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Prevalence of co-occurring conditions in children and adults with autism spectrum disorder: A systematic review and meta-analysis

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ABSTRACT

This systematic review estimates the prevalence of co-occurring conditions (CCs) in children and adults with autism. A comprehensive search strategy consulting existing guidelines, diagnostic manuals, experts, carers, and autistic people was developed. PubMed and PsycInfo databases from inception to May 2022 were searched. PROSPERO registration: CRD42019132347. Two blind authors screened and extracted the data. Prevalence estimates for different CCs were summarized by using random effects models. Subgroup analyses were performed for age groups (children/adolescents *vs* adults) and study designs (population/registry-based *vs* clinical sample-based). Of 19,932 studies, 340 publications with about 590,000 participants were included and meta-analyzed to estimate the prevalence of 38-point prevalence, 27-lifetime, and 3 without distinction between point and lifetime prevalence. Point prevalence of developmental coordination disorder, sleep-wake problem, gastrointestinal problem, ADHD, anxiety disorder, overweight/obesity, feeding and eating disorder, elimination disorder, disruptive behavior, and somatic symptoms and related disorder were the most frequent CCs. Prevalence differed depending on the age group and study design. Knowing specific CCs linked to autism helps professional investigations and interventions for improved outcomes.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by early-onset deficits in social communication and interaction as well as the presence of repetitive or stereotypical behaviors (Autism Spectrum Disorder) (APA, 2013), with a current global prevalence of around 1% (Zeidan et al., 2022). Psychiatric, medical, and neurological co-occurring conditions (CCs) result in a wide range of diagnoses, with assessment and treatment care a complex and costly process. Knowledge of the prevalence of CCs among the autistic population is crucial to inform professionals which CCs to investigate most carefully during the assessment, improving their recognition and treatment and enhancing the care and quality of life of autistic individuals and their carers. To date is unavailable a valid estimate of the full spectrum of CCs in both children and adults with ASD.

Psychiatric CCs have been recently investigated in a systematic review and meta-analysis of 96 studies including mixed samples of children and adults with ASD (Lai et al., 2019). Findings ranked Attention-Deficit/Hyperactivity Disorder (ADHD) with the higher overall pooled estimates, followed by anxiety disorders, sleep-wake disorders, disruptive/impulse-control/conduct disorders, depressive disorders, obsessive-compulsive disorder, bipolar disorders, and

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schizophrenia spectrum disorders. Psychiatric CCs were also associated with greater impairment in adaptive functioning, quality of life, and amplification of autistic symptoms (Davignon et al., 2018; Gillberg et al., 2016; Gordon-Lipkin et al., 2018). Medical and neurological CCs, such as sleep problems, epilepsy, sensory impairments, atopy, autoimmune disorders, and obesity, have been reported to be more common in autism than in general population (Al-Beltagi, 2021; Muskens et al., 2017). CCs contribute to worsening quality of life from childhood into adulthood; knowing their prevalence in different age groups can facilitate adequate diagnostic assessment, the individuation of personalized and targeted intervention and the access to the needed services (Poon et al., 2017; Rydzewska et al., 2021). This systematic review and meta-analysis aim to estimate the point and lifetime prevalence for both mental health/psychiatric and medical/neurological conditions for ASD with a further comparison among children or adults and the registry or clinical-based samples and it was developed within the scope of the Italian Guidelines on diagnosis and management of individuals with ASD (Morgano et al., 2020).

2. Methods

The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see checklist in eTable 1 in Supplement 1). The present systematic review was registered in the PROSPERO International prospective register of systematic reviews (registration number: CRD42019132347; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=132347). The systematic review team included researchers with experience in ASD with different professional backgrounds (Psychologists, Neuro and Psychomotor Therapist, Child Neuropsychiatrist, Neurobiologist, Biologist, Statistician). Experts in the field of systematic reviews and meta-analyses supported the literature search development and data extraction form definition.

The funder of the study had no role in study design, data collection, data analysis, data interpretation, and writing of the report.

2.1. Literature search

The research team developed the search strategy to identify publications reporting the prevalence of CCs in individuals with ASD. To ensure a comprehensive search strategy, the set of keywords for CCs included the inputs from National Institute for Health and Care Excellence ASD guidelines, DSM-5, and expert working group, including autistic adults and carers of autistic children/adolescents. Further integration of terms was through stakeholders' suggestions (*i.e.*, presidents or chairs of Italian parental and professional associations and scientific societies) over a four-week period. The comprehensive search strategy allowed to identify published works on CCs in autism. eMethods 1 in Supplement 1 shows the key terms used to search databases. The search strategy aimed at finding publications reporting the prevalence (*point* – the proportion of a population that has the characteristic at a specific point in time; *lifetime* – the proportion of a population who, at some point in life has ever had the characteristic (National Institute of Mental Health, 2022) of any CCs. The search strategy was adapted for each database and included a combination of MeSH and terms to capture the available literature on the topic (for the search strategy of each database, see eMethods 1 in the Supplement 1). A comprehensive literature search of the PubMed and PsycINFO databases was carried out from inception to 15 May 2022. No date limit and no language restrictions were applied.

