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Review article

# Associations between mental and physical conditions in children and adolescents: An umbrella review

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ABSTRACT

We mapped the evidence on the type and strength of associations between a broad range of mental and physical conditions in children and adolescents, by carrying out an umbrella review, i.e., a quantitative synthesis of previous systematic reviews and meta-analyses. We also assessed to which extent the links between mental and physical conditions vary across disorders or, by contrast, are transdiagnostic. Based on a pre-established protocol, we retained 45 systematic reviews/meta-analyses, encompassing around 12.5 million of participants. In analyses limited to the most rigorous estimates, we found evidence for the following associations: ADHD-asthma, ADHD-obesity, and depression-asthma. A transdiagnostic association was confirmed between asthma and anxiety/ASD/depression/bipolar disorder, between obesity and ADHD/ASD/depression, and between dermatitis and ASD/ADHD. We conclude that obesity and allergic conditions are likely to be associated with mental disorders in children and adolescents. Our results can help clinicians explore potential links between mental and physical

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conditions in children/adolescent and provide a road map for future studies aimed at shading light on the underlying factors.

## 1. Introduction

Increasingly studies point to significant associations between mental and physical conditions, but evidence remains inconclusive (Qureshi and Mehler, 2013). This putative link is likely underpinned by multiple factors. Either, physical conditions may contribute to mental disorders (e.g., hypothyroidism underlying depression) (Hage and Azar, 2012). Alternatively, mental disorders may increase the risk of physical conditions (e.g., increased risk of sexually transmitted infections in bipolar disorder) (Chen et al., 2019). Then again, mental and physical disorders may share common risk factors, including early trauma, chronic stress, inflammation, and socioeconomic factors (e.g., low income and poor educational attainment) (Druss and Walker, 2011). With a global peak age at onset of any mental disorders of 14.5 years and 63% of mental disorders occurring prior to age 25 (Solmi et al., 2021b), and with associated physical health burden being frequently observed in children and adolescents, prevention and early intervention in young people has the potential to synergistically maximise the benefit for both mental and physical health (Fusar-Poli et al., 2021).

There has been a large number of individual studies (Patten et al., 2009) and systematic reviews/meta-analyses (Cortese et al., 2018) on the association between specific mental disorders and specific physical conditions. For some associations, e.g., attention-deficit/hyperactivity disorder (ADHD)-obesity, evidence from primary studies and even from meta-analyses is mixed (Cortese et al., 2018; Nigg et al., 2016).

Umbrella reviews aim to summarise data from systematic reviews and/or meta-analysis following a systematic evidence synthesis approach. Umbrella reviews may also entail the repetition of the statistical pooling of relevant effect sizes from available meta-analyses (Fusar-Poli and Radua, 2018). As such, the quality of an umbrella review depends on the coverage of the literature and quality of the previous systematic reviews/meta-analyses. A possible limitation of umbrella reviews is related to the risk of pooling multiple times the same data, although this issue can be minimised by checking the data from the primary studies included in the umbrella review. Finally, and similarly to what occurs in a typical meta-analysis, the results of an umbrella review should be considered in the light of the heterogeneity across populations or outcome assessments in the systematic reviews/meta-analyses retained for the umbrella review.

These potential limitations need to be weighed against the arguable advantages of umbrella reviews, namely the fact that they: 1) provide the most comprehensive quantitative overview on a specific topic or ranges of topics; 2- collate all the previous literature appraisals and individual studies and, hence, can comprehensively point to guideline-relevant, robust and consistent, high-quality evidence as well as relevant gaps, guiding future avenues of research on specific topics.

A quantitative synthesis of the literature across mental disorders and physical conditions, highlighting the strength of the evidence for each association, is currently lacking. Furthermore, whereas transdiagnostic research is gaining traction in psychiatry (Fusar-Poli, 2019; Fusar-Poli et al., 2019), it is unclear to which extent the links between mental and physical conditions vary across disorders or, by contrast, are transdiagnostic.

To fill these gaps, we conducted an umbrella review of systematic reviews (SRs) and/or meta-analyses (MAs) to assess the credibility of the associations between individual mental disorders and physical conditions, and ascertain if specific mental disorders are selectively associated with specific physical conditions or if there are transdiagnostic, across-spectra, or diagnostic spectrum-specific associations. We aimed to create the largest and most comprehensive quantitative atlas on the associations between mental and physical problems in order to summarise relevant areas of available evidence and to highlight missing meta-analytic data in the field of psychiatric morbidity. Given the magnitude of the work, its purpose is not to elucidate mechanisms, but to provide the best quantitative synthesis that will guide future work on mechanisms. Gaining in-depth quantitative insights into the associations between mental and physical conditions has important implications for the understanding of the pathophysiology of these conditions, the clinical management of patients with both mental and physical disorders, and for preventive efforts (Fazel et al., 2021; Qureshi and Mehler, 2013). Here, we focus specifically on the associations between mental and physical disorders in children/adolescents, although the current report is part of a larger research project that also aims to investigate similar associations in adults. These two sections (children/adolescents and adults) are not reported together for conciseness, and also because there are specificities in terms of type and risk of mental and physical conditions in children/adolescents as opposed to adults.

## 2. Methods

We followed the PRISMA 2020 and MOOSE recommendations (Liberati et al., 2009; Moher et al., 2015; Page et al., 2021; Stroup et al., 2000), and published the protocol (Cortese et al., 2020).

### 2.1. Data sources and searches

We searched PubMed, OVID, and Web of Knowledge databases (details in eTables 1–4) with no language/date/type of publication restrictions, up to January 1st, 2021. We also hand-searched references of relevant SRs/MAs.

The search syntax had the following structure: *("term for physical disorder"$_1$ OR "term for physical disorder"$_2$ … OR "term for physical disorder"$_n$) AND ("term for mental disorder"$_1$ OR "term for mental disorder"$_2$ … OR "term for mental disorder"$_n$) AND ("term for SR/MA"$_1$ OR "term for SR/MA"$_2$ … OR "term for SR/MA"$_n$) AND ("term for children/adelescent"$_1$ OR "term for children/adelescent"$_2$ … OR term for "children/adolescent"$_n$);* and its creation was supervised by an expert librarian from the University of Southampton. Details on the search are reported in eTables 1–4.

### 2.2. Types of studies to be included

We included SRs, with or without MAs, of observational studies (case-control, cohort, cross-sectional studies) reporting on the association between mental disorders and physical conditions. The list of mental disorders is reported in eTable 5. The list of physical disorders, based on Correll et al. (2015), and expanded with the advice of a paediatrician (MR-G), included a broad range of physical disorders (eTable 6). Eligibility criteria for SRs/MAs are provided in *eMethods* 1.

### 2.3. Conditions being studied

Eligible mental disorders were those defined based on standardised criteria, codes in electronic records, clinical diagnosis in medical files, self-reported diagnosis, or a score above a threshold on a validated scale/questionnaire. Hence, diagnostic procedures had to be categorical, dividing the samples among those with and without the disorder. Conversely, studies using continuous measures of symptomatology without a dichotomisation were excluded. While all these definitions of mental disorders were accepted, those clearly following DSM or ICD criteria were deemed to be more reliable. We considered that a gold-standard diagnosis had been carried out when articles specifically

indicated that a clinical diagnosis following the mentioned criteria had been performed, or when a classification in a medical file followed DSM or ICD codes. Any categorical definition of physical conditions was accepted.

