**Risk and protective factors for mental disorders with onset in childhood/adolescence: an umbrella review of published meta-analyses of observational longitudinal studies**

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**Abstract 170/170**

The patho-etiology of mental disorders with onset in childhood or adolescence other than autism spectrum disorder and attention-deficit/hyperactivity disorder remains largely unknown. We conducted an umbrella review of meta-analyses (MAs) on environmental factors associated with mental disorders with onset in childhood/adolescence. We searched Pubmed-MEDLINE/EMBASE/PsycInfo databases. Quality of MAs was measured with AMSTAR-2.Out of 6,851 initial references, ten articles met inclusion criteria, providing 23 associations between 12 potential environmental factors and nine disorders (cases: 8,884; N= 3,660,670). While almost half of the associations were nominally significant, none of them met criteria from either convincing or highly suggestive evidence. A single association was supported by suggestive evidence (maternal exposure to lithium and antipsychotics with neuromotor deficits), but it was affected by confounding by indication. Ten more associations had weak evidence, and 12 associations were not statistically significant. Quality of meta-analyses was rated as high in two, moderate in one, low in four, critically low in two, and not pertinent in one (individual participant data).Methodologically-sound research is needed in this field.

**Introduction**

It is commonly recognized that a large portion of mental disorders have their onset before age 18.1 However, some of them have an even earlier onset. Mental disorders with onset in childhood are grouped differently in the 10th and 11th versions of the International Classification of Diseases ((ICD)-102 and ICD-113, respectively). In ICD-10, they are classified under “V - Mental and behavioural disorders”, “F80-F89 Disorders of psychological development”, and “F90-F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence”, while in the ICD-11 they are grouped under “06 - Mental, behavioural or neurodevelopmental disorders”, “Neurodevelopmental disorders”, and “Disruptive behaviour or dissocial disorders”. Despite being defined as individual categorical entities, or even being clustered in different blocks within and across ICD-10 and ICD-11, the above listed disorders are characterised by their onset, which is typically in childhood. Importantly, in terms of clinical presentation, there is a high degree of overlap among some of these disorders, which provides a strong rationale for considering them together when exploring their putative patho-etiology.4 These childhood-onset disorders present complex and heterogeneous patho-etiology, and, although highly heritable,5–8 their aetiology is typically multifactorial (with the exception of cases with single major causes, such as patients with fetal alcohol syndrome or specific genetic syndromes). Several putative environmental risk and protective factors have been proposed and assessed in several meta-analyses, with conflicting results. Gaining insight on credible risk or protective factors for neurodevelopmental disorders is a crucial initial step to illuminate the development of preventative strategies for these disorders aimed at reducing the significant financial and societal burden related to mental disorders with onset in childhood.9,10 While two recent umbrella reviews11,12 have graded the available evidence from meta-analyses of observational studies on risk factors for autism-spectrum disorder (ASD),11 and attention-deficit/hyperactivity disorder (ADHD),12 respectively, the credibility of the claimed associations between putative risk factors for other neurodevelopmental disorders and disorders with onset in childhood remains unknown. To fill this gap in the literature, we conducted an umbrella review focused on environmental risk and protective factors for disorders with onset in childhood other than ADHD or ASD. Of note, we endeavoured to address possible methodological issues when assessing putative risk factors. Indeed, as shown in several previous umbrella reviews on risk factors for mental disorders or obesity,11,13–16 several sources of bias are present across studies, which individually or altogether can contribute to over- or underestimate the associations between socio-demographic, health, environmental, and other risk factors and disorders. Additionally, when medications are considered as potential risk factors, confounding by indication can affect several false positive claimed associations between medications and disorders’ onset.17 Therefore, the aim of this umbrella review was to grade the evidence from meta-analyses of cohort and case-control studies on protective and risk factors for the most important mental disorders with onset in childhood accounting for several sources of bias and applying established quantitative criteria.