2.2. Eligibility criteria

Inclusion criteria were: (1) Population: individuals, regardless of age or sex, with a diagnosis of ASD and CCs assessed by any edition of the DSM or ICD or scores above a clinical threshold obtained using standardized instruments for the condition's assessment. For this study, conditions diagnosed through medical assessment or/and non-standardized interview (*i.e.*, feeding and eating disorder, sleep-wakes disorder, tic disorder, chromosomal disorder, genetic disorder, Down syndrome, elimination disorder, epilepsy, food intolerance, gastrointestinal (GI) disorder, hearing disorder, metabolic disorder, neurocutaneous disorder, organic nutrition disorder, overweight/obesity, Rett's syndrome, Fragile X syndrome) and sleep-wake, GI, and motor problems were treated as CCs and included. The diagnosis of intellectual disability (ID) could have been primary together with ASD. (2) Study design and context: observational studies (cohort, cross-sectional, case-control, or health surveys) assessing the current or lifetime proportion prevalence (number of individuals with ASD that have a CC divided by individuals with ASD at a given point in time or during their entire life) of CCs among individuals with ASD. Exclusion criteria were: (1) Population: (a) missing ASD or/and co-occurring diagnosis information; and (b) lack of information that could inform the inclusion of the study in one of the three age groups (children and adolescents<18 years old, adults, mixed: age range not included in the two previous groups). (2) Study design and context: (a) aggregated data that do not allow determining individual CC prevalence in autism samples; (b) studies not reporting prevalence rates or data to calculate the prevalence of CCs; and (c) studies whose purpose was not to measure prevalence; (d) case reports, comments, editorials, systematic reviews, and meta-analyses. Unpublished studies were not included to ensure that the works had undergone a peer-review process. The label "awaiting assessment" was attributed to the studies whose full text could not be retrieved after a reasonable time (six months) after contacting the authors.

2.3. Selection process

The reports retrieved from the search strategies were collected in the Systematic Review web app Rayyan QCRI (Ouzzani et al., 2016). After removing duplicates, the screening and selection process was divided into three stages. First, titles and abstracts of each record retrieved from the search strategy and from additional sources were screened for inclusion and exclusion criteria by two of the six blinded authors (MM, LG, AC, LMF, AntC, and FF). The authors attributed the label "maybe" to the records that need to be checked for their full text. In the second stage, the full texts of the records with the label "maybe" were explored by the authors. At each stage, at least two blinded authors excluded each study that clearly did not meet the inclusion criteria and included records that met the inclusion criteria. Conflicts were discussed between the two authors and if necessary, the full texts were addressed independently by a third author. In the third stage, references of systematic reviews and meta-analysis exploring the prevalence of CCs in autism were hand-searched to identify any relevant records missed in the search strategy. Articles in languages other than English were translated by a language certified reviewer (MM). A flow chart showing details of studies included and excluded at each stage of the study selection process is provided in Fig. 1.

2.4. Data collection process

Data were extracted in a standardized data extraction form, assessed, and integrated by experts in the field of systematic reviews and meta-analyses. The following studies' information was collected. *Study characteristics*: first author, year of publication, title, the country where the study was conducted (if missing, the affiliation country of the first author was reported), funding source (declared, none, not declared), conflict of interests (declared, none, not declared), study design: population/registry-based studies, *Pop Reg* – containing records for people diagnosed with a specific type of disease who reside within a defined geographic region or *via* random sampling in the population, in the form of census studies or health registries (Lai et al., 2019); clinical studies from community samples, *Clin Com* – evaluating individuals

Table 1
Pooled estimate of point and combined (point and lifetime) prevalence and subgroup analyses.

