Supplementary Material

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

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**References**

**Methods**

*Search strategy and eligibility criteria*

Two researchers (MAF and MTF or JC) independently conducted the search using the keywords (“systematic review” OR “meta-analysis”) for each of the disorders (“specific phobia” or “simple phobia”; “social phobia” or “social anxiety disorder”; “generalized anxiety disorder” or “generalised anxiety disorder”; "panic disorder"; and "obsessive-compulsive disorder"). The two researchers then screened the titles and abstracts and selected the eligible systematic reviews and meta-analyses for full-text review based on the inclusion criteria mentioned in the main manuscript. We did not include systematic reviews and meta-analyses were the outcome was "anxiety disorders" if no data were presented for specific disorders.

Example of full electronic search strategy for “social anxiety disorder” (PubMed):

(("meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]) OR ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "systematic review"[All Fields])) AND (("phobia, social"[MeSH Terms] OR ("phobia"[All Fields] AND "social"[All Fields]) OR "social phobia"[All Fields] OR ("social"[All Fields] AND "phobia"[All Fields])) OR ("phobia, social"[MeSH Terms] OR ("phobia"[All Fields] AND "social"[All Fields]) OR "social phobia"[All Fields] OR ("social"[All Fields] AND "anxiety"[All Fields] AND "disorder"[All Fields]) OR "social anxiety disorder"[All Fields])) AND ("0001/01/01"[PDAT] : "2018/04/30"[PDAT])

When more than one systematic review or meta-analysis were available for the same factor, we selected the most recent publication, but checked that it included all the studies included in the earlier systematic review or meta-analysis (and in case any study was missing, we also retained the earlier systematic review or meta-analysis).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 thus await the publication of large genome-wide association studies.

Although in some DSM classifications previous to DSM-5 “panic disorder” and “panic disorder with agoraphobia” have been classified separately, we included both nomenclatures under 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 (newly classed under the “anxiety disorders” category in the DSM-5), but they were not included due to the lack of systematic reviews and meta-analyses (**Figures S6-S7**). Posttraumatic stress disorder, grouped as an anxiety disorder until the publication of DSM-5, will be covered in a separate manuscript.

*Data extraction and selection*

Authors APV, JC, LFC, MAF, and MTF conducted the data extraction and selection as reported in the “Data extraction and selection” section of the Methods in the main manuscript. Additionally, the following rules were also followed to extract the data:

* We made sure that, if the same individual study was included in more than one systematic review or meta-analysis (for the same factor and disorder), it was only counted once.
* When there was an inconsistency between the risk estimate reported in the systematic review or meta-analysis and the same value in the individual study, we used the original data from the individual study.
* When a systematic review reported that "there was no association" between a risk factor and the anxiety disorder under study – or presented only those results that were significant – we extracted the non-reported figures from the individual paper(s).
* Where the data were only graphically reported, they were digitally measured from the original publication by using WebPlotDigitizer.
* For epidemiological studies with stable risk factors (e.g., sex) and reporting both lifetime and current/past year prevalence values, we used current/past year values. If the same individual study reported two different prevalences/temporal frames (e.g., 3 and 6 months after the risk factor), we used the more distal (i.e., 6 months).
* When several risk estimates with different degrees of adjustment were included for the same risk factor in a individual study, we used the risk estimate with the lowest degree of adjustment for comparison purposes (since in most studies the reported values were unadjusted).
* When an individual study used different operationalizations of a similar variable (e.g., “regular smoking”, “smoking”, “dependent regular smoking”), we used the variable with the closest definition to the one given in the systematic review or meta-analysis. In case of doubt, all the different operationalizations were included as separate risk factors.
* Risk factors from individual studies reporting 0 exposed individuals were not included in the analyses.

*Quality assessment*

The AMSTAR is an instrument developed to measure the methodological quality of systematic reviews which consists of 11 items assessing the presence of: an a priori design; duplicate study selection and data extraction; a comprehensive literature search; the use of status of publication as an inclusion criteria; a list of included/excluded studies; characteristics of included studies; documented assessment of the scientific quality of included studies; appropriate use of the scientific quality in forming conclusions; appropriate use of methods to combine findings of studies; assessment of the likelihood of publication bias; and documentation of conflict of interest. Several studies have confirmed that the AMSTAR has sound psychometric properties, including good agreement, reliability, construct validity, and feasibility. AMSTAR scores (rounded-up average of two raters) for each systematic review or meta-analysis are reported in the main manuscript (**Table 2**).

**Summary of data reporting**

In addition to this text file, we also provide as supplementary material to our manuscript five separate spreadsheets (one for each of the disorders included in the umbrella review): <https://www.umbrellaevidence.com/anxiety/riskfactors/>. Each spreadsheet contains a list of all systematic reviews and meta-analyses included, all individual studies included and excluded for each systematic review and meta-analysis (with reasons for exclusion), all data extracted for each individual study, and the results of the statistical analyses.

**Table S1. PRISMA Checklist.**

|  |
| --- |
| **PRISMA 2009 Checklist** |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page** |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | 1 (identified as “umbrella review”) |
| **ABSTRACT**  |  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | 2,3 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | 5 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 5,6 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | 6 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 6,7 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 6 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | 3 (Supplement) |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | 6; appendix |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 8,9; appendix |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | eTable 3; online spreadsheets |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 9 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | 8,9 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | 10 |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | 10 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | 10 |
| **RESULTS**  |  |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | eFigures 1-7 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | Table 1 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Online spreadsheets |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | Table 3; online spreadsheets; 38 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | Table 3; online spreadsheets |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | Table 3; online spreadsheets |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | Table 3; online spreadsheets |
| **DISCUSSION**  |  |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | 14 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 17 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 16, 18 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | 19 |

