Risk factors for the development of mental illnesses: An agile scope of the literature

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Introduction

The lead consultant in mental wellbeing for Public Health Wales requested the Public Health Wales Evidence Service to undertake a series of scoping reports on prevention of mental health inequalities. The evidence from these reports is to be used to inform the upcoming Wales Mental Health strategy update. During a meeting to discuss the stakeholder's needs for this scoping review, it was decided that an understanding of the risk factors for developing mental illnesses would be a necessary first step, to enable and target preventive interventions. This scoping report provides an overview of the available secondary evidence on the risk factors for predicting the development of diagnosable mental illnesses.

The findings and conclusions included are those of the source authors and not an interpretation by the Evidence Service. Factors relevant to answering the above question identified from the included systematic reviews have been extracted and briefly summarised within this report. If a specific factor is of interest, it is advisable to read the sources from where they were taken in more detail. If utilising any reviews included in this scope to inform policy, it is important to consider the generalisability of their findings to your context.

The search undertaken for this scope is unlikely to have identified all evidence relating to this topic, as searches were not exhaustive, but instead focussed on identifying robust systematic reviews.

Objectives

To conduct a scoping review to identify secondary evidence on the risk factors for predicting the development of diagnosable mental illnesses.

Key Messages

- Our searches identified many umbrella reviews and systematic reviews of primary studies published in the last 10 years focusing on a range of mental illnesses in different population groups
- All the umbrella reviews identified focused on non-genetic risk factors for mental illnesses, and none focused on genetic causality
- All the evidence identified in this review was identified from a meta-umbrella systematic review of umbrella reviews focussing on non-purely genetic risk or protective factors for any ICD/DSM mental disorders
- The most robust risk factors for dementia included type 2 diabetes mellitus, depression, and low frequency of social contacts
- For non-organic psychotic disorders, the most robust risk factors were clinical high-risk state for psychosis, cannabis use, and childhood adversities
- For opioid use disorders, the most robust risk factor was tobacco smoking
- Risk factors for depressive disorders included widowhood, sexual dysfunction, three to five metabolic factors, childhood physical and sexual abuse, job strain, obesity, and sleep disturbances
- For attention deficit/hyperactivity disorder (ADHD), the most robust risk factors were maternal pre-pregnancy obesity, maternal smoking during pregnancy, and maternal overweight pre/during pregnancy
- The most robust risk factor for autism spectrum disorder was maternal overweight pre/during pregnancy.

Findings

Our searches identified a large number of systematic reviews of primary studies focusing on a range of mental illnesses in different population groups. To ensure that our review was manageable, we decided to focus only on umbrella reviews of risk factors for mental illnesses. Seventeen reviews were identified: one meta-umbrella systematic review of umbrella reviews and 16 umbrella reviews. The meta-umbrella review (Arango et al., 2021) had searches conducted up to January 1st, 2021, and contained six of the 16 umbrella reviews identified in our searches. This large review focused purely on non-genetic risk and protective factors for mental disorders and conducted a rigorous assessment of the credibility of the evidence. We decided to focus on the meta-umbrella review due to its recency, its use of robust classification

criteria for the credibility of evidence, and its inclusion of umbrella reviews identified in our searches. The findings presented in this scoping report are therefore, based on the evidence identified in Arango et al. (2021).

Evidence for association between risk factors and mental disorders

Twenty-one associations met the most robust classification criteria for the credibility of evidence from prospective studies, i.e., class I: convincing (number of cases >1,000, p<10–6, I2<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). Table 1 summarises the associations of risk factors and mental disorders, stratified by ICD-10 diagnostic blocks.

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. However, only three risk factors were supported by class I or II evidence: **type 2 diabetes mellitus**, **depression, and low frequency of social contacts**. Six risk factors were supported by class III evidence: obesity in midlife, low education, low frequency electromagnetic fields, aluminium exposure, depression in childhood, and herpes viruses infection. However, no prospective analysis data were available to support the associations.

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. None of the associations across tobacco related disorder, alcohol related disorder and opioid use disorder 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**. Eight risk factors were supported by class III evidence - three risk factors for tobacco related disorder: attention-deficit/hyperactivity disorder (ADHD), peer smoking behaviour, and smoking in movies; and five risk factors for alcohol related disorder: impulsivity-related personality traits in college or school or community adolescents, parental alcohol supply, and externalising symptoms in adolescents. No prospective analysis data were available to support the class III evidence associations.