Pooled estimate of prevalence			Subgroup analysis: Age group			Subgroup analysis: Study design		
Co-occurring condition prevalence type	*Prevalence in autistic population*	*I^2% (Q Test p-value)*	*Child/ Adolescent*	*Adult*	*[a]Qb (1) (p-value)*	*Clin Com*	*Pop Reg*	*Qb (1) (p-value)*
Mental health and psychiatric								
ADHD N = 72 n = 208,789	37% (28–46%)	99.93 (<0.0001)	N = 44 n = 108,301 45% (32–58%)	N = 13 n = 35,612 22% (8–41%)	3.93 (0.05)	N = 49 n = 9658 43% (35–52%)	N = 23 n = 199,131 25% (13–39%)	4.89 (0.03)
Affective Disorder N = 22 n = 16,195	19% (11–28%)	99.37 (<0.0001)	N = 12 n = 8732 21%, (8–38%)	N = 6 n = 7090 16% (6–28%)	0.23 (0.63)	N = 15 n = 1768 12% (7–18%)	N = 7 n = 14,427 35% (18–54%)	6.26 (0.01)
Anxiety Disorder N = 60 n = 45,978	35% (30–39%)	98.54 (<0.0001)	N = 34 n = 15,896 42% (34–51%)	N = 12 n = 4291 28% (15–42%)	3.09 (0.08)	N = 48 n = 8766 38% (30–46%)	N = 12 n = 37,212 25% (19–32%)	6.53 (0.01)
Bipolar Disorder N = 25 n = 108,224	7% (4–9%)	98.85 (<0.0001)	N = 10 n = 83,720 7% (4–10%)	N = 6 n = 2243 9% (1–21%)	0.58 (0.45)	N = 19 n = 5881 9% (5–13%)	N = 6 n = 103,243 3% (1–6%)	8.27 (0.004)
Depressive Disorder N = 55 n = 41,923	18% (15–21%)	97.60 (<0.0001)	N = 25 n = 12,954 14% (9–19%)	N = 15 n = 2834 34% (26–43%)	18.09 (<0.0001)	N = 46 n = 8079 21% (17–26%)	N = 9 n = 33,844 8% (4–12%)	15.89 (<0.0001)
Developmental Coordination Disorder N = 2 n = 11,857	87% (87–88%)	0	N = 2 n = 11,857 87% (87–88%)	NA	NA	N = 2 n = 11,857 87% (87–88%)	NA	NA
Disruptive Behavior N = 24 n = 18,842	28% (21–36%)	98.94 (<0.0001)	N = 18 n = 13,339 28% (24–33%)	N = 3 n = 4778 18% (1–46%)	0.58 (0.45)	N = 18 n = 2233 31% (24–38%)	N = 6 n = 16,249 22% (10–37%)	1.06 (0.30)
Disruptive Impulse Control Disorder N = 42 n = 163,225	17% (13–22%)	99.73 (<0.0001)	N = 28 n = 106,189 20% (14–26%)	N = 5 n = 31,015 7% (1–17%)	3.50 (0.06)	N = 26 n = 6117 25% (13–38%)	N = 16, n = 157,108 9% (4–14%)	7.45 (0.01)
Feeding and Eating Disorder N = 32 n = 19,233 Anorexia nervosa, bulimia nervosa, binge eating disorder N = 14 n = 12,721	32% (20–46%) 5% (2–10%)	99.72 (<0.0001) 98.55 (<0.0001)	N = 25 n = 12,724 42% (30–54%) N = 8 n = 6333 7% (2–14%)	N = 4 n = 651 5% (0–16%) N = 4 n = 651 5% (0–16%)	18.26 (<0.0001) 0.05 (0.82)	N = 26 n = 9758 30% (18–44%) N = 13 n = 7070 6% (2–11%)	N = 6 n = 9475 41% (9–78%) N = 1 n = 5651 1% (1–1%)	0.24 (0.62) 10.81 (0.001)
Gender Identity Disorder N = 1 n = 34	3% (1–15%)	NA	N = 1 n = 34 3% (1–15%)	NA	NA	N = 1 n = 34 3% (1–15%)	NA	NA
Intellectual Disability N = 27 n = 162,997	33% (26–41%)	99.87 (<0.0001)	N = 18 n = 108,618 35% (28–43%)	N = 6 n = 29,954 39% (24–56%)	0.22 (0.64)	N = 11 n = 5688 38% (20–58%)	N = 16 n = 157,309 31% (22–40%)	0.42 (0.52)
Language Disorder N = 4 n = 8979	16% (0–53%)	99.93 (<0.0001)	N = 2 n = 4442 39% (38–40%)	NA	NA	N = 1 n = 4123 2% (1–2%)	N = 3 n = 4856 23% (0–67%)	2.55 (0.11)
Obsessive Compulsive Disorder N = 44 n = 36,467	9% (7–10%)	92.40 (<0.0001)	N = 25 n = 28,962 10% (8–12%)	N = 11 n = 2443 10% (6–15%)	0.48 (0.49)	N = 38 n = 13,473 10% (8–13%)	N = 6 n = 22,994 5% (3–7%)	13.24 (<0.0001)
Personality Disorder (any kind) N = 14 n = 8306	7% (4–10%)	94.59 (<0.0001)	N = 1 n = 89 9% (5–17%)	N = 9 n = 7398 6% (3–10%)	0.67 (0.41)	N = 10 n = 1327 7% (2–15%)	N = 4 n = 6979 7% (3–12%)	0.06 (0.81)
Schizophrenia N = 29 n = 65,841	10% (7–13%)	99.23 (<0.0001)	N = 5 n = 9420 10% (1–25%)	N = 13 n = 9093 10% (7–14%)	0.01 (0.92)	N = 20 n = 6075 11% (7–16%)	N = 9 n = 59,766 9% (4–14%)	0.69 (0.41)
Sleep-Wake Disorder N = 29 n = 203,287	25% (18–34%)	99.93 (<0.0001)	N = 17 n = 144,844	N = 8 n = 33,968	1.30 (0.25)	N = 16 n = 5330	N = 13 n = 197,957	7.25 (0.01)

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Table 1 (*continued*)