### 2.4. Participants

At least one of the conditions (i.e., mental or physical) had to occur in childhood or adolescence (mean/median/mid-range $< 18$ years).

### 2.5. Outcome selection

Per protocol, the primary outcome included the unadjusted or adjusted odds ratio (OR) or other ESs (i.e., risk ratios and hazard ratios) of physical-mental disorder associations, provided in the article or calculated based on the raw data reported in the article. In longitudinal studies, we selected the outcome at the first follow-up. Whenever the same outcome was reported across multiple reviews, it was extracted from the largest MA/SR in order to avoid double-counting it.

### 2.6. Data screening and extraction

Two authors conducted screening and data extraction independently; conflicts were resolved by consensus, or with a third author. Individual studies' and pooled ESs were obtained from included MAs, or SRs. We first extracted data on the characteristics of the SR/MAs included in our umbrella review, and then, when needed (i.e., data not reported at the SR/MA level) relevant data from the primary studies.

We extracted the country/ies the primary study was conducted in and excluded any effect sizes with overlapping databases for the same association. Whenever two reports were based on the same database when calculating an association, we kept the largest study. Methodology and tools employed for the diagnosis of the mental disorder were also extracted. Importantly, we extracted data that allowed us to calculate the unadjusted odds ratio (our primary effect measure) even if it was not present at the SR or MA level. Likewise, we extracted the adjusted measure of association. Data were obtained from the largest SR/MA whenever possible, from other SR/MAs, or if they were not present in any of these, they were obtained from the primary papers. We also assessed, using the Newcastle-Ottawa scale (NOS) (Wells et al., 2000), the bias of any primary study that had not been appraised at the SR/MA level. Whenever the calculation of the unadjusted OR obtained from the data in the primary study did not match the one reported in the SR/MA, and/or it was unclear how the measures of association had been obtained, we retained the ones reported in the SR/MA as we deemed that they were derived following contact with the authors of the primary study. The same procedure was followed if a primary study was not accessible or was in any language other than English, Spanish, French, German or Italian (languages the authors are fluent in). Hence, authors of primary papers were not contacted, relying instead on the extractions carried out in the SRs/MAs.

We systematically checked whether each primary study fulfilled our inclusion criteria, and extracted data that allowed us to calculate the unadjusted ES even if it was not reported at the SR/MA level, as well as the maximally adjusted ES (i.e., statistically adjusted for the largest number of variables). We also assessed, using the Newcastle-Ottawa scale (NOS) (Wells et al., 2000), the risk of bias of any primary study that had not been appraised at the SR/MA level. Extracting information from primary articles is not a common procedure in umbrella reviews (Fusar-Poli and Radua, 2018), but we deemed that it provided additional information on the primary studies that could not be found at the SR/MA level.

The risk of bias of the included SRs/MAs was rated with the AMSTAR-2 (Shea et al., 2017).

### 2.7. Data synthesis

For each association, we conducted a random-effects meta-analysis (DerSimonian and Laird, 1986), with ESs obtained from the largest available MA and any relevant additional ES found in the primary studies included in the remaining SRs/MAs. Databases used, as reported in the primary studies, were taken into account in order to only include one outcome per database in each meta-analytic computation, and hence, minimising the risk of combining non-independent data. The combination of non-independent data may skew the results of a meta-analysis and overstate the confidence in the results. In this umbrella review, pooling the same data multiple times for the same analysis might have occurred for two main reasons: 1-Two different SR/MAs on the same association may have pooled different versions of the same study (e.g., a conference proceeding in one SR/MA and the full article in the other SR/MA), or two different studies using the same database; 2-A single SR/MA combined non-independent data within the same analysis. While the former would not affect the estimates provided in the different meta-analyses, it could affect our meta-analytic result. The latter case would affect both our results and the estimate of the original meta-analysis. In our study, we aimed to be stringent in this regard and err on the safe side. For every combination of mental and physical disorders, we only pooled the effect size that was derived from the study with the largest number of participants with mental disorder among those studies using the same cohort or database.

$I^2$ and Q were computed to estimate the presence of significant heterogeneity and the proportion of total variability due to between-study heterogeneity, respectively. Egger's test was used to estimate publication bias. Publication bias plus ES being larger than that of the largest study in each association indicated small study effects (Dragioti et al., 2019). The 95% prediction intervals for the ESs were computed to estimate the possible range in which the ESs of future studies were anticipated to fall (Riley et al., 2011). We finally measured excess significance bias by assessing whether the observed number of studies with nominally statistically significant results was different from the expected number of studies with statistically significant results. For excess significance bias, a p-value $\leq 0.10$ was considered statistically significant (Ioannidis and Trikalinos, 2007; Ioannidis, 2013). Analyses were carried out using STATA 17.0 (StataCorp. 2017. Stata Statistical Software: Release 17. College Station, TX) and R (version 4.0.3).

Since the distinction between adjusted and unadjusted is more blurred than it would appear, as studies presenting "unadjusted" ES typically match participants during recruitment based on a number of factors, in the primary analysis we included adjusted ESs when unadjusted ESs were not available after systematically checking the primary studies included in each retained SR/MA. The hierarchy of selection of outcomes for the primary analysis was as follows: 1-unadjusted OR, 2-adjusted OR, 3-Other types of unadjusted risk measures (i.e., hazard ratio or relative risk), 4-adjusted hazard ratios. No transformations were carried out when combining ORs, HR and RR into the same analysis, as frequencies of disorders for which HRs were reported was low or ESs were small. The underlying rationale was that the gains in the robustness of the estimates from including additional effect sizes outweighed the bias derived from combining multiple statistical metrics that are not equal but tend to converge when the mentioned factors occur. However, it must be noted that this combination was only carried out when it was impossible to obtain or calculate ORs from the data reported at the SR/MA or primary article level.

A secondary analysis, combining adjusted ORs derived from studies using gold-standard diagnoses, was considered as particularly rigorous. Sensitivity analyses focused on: 1) unadjusted ESs only; 2) maximally adjusted ESs only; 3) studies using formal (i.e., based on DSM or ICD) diagnoses only; 5) studies with a low risk of bias (consistent with previous studies (Brady et al., 2017; Rønnstad et al., 2018), we used a threshold of $< 66\%$ of the total score of the individual tool used to assess study quality to judge a study as at high risk of bias (see *eMethods 1* for

details); 6) overweight (age and sex-adjusted BMI ≥85th percentile) rather than obesity used in the primary analysis of studies reporting on association with increased weight. In an additional sensitivity analysis, we removed studies for which the OR had been calculated in the retained SRs/MAs through a conversion from continuous measures. We had also planned a-priori to carry out a sensitivity analysis on drug-naïve participants, however there were insufficient data to pursue this analysis. While performing the project, we came to the conclusion that it was not feasible to carry out a sensitivity analysis taking into account the temporality of the associations due to several reasons. 1-Most studies were either cross-sectional (and evaluated the presence of the two disorders at a given time point) or evaluated the presence of one or both disorders over long time periods (in many cases over the entire life), with both designs hindering the possibility of evaluating temporality. 2-Additionally, while some disorders are pervasive and/or have an unclear onset time (e.g., type I diabetes or ADHD), others have a clearer time demarcation (e.g. cancer or PTSD), and other disorders may run over long periods of time (high BMI, depression). Moreover, some disorders mostly occur in childhood, while others are typical of adulthood. Importantly, different combinations of these characteristics would require different designs to evaluate temporality. 3-This information was not available in most cases at the SR/MA level in a reliable form.

