What causes psychosis? An umbrella review of risk and protective factors

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Psychosis is a heterogeneous psychiatric condition for which a multitude of risk and protective factors have been suggested. This umbrella review aimed to classify the strength of evidence for the associations between each factor and psychotic disorders whilst controlling for several biases. The Web of Knowledge database was searched to identify systematic reviews and meta-analyses of observational studies which examined associations between socio-demographic, parental, perinatal, later factors or antecedents and psychotic disorders, and which included a comparison group of healthy controls, published from 1965 to January 31, 2017. The literature search and data extraction followed PRISMA and MOOSE guidelines. The association between each factor and ICD or DSM diagnoses of non-organic psychotic disorders was graded into convincing, highly suggestive, suggestive, weak, or non-significant according to a standardized classification based on: number of psychotic cases, random-effects p value, largest study 95% confidence interval, heterogeneity between studies, 95% prediction interval, small study effect, and excess significance bias. In order to assess evidence for temporality of association, we also conducted sensitivity analyses restricted to data from prospective studies. Fifty-five meta-analyses or systematic reviews were included in the umbrella review, corresponding to 683 individual studies and 170 putative risk or protective factors for psychotic disorders. Only the ultra-high-risk state for psychosis (odds ratio, OR=9.32, 95% CI: 4.91-17.72) and Black-Caribbean ethnicity in England (OR=4.87, 95% CI: 3.96-6.00) showed convincing evidence of association. Six factors were highly suggestive (ethnic minority in low ethnic density area, second generation immigrants, trait anhedonia, premorbid IQ, minor physical anomalies, and olfactory identification ability), and nine were suggestive (urbanicity, ethnic minority in high ethnic density area, first generation immigrants, North-African immigrants in Europe, winter/spring season of birth in Northern hemisphere, childhood social withdrawal, childhood trauma, Toxoplasma gondii IgG, and non-right handedness). When only prospective studies were considered, the evidence was convincing for ultra-high-risk state and suggestive for urbanicity only. In summary, this umbrella review found several factors to be associated with psychotic disorders with different levels of evidence. These risk or protective factors represent a starting point for further etiopathological research and for the improvement of the prediction of psychosis.

Key words: Schizophrenia, psychosis, risk, environment, socio-demographic factors, parental factors, perinatal factors, antecedents, ultra-high-risk state for psychosis, Black-Caribbean ethnicity, urbanicity

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Psychotic disorders like schizophrenia are among the world's leading causes of disability[1]. They have a mean incidence of 31.7 per 100,000 person-years in England[2] and a 12-month prevalence of 1.1% among the US population[3]. Despite many decades of research, the etiology of these disorders remains undetermined[4].

The model that has received most empirical support suggests that the etiology of psychotic disorders, schizophrenia for example, involves direct genetic and environmental risk factors along with their interaction[5,6]. In reality, some of the risk factors that have been associated with psychotic disorders – such as family history of mental illness – include both a genetic and an environmental component, and hence a distinction between genetic and environmental risk factors may be spurious.

With this in mind, in this study we adopted a pragmatic approach and used the term "non-purely genetic factors" to define socio-demographic, parental, perinatal, later factors and antecedents[7-9] that may increase (risk factors) or decrease (protective factors) the likelihood of developing psychotic disorders. The clinical importance of investigating these factors is threefold. First, they could potentially be used to advance the prediction of psychosis in populations at risk of developing the disorder[10,11]. Second, some, albeit not all, of these factors may be potentially modifiable by preventive interventions[4]. Third, they could inform outreach campaigns targeting the general public to raise awareness of risk factors for psychosis and to promote mental health.

Numerous studies investigating the association between potential risk or protective factors and psychotic disorders have been published. The body of literature in this area is substantial, presumably due to the severe societal burden that is associated with these disorders and thus the urgent need to understand their causes. However, to date, for all of those factors, there is no conclusive evidence with respect to both the association itself and its direction (i.e., risk or protective), because published findings have often been conflicting.

Furthermore, some of these results have been found to be affected by several types of biases[12,13]. These are particularly

relevant to this area of research because experimental support for etiology, in the sense of randomized allocation to the above-mentioned exposures[13], is naturally lacking, and most evidence is based on observational studies. Finally, previously published literature did not generate clear hierarchies of evidence across those factors, rendering the overall interpretation of the findings particularly complex. In fact, until recently there were no stringent evaluation criteria by which to hierarchically stratify the robustness of the evidence whilst at the same time controlling for the presence of biases.

Umbrella reviews can overcome these problems by assessing the level of the evidence provided by systematic reviews and meta-analyses[14] for each risk or protective factor, through strict criteria that probe a standard list of potential biases. These criteria have been extensively validated in various areas of medicine, such as neurology, oncology, nutrition medicine, internal medicine, psychiatry, paediatrics, dermatology and neurosurgery[15-33]. In the current study, we applied the umbrella review approach to the published evidence on risk or protective factors for psychotic disorders.

Our umbrella review advances knowledge in the field of psychosis etiology, providing the first state-of-the-art classification based on the robustness of associations between putative risk or protective factors and psychotic disorders, controlling at the same time for several biases. The use of classification criteria for levels of evidence can help overcome some of the ambiguity experienced by clinicians and researchers when confronted with conflicting meta-analyses[34] on complex topics and trying to base their decisions on them. Furthermore, our analysis will hopefully promote further etiological clinical research in psychosis, support the refinement of risk prediction in at-risk populations, and inform future preventive strategies.

METHODS

The protocol of the study was registered on PROSPERO 2016: CRD42016054101.

Search strategy and selection criteria

An umbrella review (i.e., a systematic collection and assessment of multiple systematic reviews and meta-analyses published on a specific research topic)[35] was conducted. We searched the Web of Knowledge database (incorporating Web of Science and MEDLINE) to identify systematic reviews or meta-analyses of observational studies that examined the association between a number of factors and psychotic disorders, published from 1965 to January 31, 2017. The search strategy used the keywords ("systematic review" OR "meta-analysis") and ("psychosis" OR "schizophrenia"). We then conducted a manual search of the reference lists of the retrieved articles.

Articles were initially screened on the basis of title and abstract reading. The full texts of potentially eligible articles were then independently scrutinized by two investigators (PFP, VRC), with no language restrictions. We selected systematic reviews or meta-analyses of individual observational studies (case-control, cohort, cross-sectional and ecological studies) that examined the association between socio-demographic, parental, perinatal, later factors or antecedents and any non-organic psychotic disorder as defined by any edition of the ICD or the DSM, including a comparison group of non-psychotic healthy controls, and reporting enough data to perform the analyses.

When data were incomplete, the corresponding author was contacted and invited to send additional information. When two articles presented overlapping datasets on the same factor, only the article with the largest dataset was retained for the main analysis. However, if the overlap was minimal, the articles were used conjointly, counting overlapping individual studies once only[36-43]. Moreover, we also excluded articles that did not report quantitative data, and articles with an outcome other than the onset of an established psychotic disorder, such as those related to relapse, remission or treatment response.

Articles that investigated pure genetic markers of psychotic disorders were excluded, because they have been examined extensively elsewhere[44,45]. Articles that investigated the association between biomarkers and psychotic disorders were not included, because this would have required specific methodological approaches and separate analyses. However, some putative biomarkers have been defined as antecedents (e.g., premorbid IQ[38,39], minor physical anomalies[46], non-right handedness[47], dermatoglyphic abnormalities[48] and neurological soft signs[49]) or perinatal factors (vitamin D[50]), and the relevant articles were therefore included.

The same inclusion/exclusion criteria were checked for each individual study comprised in every eligible meta-analysis or systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations[51] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[52] were followed.

Data extraction

Data extraction was performed independently by at least two investigators. Any existing discrepancies were resolved in consensus meetings with two of the authors (VRC, PFP). Factors were extracted as defined in the corresponding meta-analysis or systematic review. We did not combine similar factors if they were considered and analyzed separately by meta-analyses/systematic reviews[53]. Similarly, we did not split factors into subgroups if they were considered as a whole[54]. When a meta-analysis or systematic review reported both pooled results and results divided according to subgroups, pooled results were preferred, since they had a larger sample size.