**Table S2. MOOSE checklist.**

|  |  |
| --- | --- |
| **Criteria** | **Brief description of how the criteria were handled in the umbrella review** |
|  |  |
| **Reporting of background should include** |
|  |  |  |
| √ | Problem definition | Several genetic and non-genetic variables have been proposed as potential protective/risk factors for anxiety disorders but data are inconclusive and there have been no previous attempts to summarize in a single report the strength of the evidence for both genetic and non-genetic risk and protective factors for each anxiety disorder, as well as to assess possible biases in the literature.  |
| √ | Hypothesis statement | This umbrella review summarizes the effects of several genetic and non-genetic variables as protective/risk factors for anxiety disorders, including specific phobia, panic disorder, social phobia, generalized anxiety disorder, and obsessive-compulsive disorder.Complementary analyses are conducted to assess the robustness of the findings.  |
| √ | Description of study outcomes | The outcomes of the meta-analyses were the effect sizes with their confidence intervals (CIs) and p-values, and the statistics required to assess the level of evidence. Depending on the risk/protective factor, we used incidence rate ratios (IRR), odds ratios (OR), risk ratios (RR), or Hedges’ *g*.The umbrella review also includes the study of between-study heterogeneity (95% prediction interval), residual heterogeneity (I2), publication bias, small-study effects, and excess significance bias. |
| √ | Type of exposure or intervention used | Exposure to a risk/protective factor in the patient group in comparison to a healthy control group.  |
| √ | Type of study designs used | Individual observational studies (case-control, cohort, and cross-sectional). |
| √ | Study population | Participants with ICD or DSM diagnoses of any of the following anxiety disorders: specific phobia, social anxiety disorder, generalized anxiety disorder, panic disorder, or obsessive-compulsive disorder, and healthy controls. |
| **Reporting of search strategy should include** |
|  |  |  |
| √ | Qualifications of searchers | All searchers (MAF, MTF, JC) are PhD. |
| √ | Search strategy, including time period included in the synthesis and keywords | Time period: from inception to 31 October 2017. The search adopted several combinations of the following keywords: “specific phobia”, “simple phobia”, “social phobia”, “social anxiety disorder”, “generalized anxiety disorder”, “obsessive-compulsive disorder", "meta-analysis", and "systematic review”.  |
| √ | Databases and registries searched | PubMed, Web of Science (all databases), and Scopus  |
| √ | Search software used, name and version, including special features | Web of Scienceand Scopus |
| √ | Use of hand searching | We hand-searched the reference lists of retrieved systematic review/meta-analyses for additional, relevant studies. |
| √ | List of citations located and those excluded, including justifications | Details of the literature search process are outlined in eFigures 1-5.  |
| √ | Method of addressing articles published in languages other than English | No language restrictions were applied.  |
| √ | Method of handling abstracts and unpublished studies | Abstracts and unpublished studies were excluded. |
| √ | Description of any contact with authors | We contacted the corresponding authors to provide additional data when needed. |
| **Reporting of methods should include** |
|  |  |  |
| √ | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Detailed inclusion and exclusion criteria are described in the methods section.  |
| √ | Rationale for the selection and coding of data | Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcome. |
| √ | Assessment of confounding | We assessed the quality of the systematic review/meta-analyses using the AMSTAR tool. A sensitivity analysis including only prospective studies was conducted.  |
| √ | Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | We assessed the quality of the selected systematic review/meta-analyses using a validated scale (AMSTAR). Results are presented in the main manuscript and online spreadsheets. Details of the AMSTAR are outlined in the appendix section. |
| √ | Assessment of heterogeneity | Heterogeneity was assessed by calculating the *I*2 statistic.  |
|  |  |  |
| √ | Description of statistical methods in sufficient detail to be replicated | Description of methods of the umbrella review are detailed in the Methods section of the main manuscript. |
| √ | Provision of appropriate tables and graphics | We include the PRISMA flow-charts to describe the literature search and its results. Several tables are used to describe the main findings.  |
| **Reporting of results should include** |  |
|  |  |  |
| √ | Graph summarizing individual study estimates and overall estimate | We include forest plot in the main manuscript (Figure 1) and in the Supplement (Figure 8) |
| √ | Table giving descriptive information for each study included | It is appended in the main text (for systematic review/meta-analyses). All individual studies are reported in the online spreadsheets.  |
| √ | Results of sensitivity testing | A summary is included in the main text. Results from the sensitivity analyses are reported in the online spreadsheets.  |
| √ | Indication of statistical uncertainty of findings | P-values, confidence intervals, prediction intervals, assessment of heterogeneity, assessment of potential biases, and sensitivity analyses. |
| **Reporting of discussion should include** |
|  |  |  |
| √ | Quantitative assessment of bias | We conducted Egger tests and excess significance bias tests. |
| √ | Justification for exclusion | This is provided in the discussion.  |
|  |  |  |
| √ | Assessment of quality of included studies | The quality assessments can be found in the main text and the online spreadsheets.  |
| **Reporting of conclusions should include** |
|  |  |  |
| √ | Consideration of alternative explanations for observed results | We discuss potential mechanisms of our findings.  |
| √ | Generalization of the conclusions | We include statements about the generalization of our results and suggest potential developments for future studies in the discussion. |
| √ | Guidelines for future research | They are provided in the discussion. |
| √ | Disclosure of funding source | All funding is declared in the main text. |
|  |  |  |

**Table S3. Specific risk and protective factors examined in each systematic review or meta-analysis included in the umbrella review**

