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PRENATAL AND PERINATAL RISK FACTORS FOR PSYCHOSIS: A META-ANALYSIS

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ABSTRACT

Background

Prenatal and perinatal insults are implicated in the aetiology of psychotic disorders but the consistency and magnitude of their associations with psychosis have not been updated for nearly two decades.

Methods

Independent Web of Science search (up to 20th July 2019) and data extraction according to EQUATOR/PRISMA guidelines to identify cohort and case-control studies examining the association (odds ratio, OR) between prenatal/perinatal factors and any ICD/DSM non-organic psychotic disorder with a healthy comparison group. Random-effects pairwise meta-analyses, Q statistics, I^2 index, sensitivity analyses, and assessment of study quality and publication bias were employed. The study protocol was pre-registered (PROSPERO: CRD42017079261).

Findings

152 studies relating to 98 factors were included. Significant risk factors were: maternal ages <20 (OR=1.17) and 30–34 (OR=1.05), paternal age <20 (OR=1.31) and >35 (OR=1.28), any maternal (OR=4.60) or paternal (OR=2.73) psychopathology, maternal psychosis (OR=7.61) and affective disorder (OR=2.26), ≥3 pregnancies (OR=1.30), herpes simplex 2 (OR=1.35), maternal infections not otherwise specified (NOS) (OR=1.27), suboptimal number of antenatal visits (OR=1.83), winter (OR=1.05) and winter/spring (OR=1.05) season of birth in northern hemisphere, maternal stress NOS (OR=2.40), famine (OR=1.61), any famine/nutritional deficits in pregnancy (OR=1.40), maternal hypertension (OR=1.40), hypoxia (OR=1.63), ruptured (OR=1.86) and premature rupture (OR=2.29) of membranes, polyhydramnios (OR=3.05), definite obstetric complications NOS (OR=1.83), birthweights <2000g (OR=1.84), <2500g (OR=1.53), 2500–2999g (OR=1.23), birth length <49cm (OR=1.17), small for gestational age (OR=1.40), premature birth (OR=1.35) and congenital malformations (OR=2.35). Significant protective factors were: maternal ages 20–24 (OR=0.93) and 25–29 (OR=0.92), nulliparity (OR=0.91) and birthweights 3500–3999g (OR=0.90) and >4000g (OR=0.86).

Interpretation

Numerous prenatal and perinatal factors are associated with the later onset of psychosis. The updated knowledge emerging from this study may refine our understanding of psychosis aetiopathology, enhance multivariable risk prediction and inform preventive strategies.

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INTRODUCTION

The neurodevelopmental model of psychosis[1,2] was first born into existence over 30 years ago, positing that genetic predisposition, combined with prenatal and perinatal insults, programmed the developing brain towards later psychosis[3]. The central tenet of this "two-hit" model was that the initial insult occurs *in utero*, prompting cascades of aberrant neurodevelopmental processes and alterations in neural architecture and function, leading to a trajectory of vulnerability to later insults during puberty or adolescence[4,5]. In a refinement of these early and simplistic models, the current Developmental Risk Factor Model[6,7] accounts for many epidemiological, genetic, neuroimaging and environmental factors implicated or associated with the psychosis spectrum[8].

Although the pre- and perinatal environment—and associated insults—maintained their proposed position of importance over this aetiopathological journey, their specific contribution to the emergence of psychosis has remained elusive. The earliest findings reported that periventricular bleeding and ischemic injury, hypoxia, and winter birth were more common in affected discordant twins and singletons with schizophrenia[2,9-12]. Later, as large-scale cohort studies came to fruition, it became clear that low birthweight, maternal infection during pregnancy, maternal exposure to severe stress, such as famine or genocide, and many other obstetric complications were positively associated with offspring psychosis[13-23]. A comprehensive meta-analysis of obstetric complications was last conducted in 2002[19], showing that pregnancy complications (such as bleeding, diabetes, rhesus incompatibility), abnormal foetal growth and development (low birthweight, congenital malformations) and delivery complications (such as asphyxia, emergency caesarean) were all associated with schizophrenia.

Since that time, prospective studies have established the long-term consequences of pre- and perinatal hazards on exposed infants[24,25]. These, and also umbrella reviews[26] (meta-analyses of meta-analyses) have revealed that numerous pre- and perinatal risk factors are associated not only with psychosis but with a range of cognitive and neurological abnormalities as well as other psychiatric and neurodevelopmental disorders[27-32]; neuroimaging studies have demonstrated that when such infants reach adulthood they show an excess of brain structural and dopaminergic abnormalities reminiscent of those found in patients with schizophrenia[25,33]. Despite this substantial and accumulating literature, no comprehensive meta-analysis of pre- and perinatal risk factors for psychosis has been published in nearly 20 years[19,22,23].

Having robust, updated, publication bias-corrected estimates of these associations would advance aetiopathological knowledge, inform multivariable individualised risk prediction

models[34,35] and facilitate identification of potentially modifiable factors that could be the target of preventive strategies. To fill this gap in knowledge, we conducted a systematic review and meta-analysis to quantify the consistency and magnitude of the associations between prenatal and perinatal risk factors and all non-organic psychotic disorders (including non-affective/schizophrenia-spectrum and affective psychoses).

METHODS

The study protocol was registered on PROSPERO (CRD42017079261) and followed EQUATOR Meta-analysis of Observational Studies in Epidemiology (MOOSE)[36] (eTable 1) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[37] guidelines (eTable 2).

Search Strategy and Selection Criteria

In a multistep literature search, we first searched the Web of Science (including MEDLINE/Pubmed) database to identify original studies examining the association between prenatal and perinatal risk factors (exposures) and psychotic disorders (outcomes), published in English from database inception to 20th July 2019 (see details in eMethods 1). Second, additional records were identified through manual searches of the reference lists of included articles.

