Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas

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Decades of research have revealed numerous risk factors for mental disorders beyond genetics, but their consistency and magnitude remain uncertain. We conducted a "meta-umbrella" systematic synthesis of umbrella reviews, which are systematic reviews of meta-analyses of individual studies, by searching international databases from inception to January 1, 2021. We included umbrella reviews on non-purely genetic risk or protective factors for any ICD/DSM mental disorders, applying an established classification of the credibility of the evidence: class I (convincing), class II (highly suggestive), class III (suggestive), class IV (weak). Sensitivity analyses were conducted on prospective studies to test for temporality (reverse causation), TRANSD criteria were applied to test transdiagnosticity of factors, and A Measurement Tool to Assess Systematic Reviews (AMSTAR) was employed to address the quality of meta-analyses. Fourteen eligible umbrella reviews were retrieved, summarizing 390 meta-analyses and 1,180 associations between putative risk or protective factors and mental disorders. We included 176 class I to III evidence associations, relating to 142 risk/protective factors. The most robust risk factors (class I or II, from prospective designs) were 21. For dementia, they included type 2 diabetes mellitus (risk ratio, RR from 1.54 to 2.28), depression (RR from 1.65 to 1.99) and low frequency of social contacts (RR=1.57). For opioid use disorders, the most robust risk factor was tobacco smoking (odds ratio, OR=3.07). For non-organic psychotic disorders, the most robust risk factors were clinical high risk state for psychosis (OR=9.32), cannabis use (OR=3.90), and childhood adversities (OR=2.80). For depressive disorders, they were widowhood (RR=5.59), sexual dysfunction (OR=2.71), three (OR=1.99) or four-five (OR=2.06) metabolic factors, childhood physical (OR=1.98) and sexual (OR=2.42) abuse, job strain (OR=1.77), obesity (OR=1.35), and sleep disturbances (RR=1.92). For autism spectrum disorder, the most robust risk factor was maternal overweight pre/during pregnancy (RR=1.28). For attention-deficit/hyperactivity disorder (ADHD), they were maternal pre-pregnancy obesity (OR=1.63), maternal smoking during pregnancy (OR=1.60), and maternal overweight pre/during pregnancy (OR=1.28). Only one robust protective factor was detected: high physical activity (hazard ratio, HR=0.62) for Alzheimer's disease. In all, 32.9% of the associations were of high quality, 48.9% of medium quality, and 18.2% of low quality. Transdiagnostic class I-III risk/protective factors were mostly involved in the early neurodevelopmental period. The evidence-based atlas of key risk and protective factors identified in this study represents a benchmark for advancing clinical characterization and research, and for expanding early intervention and preventive strategies for mental disorders.

Key words: Risk factors, protective factors, mental disorders, dementia, psychotic disorders, mood disorders, autism spectrum disorder, attention-deficit/hyperactivity disorder, early intervention, preventive strategies

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Mental disorders are complex conditions of uncertain aetiopathology. Although a genetic predisposition is evident (e.g., for psychotic disorders[1-3], bipolar disorders[4,5], depressive and anxiety disorders[6,7]), even polyrisk genetic scores, on their own, explain only a small proportion of the phenotypic variance[8-10]. There is strong evidence that environmental factors underlie much of the variation in clinical and neurobiological phenotypes of mental disorders and their outcomes[11], and there are suggestions for dynamic three-dimensional gene-by-environment-by-time interactions.

Aetiopathological knowledge in psychiatry has often been plagued by scientific pessimism. However, there have been recent exponential developments in research, to the point that numerous non-purely genetic risk factors for mental disorders have been identified. The timing of their effect encompasses prenatal or perinatal, childhood, later (adolescent/young adult) or antecedent (shortly preceding the onset of a disorder) phases.

The number of individual studies exploring risk or protective factors for mental disorders has grown over the past decades,

and several meta-analyses have been published. More recently[12], umbrella review methods (i.e., systematic reviews of meta-analyses[13]) have allowed comparisons between different meta-analyses, by summarizing the findings with a uniform approach for all risk/protective factors, including expected variability in the quality, focus of interest, and several types of biases in the meta-analyses[14-16].

Umbrella reviews can also apply robust classification criteria[17] to rank the credibility of the evidence, controlling at the same time for several biases[18-21], which helps overcome conflicting meta-analytic findings on complex topics[13]. Accordingly, umbrella reviews with a classification of the credibility of evidence are employed to help synthesize the available literature in order to guide both clinical care and public health policies. Collectively, umbrella reviews are at the top of the hierarchy in the evaluation of evidence[16,22].

While several recent umbrella reviews have evaluated the consistency and magnitude of risk and protective factors for each specific mental disorder, no systematic synthesis has yet collectively appraised the evidence across all existing mental disorders. Therefore, the extent to which these factors may differently exert their influence within specific disorders or across different disorders is currently unknown.

We present here the first systematic synthesis of umbrella reviews of non-purely genetic risk and protective factors for mental disorders. This approach has been termed "meta-umbrella" and offers an overarching field-wide overview to comprehensively assess a certain topic[23]. Our aims were to provide an evidence-synthesis comparative atlas of the consistency and magnitude of risk and protective factors for mental disorders beyond genetics, and to formulate recommendations for the next generation of aetiopathological research and preventive psychiatry.

METHODS

Search strategy and selection criteria

We conducted a meta-umbrella systematic review of umbrella reviews[23]. The search strategy followed the PRISMA guidelines[24]. A multi-step systematic literature search was performed by independent researchers to explore Web of Science (Clarivate Analytics) databases (including the Web of Science Core Collection, BIOSIS Citation Index, MEDLINE, KCI-Korean Journal Database, SciELO Citation Index, and Russian Science Citation Index), PubMed, the Cochrane Central Register of Reviews, and Ovid/PsycINFO databases, from inception to January 1, 2021.

The following broad search terms were applied: "umbrella review" and ("risk" OR "protect*"). Papers identified were initially screened based on title and abstract reading. After the exclusion of those which were not relevant based on the topic investigated, full texts of the remaining papers were further assessed for inclusion. The references of umbrella reviews included in the final dataset were also reviewed to identify additional eligible papers.

Studies included were: a) umbrella reviews, defined as systematic collections and assessments of multiple systematic reviews and/or meta-analyses published on a specific research topic[14,15], b) reporting quantitative data from observational individual studies (i.e., case-control, cohort, cross-sectional or ecological studies) on non-purely genetic risk and/or protective factors for mental disorders based on established criteria for classifying the credibility of the evidence[18-21] (see below), and c) primarily investigating the association between these risk and/or protective factors and ICD (any version) or DSM (any version) mental disorders.

Mental disorders were stratified by using the corresponding ICD-10 diagnostic blocks: organic, including symptomatic, mental disorders; mental and behavioural disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood (affective) disorders; neurotic, stress-related and somatoform disorders; behavioural syndromes associated with psychological disturbances and physical factors; disorders of adult personality and behaviour; mental retardation; disorders of psychological development; and behavioural and emotional disorders with onset usually occurring in childhood and adolescence.

Studies excluded were: a) systematic reviews or meta-analyses other than umbrella reviews, individual studies (including Mendelian randomization studies and randomized controlled trials), clinical cases, conference proceedings, and study protocols; b) umbrella reviews not reporting quantitative data; c) umbrella reviews addressing outcomes other than the onset of an established mental disorder (e.g., those related to clinical outcomes such as relapse, remission or treatment response[15,23], or biomarkers); d) umbrella reviews employing other classification approaches, such as GRADE[25], because these mostly apply to interventional effects, not aetiology[26].

We did not include pure genetic factors or biomarkers, because genetic/biomarker causality is tested with other analytical approaches (such as genome-wide association studies and meta/mega-analyses). When there were two or more umbrella reviews from the same centre, authors were contacted to clarify overlaps. When two papers presented overlapping datasets on the same risk/protective factor for the same disorder, only the paper with the largest dataset was retained for the analysis. Disagreements in search and selection were resolved through discussion and consensus.

Measures and data extraction

At least two independent researchers extracted a predetermined set of variables characterizing each umbrella review, including the first author and year of publication, the corresponding ICD-10 diagnostic block(s), the number of meta-analyses included, the median number of individual studies and of cases (with interquartile range) per association, the overall number of risk/protective factors investigated, and the range of years for which the evidence was reviewed.

Further variables were extracted to characterize the associa-

tion between each specific risk/protective factor and each mental disorder. We recorded each risk/protective factor (if the timing of effect was specified, this was additionally reported, e.g., childhood, midlife, elderhood). Following a pragmatic approach, each risk/protective factor was defined as originally operationalized by each individual study, without redefining it unless strictly necessary to improve the clarity of reporting. Since each factor (e.g., smoking) can be associated with multiple outcomes (e.g., lung and pancreatic cancer), the total number of associations tested in umbrella reviews typically exceeds that of factors[27].

We recorded the specific mental disorder which was the focus of each umbrella review and matched it with the corresponding ICD-10 diagnostic block. Furthermore, we recorded the number of individual studies and cases analyzed per each association, the strength of the association and its measurement – odds ratio (OR), risk ratio (RR), incidence rate ratio (IRR), hazard ratio (HR), Hedges' g, Cohen's d, and r – with the corresponding 95% confidence intervals (CI). A value of OR, RR, IRR or HR and its 95% CI higher than 1, or a value of Hedges' g, Cohen's d, or r higher than 0 indicates an association with an increased likelihood of a mental disorder (i.e., risk factor). A value of OR, RR, IRR or HR and its 95% CI lower than 1, or a value of Hedges' g, Cohen's d, or r lower than 0 indicates an association with a reduced likelihood of a mental disorder (i.e., protective factor). We also provided the equivalent OR (eOR) for all metrics: an eOR higher than 1 indicates an association with an increased likelihood of a mental disorder (i.e., risk factor), while an eOR lower than 1 indicates an association with a reduced likelihood of a mental disorder (i.e., protective factor)[15]. Finally, we extracted the overall class of evidence as reported for each association and the class of evidence reported in prospective studies of each association (see below).