Such a conservative approach was adopted to minimize the chance of introducing risk or protective factors that had not been defined by the corresponding articles, and that may have been too heterogeneous to allow meaningful interpretation. This approach also minimized the risk of artificially inflating

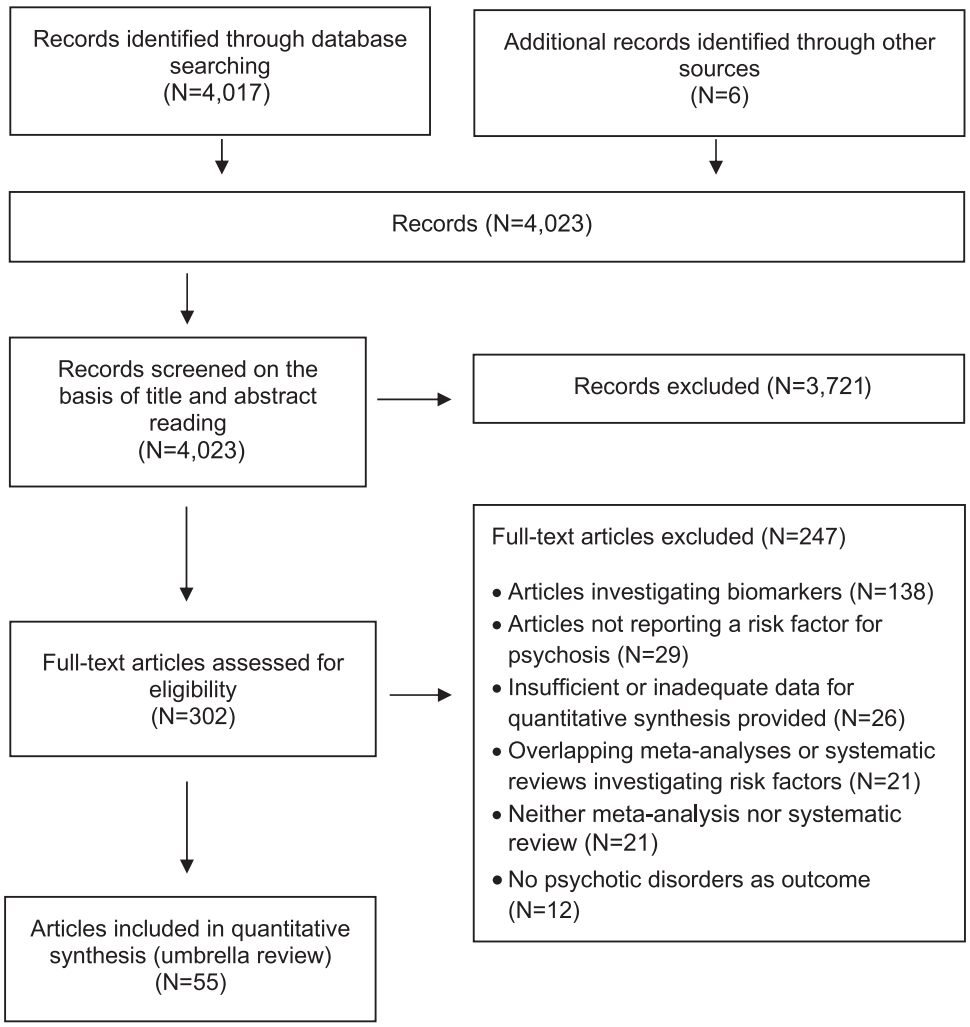

Figure 1 PRISMA flow chart

the sample size and therefore biasing the hierarchical classification of the evidence. The exception was for analyses not based on individual-level data, for which we specifically created new risk factors[55,56], as detailed in the statistical analysis section.

For descriptive purposes, risk/protective factors for psychotic disorders were clustered as previously suggested: socio-demographic and parental factors, perinatal factors, later factors (i.e., factors intervening in the post-perinatal period) and antecedents[7-9]. In line with previous definitions[7,8], antecedents were conceptualized as premorbid deviations in functioning and developmental milestones that could indicate an early expression of the disorder or active risk-modifying mechanisms and processes involved in psychosis onset. Risk factors, instead, would indicate a passive exposure to environmental agents that could play a role in the development of psychosis. One could argue that this distinction remains arbitrary, since the exact timing and mechanisms involved in the etiology of psychotic disorders remain to be elucidated, but this issue is beyond the aim of this review.

Several variables were recorded: the type of factor studied, the first author of the paper, the year of publication, the type of psychotic diagnosis, and the measure of association between the factor and psychotic disorders (preferably unadjusted), with the corresponding 95% confidence interval (CI) and the sample size (where available). If studies contained several types of control groups, data from healthy controls were used. When data were reported only in graphic form, they were digitally measured and extracted using WebPlotDigitizer[57]. The methodological quality of included studies was assessed using the validated AMSTAR (A Measurement Tool to Assess Systematic Reviews) instrument[58-60].

Statistical analysis

This umbrella review is composed of a number of meta-analyses of the included articles conducted separately with a series of scripts in R[61]. The effect size measures of the associa-

Table 1 Characteristics of meta-analyses and systematic reviews studying the association between psychotic disorders and socio-demographic and parental factors

Study	Factors examined	k	Diagnosis	AMSTAR index
Bosqui et al[71]	Ethnic minority in high ethnic density area; ethnic minority in low ethnic density area	5, 5	FEP, SZ, NAP, AP	9/11
Bourque et al[53]	First generation immigrants; second generation immigrants	12, 9	SZ, NAP, AP	10/11
Torrey et al[72]	Paternal age >35 years; paternal age >45 years; paternal age >55 years	8, 7, 4	SZ, NAP, AP	3/11
Kinney et al[55]	Disadvantaged group; latitude	2, 29	SZ	2/11
Kirkbride et al[2]	Age/gender; African ethnicity; Asian ethnicity; mixed ethnicity; other white ethnicity (all examined only in England)	9, 4, 4, 2, 3	FEP, SZ, NAP, AP	11/11
Kwok[73]	Low paternal socio-economic status	9	FEP, SZ, NAP	6/11
O'Donoghue et al[74]	Neighbourhood level social deprivation	3	FEP	8/11
Rasic et al[75]	Parental severe mental illness	9	FEP, SZ, NAP, AP	6/11
Saha et al[56]	Gross national income per capita	88	SZ	9/11
Tortelli et al[76]	Black-Caribbean ethnicity in England	7	FEP, SZ, NAP, AP	10/11
van der Ven et al[77]	North African immigrants in Europe	5	NAP	9/11
Vassos et al[78]	Urbanicity	8	SZ, NAP	6/11

k – number of studies for each factor, FEP – first episode of psychosis, SZ – schizophrenia, NAP – non-affective psychosis other than schizophrenia, AP – affective psychosis, AMSTAR – A Measurement Tool to Assess Systematic Reviews

tion between each factor and psychotic disorders were: incidence rate ratio (IRR), odds ratio (OR), risk ratio (RR), and standardized mean difference (Hedges' g) for continuous measures. Primarily, the effect size measure and its CI were used.

Since authors usually round off the measures, the first step was to "unround" them by estimating a more exact measure and CI, in which the (logarithm of the) lower and upper bounds were symmetrical around the (logarithm of the) measure. Subsequently, the variance was calculated from the standard formula for the CI. If two or more studies shared the non-exposed sample, the size of this sample was divided equally between these studies. This approach minimized the dependence produced by the sharing of the non-exposed sample, whilst allowing estimation of heterogeneity across the exposed samples[62].

Some factors required special adjustments, such as: a) the transformation of measures other than OR into OR in factors where effect size was reported using different types of measures (to have a single outcome measure), and b) the combination of effect sizes for left and right nostrils in olfaction studies[63], conservatively assuming a weak to moderate correlation (r=0.3)[64]. Ultimately, we used the "metainc" (IRR), "metabin" (RR and OR), or "metacont" (Hedges' g) functions in the R "meta" package[65] to calculate the meta-analytic effect size and its p value, the CI, and the heterogeneity (summarized with the I^2 statistic and the p value associated with the Q value). Resulting statistics were also used to calculate the prediction interval[66].

A few specific adjustments were also adopted for age and gender, where IRRs were available for schizophrenia and affective psychosis separately, and stratified by 5 or 10-year age ranges and gender[2,67]. We combined schizophrenia and affective psychoses and then meta-analyzed the IRR of each 10-year age range (vs. other ages), and the IRR of males (vs. females, globally and within each 10-year age range). Since age and gender were considered as basic factors and excluded by previous reviews on psychosis[8,9] and by umbrella reviews on other neuropsychiatric conditions[23,25,27], these analyses were considered exploratory.

Alternative analyses were also conducted for latitude[55] and gross national income per capita (GNI)[56], when the prevalence rates were provided in a series of locations. Specifically, the incidence in each location was (logistic) regressed by the latitude or GNI, obtaining the OR of 10° increase in latitude or 10,000 USD increase in GNI. These results were also considered exploratory because they are based on ecological analyses rather than individual-level data, and were traditionally excluded from previous umbrella reviews of risk factors[23,25,27].

Complementary analyses included: a) an Egger test to assess small-study effects that lead to potential reporting or publication bias[68]; b) a test of excess significance bias[69] as described below, and c) an OR equivalent. The test of excess significance bias consisted of a binomial test to compare the observed vs. the expected number of studies yielding statistically significant results. This expected number was calculated as the sum of the statistical power of the studies, which was estimated using the standard t-test formulas for Hedges' g, and random simulations for OR, RR and IRR. Specifically, the statistical power of study A was estimated as the proportion of times in which a

Table 2 Characteristics of meta-analyses and systematic reviews studying the association between psychotic disorders and perinatal factors