Articles were initially screened on the basis of titles and abstracts. Full texts of potentially eligible articles were then scrutinised against these inclusion criteria: (i) observational (case-control and cohort) primary studies published in peer-review journals that examined the association between prenatal and perinatal risk or protective factors (see below) and psychotic disorders, (ii) definition of any non-organic psychotic disorder according to the ICD or the DSM, (iii) inclusion of a comparison group of non-psychotic (preferably healthy) controls, (iv) enough data available to perform the analyses (i.e. raw binary data or pre-calculated odds ratio, see below), (v) non-overlapping datasets. Exclusion criteria were: (i) reviews, meta-analyses, abstracts/conference proceedings, and study designs other than the above (i.e. cross-sectional studies), and (ii) overlapping datasets. When two articles presented overlapping datasets (i.e. analyses of the same subjects/samples) on the same factor, the article with the largest dataset, most similar risk/protective factor definition compared to other studies, or longest follow-up period was retained for that risk factor. Risk or protective factors were considered eligible if they occurred within the prenatal or perinatal period as defined by the World Health Organization; prenatal factors were those operating from the time of conception to birth; perinatal factors were those operating from 22 completed weeks (154 days) of gestation to seven completed days after birth[38]. Because distinctions between prenatal vs perinatal factors are arbitrary, we did not attempt to separate these factors in this way. Importantly, selection of factors was pragmatic with no assumption that they were pure environmental factors. Consequently, some of them (e.g. familial psychopathology) could include composite genetic, environmental effects, or their interaction.

Outcome Measures and Data Extraction

Literature search, data selection and data extraction were performed independently by at least two investigators (CD, GS, AE, AdM, UP, VR-C, MB, GC, CS, GCr, AI) and discrepancies resolved by consensus with a senior researcher (PFP). Extracted variables included: first author, publication year, study type, sample size, type of psychotic diagnosis (non-affective psychoses/schizophrenia spectrum disorders, affective psychoses; eTable 3) and diagnostic instrument (DSM or ICD and version), the risk/protective factor and measure of association (primary outcome). Our preference for the latter was the binary data needed to calculate an odds ratio (OR). When not available, we extracted reported OR or Risk Ratios (preferably unadjusted for any covariates) with 95% confidence intervals (CI), or means and standard deviations, and transformed them to OR (eMethods 2). Specifically, risk ratios were considered equivalent to OR given the low incidence of psychotic disorders. When only means and standard deviations for each group were available, we assumed a continuous probability distribution and derived the frequencies of individuals needed in each group to calculate the OR of interest (eMethods 2). No other imputations or transformations were conducted. Risk/protective factor data were initially extracted as defined in the original papers. When possible, factors were then pooled into larger categories using established definitions (e.g. World Health Organization) and through consultation with expert clinician-researchers in perinatal psychiatry (PD, MM). The factors were clustered for reporting (i.e. not meta-analytical) purposes into four descriptive categories: parental and familial factors, pregnancy factors, labour and delivery factors, and foetal growth and development factors.

Risk of Bias Assessment

Bias was assessed using a modified version of the Newcastle-Ottawa Scale for cohort and case-control studies, in line with our previous meta-analyses[29]. Studies were awarded a maximum of nine points on items related to the selection of the cohort/cases, comparability of exposed and non-exposed groups, ascertainment of exposure and outcome, and adequacy of follow-up (eMethods 3). Risk of bias scores were used only as covariate in meta-regression analyses (see below).

Statistical Analysis

For each risk/protective factor (e.g. “exposure to toxoplasma”) with data from at least 3 independent samples, we conducted a quantitative random-effects meta-analysis to summarise the results[39]. The main outcome of the meta-analysis was the pooled odds ratio (OR) of the risk/protective factor. OR greater than 1 indicated that the factor was associated with increased likelihood of psychotic disorders (risk factor), whereas OR lower than 1 indicated that the factor was associated with decreased likelihood of psychotic disorders (protective factor). We also calculated the 95% CI and the *P*-value of the OR. All risk factors

were operationalised as dichotomous exposures (present vs absent). For ordinal variables, each ordinal level was vs all other levels (i.e. no referent group). To assess between-study heterogeneity, we looked at the I^2 index[40] (I^2>50% is commonly considered to indicate serious heterogeneity), and conducted the Q test (P<.05 might indicate potential heterogeneity). To assess publication bias, we looked for asymmetry in the funnel plots, used the Duval and Tweedie's trim-and-fill[41,42] method to estimate potential unpublished studies with negative results, and conducted the Egger's test[43] (P<.05 might indicate potential publication bias). When the trim-and-fill method estimated one or more potential unpublished studies, we recalculated the OR and its 95% CI with these estimated studies. Significant risk factors did not 'survive' publication bias adjustment if the 95% CI became non-significant (i.e. included the null hypothesis, OR=1) following the trim-and-fill procedure. For those factors with serious heterogeneity and at least 10 samples, we conducted meta-regressions by risk of bias scores and study design. Sensitivity analyses of the core findings were conducted after excluding studies that ascertained exposure using retrospective recall/questionnaires (e.g. maternal recall after the outcome was known). Statistical significance was set at P<.05 (two-tailed) and analyses conducted using Comprehensive Meta-Analysis software version 3.

RESULTS

Database

Overall, 14,799 records were identified, 440 full-texts were screened and 152 were eligible for inclusion (Figure 1). The 152 included articles were published between 1977 and July 2019 (see eTable 4 for details of included studies). Study sample sizes ranged from 52 to 29,209,710 and bias (quality) assessment scores ranged from 4–9 (eTable 4). The included studies reported on 98 putative risk/protective factors for psychotic disorders (see eTable 5 for further risk factor definitions).

Meta-Analytic Results

Overall, 30 risk factors (and 4 more that we discarded due to potential publication bias) and 5 protective factors were associated with psychotic disorders (see Tables 1–4 for full meta-analytic, publication bias and heterogeneity results).

Parental & Familial Factors (Table 1)

Maternal ages <20 (OR=1.17) or 30–34 (OR=1.05) were statistically significant risk factors, while ages 20–24 (OR=0.93) and 25–29 (OR=0.92) were statistically significant protective factors. Both young and later paternal age were statistically significant risk factors: <20 years (OR=1.31) and >35 (OR=1.28). Maternal nulliparity was a statistically significant protective factor (OR=0.91), while 3 or more previous pregnancies was a statistically significant risk factor (OR=1.30). Familial psychopathology, including any maternal (OR=4.60) or paternal (OR=2.73) psychopathology, maternal psychosis (OR=7.61) and maternal affective disorder (OR=2.26) were statistically significant risk factors. We did not detect publication bias for these factors.