Pooled estimate of prevalence			Subgroup analysis: Age group			Subgroup analysis: Study design		
			30% (10–44%)	21% (12–30%)		40% (21–62%)	12% (4–22%)	
Sleep-Wake Problem N = 26 n = 18,482	43% (36–50%)	98.34 (<0.0001)	N = 25 n = 18,399 44% (38–51%)	N = 1 n = 83 16% (9–25%)	23.85 (<0.0001)	N = 18 n = 5123 51% (38–64%)	N = 8 n = 13,359 26% (19–34%)	10.17 (0.001)
Specific Learning Disorder N = 1 n = 122	13% (8–20%)	NA	NA	NA	NA	NA	NA	NA
Somatic Symptom and related disorders N = 4 n = 186	28% (5–58%)	93.48 (<0.0001)	N = 2 n = 127 29% (22–38%)	N = 2 n = 59 10% (3–20%)	8.10 (0.004)	N = 3 n = 130 17% (3–37%)	N = 1 n = 56 55% (42–68%)	9.24 (0.002)
Substance Use Disorder N = 18 n = 20,311	5% (2–8%)	98.39 (<0.0001)	N = 4 n = 8591 2% (0–8%)	N = 10 n = 7042 5% (3–8%)	1.61 (0.21)	N = 13 n = 5272 4% (2–7%)	N = 5 n = 15,039 4% (0–13%)	0.01 (0.91)
Tic Disorder N = 38 n = 36,749	10% (8–13%)	97.36 (<0.0001)	N = 22 n = 5014 14% (8–21%)	N = 6 n = 310 11% (1–28%)	0.00 (0.96)	N = 30 n = 7320 11% (7–16%)	N = 8 n = 29,429 9% (5–14%)	0.92 (0.34)
Trauma Stress Related Disorder N = 12 n = 21,162	4% (0–10%)	99.18 (<0.0001)	N = 5 n = 19,769 6% (0–20%)	N = 4 n = 649 3% (0–8%)	0.45 (0.50)	N = 9 n = 1068 3% (1–8%)	N = 3 n = 20,094 5% (0–21%)	0.01 (0.92)
Medical and neurological								
Celiac Disease N = 6 n = 8419	4% (1–9%)	96.55 (<0.0001)	N = 4 n = 8017 6% (2–12%)	N = 1 n = 255 0% (0–2%)	8.51 (0.004)	N = 4 n = 1086 1% (1–3%)	N = 2 n = 7333 10% (9–11%)	68.24 (<0.0001)
Chromosome abnormality N = 9 n = 56,118	2% (1–4%)	98.04 (<0.0001)	N = 7 n = 55,748 1% (0–3%)	N = 1 n = 92 2% (1–8%)	0.46 (0.50)	N = 4 n = 833 4% (0–14%)	N = 5 n = 55,285 1% (0–3%)	1.30 (0.25)
Genetic Disorder N = 12 n = 19,692	3% (1–6%)	98.55 (<0.0001)	N = 7 n = 13,448 2% (0–7%)	N = 4 n = 2121 4% (2–8%)	0.76 (0.38)	N = 6 n = 4964 3% (2–6%)	N = 6 n = 14,728 2% (0–7%)	0.43 (0.51)
Down Syndrome N = 16 n = 74,916	1% (1–1%)	72.09 (<0.0001)	N = 10 n = 67,518 1% (1–1%)	N = 3 n = 6875 1% (0–2%)	0.14 (0.71)	N = 6 n = 1357 2% (1–4%)	N = 10 n = 73,559 1% (1–1%)	2.99 (0.08)
Elimination Disorder N = 27 n = 2246)	29% (19–40%)	96.36 (<0.0001)	N = 20 n = 1686 29% (18–42%)	N = 6 n = 518 33% (11–59%)	0.10 (0.75)	N = 23 n = 1971 31% (19–44%)	N = 4 n = 275 19% (9–32%)	1.90 (0.17)
Epilepsy N = 84 n = 250,800	16% (14–18%)	98.94 (<0.0001)	N = 49 n = 164,252 13% (11–15%)	N = 15 n = 9185 23% (19–27%)	19.92 (<0.0001)	N = 55 n = 18,824 18% (15–22%)	N = 29 n = 231,976 12% (10–15%)	9.35 (0.002)
Food Intolerance N = 7 n = 7094	13% (3–29%)	99.17 (<0.0001)	N = 4 n = 938 19% (4–40%)	N = 2 n = 591 20% (16–23%)	0.01 (0.94)	N = 4 n = 835 19% (4–41%)	N = 3 n = 6259 7% (0–28%)	1.00 (0.32)
Gastrointestinal Disorder N = 18 n = 27,249	21% (11–33%)	99.77 (<0.0001)	N = 8 n = 9694 12% (2–28%)	N = 8 n = 8642 37% (23–51%)	5.59 (0.02)	N = 11 n = 6706 24% (13–38%)	N = 7 n = 20,543 16% (3–37%)	0.46 (0.50)
Gastrointestinal Problem N = 43 n = 23,908	39% (32–46%)	99.07 (<0.0001)	N = 33 n = 18,961 41% (34–48%)	N = 7 n = 670 32% (20–45%)	1.67 (0.20)	N = 37 n = 21,879 40% (32–37%)	N = 6 n = 2029 32% (14–55%)	0.41 (0.52)
Gluten Intolerance N = 2 n = 338	1% (0–3%)	0	N = 1 n = 191 1% (0–3%)	NA	NA	N = 2 n = 338 1% (0–3%)	NA	NA
Hearing Disorder N = 14 n = 22,213	4% (2–7%)	98.37 (<0.0001)	N = 5 n = 12,828 1% (0–3%)	N = 4 n = 3514 11% (4–22%)	7.74 (0.01)	N = 8 n = 4832 5% (2–10%)	N = 6 n = 17,381 3% (1–8%)	0.83 (0.36)
Metabolic Disorder N = 5 n = 5014	3% (1–5%)	88.54 (<0.0001)	N = 3 n = 799 3% (0–10%)	N = 1 n = 92 1% (0–6%)	0.50 (0.48)	N = 4 n = 4958 2% (0–5%)	N = 1 n = 56 9% (4–19%)	4.72 (0.03)