Study	Factors examined	k	Diagnosis	AMSTAR index
Cai et al[40]	Gestational influenza	6	SZ, NAP, AP	10/11
Cannon et al[37]	Anaemia in pregnancy; antepartum haemorrhage; asphyxia; baby detained in hospital; birth weight <2000 g; birth weight <2500 g; birth weight <2500 g + prematurity; breech delivery; caesarean section; cephalopelvic disproportion; congenital malformations; diabetes in pregnancy; emergency caesarean section; forceps/vacuum delivery; gestational age <37 weeks; gestational age >42 weeks; induction of labour; low Apgar score; non-vertex presentation; placental abruption; preeclampsia; Rhesus incompatibility; small birth length; being small for gestational age; small head circumference; smoking in pregnancy; threatened premature delivery; urinary infection in pregnancy; uterine atony	2, 4, 3, 2, 2, 4, 3, 3, 5, 2, 3, 2, 3, 6, 4, 3, 2, 2, 5, 2, 5, 2, 3, 5, 2, 1, 2, 2, 3	SZ	6/11
Christesen et al[50]	Neonatal vitamin D (<19.7 vs. 40.5-50.9 nmol/L); neonatal vitamin D (19.7-30.9 vs. 40.5-50.9 nmol/L); neonatal vitamin D (30.9-40.4 vs. 40.5-50.9 nmol/L); neonatal vitamin D (>50.9 vs. 40.5-50.9 nmol/L)	1, 1, 1, 1	SZ	6/11
Davies et al[79]	Winter/spring season of birth in Northern hemisphere	7	SZ	6/11
Geddes & Lawrie[81]	Obstetric complications	10	SZ	6/11
Geddes et al[36]	Antepartum haemorrhage; birth weight <2500 g; caesarean section; congenital malformations; cord complications; forceps delivery; gestational age <37 weeks; incubator or resuscitation; labour >24 hours; non-vertex presentation; preeclampsia; Rhesus incompatibility; rubella or syphilis; twin birth	9, 9, 9, 7, 9, 9, 3, 8, 4, 9, 9, 7, 9, 9	SZ	4/11
McGrath & Welham[80]	Winter/spring season of birth in Southern hemisphere	7	SZ	9/11
Selten et al[106]	Maternal stress during pregnancy	4	SZ	5/11
Selten & Termoshuizen[41]	Gestational influenza	7	SZ, AP	7/11
Van Lieshout et al[82]	Pre-pregnancy and pregnancy maternal obesity	4	SZ, NAP	10/11

k – number of studies for each factor, FEP – first episode of psychosis, SZ – schizophrenia, NAP – non-affective psychosis other than schizophrenia, AP – affective psychosis, AMSTAR – A Measurement Tool to Assess Systematic Reviews

simulated study using binomial or Poisson random cases was considered "statistically significant"; the simulated studies had the same mean incidence and person-times or sample sizes as study A (using the full sample sizes in case of sharing a sample), and the same effect size as the largest study in the meta-analysis.

Small-study effects and excess significance bias were claimed at one-sided p values <0.05, as in previous studies[27]. In order to easily compare meta-analyses using different outcome measures, OR equivalents were provided for the above measures. Given the low incidence of psychotic disorders, RR was assumed to be equivalent to OR, after checking that the difference between an OR and a RR of the same data was negligible. IRR was assumed to be equivalent to RR, and Hedges' g was converted to OR using a standard formula[70].

IRR, OR and RR greater than 1 or Hedges' g greater than 0 indicated that the factor was associated with an increased likelihood of psychotic disorders. IRR, OR and RR lower than 1 or Hedges' g lower than 0 indicated that the factor was associated with a reduced likelihood of psychotic disorders, i.e. it was protective.

The levels of evidence of the associations between putative risk (or protective) factors and psychotic disorders were classified in accordance with previous umbrella reviews[23,25,27]: convincing (class I) when number of cases >1000, $p < 10^{-6}$, $I^2 < 50\%$, 95% prediction interval excluding the null, no small-study effects, and no excess significance bias; highly suggestive (class II) when number of cases >1000, $p < 10^{-6}$, largest study with a statistically significant effect, and class I criteria not met; suggestive (class III) when number of cases >1000, $p<10^{-3}$, and class I-II criteria not met; weak (class IV) when $p < 0.05$ and class I-III criteria not met; non-significant when $p > 0.05$.

Finally, a sensitivity analysis was conducted for the factors classified as class I-III by using only prospective studies (as defined in each meta-analysis/systematic review or, when this was not provided, as defined by each individual study). Prospective studies allow one to address the temporality of the

Table 3 Characteristics of meta-analyses and systematic reviews studying the association between psychotic disorders and later factors

Study	Factors examined	k	Diagnosis	AMSTAR index
Arias et al[83]	BK virus; Borna disease virus; Chlamydia psittaci; Chlamydia trachomatis; cytomegalovirus; Epstein-Barr virus; human endogenous retrovirus; human endogenous retrovirus type k115; human endogenous retrovirus type W; human herpes virus 2; influenza; JC virus; Toxocara spp; varicella zoster virus	1, 8, 2, 2, 8, 3, 4, 1, 4, 5, 2, 1, 1, 4	SZ	8/11
Attademo et al[84]	Benzene; carbon monoxide; nitrogen dioxide; nitrogen oxides; tetrachloroethylene; traffic	1, 1, 1, 1, 1, 1	SZ	2/11
Beards et al[85]	Adult life events	6	FEP, SZ, NAP, AP	8/11
Clancy et al[86]	Epilepsy	1	SZ	6/11
Cunningham et al[87]	Bullying	1	SZ, NAP	7/11
De Sousa et al[88]	Parental communication deviance	4	SZ	6/11
Gurillo et al[89]	Tobacco use	5	FEP, SZ, NAP, AP	11/11
Gutierrez-Fernandez et al[90]	Chlamydia pneumoniae; human herpes virus 1; human herpes virus 6	3, 11, 3	SZ, NAP	8/11
Khandaker et al[91]	Central nervous system infection during childhood	2	SZ, NAP	10/11
Linszen et al[92]	Hearing impairment	5	SZ	8/11
Marconi et al[93]	Heavy cannabis use	2	FEP, SZ, NAP	7/11
Molloy et al[94]	Traumatic brain injury	8	SZ	7/11
Sutterland et al[95]	Toxoplasma gondii IgG; Toxoplasma gondii IgM	40, 15	FEP, SZ	9/11
Varese et al[54]	Childhood trauma	20	FEP, SZ, NAP, AP	10/11

k – number of studies for each factor, FEP – first episode of psychosis, SZ – schizophrenia, NAP – non-affective psychosis other than schizophrenia, AP – affective psychosis, AMSTAR – A Measurement Tool to Assess Systematic Reviews, Ig – immunoglobulin

association, thus dealing with the problem of reverse causation that may affect, for example, case-control studies[23,25,27].

RESULTS

Database

Overall, 4,023 records were searched, 302 were screened and 55 articles were eligible[2,36-43,46-50,53-56,63,71-106] (see Figure 1). The eligible articles were published between 1995 (when meta-analyses in this field first became available)[107] and 2017. All of the studies utilized a healthy control group except one, investigating the ultra-high-risk state[98]. This latter study used as controls help-seeking individuals undergoing an ultra-high-risk assessment but not meeting the relevant criteria. The mental health status of this control group was not well defined.

Overall, the 55 eligible meta-analyses or systematic reviews, including 683 individual studies, reported on 170 putative risk/protective factors of psychotic disorders (Tables 1-4). For paternal socio-economic status[73], neighbourhood-level social deprivation[74], pre-pregnancy and pregnancy maternal obesity[82], neonatal levels of vitamin D[50], polluting agents (benzene, carbon monoxide, nitrogen dioxide, nitrogen oxides, tetrachloroethylene, traffic)[84] and the ultra-high-risk state[98], the studies did not provide a quantitative synthesis of individual findings, but reported adequate data to allow meta-analyses.

Summary of associations

The number of cases was greater than 1,000 for 48 factors (28.2%). One hundred three of the 170 analyzed factors (60.6%) presented a statistically significant effect ($p<0.05$) under the random-effects model, but only 39 (22.9%) reached $p<10^{-6}$. Fifty-three factors (31.2%) presented a large heterogeneity ($I^2>50\%$), while for 28 (16.5%) the 95% prediction interval did not include the null. Additionally, the evidence for small-study effects and excess significance bias was noted for 16 (9.4%) and 17 (10.0%) factors, respectively.

Classification of level of evidence of associations between socio-demographic and parental, perinatal, later factors or antecedents and psychotic disorders

Among the 170 factors, one socio-demographic factor (Black-Caribbean ethnicity in England: OR=4.87, 95% CI: 3.96-6.00) and

Table 4 Characteristics of meta-analyses and systematic reviews studying the association between psychotic disorders and antecedents

Study	Factors examined	k	Diagnosis	AMSTAR index
Dickson et al[96]	Motor function pre-onset of psychosis; poor academic achievement pre-onset of psychosis; poor mathematic academic achievement pre-onset of psychosis	4, 4, 3	FEP, SZ, NAP	7/11
Filatova et al[97]	Delay in grabbing object; delay in holding head up; delay in sitting unsupported; delay in standing unsupported; delay in walking unsupported	3, 3, 4, 4, 5	SZ, NAP	9/11
Fusar-Poli et al[98]	Ultra-high-risk state for psychosis	9	FEP	9/11
Golembo-Smith et al[48]	ATD angle; fingertip pattern asymmetry; fluctuating asymmetry A-B ridge count; fluctuating asymmetry finger ridge count; total A-B ridge count; total finger ridge count	5, 4, 3, 3, 13, 13	SZ	6/11
Hirnstein & Hugdahl[47]	Non-right handedness	41	SZ, NAP	5/11
Khandaker et al[39]	Premorbid IQ	5	SZ, NAP	8/11
Kaymaz et al[99]	Psychotic-like experiences	4	FEP, SZ, NAP, AP	10/11
Koning et al[100]	Dyskinesia in antipsychotic-naïve schizophrenic patients; parkinsonism in antipsychotic-naïve schizophrenic patients	5, 3	FEP, SZ	5/11
Matheson et al[43]	Childhood social withdrawal	5	SZ, NAP	8/11
Moberg et al[63]	Olfactory detection ability; olfactory identification ability; olfactory discrimination ability; olfactory memory ability; olfactory hedonics ability (pleasant odours); olfactory hedonics ability (unpleasant odours); olfactory hedonics ability (unspecified odours)	18, 51, 8, 2, 9, 8, 7	SZ, NAP	9/11
Neelam et al[49]	Neurological soft signs	7	SZ, NAP	8/11
Ohi et al[101]	Cooperativeness; harm avoidance; novelty seeking; persistence; reward dependence; self-directedness; self-transcendence	7, 7, 7, 7, 7, 7, 7	SZ	4/11
Ohi et al[102]	Agreeableness; conscientiousness; extraversion; neuroticism; openness	6, 7, 8, 8, 7	SZ	6/11
Potvin & Marchand[103]	Hypoalgesia	9	SZ	5/11
Tarbox & Pogue-Geile[42]	Childhood antisocial and externalizing behaviour; childhood social withdrawal and internalizing behaviour	2, 6	SZ, NAP	3/11
Ward et al[104]	Extracranial size	7	SZ, NAP	3/11
Woodberry et al[38]	Premorbid IQ	11	SZ	7/11
Xu et al[46]	Minor physical anomalies	14	SZ	4/11
Yan et al[105]	Trait anhedonia	44	SZ, NAP	6/11