Pregnancy Factors (Table 2)

Exposure to infective agents, including herpes simplex (HSV) type 2 (OR=1.35), toxoplasma (OR=1.30) and maternal infections not otherwise specified (NOS) (OR=1.27) were all statistically significant risk factors. Suboptimal number of antenatal care visits (OR=1.83), winter (OR=1.05) and winter/spring season of birth in northern hemisphere (OR=1.05), maternal stress NOS (OR=2.40), famine (OR=1.61), or any famine or nutritional deficits during pregnancy (OR=1.40) were all statistically significant risk factors. Obstetric complications, including maternal hypertension (OR=1.40), hypoxia (OR=1.63), ruptured membranes (OR=1.86) and particularly premature rupture of membranes (OR=2.29), polyhydramnios (OR=3.05), obstetric complications NOS (OR=1.52), “definite” obstetric complications NOS (defined by the Lewis-Murray Scale[9,44]) (OR=1.83) and blood loss during pregnancy

(OR=1.54) were all significant risk factors. We detected potential publication bias for exposure to toxoplasma (trim-and-fill corrected OR=1.25, 95%CI 0.98–1.58), obstetric complications NOS (trim-and-fill corrected OR=1.25, 95%CI 0.97–1.62) and blood loss during pregnancy (trim-and-fill corrected OR=1.42, 95%CI 0.96–2.11).

Labour & Delivery Factors (Table 3)

Numerous labour and delivery complications were analysed, but a statistically significant risk factor association was found only for asphyxic state (OR=1.93). However, we detected potential publication bias for this factor (trim-and-fill corrected OR=1.36, 95%CI 0.90–2.07).

Foetal Growth & Development Factors (Table 4)

Lower birthweights were significant risk factors: <2000g (OR=1.84), <2500g (OR=1.53), 2500–2999g (OR=1.23), while higher birthweights were statistically significant protective factors: 3500–3999g (OR=0.90) and >4000g (OR=0.86). In addition, birth length <49cm (OR=1.17), small for gestational age (OR=1.40), premature birth (OR=1.35) and congenital malformations (OR=2.35) were all statistically significant risk factors. We did not detect publication bias for any of these factors.

Heterogeneity, Bias Assessment and Meta-Regressions

High heterogeneity (I^2>50%) was detected for several factors (see Tables 1–4), but forest plots showed that this heterogeneity was mostly due to some studies finding smaller effect sizes and other studies finding larger effect sizes in the same direction (eResults 1). The only exceptions where heterogeneity was due to studies finding opposite effect sizes were paternal age at delivery >35, maternal infections NOS, any famine/nutritional deficits, obstetric complications NOS and gestational age <37 weeks. Meta-regressions revealed that study risk of bias significantly accounted for 24% of the variance in obstetric complications NOS (better quality studies suggested a smaller OR), and 57% of the variance in winter season of birth in northern hemisphere (better quality studies suggested larger OR, eResults 2). Risk of bias scores are presented in eTable 4.

Sensitivity Analyses

Full sensitivity analyses are presented in eResults 3 and eTables 6–9. In brief, after excluding studies using retrospective recall, conclusions remained the same for 94 of the 98 original risk/protective factors, with the significance and direction of effects concordant with the main results. However, toxoplasma (OR=1.31, P=.14), maternal stress NOS (OR=2.05, P=.09) and ruptured membranes (all) (OR=1.58, P=.07) were no longer statistically significant risk factors.

There were not enough studies evaluating the need for incubator to conduct a sensitivity analysis for this factor.

DISCUSSION

This study is the first comprehensive meta-analysis of prenatal and perinatal risk factors for psychotic disorders to be conducted in nearly 20 years[19,22,23]. Overall, 152 studies were included, contributing data on a total of 98 risk/protective factors. There were 30 significant risk factors: maternal ages <20 and 30–34 years, paternal age <20 and >35 years, any maternal or paternal psychopathology, maternal psychosis and affective disorder, ≥3 pregnancies, HSV-2, maternal infections NOS, suboptimal number of antenatal care visits, winter or winter/spring season of birth in northern hemisphere, maternal stress NOS, famine, any famine/nutritional deficits in pregnancy, maternal hypertension, hypoxia, ruptured and premature rupture of membranes, polyhydramnios, definite obstetric complications NOS[9,44], birthweights <2000g, <2500g, 2500–2999g, birth length <49cm, small for gestational age, premature birth and congenital malformations. There were 5 significant protective factors: maternal ages 20–24 and 25–29, nulliparity, birthweights 3500–3999g and >4000g. These results were controlled for publication biases.

The first overarching finding of the current meta-analysis is that the significant risk factors had ORs generally below 2, which is broadly consistent with the effect sizes reported in previous meta-analyses of this topic[19,22,23] and indicates that they each modulate risk by a relatively small amount. Exceptions included any maternal or paternal psychopathology, maternal psychosis, affective disorder, maternal stress, premature rupture of membranes, polyhydramnios and congenital malformations. Protective factors were even weaker in magnitude, with the largest OR (birthweight >4000g) of only 0.86. These findings expand on the previous 2002 meta-analysis[19], which synthesised data from 8 prospective population-based studies with schizophrenia as the outcome. The current meta-analysis includes 152 papers, conferring significantly higher power and some key differences: we (a) included both cohort and case-control studies, and (b) used a broader outcome definition (all non-organic psychotic disorder) to better inform clinical practice which is focused on early intervention in psychosis[45,46] (eDiscussion).

Within parental and familial factors, both young (<20 years) and later parental (30–34 maternal; >35 paternal) age were risk factors for psychosis, while maternal ages 20–24 and 25–29 were protective factors. Recent umbrella reviews demonstrate that paternal age >35 is a significant risk factor for psychosis[27] and anxiety disorders[32], and higher paternal ages are associated with autism spectrum disorder[30]. Conversely, only one primary study showed a significant association between maternal ages 30–34 and psychosis[47], but most studies did have ORs slightly above 1. Maternal age 30–34 has also been associated with autism spectrum disorder in a recent umbrella review[30]. However, as noted in the Limitations, we

make no assumption that maternal and paternal ages—or any other two risk factors—are necessarily independent, and our ORs should be understood as the risk associated with each factor without adjusting for other variables. Relatedly, our finding that multiparity and nulliparity were risk and protective factors, respectively, should be viewed with caution, because while it is possible that the risk associated with multiparity acts, for example, through reduced allocation (share) of parental resources per offspring[48] or lower socioeconomic status[18,49], multiparity is also highly correlated with maternal and paternal age (see Limitations).

