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Risk and protective factors for anxiety and obsessive-compulsive disorders: an umbrella review of systematic reviews and meta-analyses

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ABSTRACT

BACKGROUND: A multitude of risk/protective factors for anxiety and obsessive-compulsive disorders have been proposed. We conducted an umbrella review to summarize the evidence of the associations between risk/protective factors and each of the following disorders: specific phobia, social anxiety disorder, generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder (OCD), and to assess the strength of this evidence whilst controlling for several biases. **METHODS:** Publication databases were searched for systematic reviews and meta-analyses examining associations between potential risk/protective factors and each of the disorders investigated. The evidence of the association between each factor and disorder was graded into convincing, highly suggestive, suggestive, weak, or non-significant according to a standardized classification based on: number of cases (>1000), random-effects p-values, 95% prediction intervals, confidence interval of the largest study, heterogeneity between studies, study effects, and excess of significance. **RESULTS:** Nineteen systematic reviews and meta-analyses were included, corresponding to 216 individual studies covering 427 potential risk/protective factors. Only one factor association (early physical trauma as a risk factor for social anxiety disorder, OR=2.59, 95% CI: 2.17-3.1) met all the criteria for convincing evidence. When excluding the requirement for more than 1000 cases, five factor associations met the other criteria for convincing evidence and 22 met the remaining criteria for highly suggestive evidence. **CONCLUSIONS:** Although the amount and quality of the evidence for most risk/protective factors for anxiety and obsessive-compulsive disorders is limited, a number of factors significantly increase the risk for these disorders, may have potential prognostic ability and inform prevention.

INTRODUCTION

Anxiety disorders are the most common group of mental disorders and are associated with enormous societal costs (Kessler *et al.* 2010; Craske & Stein 2016). Both "genetic" and "non-genetic" (i.e., environmental) variables (as well as their interaction) have been proposed as potential risk/protective factors for anxiety disorders (Craske *et al.* 2017), although such a distinction may be somewhat artificial, given that many risk/protective factors include both genetic and non-genetic components. The evidence on risk/protective factors for anxiety disorders has been summarized in several systematic reviews and meta-analyses. However, findings are conflicting and there have been no previous attempts to summarize in a single report the strength of the evidence for the different potential risk/protective factors for each anxiety disorder or to assess possible biases in the literature.

We present the results of an umbrella review of risk/protective factors for the most common anxiety disorders. We will focus on specific phobia, social anxiety disorder (SAD), generalized anxiety disorder (GAD), panic disorder (PD), and obsessive-compulsive disorder (OCD) —the latter having been classified as an anxiety disorder until the publication of the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association 2013). Umbrella reviews systematically collect and assess the existing evidence from individual studies included in systematic reviews and/or meta-analyses and have an increasing role in evidence-based health care and evidence-based assessments (Ioannidis 2009; Fusar-Poli & Radua 2018).

In the current absence of valid biomarkers or clear mechanistic explanations for most mental disorders (Kapur *et al.* 2012), the identification of putative (and, at least for some, modifiable) risk/protective factors may lead to the development of

more efficient risk prediction models, and may offer clues for prevention and treatment (Paulus 2015; Moreno-Peral *et al.* 2017; Fusar-Poli *et al.* 2018). Our aim was to systematically assess the amount of evidence and the robustness of associations between potential risk/protective factors and each of the aforementioned disorders.

METHODS

We conducted an umbrella review (Ioannidis 2009; Fusar-Poli & Radua 2018) to assess the relation between potential risk/protective factors and anxiety and obsessive-compulsive disorders. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.* 2009) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup *et al.* 2000) (**Tables S1** and **S2** in the supplementary material). The study protocol was pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42017060090).

Search strategy and eligibility criteria

We searched *PubMed*, *Web of Science*, and *Scopus* from inception to April 30, 2018 for systematic reviews and meta-analyses of observational studies examining associations between potential risk/protective factors (see below) separately for each disorder. The search strategy used the keywords "systematic review" or "meta-analysis" and each of the disorders of interest. We also hand searched the reference lists of all systematic reviews and meta-analysis reaching full-text review.

Eligibility criteria were: 1) a systematic review or meta-analysis of risk/protective factors for specific phobia, SAD, GAD, PD, or OCD as defined in any

edition of the International Classification of Diseases (ICD) manual or the DSM; 2) inclusion of a healthy comparison group; and 3) studies reporting sufficient data (or that were retrievable after contacting the authors) to perform the analyses. We did not apply any language restrictions in the selection of systematic reviews or meta-analyses.

Even though we had hoped to include molecular genetic studies in the umbrella review, we found that the literature for the disorders investigated is dominated by candidate gene studies, which are known to have low credibility. Such risk factor assessment should await thus the publication of large genome-wide studies (Ioannidis *et al.* 2008). Moreover, different analytical methods and assessment criteria are required for umbrella reviews of genetic variables (Ioannidis *et al.* 2008).

Although in some DSM classifications previous to DSM-5 "panic disorder" and "panic disorder with agoraphobia" have been classified separately, we included both in our "panic disorder" category. However, we have analyzed them separately where a study reported separate factors for each of these categories. We also considered separation anxiety disorder and selective mutism ("anxiety disorders" in the DSM-5), but they were not included due to the lack of systematic reviews and meta-analyses (**Figures S6** and **S7**). Posttraumatic stress disorder (PTSD), grouped as an anxiety disorder until the publication of DSM-5, will be covered in a separate manuscript.

Further information about the search strategy and the eligibility criteria can be found in the supplementary material.