k – number of studies for each factor, FEP – first episode of psychosis, SZ – schizophrenia, NAP – non-affective psychosis other than schizophrenia, AP – affective psychosis, AMSTAR – A Measurement Tool to Assess Systematic Reviews, ATD angle – dermatoglyphic feature that compares the length of the hand to the width

one antecedent (ultra-high-risk state: OR=9.32, 95% CI: 4.91-17.72) presented a convincing level of association (class I: >1000 cases, $p < 10^{-6}$, no evidence of small-study effects or excess significance bias, 95% prediction interval not including the null, and no large heterogeneity).

For six factors there was highly suggestive evidence for association (class II: >1000 cases, $p<10^{-6}$, largest study with a statistically significant effect, and class I criteria not met). These were two socio-demographic and parental factors (ethnic minority in low ethnic density area: OR=3.71; and second generation immigrants: OR=1.68); none of the perinatal and later factors; and four antecedents (minor physical anomalies: OR=5.30; trait anhedonia: OR=4.41; olfactory identification ability: OR=0.19; and premorbid IQ: OR=0.47).

There was suggestive evidence for association (class III) for nine further factors: four socio-demographic and parental factors (North-African immigrants in Europe: OR=2.22; urbanicity: OR=2.19; ethnic minority in high ethnic density area: OR=2.11; and first generation immigrants: OR=2.10); one perinatal factor (winter/spring season of birth in Northern hemisphere: OR=1.04); two later factors (childhood trauma: OR=2.87; and Toxoplasma gondii IgG: OR=1.82); and two antecedents (childhood social withdrawal: OR=2.91; and non-right handedness: OR=1.58). There was either weak (class IV)

Table 5 Level of evidence for the association of socio-demographic and parental factors and psychotic disorders

			Features used for classification of level of evidence							
Factor	k	Random-effects measure, ES (95% CI)	N	p random-effects	I^2 (p)	PI (95% CI)	SSE/ESB	LS	eOR	CE
Black-Caribbean ethnicity in England[76]	9	IRR, 4.87 (3.96-6.00)	3,446	2.8×10^{-50}	38% (0.12)	2.95-8.03	No/No	Yes	4.87	I
Ethnic minority in low ethnic density area[71]	5	IRR, 3.71 (2.47-5.58)	1,328	3.1×10^{-10}	70% (0.09)	0.95-14.43	Yes/No	Yes	3.71	II
Second generation immigrants[53]	26	IRR, 1.68 (1.42-1.92)	28,753	7.6×10^{-10}	77% (<0.001)	0.92-3.06	No/No	Yes	1.68	II
North African immigrants in Europe[77]	12	IRR, 2.22 (1.58-3.12)	2,577	4.2×10^{-6}	65% (0.001)	0.77-6.41	No/NA	Yes	2.22	III
Urbanicity[78]	8	OR, 2.19 (1.55-3.09)	45,791	8.9×10^{-5}	99% (<0.001)	0.62-7.77	No/No	Yes	2.19	III
Ethnic minority in high ethnic density area[71]	5	IRR, 2.11 (1.39-3.20)	1,328	4.3×10^{-4}	58% (0.04)	0.57-7.81	No/No	Yes	2.11	III
First generation immigrants[53]	42	IRR, 2.10 (1.72-2.56)	25,063	1.9×10^{-13}	89% (<0.001)	0.75-5.89	No/Yes	No	2.10	III
Parental severe mental illness[75]	9	RR, 5.94 (2.99-11.79)	90	3.5×10^{-7}	0% (0.85)	2.60-13.59	No/No	Yes	5.94	IV
Black African ethnicity in England[2]	4	IRR, 4.72 (3.30-6.77)	452	2.3×10^{-17}	49% (0.12)	1.25-17.82	No/NA	Yes	4.72	IV
Asian ethnicity in England[2]	6	IRR, 2.83 (1.59-5.05)	613	4.2×10^{-4}	55% (0.05)	0.53-15.00	No/Yes	No	2.83	IV
Other white ethnicity in England[2]	3	IRR, 2.62 (1.35-5.10)	274	0.004	87% (<0.001)	0.93-21.88	No/NA	Yes	2.62	IV
Paternal age >45 years[72]	4	OR, 2.36 (1.35-4.11)	392	0.003	0% (0.66)	0.69-8.01	No/Yes	No	2.36	IV
Disadvantaged vs. advantaged groups[55]	3	RR, 2.27 (1.21-4.27)	532	0.010	69% (0.04)	0-2016.72	No/No	Yes	2.27	IV
Mixed ethnicity in England[2]	3	IRR, 2.19 (1.08-4.44)	330	0.030	0% (0.41)	0.02-14.53	No/NA	No	2.19	IV
Low paternal socio-economic status[73]	9	OR, 1.30 (1.02-1.65)	15,922	0.032	94% (<0.001)	0.58-2.90	No/No	Yes	1.30	IV
Paternal age >35 years[72]	9	OR, 1.22 (1.06-1.41)	2,181	0.007	30% (0.18)	0.89-1.67	No/Yes	No	1.22	IV
Neighbourhood level social deprivation[74]	3	OR, 1.64 (0.83-3.23)	5,560	0.156	88% (<0.001)	0-5961.52	No/No	No	1.64	ns
Paternal age >55 years[72]	7	OR, 1.21 (0.82-1.78)	57	0.341	47% (0.07)	0.45-3.22	No/No	No	1.21	ns

k – number of samples for each factor, ES – effect size, N – number of cases, PI – prediction interval, CI – confidence interval, SSE – small-study effect, ESB – excess significance bias, LS – largest study with significant effect, eOR – equivalent odds ratio, CE – class of evidence, IRR – incidence rate ratio, OR – odds ratio, RR – relative risk, NA – not assessable, ns – not significant

or no evidence of association with psychotic disorders for all other factors (see Tables 5-8).

Exploratory analyses

Results of the exploratory analyses on the association between age and gender strata (total of 23 strata) showed a main effect for male gender (males vs. females: IRR=1.34, 95% CI: 1.05-1.71, class IV). There was also a main effect for 15-35 year-old age (25-34 year-old vs. other: IRR=1.45, 95% CI: 1.29-1.63, class II; 20-29 year-old vs. other: IRR=2.43, 95% CI: 1.58-3.74, class IV; 15-24 year-old vs. other: IRR=1.46, 95% CI: 1.14-1.87, class IV). Age older than 35 was found to be a protective factor (60-69 year-old vs. other: IRR=0.26, 95% CI: 0.14-0.51, class IV; 55-64 year-old vs. other: IRR=0.30, 95% CI: 0.17-0.51, class IV; 50-59 year-old vs. other: IRR=0.50, 95% CI: 0.27-0.93, class IV; 40-49 year-old vs. other: IRR=0.54, 95% CI: 0.35-0.83, class IV; 35-44 year-old vs. other: IRR=0.80, 95% CI: 0.70-0.93, class IV).

There was also weak (class IV) association between psychotic disorders and male gender for 15-40 year-old age (male vs. female within 20-29 year-old: IRR=2.19, 95% CI: 1.69-2.84; male vs. female within 15-24 year-old: IRR=1.98, 95% CI: 1.62-2.41; male vs. female within 30-39 year-old: IRR=1.72, 95% CI: 1.22-2.41; male vs. female within 25-34 year-old: IRR=1.60, 95% CI: 1.26-2.03). The other ten strata were all not associated with psychotic disorders.

Additional exploratory analyses on latitude (per 10°)[55] and GNI per capita (per 10,000 USD)[56] found significant associations, with ORs of 1.22 and 0.80, respectively. Although these factors include >1000 patients and have a p<0.001, it was not possible to apply the classification of the evidence.