|  |  |
| --- | --- |
|  | **Risk and protective factors examined** |
|  Brander *et al.* 2016  | **Birth order:** first or only child; first child; second child; third child; sixth child. **Family size:** 1 child; 1 or 2 siblings; 2 children; 3 children; 3 to 6 children; more than 4 children; 5 children; 7 to 9 children. **Household crowding. Infections:** GABHS previous 3months; GABHS previous year; strep previous 2 years; strep previous 3 months; strep previous 5 years; strep previous year. **Parental age:** maternal age: 30 to 34; 35 to 51; <25;> 35; paternal age: 30 to 34, 35 to 67, >35. **Parental rearing style/attachment experience:** role reversal (father, mother); love (father, mother); rejection (father, mother); trauma; care (father, mother); control (father, mother); interference (father, mother); overprotection (father, mother, both); preference (father, mother); punish (father, mother); refusal (father, mother); rejection (father, mother); warmth (father, mother, both). **Perinatal complications**: perinatal complications; prenatal accidents; postnatal allergies; postnatal amnesia; prenatal amniorrhexis; postnatal anemia; prenatal anemia; anomalous fetal presentation; postnatal asthma; postnatal autoimmune diseases; prenatal heavy bleeding; postnatal brain trauma; breech delivery; cesarean delivery; cesarean section; postnatal chicken pox; postnatal coma; complications of pregnancy; prenatal convulsions; postnatal convulsions; nuchal cord entanglement; postnatal excessive crying; postnatal delayed bladder control; postnatal complications; postnatal dermatological problems; difficulty conceiving; drugs during pregnancy; postnatal ear infection; postnatal early developmental problems; edema during pregnancy; epilepsy; excessive weight gain during pregnancy; excessive consumption of caffeine; excessive weight during pregnancy; postnatal infant floppy or limp; postnatal heart disease; home delivery; hospital delivery; hyperemesis; postnatal hypertension; postnatal hyperthyroidism; postnatal hypotension; postnatal hypothyroidism; postnatal incubator required; postnatal infection; postnatal infection of the upper airways; complications during labor; postnatal low birth; maternal problems; medication during pregnancy; postnatal meningitis; postnatal migraine headaches; postnatal mumps; prenatal excessive nausea; prenatal negative emotional state; neonatal hospitalization; neonatal surgery; no prenatal care; normal delivery; not prescribed drug during pregnancy; other illnesses during pregnancy; other infant events; other labor problems; other postnatal problems; prenatal complications not directly related to pregnancy; need for oxygen therapy; postnatal pertussis; postnatal pneumonia; postnatal complications; prenatal complications; prenatal medications; primiparity; special medication or procedure to conceive; prenatal proteinuria; protracted labor; postnatal rubella; prenatal smoking; postnatal controlling anal sphincter; prenatal spotting; Infant stiffened up when help or seemed to push away; postnatal streptococcal infection; postnatal switched milk formulas > or = 3 times; postnatal talking; postnatal frequent throat infection; prenatal tobacco use; Infant too quiet; postnatal tremors; excessive gain weight during pregnancy; excessive weight loss during pregnancy. **Season of birth:** ascending year of birth; birth between March and July; birth between August and November; **birth month**: January; February; March; April; May; June; July; August; September; October; November; December. **Stressful life events**: at least one life event 1 year before onset; life event 1 year before onset; severe life event 1 year before onset; life event 6 months before onset; **Substance use disorders**: alcohol use disorder; cocaine/marijuana/other use; cocaine/marijuana use; cocaine/other (no marijuana) use; cocaine only use; marijuana/other (no cocaine) use; marijuana only use. **Traumatic life events:** childhood emotional abuse; childhood emotional neglect; childhood interpersonal trauma;childhood physical abuse; childhood physical neglect; childhood sexual abuse; childhood sexual assault (molestation); childhood sexual assault (non-contact); childhood sexual assault (rape); interpersonal violence;  **l**oss of important person other than father; loss of parent; number of traumatic events and losses; number of residence changes; peer cruelty; physical abuse in the family; verbal abuse in the family; rape victim |
|  Brown *et al.* 2000  | **Civilian trauma** |
|  Clarner *et al.* 2015  | **Work-related trauma** |
|  Clauss & Blackford 2012  | **Behavioral inhibition in childhood** |
|  Colonnesi *et al.* 2011  | **Insecure attachment in childhood** |
|  Fernandes *et al.* 2015  | **Early emotional trauma:** emotional trauma; general trauma; physical trauma; sexual trauma |
|  Gariepy *et al.* 2010  | **Obesity** |
|  Guo *et al.* 2016  | **Gender**: male. **Urbanicity**: urban area |
|  Jacobson & Newman 2017  | **Dysthymia; major depression; mixed depression** |
|  Kedzior & Laeber 2014  | **Cannabis use** |
|  Kisely *et al.* 2017  | **Indigenous ethnicity** |
|  Kossowsky *et al.* 2013  | **Separation anxiety in childhood** |
|  Kotov *et al.* 2010  | **Personality traits**: disinhibition; extraversion; neuroticism |
|  Micco *et al.* 2009  | **Parental anxiety disorder** |
|  Moreno-Peral *et al.* 2014  | **Age:** 20-29; 30-54; >74. **Alcohol problems**: abuse; dependence; binge drinking in females. **Any chronic disease; number of physical diseases. Educational level**: high school; only basic education; less than high school. **Gender:** female; male. **Race/ethnicity** (non-Hispanic/Black). **History psychological problems**: 1 childhood disorder; 2 childhood disorders; externalising disorder at age 7; externalising disorder at age 11; externalising disorder at age 16; family history of psychiatric disease; internalising disorder at age 7; internalising disorder at age 11; internalising disorder at age 16; malaise at age 33; more than 3 childhood disorders; personal history of depression or anxiety. **Inhibited temperament** (from 3 to 5). **Joint hypermobility syndrome. Limitation/disabilities**: IADL score; ADL score; MMSE<26; recent decrease in ADL functioning; recent decrease in IADL functioning. **Marital status**: not married; separated/divorced/widowed. **Miscarriage. Other anxiety disorders**: disease phobia; generalized anxiety disorder; panic attacks; panic disorder;post-traumatic stress disorder; social phobia; specific phobia. **Other mental health problems**: any drug abuse; any drug dependence; ADHD; antisocial personality disorder; avoidant personality disorder; bipolar disorder type 1; bipolar disorder type 2; borderline personality disorder; dependent personality disorder; dysthymia; histrionic personality disorder; major depression; narcissistic personality disorder; obsessive compulsive personality disorder; paranoid personality disorder; schizoid personality disorder; schizotypal personality disorder; more than 1 personality disorder; subsyndromal depression; subsyndromal depression with no distress. **Parental characteristics**: emotional warmth; overprotection; rejection. **Parental history of mental disorders**: agoraphobia; antisocial personality disorder; anxiety and depressive disorders; anxiety but not depressive disorders; depressive but not anxiety disorders; generalized anxiety disorder; generalized anxiety disorder without comorbidity; major depressive episode; panic disorder; panic disorder with agoraphobia; major depression in both parents; major depression in one parent; panic disorder; substance disorder. **Personality traits**: behavioral inhibition, extraversion, harm avoidance, neuroticism, novelty seeking, openness to experience, resilience, reward dependence. **Psychiatric care:** medication from 20 to 32; mental health treatment from 20 to 32. **Social support. Socioeconomic level**: income <19999USD. **Somatic symptoms (body sensations); somatic symptoms. Stressful life events in childhood:** death of parent; divorce of parents; dysfunctional family; long term separation; maltreatment before 11; neglect; physical abuse; separation events; sexual abuse; loss of parent before 11 |
|  Moylan *et al.* 2012  | **Cigarette smoking;** daily smoking;nicotine dependence; regular smoking; smoking;smoking with no dependence; smoking without previous mental disorder; smoking dependence in previous daily smokers; smoking persistence in daily smokers |
|  Osborn *et al.* 2016  | **Adult traumatic brain injury** |
|  Tarricone *et al.* 2012  | **Ethnic minority** |
|  van Steensel *et al.* 2011  | **Autism-spectrum disorder in childhood** |