Strategy for data synthesis

The results were systematically stratified across the corresponding ICD-10 diagnostic blocks and described across three sections: a) evidence for associations between risk/protective factors and individual mental disorders, b) evidence for transdiagnostic associations of risk/protective factors, c) evidence for factors that have both risk and protective associations with various mental disorders.

For the first analysis, we reported the classification of the credibility of the evidence in the included umbrella reviews according to established criteria[13,18-20]: class I, convincing (number of cases >1,000, $p<10^{-6}$, $I^2<50\%$, 95% prediction interval excluding the null, no small-study effects, and no excess significance bias); class II, highly suggestive (number of cases >1,000, $p<10^{-6}$, largest study with a statistically significant effect, and class I criteria not met); class III, suggestive (number of cases >1,000, $p<10^{-3}$, and class I-II criteria not met); class IV, weak ($p<0.05$ and class I-III criteria not met); and non-significant ($p>0.05$). We considered only factors with a class of evidence from I to III, and primarily focused on those with robust evidence (i.e., class I and II). We additionally reported the class of evidence for each association when the analyses were restricted to prospective studies (if provided by the umbrella reviews included). This sensitivity analysis deals with the problem of reverse causation that may affect, for example, case-control studies[20]. Furthermore, we indicated whether the associations involving medical treatments were likely confounded by underlying conditions which might themselves increase the risk of mental disorders (confounding by indication)[28]. We also reported the quality of the included meta-analyses measured by the AMSTAR (A Measurement Tool to Assess Systematic Reviews) tool[29].

The second analysis (transdiagnostic associations) was conducted only for those risk factors that were shared by at least two disorders. We applied the TRANSD criteria, which empirically evaluate the consistency and extent of putative transdiagnostic constructs across six domains[30,31]. In order to be validated, a transdiagnostic association had to adopt a transparent (criterion T) diagnostic definition according to the gold standard; clearly report (criterion R) the primary outcome of the study; be appraised (criterion A) as "across diagnoses and within spectrum" or "across diagnostic spectra"; numerate (criterion N) the corresponding ICD-10 diagnostic categories and spectra; and show (criterion S) a transdiagnostic class of evidence of at least III, and not inferior to the lowest class of evidence for the corresponding disorder-specific associations. The transdiagnostic class of evidence within prospective studies was additionally reported in order to demonstrate (criterion D) the generalizability of the transdiagnostic factor.

The third analysis was based on a systematic description of the findings.

RESULTS

Database

Overall, 1,361 records were retrieved, 800 suitable papers were screened, and 14 umbrella reviews were eligible[6,15,27,32-42] (see Figure 1). The eligible umbrella reviews were published between 2017 and 2021, and reviewed individual studies published from 1995 to 2020. The 14 eligible umbrella reviews (Table 1) included 390 meta-analyses. The median number of meta-analyses per umbrella review was 26 (interquartile range: 9-43).

Evidence for association between risk/protective factors and mental disorders

Altogether, 1,180 associations between putative risk or protective factors and mental disorders were analyzed. Among them, 497 were non-significant and 507 of class IV, leaving 176 risk/protective associations of class I-III, which were included in the current study. Twenty-one associations met class I or II from prospective designs (most robust associations). Table 2 summarizes the associations of risk/protective factors and mental disorders, stratified by ICD-10 diagnostic blocks.

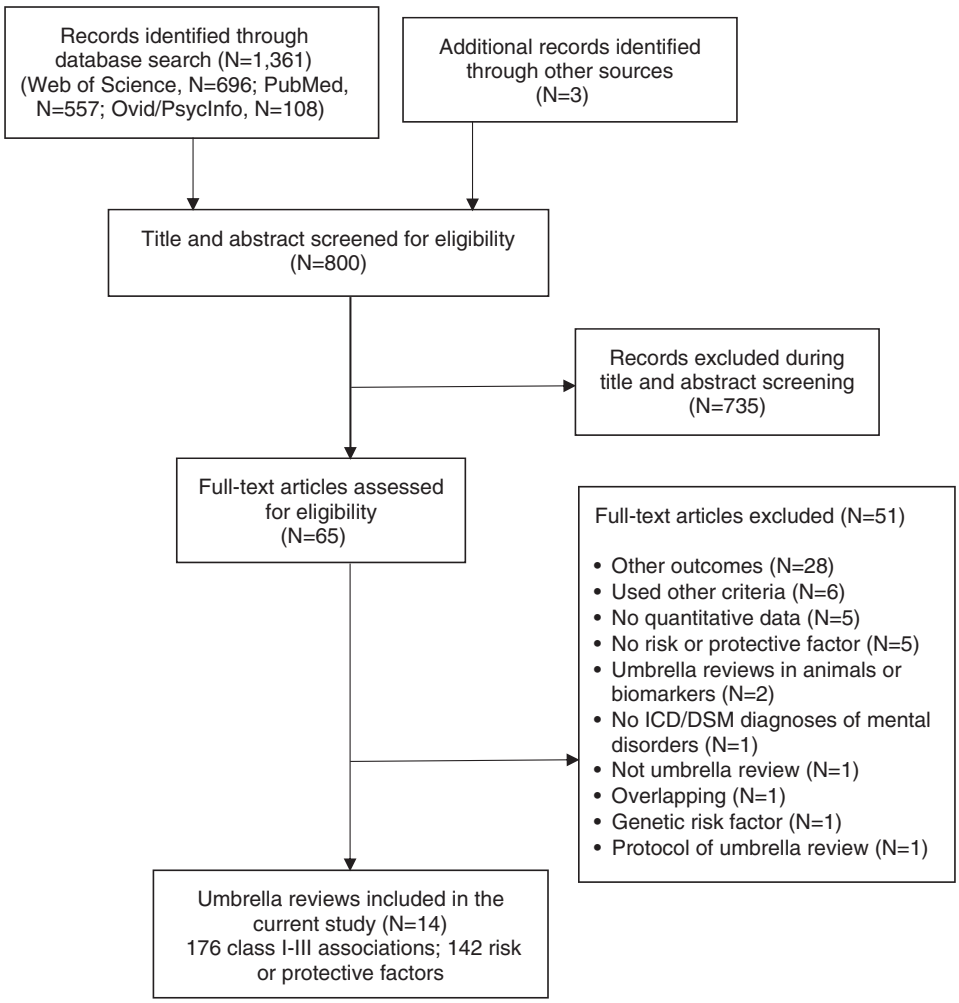

Figure 1 PRISMA flow chart outlining study selection process

Organic, including symptomatic, mental disorders

Twenty-one associations with any dementia, Alzheimer's disease, or vascular dementia were evaluated within this ICD-10 diagnostic block[27]. Seven associations were supported by class I evidence (Table 2). Four risk factors were involved in these associations: type 2 diabetes mellitus (with vascular dementia, RR=2.28, and with Alzheimer's disease, RR=1.54); depression (with any dementia, RR=1.99); depression in elderhood (with any dementia, RR=1.85, and with Alzheimer's disease, RR=1.65); low frequency of social contacts (with any dementia, RR=1.57); and benzodiazepine use (with any dementia, RR=1.49; likely confounding by indication such as difficulties with sleep and chronic anxiety with or without depression).

Four associations were supported by class II evidence (Table 2). These involved two risk factors, namely depression at any age (with Alzheimer's disease, RR=1.77) and type 2 diabetes mellitus (with any dementia, RR=1.60); and two protective factors, i.e. history of cancer (with Alzheimer's disease, HR=0.62, possibly due to survival bias) and high physical activity (with Alzheimer's disease, HR=0.62).

Ten associations were supported by class III evidence (Table 2), involving six risk factors (obesity in midlife, low education, low frequency electromagnetic fields, aluminium exposure, depression in childhood, and herpes viruses infection); and three protective factors (statin use, high physical activity, and non-steroidal anti-inflammatory drug use).

All factors with class I and II evidence remained at the same level of evidence in prospective analyses. For factors with class III evidence, no prospective analysis data were available (Table 2).

Mental and behavioural disorders due to psychoactive substance use

Twelve associations across tobacco related disorder, alcohol related disorder and opioid use disorder were evaluated within this ICD-10 diagnostic block[38,41]. None of the associations was supported by class I evidence. Only one association was supported by class II evidence, involving tobacco smoking as a risk factor for opioid use disorder (OR=3.07).