Classification of level of evidence of associations between socio-demographic and parental, perinatal, later factors or antecedents and psychotic disorders after sensitivity analysis

A sensitivity analysis was not possible for four of the associations categorized as class I-III in the overall analysis (winter/spring season of birth in Northern hemisphere, olfactory iden-

Table 6 Level of evidence for the association of perinatal factors and psychotic disorders

Factor	k	Random-effects measure, ES (95% CI)	Features used for classification of level of evidence						eOR	CE
			N	p random-effects	I^2 (p)	PI (95% CI)	SSE/ESB	LS		
Winter/spring season of birth in Northern hemisphere[79]	27	OR, 1.04 (1.02-1.06)	115,010	2.1×10^{-6}	0% (0.99)	1.02-1.06	No/No	Yes	1.04	III
Diabetes in pregnancy[37]	2	OR, 10.12 (1.84-55.72)	243	0.008	0% (0.69)	NA	NA/NA	No	10.12	IV
Emergency caesarean section[37]	3	OR, 3.36 (1.48-7.63)	825	0.004	0% (0.92)	0.02-685.69	No/No	No	3.36	IV
Birth weight <2000 g[37]	2	OR, 2.46 (1.11-5.46)	507	0.027	0% (0.85)	NA	NA/NA	Yes	2.46	IV
Congenital malformations[36,37]	10	OR, 2.31 (1.29-4.13)	1,080	0.005	0% (0.99)	1.16-4.57	No/Yes	Yes	2.31	IV
Incubator or resuscitation[36]	8	OR, 2.12 (1.29-3.47)	438	0.003	0% (0.85)	1.14-3.92	No/No	No	2.12	IV
Neonatal vitamin D (<19.7 vs. 40.5-50.9 nmol/L)[50]	1	RR, 2.11 (1.28-3.49)	424	0.004	NA (1.00)	NA	NA/NA	Yes	2.11	IV
Neonatal vitamin D (30.9-40.4 vs. 40.5-50.9 nmol/L)[50]	1	RR, 2.10 (1.30-3.40)	424	0.003	NA (1.00)	NA	NA/NA	Yes	2.10	IV
Threatened premature delivery[37]	2	OR, 2.05 (1.02-4.10)	314	0.043	0% (0.56)	NA	NA/NA	Yes	2.05	IV
Neonatal vitamin D (19.7-30.9 vs. 40.5-50.9 nmol/L)[50]	1	RR, 2.02 (1.27-3.19)	424	0.003	NA (1.00)	NA	NA/NA	Yes	2.02	IV
Pre-pregnancy and pregnancy maternal obesity[82]	4	OR, 1.99 (1.26-3.14)	305	0.003	27% (0.24)	0.47-8.50	No/No	No	1.99	IV
Uterine atony[37]	3	OR, 1.93 (1.35-2.76)	836	3.3×10^{-4}	0% (0.37)	0.19-19.78	No/No	Yes	1.93	IV
Obstetric complications[81]	10	OR, 1.84 (1.25-2.70)	373	0.002	25% (0.21)	0.80-4.22	Yes/Yes	No	1.84	IV
Neonatal vitamin D (>50.9 vs. 40.5-50.9 nmol/L)[50]	1	RR, 1.71 (1.04-2.80)	424	0.033	NA (1.00)	NA	NA/NA	Yes	1.71	IV
Antepartum haemorrhage[36,37]	14	OR, 1.63 (1.12-2.38)	1,489	0.011	6% (0.38)	0.92-2.89	No/No	No	1.63	IV
Birth weight <2500 g[36,37]	13	OR, 1.57 (1.20-2.07)	1,815	0.001	0% (0.45)	1.16-2.14	No/Yes	Yes	1.57	IV
Small head circumference[37]	2	OR, 1.41 (1.00-1.97)	762	0.048	0% (0.58)	NA	NA/NA	No	1.41	IV
Placental abruption[37]	2	OR, 4.54 (0.32-64.63)	314	0.264	72% (0.05)	NA	NA/NA	No	4.54	ns
Rhesus incompatibility[36,37]	9	OR, 1.96 (0.88-4.33)	1,097	0.098	0% (0.98)	0.75-5.11	No/NA	No	1.96	ns
Asphyxia[37]	3	OR, 1.95 (0.77-4.97)	1,122	0.160	76% (0.01)	0-108727	No/No	Yes	1.95	ns
Forceps delivery[36]	9	OR, 1.67 (0.90-3.08)	554	0.103	42% (0.08)	0.34-8.15	Yes/No	Yes	1.67	ns
Rubella or syphilis[36]	9	OR, 1.64 (0.47-5.71)	567	0.435	0% (0.099)	0.37-7.39	No/No	No	1.64	ns
Twin birth[36]	9	OR, 1.53 (0.79-2.97)	558	0.208	0% (0.45)	0.69-3.40	Yes/No	No	1.53	ns
Gestational age <37 weeks[36,37]	7	OR, 1.35 (0.99-1.84)	1,502	0.057	0% (0.66)	0.90-2.03	Yes/No	No	1.35	ns
Being small for gestational age[37]	5	OR, 1.34 (0.82-2.19)	1,436	0.240	58% (0.04)	0.28-6.41	No/No	Yes	1.34	ns
Smoking in pregnancy[37]	1	OR, 1.29 (0.72-2.31)	76	0.393	NA (1.00)	NA	NA/NA	No	1.29	ns
Birth weight <2500 g and prematurity[37]	4	OR, 1.25 (0.52-3.00)	959	0.610	65% (0.03)	0.03-46.31	No/No	Yes	1.25	ns
Anaemia in pregnancy[37]	3	OR, 1.22 (0.46-3.28)	528	0.688	56% (0.10)	0- 41770	No/No	No	1.22	ns
Maternal stress during pregnancy[106]	5	RR, 1.16 (0.94-1.43)	4,412	0.166	71% (0.01)	0.60-2.25	No/No	No	1.16	ns
Low Apgar score[37]	2	OR, 1.13 (0.69-1.84)	405	0.622	0% (0.67)	NA	NA/NA	No	1.13	ns
Preeclampsia[36,37]	15	OR, 1.07 (0.78-1.46)	2,277	0.690	22% (0.20)	0.53-2.15	No/No	Yes	1.07	ns
Forceps/vacuum delivery[37]	7	OR, 1.07 (0.81-1.42)	1,888	0.643	34% (0.16)	0.55-2.09	No/No	Yes	1.07	ns
Cord complications[36]	9	OR, 1.06 (0.47-2.39)	549	0.894	0% (0.54)	0.40-2.83	No/No	No	1.06	ns
Small birth length[37]	3	OR, 1.05 (0.86-1.30)	929	0.619	0% (0.91)	0.28-4.03	No/No	No	1.05	ns
Baby detained in hospital[37]	3	OR, 1.04 (0.59-1.86)	976	0.883	76% (0.01)	0-903.90	No/No	Yes	1.04	ns
Winter/spring season of birth in Southern hemisphere[80]	7	OR, 1.03 (0.88-1.19)	15,023	0.738	16% (0.30)	0.77-1.37	No/NA	No	1.03	ns
Influenza during pregnancy[40,41]	14	OR, 0.99 (0.91-1.08)	7,620	0.867	46% (0.03)	0.79-1.24	No/No	No	0.99	ns

Table 6 Level of evidence for the association of perinatal factors and psychotic disorders *(continued)*

			Features used for classification of level of evidence							
Factor	**k**	**Random-effects measure, ES (95% CI)**	**N**	**p random-effects**	**I^2 (p)**	**PI (95% CI)**	**SSE/ESB**	**LS**	**eOR**	**CE**
Non-vertex presentation[36,37]	15	OR, 0.99 (0.75-1.31)	2,272	0.953	6% (0.38)	0.65-1.51	No/No	No	0.99	ns
Gestational age >42 weeks[37]	3	OR, 0.97 (0.48-1.95)	1,193	0.933	42% (0.18)	0-1000	No/No	No	0.97	ns
Caesarean section[36,37]	15	OR, 0.95 (0.71-1.28)	1,920	0.734	0% (0.46)	0.68-1.32	No/No	No	0.95	ns
Breech delivery[37]	3	OR, 0.95 (0.49-1.84)	470	0.879	0% (0.78)	0.01-68.26	No/No	No	0.95	ns
Urinary infection in pregnancy[37]	3	OR, 0.90 (0.44-1.84)	690	0.776	29% (0.24)	0-498.73	No/No	No	0.90	ns
Induction of labor[37]	3	OR, 0.82 (0.53-1.28)	528	0.387	24% (0.26)	0.02-35.30	No/No	No	0.82	ns
Cephalopelvic disproportion[37]	2	OR, 0.60 (0.18-1.99)	243	0.407	0% (0.48)	NA	NA/NA	No	0.60	ns
Labour >24 hours[36]	4	OR, 0.84 (0.39-1.78)	266	0.643	20% (0.28)	0.09-8.11	No/No	No	0.84	ns

k – number of samples for each factor, ES – effect size, N – number of cases, PI – prediction interval, CI – confidence interval, SSE – small-study effect, ESB – excess significance bias, LS – largest study with significant effect, eOR – equivalent odds ratio, CE – class of evidence, IRR – incidence rate ratio, OR – odds ratio, RR – relative risk, NA – not assessable, ns – not significant

tification ability, trait anhedonia and minor physical anomalies), because they did not include any prospective studies.

Within class I factors, only ultra-high-risk state maintained the same level of evidence, whereas Black-Caribbean ethnicity in England downgraded to a weak (class IV) level of evidence. Equally, all other available class II and III factors were downgraded either to a weak (ethnic minority in low ethnic density area, North-African immigrants in Europe, childhood trauma, ethnic minority in high ethnic density area, childhood social withdrawal, first and second generation immigrants, Toxoplasma gondii IgG, and premorbid IQ) or a non-significant (non-right handedness) level of evidence, except urbanicity, that remained a class III risk factor (Table 9).

DISCUSSION

To our knowledge, this is the first umbrella review of risk and protective factors for psychotic disorders that includes a robust hierarchical classification of the published evidence. Overall, 55 meta-analyses or systematic reviews, with a total of 683 individual studies and 170 socio-demographic and parental, perinatal, later factors or antecedents of psychotic disorders, were included. There was convincing evidence (class I) for only two factors, which were the ultra-high-risk state for psychosis and Black-Caribbean ethnicity in England. However, six other factors were characterized by highly suggestive evidence (class II), and another nine by suggestive evidence (class III). Sensitivity analyses that limited data to prospective studies indicated that ultra-high-risk state and urbanicity showed the largest evidence of association (class I and class III, respectively) with psychotic disorders.