**Table S4. Significant (p<0.05) risk/protective factors, by disorder**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **DISORDER** | **FACTOR GROUP** | **RISK / PROTECTIVE FACTOR** | **K** | **N** | **Measure** | **ES (95% CI)** | **p** | **PI sign,** | **I2** | **ET sign,** | **ESB sign,** | **LS sign,** | **eOR** | **Class** | **Class (->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 |
| **Psychopathology** | Autism-spectrum disorder in childhood | 1 | 27 | OR | 2,4 (1,06, 5,44) | 0,036 | NA | NA | NA | no | yes | 2,40 | IV | IV | NA |
|  | **Personality dimensions** | Extraversion | 1 | 79 | g | -0,39 (-0,62, -0,15) | 0,0013 | NA | NA | NA | no | yes | 0,49 | IV | IV | IV |
|  |  | Neuroticism | 1 | 79 | g | 0,81 (0,57, 1,05) | <0,000001 | NA | NA | NA | no | yes | 4,35 | IV | II | II |
|  | **Substance use** | Cigarette smoking (non dependence) | 1 | 64 | OR | 2,01 (1,09, 3,68) | 0,024 | NA | NA | NA | no | yes | 2,01 | IV | IV | IV |
|  |  | Cigarette smoking (regular) | 1 | 63 | OR | 2,47 (1,35, 4,53) | 0,0035 | NA | NA | NA | no | yes | 2,47 | IV | IV | IV |
| **SAD** | **Socio-demographic** | Male gender | 9 | 301 | OR | 0,68 (0,54, 0,86) | 0,0014 | yes | 0 % | no | no | no | 0,68 | IV | IV | NA |
| **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** | Extraversion | 1 | 89 | g | -0,28 (-0,51, -0,06) | 0,013 | NA | NA | NA | no | yes | 0,60 | IV | IV | IV |
|  |  | Neuroticism | 1 | 89 | g | 0,89 (0,67, 1,12) | <0,000001 | NA | NA | NA | no | yes | 5,02 | IV | II | II |
|  | **Substance use** | Cigarette smoking (regular) | 1 | 33 | OR | 2,48 (1,14, 5,4) | 0,021 | NA | NA | NA | no | yes | 2,48 | IV | IV | IV |
|  | **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 |
|  | Hispanic ethnicity | 1 | 390 | OR | 0,5 (0,27, 0,91) | 0,023 | NA | NA | NA | no | yes | 0,50 | IV | IV | IV |
|  | Income lower than 19,999 USD | 1 | 390 | OR | 2,1 (1,15, 3,85) | 0,016 | NA | NA | NA | no | yes | 2,10 | IV | IV | IV |
|  |  | Male gender | 15 | 999 | OR | 0,5 (0,41, 0,59) | <0,000001 | yes | 0 % | no | no | yes | 0,5 | IV | I | NA |
|  |  | Separated, divorced, or widowed | 1 | 390 | OR | 1,59 (1,04, 2,42) | 0,032 | NA | NA | NA | no | yes | 1,59 | IV | IV | IV |
|  | **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 |
|  |  | Externalizing disorder at age 11 | 1 | 288 | OR | 1,65 (1,12, 2,44) | 0,011 | NA | NA | NA | no | yes | 1,65 | IV | IV | IV |
|  |  | Externalizing disorder at age 16 | 1 | 288 | OR | 1,61 (1,08, 2,41) | 0,019 | NA | NA | NA | no | yes | 1,61 | IV | IV | IV |
|  |  | History of depression or anxiety | 1 | 24 | OR | 2,58 (1,02, 6,58) | 0,046 | NA | NA | NA | no | yes | 2,58 | IV | IV | IV |
|  |  | 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 |
|  |  | Histrionic personality disorder | 1 | 390 | OR | 0,2 (0,06, 0,66) | 0,0076 | NA | NA | NA | no | yes | 0,20 | IV | IV | IV |
|  |  | 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 |
|  |  | Major depression | 3 | 1422 | OR | 1,74 (1,06, 2,85) | 0,029 | NA | 0 % | NA | no | yes | 1,74 | IV | IV | IV |
|  |  | More than one personality disorder | 1 | 19 | OR | 14,92 (2,7, 82,41) | 0,0019 | NA | NA | NA | no | yes | 14,92 | IV | IV | IV |
|  |  | Narcissistic personality disorder | 1 | 390 | OR | 2,31 (1,49, 3,6) | 0,00019 | NA | NA | NA | no | yes | 2,31 | IV | III | III |
|  |  | Panic attacks | 1 | 987 | OR | 1,7 (1,21, 2,39) | 0,0022 | NA | NA | NA | no | yes | 1,70 | IV | IV | IV |
|  |  | Panic disorder | 1 | 390 | OR | 1,72 (1,01, 2,94) | 0,047 | NA | NA | NA | no | yes | 1,72 | IV | IV | IV |
|  |  | 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 |
|  |  | Social phobia | 1 | 390 | OR | 1,8 (1,01, 3,2) | 0,046 | NA | NA | NA | no | yes | 1,80 | IV | IV | IV |
|  |  | Subsyndromal depression | 1 | 611 | OR | 1,42 (1,08, 1,86) | 0,011 | NA | NA | NA | no | yes | 1,42 | IV | IV | IV |
|  |  | 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 |
|  |  | Three or more childhood disorders | 1 | 288 | OR | 2,39 (1,28, 4,48) | 0,0064 | NA | NA | NA | no | yes | 2,39 | IV | IV | IV |
|  |  | Two childhood disorders | 1 | 288 | OR | 1,72 (1,13, 2,63) | 0,011 | NA | NA | NA | no | yes | 1,72 | IV | IV | IV |
|  | **Parental psychopathology** | Anxiety | 8 | 254 | OR | 3,45 (1,97, 6,02) | 0,000013 | yes | 0 % | no | no | yes | 3,45 | IV | III | NA |
|  |  | Depressive (but not anxiety) disorders | 1 | 106 | HR | 1,77 (1,05, 2,98) | 0,031 | NA | NA | NA | no | yes | 1,77 | IV | IV | IV |
|  |  | GAD | 1 | 165 | OR | 1,59 (1,17, 2,18) | 0,0032 | NA | NA | NA | no | yes | 1,59 | IV | IV | IV |