(*continued on next page*)

Table 1 (*continued*)

Pooled estimate of prevalence			Subgroup analysis: Age group			Subgroup analysis: Study design		
Motor Problem N = 12 n = 25,945	40% (19–64%)	99.91 (<0.0001)	N = 9 n = 25,163 36% (13–64%)	N = 1 n = 50 68% (54–79%)	3.95 (0.05)	N = 6 n = 12,301 59% (25–88%)	N = 6 n = 13,644 23% (15–33%)	4.15 (0.04)
Neurocutaneous Disorder N = 12 n = 21,682	0% (0–1%)	81.48 (<0.0001)	N = 10 n = 21,542 0% (0–1%)	N = 2 n = 140 3% (1–7%)	8.29 (0.004)	N = 5 n = 502 3% (1–6%)	N = 7 n = 21,180 0% (0–0%)	10.86 (0.001)
Organic Nutrition Disorder N = 3 n = 6038	22% (0–76%)	99.92 (<0.0001)	NA	N = 2 n = 1915 1% (1–2%)	NA	N = 2 n = 4266 53% (51–54%)	N = 1 n = 1772 1% (1–1%)	2.599 (<0.0001)
Overweight/Obesity N = 26 n = 70598	33% (25–41%)	99.63 (<0.0001)	N = 22 n = 61,175 34% (24–45%)	N = 3 n = 6447 28% (13–45%)	0.40 (0.53)	N = 18 n = 7497 35% (28–42%)	N = 8 n = 63,101 30% (17–44%)	0.36 (0.55)
Rett Syndrome N = 1 n = 92	2% (1–8%)	NA	NA	N = 1 n = 92 2% (1–8%)	NA	N = 1, n = 92 2% (1–8%)	NA	NA
Fragile X Syndrome N = 20 n = 20,802	2% (1–3%)	89.14 (<0.0001)	N = 11 n = 14,929 1% (0–2%)	N = 3 n = 5416 1% (0–5%)	0.15 (0.70)	N = 12 n = 878 5% (2–8%)	N = 8 n = 19,924 0% (0–1%)	24.00 (<0.0001)

N = number of studies in meta-analyses; n = sample size for individuals with autism included across studies; a. Qb=test for heterogeneity between subgroups; Clin Com=clinical studies from community samples; Pop Reg=population/registry-based studies; NA=Not Applicable; Child/adolescent group aged < 18 years; Adult group aged > 18 years.