Overall, our umbrella review indicates that, although a large number of risk factors for psychotic disorders have been evaluated in multiple studies, reviews and meta-analyses, the number of those that have suggestive or stronger support is far more limited. This is consistent with previous findings about the etiology of other neuropsychiatric conditions where umbrella reviews have been performed, such as dementia, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis and bipolar disorder[16,23,25-27].

Although the past two decades have clearly shown that the ultra-high-risk state is substantially associated with an increased risk of psychosis[11,108,109], this result should be interpreted with caution. Firstly, this state is the closest antecedent of psychosis by definition, with onset of the disorder occurring from within a few months of ultra-high-risk diagnosis[110]. Indeed, some ultra-high-risk individuals already present with severe symptoms, including short-lived psychotic episodes[111,112], affective symptoms[113] and impaired functioning[114]. Secondly, the ultra-high-risk state is intrinsically heterogeneous[10,115], including different subgroups[115] and varying diagnostic operationalizations[116]. Furthermore, from an epidemiological perspective, it is a spurious condition, characterized by the accumulation of a number of risk factors[117] which enrich the risk in an uncontrolled manner[118-122].

Ethnic minority status and urbanicity may better represent true risk factors, contributing to the development of psychotic disorders through increased socio-environmental adversities[123]. In fact, the effect of both factors on the risk of developing psychotic disorders may be explained (mediated) by environmental exposures at an individual level, such as substance use, social isolation, social defeat, social fragmentation, and discrimination[124]. Interestingly, many of these exposures appear to share a common factor of social stress and defeat[125,126], and have been – mostly indirectly – associated with various neurobiological sequelae of potential relevance to psychotic disorders[127], such as alterations in the hypothalamic-pituitary-adrenal axis[128,129], inflammation[130], altered brain functioning[131,132], reduced brain volumes[133], and neurochemical dysfunctions[126,134,135]. However, studies to directly assess the correlations between these factors

Table 7 Level of evidence for the association of later factors and psychotic disorders

Factor	k	Random-effects measure, ES (95% CI)	Features used for classification of level of evidence						eOR	CE
			N	p random-effects	I^2 (p)	PI (95% CI)	SSE/ESB	LS		
Childhood trauma[54]	20	OR, 2.87 (2.07-3.98)	2,363	2.5×10^{-14}	77% (<0.001)	0.75-11.01	No/Yes	No	2.87	III
Toxoplasma gondii IgG[95]	42	OR, 1.82 (1.51-2.18)	8,796	2.1×10^{-10}	78% (<0.001)	0.68-4.88	Yes/Yes	No	1.82	III
Toxocara spp[83]	1	OR, 41.61 (9.71-178.32)	98	5.1×10^{-7}	NA (1.00)	NA	NA/NA	Yes	41.61	IV
Chlamydia psittaci[83]	2	OR, 29.05 (8.91-94.69)	82	2.2×10^{-8}	0% (0.71)	NA	NA/NA	Yes	29.05	IV
Human endogenous retrovirus type W[83]	5	OR, 19.78 (6.50-60.22)	256	1.4×10^{-7}	33% (0.20)	1.05-372.34	No/No	Yes	19.78	IV
Parental communication deviance[88]	4	g, 1.35 (0.97-1.73)	74	2.3×10^{-12}	0% (0.41)	0.51-2.19	No/No	No	11.55	IV
Chlamydia pneumoniae[90]	3	OR, 6.02 (2.86-12.66)	116	2.1×10^{-6}	0% (0.57)	0.05-745.30	No/No	Yes	6.02	IV
Traffic[84]	1	RR, 5.55 (1.63-18.87)	29	0.006	NA (<0.001)	NA	NA/NA	Yes	5.55	IV
Adult life events[85]	6	OR, 5.34 (3.84-7.43)	317	2.1×10^{-23}	3% (0.39)	3.22-8.87	No/No	Yes	5.34	IV
Heavy cannabis use[93]	2	OR, 5.17 (3.64-7.36)	748	6.3×10^{-20}	42% (0.18)	NA	NA/NA	Yes	5.17	IV
Benzene[84]	1	RR, 3.20 (1.01-10.12)	29	0.048	NA (1.00)	NA	NA/NA	Yes	3.20	IV
Tobacco use[89]	6	RR, 2.19 (1.36-3.53)	8,488	0.001	99% (<0.001)	0.38-12.50	No/No	Yes	2.19	IV
Borna disease virus[83]	21	OR, 1.94 (1.30-2.91)	1,919	0.001	36% (0.05)	0.65-5.81	No/No	Yes	1.94	IV
Traumatic brain injury[94]	8	OR, 1.49 (1.09-2.05)	9,653	0.013	78% (<0.001)	0.57-3.89	Yes/No	No	1.49	IV
Human herpes virus 2[83]	5	OR, 1.44 (1.14-1.81)	901	0.002	0% (0.97)	0.99-2.09	No/No	Yes	1.44	IV
Chlamydia trachomatis[83]	2	OR, 4.39 (0.03-587.92)	82	0.554	85% (0.01)	NA	NA/NA	No	4.39	ns
Human endogenous retrovirus[83]	4	OR, 3.64 (0.72-18.37)	128	0.117	36% (0.19)	0.01-1019	No/No	Yes	3.64	ns
Tetrachloroethylene[84]	1	RR, 3.41 (0.48-24.24)	4	0.219	NA (1.00)	NA	NA/NA	No	3.41	ns
Carbon monoxide[84]	1	RR, 3.07 (0.96-9.82)	29	0.059	NA (1.00)	NA	NA/NA	No	3.07	ns
Epilepsy[86]	1	OR, 3.06 (0.31-29.95)	4	0.337	NA (1.00)	NA	NA/NA	No	3.06	ns
Nitrogen oxides[84]	1	RR, 2.02 (0.74-5.53)	29	0.171	NA (1.00)	NA	NA/NA	No	2.02	ns
Central nervous system infection during childhood[91]	2	RR, 1.99 (0.31-12.78)	2,369	0.466	80% (0.02)	NA	NA/NA	No	1.99	ns
Epstein-Barr virus[83]	3	OR, 1.98 (0.23-16.85)	55	0.532	0% (0.81)	0-2121495	No/No	No	1.98	ns
Nitrogen dioxide[84]	1	RR, 1.91 (0.70-5.19)	29	0.205	NA (1.00)	NA	NA/NA	No	1.91	ns
Hearing impairment[92]	5	OR, 1.64 (0.85-3.15)	597	0.141	76% (0.002)	0.18-15.17	No/No	Yes	1.64	ns
Toxoplasma gondii IgM[95]	15	OR, 1.24 (0.97-1.59)	2,867	0.083	2% (0.43)	0.91-1.70	No/No	No	1.24	ns
Human herpes virus 1[90]	11	OR, 1.24 (0.98-1.58)	1,117	0.074	5% (0.39)	0.87-1.78	No/No	No	1.24	ns
Cytomegalovirus[83]	8	OR, 1.20 (0.65-2.20)	171	0.558	0% (1.00)	0.56-2.56	No/No	No	1.20	ns
Varicella zoster virus[83]	4	OR, 1.17 (0.16-8.58)	69	0.878	0% (0.99)	0.01-92.93	No/No	No	1.17	ns
BK virus[83]	1	OR, 1.05 (0.02-55.41)	20	0.979	NA (1.00)	NA	NA/NA	No	1.05	ns
JC virus[83]	1	OR, 1.05 (0.02-55.41)	20	0.979	NA (1.00)	NA	NA/NA	No	1.05	ns
Human endogenous retrovirus type k115[83]	1	OR, 0.89 (0.43-1.84)	178	0.753	NA (1.00)	NA	NA/NA	No	0.89	ns
Influenza[83]	2	OR, 0.87 (0.05-15.48)	33	0.925	0% (0.92)	NA	NA/NA	No	0.87	ns
Human T-lymphotropic virus 1[83]	2	OR, 0.57 (0.20-1.62)	209	0.294	0% (0.87)	NA	NA/NA	No	0.57	ns
Bullying[87]	1	OR, 0.38 (0.13-1.10)	30	0.075	NA (1.00)	NA	NA/NA	No	0.38	ns
Human herpes virus 6[90]	3	OR, 0.34 (0.05-2.42)	55	0.284	0% (0.71)	0-106440	No/No	No	0.34	ns

k – number of samples for each factor, ES – effect size, N – number of cases, PI – prediction interval, CI – confidence interval, SSE – small-study effect, ESB – excess significance bias, LS – largest study with significant effect, eOR – equivalent odds ratio, CE – class of evidence, IRR – incidence rate ratio, OR – odds ratio, RR – relative risk, Ig – immunoglobulin, NA – not assessable, ns – not significant

Table 8 Level of evidence for the association of antecedents and psychotic disorders