Table 1 Overall characteristics of the umbrella reviews included in the current study

	ICD-10 diagnostic block	Number of included meta-analyses	Median number of individual studies (IQR) per association	Median number of cases (IQR) per association	Number of risk or protective factors tested	Evidence reviewed (years range)
Bellou et al[27]	Organic, including symptomatic, mental disorders	43	7 (5-13)	1,139 (590-3,537)	53	2008-2016
Bortolato et al[32]	Mood (affective) disorders	7	8 (4-11)	1,163 (313-50,358)	7	2006-2016
Belbasis et al[33]	Schizophrenia, schizotypal and delusional disorders	41	7 (5-10)	384 (254-939)	41	1995-2016
Kohler et al[34]	Mood (affective) disorders	70	7.5 (5-11)	2,269 (621- 9,090)	134	2003-2017
Radua et al[15]	Schizophrenia, schizotypal and delusional disorders	55	5 (3-9)	424 (226-1,193)	170	1995-2017
Kim et al[35]	Disorders of psychological development	46	8 (2-24)	3,764(1,000-8,831)	67	2011-2019
Tortella-Feliu et al[6]	Neurotic, stress-related and somatoform disorders	33	1 (1-4)	46 (22-82)	130	2000-2018
Fullana et al[36]	Neurotic, stress-related and somatoform disorders	19	1 (1-1)	100 (54-224)	427	2000-2017
Kim et al[37]	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	35	6 (4-8)	16,850 (1,490–37,086)	40	2012-2020
Solmi et al[39]	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	10	6 (4-9)	485 (70-2,081)	12	2013-2018
Solmi et al[38]	Mental and behavioural disorders due to psychoactive substance use	12	8 (4-12)	1348 (842-2,064)	12	2003-2019
Solmi et al[40]	Behavioural syndromes associated with physiological disturbances and physical factors	9	32 (17-82)	514 (196-1,103)	49	2002-2019
Solmi et al[41]	Mental and behavioural disorders due to psychoactive substance use	5	10 (7-14)	634 (366-1,621)	12	2011-2019
Solmi et al[42]	Disorders of adult personality and behaviour; mental retardation	5	5 (3-14)	214 (98-2,420)	26	1999-2020

IQR – interquartile range

Eleven associations were supported by class III evidence (Table 2), involving eight risk factors and two protective factors. The three risk factors for tobacco related disorder were attention-deficit/hyperactivity disorder (ADHD), peer smoking behaviour, and smoking in movies; the five risk factors for alcohol related disorder were impulsivity-related personality traits in college or school or community adolescents, parental alcohol supply, and externalizing symptoms in adolescents. The two protective factors were surviving childhood cancer (for alcohol and tobacco related disorder) and parental stricter alcohol rules (for alcohol related disorder).

For class II evidence, the prospective analysis showed that tobacco smoking remained at the same level of evidence as a risk factor for opioid use disorder. For the remaining class III evidence factors, no prospective analysis data were available (Table 2).

Schizophrenia, schizotypal and delusional disorders

Twenty-two associations with any non-organic psychotic disorder and schizophrenia spectrum disorders were evaluated within this ICD-10 diagnostic block[15,33]. Only three associations were supported by class I evidence (Table 2). These all included risk factors: clinical high risk state for psychosis (with any non-organic psychotic disorder, OR=9.32), Black-Caribbean ethnicity in England (with any non-organic psychotic disorder, IRR=4.87), and obstetric complications (with schizophrenia spectrum disorders, OR=1.97).

Nine associations were supported by class II evidence (Table 2). Seven of these involved risk factors, namely minor physical anomalies (Hedges' g=0.92), trait anhedonia (Hedges' g=0.82), ethnic minority in low ethnic density area (IRR=3.71), and being a second generation immigrant (IRR=1.68), with any non-organic psychotic disorder; and cannabis use (OR=3.90), stressful events (OR=3.11), and adversities in childhood (OR=2.80), with schizophrenia spectrum disorders. Two associations involved protective factors: premorbid IQ (Hedges' g = –0.42) and olfactory identification ability (Hedges' g = –0.91) with any non-organic psychotic disorder.

Ten associations were supported by class III evidence (Table 2). These all involved risk factors: social withdrawal in childhood,

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Organic, including symptomatic, mental disorders							
Type 2 diabetes mellitus	Vascular dementia	14 (1,396)	2.28, RR	1.94-2.66	I (I)	High	2.28
Depression	Any dementia	33 (25,106)	1.99, RR	1.84-2.16	I (I)	High	1.99
Depression in elderhood	Any dementia	25 (4,957)	1.85, RR	1.67-2.05	I (I)	Medium	1.85
Depression in elderhood	Alzheimer's disease	16 (3,358)	1.65, RR	1.42-1.92	I (I)	Medium	1.65
Low frequency of social contacts	Any dementia	8 (1,122)	1.57, RR	1.32-1.85	I (I)	Medium	1.57
Type 2 diabetes mellitus	Alzheimer's disease	21 (3,537)	1.54, RR	1.39-1.72	I (I)	High	1.54
Benzodiazepines use*	Any dementia	5 (11,741)	1.49, RR	1.30-1.72	I (I)	High	1.49
Depression	Alzheimer's disease	25 (5,101)	1.77, RR	1.48-2.13	II (II)	High	1.77
Type 2 diabetes mellitus	Any dementia	22 (15,707)	1.60, RR	1.43-1.79	II (II)	High	1.60
High physical activity	Alzheimer's disease	9 (1,358)	0.62, HR	0.52-0.72	II (II)	Medium	0.62
History of cancer	Alzheimer's disease	7 (4,635)	0.62, HR	0.53-0.74	II (II)	Medium	0.62
Obesity in midlife	Any dementia	5 (1,914)	1.91, RR	1.40-2.62	III (NA)	Medium	1.91
Low education	Any dementia	23 (8,739)	1.88, RR	1.51-2.33	III (NA)	High	1.88
Low education	Alzheimer's disease	16 (2,769)	1.82, RR	1.36-2.43	III (NA)	High	1.82
Low frequency electromagnetic fields	Alzheimer's disease	25 (3,238)	1.74, RR	1.37-2.21	III (NA)	High	1.74
Aluminium exposure	Alzheimer's disease	8 (1,383)	1.72, OR	1.33-2.21	III (NA)	Medium	1.72
Depression in childhood	Any dementia	9 (3,538)	1.63, RR	1.27-2.11	III (NA)	High	1.63
Herpes viruses infection	Alzheimer's disease	33 (1,330)	1.38, OR	1.14-1.65	III (NA)	Medium	1.38
Statins use	Any dementia	12 (37,798)	0.83, RR	0.76-0.91	III (NA)	High	0.83
High physical activity	Any dementia	21 (3,845)	0.76, RR	0.66-0.86	III (NA)	Medium	0.76
NSAID use	Alzheimer's disease	16 (53,372)	0.74, RR	0.64-0.86	III (NA)	High	0.74
Mental and behavioural disorders due to psychoactive substance use							
Tobacco smoking	Opioid use disorder	10 (2,447)	3.07, OR	2.27-4.14	II (II)	Low	3.07
Impulsivity-related personality traits in college adolescents	Alcohol related disorder	15 (NA)	0.53, d	0.43-0.64	III (NA)	Medium	2.63
ADHD	Tobacco related disorder	4 (NA)	2.36, OR	1.71-3.27	III (NA)	Medium	2.36
Impulsivity-related personality traits in community adolescents	Alcohol related disorder	9 (NA)	0.45, d	0.33-0.56	III (NA)	Medium	2.26
Impulsivity-related personality traits in school adolescents	Alcohol related disorder	12 (NA)	0.43, d	0.34-0.52	III (NA)	Medium	2.18
Parental alcohol supply	Alcohol related disorder	8 (NA)	2.00, OR	1.72-2.32	III (NA)	Medium	2.00
Peer smoking behaviour	Tobacco related disorder	71 (NA)	1.92, OR	1.76-2.09	III (NA)	Medium	1.92
Externalizing symptoms in adolescents	Alcohol related disorder	23 (NA)	1.63, OR	1.39-1.90	III (NA)	Medium	1.63
Smoking in movies	Tobacco related disorder	9 (4,398)	1.46, RR	1.23-1.73	III (NA)	Medium	1.46
Surviving childhood cancer	Alcohol related disorder	3 (1,348)	0.78, OR	0.68-0.88	III (NA)	Medium	0.78
Surviving childhood cancer	Tobacco related disorder	6 (2,064)	0.54, OR	0.42-0.70	III (NA)	Medium	0.54
Parental stricter alcohol rules	Alcohol related disorder	2 (NA)	0.41, OR	0.33-0.51	III (NA)	Medium	0.41
Schizophrenia, schizotypal and delusional disorders							
Clinical high-risk state for psychosis	Any non-organic psychotic disorder	9 (1,226)	9.32, OR	4.91-17.72	I (I)	High	9.32

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders *(continued)*

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Black-Caribbean ethnicity in England	Any non-organic psychotic disorder	9 (3,446)	4.87, IRR	3.96-6.00	I (IV)	High	4.87
Obstetric complications	Schizophrenia spectrum disorders	18 (1,000)	1.97, OR	1.55-2.50	I (NA)	Low	1.97
Minor physical anomalies	Any non-organic psychotic disorder	14 (1,212)	0.92, g	0.61-1.23	II (NA)	Medium	5.30
Trait anhedonia	Any non-organic psychotic disorder	44 (1,601)	0.82, g	0.72-0.92	II (NA)	Medium	4.41
Cannabis use	Schizophrenia spectrum disorders	10 (4,036)	3.90, OR	2.84-5.35	II (II)	High	3.90
Ethnic minority in low ethnic density area	Any non-organic psychotic disorder	5 (1,328)	3.71, IRR	2.47-5.58	II (IV)	High	3.71
Stressful events	Schizophrenia spectrum disorders	13 (2,218)	3.11, OR	2.31-4.18	II (NA)	Medium	3.11
Adversities in childhood	Schizophrenia spectrum disorders	34 (7,738)	2.80, OR	2.34-3.34	II (II)	Medium	2.80
Second generation immigrant	Any non-organic psychotic disorder	26 (28,753)	1.68, IRR	1.42-1.92	II (IV)	High	1.68
Premorbid IQ	Any non-organic psychotic disorder	16 (4,459)	–0.42, g	–0.52 to –0.33	II (IV)	Medium	0.47
Olfactory identification ability	Any non-organic psychotic disorder	55 (1,703)	–0.91, g	–1.05 to –0.78	II (NA)	High	0.19
Social withdrawal in childhood	Any non-organic psychotic disorder	15 (1,810)	0.59, g	0.33-0.85	III (IV)	High	2.91
Tobacco smoking	Schizophrenia spectrum disorder	17 (NA)	2.34, OR	1.65-3.33	III (NA)	High	2.34
North African immigrant in Europe	Any non-organic psychotic disorder	12 (2,577)	2.22, IRR	1.58-3.12	III (IV)	High	2.22
Urbanicity	Any non-organic psychotic disorder	8 (45,791)	2.19, OR	1.55-3.09	III (III)	Medium	2.19
Ethnic minority in high ethnic density area	Any non-organic psychotic disorder	5 (1,328)	2.11, IRR	1.39-3.20	III (IV)	High	2.11
First generation immigrant	Any non-organic psychotic disorder	42 (25,063)	2.10, IRR	1.72-2.56	III (IV)	High	2.10
Toxoplasma gondii IgG	Any non-organic psychotic disorder	42 (8,796)	1.82, OR	1.51-2.18	III (IV)	High	1.82
Non-right handedness	Any non-organic psychotic disorder	41 (2,652)	1.58, OR	1.35-1.86	III (NS)	Medium	1.58
Paternal age >35	Schizophrenia spectrum disorders	10 (NA)	1.28, OR	1.11-1.48	III (NA)	Medium	1.28
Winter/spring season of birth in the Northern hemisphere	Any non-organic psychotic disorder	27 (115,010)	1.04, OR	1.02-1.06	III (NA)	High	1.04
		Mood (affective) disorders					
Widowhood	Depressive disorders	5 (2,720)	5.59, RR	3.79-8.23	I (I)	Low	5.59
Sexual dysfunction	Depressive disorders	6 (5,488)	2.71, OR	1.93-3.79	I (I)	High	2.71
Irritable bowel syndrome	Bipolar disorders	6 (177,117)	2.48, OR	2.35-2.61	I (NA)	High	2.48
Four or five metabolic risk factors	Depressive disorders	8 (1,191)	2.06, OR	1.59-2.68	I (I)	Low	2.06
Physical abuse in childhood	Depressive disorders	10 (3,886)	1.98, OR	1.68-2.33	I (I)	Medium	1.98