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. Three

associations were supported by class I evidence. These all included risk factors: clinical high-risk state for psychosis (with any non-organic psychotic disorder), Black-Caribbean ethnicity in England (with any non-organic psychotic disorder), and obstetric complications (with schizophrenia spectrum disorders). However, prospective analysis of risk factors showed that only **clinical high-risk state for psychosis** (with any non-organic psychotic disorder) remained at the same level of evidence.

Nine associations were supported by class II evidence. Seven of these involved risk factors: minor physical anomalies, trait anhedonia, ethnic minority in low ethnic density area, and being a second-generation immigrant, with any non-organic psychotic disorder; and cannabis use, stressful events, and adversities in childhood, with schizophrenia spectrum disorders. However, prospective analysis of risk factors showed that only **cannabis use** and **adversities in childhood** remained at the same level of evidence, while the other risk factors were either downgraded to class IV evidence or prospective studies were not available to support any associations.

Mood (affective) disorders

Forty-eight associations with depressive or bipolar disorders were evaluated within this ICD-10 diagnostic block. Seven associations were supported by class I evidence. Six were risk factors for depressive disorders: widowhood, sexual dysfunction, four or five metabolic risk factors, physical abuse in childhood, job strain, and obesity. One was a risk factor for bipolar disorders: irritable bowel syndrome. 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.

Sixteen associations were supported by class II evidence. These included nine risk factors for depressive disorders: dry eye disease with Sjögren's syndrome, emotional abuse in childhood, intimate partner violence against women, sexual abuse in childhood, being a Gulf War veteran, three metabolic risk factors, psoriasis, metabolic syndrome, and sedentary behaviour. There were five risk factors for depressive disorders in elderhood: poor physical health, chronic disease, poor vision, sleep disturbances, and low education. There was one risk factor for depressive disorders in childhood: asthma. There was one risk factor for bipolar disorders: adversities in childhood. 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.

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. Four associations were supported by class I evidence. These involved one risk factor for social anxiety disorder, namely physical abuse in childhood; and three risk factors for PTSD: physical disease history, family history of psychiatric disorder, and being an indigenous American. 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 available.

Four associations were supported by class II evidence. These all involved risk factors for PTSD: cumulative exposure to potentially traumatic experiences, trauma severity, being trapped in an earthquake, and female sex. Prospective analysis showed that trauma severity as a risk factor for PTSD was downgraded to class IV evidence.

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. None of the associations was supported by class I evidence. Two associations were supported by class II evidence, involving two risk factors: appearance-related teasing victimization (with any eating disorder) and sexual abuse in childhood (with bulimia nervosa). **No prospective analysis data were available for any of the factors**.

Disorders of adult personality and behaviour

Six associations with borderline personality disorder were evaluated within this ICD-10 diagnostic block. The associations were all supported by class II evidence, involving emotional, physical and sexual abuse; emotional and physical neglect; and adversities in childhood. However, **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

Twenty-six associations with autism spectrum disorder were evaluated within this ICD-10 diagnostic block. Seven associations were supported by class I evidence. These involved seven risk factors: maternal selective serotonin reuptake inhibitor (SSRI) use during pregnancy (confounding by indication such as underlying maternal mental disorders), maternal pre-pregnancy antidepressant use (confounding by indication as above), maternal chronic hypertension, maternal gestational hypertension, maternal pre-eclampsia, maternal age ≥35 years, and maternal overweight pre/during pregnancy. Prospective analysis showed that none of the risk

factors remained at the same level. **Maternal overweight pre/during pregnancy was downgraded to class II evidence**, while all other class I factors were downgraded to non-significant levels or prospective evidence was not available.

Eight associations were supported by class II evidence. These involved risk factors: highest paternal age group vs. reference group, paternal age >45 years, highest maternal age group vs. reference group, paternal age 40-45 years, maternal autoimmune disease, higher paternal age per 10-years increase, maternal paracetamol use during pregnancy (likely confounding by indication such as maternal comorbidities involving inflammation or infection), and maternal age 30-34 years. Prospective analysis showed that none of the risk factors remained at the same level of evidence and were either downgraded to class III or IV evidence.