### 2.8. Classification of the level of evidence

Following our protocol, we stratified available evidence (Fusar-Poli and Radua, 2018; Tsilidis et al., 2015) as follows: Class I, convincing (number of cases >1000, $p < 10^{-6}$, I 2 <50%, 95% prediction interval excluding the null, no small-study effects, and no excess significance bias); class II, highly suggestive (number of cases >1000, $p < 10^{-6}$, largest study with a statistically significant effect, and class I criteria not met); class III, suggestive (number of cases >1000, $p < 10^{-3}$, and class I-II criteria not met); class IV, weak ($p < 0.05$ and class I-III criteria not met); and non-significant ($p > 0.05$).

**Table 1**
Definition and operationalization of TRANSD criteria.

| Criterion | Definition | Operationalization |
|---|---|---|
| T | Transparent definition of disorders | Analysis focuses on studies defining disorders according to gold-standard definitions only |
| R | Reporting of the primary outcome of the study, as well as the study design and the definition of the transdiagnostic construct in the abstract and main text (criterion R) | Criterion R was met through the inclusion criteria adopted by the current study |
| A | necessity of Appraising the conceptual transdiagnostic framework/approach as "across diagnoses and within spectrum" or "across diagnostic spectra" | Analysis focuses on relationships across all disorders and spectra |
| N | for Numerating the diagnostic categories, spectra and non-clinical samples in which the transdiagnostic construct is being tested and then validated | Diagnostic categories are included in supplementary material, eTable 7 |
| S | Necessity of Showing the degree of improvement or non-inferiority of the transdiagnostic approach against the specific diagnostic approach through specific comparative analyses | A transdiagnostic class of evidence of at least III, and not inferior to the lowest class of evidence for the corresponding disorder-specific associations is required |
| D | Demonstrate the generalisability of the transdiagnostic construct through external validation studies | Associations had to be confirmed in more than one study in eligible meta-analyses |

### 2.9. Transdiagnostic analysis

We used the TRANSD-iagnostic criteria (Table 1), to assess to which extent the associations between mental disorders and physical conditions were disorder-specific or transdiagnostic (Arango et al., 2021; Fusar-Poli, 2019; Fusar-Poli et al., 2019). Diagnostic spectra were defined according to the ICD-11 diagnostic blocks (eTable 7). For the TRANSD analyses, we used studies adopting only gold-standard (i.e., formal) diagnoses.

Additions/amendments to the pre-registered protocol are reported in eMethods 1, alongside additional methodological details.

## 3. Results

The screening of 26,711 records led to the final inclusion of 45 SRs/MAs (Fig. 1, eResults, eTables 8–10), which included close to of 12.5 million individuals (1.5 million with physical conditions and 500,000 with mental disorders, respectively). Out of 341 records the full-text of which was assessed for eligibility, 290 reports were excluded (eTable 9) as they did not: 1) evaluate risk (78 articles); 2) include primary studies in children/adolescents (59 articles); 3) include eligible mental or physical conditions (35 articles in both cases). Six additional records were obtained from the list of references of included articles and umbrella reviews. See eTables 11–14 for details on the included SR/MAs, and eMethods for the methodology to estimate sample counts in our study. Using the AMSTAR-2 tool (eTable 15 and eFig. 2), nine MAs were deemed of overall high or moderate quality, and 36 of low or critically low quality. Relevant summary ESs found in each MA for each association are presented in eTable 16. The retained SRs/MAs included a median of 15 studies (interquartile range: 11–27). Most SRs/MAs reported ORs, implemented a random effects model when pooling data, and carried out an appraisal evaluation of the risk of bias. Eighteen SRs/MAs conducted the search between 2017 and 2021. Twenty-four SRs/

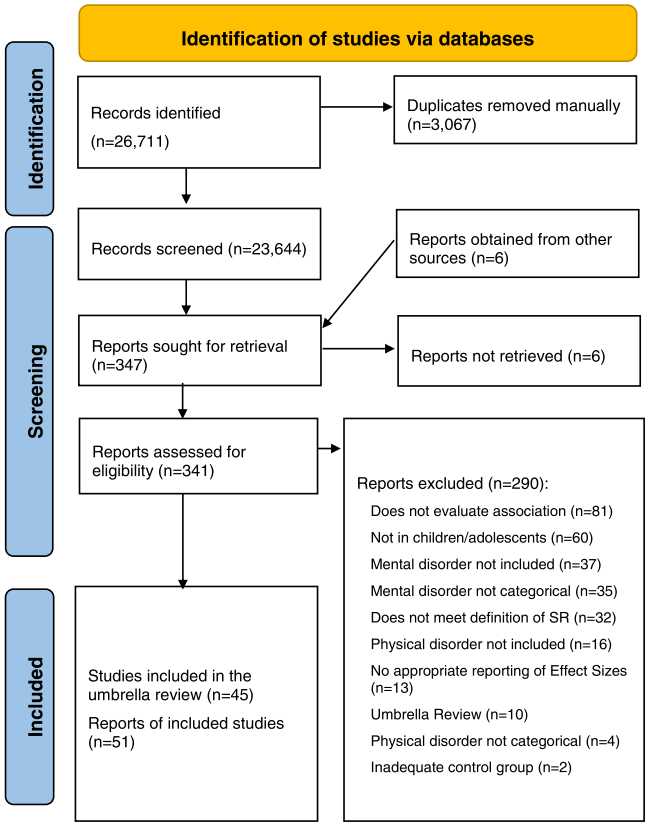


**Fig. 1.** Study selection flowchart.

MAs only included studies in which both disorders occurred in childhood and/or adolescence. In three SRs/MAs, only the physical disorder had to occur in individuals under the age of 18. The remaining SRs/MAs accepted any age of diagnosis or measurement of the association and varying definitions of the mental and physical disorders. An evaluation of the risk of bias was implemented in 37 SRs/MAs. The most frequently chosen tool was the NOS, which was used in 54% of those SRs/MAs performing a quality appraisal (in some cases with modifications). It must be noted that the total number of included participants that we present is this report is derived from summing samples included in the primary studies and inevitably an approximation. However, the total number does not count studies for which we were unable to extract the sample sizes. Conversely, if two studies used the same database for different mental-physical combinations of outcomes, the individuals would be included in this count more than once.

### 3.1. Outcomes

Criteria from a number of included SR/MAs differed from those in our umbrella review. For example, SR/MAs might have pooled together studies on children and on adults or have included conditions that were not relevant to the umbrella review. Overall, 363 outcomes reported in the primary studies and included in the retained SRs/MAs were excluded (eTables 17 and 18), as determined when evaluating the descriptive tables of the SRs/MAs or the primary studies themselves. The most frequent reasons for outcome exclusion were that they referred to adults (109 outcomes), were based on overlapping databases (75 outcomes), did not have a control group or it was inadequate (68 outcomes), or used an inadequate measure for diagnosis (50 outcomes). Six hundred twenty-one outcomes, deriving from 290 samples in 276 primary studies from all continents, were retained in the umbrella review (eTables 19–21). The larger number of outcomes in relation to that of samples derives from the fact that many studies evaluated the risk of multiple mental-physical associations in the same sample. Moreover, some primary studies reported on multiple samples.