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders *(continued)*

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Job strain	Depressive disorders	7 (1,909)	1.77, OR	1.46-2.13	I (I)	Medium	1.77
Obesity	Depressive disorders	8 (7,673)	1.35, OR	1.21-1.50	I (I)	Low	1.35
Dietary zinc	Depressive disorders	8 (3,708)	0.65, RR	0.57-0.75	I (NA)	Medium	0.65
Tea intake	Depressive disorders	13 (4,373)	0.68, RR	0.61-0.77	I (NA)	Medium	0.68
Dry eye disease with Sjögren's syndrome	Depressive disorders	7 (3,062)	4.25, OR	2.67-6.76	II (NA)	Low	4.25
Poor physical health	Depressive disorders in elderhood	11 (8,630)	4.08, OR	3.25-5.12	II (NA)	Low	4.08
Adversities in childhood	Bipolar disorders	13 (1,146)	2.86, OR	2.03-4.04	II (NA)	High	2.86
Emotional abuse in childhood	Depressive disorders	8 (4,112)	2.78, OR	1.89-4.09	II (III)	Medium	2.78
Chronic disease	Depressive disorders in elderhood	10 (9,090)	2.59, OR	1.78-3.76	II (III)	Low	2.59
Intimate partner violence against women	Depressive disorders	9 (3,003)	2.57, RR	2.25-2.94	II (NA)	Low	2.57
Sexual abuse in childhood	Depressive disorders	14 (4,586)	2.42, OR	1.94-3.02	II (II)	Medium	2.42
Gulf war veterans	Depressive disorders	11 (16,826)	2.37, OR	1.91-2.93	II (NA)	Low	2.37
Asthma	Depressive disorders in childhood	7 (2,828)	2.08, OR	1.56-2.77	II (NA)	Low	2.08
Three metabolic risk factors	Depressive disorders	8 (3,014)	1.99, OR	1.60-2.48	II (II)	Low	1.99
Poor vision	Depressive disorders in elderhood	12 (11,066)	1.94, OR	1.67-2.25	II (NA)	Medium	1.94
Sleep disturbances	Depressive disorders in elderhood	11 (2,610)	1.92, RR	1.59-2.33	II (II)	High	1.92
Psoriasis	Depressive disorders	9 (86,945)	1.64, OR	1.41-1.90	II (NA)	Medium	1.64
Low education	Depressive disorders in elderhood	24 (16,590)	1.58, OR	1.38-1.82	II (IV)	Low	1.58
Metabolic syndrome	Depressive disorders	27 (20,924)	1.42, OR	1.28-1.57	II (IV)	Medium	1.42
Sedentary behaviour	Depressive disorders	24 (60,526)	1.25, RR	1.16-1.35	II (NA)	Medium	1.25
Neglect in childhood	Depressive disorders	6 (1,668)	2.75, OR	1.59-4.74	III (NA)	Medium	2.75
Insomnia	Depressive disorders	21 (NA)	2.60, OR	1.98-3.42	III (NA)	Low	2.60
Chronic lung disease	Depressive disorders	4 (297,031)	2.38, RR	1.47-3.85	III (NA)	Medium	2.38
Dry eye disease without Sjögren's syndrome	Depressive disorders	6 (611,517)	2.24, OR	1.50-3.34	III (NA)	Low	2.24
Vitamin D deficiency	Depressive disorders	3 (NA)	2.22, HR	1.42-3.47	III (III)	High	2.22
Asthma	Bipolar disorders	4 (50,358)	2.12, OR	1.57-2.87	III (NA)	Medium	2.12
Maltreatment in childhood	Depressive disorders in childhood	5 (1,400)	2.03, OR	1.37–3.01	III (NA)	High	2.03
Terrorist act exposure	Depressive disorders	6 (NA)	2.02, OR	1.38-2.96	III (NA)	High	2.02
Diabetes	Depressive disorders in elderhood	9 (1,814)	1.88, OR	1.31-2.70	III (NA)	Medium	1.88
Heart disease	Depressive disorders in elderhood	6 (1,911)	1.81, OR	1.41-2.31	III (NA)	Medium	1.81
Obesity	Bipolar disorders	9 (12,259)	1.77, OR	1.40-2.23	III (NA)	Low	1.77
Hearing impairment	Depressive disorders in elderhood	7 (4,448)	1.71, OR	1.28-2.27	III (NA)	Medium	1.71

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders *(continued)*

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Age >65	Depressive disorders in elderhood	6 (15,017)	1.63, OR	1.24-2.16	III (NA)	Low	1.63
Living alone	Depressive disorders in elderhood	16 (10,478)	1.55, OR	1.23-1.95	III (NA)	Low	1.55
Age >85	Depressive disorders in elderhood	12 (4,559)	1.52, OR	1.20-1.93	III (NA)	Low	1.52
Two metabolic risk factors	Depressive disorders	8 (6,691)	1.45, OR	1.17-1.80	III (NA)	Low	1.45
Low birth weight (≤2,500 g)	Depressive disorders	21 (NA)	1.38, OR	1.16-1.65	III (NA)	Low	1.38
Age >75	Depressive disorders in elderhood	19 (11,219)	1.35, OR	1.17-1.56	III (NA)	Low	1.35
Type 2 diabetes mellitus	Depressive disorders	11 (37,964)	1.24, OR	1.09-1.40	III (NA)	Medium	1.24
Unemployment	Depressive disorders	13 (40,679)	1.16, OR	1.09-1.23	III (NA)	Medium	1.16
Fruit intake	Depressive disorders	8 (NA)	0.85, RR	0.77-0.93	III (NA)	Low	0.85
Traditional/healthy dietary patterns	Depressive disorders	17 (NA)	0.76, RR	0.68-0.86	III (NA)	Low	0.76
Iron intake	Depressive disorders	3 (1,045)	0.40, RR	0.24-0.65	III (NA)	Medium	0.40
Neurotic, stress-related and somatoform disorders							
Physical abuse in childhood	Social anxiety disorder	4 (1,191)	2.59, OR	2.17-3.10	I (IV)	High	2.59
Physical disease history	PTSD	4 (2,161)	2.29, OR	2.07-2.52	I (NA)	High	2.29
Family history of psychiatric disorder	PTSD	12 (1,765)	1.80, OR	1.48-2.19	I (NA)	Medium	1.80
Being an Indigenous American	PTSD	5 (3,214)	1.47, OR	1.28-1.69	I (NA)	High	1.47
Cumulative exposure to potentially traumatic experiences	PTSD	17 (3,094)	5.24, OR	3.54-7.76	II (NA)	High	5.24
Trauma severity	PTSD	25 (2,017)	0.66, g	0.44-0.88	II (IV)	Medium	3.32
Being trapped in an earthquake	PTSD	1 (2,028	2.86, OR	2.52-3.25	II (NA)	High	2.86
Female sex	PTSD	112 (9,137)	1.65, OR	1.45-1.87	II (NA)	Medium	1.65
Torture exposure	PTSD	10 (1,357)	4.46, OR	2.39-8.31	III (NA)	Low	4.46
Sexual abuse in childhood	Social anxiety disorder	5 (1,239)	3.18, OR	1.73-5.86	III (IV)	High	3.18
Personal psychiatric history	PTSD	27 (1,753)	2.45, OR	1.67-3.61	III (IV)	Medium	2.45
Overprotection from father	Obsessive-compulsive disorder	6 (716)	0.44, g	0.21-0.68	III (NA)	High	2.24
Behavioural syndromes associated with physiological disturbances and physical factors							
Appearance-related teasing victimization	Any eating disorder	10 (1,341)	2.91, OR	2.05-4.12	II (NA)	Medium	2.91
Sexual abuse in childhood	Bulimia nervosa	26 (1,103)	2.73, OR	1.96-3.79	II (NA)	Medium	2.73
ADHD	Any eating disorder	12 (3,618)	4.24, OR	2.62-6.87	III (NA)	Medium	4.24
Physical abuse in childhood	Binge eating disorder	4 (NA)	3.10, OR	2.48-3.88	III (NA)	Medium	3.10
Sexual abuse in childhood	Binge eating disorder	7 (NA)	2.31, OR	1.66-3.20	III (NA)	Medium	2.31
Self-reported dieting	Bulimia nervosa	7 (NA)	0.22, r	0.14-0.30	III (NA)	Medium	2.26
Body dissatisfaction	Any eating disorder	11 (NA)	0.14, r	0.11-0.17	III (NA)	Medium	1.67
Perceived pressure to be thin	Any eating disorder	4 (NA)	0.11, r	0.08-0.14	III (NA)	Medium	1.51
Negative affect	Any eating disorder	11 (NA)	0.09, r	0.06-0.12	III (NA)	Medium	1.38
5-min Apgar score <7	Anorexia nervosa	33 (2,701)	1.32, OR	1.17-1.49	III (NA)	Medium	1.32