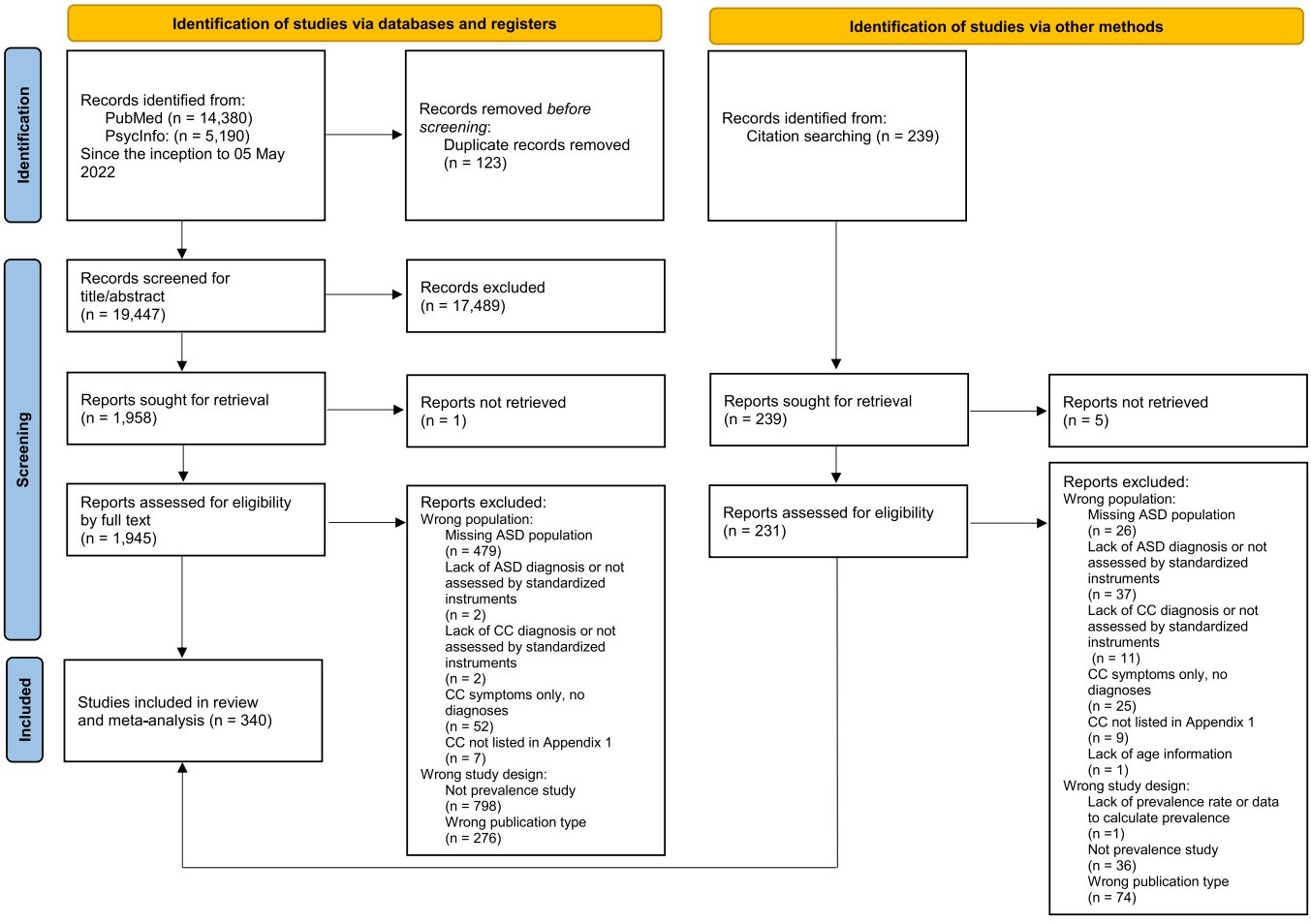

Fig. 1. Flow chart of the literature selection process.".

from clinical, treatment centers, or hospitals describing a non-randomly sampled subset of ASD population which may have higher rates of CCs than the general population (Lai et al., 2019), type of prevalence (point or/and lifetime). *ASD population characteristics*: diagnosis type, tools/-methods used for the ASD diagnosis, sample size, gender (% of females), age (mean, SD, range), ID (% of ASD with ID – below a score of 70 in the intelligent quotient), language disorder (% of ASD with language disorder). *ASD with CC(s) population characteristics*: sample size (number of ASD with the CC), CC label as reported in the study, tools/methods used for the diagnosis of the CC, gender, age, ID, and language disorder. When follow-up studies measured prevalence rates in different time points, the prevalence of the last time point was reported. CCs were grouped based on the diagnostic broad categories (eTables 2 in the Supplement 1). In addition to presenting the prevalence of feeding and eating and disorders, the prevalence of typical eating disorders (*i.e.*, anorexia nervosa, bulimia nervosa, and binge eating disorder) is presented separately since they have a lengthy history of specific nosologic conceptualization and have been reported to have different prevalence rates in comparison to the other "atypical" forms of these disorders. The data extraction and risk of bias assessment were performed by two of the six blinded authors for each study. The data extracted from each included study were checked by a second independent author. To ensure consistency across all authors, calibration exercises before starting to extract the data were conducted. Conflicts or doubts were discussed between the two authors and if necessary, the involvement of a third author was required.

2.5. Study quality

To assess the study quality and indirectness (external validity) of the included studies, the Hoy Risk of Bias Tool (Hoy et al., 2012) was used. This tool measures internal and external validity and has been used extensively to evaluate prevalence studies. It is a 10 questions tool providing a summary score representing risk of bias. Each item can be answered with "yes" (low risk) or "no" (high risk). Summary scores indicate low (further research is very unlikely to change our confidence in the estimate), moderate (further research is likely to have an important impact on our confidence in the estimate and may change the estimate), and high (further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate) risk of bias (Hoy et al., 2012) Inter-rater reliability was calculated using intraclass correlations.

2.6. Data analysis

All CCs detected by the search strategy were considered. Data for each CCs listed in the search strategy were meta-analyzed if the population and diagnostic criteria were homogeneous enough within each CC. The remaining ones, along with a group of minor CCs were not described but listed in eMethods 2 in the Supplement 1.

Reports presenting summary estimates of prevalence were included in the systematic review.

A meta-analysis with a random-effects model was used to determine the prevalence of any CCs in the autistic population. The metaprop command was used for pooling proportions in the meta-analysis. Heterogeneity was assessed using the I^2 statistic and the Cochrane Q test. We explored heterogeneity in subgroup analysis if I2 was $>$ 25% (Higgins et al., 2003).