Within pregnancy-related risk factors, suboptimal/fewer number of antenatal care visits emerged as risk factor. Fewer antenatal visits by mothers of offspring who later develop psychosis (vs those who do not) may underlie the higher prevalence of obstetric events in these individuals[18,50]. However, suboptimal number of antenatal visits may be a proxy for maternal ill health/psychopathology or disadvantaged socioeconomic status, which could affect provision or attendance at antenatal clinics or make compliance with antenatal advice/health behaviours more challenging[18,50].

Obstetric complications represent some of the longest-studied and best-replicated environmental risk factors for psychosis[51], and foetal hypoxia and anoxia-related factors, where the foetal brain is deprived of oxygen, are among those most consistently implicated[52-54]. Our meta-analysis confirmed that hypoxia and some related blood supply markers, such as premature rupture of membranes and maternal hypertension during pregnancy, are significant risk factors for psychosis[19,23]. Premature rupture of membranes was the strongest risk factor in a previous individual-patient data meta-analysis of obstetric factors for psychosis[23]. Two further related risk factors, asphyxia and blood loss during pregnancy, became non-significant in our analyses after adjusting for publication bias. Both of these factors were significant (and had larger ORs) in the previous meta-analysis[19], where 3 and 6 studies were included, respectively, compared to the 9 and 13 studies included in the current meta-analysis. A further pertinent limitation, particularly for hypoxia, relates to the markedly heterogeneous risk factor definitions used across studies. However, with only 6 studies included, it was not possible to parcellate into specific (and likely more proximal) definitions. Finally, despite the relatively large number of studies that have now investigated pre-eclampsia (16 in our analyses), the results appear decidedly null, consistent with previous meta-analyses[19,23].

Although not evaluated in the previous meta-analysis[19], famine and any nutritional deficits/famine also emerged as significant risk factors. However, it should be noted that the studies contributing to the ‘any nutritional deficits’ risk factor were assessing many different

nutritional deficits, which we could not separate out due to the low number of studies. While only 3 studies contributed to the famine summary effect, these were, at least, large cohorts from geographically and ethnically disparate settings[21,55,56].

Despite the strong historic interest in maternal prenatal infections and psychosis, it is somewhat surprising that we found significant associations only for HSV-2 and maternal infections NOS. Of note, we found no indication, when assessed for any time during pregnancy nor for individual trimesters, of a significant effect of influenza. There was some evidence for toxoplasma, but adjustment for publication bias (and sensitivity analyses) rendered it non-significant. The teratogenic role of infective agents is well established[57,58] and epidemiological evidence specifically implicates maternal infection in the aetiology of schizophrenia/psychosis[59]. However, a 2016 study of more than 2 million individuals found no association between maternal infection and nonaffective psychosis in offspring[60]. The association between maternal infection and offspring psychosis also varies by infection severity and foetal sex, with males at significantly higher risk[61]. Finally, studies varied in terms of ascertainment method, with a tendency for ecological vs serological ascertainment in earlier than more recent studies, respectively[62]. These factors could well contribute to a lack of significant effects in our meta-analysis.

Further significant pregnancy-related risk factors included polyhydramnios and maternal stress, but maternal stress was no longer significant after sensitivity analyses[63-65]. The association between maternal stress and psychosis may implicate cortisol, although recent evidence found no association between maternal cortisol levels during pregnancy and offspring schizophrenia[66]. Finally, in line with previous work[27], we found a small (OR=1.05) but significant association between winter/spring season of birth in northern hemisphere and psychosis.

Within labour and delivery-related risk factors, only asphyxia showed some evidence of association but became non-significant after controlling for publication bias. Notably, emergency caesarean section and uterine atony—significant risk factors in the previous meta-analysis[19]—were not supported in the present study.

Within foetal growth and development factors, lower birthweights (<2000g, <2500g, 2500–2999g) were significant risk factors while higher birthweights (>3500g) were significant protective factors. Birthweights <2000g and <2500g were significant risk factors in our recent umbrella review[27] and in the previous meta-analysis[19]. However, the current point estimates are smaller than those previously reported[19], particularly for birthweight <2000g (OR=1.84 vs

OR=3.89), which may be due to the significantly enhanced sample size in the current analyses (14 and 25 studies for <2000g and <2500g, respectively, compared to the previous 2 and 5 studies) or our broader diagnostic outcome. Birthweight can modulate cognitive ability at age 6–8 years[67-69] and one population-based cohort study reported a significant linear trend of increasing odds ratios for psychosis with decreasing birth weights[67], a pattern reflected by the current meta-analytic results. In contrast to the previous meta-analysis[19], we found significant associations between prematurity, small birth length (<49cm) and being small for gestational age with later psychotic disorder. The processes linking foetal growth and development to psychosis risk remain undetermined, but metabolic or endocrine dysregulation, cellular stress and inflammation may be implicated[58,67,70]. For example, it has been claimed that a subset of some of the most significant genetic variants associated with schizophrenia converge on impaired placental biology and its response to cellular stress[70]. Activation of these schizophrenia genes in the placenta, particularly in male foetuses, has been associated with foetal growth restriction[70]. Separate work indicates that numerous pre- and perinatal risk factors, such as maternal infection and foetal hypoxia, may all lead to impaired foetal growth in those who later develop psychosis[71]. Finally, congenital malformations had the largest OR of all development-related risk factors, which was also identified by our recent umbrella review and the previous meta-analysis[19], with markedly similar effect sizes[27].