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

Nineteen associations with ADHD were evaluated within this ICD-10 diagnostic block. Five associations were supported by class I evidence, all including risk factors: maternal pre-pregnancy obesity, eczema in childhood, maternal hypertensive disorders during pregnancy, maternal pre-eclampsia, and maternal paracetamol use during pregnancy (likely confounding by indication). 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.

Three associations were supported by class II evidence, involving three risk factors: maternal smoking during pregnancy, asthma in childhood, and maternal overweight pre/during pregnancy. 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. For the remaining class II evidence factors, no prospective analysis data were available.

Table 1: Evidence for associations between non-purely genetic risk factors and mental disorders

Risk factor	Mental disorder	Class of evidence (prospective evidence class)
Organic, including symptomatic, mental disorders		
Type 2 diabetes mellitus	Vascular dementia, Alzheimer's disease, any dementia	Class I (Vascular dementia, Alzheimer's disease) Class II (Any dementia)
Low frequency of social contacts	Any dementia	Class I
Mental and behavioural disorders due to psychoactive substance use		
Tobacco smoking	Opioid use disorder	Class II
Schizophrenia, schizotypal and delusional disorders		
Clinical high-risk state for psychosis	Any non-organic psychotic disorder	Class I
Cannabis use	Schizophrenia spectrum disorders	Class II
Adversities in childhood	Schizophrenia spectrum disorders	Class II
Mood (affective) disorders		
Widowhood	Depressive disorders	Class I
Sexual dysfunction	Depressive disorders	Class I
Four or five metabolic risk factors	Depressive disorders	Class I
Physical abuse in childhood	Depressive disorders	Class I
Job strain	Depressive disorders	Class I
Obesity	Depressive disorders	Class I
Sexual abuse in childhood	Depressive disorders	Class II
Three metabolic risk factors	Depressive disorders	Class II
Sleep disturbances	Depressive disorders in elderhood	Class II
Neurotic, stress-related and somatoform disorders		
None of the factors was supported by class I or II evidence		
Behavioural syndromes associated with physiological disturbances and physical factors		

None of the factors was supported by class I or II evidence		
Disorders of adult personality and behaviour		
None of the factors was supported by class I or II evidence		
Mental retardation		
None of the factors was supported by class I or II evidence		
Disorders of psychological development		
Maternal overweight pre/during pregnancy	Autism spectrum disorder	Class II
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence		
Maternal pre-pregnancy obesity	ADHD	Class I
Maternal overweight pre/during pregnancy	ADHD	Class I
Maternal smoking during pregnancy	ADHD	Class II

Please note, unless otherwise stated, no quality appraisal has been undertaken so the Evidence Service cannot comment on the methodological quality of sources outlined in table 1. If any paper is to be utilised for policy and/or practice, please conduct a quality assessment and consider the generalisability of findings to your context.

Options for further work

Our searches identified evidence directly relevant to answering the research question on the risk factors for predicting the development of diagnosable mental illnesses. However, we were not able to find evidence on genetic risk factors for mental illnesses. Genetic causality is tested with other analytic approaches such as genome-wide association studies which may not have been picked up in our search strategy. It may be appropriate to conduct a scoping review to identify research on genetic causality if needed.

Alternatively, since targeting modifiable (non-genetic) risk factors are better placed to inform intervention efforts, a scoping review of the literature to identify research on interventions for preventing mental illnesses is recommended.

Methods

Appendix A (technical appendix) provides an outline of the general rationale and methods used to develop agile scopes. The following methodology outlines the approach undertaken for this agile scoping report.

As this is a broad topic, this agile scope was limited to only include reviews produced using explicit and reproducible methods of systematic searching, critical appraisal of quality and synthesis of the primary literature on the topic. This is an acceptable way to rapidly assess the majority of the evidence base, and although it does not intend to identify every publication on a topic, it would allow for the production of an overview. Primary studies were excluded as including both primary and secondary sources of evidence on such a broad topic would have made this report unmanageable within the timeframe of this research.

Data sources: Four reliable evidence sources were searched that adhere to robust systematic review principles[1]. In addition, Google scholar and Medline were searched for published evidence (Table 3) using search terms and strategies designed specifically for each data source. Searches were conducted using a combination of the following terms:

- mental illness*
- depression or anxiety or "obsessive compulsive disorder" or phobia* or psychosis or schizophrenia or "bi-polar disorder" or "personality disorder*" or "eating disorder*" or anorexia or bulimia or "disordered eating" or "binge eating disorder
- risk factor*

A full search strategy for Medline along with a full list of resources searched is included in appendix B (table 3).