**Methods**

This study was conducted according to state-of-the-art methods of previously published umbrella reviews. 11,18–22 The study followed an a-priori protocol uploaded in Center for Open Science (<https://osf.io/ejrfs/?view_only=41603e4db20d40538b32d542010bb79c>). The Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) were followed in conducting and reporting this umbrella review (eTable 1-2).23,24 Four investigators (MS, ED, EO, OK) performed independently the search screening, data extraction, and methodological appraisal of the included studies.

*Literature search strategy*

We systematically searched PubMed, Embase, and PsycINFO from inception to April 29th, 2020 to identify eligible meta-analyses of prospective and retrospective observational studies that assessed risk or protective factors for F80-89 Disorders of psychological development, F90-F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence according to ICD-10, or neurodevelopmental, disruptive behaviour or dissocial disorders according to ICD-11. Our search strategy used a combination of key terms available in eTable 3. The correspondence between search term and respective ICD-10/11 blocks is reported in eTable 4. No restrictions regarding language, ethnicity, or specific groups (e.g., only girls, at-risk populations, or minority samples) were applied during the search process. Hand search was also performed on the cited references of the retrieved relevant studies to identify any further eligible article. Any discrepancies during this process were resolved by consensus among investigators.

*Eligibility criteria*

We included systematic reviews with a meta-analysis that evaluated observational studies with longitudinal (prospective or retrospective, i.e., case-control or cohort studies) design reporting on environmental factors that may affect the risk of the disorders of interest, as per the ICD-10/11 definition, other than ADHD or ASD. ASD and ADHD were not considered for this umbrella review since two umbrella reviews assessing risk and protective factors have been recently published for these disorders. 11,12 Specifically, included disorders were ICD-10 disorders under “V - Mental and behavioural disorders”, specifically “F80-F89 Disorders of psychological development”, and “F90-F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence”, while in the ICD-11 disorders under “06 - Mental, behavioural or neurodevelopmental disorders”, specifically “Neurodevelopmental disorders”, and “Disruptive behaviour or dissocial disorders”. Putative factors were considered eligible, regardless of whether they increase (risk factors) or decrease (protective factors) disease incidence or whether they had an unclear association with disease onset. Individual patient data meta-analyses were included as well.

We excluded non-human studies, cross-sectional studies, genome-wide association, or polymorphism meta-analyses of disorders of interest, systematic reviews without a quantitative meta-analytic data synthesis, narrative reviews, and commentaries/letters to the editor.

When two or more meta-analyses examined the same association, we selected only the one that included the largest data set for analysis.

*Data extraction*

Extracted information included PMID/DOI of the publication, first author, year of publication, design of included studies (cohort, case-control), number of included studies in the meta-analysis, specific population under investigation (i.e., general population, primary school, secondary school, university students, hospital sample, or a sample with a specific somatic, mental, or somatic/mental comorbid condition, etc.) and the reference/comparison population (i.e. no risk factor in cohort studies, no disorder in case-control studies), tools for the definition of both population and risk/protective factor (DSM, ICD, clinical records, rating scales), specific protective or risk factor, outcome (ICD or DSM code if available, or definition of specific disorders as reported by authors given inclusion criteria were met), and its risk estimate. If an article presented separate meta-analyses on more than one reported neurodevelopmental disorder or setting, we assessed each separately. The methodological quality of each included article was assessed by couples of two investigators (MS, ED, OK, EO) using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) version 2. 25

