	7 (6)	36 (6)	0.94	0.40–2.17	-	-	-	-	-	-	-	-	
<i>2.) Pregnancy complications</i>													
Diabetes	4 (4)	5 (1)	4.00	1.10–15.10	-	-	-	-	10,253	0	58 (1)	a	a
Pregnancy bleeding	-	-	-	-	5 (7)	6 (7.3)	1	0.30–3.4	-	-	-	-	-
Maternal anaemia	12 (11)	30 (5)	2.10	1.00–4.10	-	-	-	-	7647	11(16)	991 (13)	1.1	0.50–2.40
<i>3.) Delivery complications</i>													
Breech delivery	5 (4)	26 (5)	0.93	0.35–2.47	-	-	-	-	-	-	-	-	-
Induced labour	-	-	-	-	16 (20.9)	15 (19.8)	1.08	0.50–2.33	-	-	-	-	-
Premature rupture of the membrane	16 (14)	60 (11)	1.34	0.74–2.43	13 (16.5)	10 (13.6)	a	a	-	-	-	-	-
Vaginal instrumental delivery	4 (4)	20 (4)	0.97	0.32–2.89	10 (11)	16 (19)	0.58	0.25–1.35	-	-	-	-	-
Caesarean section	2 (2)	12 (2)	0.81	0.18–3.65	7 (8.8)	3 (3.5)	0.2	0.60–4.70	-	-	-	-	-
Cephalhaematoma	3(3)	5 (1)	a	a	-	-	-	-	-	-	-	-	-
<i>4.) Abnormal foetal growth and development</i>													
Apgar score at 5 min (score <7)	-	-	-	-	-	-	-	-	-	-	-	-	-
Jaundice	13 (11)	67 (12)	0.9	0.50–1.80	-	-	-	-	-	-	-	-	-
Need for oxygen	17 (15)	45 (8)	2.00	1.10–3.60	-	-	-	-	-	-	-	-	-
Birth weight (<2500 g)	9 (8)	38 (7)	1.20	0.60–2.50	4 (4.7)	4(4.5)	1	0.24–4.12	-	-	-	-	-
Gestational age (<37 weeks)	7 (6)	33 (6)	1.1	0.40–2.70	8 (14.8)	5 (5.3)	a	a	10,347	16 (17)	2160 (22)	0.80	0.40–1.60

OR: odds ratio; 95% CI: 95% confidence interval.

<sup>a</sup>Odds ratios not calculated as no cases in either of the two groups (cases and/or controls) or because of no convergence.



found in the other studies and is likely to be due to low prevalence of the predictor or a small sample size. Asymmetry in the plot created by a lack of smaller studies reporting a negative effect size ( $OR < 1$ ) is suggestive of a publication bias. This was not found to be significant by using Begg's adjusted rank test ( $p = 0.33$ ), although this test lacks power with small number of studies.

#### 4.4.2. Prematurity

The meta-analysis also showed a non-significant effect ( $OR$  1.17, 95%CI: 0.91–1.52) for prematurity (OC defined as  $< 37$  weeks of gestation). The robustness of this estimate was again investigated by using *metainf*. When excluding the study by Nicholls and Viner [6] from the analyses, the pooled  $OR$  became significant ( $OR$  1.35, 95% CI: 1.05–1.65). This large study reported a small, non-significant  $OR$  and reduced the pooled  $OR$  when included.

The studies were again not found to be substantially heterogeneous. An  $I^2$  of  $< 0.1\%$  was calculated from the analysis.

Fig. 2b shows the funnel plot for prematurity. Smaller, negative studies appeared to be missing, which is suggestive of a publication bias. However, Begg's adjusted rank test was non-significant and showed no evidence of a publication bias, although this is once again underpowered due to the number of studies included.

## 5. Discussion

To our knowledge, this is the first review assessing systematically the association between OCs as risk factors for EDs. Our first main finding was that our meta-analysis on instrumental delivery and prematurity showed no evidence of an effect most probably because of the low statistical power. As regards to the systematic review we found that the majority of OC factors assessed in the 14 studies yielded conflicting findings, with some studies [4,5,26,40] reporting a significant relationship between OC and ED diagnoses and/or ED symptomatology, while others were refuting it [6,37–39,41]. Although a few OCs have been reported to be associated to EDs (see Table 2), no particular OC has been consistently associated with EDs and replicated. We will first of all briefly recapture our main findings and will then elaborate on the main limitations of the studies included in the review. Finally we will provide recommendations for future studies.

### 5.1. Which OCs might be related to AN, BN and/or ED symptomatology?

Even though some perinatal risk factors for AN and BN seem to overlap, specific disparities have also been obtained in the studies reviewed. This might indicate that distinct pathways are implicated in the aetiology of these disorders or it might reflect different methodologies employed. OCs related to AN include pregnancy complications (e.g., maternal anaemia, diabetes mellitus, placental infarction), the actual delivery (cephalhaematoma, preeclampsia, and wrapping of the umbilical cord around the neck) and infant parameters/prematurity (prematurity, birth weight, neonatal cardiac problems, hypothermia, tremors, hyporeactivity, hypotonia and demand for oxygen) [4,5,26,40]. However, given the failure to replicate these findings [6] further studies are needed to clarify these inconsistencies.