Study selection: Reviews produced using systematic methodology (including critical appraisal) i.e., systematic reviews, scoping reviews, rapid reviews etc. were assessed for inclusion. One reviewer independently screened the reviews for relevance at title, abstract and full-text level against the inclusion criteria outlined in table 2.

Data extraction: Data were extracted from the secondary research studies identified in the search and discussed in the findings section of this report. A full reference and

[1] Follows core systematic review principles: comprehensive and stated search strategy, selection of sources based on objective criteria, assessment of risk of bias of primary sources and/or is a methodology developed by an expert body e.g. NICE. For a full list of sources searched, please refer to Sources searched section of the report.

hyperlink are provided for each study, and their respective aims and abstracts have been extracted. Date extraction is shown in table 4.

Quality assessment: No quality assessment was performed.

Table 2: Inclusion Criteria	
Review question	
What are the risk factors for predicting the development of diagnosable mental illnesses?	
Participants	Individuals of all ages (any gender, ethnicity, SE status), including institutionalised individuals (prisoners) and people with learning difficulties.
Exposure	Specific risk factors for developing mental illness (both common and severe)
Comparison	n/a
Outcomes	Diagnosable mental illness (both common and severe). To include specific mental illnesses
Other Study Considerations	
Settings – all settings except residential care Study design – secondary evidence (systematic reviews, guidance) Language of publication – English Date limit – since 2013 (last 10 years) Countries – OECD	

References

ARANGO, C., DRAGIOTI, E., SOLMI, M., CORTESE, S., DOMSCHKE, K., MURRAY, R. M., JONES, P. B., UHER, R., CARVALHO, A. F., REICHENBERG, A., SHIN, J. I., ANDREASSEN, O. A., CORRELL, C. U. & FUSAR-POLI, P. 2021. Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas. World Psychiatry, 20, 417-436.

Appendix A: Technical document

AGILE SCOPES are stakeholder-driven, rapid, systematic overviews of the evidence on a topic. They provide a transparent and reliable overview of the evidence landscape and are useful to:

- establish what literature exists
- help to refine a broad question
- identify gaps in the evidence
- inform further work by stakeholders.

The scopes employ a process of *up to* three steps, depending on what evidence is available for the topic. Progress from one step to another is discussed and agreed with stakeholders.

1. The first step is to draw on existing systematic review evidence identified from trusted sources[2] (secondary evidence sources that use robust methodologies) where this exists. The Evidence Service does not undertake critical appraisal of these reviews. A brief report outlining evidence identified is produced.
2. If little or no evidence has been identified at this stage, a very simple search will be conducted in Medline using key words only to establish the benefit of conducting further searches in a broader range of databases. A summary of the search results (i.e., number, study design, relevancy etc.) will be provided in the agile scope to help inform stakeholders.
3. Where little or no trusted secondary evidence exists, and if identified as potentially beneficial from the Medline search conducted in step 2, the scope may be extended, at the request of the stakeholder to include a search for systematic reviews or primary literature in Google Scholar, Scopus or Medline, as appropriate. At this and any subsequent step, quality assessment of the identified evidence would be required.
4. Primary studies are not usually included, unless few or no systematic reviews are identified in the preliminary phase of step 1, or stakeholders request it following earlier work they have undertaken.

Considerations

- The scope does not attempt to identify all evidence on a given topic.
- Not all outcomes identified in the literature will necessarily be included in this scoping report for a number of reasons, including:
    - Outcomes included in the scope are limited to those that are relevant to the stakeholders' original question.

[2] The sources on the Evidence Service list of trusted secondary evidence resources are provided in Table 1

  - Outcomes may not have been reported in the secondary sources, although it may exist in the primary literature. These outcomes will therefore not be included within the scoping report.
- Findings within included reviews are not assessed for generalisability to the Welsh context. [*It would be a complex process as secondary evidence is likely to include studies from multiple countries*.] This would need to be considered by stakeholders if using secondary evidence to inform policy and practice. Additional work could be requested if necessary.
- The scope summarises the findings and conclusions of the source authors. If a specific element of the report is of particular interest, it is advisable to read the source(s) from which it originates in more detail, as this will provide more context. Further work may be undertaken on specific areas if required.
- Hyperlinks to the included evidence are provided in the data summary table. In many instances, that evidence is freely available. If not, your Trust's Knowledge and Library service can help. NHS Wales Library Service | NHSWLS