*Data analysis*

For each association (i.e., between a specific risk factor and a specific neurodevelopmental disorder), we obtained effect sizes of individual studies reported in each meta-analysis, recalculating the pooled effect sizes and 95% confidence intervals (Cis), using random-effects models. 26 We transformed the initial effect sizes or modified the direction of associations presented by the original authors only for the associations with continuous or correlational data (e.g., Hedges g, beta coefficients) in order to present comparable estimates (i.e., equivalent Odds Ratio - eOR). 22 Between-study heterogeneity was tested with the I2 statistic.27 Moreover, 95% prediction intervals for the summary random effect sizes were computed to estimate the possible range in which the effect sizes of future studies were anticipated to fall.28 Then, we examined small-study effect bias, i.e., whether smaller studies generated larger effect sizes compared with larger studies. 11,18–22,29 We used as indicators of small-study effect when regarding a specific association both the Egger regression asymmetry test (p-value ≤ 0.10) and the random-effects summary effect size were larger than the effect size of the largest study contributing to that association .18,20,21,29 We finally evaluated the existence of excess significance bias by assessing whether the observed number of studies with nominally statistically significant results was different from the expected number of studies with statistically significant results.30,31 The expected number of statistically significant studies per association was computed by summing the statistical power estimates for each component study. The power estimates of each component study depend on the plausible effect size for the examined association, which we assumed to be the effect size of the largest study (i.e., the smallest SE) per association.31 For excess significance bias, a p-value ≤ 0.10 was considered statistically significant. 30 All analyses were conducted in Stata/ MP, version 10.0 (StataCorp LLC).

*Assessment of the credibility of evidence*

In accordance with previous umbrella reviews,14–16,32 eligible associations for neurodevelopmental disorders were classified into five levels according to the strength of the evidence of potential environmental risk/protective factors : convincing (class I), highly suggestive (class II), suggestive (class Ⅲ), weak (class Ⅳ), and not significant (NS) (Table 1).

**Results**

*Search results*

We initially identified 6,581 possibly relevant articles, screened 272 full-text articles, and eventually included ten articles in this umbrella review (Figure 1; Table 2). 33–42 Reasons for exclusion for each reference for which full text was checked are presented in eTable 5.

*Descriptive results of the included associations*

The ten eligible articles yielded 23 associations between 12 potential environmental risk factors and nine neurodevelopmental disorders/problems, including altogether 192 primary observational studies (Table 2; Table 3). Twenty associations (87%) included cohort design studies, two (9%) included both cohort and case-control design studies, and one (4%) used case-control designs (Table 2). Six (26%) of 23 associations were associations between risk/protective factors and conduct problems. Additionally, other associations focused on risk factors for psychological development (n=4), intellectual disability (n=3), neuromotor deficits (n=2). The remaining eight associations examined various mental disorders (Table 2). All eligible associations used summary-level data from published meta-analyses, with the exception of one with access to individual participant data level. 42 No protective factors were found.

The median of the total population was 14,592 participants per association (inter-quartile range [IQR]= 1,263 to 65,301, range 251 to 2,951,197), and the median number of studies per association was six (IQR= 4 to 9, range 2 to 26). The 23 associations involving environmental risk factors were based on data from 8,884 total neurodevelopmental disorders cases, 3,660,670 general population controls, and a median of 485 neurodevelopmental disorders cases per association (IQR= 70 to 2,081, range 67 to 6,181). The number of cases was >1,000 in two associations, while in 18 associations the number of cases was not reported (Table 3).

The majority of these associations (n=17; 74%) used categorical metrics, such as RR, OR, HR, while six associations used continuous metrics, such as beta or SMD. 33 35 36 The effect size was >2 in five associations. None of the factors were associated with a decreased risk of neurodevelopmental disorders.

*Summary of Associations*

Using the random-effects model, altogether 11 (48%) out of 23 associations were significant at p<0.05, of which three (13%) were at p<10-3, and three (13%) were at p<10-6 (Table 3). Nine (39%) associations showed large heterogeneity i.e., I2 > 50%. The statistically significant associations with very large heterogeneity (i.e., I2 >75%) were related to the links of maternal smoking and alcohol exposure with conduct problems,37 maternal hypothyroxinaemia and intellectual disability, 39 and postural stability scores and dyslexia. 36

The 95% prediction interval excluded null in only five (21%) associations. Seven (30%) associations had small study effects, while only two (9%) associations had an excess of significance bias (Table 3).