Risk/protective factor definition

We used the following definition of risk factor: "that characteristic, variable, or hazard preceding the outcome of interest that, if present for a given individual, makes it more likely that this individual, rather than someone selected from the general population, will develop a given disorder" (Mrazek & Haggerty 1994; Kraemer *et al.* 1997). Similarly, protective factors are those where risk is found to be decreased. We assessed both stable factors (e.g., sex), for which time precedence does not need to be established, and factors that are subject to change within-subject. For the latter, we required that the determination of the factor preceded the diagnosis of the outcome (i.e., the disorder) even if the information on the factor and the outcome was collected at the same time point (as in the case of cross-sectional studies). This rule ensured that there would be time precedence for the assessments of factors and outcomes, although factors may have existed even before their determination, and disorders may have also existed before their diagnosis. Furthermore, when the factor investigated was related to personality dimensions (e.g., neuroticism), we also required that personality was *assessed* before the disorder was diagnosed in order to avoid state-trait influences (Reich *et al.* 1987). The definitions for each factor were those given in the corresponding systematic review or meta-analysis.

Following previous work (Radua *et al.* 2018) we grouped factors into several descriptive categories: sociodemographic, psychopathology, parental psychopathology, personality dimensions, substance use, life events, perinatal complications, parental rearing styles/attachment, and others.

Data extraction and selection

We used a systematic approach to extract and select the data. First, we identified the factors assessed in each systematic review or meta-analysis. Second, two investigators

independently checked that each individual article included in the systematic review or meta-analysis met the same eligibility criteria applied to the systematic review or meta-analysis. Third, two investigators independently extracted the following data (from the systematic review or meta-analysis or, in most cases, from the individual studies): first author and year of publication; number of cases and controls; measure and size of the risk and corresponding 95% confidence intervals (CIs); specific variables depending on the measure of effect size; and whether the study was a prospective cohort. Specific variables depending on the measure of effect size were: number of cases and person-times in exposed and unexposed for incidence rate ratios (IRR), number of cases and total number of exposed and unexposed for risk ratios (RR), number of exposed and unexposed and cases and controls for odds ratios (OR), and means and standard deviations for cases and controls for standardized mean differences (SMD). Fourth, two investigators independently rated the quality of the systematic review or meta-analysis using the Assessment of Multiple Systematic Reviews (AMSTAR; Shea *et al.* 2007) tool, with substantial interrater agreement (both weighted Cohen's kappa and intraclass correlation = 0.71; see Supplementary Material). A third investigator reviewed the extracted data to check for inconsistencies, and disagreements were resolved by consensus. For further details on the data extraction, selection, and quality assessment, see the supplementary material.

Statistical analysis

We performed statistical analyses commonly used in standard meta-analyses. However, we did not use the statistics provided in the included systematic review or meta-analyses because there are differences across-studies in the methods employed and because some analyses are often not conducted (e.g., the test for an excess of

significant findings).

We conducted a separate random-effects meta-analysis for each factor and disorder. The outcomes of the meta-analyses were the effect sizes with their CIs and p-values, and the statistics required to assess the level of evidence (see below). Depending on the factor, we used IRR, RR, OR, or SMD Hedges' *g*. For descriptive purposes, we also report OR equivalents (eOR) of IRR, RR, and Hedge's *g* (see Fusar-Poli & Radua (2018) for additional details).

We assessed between-study heterogeneity by estimating the 95% prediction interval – which evaluates the uncertainty for the effect that would be expected in a new study addressing that same association – and the I^2 metric (Ioannidis *et al.* 2007). $I^2 > 50\%$ were considered to represent substantial heterogeneity (Higgings & Green 2009). We also assessed whether there was evidence of small-study effects with Egger tests (Egger *et al.* 1997), where statistical significance would mean potential reporting or publication bias in the smaller studies. Finally, excess significance (a relative excess of statistically significant findings) was assessed with a binomial test that compared the observed *vs* the expected number of studies yielding statistically significant results (Radua *et al.* 2018).

The levels of evidence of the associations between each factor and disorder were classified into *convincing* (class I), *highly suggestive* (class II), *suggestive* (class III), or *weak* (class IV) (Fusar-Poli & Radua 2018). *Convincing* evidence required a number of cases (n) >1000, a highly significant association ($p<10^{-6}$), $I^2<50\%$, a statistically significant 95% prediction interval, and the absence of small-study effects and excess significance bias. *Highly suggestive* evidence also required n >1000, a highly significant association ($p<10^{-6}$), and that the largest study had a statistically significant effect. *Suggestive evidence* required n >1000 and $p<10^{-3}$. *Weak evidence*

required no specific number of cases and $p<0.05$. Furthermore, after collecting all the available evidence, we noticed that, with few exceptions, there were fewer than 1000 cases for most factors. Therefore, we also examined these criteria removing the requirement of n >1000, so as to obtain a more fine-grained appraisal of the evidence. For associations with significant evidence (classes I-IV), we also conducted a sensitivity analysis by using only prospective cohort studies.

RESULTS

We included 19 systematic reviews and meta-analyses **(Figure 1** and **Figures S1-S5** in the supplementary material**)**. AMSTAR scores are presented in **Table 1**. All extracted data and results are available at: https://www.umbrellaevidence.com/anxiety/riskfactors/.

We extracted data for 427 factors from 216 individual studies. The number of systematic reviews and meta-analyses, individual studies assessed and included, and factors included are presented in **Table 2**. The groups of factors assessed in each systematic review or meta-analysis are reported in **Table 1** and the specific factors in **Table S3** (see supplementary material). Factors showing convincing, highly suggestive, or suggestive evidence of association with each disorder are presented in **Table 3**. All significant factors (including those showing weak evidence of association) are presented in **Table S4** (see supplementary material).

Overall, the number of cases was greater than 1000 for 20 factors (4.68%). One-hundred eighty-three of the 427 factors (42.84%) presented a statistically significant effect ($p<0.05$) under the random-effects model, but only 91 (21.31%) had a $p<0.005$ and only 27 (6.32 %) reached $p<10^{-6}$. Twenty-five factors (36.76%)

presented a large estimate of heterogeneity (I^2>50%), while for 29 factors (78.37%) the 95% prediction interval did not include the null. Additionally, evidence for small-study effects and excess significance bias was noted for 2 (5.40%) and 8 (1.87%) factors, respectively (see **Table S4** in the supplementary material).