Methods

All agile scopes follow a broad methodology and structure, with only small variations according to the question and evidence base identified. Through discussions with stakeholders, a research question and inclusion/exclusion criteria are developed using the PICO/PECO format (population, intervention/exposure, comparator, outcome). **Note: stakeholders are requested to indicate evidence/information they have already identified.**

As noted above, the methodology utilised is designed to provide rapid information to stakeholders. In the first step, restricting the search to sources from the trusted secondary evidence resources list reduces the time taken both in terms of search scope and by excluding the need for critical appraisal.

The search strategy developed is based on the inclusion criteria and uses key words. The scope is restricted to including only English language evidence and publication date limits may be imposed when the search results are too large to manage in a short timeframe, or where the stakeholder requires work to be completed within a specific timeframe. Additionally, the countries included may be limited, particularly where generalisability to a Welsh context is a particular concern.

All search results and screening for relevant systematic reviews are maintained in an EndNote library or suitable reference management system. Inclusion at title and abstract are calibrated by two reviewers independently screening the first 10% to 20% of systematic reviews for relevance, with the remainder being screened by a single reviewer. Full text screening decisions are made by two reviewers. Data on study characteristics and findings relevant to the question are extracted by one

reviewer and checked by a second. The evidence is them summarised narratively to answer stakeholder questions. Evidence gaps within the secondary literature are reported.

If none, or limited evidence is identified from the trusted secondary sources list, a brief search is conducted in Medline using basic key word searches to establish the benefit of conducting further searches in a broader range of databases. A summary of the search results (i.e., number, study design, relevancy etc.) will be provided in the agile scope.

Findings

The agile scoping report contains a narrative summary and a data table. The narrative summary is a broad overview of the evidence identified, with a particular focus on elements highlighted as important by stakeholders. Data tables include the reference (with a hyperlink), information on study characteristics and findings. The information in the data tables will vary according to the question, types of included studies and requirements of stakeholders. The table also includes a comment section highlighting any elements of particular interest to stakeholders along with any limitations that should be considered.

The report concludes with an ‘options for further work’ section. These suggestions are based on the evidence identified and provide an explicit rationale where further evidence review work is recommended. This information will be informed by the additional brief search conducted in Medline to help assess how much additional information, and the likely benefits of conducting additional work are. These findings will be provided to stakeholders to ensure they can make an informed decision on what to do next.

Appendix B: Search Appendix

Table 3: Resources searched	
Joanna Briggs Institute - https://journals.lww.com/jbisrir/pages/advancedsearch.aspx This organisation's journal, JBI Evidence Synthesis includes systematic and scoping reviews of both quantitative and qualitative evidence on healthcare and public health topics. All fields: "mental health condition" OR "mental illness" OR "mental health illness" OR "mental disorder" OR "mental health disorder" OR "mental health issue" OR depression or anxiety or "obsessive compulsive disorder" or phobia or psychosis or schizophrenia or "bi polar disorder" or "personality disorder" or "eating disorder" or anorexia or bulimia or "disordered eating" or "binge eating disorder" Abstract: risk Title: systematic review Limited to last 3 years	Date of search: 24/05/2023 **Results: 1**
Prospero – https://www.crd.york.ac.uk/prospero/ ("mental health condition" OR "mental illness" OR "mental health illness" OR "mental disorder" OR "mental health disorder" OR "mental health issue" OR depression or anxiety or "obsessive compulsive disorder" or phobia or psychosis or schizophrenia or "bi polar disorder" or "personality disorder" or "eating disorder" or anorexia or bulimia or "disordered eating" or "binge eating disorder"):TI AND (Epidemiologic):RT AND (Mental health and behavioural conditions):HA WHERE CD FROM 01/01/2021 TO 01/06/2023 AND "risk factor" AND (Epidemiologic):RT AND (Mental health and behavioural conditions):HA WHERE CD FROM 01/01/2021 TO 01/06/2023	Date of search: 24/05/2023 **Results: 22**
Public Health/ Wider Determinants Focus [select if relevant to your question]	
National Institute for Health Research (NIHR) Public Health Research – https://www.journalslibrary.nihr.ac.uk/phr/about-the-phr-journal.htm *Some reports in this journal are systematic reviews of interventions to improve public health.* "mental health condition" OR "mental illness" OR "mental health illness" OR "mental disorder" OR "mental health disorder" OR "mental health issue"	Date of search: 24/05/2023 **Results: 5,** manual screen - none relevant as either out of scope or intervention type research