*Quality assessment of included articles*

According to the AMSTAR 2 rating, quality was high in two meta-analyses, moderate in one, low in four, and critically low in two meta-analysis. Quality was low mainly because articles did not report a protocol for the systematic review and the review authors did not report the funding sources for the studies included in the review. For one meta-analysis (maternal cell phone use), it was not possible to apply AMSTAR 2 because it used individual participant data42 (Table 2 and 3).

*Convincing Evidence and highly suggestive evidence*

No association between putative risk factors and other-than-ASD/ADHD disorders with onset in childhood were deemed at convincing or highly level of evidence.

*Suggestive, Weak, and No Evidence*

Suggestive evidence was found only for one association (4%), i.e., maternal exposure to lithium/antipsychotics and neuromotor deficits (Table 3).34 Ten associations (44% ) were graded as weak evidence. These included maternal exposure to lithium/antipsychotics for six months assessments and neuromotor deficits, 34 maternal smoking exposure (including light and heavy smoking) and conduct problems, 37 maternal alcohol use exposure and conduct disorders, 37 maternal obesity and cognitive and intellectual delay or conduct disorders, 38 maternal subclinical hypothyroidism/hypothyroxinaemia and intellectual disability, 39 and finally postural stability and dyslexia. 36 For the remaining 12 associations (52%), no statistically significant evidence was found.

**Discussion**

To our knowledge, this is the first umbrella review assessing systematic reviews with meta-analysis on risk or protective factors for mental disorders with onset in childhood (other than ASD and ADHD), exclusively focusing on case-control and retrospective/prospective cohort studies. This umbrella review shows that no convincing nor highly suggestive evidence supports any risk or protective factor, that the only risk factor supported by suggestive evidence is affected by confounding by indication, and that all other reported associations are either weak, or not significant.

Results of the present umbrella review are of relevance for several reasons. First, they clearly show the current lack of high-quality research identifying risk factors for mental disorders with onset in childhood (other than in ASD and ADHD). Contrary to our results, an umbrella review of 46 eligible meta-analyses on ASD, reporting data on 67 environmental risk factors (544 212 cases, 81 708 787 individuals) and 52 biomarkers (15 614 cases, 15 433 controls), identified several convincing risk factors, namely maternal age of ≥35 years (relative risk=1·31), maternal chronic hypertension (odds ratio [OR]=1.48), maternal gestational hypertension (OR=1.37), maternal overweight before or during pregnancy (RR=1.28), pre-eclampsia (RR=1.32), pre-pregnancy maternal antidepressant use (RR=1.48), and maternal selective serotonin reuptake inhibitor use during pregnancy (OR=1.84).11 Similarly, an umbrella review of 63 meta-analyses on ADHD, reporting data on 40 environmental risk/protective factors and 23 peripheral biomarkers, identified several risk factors supported by convincing evidence, namely maternal pre-pregnancy obesity (OR=1.63), childhood eczema (OR=1.31), maternal hypertensive disorders during pregnancy (OR=1.29), maternal preeclampsia (OR=1.28), and maternal acetaminophen exposure during pregnancy (RR=1.25), and highly suggestive risk factors (class II) for maternal smoking during pregnancy (OR=1.60), childhood asthma (OR=1.51), maternal pre-pregnancy overweight (OR=1.28), and serum vitamin D levels (WMD=−6.93).12

The highest level of evidence (suggestive) is available for exposure to antipsychotics/lithium during pregnancy and neuromotor deficits. However, as already shown in a previous large-scale meta-analysis,43 the claimed detrimental effects on offspring of exposure to lithium during pregnancy is inflated by confounding by indication bias. In general, when comparing the health outcomes of a medication, the two compared groups should be matched by underlying conditions; without matching, then the measured association might be between underlying disease (rather than between the medication) and outcome.17

