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Review article

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

The patho-etiology of mental disorders with onset in childhood or adolescence 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, last search April 29th, 2020. Quality of MAs was measured with AMSTAR-2. Out of 6851 initial references, ten articles met inclusion criteria, providing 23 associations between 12 potential environmental factors and nine disorders (cases: 8884; N = 3,660,670). While almost half of the associations were nominally significant, none of them met

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criteria from either convincing or highly suggestive evidence. A single association was supported by suggestive evidence (maternal exposure to lithium or 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.

1. Introduction

It is commonly recognized that a large portion of mental disorders have their onset before age 18 (Paus et al., 2008). 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)-10 (WHO, 2019a) and ICD-11 (WHO, 2019b), 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 (Thapar et al., 2017). These childhood-onset disorders present complex and heterogeneous patho-etiology, and, although highly heritable (Lord et al., 2018; Yousaf et al., 2020; Demontis et al., 2019; Lichtenstein et al., 2010), 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 (Arim et al., 2017; Arango et al., 2018). While two recent umbrella reviews (Kim et al., 2019, 2020) have graded the available evidence from meta-analyses of observational studies on risk factors for autism-spectrum disorder (ASD) (Kim et al., 2019), and attention-deficit/hyperactivity disorder (ADHD), Kim et al., 2020) 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, (Kim et al., 2019; Solmi et al., 2020; Köhler et al., 2018; Bortolato et al., 2017; Solmi et al., 2018a) 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 (Solmi et al., 2018b). 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.

2. Methods

This study was conducted according to state-of-the-art methods of previously published umbrella reviews (Kim et al., 2019; Dragioti et al., 2019, 2017; Bellou et al., 2017; Belbasis et al., 2015; Radua et al., 2018). 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 (eTables 1,2) (Stroup et al., 2000; Moher et al., 2009). Four investigators (MS, ED, EO, OK) performed independently the search screening, data extraction, and methodological appraisal of the included studies.

2.1. 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.

2.2. 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 (Kim et al., 2019, 2020). 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.

2.3. 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 (Shea et al. (2017)).

2.4. 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 (DerSimonian and Laird, 1986). 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) (Radua et al., 2018). Between-study heterogeneity was tested with the I^2 statistic (Higgins et al., 2003). 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 (Riley et al., 2011). Then, we examined small-study effect bias, i.e., whether smaller studies generated larger effect sizes compared with larger studies (Kim et al., 2019; Dragioti et al., 2019; Radua et al., 2018), (Dragioti et al., 2018). We used as indicators of small-study effect when regarding a specific association both the Egger regression asymmetry test (p-value $\leq$ 0.10) and the random-effects summary effect size were larger than the effect size of the largest study contributing to that association (Dragioti et al., 2019; Bellou et al., 2017; Belbasis et al., 2015; Dragioti et al., 2018). 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 (Ioannidis and Trikalinos, 2007; Ioannidis, 2013). 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 Ioannidis, 2013). For excess significance bias, a p-value $\leq$ 0.10 was considered statistically significant (Ioannidis and Trikalinos, 2007). All analyses were conducted in Stata/MP, version 10.0 (StataCorp LLC).

2.5. Assessment of the credibility of evidence

In accordance with previous umbrella reviews, (Köhler et al., 2018; Bortolato et al., 2017; Solmi et al., 2018a; Papola et al., 2019), 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).

3. Results

3.1. Search results

We initially identified 6581 possibly relevant articles, screened 272 full-text articles, and eventually included ten articles in this umbrella review (Fig. 1; Table 2) (Lee et al., 2018; Papola et al., 2019; Lee et al., 2018; Poels et al., 2018; Radke et al., 2020; Rochelle and Talcott, 2006; Ruisch et al., 2018; Sanchez et al., 2018; Thompson et al., 2018; Yew and O'Kearney, 2013; Zhang et al., 2019; Birks et al., 2017). Reasons for exclusion for each reference for which full text was checked are presented in eTable 5.