Limits: Research Type - evidence synthesis; Published After - January 2013	
The Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre) – http://eppi.ioe.ac.uk/cms/ Manual search of ▸Publications▸Index of systematic review topics▸Link pages▸ Mental health 10 topic headings Depression, anxiety, pain and quality of life in people living with chronic hepatitis C: a systematic review and meta-analysis (2015)	24/05/2023 **Results: 1 relevant**
Medline Ovid MEDLINE(R) ALL <1946 to May 17, 2023> 1. ("mental health condition*" and risk*).tw. (1648) 2. (("mental illness*" or "mental health illness*") and risk*).tw. (8796) 3. (("mental disorder*" or "mental health disorder") and risk*).tw. (11921) 4. 1 or 2 or 3 (21180) 5. "umbrella review*".tw. (1383) 6. 4 and 5 (29) 7. limit 6 to yr="2013 -Current" (29) 8. ((depression or anxiety or "obsessive compulsive disorder" or phobia* or psychosis or schizophrenia or "bi-polar disorder" or "personality disorder*" or "eating disorder*" or anorexia or bulimia or "disordered eating" or "binge eating disorder") and risk factor*).tw. (41390) 9. 5 and 8 (34) 10. limit 9 to yr="2013 -Current" (34) 11. 7 or 10 (55)	Date of search: 18/05/2023 **Results: 55**

Appendix C: Data extraction

Table 4: Data extraction of the reviews identified in the scoping search (in alphabetical order)

Review of umbrella reviews			
Reference	**Aim/Question**	**Abstract or summary**	**Comments**
Arango, C. et al. (2021). Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas. World Psychiatry, 20(3), 417-436.	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** A multi-step systematic literature search was performed by independent researchers to explore Web of Science 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. An established classification of the credibility of the evidence in the included umbrella reviews was applied : 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. **Results** Fourteen eligible umbrella reviews were retrieved, summarizing 390 meta-analyses and 1,180 associations between putative risk or protective factors and mental disorders. Twenty-one associations met class I or II from prospective designs (most robust associations). **Organic, including symptomatic, mental disorders**	This review is a meta-umbrella systematic review of umbrella reviews. The review authors did not include pure genetic risk or protective factors or biomarkers, because genetic/biomarker causality is tested with other analytical approaches (such as genome-wide association studies and meta/mega-analyses). The eligible umbrella reviews were published between 2017 and 2021, and reviewed individual

		Seven associations with any dementia, Alzheimer's disease, or vascular dementia were supported by class I evidence. 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. 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). **Mental and behavioural disorders due to psychoactive substance use** None of the associations across tobacco related disorder, alcohol related disorder and opioid use disorder 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). **Schizophrenia, schizotypal and delusional disorders** For non-organic psychotic disorders, the most robust risk factors were **clinical high-risk state for psychosis** (Class I evidence, OR=9.32), **cannabis use** (Class II evidence, OR=3.90), and **adversities in childhood** (Class II evidence, OR=2.80). **Mood (affective) disorders** Six risk factors for depressive disorders were supported by class I evidence. These were **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).	studies published from 1995 to 2020

		Two risk factors for depressive disorders (**sexual abuse in childhood** (OR=2.42), and **three metabolic risk factors** (OR=1.99)), and one risk factor for depressive disorders in elderhood (**sleep disturbances** (RR=1.92)) were supported by class II evidence. **Disorders of psychological development** For autism spectrum disorder, the most robust risk factor was **maternal overweight pre/during pregnancy** (Class II evidence, RR=1.28). **Behavioural and emotional disorders with onset usually occurring in childhood and adolescence** For attention deficit/hyperactivity disorder (ADHD), the most robust risk factors were **maternal pre-pregnancy obesity** (Class I evidence, OR=1.63), **maternal overweight pre/during pregnancy** (Class I evidence, OR=1.28) and **maternal smoking during pregnancy** (Class II evidence, OR=1.60).	

ISBN: 978-1-83766-208-1