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders *(continued)*

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Disorders of adult personality and behaviour							
Emotional abuse in childhood	Borderline personality disorder	27 (3,525)	28.15, OR	17.46-53.68	II (NA)	Medium	28.15
Emotional neglect in childhood	Borderline personality disorder	21 (3,225)	22.86, OR	11.55-45.22	II (NA)	Medium	22.86
Adversities in childhood	Borderline personality disorder	97 (16,098)	14.32, OR	10.80-18.98	II (NA)	Medium	14.32
Physical abuse in childhood	Borderline personality disorder	30 (2,869)	9.30, OR	6.57-13.17	II (NA)	Medium	9.30
Sexual abuse in childhood	Borderline personality disorder	31 (3,748)	7.95, OR	6.21-10.17	II (NA)	Medium	7.95
Physical neglect in childhood	Borderline personality disorder	20 (3,072)	5.73, OR	3.21-10.21	II (NA)	Medium	5.73
Mental retardation							
None of the factors was supported by class I, II or III evidence							
Disorders of psychological development							
Maternal SSRI use during pregnancy*	Autism spectrum disorder	7 (19,670)	1.84, OR	1.60-2.11	I (II)	Medium	1.84
Maternal pre-pregnancy antidepressant use*	Autism spectrum disorder	7 (22,877)	1.48, RR	1.29-1.71	I (NA)	Medium	1.48
Maternal chronic hypertension	Autism spectrum disorder	4 (22,864)	1.48, OR	1.29-1.70	I (NA)	Medium	1.48
Maternal gestational hypertension	Autism spectrum disorder	9 (4,334)	1.37, OR	1.21-1.54	I (NA)	Medium	1.37
Maternal pre-eclampsia	Autism spectrum disorder	10 (10,699)	1.32, RR	1.20-1.45	I (NA)	Medium	1.32
Maternal age ≥35 years	Autism spectrum disorder	11 (>1,000)	1.31, RR	1.18-1.45	I (NA)	Low	1.31
Maternal overweight pre/during pregnancy	Autism spectrum disorder	5 (7,872)	1.28, RR	1.19-1.36	I (II)	Low	1.28
Highest paternal age group vs. reference group	Autism spectrum disorder	20 (2,920)	1.55, OR	1.39-1.73	II (NA)	Medium	1.55
Paternal age >45 years	Autism spectrum disorder	18 (>1,000)	1.43, OR	1.33-1.53	II (III)	High	1.43
Highest maternal age group vs. reference group	Autism spectrum disorder	19 (2,254)	1.42, OR	1.29-1.55	II (IV)	Medium	1.42
Paternal age 40-45 years	Autism spectrum disorder	12 (>1,000)	1.37, OR	1.23-1.53	II (IV)	High	1.37
Maternal autoimmune disease	Autism spectrum disorder	10 (9,775)	1.37, OR	1.21-1.54	II (NA)	Medium	1.37
Higher paternal age (per 10-years increase)	Autism spectrum disorder	17 (47,373)	1.21, OR	1.18-1.24	II (NA)	Medium	1.21
Maternal paracetamol use during pregnancy*	Autism spectrum disorder	5 (>100)	1.20, RR	1.14-1.26	II (NA)	Medium	1.20
Maternal age 30-34	Autism spectrum disorder	8 (>1,000)	1.14, RR	1.09-1.18	II (NA)	Low	1.14
Hearing impairment	Autism spectrum disorder	7 (4,370)	14.16, RR	4.53-44.22	III (NA)	Medium	14.16
5-min Apgar score <7	Autism spectrum disorder	6 (3,676)	1.67, OR	1.34 -2.09	III (NA)	Medium	1.67
Family history of psoriasis	Autism spectrum disorder	8 (>1,000)	1.59, OR	1.28-1.97	III (NA)	Medium	1.59
Family history of rheumatoid arthritis	Autism spectrum disorder	8 (>1,000)	1.51, OR	1.19-1.91	III (NA)	Medium	1.51
Maternal diabetes	Autism spectrum disorder	16 (8,872)	1.49, RR	1.28-1.74	III (NA)	High	1.49
Family history of type 1 diabetes	Autism spectrum disorder	13 (>1,000)	1.49, OR	1.23-1.81	III (NA)	Medium	1.49
Maternal infection requiring hospitalization	Autism spectrum disorder	3 (34,547)	1.30, OR	1.14-1.50	III (NA)	Medium	1.30
Family history of any autoimmune disease	Autism spectrum disorder	17 (1,894)	1.28, OR	1.12-1.48	III (NA)	Medium	1.28
Reference group vs. lowest paternal age group	Autism spectrum disorder	15 (2,295)	1.24, OR	1.12-1.37	III (NA)	Medium	1.24

Table 2 Evidence for associations between non-purely genetic risk or protective factors and mental disorders *(continued)*

Risk or protective factor	Mental disorder	Number of individual studies (cases)	Strength of association, measure	95% CI	Class of evidence (prospective evidence class)	Quality (AMSTAR)	eOR
Higher maternal age (per 10-years increase)	Autism spectrum disorder	14 (46,025)	1.18, OR	1.10-1.26	III (NA)	Medium	1.18
Paternal age 35-40 years	Autism spectrum disorder	16 (>1,000)	1.14, OR	1.08-1.21	III (NA)	High	1.14
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence							
Maternal pre-pregnancy obesity	ADHD	11 (40,880)	1.63, OR	1.49-1.77	I (I)	Low	1.63
Eczema in childhood	ADHD	6 (10,636)	1.31, OR	1.20-1.44	I (IV)	Low	1.31
Maternal hypertensive disorders during pregnancy	ADHD	8 (37,128)	1.29, OR	1.22-1.36	I (NA)	High	1.29
Maternal pre-eclampsia	ADHD	6 (>1,000)	1.28, OR	1.21-1.35	I (NA)	High	1.28
Maternal paracetamol use during pregnancy*	ADHD	8 (>1,000)	1.25, RR	1.17-1.34	I (I)	High	1.25
Maternal smoking during pregnancy	ADHD	20 (50,044)	1.60, OR	1.45-1.76	II (II)	High	1.60
Asthma in childhood	ADHD	11 (32,539)	1.51, OR	1.40-1.63	II (NA)	High	1.51
Maternal overweight pre/during pregnancy	ADHD	9 (23,525)	1.28, OR	1.21-1.35	II (I)	Low	1.28
Preterm birth	ADHD	11 (1,542)	1.84, OR	1.36-2.49	III (NA)	High	1.84
Maternal stress during pregnancy	ADHD	8 (25,547)	1.72, OR	1.27-2.34	III (NA)	High	1.72
Maternal SSRI use during pre-pregnancy period*	ADHD	3 (39,097)	1.59, RR	1.23-2.06	III (NA)	High	1.59
Maternal non-SSRI antidepressants use during pregnancy*	ADHD	6 (23,064)	1.50, RR	1.24-1.82	III (NA)	High	1.50
Maternal SSRI use during pregnancy*	ADHD	5 (56,502)	1.37, RR	1.16-1.63	III (NA)	High	1.37
Child 4 months younger than school classmates	ADHD	30 (>1,000)	1.36, RR	1.25-1.47	III (NA)	High	1.36
Maternal diabetes	ADHD	2 (>1,000)	1.36, HR	1.19-1.55	III (NA)	High	1.36
5-min Apgar score <7	ADHD	7 (37,414)	1.30, OR	1.11-1.52	III (NA)	High	1.30
High frequency of maternal cell phone use during pregnancy	ADHD	5 (6,922)	1.29, OR	1.12-1.48	III (NA)	Low	1.29
Caesarean delivery	ADHD	14 (92,426)	1.17, OR	1.08-1.26	III (NA)	High	1.17
Breech/transverse presentation	ADHD	5 (29,051)	1.14, OR	1.06-1.22	III (NA)	High	1.14

AMSTAR – A Measurement Tool to Assess Systematic Reviews, OR – odds ratio, RR – risk ratio, IRR – incidence rate ratio, HR – hazard ratio, eOR – equivalent OR, NA – not available, ADHD – attention-deficit/hyperactivity disorder, PTSD – post-traumatic stress disorder, NSAID – nonsteroidal anti-inflammatory drug, SSRI – selective serotonin-reuptake inhibitor, * documented or likely confounding by indication

tobacco smoking, being a North African immigrant in Europe, urbanicity, ethnic minority in high ethnic density area, being a first generation immigrant, Toxoplasma gondii IgG, non-right handedness, paternal age >35, and winter/spring season of birth in the Northern hemisphere.

For class I evidence, the prospective analysis of risk factors showed that only clinical high risk state for psychosis remained at the same level of evidence, while Black-Caribbean ethnicity in England was downgraded to class IV evidence, and for obstetric complications the level of evidence was not available. For class II evidence, the prospective analysis of risk factors showed that cannabis use and adversities in childhood remained at the same level of evidence, while ethnic minority in low ethnic density area and being a second generation immigrant were downgraded to class IV evidence. One class II evidence protective factor, premorbid IQ, was also downgraded to class IV evidence. For the remaining class II factors, the level of evidence in prospective studies was not available.