|  |  | 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 | 1 | 165 | OR | 1,52 (1,12, 2,08) | 0,008 | NA | NA | NA | no | yes | 1,52 | IV | IV | IV |
|  |  | 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 |
|  |  | PD | 1 | 165 | OR | 1,49 (1,09, 2,04) | 0,011 | NA | NA | NA | no | yes | 1,49 | IV | IV | IV |
|  |  | Substance disorder | 1 | 165 | OR | 1,49 (1,09, 2,04) | 0,011 | NA | NA | NA | no | yes | 1,49 | IV | IV | IV |
|  | **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 |
|  |  | Neuroticism | 3 | 406 | g | 0,86 (0,1, 1,61) | 0,026 | no | 98 % | no | yes | yes | 4,73 | IV | IV | IV |
|  |  | Reward dependence | 1 | 106 | HR | 1,43 (1,07, 1,9) | 0,014 | NA | NA | NA | no | yes | 1,43 | IV | IV | IV |
|  | **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 |
|  |  | Cigarette smoking (non dependent) | 1 | 5 | OR | 0,1 (0,02, 0,61) | 0,012 | NA | NA | NA | no | yes | 0,10 | IV | IV | IV |
|  |  | Cigarette smoking (without previous mental disorder) | 1 | 17 | IRR | 4,57 (1,53, 13,67) | 0,0065 | NA | NA | NA | no | yes | 4,57 | IV | IV | IV |
|  | **Life events** | Childhood maltreatment before 11 | 1 | 52 | OR | 4,4 (1,47, 13,17) | 0,0080 | NA | NA | NA | no | yes | 4,40 | IV | IV | IV |
|  |  | Divorce of parents in childhood | 1 | 165 | OR | 1,4 (1,03, 1,92) | 0,032 | NA | NA | NA | no | yes | 1,40 | IV | IV | IV |
|  |  | Dysfunctional family in childhood | 1 | 106 | HR | 1,48 (1,05, 2,07) | 0,023 | NA | NA | NA | no | yes | 1,48 | IV | IV | IV |
|  |  | 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 |
|  |  | Neglect in childhood | 1 | 165 | OR | 1,66 (1,21, 2,26) | 0,0014 | NA | NA | NA | no | yes | 1,66 | IV | IV | IV |
|  |  | 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 |
|  |  | Sexual abuse in childhood | 1 | 165 | OR | 1,58 (1,13, 2,21) | 0,0079 | NA | NA | NA | no | yes | 1,58 | IV | IV | IV |
|  | **Parental rearing styles/attachment** | Parental overprotection | 1 | 106 | HR | 1,48 (1,07, 2,05) | 0,018 | NA | NA | NA | no | yes | 1,48 | IV | IV | IV |
|  | **Other** | Joint hypermobility syndrome | 1 | 16 | RR | 2,97 (1,2, 7,37) | 0,018 | NA | NA | NA | no | no | 2,97 | IV | IV | IV |
|  |  | Obesity | 1 | 27 | OR | 4,49 (1,21, 16,69) | 0,024 | NA | NA | NA | no | yes | 4,49 | IV | IV | IV |
|  |  | 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** | Age (20 to 29) | 1 | 224 | OR | 2,7 (1,2, 6,09) | 0,016 | NA | NA | NA | no | yes | 2,7 | IV | IV | IV |
|  |  | Age (30 to 54) | 1 | 224 | OR | 2,6 (1,28, 5,28) | 0,0079 | NA | NA | NA | no | yes | 2,6 | IV | IV | IV |
|  |  | Income lower than 19999 USD | 1 | 224 | OR | 2,3 (1,13, 4,68) | 0,021 | NA | NA | NA | no | yes | 2,3 | IV | IV | IV |
|  |  | Male gender | 11 | 439 | OR | 0,5 (0,39, 0,64) | <0,000001 | yes | 0 % | no | no | yes | 0,5 | IV | I | NA |
|  | **Psychopathology** | Any psychological disorder | 1 | 24 | OR | 2,48 (1,1, 5,57) | 0,028 | NA | NA | NA | no | yes | 2,48 | IV | IV | IV |
|  |  | Bipolar I disorder | 1 | 224 | OR | 2,31 (1,08, 4,93) | 0,03 | NA | NA | NA | no | yes | 2,31 | IV | IV | IV |
|  |  | Borderline personality disorder | 1 | 224 | OR | 2,3 (1,17, 4,5) | 0,015 | NA | NA | NA | no | yes | 2,3 | IV | IV | IV |
|  |  | GAD | 1 | 224 | OR | 2,6 (1,27, 5,29) | 0,0085 | NA | NA | NA | no | yes | 2,6 | IV | IV | IV |
|  |  | Major depression | 2 | 771 | OR | 2,03 (1,66, 2,49) | <0,000001 | NA | 0 % | NA | no | yes | 2,03 | IV | II | II |
|  |  | Mixed depression | 1 | 6 | OR | 10,03 (1,77, 56,68) | 0,009 | NA | NA | NA | no | yes | 10,03 | IV | IV | IV |
|  |  | More than one personality disorder | 1 | 30 | OR | 3,27 (1,13, 9,48) | 0,029 | NA | NA | NA | no | yes | 3,27 | IV | IV | IV |
|  |  | 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 |
|  |  | Schizotypal personality disorder | 1 | 224 | OR | 2,6 (1,33, 5,09) | 0,0054 | NA | NA | NA | no | yes | 2,6 | IV | IV | IV |
|  |  | 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 |
|  |  | Subsyndromal depression | 1 | 395 | OR | 1,59 (1,11, 2,29) | 0,012 | NA | NA | NA | no | yes | 1,59 | IV | IV | IV |
|  | **Parental psychopathology** | Anxiety | 4 | 25 | OR | 3,48 (1,24, 9,74) | 0,017 | no | 0 % | no | no | yes | 3,48 | IV | IV |  |
|  |  | Major depression in both parents | 1 | 39 | OR | 2,91 (1,39, 6,09) | 0,0044 | NA | NA | NA | no | yes | 2,91 | IV | IV | IV |
|  |  | 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 |
|  |  | PD (for PDA) | 1 | 54 | OR | 3,55 (1,38, 9,13) | 0,0087 | NA | NA | NA | no | yes | 3,55 | IV | IV | IV |