Sixty-four percent of the primary studies were considered to be at a low risk of bias. Median and interquartile ranges for sample sizes were 752 (196−6836) for the total sample, 121 (46−591) for the number of individuals with a mental disorder, and 154 (42−683) for the number of individuals with a physical disorder. Almost all studies reported ORs. Only 5 HRs or RR were included in the main analyses. For the majority of these, the frequency of the events was low (under 10%) making the reported ES arguably equal to ORs (Cummings, 2009). In three cases were frequency could be expected to be higher, ES were under 2, and hence the expected OR would be only slightly higher.

### 3.2. Association between mental disorders and physical conditions

While searches were created to retrieve any SR/MA evaluating combinations between broad lists of physical and mental disorders, the included outcomes evaluated the association between ten mental disorders and 18 physical disorders (Table 2).

There were data in SR/MAs for 42 combinations of mental and physical disorders for the main analysis. The median number of outcomes included in the re-analyses (and interquartile range: IQR) was 6 (IQR=2.25–9.75). The median number of participants was 44,335 (IQR=8687–444,452), whereas the median number of cases with the physical disorder was 6805 (IQR=879–16,593). The pooled effect sizes ranged between 0.68 and 7.74, with 30 effects (71%) laying between an equivalent OR of 1 and 2. Pooled effects were significant in 31 analyses (74%). The percentage of heterogeneity due to true variation was important: eleven studies had either low (<25%) or moderate (25–50%), while twelve had substantial (50–75%) and 15 very substantial heterogeneity (>75%). The prediction interval (the estimate of the interval in which a future observation will fall in 95% of the occasions) was significant for six out of 31 effects (19%) with more than 2 outcomes, whereas five of them showed evidence of small study effects/publication bias (16%). Excess significance bias was found for three out of 38 effects (8%). In 18 (47%) effects, E was larger than O, indicating that an excess of significant findings was not pertinent and in eight effects (21%) there was no evidence of excess significance bias. This test could not be estimated for nine effects (24%). Regarding the class of evidence, two associations showed convincing evidence, ten highly suggestive evidence, six had convincing evidence and for thirteen there was weak evidence on their association.

There were data in SR/MAs for 22 combinations of mental and physical disorders for the analysis including adjusted effect sizes obtained with a gold-standard diagnosis. The median number of outcomes included in this set of analysis was 2 (IQR=1–4). The median number of participants was 31,132 (IQR=5142–247,672), whereas the median number of cases with the physical disorder was 3367 (IQR=992–15,405). The pooled effect sizes ranged between 0.22 and 3.04, with 16 effects laying between an equivalent OR of 1 and 2. Pooled effects were significant in 12 analyses, although 4 derived from single studies where no meta-analysis was carried out. Heterogeneity was lower than for the main analyses: eight studies had either low (<25%) or moderate (25–50%), while two had substantial (50–75%) and four very substantial heterogeneity (>75%). The prediction interval was significant for 2 out of 9 effects with more than 2 outcomes, whereas none of them showed evidence of small study effects/publication bias. There was no excess significance bias for the 14 effects (0%). In six (42%) effects, E was larger than O, indicating that an excess of significant findings was not pertinent and in four effects (29%) there was no evidence of excess significance bias. Also, this test could not be estimated for four effects (29%). Regarding the class of evidence, two associations showed convincing evidence, one highly suggestive evidence, one convincing evidence and for four there was weak evidence on their association.

Results of the primary (unadjusted-if-possible ES) and secondary analysis based on adjusted ES only with gold standard diagnoses can be found in Tables 2 and 3, respectively.

Sensitivity analyses are shown in eTables 22–28. We summarise here the results by groups of mental disorders.

*Neurodevelopmental/disruptive disorders* (21 SRs/MAs): In the primary analysis, there was convincing (class I) or highly suggestive (class II) evidence for an association of ASD with rhinitis (OR=1.66; CI-=1.49, 1.85), obesity (OR=1.90; CI=1.51, 2.39), and food allergy (OR=2.65; CI=1.97, 3.56), of ADHD with rhinitis (OR=1.58; CI=1.32, 1.90), obesity (OR=1.32; CI=1.18, 1.47; with evidence of excess significance bias), and dermatitis (OR=1.41; CI=1.31, 1.51; with evidence of small study effects/publication bias), and of disruptive behaviour with dermatitis (OR=1.54; CI=1.31, 1.80). ADHD-obesity was the association based on the largest evidence (43 primary studies; 1,390,311 individuals). In the sensitivity analysis focusing on adjusted ESs only, with gold standard diagnoses, there was convincing or highly suggestive evidence for an association of ADHD with asthma (OR=1.47; CI=1.38, 1.57) and obesity (OR=1.81; CI=1.40, 2.33). The other sensitivity analyses were, in general, quite consistent with the primary analysis.

*Mood disorders* (20 SRs/MAs): When considering unadjusted-if-possible ORs, there was convincing or highly suggestive evidence for an association between depressive disorders and cancer (OR=1.40; CI=1.21, 1.61), obesity (OR=1.53; CI=1.39, 1.70; with evidence of small study effects/publication bias) and rhinitis (OR=1.87; CI=1.47, 2.38), as well as between bipolar disorder and asthma (OR=1.87; CI=1.47, 2.38). Evidence for the largest association (obesity-depression) was based on 57 primary studies (159,767 participants). In the sensitivity analysis considering adjusted ES with gold-standard diagnoses, the association depression-asthma was rated as convincing (OR=1.63; CI=1.35, 1.97). All other associations were considered suggestive or weak. The other sensitivity analyses were in general in line with the primary analysis, except for the association depression-cancer that was downgraded to suggestive or weak. Importantly, out of 45 SR/MAs only

**Table 2**
Associations between psychiatric and physical outcomes by class of evidence (unadjusted-if-possible ES), listed by group of disorders and, within group, by class level.