As regards to BN, two studies [5,26] indicated a significant relationship between BN and a general OC composite score [5] as well as more specific OC factors such as low birth weight, small length, and small head circumference [26]. These results are suggestive of a possible association between BN and poor foetal growth which is also known to be associated with a greater risk of developing mood disorders [55,56], suicidality [57] and obesity [58]. All of these factors have been shown to be important risk and/or maintaining factors for BN [1,59–61].

### 5.2. What are the possible pathways underlying the relationship between OCs and EDs?

Even though our systematic review only partly retrieved positive findings, it might nevertheless be worth, to briefly outline the possible pathways that may underlie the relationship between OCs and EDs. Firstly, a neurodevelopmental model of EDs, which highlights biological features, such as permanent brain alterations and impairment of the HPA axis and appetite control [8,18], has been outlined as a possible mechanism. Secondly, maternal behaviours and/or physical as well as psychological health during pregnancy have commonly been associated with OCs and the development of the foetus [39,62–64]. Thirdly, an interaction between perinatal complications and a genetic susceptibility might explain the development of EDs [40]. However, it should be noted that maternal genetic risk factors, could also influence this susceptibility, which depending on the timing and severity may result in diverse thresholds for the influence of OCs [6,7,26]. Finally, epigenetic dysregulation [65] caused through stress during pregnancy, OCs and nutrition early in life might be a further factor responsible for the association between OCs and EDs.

### 5.3. What are the limitations to studying OCs as risk factors for EDs?

As can be seen from the present review, the literature assessing the relationship between OCs and EDs suffers from various important limitations, which are important to highlight. Primarily, some of the variability of the findings obtained might be attributable to the low power caused by the small sample sizes and the varying methodologies employed. Both OCs as well as EDs are low prevalence occurrences and therefore very large general population sample sizes are needed to study both manifestations in combination. In Table 3 we calculated the required sample sizes for the 6 studies included in our meta-analysis. Precisely we assumed that the prevalence of our outcome (OCs) is  $X$  and the ratio of our groups is  $N1$  (ED group)/ $N2$  (control group). We were interested to find out how many individuals we will need for  $N1$  and  $N2$  to show a difference with 90% power at an alpha of 5%. It is clearly visible from these calculations that all of the 6 studies are underpowered. We hope that these estimations might provide guidance for future researchers to ascertain larger sample sizes, which most probably will only be achievable through the pooling of different datasets.

The samples examined in the studies reviewed differed in terms of geography, cohort and period effects, as well as how the OCs and EDs were assessed. In specific there is a lack of homogeneity of the comparison groups employed, which ranged from twins, sisters, other psychiatric populations, healthy controls, to no comparison group at all. Even though the majority of studies tried to employ a population-based design, the final samples were selected to a certain extent.

It is also worth noting that various ascertainment biases might have hampered the ability of the above outlined studies to identify OC as risk factors for EDs. The retrospective OC recording employed in various studies by either structured or semi-structured interviews and/or self-report questionnaires may be subject to recall-bias. Some studies [6,41] used self-report assessment to establish ED diagnoses, which may provide less accurate diagnoses than formal interviews. For the OC assessment, a differential recall bias might exist, where the outcome of the pregnancy can influence the mother's ability to remember and accurately report OCs [66]. Only two [26,37] out of the 14 studies employed scales or scoring methods specifically designed to record OCs. The gold standard would be to use obstetric register data, but this was only provided in half of the studies. Furthermore, studies [67] from the schizophrenia literature have found that the accuracy of maternal recall varies greatly in relation to the type of pregnancy event, with major medical events such as caesarean section, breech delivery, birth weight and length of gestation being remembered more accurately than more complicated events such as placental and cord difficulties.

**Table 3**  
Required samples sizes for the case control studies included in the meta-analysis to yield 90% power at an alpha of 5%.