Results by disorder

Specific phobia

No factor showed convincing or highly suggestive evidence as a risk/protective factor for specific phobia using the original umbrella review criteria. Removing the n>1000 criterion, being male showed convincing evidence as protective factor. Moreover, neuroticism showed highly suggestive evidence as risk factor for the disorder, which was maintained after the sensitivity analyses (**Table 3, Figure 2,** and **Table S4**).

Social anxiety disorder

Early physical and sexual trauma showed, respectively, convincing and suggestive evidence as risk factors for SAD. Additionally, when removing the n>1000 criterion, dysthymia, insecure attachment in childhood, major depression, and neuroticism showed highly suggestive evidence as risk factors for SAD. After sensitivity analyses, evidence for both trauma-related factors became weak, but the rest of factors–except insecure attachment in childhood- maintained the same level of evidence (**Table 3, Figure 2,** and **Table S4**).

Generalized anxiety disorder

No factor showed convincing or highly suggestive evidence as a risk/protective factor for GAD. Removing the n>1000 criterion, being male showed convincing evidence as protective factor for GAD and the following factors showed highly suggestive evidence as risk factors for the disorder: psychological malaise at age 33, borderline personality disorder, parental GAD without comorbidity, early physical and sexual trauma, and behavioral inhibition (assessed as a personality dimension). After sensitivity analyses, all these factors – except both trauma-related variables – maintained the same level of evidence (**Table 3, Figure 2,** and **Table S4**).

Panic disorder

No factor showed convincing or highly suggestive evidence as risk/protective factor for PD. Removing the n>1000 criterion, being male, separation anxiety in childhood, and early physical trauma showed convincing evidence as risk/protective factors for PD. The evidence was not maintained, however, after sensitivity analyses. Furthermore, daily cigarette smoking, panic attacks, and major depression showed highly suggestive evidence as risk factors for PD, which was maintained after sensitivity analyses (**Table 3, Figure 2,** and **Table S4**).

Obsessive-compulsive disorder

No factor showed convincing or highly suggestive evidence as risk/protective factor for OCD. Removing the n>1000 criterion, several parental rearing style variables, neuroticism, and use of cocaine together with another drug (except marijuana) showed highly suggestive evidence as risk/protective factors for OCD. However, the latter was based on a single study reporting one single case in the exposed group. Only

neuroticism and use of cocaine together with another drug (except marijuana) maintained the same level of evidence after the sensitivity analyses (**Table 3, Figure 2,** and **Table S4**).

DISCUSSION

This is, to the best of our knowledge, the first umbrella review of risk/protective factors for anxiety and obsessive-compulsive disorders. Our study provides a state-of-the-art classification of risk/protective factors based on the robustness of associations between these factors and five separate disorders, while controlling for several biases.

Using the original umbrella review criteria, early physical trauma was the single most consistent risk factor – class I – for SAD. Early sexual trauma was also associated – class III –with SAD. Several "traditional" risk/protective factors for anxiety and obsessive-compulsive disorders were among those that had nominally statistically significant results (Beesdo *et al.* 2009; Craske & Stein 2016). Although we could not assess exactly the same factors for all disorders, a number of factors showed a similar association with several of the disorders investigated (**Figure 3**). For example, being male was associated with decreased risk for specific phobia, SAD, GAD, and PD; and neuroticism was associated with increased risk for specific phobia, SAD, GAD, and OCD. Moreover, early traumatic experiences increased the risk of all disorders in which they were investigated (SAD, GAD, PD, and OCD). Although the evidence for most of these associations was rated as weak, the consistency of these signals across multiple disorders strengthens the case that they do carry prognostic potential. The fact that the same factors increased the risk for different disorders may indicate a shared liability *within* anxiety and obsessive-compulsive disorders (Blanco *et al.* 2014). Moreover, some factors may be shared *across* mental disorders (i.e., be

"transdiagnostic"). For example, early traumatic experiences are a significant risk factor for depressive (Köhler *et al.* 2018), psychotic (Belbasis *et al.* 2018; Radua *et al.* 2018), and bipolar disorders (Bortolato *et al.* 2017). Importantly, the results of our umbrella review provide hints not only on the presence/absence of a particular factor but also on the *loading* (weight) of that factor, which may be still unique (Uher & Zwicker 2017).

The non-specificity of the findings for most risk factors investigated here (and probably for most risk factors for mental disorders in general) may also be partially explained by the fact that developmental effects (including temporal dynamics and the development of comorbidity over time) are often ignored in current nosological systems. The use of longitudinal "staging models" – that describe the progression from more simple or "pure" disorders to more complex or comorbid disorders – has been proposed to deal with these issues. Such models could offer a better description of the developmental patterns typical to most mental disorders (Beesdo *et al.* 2009).

Our data suggest that rather than "a few" risk or protective factors with large effects, large sets of common "variants" of small effects account for the risk for anxiety and obsessive-compulsive disorders. This idea, which is well established in psychiatry genetics (Anttila *et al.* 2018; Sullivan *et al.* 2018), seems to be also true for "non-purely genetic" factors (Uher & Zwicker 2017). Furthermore, our findings open the door to the potential development of enhanced risk prediction models (Bernardini *et al.* 2017) and individual risk prediction scores (see Kessler et al., 2014, and Shalev et al., 2019 for specific examples in PTSD). In recent years, the use of polygenic risk scores has been validated in disorders such as schizophrenia (International Schizophrenia Consortium *et al.* 2009). More recently, the use of "poly-environmental scores" has been proposed (Padmanabhan *et al.* 2017; Uher & Zwicker 2017). Given

that multiple genetic and non-genetic factors have much greater explanatory power than considering them one at a time in most mental disorders (Uher & Zwicker 2017), it is likely that "poly-risk" scores (containing both genetic and non-genetic factors) improve the prediction of mental disorders. Our data may help developing such scores for anxiety and obsessive-compulsive disorders, although the time of exposure and the cumulative nature of non-genetic risk will need to be taken into account to improve such prediction abilities (Moffitt *et al.* 2005; Sharma *et al.* 2016). Developmental effects – and their potential interaction with genetic variables- are difficult to study using epidemiological data, but they could be investigated using animal models (Leonardo and Hen, 2008).