3.2. 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 (Birks et al., 2017). No protective factors were found.

The median of the total population was 14,592 participants per association (inter-quartile range [IQR] = 1263 to 65,301, range 251 to 2,951,197), and the median number of studies per association was six (IQR = 4–9, range 2–26). The 23 associations involving environmental risk factors were based on data from 8884 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 6181). The number of cases was >1000 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 (Lee et al., 2018; Radke et al., 2020;

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

Classification	Criteria
Convincing evidence (Class I)	More than 1000 cases Significant summary associations ($p<1 \times 10^{-6}$) per random-effects calculations No evidence of small-study effects No evidence of excess of significance bias Prediction intervals not including the null value Largest study nominally significant ($p < 0.05$) No large heterogeneity (i.e., $I^2< 50\%$)
Highly Suggestive evidence (Class II)	More than 1000 cases Significant summary associations ($p<1 \times 10^{-6}$) per random-effects calculation Largest study nominally significant ($p < 0.05$)
Suggestive Evidence (Class III)	More than 1000 cases Significant summary associations ($p<1 \times 10^{-3}$) per random-effects calculations
Weak evidence (Class IV)	All other associations with $p \leq 0.05$
Non-significant associations (NS)	All associations with $p > 0.05$

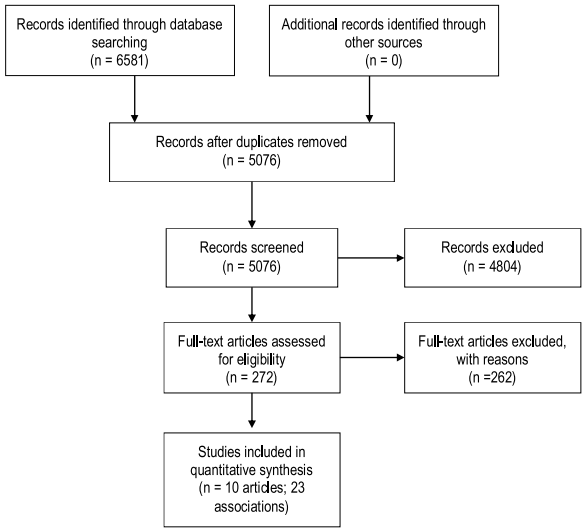

Fig. 1. PRISMA 2009 Flow Diagram.

Rochelle and Talcott, 2006). The effect size was >2 in five associations. None of the factors were associated with a decreased risk of neurodevelopmental disorders.

3.3. 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., $I^2 > 50$ %. The statistically significant associations with very large heterogeneity (i.e., $I^2 >75$ %) were related to the links of maternal smoking and alcohol exposure with conduct problems, (Ruisch et al., 2018) maternal hypothyroxinaemia and intellectual disability (Thompson et al., 2018), and postural stability scores and dyslexia (Rochelle and Talcott, 2006).

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).

3.4. 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 data (Birks et al., 2017) (Tables 2 and 3).

3.5. 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.

3.6. 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) (Poels et al., 2018). Ten associations (44 %) were graded as weak evidence. These included maternal exposure to lithium/antipsychotics for six months assessments and neuromotor deficits (Poels et al., 2018), maternal smoking exposure (including light and heavy smoking) and conduct problems (Ruisch et al., 2018), maternal alcohol use exposure and conduct disorders (Ruisch et al., 2018), maternal obesity and cognitive and intellectual delay or conduct disorders (Sanchez et al., 2018), maternal subclinical hypothyroidism/hypothyroxinaemia and intellectual disability (Thompson et al., 2018), and finally postural stability and dyslexia (Rochelle and Talcott, 2006). For the remaining 12 associations (52 %), no statistically significant evidence was found.