OC	Kaye [32]		Cnattingius [4]		Shoebriidge [38]		Favaro [26]		Taborelli (submitted) [39]		Nicholls [6]	
	AN (n = 16)	Controls (n = 8)	AN (n = 781)	Controls (n = 3905)	AN (n = 40)	Controls (n = 40)	AN (n = 114)	Controls (n = 554)	AN (n = 94)	AN sisters (n = 94)	AN	Controls
<i>1.) Previous complications</i>												
Previous miscarriages	–	–	–	–	64	21,334	691	230,332	<sup>a</sup>	<sup>a</sup>	–	–
Previous OC	–	–	–	–	–	–	<sup>a</sup>	<sup>a</sup>	–	–	–	–
<i>2.) Pregnancy complications</i>												
Diabetes	–	–	2249	749,660	–	–	255	85,000	–	–	5071	1,690,317
Pregnancy bleeding	–	–	4297	1,432,320	143	47,667	–	–	104	10,400	1454	484,662
Maternal anaemia	–	–	–	–	–	–	208	69,333	–	–	–	–
<i>3.) Delivery complications</i>												
Breech delivery	44	14,667	–	–	–	–	4714	1,571,318	–	–	–	–
Induced labour	21	7000	–	–	–	–	–	–	21,202	7,067,263	–	–
Premature rupture of the membrane	–	–	6379	2,126,313	–	–	1281	426,996	1537	512,329	–	–
Vaginal instrumental delivery	14	4667	1680	559,995	818	272,664	<sup>a</sup>	<sup>a</sup>	227	75,666	–	–
Caesarean section	–	–	797,812	2.7e + 08	904	301,331	<sup>a</sup>	<sup>a</sup>	247	82,333	–	–
Cephalhaematoma	–	–	1029	342,997	–	–	479	159,666	–	–	–	–
<i>4.) Abnormal foetal growth and development</i>												
Apgar score at 5 min (score < 7)	–	–	21,210	7,069,930	<sup>a</sup>	<sup>a</sup>	–	–	–	–	–	–
Jaundice	–	–	49,157	16,385,503	–	–	10,905	3,634,964	–	–	–	–
Need for oxygen	–	–	–	–	–	–	215	71,666	–	–	–	–
Birth weight (< 2500 g)	–	–	940	313,331	–	–	7310	2,436,643	–	–	–	–
Gestational age (< 37 weeks)	–	–	77	25,667	218	72,666	<sup>a</sup>	<sup>a</sup>	101	10,100	–	–

<sup>a</sup> Sample size could not be assessed because the proportion in both samples was the same.

In addition, it has generally been found that women with higher educational level were more precise in their recall than women with a lower educational background [67]. For medical records a pervasive methodological bias might also exist if the doctor noted OCs more accurately for the women with a family history of psychiatric disorders than the women without such a history (70). Finally, it should be noted that various studies used a composite variable for OCs, which made it impossible to assess the individual OCs in these studies. These ascertainment problems and biases might lead to the repeated, indication of elevated rates of OCs. Significant associations might also have emerged by chance [e.g., the true null hypothesis was incorrectly rejected (Type I error)] because most studies were inclined to assess all existing prenatal information without incorporating a priori hypotheses.

#### 5.4. What are the shortcomings of the present review?

There are several limitations to this review, which are worth outlining. Of the 14 papers reviewed only 6 studies reported the data needed for inclusion in the meta-analysis. A further problem was that these studies did not always report on the same OC exposures. Only with instrumental delivery and prematurity were reported in 5 studies and hence statistical analyses were only run on these OC variables. The statistical power to assess possible changes in effect size according to different study characteristics was restricted as a result of the small number of studies included in the analyses. Finally, it should be acknowledged that, because some of the OCs assessed were extremely rare and the sample sizes of the majority of studies was very small, there were occurrences of zero cell counts within the studies.

#### 5.5. What are the implications for future research?

According to previous suggestions from the schizophrenia literature [11,68], we hope that by grouping key OCs into the following four groups: 1.) pregnancy complications, 2.) labour- and 3.) delivery complications and 4.) foetal distress signs/neonatal complications and by postulating a more meticulous definition of obstetric exposures within these four groups, the quality of the data will be significantly enhanced. To some extent Tables 2 and 3 already provide a reference for such type of grouping, however, due to the sporadic reporting of different OCs across papers, it was not possible to combine these groups and calculate a composite score. Ideally, the literature on OCs and EDs should progress similarly to the one in schizophrenia by assessing primarily a rather global hypothesis (which in most instances has already been done) to a collection of more refined questions. In this sense, future studies should examine OCs in relation to family history, premorbid adjustment, age at onset of illness, gender and ethnicity among others. Upcoming research is also required to elucidate the role of OCs in augmenting the susceptibility for EDs and their interactions with other genetic and/or environmental risk factors. Multicentre collaborations among investigators are required to attain a comprehensive dataset of the raw data of case-control studies, including if possible both maternal and child risk factors related to OCs. However, since OCs are difficult to standardize and their presence is rated in diverse ways in different countries and even in different hospitals we encourage especially the study of larger homogeneous cohorts from one country or geographical region. Novel methods of examining OCs should also include animal models, which can be a valuable device to directly assess if a particular OC can cause abnormal eating behaviours and ED related behaviours as well as brain changes in rodents. Ideally, there should

be an interaction between animal modelling and human studies, with progresses in one working in synergy with the other.

## 6. Conclusions

In conclusion, while our meta-analysis showed a negative association between delivery method, prematurity and AN, the findings for our systematic review are ambiguous, with some studies showing a positive relationship between EDs and OCs and others disproving it. No specific OC has been consistently reported in the literature, which might be due to small sample sizes and differences in ED and OC assessments. In particular lack of raw data in the published articles hinders secondary data analyses. A combination of approaches and study designs evaluating larger homogeneous cohorts from the same geographical region will be necessary to disentangle these inconsistencies.

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