|  |  | PDA (for PDA) | 1 | 54 | OR | 3,38 (1,05, 10,87) | 0,041 | NA | NA | NA | no | yes | 3,38 | IV | IV | IV |
|  |  | Specific phobia (for PD) | 1 | 47 | OR | 2,07 (1,06, 4,02) | 0,031 | NA | NA | NA | no | yes | 2,07 | IV | IV | IV |
|  | **Substance use** | Binge drinking (in females) | 1 | 179 | OR | 2,23 (1,03, 4,83) | 0,042 | NA | NA | NA | no | yes | 2,23 | IV | IV | IV |
|  |  | Cannabis use | 1 | 66 | OR | 2,37 (1,21, 4,66) | 0,012 | NA | NA | NA | no | yes | 2,37 | IV | IV | IV |
|  |  | 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 |
|  |  | Cigarette smoking (regular) | 1 | 15 | OR | 3,28 (1,03, 10,47) | 0,045 | NA | NA | NA | no | yes | 3,28 | IV | IV | IV |
|  | **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 |
|  |  | Traumatic event at work | 2 | 10 | OR | 5,94 (1,26, 28,09) | 0,024 | NA | 0 % | NA | yes | no | 5,94 | IV | IV | NA |
|  | **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** | Birth between August and November | 1 | 1047 | RR | 1,19 (1,05, 1,36) | 0,0077 | NA | NA | NA | no | yes | 1,19 | IV | IV | NA |
|  |  | Birth between March and July | 1 | 1047 | RR | 0,84 (0,74, 0,95) | 0,0057 | NA | NA | NA | no | yes | 0,84 | IV | IV | NA |
|  |  | Family size (3 to 6 siblings) | 1 | 89 | OR | 0,64 (0,42, 0,98) | 0,039 | NA | NA | NA | no | yes | 0,64 | IV | IV | NA |
|  |  | Family size (1 or 2 siblings) | 1 | 89 | OR | 2,07 (1,25, 3,42) | 0,0043 | NA | NA | NA | no | yes | 2,07 | IV | IV | NA |
|  |  | Family size (2 children) | 2 | 36 | OR | 0,4 (0,19, 0,85) | 0,017 | NA | 0 % | NA | no | yes | 0,40 | IV | IV | NA |
|  |  | Family size (3 children) | 2 | 36 | OR | 2,48 (1,23, 5) | 0,01 | NA | 0 % | NA | no | no | 2,48 | IV | IV | NA |
|  |  | Family size (4 or more children) | 1 | 25 | OR | 2,75 (1,1, 6,91) | 0,031 | NA | NA | NA | no | yes | 2,75 | IV | IV | NA |
|  |  | Maternal age 35 to 51 | 1 | 2057 | OR | 1,25 (1,04, 1,5) | 0,016 | NA | NA | NA | no | yes | 1,25 | IV | IV | NA |
|  |  | Paternal age <25 | 1 | 122 | OR | 0,29 (0,1, 0,82) | 0,019 | NA | NA | NA | no | yes | 0,29 | IV | IV | NA |
|  |  | Paternal age >35 | 1 | 122 | OR | 5,34 (2,15, 13,27) | 0,00030 | NA | NA | NA | no | yes | 5,34 | IV | III | NA |
|  |  | Paternal age 30 to 34 | 1 | 122 | OR | 2,21 (1,26, 3,89) | 0,0057 | NA | NA | NA | no | yes | 2,21 | IV | IV | NA |
|  | **Parental psychopathology** | Anxiety | 1 | 11 | OR | 10,3 (1,25, 85,04) | 0,03 | NA | NA | NA | no | yes | 10,30 | IV | IV | IV |
|  | **Perinatal complications** | Cesarean section | 1 | 68 | OR | 2,83 (1,36, 5,89) | 0,0055 | NA | NA | NA | no | yes | 2,83 | IV | IV | NA |
|  |  | Delivery with neonatal complications | 1 | 126 | OR | 2,12 (1,04, 4,3) | 0,037 | NA | NA | NA | no | yes | 2,12 | IV | IV | NA |
|  |  | Drugs during pregnancy | 1 | 124 | OR | 2,28 (1,1, 4,71) | 0,026 | NA | NA | NA | no | yes | 2,28 | IV | IV | NA |
|  |  | 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 |
|  |  | Edema in pregnancy | 1 | 68 | OR | 5,86 (1,23, 27,84) | 0,026 | NA | NA | NA | no | yes | 5,86 | IV | IV | 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 |
|  |  | Home delivery | 1 | 68 | OR | 0,25 (0,08, 0,8) | 0,019 | NA | NA | NA | no | yes | 0,25 | IV | IV | NA |
|  |  | Hospital delivery | 1 | 68 | OR | 4 (1,24, 12,86) | 0,019 | NA | NA | NA | no | yes | 4,00 | IV | IV | NA |
|  |  | Hyperemesis | 1 | 68 | OR | 8 (3,21, 19,97) | 0,000008 | NA | NA | NA | no | yes | 8,00 | IV | III | NA |
|  |  | Infection | 2 | 195 | OR | 3,06 (1,03, 9,12) | 0,044 | NA | 16 % | NA | no | no | 3,06 | IV | IV | NA |
|  |  | Infection of the upper airways | 1 | 68 | OR | 5,04 (1,76, 14,44) | 0,0025 | NA | NA | NA | no | yes | 5,04 | IV | IV | 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 |
|  |  | Migraine | 1 | 68 | OR | 2,5 (1,07, 5,84) | 0,034 | NA | NA | NA | no | yes | 2,50 | IV | IV | NA |
|  |  | Mumps | 1 | 68 | OR | 11,41 (3,23, 40,28) | 0,00015 | NA | NA | NA | no | yes | 11,41 | IV | III | NA |
|  |  | Negative emotionality | 1 | 68 | OR | 4,6 (1,82, 11,64) | 0,0012 | NA | NA | NA | no | yes | 4,60 | IV | IV | NA |
|  |  | Normal delivery | 1 | 68 | OR | 0,35 (0,17, 0,74) | 0,0055 | NA | NA | NA | no | yes | 0,35 | IV | IV | NA |
|  |  | Other illnesses | 1 | 120 | OR | 12 (1,58, 91,38) | 0,016 | NA | NA | NA | no | yes | 12,00 | IV | IV | NA |
|  |  | Other infant events | 1 | 123 | OR | 28,21 (1,69, 472,28) | 0,02 | NA | NA | NA | no | no | 28,21 | IV | IV | NA |
|  |  | Other labor problems | 1 | 123 | OR | 2,55 (1,29, 5,04) | 0,0069 | NA | NA | NA | no | yes | 2,55 | IV | IV | 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 |