4. 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

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)	1	DEHP, di-(2-ethylhexyl) phthalate	Cognitive development	Low
(Poels et al., 2018)	2	Maternal exposure to lithium or antipsychotics for all follow up assessments; Exposure to lithium and antipsychotics for 6 months assessments	Neuromotor deficits	Low
(Radke et al., 2020)	4	Butyl benzyl phthalate (BBP);Dibutyl phthalate (DBP);Diethyl phthalate (DEP); Disobutyl phthalate (DIBP)	Mental Development	Low
(Rochelle and Talcott, 2006)	1	Postural stability scores in dyslexic	Dyslexia	Critically Low
(Ruisch et al., 2018)	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)	2	Maternal obesity	Cognitive and intellectual delay; Emotional/behavioural problems	Moderate
(Thompson et al., 2018)	3	Maternal subclinical hypothyroidism; Maternal hypothyroxinaemia; Levothyroxine treatment for maternal subclinical hypothyroidism and hypothyroxinaemia	Intellectual disability; Intelligence quotient	High
(Yew and O'Kearney, 2013)	1	Specific language impairment	Conduct problems	Low
(Zhang et al., 2019)	2	Cesarean delivery	Intellectual disability; Tic disorder	High
(Birks et al., 2017)	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	I (WHO, 2019a)	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 or antipsychotics/Neuromotor deficits	Poels et al. 2018	2081/65,301	6	Cohort	RR	1.81 (1.42–2.32)	2.0×10^{-6}	0%	1.28 to 2.57	0.10	Small study effect	1.81	Low
Weak (class IV)													
Maternal exposure to lithium or antipsychotics for 6 months assessments/Neuromotor deficits	Poels et al. 2018	70/251	2	Cohort	RR	1.63 (1.22–2.19)	0.001	0%	NA	NA	None	1.63	Low
Maternal smoking exposure/ Conduct problems	Ruisch et al. 2018	NR/ 115,292	25	Cohort	OR	2.06 (1.66–2.57)	3.3×10^{-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/31,756	6	Cohort	OR	1.40 (1.25–1.57)	1.1×10^{-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/31,756	6	Cohort	OR	1.78 (1.37–2.31)	1.2×10^{-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/50,621	9	Cohort	OR	2.12 (1.42–3.15)	2.2 × 10−3	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/175,458	24	Cohort	OR	1.51 (1.37–1.66)	1.9×10^{-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/14,592	26	Cohort	OR	1.42 (1.23–1.64)	2.0×10^{-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 (1.20–3.83)	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/15,078	11	Cohort	OR	1.64 (1.04–2.57)	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/ 36,341	3	Cohort, case-control	OR	1.82 (0.89–3.71)	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/ 2,951,197	3	Cohort, case-control	OR	1.31 (0.98–1.75)	0.07	75 %	0.06 to 30.70	0.78	Large heterogeneity	1.31	High
Levothyroxine treatment for maternal subclinical	Thompson et al. 2018	NR/ 1997	4	Cohort	OR	0.92 (0.76–1.11)	0.39	0%	0.61 to 1.40	0.28	None *	0.92	High

(*continued on next page*)

Table 3 (*continued*)

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	I (WHO, 2019a)	95 % prediction interval	Egger p-value	Large heterogeneity, small study effect or excess significance bias	eOR	AMSTAR 2 quality
hypothyroidism and hypothyroxinaemia/ Intelligence quotient													
Maternal cannabis use/Conduct disorders	Ruisch et al. 2018	67/1263	3	Cohort	OR	1.29 (0.92–1.81)	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 (0.99–4.47)	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/ 83,688	5	Cohort	OR	1.24 (0.92–1.67)	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/ 69,937	5	Cohort	OR	1.03 (0.73–1.44)	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.

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) (Kim et al., 2019). 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) (Kim et al., 2020).

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, (Fornaro et al., 2020) 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 (Solmi et al., 2018b).

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 (Fombonne et al., 2020).

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) (Fusar-Poli et al., 2020). 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 (Ward et al., 2019; Forouzanfar et al., 2017). 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, (Afshin et al., 2017) 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 (Waye and Cheng, 2018). 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 (Fusar-Poli et al., 2019). 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 (Hoyos et al., 2020).

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.

Declaration of Competing Interest

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

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.09.002.

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