Factor	k	Random-effects measure, ES (95%CI)	Features used for classification of level of evidence							
			N	p random-effects	I^2 (p)	PI (95% CI)	SSE/ESB	LS	eOR	CE
Ultra-high-risk state for psychosis[98]	9	RR, 9.32 (4.91 to 17.72)	1,226	9.5×10^{-12}	0% (0.91)	4.30 to 20.24	No/No	No	9.32	I
Minor physical anomalies[46]	14	g, 0.92 (0.61 to 1.23)	1,212	5.8×10^{-9}	91% (<0.001)	−0.34 to 2.18	No/Yes	Yes	5.30	II
Trait anhedonia[105]	44	g, 0.82 (0.72 to 0.92)	1,601	9.2×10^{-57}	43% (0.002)	0.37 to 1.27	No/Yes	Yes	4.41	II
Olfactory identification ability[63]	55	g, −0.91 (–1.05 to −0.78)	1,703	4.0×10^{-41}	67% (<0.001)	−1.72 to −0.10	Yes/Yes	Yes	0.19	II
Premorbid IQ[38,39]	16	g, −0.42 (−0.52 to −0.33)	4,459	1.1×10^{-18}	73% (<0.001)	−0.70 to −0.14	No/No	Yes	0.47	II
Childhood social withdrawal[42,43]	15	g, 0.59 (0.33 to 0.85)	1,810	6.4×10^{-6}	93% (<0.001)	−0.44 to 1.62	No/No	Yes	2.91	III
Non-right handedness[47]	41	OR, 1.58 (1.35 to 1.86)	2,652	2.0×10^{-8}	21% (0.12)	0.99 to 2.54	No/No	No	1.58	III
Neurological soft signs[49]	8	g, 1.83 (1.28 to 2.38)	564	7.7×10^{-11}	93% (<0.001)	−0.15 to 3.81	Yes/No	Yes	27.59	IV
Neuroticism[102]	8	g, 1.20 (0.88 to 1.52)	430	2.7×10^{-13}	73% (<0.001)	0.18 to.21	No/No	Yes	8.76	IV
Harm avoidance[101]	7	g, 0.98 (0.78 to 1.18)	384	4.5×10^{-21}	48% (0.07)	0.43 to 1.53	No/No	Yes	5.92	IV
Parkinsonism in antipsychotic-naïve schizophrenic patients[100]	3	OR, 5.33 (1.75 to 16.23)	84	0.003	0% (0.81)	0 to 7310	No/No	Yes	5.33	IV
Psychotic like experiences[99]	4	RR, 3.84 (2.55 to 5.79)	118	1.2×10^{-10}	0% (0.65)	1.56 to 9.45	No/No	No	3.84	IV
Dyskinesia in antipsychotic-naïve schizophrenic patients[100]	5	OR, 3.59 (1.53 to 8.42)	189	0.003	0% (0.75)	0.90 to 14.32	No/No	Yes	3.59	IV
Self-transcendence[101]	7	g, 0.61 (0.48 to 0.75)	384	7.8×10^{-19}	0% (0.67)	0.43 to 0.79	No/No	Yes	3.03	IV
Antisocial and externalizing behaviour[42]	3	g, 0.48 (0.22 to 0.74)	68	3.1×10^{-4}	36% (0.20)	−1.97 to 2.93	No/No	Yes	2.39	IV
Delay in walking unsupported[97]	5	g, 0.48 (0.27 to 0.68)	368	4.3×10^{-6}	81% (<0.001)	−0.27 to 1.22	Yes/NA	Yes	2.37	IV
Hypoalgesia[103]	9	g, 0.46 (0.13 to 0.79)	204	0.006	64% (0.005)	−0.57 to 1.49	No/No	No	2.31	IV
Extracranial size[104]	7	g, 0.27 (0.05 to 0.50)	192	0.018	15% (0.31)	−0.15 to 0.70	No/No	Yes	1.64	IV
Delay in standing unsupported[97]	4	g, 0.25 (0.12 to 0.39)	307	2.6×10^{-4}	48% (0.12)	−0.26 to 0.76	Yes/NA	No	1.58	IV
Delay in sitting unsupported[97]	4	g, 0.19 (0.05 to 0.33)	386	0.006	48% (0.12)	−0.33 to 0.70	Yes/NA	No	1.41	IV
Delay in holding head up[97]	3	g, 0.13 (0.01 to 0.24)	352	0.029	0% (0.91)	−0.61 to 0.86	Yes/NA	No	1.26	IV
Olfactory memory ability[63]	2	g, −1.62 (–2.24 to −1.01)	67	2.0×10^{-7}	56% (0.13)	NA	NA/NA	Yes	0.05	IV
Self-directedness[101]	7	g, −0.96 (–1.10 to −0.82)	384	7.7×10^{-42}	0% (0.75)	−1.14 to −0.78	No/No	Yes	0.17	IV
Extraversion[102]	8	g, −0.90 (–1.05 to −0.75)	430	3.6×10^{-32}	5% (0.38)	−1.13 to −0.67	No/No	Yes	0.20	IV
Olfactory discrimination ability[63]	8	g, −0.88 (–1.16 to −0.60)	226	4.1×10^{-10}	45% (0.07)	−1.61 to −0.15	No/No	Yes	0.20	IV
Olfactory hedonics ability (pleasant odours)[63]	10	g, −0.76 (−0.99 to −0.54)	298	2.5×10^{-11}	38% (0.10)	−1.34 to −0.19	No/No	Yes	0.25	IV
Conscientiousness[102]	7	g, −0.68 (−0.92 to −0.44)	399	2.2×10^{-8}	51% (0.05)	−1.33 to −0.04	No/No	Yes	0.29	IV
Olfactory detection ability[63]	18	g, −0.63 (−0.94 to −0.32)	498	5.9×10^{-5}	80% (<0.001)	−1.92 to 0.66	Yes/Yes	No	0.32	IV
Motor function pre-onset of psychosis[96]	4	g, −0.56 (−0.73 to −0.38)	152	4.1×10^{-10}	0% (0.60)	−0.94 to −0.17	No/No	Yes	0.36	IV
Olfactory hedonics ability (unspecified odours)[63]	7	g, −0.51 (−0.78 to −0.24)	142	2.1×10^{-4}	21% (0.26)	−1.06 to 0.05	No/No	No	0.40	IV
Agreeableness[102]	6	g, −0.47 (−0.88 to −0.07)	375	0.022	81% (<0.001)	−1.82 to 0.88	No/No	Yes	0.42	IV
Cooperativeness[101]	7	g, −0.47 (−0.60 to −0.33)	384	7.9×10^{-12}	0% (0.88)	−0.64 to −0.29	Yes/Yes	Yes	0.43	IV
Reward dependence[101]	7	g, −0.43 (−0.56 to −0.30)	384	2.7×10^{-10}	0% (0.43)	−0.61 to −0.26	No/No	Yes	0.46	IV
Openness[102]	7	g, −0.40 (−0.67 to −0.13)	399	0.003	62% (0.01)	−1.18 to 0.38	No/Yes	No	0.49	IV
Olfactory hedonics ability (unpleasant odours)[63]	9	g, −0.35 (−0.53 to −0.17)	244	1.3×10^{-4}	0% (0.79)	−0.57 to −0.13	No/No	No	0.53	IV
Persistence[101]	7	g, −0.24 (−0.39 to −0.08)	384	0.003	22% (0.26)	−0.56 to 0.09	No/No	No	0.65	IV
Total A-B ridge count[48]	13	g, −0.15 (−0.28 to −0.02)	979	0.027	46% (0.35)	−0.53 to 0.23	No/No	No	0.76	IV

Table 8 Level of evidence for the association of antecedents and psychotic disorders *(continued)*

Factor	k	Random-effects measure, ES (95%CI)	Features used for classification of level of evidence							
			N	p random-effects	I^2 (p)	PI (95% CI)	SSE/ESB	LS	eOR	CE
Fluctuating asymmetry A-B ridge count[48]	4	g, 0.74 (−0.65 to 2.13)	241	0.295	98% (<0.001)	−6.00 to 7.49	No/Yes	Yes	3.84	ns
Fluctuating asymmetry finger ridge count[48]	4	g, 0.31 (−0.50 to 1.12)	233	0.448	94% (<0.001)	−3.54 to 4.17	No/No	Yes	1.76	ns
Fingertip pattern asymmetry[48]	5	g, 0.25 (−0.08 to 0.59)	249	0.138	66% (0.02)	−0.85 to 1.35	No/No	Yes	1.58	ns
Poor general academic achievement pre-onset of psychosis[96]	4	g, 0.20 (−0.12 to 0.51)	1,007	0.219	93% (<0.001)	−1.25 to 1.65	No/No	Yes	1.43	ns
ATD angle[48]	5	g, 0.16 (−0.02 to 0.34)	261	0.083	0% (0.54)	−0.13 to 0.46	No/No	No	1.34	ns
Poor mathematic academic achievement pre-onset of psychosis[96]	3	g, 0.11 (−0.24 to 0.47)	136	0.527	63% (0.06)	−3.77 to 3.99	No/No	Yes	1.23	ns
Delay in grabbing object[97]	3	g, 0.05 (−0.07 to 0.17)	351	0.440	14% (0.31)	−0.90 to 1.00	Yes/NA	No	1.09	ns
Novelty seeking[101]	7	g, −0.31 (−0.68 to 0.05)	384	0.092	85% (<0.001)	−1.56 to 0.93	No/No	No	0.57	ns
Total finger ridge count[48]	13	g, −0.12 (−0.29 to 0.04)	935	0.149	65% (0.001)	−0.69 to 0.44	No/Yes	No	0.80	ns

k – number of samples for each factor, ES – effect size, N – number of cases, PI – prediction interval, CI – confidence interval, SSE – small study effect, ESB – excess significance bias, LS – largest study with significant effect, eOR – equivalent odds ratio, CE – class of evidence, IRR – incidence rate ratio, OR – odds ratio, RR – relative risk, ATD angle – dermatoglyphic feature that compares the length of the hand to the width, NA – not assessable, ns – not significant

(e.g., urbanicity) and neurobiological alterations in psychotic disorders have only just started to emerge[133,136]. Until the exact mechanisms that lead to an increased risk of psychosis are determined, the requirement for biological or psychological plausibility for these factors cannot be fully met. Importantly, future research is required to clarify the contextual specifics of ethnic minority status and urbanicity, because their effects may also be modulated by geographical location or predominant population factors, rather than having universal value.