The majority of factors were only classified as having weak evidence (class IV). This mainly reflects the methodological limitations of the data, where less than 5% of the factors included more than 1000 cases and where the significance of the associations for each individual factor was overall low. The (weak) strength of the associations found, together with limitations inherent to the individual study designs employed to date, precludes firm causal inferences for any of the significant factors identified in our umbrella review (Paulus 2015). Future work to identify risk/protective factors could focus on large-scale family-based designs, that allow for a more stringent control of unmeasured familial confounders (D'Onofrio *et al.* 2013) and should improve the confidence in the identification of "non-purely genetic" risk/protective factors that are in the causal pathway for anxiety and obsessive-compulsive disorders. For example, recent population-based work in OCD has confirmed that a range of perinatal complications are robustly associated with the disorder, even after strict control of unmeasured genetic and environmental confounders, and that the number of perinatal complications cumulatively contribute

to risk for the disorder (Brander *et al.* 2016b). Similarly, as the field of psychiatric genetics is clearly shifting away from the candidate gene approach into the less arbitrary genome-wide association studies (GWAS) approach, the identification of genetic variants implicated in these disorders should increase dramatically in the next few years, as exemplified by the recent formation of an anxiety disorders group within the psychiatric genetics consortium (Sullivan *et al.* 2018).

We also note that we identified very few *protective* factors that were not reciprocal to risk factors. This indicates that most research so far has focused on adverse/negative factors, and highlights another important aspect that will need to be addressed in future studies.

Our results may also offer opportunities for prevention. Current prevention programs for anxiety disorders have shown modest benefits (Moreno-Peral *et al.* 2017) and there is a need for new strategies. Our findings lend support to identifying those individuals with *several* risk factors for inclusion in prevention programs (Blanco *et al.* 2014). Large sets of risk factors of small effects seem to account for the risk for anxiety and obsessive-compulsive disorders, and therefore interventions that try to modulate several of them concurrently should be devised. For example, parental psychopathology and parental rearing styles were significant risk factors for several of the disorders investigated here and could be a combined target for prevention efforts. Recent data on moderators and mediators of prevention strategies should help optimise such efforts (Ginsburg *et al.* 2015). Our results also support focusing on those modifiable risk factors with the largest effects (e.g., trauma), and whose reduction would have a greater prospective impact (Li *et al.* 2016). Claims of success should await the results of randomized trials, since observational associations may not necessarily represent causal effects.

Our study has several strengths. We used systematic search methods and both the study selection and data extraction were conducted by independent raters. Moreover, we assessed that each individual study included in the systematic review or meta-analysis fulfilled our inclusion criteria and used standard approaches to assess the methodological quality of the systematic reviews or meta-analysis (Fusar-Poli & Radua 2018). We offer as supplementary material all data collected in our umbrella review. Beyond encouraging open science, this databank may contribute to the creation of a database of risk/protective factors for anxiety and obsessive-compulsive disorders that can be updated in the future. We also note several limitations. First, we assessed each of disorders separately and did not use a mixed "anxiety disorders" category as an outcome. There have been changes in the specific disorders included under the "anxiety disorders" category, complicating the interpretation of such analyses. Second, we collected only information about factors assessed in systematic reviews and meta-analyses, and studies not included in this type of publication were not eligible for inclusion. Moreover, not all factors were evaluated for all the disorders. Third, we did not assess the quality of the individual studies included in the systematic reviews and meta-analyses (because this is beyond the scope of an umbrella review). Moreover, there may be differences across-studies in the exact definitions and methods of assessment for each factor. Finally, the almost ubiquitously limited amount of evidence made us explore also what would happen if we removed the need for >1000 cases to have highly suggestive evidence. Nevertheless, great caution is needed in trusting associations, no matter how strong and consistent, where data are sparse.

In summary, we found a number of nominally statistically significant risk and protective factors for anxiety and obsessive-compulsive disorders, although very few were supported by robust evidence. The limited amount of evidence was the main

restricting factor, and this means that there is plenty of room to improve the standards of evidence in this field. Our findings may help optimize current prediction models and may provide hints for testing prevention strategies.

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Table 1. Systematic reviews and meta-analyses included in the umbrella review, quality scores, and groups of risk/protective factors examined, by disorder.

Systematic review/meta-analysis	AMSTAR score (0-11)*	Groups of risk/protective factors examined	Disorders examined
Brander *et al.*(2016a)	6	Socio-demographic; parental rearing styles/attachment; substance use; life events; other	OCD
Brown *et al.*(2000)	3	Life events	Specific phobia, GAD, PD
Clarner *et al.* (2015)	8	Life events	PD
Clauss & Blackford (2012)	8	Other (behavioral inhibition in childhood)	SAD
Colonnessi *et al.* (2011)	8	Parental rearing styles/attachment	SAD
Fernandes *et al.*(2015)	8	Life events	SAD, GAD, PD
Gariepy *et al.* (2010)	10	Other (obesity)	GAD
Guo *et al.* (2016)	10	Socio-demographic	Specific phobia, SAD, GAD, PD, OCD
Jacobson & Newman (2017)	7	Psychopathology	Specific phobia, GAD, PD
Kedzior *et al.* (2014)	7	Substance use	Specific phobia, GAD, PD, OCD
Kissely *et al.*(2017)	11	Socio-demographic	SAD, GAD, PD
Kossowsky *et al.* (2013)	10	Psychopathology	PD
Kotov *et al.* (2010)	5	Personality dimensions	Specific phobia, SAD, GAD, OCD
Micco *et al.* (2009)	7	Parental psychopathology	SAD, GAD, PD, OCD
Moreno-Peral *et al.*(2014)	9	Socio-demographic; psychopathology; parental psychopathology; personality dimensions; substance use; life events; perinatal complications; parental rearing styles/attachment; other	GAD, PD
Moylan *et al.* (2012)	6	Substance use	Specific phobia, SAD, GAD
Osborn *et al.* (2016)	8	Other (traumatic brain injury)	GAD
Tarricone *et al.* (2012)	8	Socio-demographic	GAD
Van Steensel *et al.* (2011)	6	Psychopathology	Specific phobia

* Rounded-up average of two raters.