Point and lifetime prevalence analyses were conducted separately. Lifetime prevalence results, more susceptible to recall biases (Simon and VonKorff, 1995) as they rely on individuals' or carers' ability to accurately recall past events and diagnoses and obfuscate age-subgroup analyses (Lai et al., 2019), are reported in eTables 2, 3 in the Supplement 1 and eFigures 1 in the Supplements 2 and 3. For all tests, *p-values* $<$ 0·05 were considered as making the play of chance as very unlikely. All statistical analyses were conducted using STATA 17·0 software (Stata Statistical Software: Release 17. College Station, TX, USA: StataCorp LP).

3. Results

3.1. Studies selection

The search strategy provided 19,932 studies (PubMed, n = 14,380; PsycINFO, n = 5190, and 239 hand searching), 123 duplicates were removed. A total of 19,686 records were screened for inclusion and exclusion criteria. Based on the titles and abstracts screening, 17,489 non-pertinent works were excluded.

The remaining 2197 records were checked in their full text. Six reports were not retrieved. Studies missing ASD population (n = 505), lacking ASD (n = 39) or CC (n = 13) diagnosis or not assessed by standardized instruments, exploring CC symptoms only, no diagnoses (n = 77), CC not included in the search strategy and not subjected to metanalysis process (n = 16), lacking of age information (n = 1) or prevalence rate or data to calculate prevalence (n = 1), and not prevalence studies (n = 834) were excluded. In addition, 350 works were excluded because of reviews, case reports, comments, editorials, and letters (wrong publication type). eMethods 3 in Supplement 4, lists the records' references included and excluded after being checked in their full text with the reasons for exclusion. Finally, we evaluated 340 publications as eligible for the data extraction process and meta-analyses for the prevalence of 38-point prevalence CCs, 27-lifetime, and 3 without distinction between point and lifetime prevalence (ID, Down and Fragile X syndromes) because lifelong disorders. Fig. 1 provides the process of records identification and screening.

3.2. Study and population characteristics

A total of 340 studies (references listed in eMethods 3 in the Supplement 4), including 592,169 autistic people (ASD sample size range=9–93,639; mean=1742, SD=7281), were included in the meta-analysis. From the year 2004 to date 10 or more (except for 2007) records per year have been published on this topic (eFigure 2 in Supplement 4). Most of the studies (40%, n = 136) were conducted in the US, followed by the United Kingdom (7%, n = 25), Italy (7%, n = 24), and Sweden (7%, n = 23) (eTables 2 in the Supplement 1). Most studies were published in the English language (99·4%, n = 338), except for one in German and one in Spanish. Most of the studies included were *Clin com* (76%, n = 258), while the 24% (n = 82) *Pop reg.* Seventy-nine percent (n = 270) of the studies reported the number of female participants. Only 1% (n = 5) of these studies had more than 50% of females in their sample (mean=20.20%, SD=10.80%, range=0–100%). The number of autistic people with ID was reported in 32% (n = 108) of the studies included. 42% (n = 45) of these studies had more than 50% of autistic people with ID in their sample (mean=42.31%, SD=36.08%, range=0–100%). Forty-five percent (n = 49 studies on 108) of the studies reporting the number of ASD with ID also revealed how many of these individuals presented the CC. Only 12% (n = 42) of the studies reported the number of autistic people with language disorders. Twenty-six percent (n = 11) of these studies had more than 50% of autistic people with language disorders in their sample (mean=23.80%, SD=29.20%, range=0–100%). Forty percent (n = 17 studies on 42) of the studies reporting the number of ASD with language disorder also revealed how many of these individuals presented the CC. The age group results are presented considering the three age groups analyzed, thus it is possible that one study included more than one age group. Similarly, it is possible that one study included more than one type of prevalence (point and/or lifetime). So, the age group and prevalence type results are presented on 1118 records. Eighty-three percent (n = 931) of the included studies showed a point prevalence and 17% (n = 187) a lifetime prevalence. Fifty-nine percent (n = 661) of the records included children and adolescents $<$ 18 years old; 22% (n = 243) adults, and 19%

(n = 214) mixed age (eTables 2 in the Supplement 1). Thirty-eight percent (N = 128) of the included studies declared no conflict of interest, while 56% (n = 192) did not provide this information. Only 6% (n = 20) of the studies reported a conflict of interest. Twelve percent (n = 40) of the declared to be supported by any funding, while 37% (n = 126) did not provide this information. About half of the studies (51%, n = 174) indicated at least one source of funding.