Several other factors beyond the ultra-high-risk state, ethnic minority status, and urbanicity provided a highly suggestive or a suggestive level of evidence of association with psychotic disorders, mostly confirming the role that perinatal factors (winter/spring season of birth in Northern hemisphere) or later factors/antecedents (childhood trauma and childhood social withdrawal, Toxoplasma gondii IgG, minor physical anomalies, trait anhedonia, low olfactory identification ability, low premorbid IQ, and non-right handedness) might have in psychosis onset. At the same time, a number of the explored factors showed only weak evidence of association with psychotic disorders. Some of these factors, such as heavy cannabis use and obstetric complications, were expected to have stronger evidence. However, weak findings in these areas may simply indicate that there are not yet enough data. Our umbrella review also identified only a few putative protective factors, indicating that the vast majority of available studies have focused on the adverse or negative end of several factors. Future research is required to actively seek unstudied protective factors that are not reciprocal to risk factors, such as specific characteristics of the individual, family or wider environment that improve the likelihood of positive outcomes[137].

This study has several conceptual implications. On an etiopathological level, our findings corroborate the notion that psychotic disorders can be related to adversities in an individual's social milieu, whereby environmental exposures during critical developmental periods impact brain, neurocognition, affect, and social cognition[13,138]. It is also apparent that most of these factors are likely not specific to psychosis, but also associated with other mental disorders[139]. From a transdiagnostic perspective, the current study can provide a benchmark for comparing the magnitude of association of these factors with other non-psychotic mental disorders. On a risk prediction level, these results may substantially advance our ability to prognosticate the onset of psychosis in populations at risk, paralleling the recent advancements observed in genetics.

In this latter area, the availability of robust meta-analytical evidence of associations between genetic loci and psychotic disorders – provided by the genome-wide association study (GWAS) meta-analysis conducted by the Schizophrenia Working Group of the Psychiatric Genomics Consortium[44] – has ultimately led to the development of polygenic risk scores to assess the *en masse* genetic effect of several loci[140]. Polygenic risk scores have been used to predict case-control status at the time of a first-episode psychosis, explaining approximately 9% of the variance[140]. The small proportion of variance explained indicates that the use of polygenic risk scores in clinical routine would be unwarranted[44] without first boosting them with other non-purely genetic factors.

Table 9 Sensitivity analysis for the associations of socio-demographic and parental, perinatal, later factors, antecedents and psychotic disorders within individual prospective studies of class I-III factors

				Features used for classification of level of evidence							
Factor	CE	k	Random-effects measure, ES (95% CI)	N > 1000	p random-effects	I^2 (p)	PI (95% CI)	SSE/ESB	LS	eOR	CES
Ultra-high-risk state for psychosis[98]	I	9	RR, 9.32 (4.91 to 17.72)	Yes	9.5×10^{-12}	0% (0.91)	4.30 to 20.24	No/No	No	9.32	I
Urbanicity[78]	III	8	OR, 2.19 (1.55 to 3.09)	Yes	8.9×10^{-6}	99% (<0.001)	0.62 to 7.77	No/No	Yes	2.19	III
Black-Caribbean ethnicity in England[76]	I	7	IRR, 5.54 (4.50 to 6.82)	No	4.9×10^{-59}	0% (0.48)	4.22 to 7.27	No/No	Yes	5.54	IV
Ethnic minority in low ethnic density area[71]	II	3	IRR, 4.27 (1.89 to 9.68)	No	4.9×10^{-4}	82% (0.004)	0 to 75335	Yes/No	Yes	4.27	IV
North African immigrants in Europe[77]	III	8	IRR, 3.20 (2.36 to 4.35)	No	1.0×10^{-13}	21% (0.27)	1.73 to 5.94	No/NA	Yes	3.20	IV
Childhood trauma[54]	III	4	OR, 2.52 (1.27 to 5.02)	Yes	0.009	71% (0.016)	0.14 to 46.01	No/Yes	No	2.52	IV
Ethnic minority in high ethnic density area[71]	III	3	IRR, 2.51 (1.10 to 5.71)	No	0.028	70% (0.037)	0 to 28153	No/No	Yes	2.51	IV
Childhood social withdrawal[42,43]	III	11	g, 0.43 (0.14 to 0.71)	Yes	0.003	94% (<0.001)	−0.63 to 1.48	No/No	Yes	2.16	IV
First generation immigrants[53]	III	12	IRR, 1.83 (1.40 to 2.38)	No	9.6×10^{-6}	0% (0.82)	1.35 to 2.47	No/Yes	No	1.83	IV
Second generation immigrants[53]	II	10	IRR, 1.45 (1.05 to 2.01)	Yes	0.023	76% (<0.001)	0.54 to 3.95	Yes/No	No	1.45	IV
Toxoplasma gondii IgG[95]	III	7	OR, 1.28 (1.06 to 1.55)	Yes	0.012	22% (0.26)	0.86 to 1.91	Yes/No	No	1.28	IV
Premorbid IQ[38,39]	III	9	g, −0.43 (−0.64 to −0.22)	No	5.2×10^{-5}	62% (0.007)	−1.04 to 0.18	No/No	Yes	0.46	IV
Non-right handedness[47]	III	1	OR, 1.83 (0.62 to 5.39)	No	0.273	NA	NA	NA/NA	No	1.83	ns
Minor physical anomalies[46]	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Olfactory identification ability[63]	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Trait anhedonia[105]	II	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Winter/spring season of birth in Northern hemisphere[79]	III	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC

CE – class of evidence, k – number of samples for each factor within prospective studies, ES – effect size, CI – confidence interval, N – number of cases, PI – prediction interval, SSE – small study effect, ESB – excess significance bias, LS – largest study with significant effect, eOR – equivalent odds ratio, CES – class of evidence after sensitivity analysis, RR – relative risk, OR – odds ratio, IRR – incidence rate ratio, NA – not assessable, Ig – immunoglobulin, ns – non-significant, NC – not calculable (no prospective studies to be analyzed)

To date, the integration of multiple non-purely genetic factors into "polyrisk" scores has been limited by the lack of established and robust *a priori* knowledge on their association with psychotic disorders[139]. The current umbrella review attempted to fill this knowledge gap by providing the most robust estimates of association (ORs) between several non-purely genetic risk (or protective) factors and psychotic disorders. Assessing these predictive factors may offer some logistic advantages over more complex measurements that are based on cognitive, imaging, central or peripheral measures. Simple demographic factors have already been used to develop an individualized risk estimation tool to predict psychosis onset in at-risk individuals in clinical practice[141].

Recently, geneticists have advocated the development of polyrisk scores encompassing socio-demographic, parental, perinatal, later factors, antecedents, and genetic risk profiling[139,142]. Such an approach may ultimately reveal new, clinically useful predictors, because even the risk factors that we found to be weakly associated with psychotic disorders may eventually contribute to the predictive accuracy of the model, as previously observed for genetic associations[44]. The current umbrella review lays the groundwork for testing the predictive accuracy of integrated polyrisk scores in independent samples[139].

Finally, on a pragmatic level, the current stratification of evidence can be used by clinicians, policy makers and regulatory bodies to inform and strategically target outreach campaigns, to promote the prevention of mental disorders in the youth population, and to raise awareness of risk factors for psychotic disorders.

This study also has some limitations. First, association is not necessarily causation. Reverse causation is a particular concern[13], and thus establishing the temporality of the association is critical. It is possible that some of the later factors and antecedents are actually characteristics of psychotic disorders themselves or secondary to their appearance. To specifically address these problems and the effect of temporality, we con-

ducted a sensitivity analysis restricted to individual studies with prospective designs.

A second limitation is that the umbrella review approach may favour the selection of more commonly and readily studied factors, since they are more likely to be included in a meta-analysis. We cannot exclude the possibility that some promising factors, despite having sufficient data, do not have a corresponding eligible meta-analysis, such as mood and anxiety disorders[143-145], personality disorders[146], attachment[147], alcohol and psychoactive substances[148-151], sleep dysfunction[152], homelessness[153] or pervasive developmental disorders[154]. However, this possibility is becoming less likely in the current era, with meta-analyses being performed massively, to the point that for several topics multiple meta-analyses are available[155,156]. In any case, for most putative risk or protective factors that are difficult to study (or uncommonly studied), the current grade of evidence is unlikely to be remarkable, given the limited data.

A third limitation is that the definition of healthy control groups employed by each meta-analysis/systematic review or, when this was not provided, by each individual study, may not be entirely accurate. Moreover, some of the factors included in this umbrella review may be better conceptualized as risk markers, because they may be the result of different interacting risk factors. The ultra-high-risk state[98], ethnicity[76] and immigration status[53,77] are prototypical examples of risk markers, and their limitations have already been addressed above.

Another caution is that the categories of socio-demographic and parental, perinatal, later factors, and antecedents[7-9] were used only for descriptive purposes. As noted in the Methods section, these categories may actually overlap to some extent. Finally, the relevance of epigenetic risk factors, and the interaction between environmental and genetic factors in psychotic disorders, remains to be elucidated[157].

In conclusion, we found several factors to be associated with psychotic disorders at different levels of evidence. These factors represent a starting point of knowledge that can be used to advance etiological research and improve the prediction of psychosis.

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