|  |  | Perinatal complications | 1 | 123 | OR | 3,28 (1,42, 7,6) | 0,0055 | NA | NA | NA | no | yes | 3,28 | IV | IV | NA |
|  |  | Postnatal anemia | 1 | 68 | OR | 31,19 (1,81, 538,36) | 0,017 | NA | NA | NA | no | no | 31,19 | IV | IV | NA |
|  |  | Protracted labor | 1 | 68 | OR | 11,33 (2,5, 51,28) | 0,0016 | NA | NA | NA | no | yes | 11,33 | IV | IV | NA |
|  |  | Switch milk | 1 | 120 | OR | 17,87 (1,06, 302,61) | 0,045 | NA | NA | NA | no | no | 17,87 | IV | IV | NA |
|  |  | Throat infection | 1 | 68 | OR | 4,7 (2,28, 9,7) | 0,000028 | NA | NA | NA | no | yes | 4,70 | IV | III | NA |
|  |  | Tremors | 1 | 68 | OR | 9,2 (1,12, 75,69) | 0,039 | NA | NA | NA | no | yes | 9,20 | IV | IV | 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 abuse in childhood | 1 | 74 | g | 0,49 (0,07, 0,92) | 0,022 | NA | NA | NA | no | yes | 2,45 | IV | IV | NA |
|  |  | 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 |
|  |  | Interpersonal life events in childhood | 1 | 74 | g | 0,6 (0,17, 1,03) | 0,0061 | NA | NA | NA | no | yes | 2,97 | IV | IV | NA |
|  |  | Physical abuse in childhood | 2 | 110 | g | 0,79 (0,1, 1,47) | 0,023 | NA | 84% | NA | no | yes | 4,17 | IV | IV | III |
|  |  | Rape | 1 | 16 | OR | 3,82 (1,21, 12,06) | 0,022 | NA | NA | NA | no | yes | 3,82 | IV | IV | NA |
|  |  | Rape in childhood | 1 | 10 | RR | 4,44 (1,31, 15,05) | 0,016 | NA | NA | NA | no | yes | 4,44 | IV | IV | NA |
|  |  | Sexual abuse in childhood | 3 | 133 | g | 0,45 (0,17, 0,74) | 0,0017 | no | 37 % | no | no | no | 2,27 | IV | IV | IV |
|  |  | 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 |
|  |  | Sexual contact in childhood | 1 | 30 | OR | 3,81 (1,19, 12,16) | 0,023 | NA | NA | NA | no | yes | 3,81 | IV | IV | NA |
|  |  | Stressful life events 6 months before onset of disorder | 1 | 10 | g | 1,69 (0,64, 2,75) | 0,0016 | NA | NA | NA | no | yes | 21,44 | IV | IV | 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** | Attachment experience (love) from father | 1 | 25 | g | -0,71 (-1,28, -0,13) | 0,015 | NA | NA | NA | no | yes | 0,28 | IV | IV | NA |
|  |  | Attachment experience (love) from mother | 1 | 25 | g | -0,7 (-1,27, -0,12) | 0,017 | NA | NA | NA | no | yes | 0,28 | IV | IV | NA |
|  |  | Attachment experience (rejection) from father | 1 | 25 | g | 0,84 (0,26, 1,42) | 0,0043 | NA | NA | NA | no | yes | 4,59 | IV | IV | NA |
|  |  | Attachment experience (rejection) from mother | 1 | 25 | g | 0,97 (0,38, 1,56) | 0,0012 | NA | NA | NA | no | yes | 5,81 | IV | IV | NA |
|  |  | Care from father | 4 | 582 | g | -0,42 (-0,73, -0,11) | 0,0074 | no | 66 % | no | no | yes | 0,47 | IV | IV | NA |
|  |  | Interference from father | 1 | 94 | g | 0,85 (0,55, 1,14) | <0,000001 | NA | NA | NA | no | yes | 4,67 | IV | II | NA |
|  |  | Interference from mother | 1 | 94 | g | 0,41 (0,13, 0,69) | 0,0046 | NA | NA | NA | no | yes | 2,10 | IV | IV | 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 |
|  |  | Overprotection from mother | 5 | 623 | g | 0,38 (0,14, 0,63) | 0,015 | no | 56 % | no | no | yes | 2 | IV | IV | NA |
|  |  | Preference from mother | 1 | 94 | g | 0,3 (0,02, 0,58) | 0,037 | NA | NA | NA | no | yes | 1,72 | IV | IV | NA |
|  |  | Punishment from father | 1 | 94 | g | 0,71 (0,42, 1) | 0,000001 | NA | NA | NA | no | yes | 3,62 | IV | III | NA |
|  |  | Punishment from mother | 1 | 94 | g | 0,29 (0,01, 0,57) | 0,045 | NA | NA | NA | no | yes | 1,69 | IV | IV | 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 |
|  |  | Refusal from mother | 1 | 94 | g | 0,44 (0,16, 0,73) | 0,0022 | NA | NA | NA | no | yes | 2,22 | IV | IV | NA |
|  |  | Rejection | 1 | 40 | g | 0,62 (0,17, 1,07) | 0,0067 | NA | NA | NA | no | yes | 3,08 | IV | IV | NA |
|  |  | Rejection from father | 2 | 154 | g | 0,49 (0,11, 0,87) | 0,011 | NA | 47 % | NA | no | yes | 2,43 | IV | IV | NA |
|  |  | Rejection from mother | 2 | 162 | g | 0,35 (0,1, 0,61) | 0,0065 | NA | 0 % | NA | no | no | 1,89 | IV | IV | NA |
|  |  | Warmth | 1 | 40 | g | -0,45 (-0,89, -0,01) | 0,046 | NA | NA | NA | no | yes | 0,44 | IV | IV | 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 |
|  |  | Warmth from mother | 3 | 256 | g | -0,53 (-0,86, -0,21) | 0,0014 | no | 63 % | no | yes | yes | 0,38 | IV | IV | NA |
|  | **Other** | Postpartum | 1 | 29 | OR | 12,05 (3,5, 41,52) | 0,000081 | NA | NA | NA | no | yes | 12,05 | IV | III | NA |
|  |  | Streptococcal infection during previous year | 2 | 218 | OR | 1,64 (1,07, 2,51) | 0,022 | NA | 0 % | NA | no | yes | 1,64 | IV | IV | IV |