Note: Some risk/protective factors were assessed only for some of the disorders included in the corresponding systematic review/meta-analysis.

The specific risk/protective factors assessed in each systematic review or meta-analysis are reported in **Table S4** in the supplementary material.

Abbreviations: AMSTAR- Measurement tool to assess the methodological quality of systematic reviews, GAD-generalized anxiety disorder, PD-panic disorder, OCD-obsessive-compulsive disorder, SAD-social anxiety disorder.

Table 2. Number of systematic reviews and meta-analyses included in the umbrella review, individual studies assessed and included, and potential risk/protective factors included in the umbrella review, by disorder.

Disorder	Number of systematic reviews or meta-analyses included	Number of individual studies assessed for eligibility	Number of individual studies included	Number of potential risk/protective factors included
Specific phobia	6	63	19	13
Social anxiety disorder	10	110	34	20
Generalized anxiety disorder	13	132	57	110
Panic disorder	11	144	60	78
Obsessive-compulsive disorder	6	160	46	206

Table 3. Risk/protective factors showing *convincing* (class I), *highly suggestive* (class II), or *suggestive* (class III) evidence of association with each disorder using the original umbrella review criteria or after removing the n>1000 cases criterion, by disorder.

DISORDER	FACTOR GROUP	RISK / PROTECTIVE FACTOR	K	N	Measure	ES (95% CI)	p	PI sign.	I^2	ET sign.	ESB sign.	LS sign.	eOR	Class	Class (-n>1000)	Class (-n>1000, prosp.)
SPECIFIC PHOBIA	**Socio-demographic**	Male gender	9	689	OR	0·43 (0·36-0·51)	<0·000001	yes	0 %	no	no	yes	0·43	IV	I	NA
	Personality dimensions	Neuroticism	1	79	g	0·81 (0·57-1·05)	<0·000001	NA	NA	NA	no	yes	4·35	IV	II	II
SAD	**Psychopathology**	Dysthymia	1	52	IRR	14·81 (6·7-32·73)	<0·000001	NA	NA	NA	no	yes	14·81	IV	II	II
		Major depression	1	52	IRR	9·35 (4·71-18·54)	<0·000001	NA	NA	NA	no	yes	9·35	IV	II	II
	Personality dimensions	Neuroticism	1	89	g	0·89 (0·67-1·12)	<0·000001	NA	NA	NA	no	yes	5·02	IV	II	II
	Life events	Early emotional trauma	3	720	OR	2·8 (1·84- 4·24)	0·000001	no	36 %	no	no	yes	2·80	IV	III	III
		Early physical trauma	4	1191	OR	2·59 (2·17-3·1)	<0·000001	yes	0	no	no	yes	2·59	I	I	IV
		Early sexual trauma	5	1239	OR	3·18 (1·73-5·86)	0·00019	no	85 %	no	no	yes	3·18	III	III	IV
	Parental rearing styles/attachment	Insecure attachment in childhood	1	76	g	1·26 (0·91-1·61)	<0·000001	NA	NA	NA	no	yes	9·83	IV	II	NA
	Other	Behavioral inhibition in childhood*	7	257	OR	7·52 (3·04-18·61)	0·000013	no	78 %	no	yes	yes	7·52	IV	III	III
GAD	**Socio-demographic**	Age (30 to 54)	1	390	OR	2·92 (1·78-4·78)	0·000022	NA	NA	NA	no	yes	2·92	IV	III	III
		Male gender	15	999	OR	0·5 (0·41-0·59)	<0·000001	yes	0 %	no	no	yes	0·5	IV	I	NA
	Psychopathology	Bipolar I disorder	1	390	OR	2·58 (1·48-4·49)	0·00081	NA	NA	NA	no	yes	2·58	IV	III	III
		Borderline personality disorder	1	390	OR	4·71 (2·93-7·57)	<0·000001	NA	NA	NA	no	yes	4·71	IV	II	II
		History of one psychological disorder	1	288	OR	1·7 (1·27-2·26)	0·00029	NA	NA	NA	no	yes	1·70	IV	III	III
		Internalizing disorder at age 16	1	288	OR	2·01 (1·34-3)	0·00065	NA	NA	NA	no	yes	2·01	IV	III	III
		Internalizing disorder at age 7	1	288	OR	1·91 (1·31-2·79)	0·00081	NA	NA	NA	no	yes	1·91	IV	III	III
		Narcissistic personality disorder	1	390	OR	2·31 (1·49-3·6)	0·00019	NA	NA	NA	no	yes	2·31	IV	III	III
		Psychological malaise at age 33	1	288	OR	4·73 (3·43-6·52)	<0·000001	NA	NA	NA	no	yes	4·73	IV	II	II
		Schizotypal personality disorder	1	390	OR	2·6 (1·52-4·44)	0·00045	NA	NA	NA	no	yes	2·60	IV	III	III
		Subsyndromal depression no distress	1	563	OR	2·25 (1·56-3·24)	0·000014	NA	NA	NA	no	yes	2·25	IV	III	III
	Parental psychopathology	Anxiety	8	254	OR	3·45 (1·97-6·02)	0·000013	yes	0 %	no	no	yes	3·45	IV	III	NA
		GAD without comorbidity	1	106	HR	3·77 (2·27-6·26)	<0·000001	NA	NA	NA	no	yes	3·77	IV	II	II
		Major depression in both parents	1	65	OR	3·7 (2·01-6·79)	0·000024	NA	NA	NA	no	yes	3·70	IV	III	III
		Major depression in one parent	1	79	OR	2·51 (1·47-4·29)	0·00074	NA	NA	NA	no	yes	2·51	IV	III	III
	Personality dimensions	Behavioral inhibition*	1	106	HR	1·97 (1·66-2·33)	<0·000001	NA	NA	NA	no	yes	1·97	IV	II	II
		Harm avoidance	1	106	HR	1·69 (1·37-2·09)	0·000001	NA	NA	NA	no	yes	1·69	IV	III	III
	Substance use	Cannabis use	1	83	OR	2·79 (1·55-5·02)	0·00059	NA	NA	NA	no	yes	2·79	IV	III	III
	Life events	Early physical trauma	1	350	OR	2·39 (1·92-2·98)	<0·000001	NA	NA	NA	no	yes	2·39	IV	II	NA
		Early sexual trauma	1	350	OR	3·28 (2·6-4·14)	<0·000001	NA	NA	NA	no	yes	3·28	IV	II	NA
		Physical abuse in childhood	1	165	OR	1·82 (1·33-2·48)	0·00017	NA	NA	NA	no	yes	1·82	IV	III	IV
		Separation events in childhood	1	106	HR	2·44 (1·54-3·85)	0·00013	NA	NA	NA	no	yes	2·44	IV	III	IV
	Other	Received mental health treatment from 20 to 32	1	52	OR	6·15 (2·81-13·45)	0·000005	NA	NA	NA	no	yes	6·15	IV	III	III