Of note, no current systematic review/meta-analysis assessed the role of vaccines as a potential risk factor for mental disorders with onset in childhood, which is still highly debated and controversial in the lay public. This finding is in line with the lack of empirical evidence supporting the role of vaccine in contributing to increased rates of autism. However, despite this evidence, concerns on autism as a consequence of vaccines have led to a decline in childhood-immunization, with an unfortunate increase in the rates of preventable infectious diseases.44

Also, as seven out of ten studies were published in or after 2018 and given the limited number of included studies (ten) we could not conduct any type of cumulative analysis to assess to which extent the type of risk factors investigated in the reported studies changed over the years. This is an aspect that future evidence synthesis in the next decade should consider. We would expect that the implementation of state-of-the-art technologies will facilitate the inclusion, in studies, of risk factors related to biochemical compounds (e.g., pesticides or other biological measures) in addition to risk factors that can be assessed via history taking (e.g, preterm birth).

Among other factors, future research on risk factors for mental disorders with childhood-onset might focus on those risk factors that have proved to be associated with ASD/ADHD as summarized above. From a clinical perspective, should these relevant risk factors for ASD/ADHD be replicated across additional childhood disorders, trans-diagnostic interventions might be needed and possible, maximizing ecological sustainability (as opposed to specific interventions in subjects with high prevalence risk factors for low prevalence disorders).45 Such potential preventive strategies might target the physical health of women of child-bearing age who are intending to get pregnant or who pregnant. For instance, hypertension and obesity, and, even more so, overweight is currently affecting or expected to affect in the next years a large proportion of the global population.46,47 Both hypertension and obesity have a large number of recognized health outcomes, which include poor functioning and quality of life and work performance, cardiovascular mortality, and ultimately death,48 but also seem to adversely affect mental health outcomes of offspring.

Future research should also focus on the interaction between environmental and genetic factors and the role of epigenetics.49 Indeed, given the strong multifactorial nature of the neurodevelopmental disorders assessed in the present umbrella review, it is perhaps not surprising that none of the association specifically focusing on individual factors was deemed as convincing. Further evidence synthesis projects should investigate the role of epigenetics.

Furthermore, whilst the identification of risk factors is informative for policy makers, the detection of relevant protective factors may inform primary and secondary prevention and treatment strategies in the general population and in clinical settings.50 However, none among the included meta-analyses focused on protective factors specifically, potentially suggesting a lack of knowledge of what protective factors are, what mechanisms they might exert their putative protective action through, and calling for joint efforts towards preventive interventions.

Of note, whilst the majority of factors assessed in the identified studies were biological in nature, few psychosocial or systemic risk and protective factors have been investigated. Given that the formulation of mental health conditions should include a multisystemic approach beyond individual biological factors related to the child, this areas should be a priority for the field.51

The present work has several limitations. First, it does not consider biomarkers, and cross-sectional studies. While cross-sectional studies might be of limited value when investigating causality, they can have diagnostic and ecological validity informing clinical screening and diagnostic practice, in particular when focusing on biomarkers. However, since the focus of the present umbrella review was on risk/protective factors, a longitudinal study design was deemed a mandatory inclusion criterion. Second, compared to credibility of evidence for other disorders, very few meta-analyses (nine) and associations (21) were found, suggesting that neurodevelopmental disorders other than ASD and ADHD are largely understudied. Such limitation is due to available literature, providing an impetus for the field to fill this apparent gap. Third, it focuses on published evidence only.

In conclusion, the present work shows that according to quantitative criteria applied to a body of evidence on a population as large as 3,660,670 individuals, among all mental disorders with onset during childhood/adolescence other than ASD and ADHD no risk factor is supported by convincing evidence nor by highly suggestive evidence. One risk factor had suggestive evidence, but confounding by indication could not be ruled out. Results strongly indicate the need for further, well-designed cohort studies to identify convincing risk factors for neurodevelopmental disorders in order to identify subjects at risk and implement prevention strategies. Furthermore, knowledge about protective factors is urgently need needed in order to allow for the development and implementation of primary and/or secondary prevention.