Implications

First, as discussed above, our results may be used as a starting point for advancing aetiopathological understanding and inform future research in this field. For example, the significance and magnitude of the risk factors that we identified could form the basis of an updated assessment scale for collecting prenatal and perinatal risk exposure information (eDiscussion). Second, the measures of association provided by this evidence synthesis could be used to develop multivariable psychosis risk prediction models[34], which integrate the loading of several factors into prognostic tools[72,73] (eDiscussion). Some risk factors identified here are not only associated with psychosis but also other psychiatric and neurodevelopmental disorders (eDiscussion)[30-32], which may suggest that some risk factors are transdiagnostic[74]. Our results can therefore provide a benchmark for comparison of the magnitude of pre- and perinatal risk factors for psychosis with other disorders. A third implication is that our results can advance preventive strategies. To date, prevention of psychosis has predominantly focused on delivering psychosocial interventions[45,75] to people with subthreshold symptoms[76] of the disorder (i.e. indicated prevention[77]). Since recent evidence suggests that these are not fully effective[78,79], preventive efforts could be expanded to the 'pre-symptomatic'[80,81] or potentially the prenatal stage[51,82-84], targeting those with specific risk factors (i.e. selective prevention[77]). For example, selective outreach campaigns

(e.g. in at-risk women, such as mothers with psychosis) could be implemented to mitigate exposure to modifiable factors, such as suboptimal antenatal care, nutritional deficits and maternal infection[46]. While it is extremely unlikely that preventing exposure to any one (or combination of) these pre- and perinatal factors in isolation will prevent the development of psychosis, it is conceivable that the simultaneous prevention of multiple environmental risk factors could together confer a significant risk reduction[51].

Limitations

First, significant heterogeneity was detected across a number of risk factors. When possible, we used meta-regression to explain it, finding that study risk of bias was a significant moderator for two factors. Second, it is extremely unlikely that individual pre- or perinatal complications are independent of each other but we make no such claim or causal assumption[17,54,85,86] (eLimitations). In addition, we could not assess risk factors stratified by potentially important factors, such as foetal sex, because most primary studies did not report data separately by such factors. Finally, exposure ascertainment may be subject to recall bias in those studies using retrospective recall after the outcome (i.e. psychosis) is known. We mitigated this limitation by conducting sensitivity analyses after removing the studies based on retrospective recall, with little change to the results.

Conclusions

We found numerous prenatal and perinatal risk factors to be associated with psychotic disorders. This knowledge advances understanding of psychosis, will facilitate multivariable risk prediction profiling and may inform future preventative strategies.

AUTHOR CONTRIBUTIONS

CD, GS, AE contributed equally as co-first authors. CD, GS, AE had full access to the data and take responsibility for its accuracy and reporting. CD takes responsibility for the accuracy of the data analysis. Concept and design: PFP, VR-C. Literature search, data selection and data extraction: CD, GS, AE, AdM, UP, VR-C, MB, GC, CS, GCr, AI. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: CD, AE, PFP. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: CD, DO, GSdP. Administrative, technical, or material support: DO. Supervision: PFP, PMG, RM, PD.

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CONFLICT OF INTEREST DISCLOSURES

PFP has received advisory consultancy fees from Lundbeck outside of this work. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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Figure 1. PRISMA Flowchart of the Study Selection Process

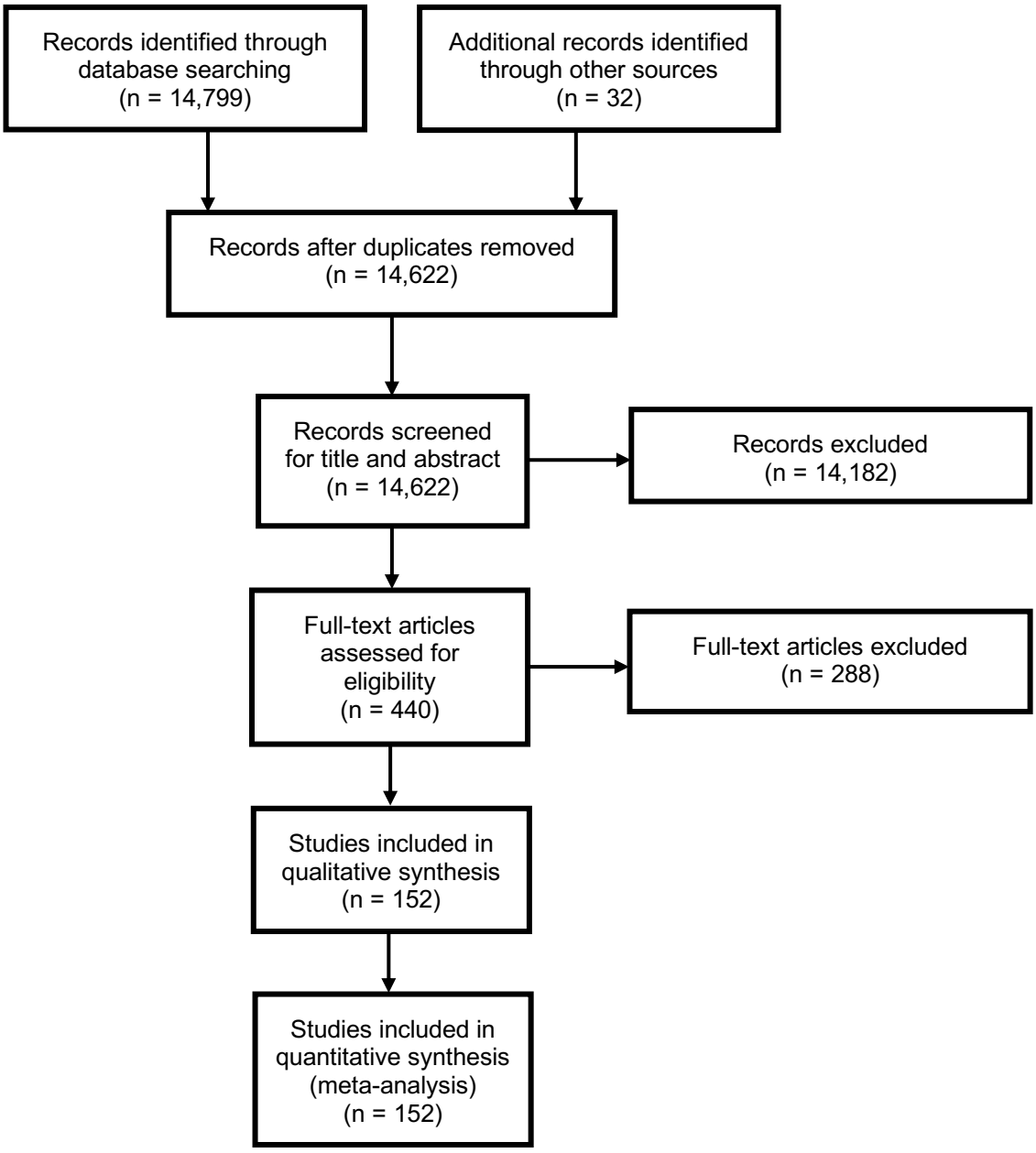

Table 1. Meta-Analytic Association between Parental and Familial Factors and Psychotic Disorders