		Received psychiatric medication from 20 to 32	1	52	OR	5·19 (1·98-13·55)	0·00078	NA	NA	NA	no	yes	5·19	IV	III	III
PD	**Socio-demographic**	Male gender	11	439	OR	0·5 (0·39-0·64)	<0·000001	yes	0 %	no	no	yes	0·5	IV	I	NA
	Psychopathology	Major depression	2	771	OR	2·03 (1·66-2·49)	<0·000001	NA	0 %	NA	no	yes	2·03	IV	II	II
		Panic attacks	1	811	OR	2·73 (1·93-3·88)	<0·000001	NA	NA	NA	no	yes	2·73	IV	II	II
		Post-traumatic stress disorder	1	224	OR	2·59 (1·5-4·47)	0·00062	NA	NA	NA	no	yes	2·59	IV	III	III
		Separation anxiety in childhood	10	880	OR	6·11 (4·31-8·66)	<0·000001	yes	5 %	no	no	yes	6·11	IV	I	NA
	Parental psychopathology	Panic attacks (for PDA)	1	54	OR	3·93 (1·91-8·07)	0·00019	NA	NA	NA	no	yes	3·93	IV	III	III
	Substance use	Cigarette smoking (daily)	2	201	HR	3·46 (2·21-5·41)	<0·000001	NA	21 %	NA	no	yes	3·46	IV	II	II
		Cigarette smoking (persistence in daily smokers)	1	51	HR	14·46 (4·81· 43·5)	0·000002	NA	NA	NA	no	yes	14·46	IV	III	III
		Cigarette smoking (persistence in prior daily smokers)	1	149	HR	3·18 (1·99-5·1)	0·000001	NA	NA	NA	no	yes	3·18	IV	III	III
	Life events	Early emotional trauma	1	123	OR	2·71 (1·57-4·68)	0·00035	NA	NA	NA	no	yes	2·71	IV	III	NA
		Early trauma	2	194	OR	3·56 (1·86-6·8)	0·00012	NA	0	NA	no	yes	3·56	IV	III	NA
		Early physical trauma	4	449	OR	2·46 (1·95-3·11)	<0·000001	yes	0 %	no	no	yes	2·46	IV	I	III
		Early sexual trauma	5	518	OR	2·91 (1·67-5·08)	0·00017	no	73 %	no	no	yes	2·91	IV	III	III
	Other	Joint hypermobility syndrome	1	14	RR	22·34 (5·3-94·29)	0·000023	NA	NA	NA	no	yes	22·34	IV	III	III
OCD	**Socio-demographic**	Paternal age >35	1	122	OR	5·34 (2·15-13·27)	0·00030	NA	NA	NA	no	yes	5·34	IV	III	NA
	Perinatal complications	Ear infection	1	68	OR	57·81 (7·59-440·61)	0·00009	NA	NA	NA	no	yes	57·81	IV	III	NA
		Early developmental problems	1	13	OR	11·53 (2·84-46·78)	0·00062	NA	NA	NA	no	yes	11·53	IV	III	NA
		Excess weight gain in pregnancy	1	68	OR	9·31 (2·62-33·1)	0·00057	NA	NA	NA	no	yes	9·31	IV	III	NA
		Hyperemesis	1	68	OR	8 (3·21-19·97)	0·000008	NA	NA	NA	no	yes	8·00	IV	III	NA
		Medication during pregnancy	1	68	OR	5·45 (2·6-11·45)	0·000007	NA	NA	NA	no	yes	5·45	IV	III	NA
		Mumps	1	68	OR	11·41 (3·23-40·28)	0·00015	NA	NA	NA	no	yes	11·41	IV	III	NA
		Other postnatal problems	1	68	OR	5·81 (2·04-16·52)	0·00096	NA	NA	NA	no	yes	5·81	IV	III	NA
		Other problems in pregnancy	1	68	OR	12·18 (3·46-42·9)	0·0001	NA	NA	NA	no	yes	12·18	IV	III	NA
		Throat infection	1	68	OR	4·7 (2·28-9·7)	0·000028	NA	NA	NA	no	yes	4·70	IV	III	NA
	Substance use	Alcohol use disorder	1	105	RR	2·41 (1·6-3·62)	0·000024	NA	NA	NA	no	yes	2·41	IV	III	III
		Use of cocaine and others (no marijuana)	1	105	RR	5·92 (4·97-7·05)	<0·000001	NA	NA	NA	no	yes	5·92	IV	II	II
	Life events	Emotional neglect in childhood	1	74	g	0·75 (0·32-1·18)	0·00066	NA	NA	NA	no	yes	3·90	IV	III	NA
		History of verbal abuse in family	1	33	OR	4·36 (1·88-10·11)	0·00061	NA	NA	NA	no	yes	4·36	IV	III	NA
		Sexual assault in childhood	2	32	RR	4·03 (1·83-8·87)	0·00052	NA	0	NA	no	yes	4·03	IV	III	NA
	Personality dimensions	Neuroticism	1	62	g	1·23 (0·96-1·5)	<0·000001	NA	NA	NA	no	yes	9·31	IV	II	II
	Parental rearing styles/attachment	Interference from father	1	94	g	0·85 (0·55-1·14)	<0·000001	NA	NA	NA	no	yes	4·67	IV	II	NA
		Overprotection from father	6	716	g	0·44 (0·21-0·68)	0·00017	no	65 %	no	no	yes	2·24	III	III	NA
		Punishment from father	1	94	g	0·71 (0·42-1)	0·000001	NA	NA	NA	no	yes	3·62	IV	III	NA
		Refusal from father	1	94	g	1·28 (0·98-1·59)	<0·000001	NA	NA	NA	no	yes	10·19	IV	II	NA
		Warmth from father	3	248	g	-0·64 (-0·87- -0·42)	<0·000001	no	23 %	no	no	yes	0·31	IV	II	NA
	Other	Postpartum	1	29	OR	12·05 (3·5-41·52)	0·000081	NA	NA	NA	no	yes	12·05	IV	III	NA