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**Conflict of interest**

MS, ED, EO, FCS, PM, LM, JR, SC have no conflict of interest to declare.

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**Table 1** Criteria for evaluation of the credibility of the evidence of observational studies

|  |  |
| --- | --- |
| **Classification** | **Criteria** |
| Convincing evidence (Class I) | 1. More than 1000 cases 2. Significant summary associations (p<1x10-6) per random-effects calculations 3. No evidence of small-study effects 4. No evidence of excess of significance bias 5. Prediction intervals not including the null value 6. Largest study nominally significant (p<0.05) 7. No large heterogeneity (i.e., *I2*< 50%) |
| Highly Suggestive evidence (Class II) | 1. More than 1000 cases 2. Significant summary associations (p<1x10-6) per random-effects calculation 3. Largest study nominally significant (p<0.05) |
| Suggestive Evidence (Class III) | 1. More than 1000 cases 2. Significant summary associations (p<1x10-3) per random-effects calculations |
| Weak evidence (Class IV) | 1. All other associations with p≤0.05 |
| Non-significant associations (NS) | 1. All associations with p >0.05 |

**Table 2. Characteristics of ten eligible articles**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author, year** | **No of associations** | **Potential environmental risk/protective factor** | **Neurodevelopmental disorder /problem** | **AMSTAR 2 quality** |
| Lee et al. 2018 33 | 1 | DEHP, di-(2-ethylhexyl) phthalate | Cognitive development | Low |
| Poels et al. 2018 34 | 2 | Maternal exposure to lithium and antipsychotics for all follow up assessments; Exposure to lithium and antipsychotics for 6 months assessments | Neuromotor deficits | Low |
| Radke et al. 2020 35 | 4 | Butyl benzyl phthalate (BBP);Dibutyl phthalate (DBP);Diethyl phthalate (DEP); Disobutyl phthalate (DIBP) | Mental Development | Low |
| Rochelle et al. 2006 36 | 1 | Postural stability scores in dyslexic | Dyslexia | Critically Low |
| Ruisch et al. 2018 37 | 5 | Maternal smoking exposure; Maternal smoking light dose exposure; Maternal smoking exposure heavy dose; Maternal alcohol use exposure; Maternal cannabis use | Conduct problems | Critically Low |
| Sanchez et al. 2018 38 | 2 | Maternal obesity | Cognitive and intellectual delay; Emotional/behavioural problems | Moderate |
| Thompson et al. 2018 39 | 3 | Maternal subclinical hypothyroidism; Maternal hypothyroxinaemia; Levothyroxine treatment for maternal subclinical hypothyroidism and hypothyroxinaemia | Intellectual disability; Intelligence quotient | High |
| Yew et al. 2013 40 | 1 | Specific language impairment | Conduct problems | Low |
| Zhang et al. 2019 41 | 2 | Cesarean delivery | Intellectual disability; Tic disorder | High |
| Birks 2017 42 | 2 | Cell phone use during pregnancy | Behavioral problems; Emotional problems | NR |