Risk Factor	N		Odds Ratio			Heterogeneity		Publication Bias			
	Studies	Samples	Value	95% CI	*P*	I^2 (%)	*P*	Funnel Plot Asymmetry[a]	Trim & Fill imputed studies	Trim & Fill adjusted OR (95% CI)	Egger *P*
PARENTAL & FAMILIAL FACTORS											
Parental age											
Maternal age at delivery (years):											
<20	22	22	1.17	1.07 – 1.27	<.001	19	.21	No	0	NA	.81
20–24	20	20	0.93	0.89 – 0.96	<.001	0	.83	No	0	NA	.48
25–29	21	21	0.92	0.88 – 0.95	<.001	5	.40	No	0	NA	.40
30–34	20	20	1.05	1.01 – 1.09	.02	0	.83	No	0	NA	.72
35+	24	24	1.44	0.98 – 2.12	.06	99	<.001	Poss. (right)	0	NA	.51
Paternal age at delivery (years):											
<20	11	11	1.31	1.17 – 1.46	<.001	0	.74	Poss. (right)	0	NA	.45
20–24	12	12	0.97	0.91 – 1.04	.45	25	.19	No	0	NA	.54
25–29	12	12	0.96	0.83 – 1.11	.57	92	<.001	No	0	NA	.79
30–34	12	12	0.97	0.94 – 1.00	.06	0	.98	No	0	NA	.72
35+	13	13	1.28	1.06 – 1.55	.01	97	<.001	Poss. (right)	0	NA	.18
Pregnancy history											
Parity/previous pregnancies:											
0 (nulliparous)	10	10	0.91	0.85 – 0.97	.004	0	.99	Poss. (left)	1	0.91 (0.85 – 0.97)	.46
1	8	8	1.05	0.79 – 1.40	.72	81	<.001	Yes (right)	0	NA	.92
2	7	7	0.92	0.82 – 1.03	.15	0	1.00	No	0	NA	.95
3 or more	10	10	1.30	1.16 – 1.45	<.001	0	.54	Poss. (right)	0	NA	.46
First born (vs other)	8	8	0.94	0.70 – 1.26	.68	53	.04	No	0	NA	.95
Twin (or multiple) birth	5	5	0.65	0.43 – 1.00	.05	25	.26	Poss.	0	NA	.77
Familial psychopathology											
Any maternal psychopathology	9	9	4.60	2.74 – 7.73	<.001	97	<.001	Poss. (right)	0	NA	.13
Maternal psychosis	6	6	7.61	6.29 – 9.21	<.001	62	.02	Yes (right)	1	7.49 (6.23 – 9.00)	.19
Maternal affective disorder	3	3	2.26	1.09 – 4.70	.03	90	<.001	No	0	NA	.91
Any paternal psychopathology	5	5	2.73	2.33 – 3.19	<.001	27	.24	Yes (left)	3	2.56 (2.20 – 2.97)	.06

All summary effects estimated using random-effects meta-analyses. N: number of studies and samples (where studies included more than one sample/independent cohort); NA, not applicable OR, odds ratio; *P*, p value (2-tailed); Poss., possible. OR > 1 indicates risk factor and OR < 1 indicates protective factor; I^2 > 50% indicates serious heterogeneity; asymmetry in the funnel plot and imputed studies in the trim and fill indicate potential publication bias.
[a] Results of visual inspection for funnel plot asymmetry (yes, no, possible [Poss.]) and the side where studies are potentially missing (left, right).

Table 2. Meta-Analytic Association between Pregnancy Factors and Psychotic Disorders

Risk Factor	N		Odds Ratio			Heterogeneity		Publication Bias			
	Studies	Samples	Value	95% CI	*P*	I^2 (%)	*P*	Funnel Plot Asymmetry[a]	Trim & Fill imputed studies	Trim & Fill adjusted OR (95% CI)	Egger *P*
PREGNANCY FACTORS											
Maternal medical conditions/ procedures											
Maternal diabetes in pregnancy	3	3	5.13	0.83 – 31.53	.08	20	.29	Poss. (left)	0	NA	.72
Admission to hospital during pregnancy	3	5	0.97	0.66 – 1.42	.88	79	<.001	Yes (right)	0	NA	.08
Fever in pregnancy	3	3	2.18	0.85 – 5.57	.10	0	.69	Yes (left)	2	1.42 (0.67 – 3.02)	.79
Suboptimal no. antenatal care visits	4	4	1.83	1.42 – 2.36	<.001	0	.73	Poss. (right)	0	NA	.06
Infective agents											
Toxoplasma	4	4	1.30	1.04 – 1.62	.02	18	.30	Yes (left)	1	1.25 (0.98 – 1.58)	.47
Herpes simplex type 1	4	4	0.97	0.75 – 1.26	.82	0	.86	Poss. (right)	0	NA	.99
Herpes simplex type 2	5	5	1.35	1.16 – 1.58	<.001	0	.80	No	0	NA	.77
Unspecified maternal infections NOS	9	9	1.27	1.06 – 1.53	.01	50	.04	Yes (left)	1	1.26 (1.04 – 1.52)	.93
Influenza infection											
Any time during pregnancy	8	8	1.13	0.94 – 1.35	.20	52	.04	Yes (left)	3	1.03 (0.83 – 1.29)	.03
First trimester	6	6	1.36	0.79 – 2.35	.27	44	.11	Yes (left)	2	1.08 (0.58 – 2.00)	.07
Second trimester	5	5	1.04	0.92 – 1.18	.55	0	.58	Poss. (left)	1	1.03 (0.88 – 1.20)	.60
Third trimester	4	4	1.37	0.91 – 2.06	.13	0	.85	No	0	NA	.96
Cytomegalovirus	3	3	1.09	0.80 – 1.48	.60	0	.74	No	0	NA	.82
Urinary tract infection	4	6	0.99	0.68 – 1.44	.95	0	.69	Yes (left)	1	0.90 (0.64 – 1.29)	.86
Sexually transmitted infections	3	3	1.51	0.58 – 3.89	.40	58	.10	Poss. (right)	0	NA	.97
Maternal drug use during pregnancy											
Smoking	8	8	1.29	0.88 – 1.90	.19	71	<.01	Yes (left)	2	1.08 (0.69 – 1.68)	.74
Alcohol	6	6	1.76	0.71 – 4.37	.22	42	.13	Poss. (left)	1	1.50 (0.59 – 3.78)	.88
Maternal stress during pregnancy											
Death/severe illness of a close relative	3	3	0.84	0.61 – 1.17	.31	0	.45	No	0	NA	.40
Exposure to catastrophic event:											
Any time during pregnancy	5	6	1.15	0.98 – 1.36	.09	74	.002	Poss. (left)	0	NA	.30
First trimester	4	4	1.12	0.97 – 1.30	.11	17	.31	Yes (right)	0	NA	.69