| Author, year | Mental | Physical | k | n/N | eOR (95% CI) | p | PI sign | $I^2$ (%) | SSE | ESB | LS sign | Class | AMSTAR-2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Miyazaki, 2015 | ASD | Rhinitis | 5 | 2592/ 9685 | 1.66 (1.49, 1.85) | $5.6 \times 10^{-20}$ | Yes | 0.0 | No | No | Yes | I | Low |
| Xie, 2019 | Disruptive Behaviour | Dermatitis | 6 | 12,925/ 92,733 | 1.54 (1.31, 1.80) | $1.7 \times 10^{-7}$ | Yes | 28.6 | No | No | Yes | I | Low |
| Miyazaki, 2017, van der Schans, 2017 MA, van der Schans, 2017 SR, Schmitt, 2010, Xie, 2019 | ADHD | Dermatitis | 22 | 435,477/ 1,190,930 | 1.41 (1.31, 1.51) | $1.9 \times 10^{-21}$ | Yes | 65.8 | Yes | NP | Yes | II | Moderate, low, low, crit low, low |
| Cortese, 2016, Li and Xie, 2020, Nigg, 2016 | ADHD | Obesity | 43 | 74,476/ 1390,311 | 1.32 (1.18, 1.47) | $5.3 \times 10^{-7}$ | No | 83.6 | No | Yes | Yes | II | High, moderate, crit low |
| Miyazaki, 2017, van der Schans, 2017 MA, van der Schans, 2017 SR | ADHD | Rhinitis | 8 | 15,197/ 83,438 | 1.58 (1.32, 1.90) | $7.3 \times 10^{-7}$ | No | 79.2 | No | NP | Yes | II | Moderate, low, low |
| Li, 2020, Miyazaki, 2015, Wang, 2020 | ASD | Food allergy | 16 | 16,593/ 419,752 | 2.64 (1.97, 3.55) | $1.2 \times 10^{-10}$ | No | 84.3 | No | NP | Yes | II | Low, low, crit low |
| Kahathuduwa, 2019, Li and Xie, 2020, Zheng, 2017 | ASD | Obesity | 21 | 32,525/ 420,382 | 1.90 (1.51, 2.39) | $3.7 \times 10^{-8}$ | No | 93.7 | No | No | Yes | II | Moderate, moderate, crit low |
| Salem, 2018 | ADHD | Headache | 8 | 4480/ 19,419 | 1.58 (1.23, 2.03) | $3.6 \times 10^{-4}$ | No | 67.7 | No | No | Yes | III | Moderate |
| Miyazaki, 2015, Xie, 2019 | ASD | Dermatitis | 8 | 418,161/ 900,854 | 1.85 (1.35, 2.55) | $1.4 \times 10^{-4}$ | No | 92.2 | No | NP | Yes | III | Low, low |
| McElhanon, 2014 | ASD | Diarrhoea | 12 | 554/ 37,303 | 3.67 (1.83, 7.35) | $2.4 \times 10^{-4}$ | No | 86.8 | No | NA | Yes | IV | Crit low |
| Cortese, 2018, Kaas, 2020, Miyazaki, 2017, van der Schans, 2017 MA | ADHD | Asthma | 29 | 572,114/ 482,2797 | 1.55 (1.17, 2.06) | 0.002 | No | 99.7 | No | NP | Yes | IV | High, low, crit low, low |
| Miyazaki, 2017 | ADHD | Conjunctivitis | 3 | 9564/ 41,908 | 1.69 (1.04, 2.75) | 0.035 | No | 92.5 | No | NP | Yes | IV | Crit low |
| McElhanon, 2014 | ASD | Abdominal Pain | 8 | 196/ 608 | 2.45 (1.18, 5.07) | 0.016 | No | 69.7 | No | NA | No | IV | Crit low |
| Kaas, 2020, Miyazaki, 2015, Zheng, 2016 | ASD | Asthma | 18 | 34,292/ 202,656 | 1.36 (1.13,1.65) | 0.002 | No | 88.0 | Yes | Yes | No | IV | Low, low, low |
| McElhanon, 2014 | ASD | Constipation | 9 | 161/ 608 | 3.87 (2.23, 6.71) | $1.5 \times 10^{-6}$ | No | 63.8 | No | NA | Yes | IV | Crit low |
| McElhanon, 2014 | ASD | General gastrointestinal problems | 9 | 353/ 1008 | 4.50 (1.76, 11.55) | 0.002 | No | 93.4 | No | NA | No | IV | Crit low |
| Nujic, 2020 | Disruptive behaviour | Obesity | 2 | 6926/ 43,442 | 1.71 (1.01, 2.90) | 0.047 | NA | 69.8 | NA | NA | Yes | IV | Moderate |
| Christie, 2017 | Intellectual disability | Bacterial meningitis | 5 | 526/ 1139 | 7.74 (2.85, 21.02) | $5.8 \times 10^{-5}$ | Yes | 0.0 | No | NP | Yes | IV | Low |
| Miyazaki, 2017 | ADHD | Food allergy | 3 | 506/ 8613 | 1.15 (0.89, 1.48) | 0.279 | No | 0.00 | No | NP | No | NS | Moderate |
| Maiano, 2016 | Intellectual disability | Obesity | 2 | 2775/ 21,256 | 1.25 (0.71, 2.21) | 0.437 | NA | 34.4 | NA | NP | No | NS | Low |
| Wu, 2016 | BD | Asthma | 2 | 49,568/ 129,741 | 2.17 (1.85, 2.54) | $7.3 \times 10^{-22}$ | NA | 0.0 | NA | NA | Yes | II | Crit low |
| Secinti, 2017 | Depression | Cancer | 14 | 10,289/ 13,503 | 1.40 (1.21,1.61) | $6.9 \times 10^{-6}$ | Yes | 16.3 | No | NP | Yes | II | Low |
| Luppino, 2010, Mannan, 2016, Moradi, 2020, Quek, 2017, Rao, 2019, Rao, 2020, Sutaria, 2019, Villagrasa Blasco, 2020 | Depression | Obesity | 57 | 23,547/ 159,767 | 1.53 (1.39, 1.70) | $1.3 \times 10^{-16}$ | No | 57.7 | Yes | NP | Yes | II | Low, moderate, low, low, crit low, crit low, low, crit low |
| Lu, 2018 | Depression | Rhinitis | 2 | 1876/ 8911 | 1.87 (1.47, 2.38) | $3.0 \times 10^{-7}$ | NA | 0.0 | NA | No | Yes | II | Crit low |
| Brady, 2017, Lu, 2012, Lu, 2018, Secinti, 2017 | Depression | Asthma | 15 | 6805/ 45,228 | 2.09 (1.63, 2.67) | $5.1 \times 10^{-9}$ | No | 84.0 | No | Yes | No | III | Crit low, crit low, crit low, low |
| Ronnstad, 2018, Xie, 2019 | Depression | Dermatitis | 8 | 47,320/ 452,475 | 1.34 (1.17, 1.53) | $9.2 \times 10^{-6}$ | No | 73.8 | No | NA | Yes | III | Crit low, low |
| Secinti, 2017 | Depression | Congenital heart disease | 2 | 388/ 577 | 1.63 (0.39, 6.78) | 0.498 | NA | 76.5 | NA | NP | Yes | NS | Low |
| Brady, 2017, Secinti, 2017 | Depression | Diabetes | 7 | 2645/ 482,591 | 1.54 (0.99, 2.41) | 0.057 | No | 78.8 | No | NP | Yes | NS | Crit low, low |
| Brady, 2017 | BD | Diabetes | 1 | | | – | – | – | – | – | – | SS | Crit low |

(*continued on next page*)