**Table 3.** **Potential environmental risk/protective factors of neurodevelopmental disorders**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Potential environmental risk/protective factor/ Neurodevelopmental disorder** | **Author, year** | **Number of cases / total population** | **Number of study estimates** | **Study design** | **Effect metrics** | **Random effects summary estimate (95% CI)** | **Random effects p-value** | **I2** | **95% prediction interval** | **Egger p-value** | **Large heterogeneity, small study effect or excess significance bias** | **eOR** | **AMSTAR 2 quality** |
| **Convincing (class I)** | | | | | | | | | | | | | |
| **No association supportive by convincing evidence** | | | | | | | | | | | | | |
| **Highly suggestive (class II)** | | | | | | | | | | | | | |
| **No association supported by highly suggestive evidence** | | | | | | | | | | | | | |
| **Suggestive (class III)** | | | | | | | | | | | | | |
| Maternal exposure to lithium and antipsychotics/Neuromotor deficits | Poels et al. 2018 | 2081/65301 | 6 | Cohort | RR | 1.81 (1.42 to 2.32) | 2.0x10-6 | 0% | 1.28 to 2.57 | 0.10 | Small study effect | 1.81 | Low |
| **Weak (class IV)** | | | | | | | | | | | | | |
| Maternal exposure to lithium and antipsychotics for 6 months assessments/Neuromotor deficits | Poels et al. 2018 | 70/251 | 2 | Cohort | RR | 1.63 (1.22 to 2.19) | 0.001 | 0% | NA | NA | None | 1.63 | Low |
| Maternal smoking exposure/Conduct problems | Ruisch et al. 2018 | NR/ 115292 | 25 | Cohort | OR | 2.06 (1.66 to 2.57) | 3.3x10-11 | 93% | 0.78 to 5.47 | 0.02 | Large heterogeneity; small study effect | 2.06 | Critically Low |
| Maternal smoking light dose exposure/Conduct problems | Ruisch et al. 2018 | NR/31756 | 6 | Cohort | OR | 1.40 (1.25 to 1.57) | 1.1x10-8 | 28% | 1.07 to 1.82 | 0.32 | None | 1.40 | Critically Low |
| Maternal smoking exposure heavy dose /Conduct problems | Ruisch et al. 2018 | NR/31756 | 6 | Cohort | OR | 1.78 (1.37 to 2.31) | 1.2x10-4 | 73% | 0.79 to 4.05 | 0.29 | Large heterogeneity | 1.78 | Critically Low |
| Maternal alcohol use exposure/Conduct disorders | Ruisch et al. 2018 | NR/50621 | 9 | Cohort | OR | 2.12 (1.42 to 3.15) | 2.2x10-3 | 76% | 0.62 to 1.17 | 0.03 | Large heterogeneity; small study effect | 2.12 | Critically Low |
| Obese mothers/Cognitive and intellectual delay | Sanchez et al. 2018 | NR/175458 | 24 | Cohort | OR | 1.51 (1.37 to 1.66) | 1.9x10-16 | 60% | 1.07 to 2.11 | 0.09 | Large heterogeneity; small study effect | 1.51 | Moderate |
| Obese mothers/conduct disorders | Sanchez et al. 2018 | NR/14592 | 26 | Cohort | OR | 1.42 (1.23 to 1.64) | 2.0x10-6 | 27% | 0.93 to 2.16 | 0.49 | Excess significance bias | 1.42 | Moderate |
| Maternal subclinical hypothyroidism/Intellectual disability | Thompson et al. 2018 | NR/8249 | 11 | Cohort | OR | 2.14 (1.20 to 3.83) | 0.010 | 72% | 0.33 to 14.13 | 0.10 | Large heterogeneity; small study effect | 2.14 | High |
| Maternal hypothyroxinaemia/Intellectual disability | Thompson et al. 2018 | NR/15078 | 11 | Cohort | OR | 1.64 (1.04 to 2.57) | 0.032 | 79% | 0.36 to 7.42 | 0.95 | Large heterogeneity | 1.64 | High |
| Postural stability/Dyslexia | Rochelle et al. 2006 | NR/ 739 | 9 | Case-control | SMD | 0.54 (0.22 to 0.86) | 0.001 | 79% | -0.43 to 1.50 | 0.01 | Large heterogeneity; small study effect; excess significance bias | 2.65 | Critically Low |