For class III evidence risk factors, the prospective analysis showed that only urbanicity remained at the same level of evidence, while social withdrawal in childhood, being a North African immigrant in Europe, ethnic minority in high ethnic density area, being a first generation immigrant and Toxoplasma gondii IgG were downgraded to class IV evidence. The remaining factors

were either downgraded to the non-significant level or the level of evidence was not available (Table 2).

Mood (affective) disorders

Forty-eight associations with depressive or bipolar disorders were evaluated within this ICD-10 diagnostic block[32,34]. Nine associations were supported by class I evidence (Table 2). Of these, six were risk factors for depressive disorders: widowhood (RR=5.59), sexual dysfunction (OR=2.71), four or five metabolic risk factors (OR=2.06), physical abuse in childhood (OR=1.98), job strain (OR=1.77), and obesity (OR=1.35). One was a risk factor for bipolar disorders: irritable bowel syndrome (OR=2.48). Two were protective factors for depressive disorders: dietary zinc (RR=0.65) and tea intake (RR=0.68).

Sixteen associations were supported by class II evidence (Table 2). These included nine risk factors for depressive disorders: dry eye disease with Sjögren's syndrome (OR=4.25), emotional abuse in childhood (OR=2.78), intimate partner violence against women (RR=2.57), sexual abuse in childhood (OR=2.42), being a Gulf War veteran (OR=2.37), three metabolic risk factors (OR=1.99), psoriasis (OR=1.64), metabolic syndrome (OR=1.42), and sedentary behaviour (RR=1.25). There were five risk factors for depressive disorders in elderhood: poor physical health (OR=4.08), chronic disease (OR=2.59), poor vision (OR=1.94), sleep disturbances (RR=1.92), and low education (OR=1.58). There was one risk factor for depressive disorders in childhood: asthma (OR=2.08). There was one risk factor for bipolar disorders: adversities in childhood (OR=2.86).

Twenty-three associations were supported by class III evidence (Table 2). These included ten risk factors for depressive disorders: neglect in childhood, insomnia, chronic lung disease, dry eye disease without Sjögren's syndrome, vitamin D deficiency, terrorist act exposure, two metabolic risk factors, low birth weight (≤2,500 g), type 2 diabetes mellitus, and unemployment. There was one risk factor for depressive disorders in childhood (maltreatment), and seven risk factors for depressive disorders in elderhood (diabetes, heart disease, hearing impairment, age >65, living alone, age >85, and age >75). There were two risk factors for bipolar disorders: asthma and obesity. There were also three protective factors for depressive disorders: fruit intake, traditional/healthy dietary patterns, and iron intake.

For class I evidence, the prospective analysis showed that six risk factors for depressive disorders – widowhood, sexual dysfunction, four or five metabolic risk factors, physical abuse in childhood, job strain, and obesity – remained at the same level of evidence, while dietary zinc and tea intake, as well as irritable bowel syndrome, which was associated with bipolar disorders, were either downgraded to the non-significant level, or the level of evidence was not available. For class II evidence, the prospective analysis showed that two risk factors for depressive disorders (sexual abuse in childhood, and three metabolic risk factors), and one risk factor for depressive disorders in elderhood (sleep disturbances) remained at the same level of evidence. Two class II risk factors for depressive disorders (emotional abuse in childhood, and metabolic syndrome), and two risk factors for depressive disorders in elderhood (chronic disease and low education) were downgraded to class III or IV evidence. For the remaining class II factors, the level of evidence in prospective studies was not available. For class III evidence, the prospective analysis showed that one risk factor for depressive disorders (vitamin D deficiency) remained at the same level of evidence, while all the other factors were either downgraded to the non-significant level or the level of evidence was not available (Table 2).

Neurotic, stress-related and somatoform disorders

Twelve associations across three mental disorders – social anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorders (PTSD) – were evaluated within this ICD-10 diagnostic block[6,36]. Four associations were supported by class I evidence (Table 2). These involved one risk factor for social anxiety disorder, namely physical abuse in childhood (OR=2.59); and three risk factors for PTSD: physical disease history (OR=2.29), family history of psychiatric disorder (OR=1.80), and being an indigenous American (OR=1.47).

Four associations were supported by class II evidence (Table 2). These all involved risk factors for PTSD: cumulative exposure to potentially traumatic experiences (OR=5.24), trauma severity (Hedges' g = 0.66), being trapped in an earthquake (OR=2.86), and female sex (OR=1.65).

Four associations were supported by class III evidence (Table 2), involving two risk factors for PTSD (torture exposure and personal psychiatric history); one risk factor for social anxiety disorder (sexual abuse in childhood); and one risk factor for obsessive-compulsive disorder (overprotection from father).

For class I evidence, the prospective analysis showed that no factor retained its class of evidence. Physical abuse in childhood as a risk factor for social anxiety disorder was downgraded to class IV evidence, while the other factors were downgraded to the non-significant level or were not computable or available. For class II evidence, the prospective analysis showed that trauma severity as a risk factor for PTSD was downgraded to class IV evidence. For class III evidence, the prospective analysis showed that personal psychiatric history as a risk factor for PTSD, and sexual abuse in childhood as a risk factor for social anxiety disorder, were downgraded to class IV evidence. For the remaining class II and III evidence factors, no prospective analysis data were available (Table 2).

Behavioural syndromes associated with physiological disturbances and physical factors

Ten associations with eating disorders (any eating disorder, bulimia nervosa, anorexia nervosa, binge eating disorder) were evaluated within this ICD-10 diagnostic block[40]. None of the associations was supported by class I evidence. Two associations

were supported by class II evidence (Table 2), involving two risk factors: appearance-related teasing victimization (with any eating disorder, OR=2.91) and sexual abuse in childhood (with bulimia nervosa, OR=2.73).

Eight associations were supported by class III evidence (Table 2), involving ADHD, physical and sexual abuse in childhood, self-reported dieting, body dissatisfaction, perceived pressure to be thin, negative affect, and 5-min Apgar score <7.

No prospective analysis data were available for any of the factors (Table 2).

Disorders of adult personality and behaviour

Six associations with borderline personality disorder were evaluated within this ICD-10 diagnostic block[42]. The associations were all supported by class II evidence, involving emotional (OR=28.15), physical (OR=9.30) and sexual (OR=7.95) abuse; emotional (OR=22.86) and physical (OR=5.73) neglect; and adversities in childhood (OR=14.32) (Table 2).

The level of evidence in prospective studies was not available.

Mental retardation

No class I-III risk factor for mental retardation was identified.

Disorders of psychological development

Within this ICD-10 diagnostic block, 26 associations with autism spectrum disorder were evaluated[35]. Seven associations were supported by class I evidence (Table 2). These involved seven risk factors: maternal selective serotonin reuptake inhibitor (SSRI) use during pregnancy (OR=1.84, confounding by indication such as underlying maternal mental disorders), maternal pre-pregnancy antidepressant use (RR=1.48, confounding by indication as above), maternal chronic hypertension (OR=1.48), maternal gestational hypertension (OR=1.37), maternal pre-eclampsia (RR=1.32), maternal age ≥35 years (RR=1.31), and maternal overweight pre/during pregnancy (RR=1.28).

Eight associations were supported by class II evidence (Table 2), all involving risk factors. These were: highest paternal age group vs. reference group (OR=1.55), paternal age >45 years (OR=1.43), highest maternal age group vs. reference group (OR=1.42), paternal age 40-45 years (OR=1.37), maternal autoimmune disease (OR=1.37), higher paternal age per 10-years increase (OR=1.21), maternal paracetamol use during pregnancy (RR=1.20, likely confounding by indication such as maternal comorbidities involving inflammation or infection), and maternal age 30-34 (RR=1.14).

Eleven associations were supported by class III evidence (Table 2), all involving risk factors: hearing impairment, 5-min Apgar score <7, family history of psoriasis, family history of rheumatoid arthritis, maternal diabetes, family history of type 1 diabetes, maternal infection requiring hospitalization, family history of any autoimmune disease, reference group vs. lowest paternal age group, higher maternal age per 10-years increase, and paternal age 35-40 years.

For class I evidence, the prospective analysis showed that none of the risk factors remained at the same level. Maternal SSRI use during pregnancy (confounding by indication) and maternal overweight pre/during pregnancy were downgraded to class II evidence, while all other class I factors were downgraded to non-significant levels or prospective evidence was not available. For class II evidence, the prospective analysis showed that none of the factors retained the same level of evidence. Paternal age >45 years, highest maternal age group vs. reference group, and paternal age 40-45 years were downgraded to class III or IV evidence. For the remaining class II evidence factors and all class III evidence factors, no prospective analysis data were available (Table 2).

Behavioural and emotional disorders with onset usually occurring in childhood and adolescence

Nineteen associations with ADHD were evaluated within this ICD-10 diagnostic block[37]. Five associations were supported by class I evidence (Table 2), all including risk factors: maternal pre-pregnancy obesity (OR=1.63), eczema in childhood (OR=1.31), maternal hypertensive disorders during pregnancy (OR=1.29), maternal pre-eclampsia (OR=1.28), and maternal paracetamol use during pregnancy (OR=1.25, likely confounding by indication).

Three associations were supported by class II evidence (Table 2), involving three risk factors: maternal smoking during pregnancy (OR=1.60), asthma in childhood (OR=1.51), and maternal overweight pre/during pregnancy (OR=1.28).

Eleven associations, all involving risk factors, were supported by class III evidence (Table 2). They were: preterm birth, maternal stress during pregnancy, maternal SSRI use during pre-pregnancy period, maternal non-SSRI antidepressant use during pregnancy, maternal SSRI use during pregnancy (confounding by indication for all antidepressant exposures), child 4 months younger than school classmates, maternal diabetes, 5-min Apgar score <7, high frequency of maternal cell phone use during pregnancy, caesarean delivery, and breech/transverse presentation.