Abbreviations: Class – class of evidence, Class (-n>1000)- class of evidence after removing the n>1000 cases criterion, Class (-n>1000, prosp.)– class of evidence after removing the n>1000 cases criterion and after sensitivity analyses (including only prospective studies), CI – confidence interval, ES – effect size, ET – Egger test, eOR – equivalent odds ratio, ESB – excess significance bias, g – Hedge's g, GAD – generalized anxiety disorder, HR – hazard ratio, I^2 – heterogeneity, IRR – incidence rate ratio, K – number of studies for each factor, LS – largest study with significant effect, N – number of cases, NA – not assessable, ns – not significant, OCD – obsessive-compulsive disorder, OR – odds ratio, PD – panic disorder, PDA – panic disorder with agoraphobia, PI – prediction interval, SAD – social anxiety disorder, sign. – significant, RR – relative risk.

***** "Behavioral inhibition" referred to "the chronic tendency to respond to novel persons, places, and objects with wariness or avoidant behaviours" in one meta-analysis (Clauss & Blackford 2012) and to a personality/character dimension referring to "consistent restraint in response to social and non social situations" in one systematic review (Moreno-Peral *et al.* 2014).

Conflict of interest

Dr. Fernández de la Cruz and Prof. Mataix-Cols receive royalties for contributing articles to UpToDate, Wolters Kluwer Health. Dr. Vieta has received grants and honoraria from AB-Biotics, Allergan, Angelini, AstraZeneca, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, Janssen, Lundbeck, Medscape, Otsuka, Pfizer, Sanofi-Aventis, Sunovion, and Takeda as well as from the CIBERSAM, Grups Consolidats de Recerca 2014 (SGR 398), the Seventh European Framework Programme (ENBREC), Horizon 2020 (R-LINK) and the Stanley Medical Research Institute.

The rest of authors report no competing interests.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008."

FIGURE CAPTIONS

Figure 1. Flow chart of the literature search (see supplementary material for the flowcharts for each specific disorder)