Risk Factor	N		Odds Ratio			Heterogeneity		Publication Bias			
	Studies	Samples	Value	95% CI	*P*	I^2 (%)	*P*	Funnel Plot Asymmetry[a]	Trim & Fill imputed studies	Trim & Fill adjusted OR (95% CI)	Egger *P*
Second trimester	4	4	1.03	0.91 – 1.18	.64	0	.76	Yes (left)	1	1.03 (0.90 – 1.17)	.88
Third trimester	4	4	1.02	0.90 – 1.16	.79	0	.89	Yes (left)	1	1.02 (0.90 – 1.15)	.98
Maternal stress NOS	4	4	2.40	1.15 – 5.01	.02	80	.002	Poss. (left)	0	NA	.09
Famine & nutritional deficits											
Any famine/nutritional deficits	11	13	1.40	1.17 – 1.68	<.001	69	<.001	Yes (left)	1	1.38 (1.14 – 1.67)	.60
Famine	3	3	1.61	1.51 – 1.71	<.001	0	.46	Yes (left)	1	1.60 (1.50 – 1.70)	.63
Maternal anaemia	4	6	0.92	0.61 – 1.40	.71	30	.21	Yes (left)	1	0.87 (0.58 – 1.32)	.39
Maternal haemoglobin:											
<10 g/dl	3	3	1.04	0.49 – 2.23	.92	81	.005	Poss.	0	NA	.15
>12 g/dl	3	3	1.05	0.60 – 1.83	.87	75	.02	Poss.	0	NA	.29
Pregnancy complications											
Maternal hypertension	5	7	1.40	1.10 – 1.78	.006	0	.74	Yes (left)	2	1.38 (1.09 – 1.74)	.77
Pre-eclampsia/toxaemia	14	16	1.32	0.99 – 1.76	.06	26	.16	Poss. (left)	1	1.29 (0.96 – 1.72)	.62
Hypoxia (as defined by authors)	6	6	1.63	1.11 – 2.40	.01	41	.13	No	0	NA	.48
Ruptured membranes (all)	5	7	1.86	1.23 – 2.83	.003	0	.77	Yes (right)	0	NA	.11
Preterm rupture	1	3	1.20	0.58 – 2.51	.62	0	.86	No	0	NA	.74
Premature rupture	4	4	2.29	1.38 – 3.80	.001	0	.80	Yes (left)	1	2.13 (1.38 – 3.30)	.35
Polyhydramnios	3	3	3.05	1.15 – 8.06	.02	0	1.0	No	0	NA	.40
Blood loss during pregnancy	11	13	1.54	1.06 – 2.25	.02	33	.12	Poss. (left)	1	1.42 (0.96 – 2.11)	.86
Unspecified obstetric complications (NOS)	19	21	1.52	1.19 – 1.94	<.001	67	<.001	Yes (left)	5	1.25 (0.97 – 1.62)	.06
"Definite" obstetric complications NOS[b]	9	9	1.83	1.21 – 2.77	.004	71	<.001	Yes (left)	0	NA	.002
Placental complications	5	5	1.52	0.42 – 5.43	.52	60	.04	No	0	NA	.46
Rhesus-related factors/ incompatibility	9	9	1.42	1.00 – 2.01	.05	0	.44	Yes (left)	3	1.32 (0.91 – 1.91)	.15
Season of birth in northern hemisphere:											
Winter/spring	8	8	1.05	1.03 – 1.08	<.001	77	<.001	Poss. (left)	2	1.04 (1.02 – 1.07)	.72
Winter	11	11	1.05	1.03 – 1.08	<.001	55	.01	Poss. (right)	0	NA	.49

All summary effects estimated using random-effects meta-analyses. N: number of studies and samples (note that some studies included more than one sample/independent cohort); NA, not applicable OR, odds ratio; *P*, p value (2-tailed); Poss., possible. OR > 1 indicates risk factor and OR < 1 indicates protective factor; I^2 > 50% indicates serious heterogeneity; asymmetry in the funnel plot and imputed studies in the trim and fill indicate potential publication bias.

[a] Results of visual inspection for funnel plot asymmetry (yes, no, possible [Poss.]) and the side where studies are potentially missing (left, right).

[b] "Definite" obstetric complications as specified in the Lewis-Murray Obstetric Complications Scale.

Table 3. Meta-Analytic Association between Labour and Delivery Factors and Psychotic Disorders