For class I evidence, the prospective analysis showed that maternal obesity pre-pregnancy and maternal paracetamol use during pregnancy (likely confounding by indication) remained at the same level of evidence, while eczema in childhood was downgraded to class IV evidence, and there were no prospective data for the remaining factors. For class II evidence, the prospective analysis showed that maternal smoking during pregnancy remained at the same level of evidence, while maternal overweight pre/during pregnancy was upgraded to class I level factor (there were no more small-study effects). For the remaining class II and all class III evidence factors, no prospective analysis data were available (Table 2).

Quality assessment

Based on the AMSTAR evaluation, 58 associations (32.9%) met the high-quality level, 86 (48.9%) were of medium quality, and 32 (18.2%) were of low quality (Table 2).

Evidence for transdiagnostic risk/protective factors

Eighteen risk factors had a consistent definition across umbrella reviews and were associated with different mental disorders, enabling us to pool them and test their transdiagnosticity against TRANSD criteria (Table 3).

Sexual abuse in childhood met TRANSD transdiagnostic criteria across at least five mental disorders: borderline personality disorder[42], bulimia nervosa[40], binge eating disorder[40], depressive disorders[34], and social anxiety disorder[36] (class II evidence; OR=3.92).

Physical abuse in childhood met TRANSD transdiagnostic criteria across at least four mental disorders: depressive disorders[34], social anxiety disorder[36], borderline personality disorder[42], and binge eating disorder[40] (class II evidence; OR=4.82).

Adversities in childhood were associated with at least three mental disorders: borderline personality disorder[42], bipolar disorders[32], and schizophrenia spectrum disorders[33] (class II evidence; OR=13.83). However, bipolar disorders did not meet the criterion T of the TRANSD framework, because the ICD/DSM gold standard was not acknowledged[32].

Five-min Apgar score <7 met TRANSD transdiagnostic criteria across three mental disorders: autism spectrum disorder[35], anorexia nervosa[40], and ADHD[37] (class III evidence; OR=1.27).

Type 2 diabetes mellitus was associated with Alzheimer's disease[27], vascular dementia[27], and depressive disorders[34] (class II evidence; OR=1.53); and obesity was associated with depressive disorders[34], bipolar disorders[32], and any dementia[27] (class II evidence; OR=1.58). However, they did not meet the TRANSD criterion T[27,32,34].

Asthma was associated with depressive disorders in childhood[34], bipolar disorders[32], and ADHD[37] (class II evidence; OR=1.79). However, bipolar disorders did not met the criterion T of the TRANSD framework[32]. Several other risk factors were associated with at least two mental disorders, as shown in Table 3.

When the transdiagnostic class of evidence was restricted to prospective analyses, 5-min Apgar score <7 remained in class III, while type 2 diabetes mellitus was downgraded from class II to class III. Prospective data were not available for the remaining transdiagnostic factors associated with at least three mental disorders.

Evidence for factors having both risk and protective associations with various mental disorders

No factors were found to have both risk and protective associations with various mental disorders. There were only reciprocal operationalizations of the same factor showing risk-increasing or protective effects (e.g., high physical activity vs. sedentary behaviour, or parental alcohol supply vs. parental stricter alcohol rules).

DISCUSSION

This is the largest available systematic evidence-based risk atlas of mental disorders. Its main strength is the rigorous assessment of the credibility of the evidence, which is essential to overcome several types of biases in aetiopathological research. Furthermore, we have adopted a lifespan approach spanning from the pre/perinatal period to childhood, adulthood and elderhood.

A first overarching finding is that 176 associations between risk/protective factors and mental disorders met the criteria for class I-III evidence. These associations reflected large-scale observational studies conducted worldwide, thus representing consolidated risk signatures for mental disorders and countering replication crisis[43] and scientific pessimism in psychiatry.

At the same time, it is essential to acknowledge that association is not necessarily causation. In particular, reverse causation can confound aetiopathological research[44]. Accordingly, assessing temporality between exposures and outcome is one of the core Bradford Hill criteria that may be considered when navigating the difficult question of causation vs. plain association[45,46]. This potential bias was controlled in sensitivity analyses. Some factors were additionally excluded because of survival biases (i.e., history of cancer[27]). Others were excluded because of confounding by indication, as documented in previous umbrella reviews and meta-analyses[21,47] (i.e., maternal SSRI use before and during pregnancy[35,37], maternal antidepressant use before pregnancy[35], maternal non-SSRI antidepressant use during pregnancy[37]) or acknowledged as likely (benzodiazepine use[27], maternal paracetamol use during pregnancy[35,37]). We found that 26 associations, relating to 20 risk factors and one protective factor, retained convincing or highly suggestive credibility of evidence (i.e., class I or II) in prospective analyses. The provision of such robust knowledge is essential to allow a more detailed characterization of mental disorders which overcomes the current diagnostic limitations[48-50], and a prerequisite for evidence-based preventive and early intervention approaches[51,52], because most of the identified risk factors are, at least theoretically, modifiable.

Specifically, we have found that type 2 diabetes mellitus, depression and low frequency of social contacts are consistently associated with dementia. These exposures should be systematically screened in the elderly and could be considered part of refined management strategies in the early phases of dementia. At the same time, our finding of the protective role of high-intensity exercise is consistent with meta-analytic evidence that this exercise improves some outcomes of dementia, such as motor performance and daily functioning[53].

Beyond dementia, impaired physical health emerged as an overarching core cluster, with three or four-five metabolic risk

Table 3 Evidence for transdiagnostic risk factors

Factor	Mental disorders	Transdiagnostic class of evidence (prospective evidence class)	Transdiagnostic odds ratio (95% CI)	Number of individual studies (cases)	TRANSD criteria met or not
Sexual abuse in childhood	Borderline personality disorder	II (NA)	3.92 (3.33-4.61)	83 (>10,676)	Yes
	Bulimia nervosa				
	Binge eating disorder				
	Depressive disorders				
	Social anxiety disorder				
Physical abuse in childhood	Depressive disorders	II (NA)	4.82 (3.92-5.91)	48 (>7,946)	Yes
	Social anxiety disorder				
	Borderline personality disorder				
	Binge eating disorder				
Adversities in childhood	Borderline personality disorder	II (NA)	13.83 (10.49-18.23)	144 (24,982)	Yes (for two disorders only)
	Bipolar disorders				
	Schizophrenia spectrum disorders				
5-min Apgar score <7	Autism spectrum disorder	III (III)	1.27 (1.11-1.46)	46 (43,791)	Yes
	Anorexia nervosa				
	ADHD				
Type 2 diabetes mellitus	Alzheimer's disease	II (III)	1.53 (1.39-1.69)	46 (42,897)	No
	Vascular dementia				
	Depressive disorders				
Obesity	Depressive disorders	II (NA)	1.58 (1.40- 1.79)	22 (21,846)	No
	Bipolar disorders				
	Any dementia				
Asthma	Depressive disorders in childhood	II (NA)	1.79 (1.62- 1.97)	22 (85,725)	Yes (for two disorders only)
	Bipolar disorders				
	ADHD				
Low education	Depressive disorders in elderhood	II (NA)	1.68 (1.46-1.93)	40 (19,359)	No
	Alzheimer's disease				
ADHD	Any eating disorder	III (NA)	3.58 (2.50-5.14)	16 (>3,618)	Yes
	Tobacco related disorder				
Tobacco smoking	Opioid use disorder	II (II)	2.61 (2.04-3.33)	27 (>2,447)	No
	Schizophrenia spectrum disorders				
Emotional abuse in childhood	Borderline personality disorder	II (NA)	15.22 (10.02-23.10)	35 (7,637)	Yes
	Depressive disorders				
Hearing impairment	Autism spectrum disorder	III (NA)	4.98 (2.17- 11.45)	14 (8,818)	No
	Depressive disorders in elderhood				
Maternal pre-eclampsia	Autism spectrum disorder	I (II)	1.29 (1.22-1.36)	16 (>11,699)	Yes
	ADHD				
Maternal paracetamol use during pregnancy*	Autism spectrum disorder	II (II)	1.23 (1.17-1.28)	13 (>2,000)	Yes
	ADHD				
Maternal SSRI use during pregnancy*	Autism spectrum disorder	I (II)	1.62 (1.44- 1.82)	12 (76,112)	Yes
	ADHD				

Table 3 Evidence for transdiagnostic risk factors *(continued)*

Factor	Mental disorders	Transdiagnostic class of evidence (prospective evidence class)	Transdiagnostic odds ratio (95% CI)	Number of individual studies (cases)	TRANSD criteria met or not
Maternal overweight pre/during pregnancy	Autism spectrum disorder	I (I)	1.26 (1.22- 1.30)	14 (31,397)	No
	ADHD				
Maternal diabetes	Autism spectrum disorder	III (III)	1.44 (1.27-1.65)	18 (>9,872)	No
	ADHD				
Surviving childhood cancer	Tobacco related disorder	III (NA)	0.61 (0.50-0.75)	9 (3,412)	No
	Alcohol related disorder				

ADHD – attention-deficit/hyperactivity disorder, SSRI – selective serotonin-reuptake inhibitor, NA – not available, * documented or likely confounding by indication

factors and obesity being associated with depressive disorders; maternal overweight before/during pregnancy with autism spectrum disorder; and maternal overweight or obesity before/during pregnancy with ADHD. These findings reflect the close interplay between environmental factors and early brain development, as well as the close interconnection of mental and physical domains[54]. The latter has the potential to offset the numerator of efforts and costs for preventive and early intervention by a denominator of multiple mental and physical disease endpoints. Physical activity is recommended[55] for improving outcomes across several mental disorders, including substance related disorders[56], and is also indicated to protect physical health of people with mental disorders[57]. The emerging field of lifestyle psychiatry recommends physical activity together with other "lifestyle factors", even beyond clinical populations, as a universal tool for public health strategies[58].