*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, I2 – 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.

**Figure S1. PRISMA flowchart of the literature search for specific phobia**

Additional records identified through other sources
(n = 2)

Records identified through database searching
(n = 627)

## Identification

Records after duplicates removed (n = 549)

Records screened on the basis of title and abstract
(n = 549)

Records excluded (n = 490)

## Screening

53 systematic reviews/meta-analyses excluded:

- no systematic review or meta-analysis (n = 20)

- insufficient/inadequate data for analysis (n = 6)

- no healthy control group (n = 1)

- no specific phobia as outcome (n = 8)

- factor does not precede disorder (n = 15)

- none of individual studies eligible (n = 3)

Full-text systematic reviews/ meta-analyses assessed for eligibility
(n = 59)

## Eligibility

Systematic reviews/meta-analyses included in the umbrella review

(n = 6)

Individual studies included in the umbrella review

 (n= 19)

## Included

**Figure S2. PRISMA flowchart of the literature search for social anxiety disorder**

Additional records identified through other sources
(n = 2)

Records identified through database searching
(n = 3263)

## Identification

Records after duplicates removed (n = 2954)

Records screened on the basis of title and abstract
(n = 2954)

## Screening

Records excluded (n = 2851)

93 full-text systematic reviews/meta-analyses excluded:

- no systematic review or meta-analysis (n = 18)

- insufficient/inadequate data for analysis (n = 8)

- overlapping systematic review/meta-analysis (n = 1)

- no healthy control group (n = 2)

- no social anxiety disorder as outcome (n = 32)

- factor does not precede disorder (n = 28)

- none of individual studies eligible (n = 4)

Full-text systematic reviews/ meta-analyses assessed for eligibility
(n =103)

## Eligibility

Systematic reviews/meta-analyses included in the umbrella review

(n = 10)

Individual studies included in the umbrella review

(n = 34)

## Included

**Figure S3. PRISMA Flowchart of the literature search for generalized anxiety disorder**

Additional records identified through other sources
(n = 5)

Records identified through database searching
(n = 1448)

## Identification

Records after duplicates removed (n = 1299)

Records screened on the basis of title and abstract
(n = 1299)

## Screening

Records excluded (n = 1233)

 53 systematic reviews/meta-analyses excluded:

- no systematic review or meta-analysis (n = 8)

- insufficient/inadequate data for analysis (n = 13)

- no healthy control group (n = 4)

- no generalized anxiety disorder as outcome (n = 6)

- factor does not precede disorder (n = 14)

- none of individual studies eligible (n = 7)

- purely genetic (n=1)

Full-text systematic review/ meta-analyses assessed for eligibility
(n =66)

## Eligibility

Systematic reviews/meta-analyses included in the umbrella review

(n = 13)

Individual studies included in the umbrella review

(n = 57)

## Included

**Figure S4. PRISMA Flowchart of the literature search for panic disorder**

Records identified through database searching
(n = 2746)

Records screened on the basis of title and abstract
(n = 2490)

Records excluded (n = 2378)

Systematic reviews/meta-analyses included in the umbrella review

(n = 11)

Additional records identified through other sources
(n = 2)

## Identification

Records after duplicates removed (n = 2490)

## Screening

101 full-text systematic reviews/meta-analyses excluded:

- no systematic review or meta-analysis (n = 17)

- insufficient/inadequate data for analysis (n = 13)

- overlapping systematic reviews or meta-analyses

(n = 14)

- no healthy control group (n = 1)

- no panic disorder as outcome (n = 15)

- factor does not precede disorder (n = 32)

- none of individual studies eligible (n = 7)

- purely genetic (n=2)

Full-text systematic review/ meta-analyses assessed for eligibility
(n =112 )

## Eligibility

Individual studies included in the umbrella review

(n = 60)

## Included

**Figure S5. PRISMA Flowchart of the literature search for obsessive-compulsive disorder**

Additional records identified through other sources
(n = 3 )

Records identified through database searching
(n = 3948)

## Identification

Records after duplicates removed (n = 3946)

Records screened on the basis of title and abstract
(n = 3946)

## Screening

Records excluded (n = 3797)

143 systematic review/meta-analyses excluded:

-no systematic review or meta-analysis (n = 45)

- insufficient or inadequate data for analysis (n = 12)

-overlapping systematic review or meta-analysis

(n = 2)

- no healthy control group (n = 2)

- no obsessive-compulsive disorder as outcome

(n = 23)

- factor does not precede disorder (n = 54)

- none of individual studies eligible (n = 1)

- purely genetic (n=4)

Full-text systematic review/ meta-analyses assessed for eligibility
(n =149)

## Eligibility

Individual studies included in the umbrella review

(n = 46)

Systematic reviews/meta-analyses included in the umbrella review

(n = 6)

## Included

**Figure S6. PRISMA Flowchart of the literature search for separation anxiety disorder**

Additional records identified through other sources
(n = 0 )

Records identified through database searching
(n =33)

## Identification

Records after duplicates removed (n =30)

Records screened on the basis of title and abstract
(n =30)

## Screening

Records excluded (n = 30)

Full-text systematic review/ meta-analyses assessed for eligibility
(n =0)

## Eligibility

**Figure S7. PRISMA Flowchart of the literature search for selective mutism**

Additional records identified through other sources
(n = 0 )

Records identified through database searching
(n =17)

## Identification

Records after duplicates removed (n =15)

Records screened on the basis of title and abstract
(n =15)

## Screening

Records excluded (n = 15)

Full-text systematic review/ meta-analyses assessed for eligibility
(n =0)

## Eligibility

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