Risk Factor	N		Odds Ratio			Heterogeneity		Publication Bias			
	Studies	Samples	Value	95% CI	*P*	I^2 (%)	*P*	Funnel Plot Asymmetry[a]	Trim & Fill imputed studies	Trim & Fill adjusted OR (95% CI)	Egger *P*
LABOUR & DELIVERY FACTORS											
Labour and delivery complications											
Caesarean section (any)	12	14	1.13	0.90 – 1.43	.30	42	.05	Yes (left)	5	1.00 (0.78 – 1.29)	.15
Caesarean section (emergency)	9	9	1.41	0.87 – 2.30	.16	39	.11	Yes (left)	4	0.98 (0.61 – 1.57)	.06
Prolonged duration of labour	11	13	1.30	0.92 – 1.83	.14	47	.04	No	0	NA	.54
Induced labour:											
Oxytocics	2	4	1.01	0.81 – 1.27	.91	0	.58	Yes (left)	1	0.96 (0.78 – 1.19)	(<).05
Artificial rupture of membranes	2	4	1.11	0.78 – 1.57	.57	61	.05	Yes (left)	1	0.99 (0.70 – 1.42)	.45
Forceps, vacuum, instrumental delivery	14	16	1.15	0.91 – 1.46	.25	40	.05	Yes (left)	6	0.98 (0.75 – 1.27)	.02
Abnormal presentation:											
Non-vertex	10	12	1.03	0.77 – 1.39	.83	12	.33	Yes (left)	3	0.89 (0.62 – 1.28)	.15
Breech	5	5	1.00	0.52 – 1.94	.99	0	.54	No	0	NA	.50
Cephalopelvic disproportion	3	5	1.07	0.58 – 1.97	.83	21	.28	Poss. (right)	0	NA	.99
Baby detained in hospital/special care	3	5	1.06	0.72 – 1.57	.76	62	.03	Poss. (right)	0	NA	.23
Nonspontaneous delivery	3	5	0.98	0.78 – 1.24	.89	0	.46	Yes (left)	1	0.95 (0.76 – 1.18)	.53
Uterine atony	3	3	2.37	0.79 – 7.12	.12	39	.20	No	0	NA	.99
Apgar score <7 at 5 mins	5	5	1.57	0.94 – 2.63	.08	0	.45	Yes (left)	2	1.35 (0.75 – 2.43)	.14
Umbilical cord complications (any)	7	7	1.13	0.93 – 1.39	.22	0	.73	Yes (left)	2	1.11 (0.91 – 1.36)	.10
Umbilical cord around neck	4	4	1.11	0.90 – 1.37	.32	0	.66	No	0	NA	.79
Abnormal foetal heart rate/rhythm	3	3	1.17	0.80 – 1.73	.42	0	.40	Yes (left)	2	0.93 (0.62 – 1.39)	.11
Asphyxic state	8	9	1.93	1.30 – 2.88	.001	43	.08	Yes (left)	5	1.36 (0.90 – 2.07)	.07
Maternal blood loss during delivery	3	3	1.12	0.27 – 4.73	.88	61	.07	No	0	NA	.47

All summary effects estimated using random-effects meta-analyses. N: number of studies and samples (note that some studies included more than one sample/independent cohort); NA, not applicable OR, odds ratio; *P*, p value (2-tailed); Poss., possible. OR > 1 indicates risk factor and OR < 1 indicates protective factor; I^2 > 50% indicates serious heterogeneity; asymmetry in the funnel plot and imputed studies in the trim and fill indicate potential publication bias.

[a] Results of visual inspection for funnel plot asymmetry (yes, no, possible [Poss.]) and the side where studies are potentially missing (left, right).

Table 4. Meta-Analytic Association between Foetal Growth and Development Factors and Psychotic Disorders

Risk Factor	N		Odds Ratio			Heterogeneity		Publication Bias			
	Studies	Samples	Value	95% CI	*P*	I^2 (%)	*P*	Funnel Plot Asymmetry[a]	Trim & Fill imputed studies	Trim & Fill adjusted OR (95% CI)	Egger *P*
FOETAL GROWTH & DEVELOPMENT											
Gestational age:											
<37 weeks (premature birth)	21	24	1.35	1.12 – 1.62	.002	58	<.001	Poss. (left)	0	NA	.37
>42 weeks	10	12	1.14	0.96 – 1.35	.13	25	.19	Yes (left)	1	1.13 (0.96 – 1.32)	.35
Neonate birth weight & size											
Birthweight:											
<2000g	13	14	1.84	1.53 – 2.22	<.001	0	.83	No	0	NA	.95
<2500g	23	25	1.53	1.31 – 1.78	<.001	25	.13	No	0	NA	.46
2500–2999g	15	17	1.23	1.15 – 1.31	<.001	0	.92	Poss. (left)	0	NA	.15
3000–3499g	15	17	1.00	0.95 – 1.05	.92	0	.99	Poss. (left)	0	NA	.62
3500–3999g	15	17	0.90	0.85 – 0.94	<.001	0	.99	No	0	NA	.99
>4000g	15	17	0.86	0.80 – 0.92	<.001	0	76	Yes (left)	2	0.85 (0.80 – 0.92)	.29
<2500g & premature	4	4	1.53	0.90 – 2.60	.12	13	.33	Poss. (right)	0	NA	.04
Low ponderal index (≤5th centile)	2	4	1.17	0.82 – 1.67	.38	6	.36	No	0	NA	.79
High ponderal index (≥95th centile)	2	4	1.13	0.80 – 1.60	.47	0	.79	Poss. (right)	0	NA	.18
Small for gestational age	10	12	1.40	1.25 – 1.57	<.001	18	.26	No	0	NA	.97
Large/heavy for gestational age	3	3	1.10	0.75 – 1.61	.62	44	.17	No	0	NA	.64
Birth length <49cm	8	8	1.17	1.05 – 1.32	.01	21	.27	Yes (left)	3	1.15 (1.03 – 1.29)	.07
Birth length >54cm	7	7	1.03	0.83 – 1.28	.77	0	.79	Yes (left)	2	1.02 (0.82 – 1.26)	.17
Head circumference <32cm	10	10	1.37	0.99 – 1.91	.06	14	.31	Yes (left)	5	1.22 (0.88 – 1.69)	.04
Neonatal Health											
Congenital malformation	4	4	2.35	1.23 – 4.46	.009	0	.82	Yes (left)	1	2.26 (1.22 – 4.18)	.80
Need for incubator	3	3	2.54	0.69 – 9.69	.16	0	.43	No	0	NA	.77

All summary effects estimated using random-effects meta-analyses. N: number of studies and samples (note that some studies included more than one sample/independent cohort); NA, not applicable OR, odds ratio; *P*, p value (2-tailed); Poss., possible. OR > 1 indicates risk factor and OR < 1 indicates protective factor; I^2 > 50% indicates serious heterogeneity; asymmetry in the funnel plot and imputed studies in the trim and fill indicate potential publication bias.

[a] Results of visual inspection for funnel plot asymmetry (yes, no, possible [Poss.]) and the side where studies are potentially missing (left, right).