A related risk domain points to the potential impact of reducing tobacco smoking[41] or maternal smoking during pregnancy[37] in order to prevent opioid use disorder and ADHD, respectively; similarly, reducing cannabis use[33] emerges as an accessible mainstream approach to prevent psychosis[59]. Effective public health (e.g., community pharmacy-delivered interventions[60]), psychoeducation[61] and pharmacological interventions (e.g., varenicline[62-64]) are available to reduce tobacco smoking, but no interventions have yet been consolidated to reduce maternal smoking[65] or cannabis use[66,67].

A further cluster includes risk factors related to environmental stressors, with childhood adversities being associated with psychosis, and widowhood, childhood physical or sexual abuse, and job strain with depressive disorders. Early traumatic experiences have been suggested to be associated with a pro-inflammatory state in adulthood, with specific inflammatory profiles depending on the type of trauma[68]. Unfortunately, the current evidence is insufficient to recommend specific interventions to prevent early traumatic experiences[69]. Future research should prioritize population-level actions on social determinants of mental health (demographic, economic, neighbourhood, environmental events, social and cultural domains) to replace negative cycles of poverty, abuse, violence, environmental degradation and high personal stress with virtuous cycles of mental health, well-being, and sustainable development[52,70].

Another important finding is that the strongest level I risk factor surviving prospective analyses was the clinical high risk state for psychosis[15,71], with an eOR of about 9. However, this state may be better conceptualized as a risk marker, because it represents the result of different interacting risk factors[72,73] that accumulate during the recruitment phase[74] of these individuals. The clinical high risk state for psychosis is also the prototypical example of antecedent conditions[75], for which the boundaries with the onset of the disorder itself may become blurred[76-79].

According to methodological guidelines, ORs greater than 4.72 are to be considered large (assuming a prevalence rate of mental disorders in the non-exposed ranging from 1% to 5%)[80]. The vast majority of identified class I-III factors (independently of prospective sensitivity analyses) had only a small to medium effect size, with a few exceptions mostly relating to childhood trauma. This finding indicates that future aetiopathological studies need to move away from univariable analyses to rather augment polygenic risk prediction by multivariable measurements of environmental exposures in the same individuals.

In fact, mental disorders exhibit both equifinality (multiple factors can lead to the same disorder) and multifinality (the same aetiological factor can result in different mental disorders). For example, recent genome-wide association, copy number variant and exome sequencing studies have detected shared genetic risk loci among schizophrenia, bipolar disorder and autism, indicating a broad genetic vulnerability to mental disorders (i.e., genetic pleiotropy)[81,82]. On the other hand, recent transdiagnostic approaches in psychiatry have explored multifinality of environmental exposures. However, to date, transdiagnostic approaches have been limited by several methodological caveats, mostly involving reporting inaccuracies[83].

Our approach of combining robust classification of evidence with the TRANSD recommendations[30] has addressed these biases to deliver robust transdiagnostic evidence inasmuch as data were available. As shown in Table 3, we failed to identify a universal transdiagnostic factor that could account for most mental disorders (such as the "p" factor marker for general psychopa-

thology[83]). This finding is supported by the lack of convincing evidence supporting the existence of a truly transdiagnostic biomarker[84]. However, it is important to acknowledge that transdiagnostic aetiopathological research is still an emerging field and that only a few observational studies have conducted multivariable measurements that both lump (transdiagnostic) and split (specific) risk/protective factors across diagnostic dimensions[85]. The factors identified in Table 3 could represent the starting set of exposures to be tested across different mental disorders or intermediate phenotypes (e.g., those proposed by the Research Domain Criteria[86]).

Notably, about one-third of any class I-II factors listed in Table 2 and the vast majority of transdiagnostic factors listed in Table 3 impact the early neurodevelopment. This finding confirms that the maximal window of opportunity for discovering and therapeutically addressing transdiagnostic risk or protective factors is during the very early phases of neurodevelopment, where the chances of impacting the course of multiple disorders are the highest. Conceptually, these results corroborate the essential neurodevelopmental nature of many mental disorders and suggest that pre/perinatal psychiatry should become a mainstream focus of future applied clinical research and prevention psychiatry.

Genetic factors can be measured *en masse* with high precision, building on variation in specific single nucleotides in exact positions in the genome, and thus are unambiguously defined at all ages for all individuals and across all studies. In contrast, massive measurements of multiple environmental (or epigenetic) factors are challenging.

First, environmental factors pose logistic barriers, because their assessment may be particularly time consuming and lead to missing data. Recent developments in digital technologies (e.g., electronic medical records, mobile apps)[87,88] and sequential testing frameworks[89], as well as the recent availability of poly-environmental risk scores (e.g., psychosis poly-risk score[87,90] or exposome[91]), may make it possible to record multiple exposures in the same individuals in a deep phenotyping approach and over time.

Second, the distinction between clear-cut genetic and environmental factors in several circumstances may be spurious. For example, family history of mental disorders and socioeconomic status comprise both a genetic and an environmental component[90], genetic disposition for ADHD increases the risk of exposure to adverse environments[92], and polygenic risk scores for psychosis impact certain behavioural traits and risk exposures[93]. Epigenetic factors at the crossroads between genes and the environment[94] add another level of complexity. A pragmatic approach could be to define environmental factors as non-purely genetic factors, in line with the current study.

Third, while some risk factors are clearly operationalized (e.g., 5-min Apgar score <7 and low birth weight ≤2,500 g), numerous others (e.g., stressful events, childhood adversities) are not. Specifically, some of them are imprecisely defined, assessed through different instruments, or include contextual specifiers. For example, stressful events can be ascertained through multiple psychometric instruments, generally falling into two categories: checklists (e.g., the Life Events Checklist) and semi-structured interviews (e.g., the Life Events and Difficulties Schedule)[95]. While pooling these different instruments is legitimate within meta-analytical approaches, their empirical interchangeability for future use in research or clinical settings remains questionable. Similarly, while we found that advanced paternal age has been associated with autism, some associations have defined this factor by comparing the highest paternal age group vs. a reference group[96]. Interestingly, the authors themselves acknowledged that, as the reference groups were heterogeneous, it was "impossible to define a specific age range as the reference group"[96]. Because an unclear reference group is used for this factor, it is not truly measurable.

The associated caveat is that using loose operationalizations of factors will inevitably inflate their non-specificity of association across mental disorders, and therefore lead to an observed artificial transdiagnosticity across different dimensions. For example, psychotic experiences[97] measured through self-administered questionnaires[98] are relatively frequent at the population level (prevalence about 8% in young adults[99]) but poorly predictive of psychosis onset (risk of psychosis: 0.5-1% per year[99]). These manifestations cannot be conflated with the clinical high risk state for psychosis, which requires detection by an experienced and trained clinician[100], is not common in the general population (only 0.3% of individuals[101]), and is highly predictive of psychosis onset (risk of psychosis: 20% at 2 years[71,102]). The trivialization of the contextual significance of complex phenomena and their operationalization may result in non-specificity, triggering illusions of continuity and transdiagnostic phenomena[103].

In a similar vein, other factors may require temporal (e.g., childhood, midlife, elderhood) or contextual specifiers (e.g., Black-Caribbean ethnicity in England or indigenous Americans), since their validity may depend on their timing of action or different cultural scenarios. We also found that some factors may be influenced by changes in the contextual environment (e.g., cumulative exposure to potentially traumatic experiences), which may impact their durability over time. A further important methodological limitation is that there are several spurious risk markers (beyond the clinical high risk state for psychosis). For example, some experiences included among "childhood adversities", such as bullying, may be a marker of early vulnerability in social contexts[104].

The lack of standardized assessment measures to reliably record environmental exposures may prevent their usability in research and clinical settings. Accordingly, a significant advancement of knowledge would likely be reached by a global collaborative harmonization effort to standardize the multimodal (e.g., psychopathological, neurobiological, neurocognitive) measurement of these exposures, as well as a specific support from funders to achieve these goals. The set of exposures provided in Table 2 may represent the starting point for emerging international efforts promoted by research funders, such as the Common Measures in Mental Health Science Governance Board[105], which aims to drive the adoption of harmonized data collection instruments that are transferable to a variety of locations and ar-

eas of mental health research, considering aspects of diversity, inclusivity, cultural and geographical appropriateness.

The main limitation of the current study is that, because confounding (e.g., by indication, as highlighted above[21,47]) cannot be ruled out in findings of observational studies, it is not possible to establish causation from the associations. More robust epidemiological methods are needed to control for confounders and better identify causal risk factors for major mental disorders that would enhance the precision and generalizability of the current evidence[106]. Nevertheless, our findings represent an important agenda for experimental research that can do this, including intervention trials for treatments and prevention. Second, the observed risk factors have been mostly measured in univariable analyses that cannot control for their intercorrelation. Third, gene-by-environment correlations and interactions have been inadequately reported. Fourth, we could only identify a small number of protective factors (only 9% of the 176 analyzed factors), likely because current research has been disease-centred, with resilience factors and good mental health outcomes being investigated only more recently[107,108].

Finally, the umbrella review approach favours the selection of more commonly and readily studied factors, which are more likely to be meta-analyzed. However, although some emerging risk or protective factors may not have a corresponding eligible meta-analysis to be included in an umbrella review, this possibility is unlikely, since meta-analyses are now being performed frequently. In any case, for most of these emerging factors, the current grade of evidence is unlikely to be remarkable, given the limited data. Furthermore, the primary aim of the current study was to provide an evidence-based classification of the existing knowledge, as opposed to appraising emerging factors that may be consolidated by future research. The rapid progress in aetiopathological meta-research in this field will nevertheless require periodic updates of knowledge via umbrella reviews, which could leverage the methodological framework validated in the current study.

In conclusion, the evidence-based atlas of key risk and protective factors identified in the current study equips clinicians and researchers with a solid benchmark for advancing aetiopathological research and for expanding early intervention and preventive strategies for mental disorders.

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