**Table 2** (*continued*)

| Author, year | Mental | Physical | k | n/N | eOR (95% CI) | p | PI sign | $I^2$ (%) | SSE | ESB | LS sign | Class | AMSTAR-2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1989/ 471,685 | 1.67 (0.53, 5.2) | | | | | | | | |
| Secinti, 2017 | Depression | Epilepsy | 1 | 334/ 457 | 0.68 (0.23, 1.99) | – | – | – | – | – | – | SS | Low |
| Secinti, 2017 | Depression | Rheumatoid arthritis | 1 | 334/ 457 | 1.61 (0.57, 4.56) | – | – | – | – | | – | SS | Low |
| Lu, 2012, Secinti, 2017 | Anxiety | Asthma | 6 | 3231/ 12,991 | 1.66 (1.36, 2.03) | $6.3 \times 10^{-7}$ | No | 65.0 | No | NP | Yes | II | Crit low, low |
| Brady, 2017, Secinti, 2017 | Anxiety | Diabetes | 4 | 2101/ 481,709 | 1.70 (1.37, 2.12) | $1.6 \times 10^{-6}$ | Yes | 3.9 | No | NP | Yes | III | Crit low, low |
| Secinti, 2017 | Anxiety | Cancer | 10 | 8574/ 10,310 | 1.62 (1.24, 2.13) | $4.7 \times 10^{-4}$ | No | 58.1 | Yes | NP | Yes | III | Low |
| Secinti, 2017 | Anxiety | Congenital heart disease | 2 | 879/ 919 | 2.58 (1.45, 4.60) | 0.001 | NA | 0.0 | NA | NA | Yes | IV | Low |
| Xie, 2019 | Anxiety | Dermatitis | 7 | 10,797/ 80,894 | 1.34 (1.07, 1.68) | 0.011 | No | 26.1 | No | NP | Yes | IV | Low |
| Moradi, 2020 | Anxiety | Obesity | 6 | 8438/ 57,692 | 1.06 (0.83, 1.35) | 0.627 | No | 61.0 | No | No | Yes | NS | Low |
| Secinti, 2017 | Anxiety | Epilepsy | 1 | 257/ 391 | 0.7 (0.3, 1.4) | – | – | – | – | – | – | SS | Low |
| Jiang, 2020 | Psychosis | Infection | 3 | 256,106/ 2,281,723 | 1.45 (1.17, 1.79) | 0.001 | No | 89.8 | No | No | Yes | IV | Crit low |
| Xie, 2019 | Sleep disorders | Dermatitis | 6 | 702/ 1711 | 2.90 (1.59, 5.29) | 0.001 | No | 84.7 | No | NA | Yes | IV | Low |
| Jiang, 2020 | Psychosis | Infection (CNS) | 5 | 9164/ 688,277 | 1.68 (0.94, 2.98) | 0.077 | No | 71.6 | Yes | No | No | NS | Crit low |
| Brady, 2017, Galling, 2016 | Schizophrenia | Diabetes | 2 | 2489/ 483,605 | 1.99 (0.36, 11.02) | 0.431 | NA | 69.1 | NA | NP | No | NS | Crit low, moderate |

Abbreviations: Class – class of evidence, CI – confidence interval, eOR – equivalent odds ratio, ESB – excess significance bias, I2 – heterogeneity, k – number of effects per association, LS – largest study with significant effect, n – number of cases per association (those with the physical disorder), N – total number of individuals in cohort per association, NP=not pertinent, because the estimated E (Expected) is larger than the O (Observed), and there is no evidence of excess statistical significance based on the assumption made for the plausible effect size, OR – odds ratio, PI – prediction interval, SSE – small study effects, sign. – significant, SS – single study in which case cells with statistical values calculated from meta-analysis are left empty.

two (Cortese et al., 2016; Nigg et al., 2016) took into account medication in their final analyses, while a third one had planned to use it but was unable to carry out the analyses due to lack of reliable data in the primary papers (Cortese et al., 2018). Indeed, this shows that information in this regard is typically hard to extract even from primary articles. Hence, it was decided not to pursue this analysis due to insufficient data.

*Anxiety disorders* (10 SRs/MAs): There was highly suggestive evidence for an association of anxiety disorders with asthma (OR=1.66; CI=1.36, 2.03; with 6 studies and 12,991 individuals), which was generally confirmed in most sensitivity analyses, but was downgraded to weak in the sensitivity analysis focused on adjusted ES with gold standard diagnoses.

*Other disorders* (4 SRs/MAs): All associations regarding other mental disorders (psychosis/schizophrenia and sleep disorders) were weak or non-significant.

### 3.3. Transdiagnostic analysis

We were able to test if there was a transdiagnostic association for four physical disorders (obesity, asthma, dermatitis and rhinitis), as for these there was evidence of association with more than one mental disorder when only gold-standard diagnoses were considered. There was evidence for a transdiagnostic association for all of them except for rhinitis (Table 4). Considering adjusted ESs only and limiting results to class I and II, we found evidence for a transdiagnostic association only for asthma (Table 4).

## 4. Discussion

We report the most comprehensive transdiagnostic quantitative evidence synthesis on the associations between mental-physical disorder pairs in children/adolescents, grading the credibility of the evidence. Previous MAs provided inconclusive evidence and have generally been restricted to specific pairs of mental-physical conditions (e.g., ASD and food allergy (Wang et al., 2021)), small sets of disorders (e.g., depression and anxiety with obesity (Wang et al., 2019)) or just one mental or physical condition (e.g., mental disorders and dermatitis (Xie et al., 2019)) in children and adolescents. By contrast, our umbrella review included a broad set of mental and physical conditions, using the same criteria to rate the strength of the evidence for each association.

When considering unadjusted ES (when possible; otherwise, adjusted ES) and any method to diagnose mental disorders, we found convincing evidence for the association of ASD with rhinitis, disruptive behaviour disorder with dermatitis, and highly suggestive evidence for ADHD with rhinitis, dermatitis, and obesity, ASD with food allergy and obesity, anxiety with asthma, bipolar disorder with asthma, and depression with cancer, obesity, and rhinitis. We found evidence of transdiagnostic associations for asthma, dermatitis and obesity.

The results of our primary analysis in children and adolescent extend previous research, including a large-scale analysis based on ~5.9 million adults in Denmark showing that the majority of mental disorders were associated with an increased risk of a subsequent physical condition, with significant association across 76 of 90 mental-physical disorder pairs (Momen et al., 2020). Our analyses complement and extend these results showing that a number of specific associations start being significant in childhood/adolescence. Our findings are also based on more comprehensive and diverse evidence from different study designs and provide a more international perspective. Unlike the Danish study, we did not find any instance in which the presence of a mental disorder decreased the risk of physical conditions. This difference may be accounted for either by developmental effects - protective role manifesting later across the lifespan or premature death in mentally ill individuals prior to the emergence of the medical condition - or by the fact that available SRs/MAs focused mainly on increased risk of physical conditions.

The temporality of the significant associations detected in our

**Table 3**
Sensitivity analysis including only adjusted ES from studies using gold-standard diagnoses, listed by group of disorders and, within group, by class level.