| **Not significant (NS)** | | | | | | | | | | | | | |
| Butyl benzyl phthalate (BBP)/ Mental Development | Radke et al. 2020 | NR/ 1376 | 6 | Cohort | beta | -0.25 (-0.83 to 0.32) | 0.39 | 24% | -1.54 to 1.04 | 0.25 | None\* | 0.89 | Low |
| Dibutyl phthalate (DBP)/ Mental Development | Radke et al. 2020 | NR/ 1551 | 7 | Cohort | beta | -0.16 (-0.67 to 0.36) | 0.55 | 17% | -1.17 to 0.86 | 0.17 | None\* | 0.46 | Low |
| Diethyl phthalate (DEP)/ Mental Development | Radke et al. 2020 | NR/ 1126 | 5 | Cohort | beta | 0.32 (-0.25 to 0.89) | 0.28 | 0% | -0.62 to 1.25 | 0.84 | None\* | 4.24 | Low |
| Disobutyl phthalate (DIBP)/ Mental Development | Radke et al. 2020 | NR/ 1125 | 5 | Cohort | beta | -0.07 (-0.59 to 0.45) | 0.79 | 0% | 0.91 to 0.77 | 0.11 | None\* | 0.64 | Low |
| Elective and emergency cesarean delivery/ Intellectual disability | Zhang et al., 2019 | 485/ 36341 | 3 | Cohort, case-control | OR | 1.82 (0.89 to 3.71) | 0.10 | 88% | 0.00 to 8412.76 | 0.82 | Large heterogeneity | 1.82 | High |
| Elective and emergency cesarean delivery/ Tic disorder | Zhang et al. 2019 | 6181/ 2951197 | 3 | Cohort, case-control | OR | 1.31 (0.98 to 1.75) | 0.07 | 75% | 0.06 to 30.70 | 0.78 | Large heterogeneity | 1.31 | High |
| Levothyroxine treatment for maternal subclinical hypothyroidism and hypothyroxinaemia/ Intelligence quotient | Thompson et al. 2018 | NR/ 1997 | 4 | Cohort | OR | 0.92 (0.76 to 1.11) | 0.39 | 0% | 0.61 to 1.40 | 0.28 | None \* | 0.92 | High |
| Maternal cannabis use/Conduct disorders | Ruisch et al. 2018 | 67/1263 | 3 | Cohort | OR | 1.29 (0.92 to 1.81) | 0.13 | 0% | 0.15 to 11.34 | 0.05 | Small study effect | 1.29 | Critical Low |
| DEHP, di-(2-ethylhexyl) phthalate/ Cognitive development | Lee et al. 2018 | NR/1625 | 8 | Cohort | beta | -0.14 (-0.69 to 0.41) | 0.62 | 0% | -0.84 to 0.55 | 0.68 | None \* | 0.49 | Low |
| Specific language impairment/ Conduct disorders | Yew et al. 2013 | NR / 351 | 3 | Cohort | RR | 2.11 (0.99 to 4.47) | 0.06 | 0% | 0.02 to 274 | 0.29 | None\* | 2.11 | Low |
| Maternal cell phone use during pregnancy/Behavioral problems | Birks et al. 2017 | NR/ 83688 | 5 | Cohort | OR | 1.24 (0.92 to 1.67) | 0.16 | 39% | 0.55 to 2.79 | 0.35 | None\* | 1.24 | NR |
| Maternal cell phone use during pregnancy/ Emotional problems | Birks et al. 2017 | NR/ 69937 | 5 | Cohort | OR | 1.03 (0.73 to 1.44) | 0.86 | 55% | 0.38 to 2.80 | 0.50 | Large heterogeneity\* | 1.03 | NR |

*Legend. \*Presence of excess significance bias could not be assessed since necessary data were not reported; AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2; beta, standardized regression coefficients; CI, confidence interval; HR, hazard ratio; NA, not available; NR, not reported; OR, odds ratio; RR, relative risk; SMD, standardized mean difference*

Studies included in quantitative synthesis   
(n = 10 articles; 23 associations)

Full-text articles excluded, with reasons  
(n =262)

Full-text articles assessed for eligibility  
(n = 272)

Records excluded  
(n = 4804)

Records screened  
(n = 5076)

Records after duplicates removed  
(n = 5076)

Additional records identified through other sources  
(n = 0)

Records identified through database searching  
(n = 6581)

**Figure 1. PRISMA 2009 Flow Diagram**