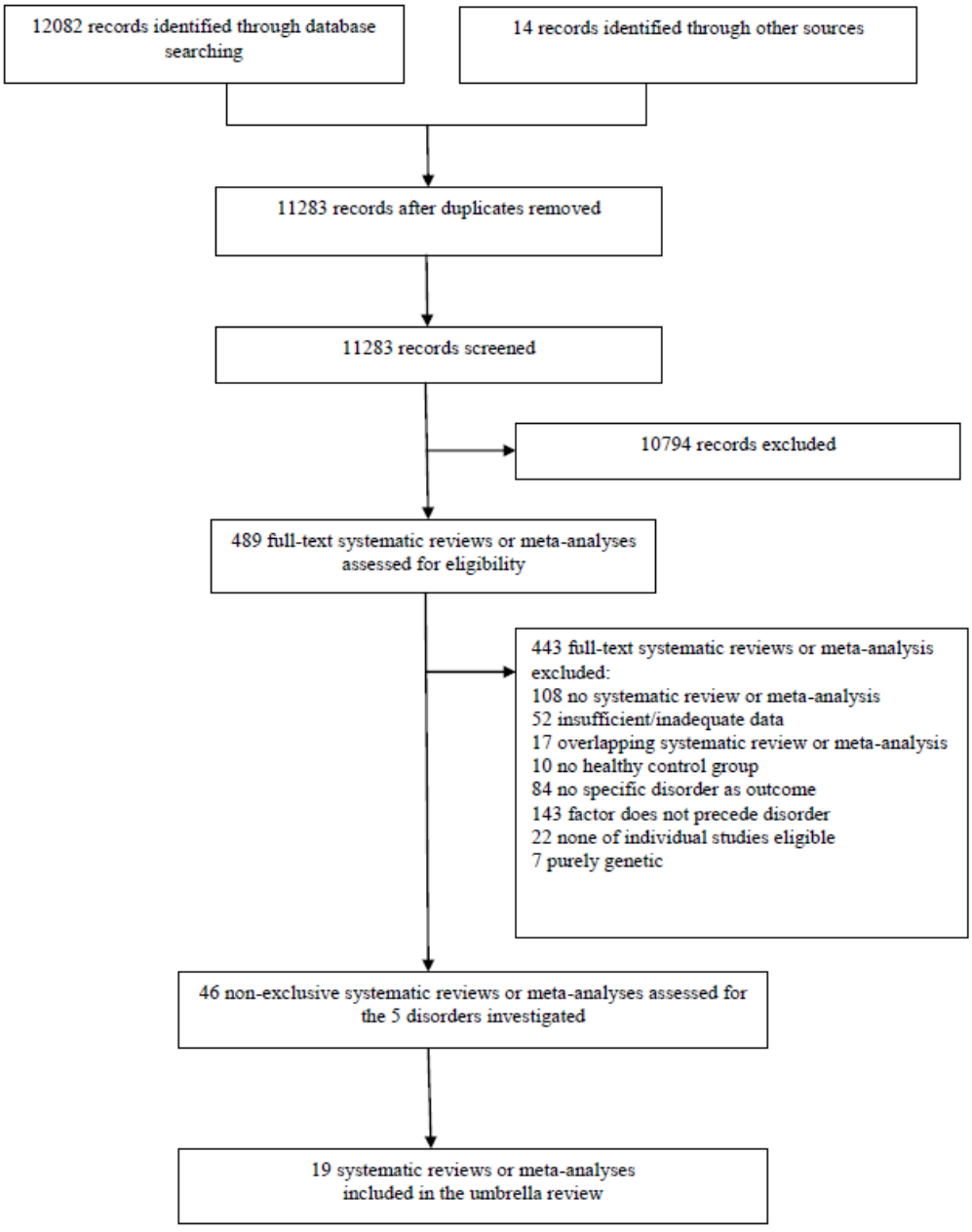

Figure 2. Forest plots of risk (in red) and protective (in green) factors showing *convincing* (class I) or *highly suggestive* (class II) evidence of association with each disorder, after removing the n>1000 cases criterion.

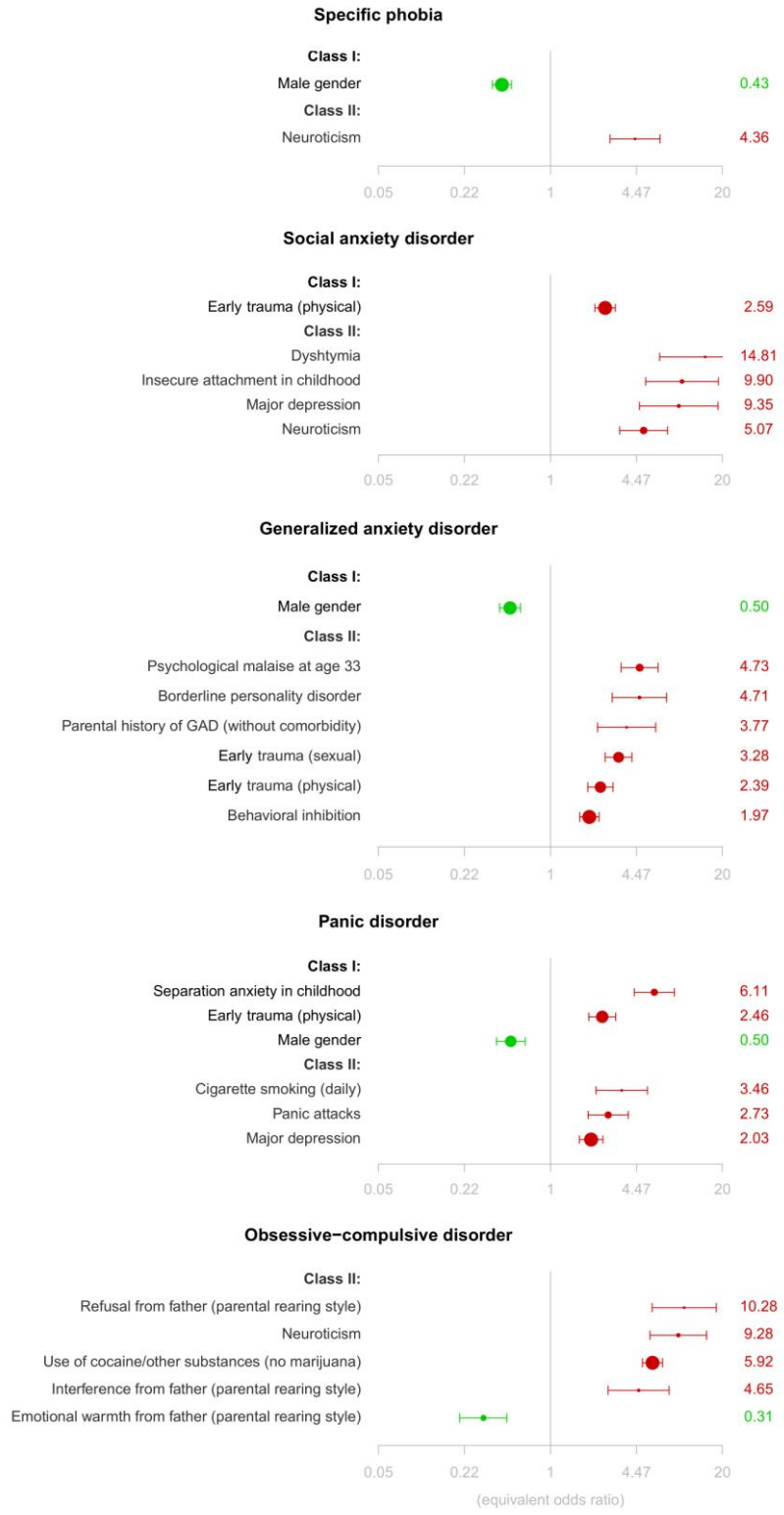

Figure 3. Forest plots of risk/protective factors assessed in at least four of the disorders under study and showing *convincing* (class I) or *highly suggestive* (class II) evidence of association with at least one of the disorders, after removing the n>1000 cases criterion.