| Author, year | Mental | Physical | k | n/ N | eOR (95% CI) | p | PI sign | $I^2$ (%) | SSE | ESB | LS sign | Class | AMSTAR-2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cortese, 2018, Kaas, 2020 | ADHD | Asthma | 8 | 12,577/ 77,300 | 1.47 (1.38, 1.57) | $9.3 \times 10^{-33}$ | Yes | 12.8 | No | NP | Yes | I | High, low |
| Cortese, 2016, Li and Xie 2020 | ADHD | Obesity | 5 | 19,511/ 499,744 | 1.81 (1.40, 2.33) | $4.2 \times 10^{-7}$ | No | 25.4 | No | NP | Yes | II | High, critically low |
| Miyazaki, 2017, Schmitt, 2010, van der Schans, 2017 MA, Xie, 2019 | ADHD | Dermatitis | 7 | 392,925/ 802,099 | 1.30 (1.14, 1.47) | $4.3 \times 10^{-5}$ | No | 43.50 | No | No | Yes | III | Moderate, critically low, low, low |
| Li and Liu, 2020, Wang, 2021 | ASD | Food allergy | 3 | 3718/ 83,961 | 1.60 (1.19, 2.15) | 0.001 | No | 34.2 | No | No | Yes | IV | Low, low |
| Zheng, 2017 | ASD | Obesity | 2 | 16,348/ 299,244 | 3.04 (1.14, 8.10) | 0.026 | NA | 99.2 | NA | NA | Yes | IV | Critically low |
| Miyazaki, 2017 | ADHD | Conjunctivitis | 2 | 1065/ 4193 | 1.41 (0.50, 3.99) | 0.520 | NA | 63.8 | NA | NP | No | NS | Moderate |
| Miyazaki, 2017 | ADHD | Food allergy | 3 | 506/ 8613 | 0.99 (0.75, 1.31) | 0.943 | No | 0.0 | No | NP | No | NS | Moderate |
| Miyazaki, 2017, van der Schans, 2017 MA | ADHD | Rhinitis | 5 | 12,234/ 45,391 | 1.30 (0.98, 1.72) | 0.073 | No | 88.8 | No | No | Yes | NS | Moderate, low |
| Kaas, 2020 | ASD | Asthma | 4 | 12,487/ 53,039 | 1.10 (0.74, 1.64) | 0.632 | No | 94.9 | No | NP | No | NS | Low |
| Miyazaki, 2017 | ADHD | Drug allergy | 1 | 84/ 4113 | 1.15 (0.62, 2.11) | – | – | – | – | – | – | SS | Moderate |
| Salem, 2018 | ADHD | Headache | 1 | 139/ 1308 | 2.43 (0.86, 6.85) | – | – | – | – | – | – | SS | Moderate |
| Miyazaki, 2017 | ADHD | Urticaria | 1 | 6/ 80 | 0.22 (0.03, 2.10) | – | – | – | – | – | – | SS | Moderate |
| Xie, 2019 | ASD | Dermatitis | 1 | 387,262/ 774,524 | 1.36 (1.26, 1.46) | – | – | – | – | – | – | SS | Low |
| Miyazaki, 2015 | ASD | Rhinitis | 1 | 2336/ 7990 | 1.70 (1.51, 1.91) | – | – | – | – | – | – | SS | Low |
| Brady, 2017, Lu, 2012 | Depression | Asthma | 4 | 3016/ 16,874 | 1.63 (1.35, 1.97) | $5.1 \times 10^{-7}$ | Yes | 0.0 | No | NP | Yes | I | Critically low, critically low |
| Mannan, 2016, Moradi, 2020, Rao, 2020, Sutaria, 2019 | Depression | Obesity | 9 | 1354/ 9393 | 1.46 (1.06, 2.02) | 0.020 | No | 41.2 | No | NA | Yes | IV | Moderate, low, critically low, low |
| Wu, 2016 | BD | Asthma | 1 | 46,443/ 92,955 | 1.82 (1.25, 2.65) | – | – | – | – | – | – | SS | Critically low |
| Lu, 2018 | Depression | Rhinitis | 1 | 1673/ 8365 | 1.59 (1.02, 2.50) | – | – | – | – | – | – | SS | Critically low |
| Miyazaki, 2017 | Anxiety | Asthma | 2 | 968/ 2609 | 1.61 (1.18, 2.20) | 0.003 | NA | 0.0 | NA | No | Yes | IV | Moderate |
| Secinti, 2017 | Anxiety | Epilepsy | 1 | 257/ 391 | 0.70 (0.00, 1.40) | – | – | – | – | – | – | SS | Low |
| Jiang, 2020 | Psychosis | Infection | 2 | 248,592/ 2,230,259 | 1.37 (0.85, 2.21) | 0.200 | NA | 87.5 | NA | NA | Yes | NS | Critically low |
| Jiang, 2020 | Psychosis | Infection (CNS) | 2 | 4738/ 662,016 | 2.09 (0.34, 12.83) | 0.425 | NA | 70.9 | NA | NA | No | NS | Critically low |

Abbreviations: Class – class of evidence, CI – confidence interval, eOR – equivalent odds ratio, ESB – excess significance bias, I2 – heterogeneity, k – number of effects per association, LS – largest study with significant effect, n – number of cases per association (those with the physical disorder), N – total number of individuals in cohort per association, NP=not pertinent, because the estimated E (Expected) is larger than the O (Observed), and there is no evidence of excess statistical significance based on the assumption made for the plausible effect size, OR – odds ratio, PI – prediction interval, SSE – small study effects, sign. – significant, SS single study, NA – not available.

**Table 4**
Evidence for transdiagnostic associations.

| | TR | AN | S | D | TRANSD |
|---|---|---|---|---|---|
| Unadjusted effect sizes if possible | | | | | |
| Physical disorder | Mental disorders (ICD-11 code), Class | Number of mental disorders (spectra) | Pooled class; equivalent Odds Ratio (95% CI); number of individual studies, cases | Number of individual studies reporting significant associations, ≥ 2 within each mental disorder | Criteria met or not |
| Asthma | Anxiety (6B0), III<br>ASD (6A02), IV<br>B (6A6) II<br>Depression (6A7), III | 4 (3) | II; 1.64 (1.35; 1.99); 25; 409,402 | 16, yes | Yes |
| Obesity | ADHD (6A05), III<br>ASD (6A02), IV<br>Depression (6A7), I | 4 (2) | II; 1.54 (1.35; 1.75); 61; 333,274 | 25, yes | Yes |
| Dermatitis | ADHD (6A05), II<br>ASD (6A02), IV | 2 (1) | II; 1.44 (1.31; 1.58); 16; 407,121 | 9, yes | Yes |
| Rhinitis | ADHD (6A05), IV<br>ASD (6A02), II | 2 (1) | II; 1.52 (1.30; 1.77); 8; 1405 | 4, no | No |
| Adjusted effect sizes | | | | | |
| Physical disorder | Mental disorders (ICD-11 code), Class | Number of mental disorders (spectra) | Pooled class; equivalent Odds Ratio (95% CI); number of individual studies, cases | Number of individual studies reporting significant associations, ≥ 2 within each mental disorder | Criteria met or not |
| Asthma | ADHD (6A02), I<br>Anxiety (6B0), IV<br>Depression (6A7), I | 3 (3) | I; 1.50 (1.43; 1.57); 14; 16,561 | 8, no | Yes* |
| Obesity | ADHD (6A05), II<br>ASD (6A02), IV<br>Depression (6A7), IV | 3 (2) | III; 1.76 (1.35; 2.29); 16; 808,381 | 8, yes | Yes |

umbrella review is complex. In our protocol we planned subgroup analyses including cross-sectional and prospective studies only, respectively. However, when carefully analyzing each of the retained SRs/MAs, we could not disentangle temporality or causality. Thus, the significant associations that we detected may be explained by several, non-mutually exclusive factors.

First, it is possible that that the links between physical and mental disorders are underpinned by shared genetic factors. For instance, for depression, in a recent population-based cohort study comprising 16,687 singletons, a higher liability to major depression was associated with increased asthma risk (Liu et al., 2020). As for ADHD, a large genome-wide association meta-analysis (20,183 individuals diagnosed with ADHD and 35,191 controls) found a small albeit significant genetic correlation between asthma and ADHD (Demontis et al., 2019). However, we are not aware of any genome-wide study assessing genetic associations of physical conditions across several mental disorders. Our results point to the need of conducting such studies. Second, mental and physical disorders might share non-purely genetic factors, i.e., factors related to the environment that may eventually include indirect genetic effects. In this regard, a meta-umbrella review summarising 1180 associations between putative risk or protective factors and mental disorders found convincing or highly suggestive evidence for a number of non-purely genetic factors and a broad set of mental conditions (Arango et al., 2021). Of note, the most robust non-purely genetic risk factors identified for childhood conditions (e.g., maternal pre-pregnancy obesity, maternal smoking during pregnancy, maternal overweight pre/during pregnancy for ADHD, and maternal overweight pre/during pregnancy for ASD) may increase the risk also for physical dysfunctions in the child/adolescent. Common genetic and non-purely genetic factors, as well as their interplay and epigenetic factor, may lead to shared pathophysiologic pathways for mental and physical conditions. These pathways may include immunological dysfunctions. Indeed, pro-inflammatory changes have been reported in children/adolescents with mental disorders, like depression (D'Acunto et al., 2019), anxiety (Khandaker et al., 2016), and ADHD (Chang et al., 2021). Such inflammatory alterations may contribute to behavioural/emotional symptoms. For instance, hyper-secretion of pro-inflammatory cytokines from allergic reactions passing through the blood-brain barrier may affect the prefrontal cortex, contributing to the clinical symptomatology of ADHD (Strom et al., 2016). Fourth, it is also possible that mental disorders increase the risk of psychological stress, which in turn would contribute to immunological dysfunctions (Ohno, 2017). Fifth, the pharmacological treatment of physical disorders may contribute to psychiatric symptoms (e.g., corticosteroid contributing to disruptive behaviours) (Warrington and Bostwick, 2006). Sixth, the pharmacological treatment of mental disorders may contribute to physical conditions (e.g., antipsychotics, mood stabilisers or certain antidepressants contributing to overweight/obesity, dyslipidemia and diabetes) (Correll et al., 2015; Firth et al., 2019). Seventh, physical dysfunctions might increase the risk of mental disorders (e.g. cancer contributing to depression). Of note, we did not find convincing evidence of increased risk of medical conditions in children due to dysregulated behaviours related to mental conditions, such as sexual infections caused by inappropriate/risky behaviours related to mental conditions (e.g. ADHD), although primary individual studies support this link in older individuals (Chen et al., 2018).

Notably, when focusing on more rigorous adjusted ES, gold standard diagnoses of mental disorder, we found convincing/highly suggestive evidence for less associations, also due to fewer such data, yet still involving conditions characterised by immunologic dysfunctions (asthma-ADHD and asthma-depression and highly suggestive evidence for ADHD-obesity).

Our results might have important clinical and public health implications in terms of screening programs. This is particularly relevant in light of the well documented disparity in the screening and management of physical conditions in individuals with vs. those without mental disorders (Solmi et al., 2021a, 2020). However, we urge caution in interpreting our results as evidence supporting the need for a systematic, universal screening of physical conditions in children with mental disorders, as this would require evidence of cause-effect relationships as well as pragmatic randomised controlled trials of universal screening showing effectiveness in the real world.

Our results should be considered in the light of several limitations. We relied on evidence provided in available SR/MAs to find significant associations. Robust evidence on other associations may be offered by primary studies that have not been included in meta-analyses yet, and key information might not be reported at the SR/MA level. Relatedly, the quality of the included SR/MAs was deemed high for two meta-

analyses only (Cortese et al., 2018, 2016). However, we note that this assessment is based on judgments that, inevitably, have a subjective component, and are also influenced by the reporting of the SR/MA, rather than exclusively by its quality.

While it could be argued that redoing a systematic search and data extraction of primary articles would be ideal, such a task at the scale of our work was clearly not be feasible. Nevertheless, it must be highlighted that our work used a mixed approach, as we relied heavily on primary articles obtained from the SRs/MAs. SRs/MAs helped to identify a list of potential articles, but then key data were checked or completed with the primary article whenever possible. A major advantage of our methodology is related to a relevant risk in umbrella reviews, namely the danger of double-counting participants or studies and, therefore, overstating the confidence in the pooled effect sizes. We took great care in minimising this risk by checking the database used in each included primary article and eliminating any effect sizes that could violate such a requirement for independence.

As previously mentioned, we were unable to disentangle the direction of the association between physical and mental conditions. Similarly, we were not able to study in depth other factors that could be influencing the results of the different pooled effects, such as the effect of combining epidemiological or clinical disorders, the fact that patients may also present with more than one co-occurring physical and mental condition, and the effect of medications (both for mental and physical disorders) in contributing to the associations. All these effects were not analyzed both due to limitations in the retained SRs/MAs and primary studies and the broadness and scope of our project. However, the results of our work now provide a roadmap to move forward in the field of evidence synthesis in developmental psychiatry, forming a strong base from which to develop and update future meta-analyses. Indeed, we explicitly planned the present work as the first step of a larger project aiming to complete, update or improve the meta-analytic evidence on relationships between mental and physical disorders. These future studies can be carried out in a much focused and in-depth way while standing on the shoulders of our present results.

In conclusion, there is converging evidence that physical conditions involving (auto)immunological and/or inflammatory processes may be related to mental disorders. Since at least half of mental disorders emerge in childhood and adolescence (Solmi et al., 2021b), these results should guide future research in the field, aimed at gaining insight into the temporal and causal links between mental and physical conditions as well as specific factors linking the two in order to devise effective preventive and intervention strategies.

## CRediT authorship contribution statement

CC and SC conceptualized the study; GA, MS, AFC, AC, PF-P, HL, CC and SC designed the protocol; GA, LE, MR-G, AMC-L, SM, SW and SC carried out the Screening, data extraction and risk of bias evaluation; GA, MS, ED and SC performed and interpreted the statistical analyses; GA and SC drafted the initial version of the article and coordinated and supervised the overall project; all authors critically revised the manuscript and approved its final version. GA and SC had full access to all the data in the study and accept responsibility to submit for publication.

## Declaration of interests

Authors in the current umbrella review have also authored SR/MAs included. SC declares reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, Canadian AADHD Alliance Resource (CADDRA), British Association of Psychopharmacology (BAP) and from Healthcare Convention for educational activity on ADHD. MS has received honoraria/has been a consultant for Angelini, Lundbeck. CC has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Cardio Diagnostics, Compass, Damitsa, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Relmada, Rovi, Seqirus, Servier, SK Life Science, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva, and Viatris. He has provided expert testimony for Bristol- Myers Squibb, Janssen and Otsuka. He served on a Data Safety-Monitoring Board for Lundbeck, Relmada, ROVI and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a stock option holder of Cardio Diagnostics, Holmusk and LB Pharma. AC has received research grants, educational and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation and Angelini Pharma, outside the submitted work. HL reports receiving grants from Shire Pharmaceuticals; personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB; and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire/Takeda Pharmaceuticals and Evolan Pharma AB, all outside the submitted work. All other authors declare no competing interests.

## Data Availability

Please contact the corresponding author if you would like to request any data that are not included in the Article or the Appendix.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104662.

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