3.3. Risk of bias in studies

For the risk of bias assessment between two reviewers, the case 2 A intra-class correlation of 20% (n = 68) of the studies was high (0.87; 95% CI=0·76–0.93). This value indicates very good reliability. The risk of bias ratings of the included studies are reported in eTable 4 inSupplement 4. The risk of bias overall rating ranged from 0 to 8 (Mean=3.26; SD=1.49). 60% (n = 203) of the included studies, were rated at low risk of bias, 38% (n = 131) at moderate, and 2% (n = 6) at high low risk of bias. Seventy-two percent (n = 245) of the studies were at high risk for random selection used to the sample, 68% (n = 232) for a close representation of the target population, 65% (n = 222) for a close representation of the national population, 35% (n = 121) for the instrument that measured the parameter of interest reliability and validity, and 28% (n = 96) for data collection performed directly from the subjects.

3.4. Overall pooled estimates

Table 1 shows the overall pooled estimates' results. Among the mental health/psychiatric CCs analyzed, the overall point prevalence from most frequent to least frequent were the following: developmental coordination disorder, 87% (95% CI 87–88%), sleep-wake problem, 43% (95% CI 36–50%), ADHD, 37% (95% CI 28–46%), anxiety disorder, 35% (95% CI 30–39%), ID (point and lifetime prevalence pooled together), 33% (95% CI 26–41%), feeding and eating disorder, 32% (95% CI 20–46%), disruptive behavior, 28% (95% CI 21–36%), somatic symptom and related disorders, 28% (95% CI 5–58%), sleep-wake disorder, 25% (95% CI 18–34%), affective disorder, 19% (95% CI 11–28%), depressive disorder, 18% (95% CI 15–21%), disruptive impulse control disorder, 17% (95% CI 13–22%), language disorder, 16% (95% CI 0–53%), specific learning disorder, 13% (95% CI 8–20%), schizophrenia, 10% (95% CI 7–13%), tic disorder, 10% (95% CI 8–13%), obsessive compulsive disorder, 9% (95% CI 7–10%), any kind of personality disorder, 7% (95% CI 4–10%), bipolar disorder, 7% (95% CI 4–9%), substance use disorder, 5% (95% CI 2–8%), trauma stress related disorder, 4% (95% CI 0–10%), and gender identity disorder, 3% (95% CI 1–15%). Anorexia nervosa, bulimia nervosa and binge eating, 5% (95% CI 2–10%), was calculated in addition to feeding and eating disorder.

Among the medical and neurological CCs analyzed, the overall point prevalence from most frequent to least frequent were the following: motor problem, 40% (95% CI 19–64%), GI problem, 39% (95% CI 32–46%), overweight/obesity, 33% (95% CI 25–41%), elimination disorder, 29% (95% CI 19–40%), organic nutrition disorder, 22% (95% CI 0–76%), GI disorder, 21% (95% CI 11–33%), epilepsy, 16% (95% CI 14–18%), food intolerance, 13% (95% CI 3–29%), celiac disease, 4% (95% CI 1–9%), hearing disorder, 4% (95% CI 2–7%), metabolic disorder, 3% (95% CI 1–5%), genetic disorder, 3% (95% CI 1–6%), Rett syndrome, 2% (95% CI 1–8%), chromosome abnormality, 2% (95% CI 1–4%), Fragile X syndrome (point and lifetime prevalence pooled together), 2% (95% CI 1–3%), Down syndrome (point and lifetime prevalence pooled together), 1% (95% CI 1–1%), gluten intolerance, 1% (95% CI 0–3%), and neurocutaneous disorder, 0% (95% CI 0–1%) (Table 1).

Raw data of studies reporting lifetime prevalence, pooled estimates, and funnel plots are reported in eTables 2, 3 in Supplement 1 and eFigures 1 in Supplements 2 and 3.

All meta-analyses showed substantial heterogeneity (I^2 >90%) except for point or combined point and lifetime prevalence of metabolic disorder (I^2 =88.54%) and neurocutaneous disorder (I^2 =81.48%), Down syndrome (I^2 =72.09%), and fragile X syndrome (I^2 =89.14%); the lifetime prevalence of feeding and eating disorder (I^2 =96.73%), bipolar disorder (I^2 =89.46%), and hearing disorder (I^2 =63.13%). The point prevalence of developmental coordination disorder and gluten intolerance, and the lifetime of feeding disorder, any kind of personality disorder, sleep-wake disorder, and sleep-wake and problem showed I^2 = 0%.

3.5. Subgroup analysis results: Age

Regarding the subgroup analysis on age groups (child/adolescent≤18 *vs* adult), studies investigating ADHD (45% *vs* 22%, p = 0.050), sleep-wake problem (44% *vs* 16%, p < 0.0001), feeding and eating disorder (42% *vs* 5%, p < 0.0001), somatic symptom and related disorders (29% *vs* 10%, p = 0.004), and celiac disease (6% *vs* 0%, p = 0.004) showed significantly higher prevalence in children/adolescents compared to those including adults.

On the contrary, motor problem (36% *vs* 68%, p = 0.05), GI disorder (12% *vs* 37%, p = 0.02), depressive disorder (14% *vs* 34%, p < 0.0001), epilepsy (13% *vs* 23%, p < 0.0001), hearing disorder (1% *vs* 11%, p = 0.01), and neurocutaneous disorder (0% *vs* 3%, p = 0.004) were found to be significantly prevalent in studies including adults compared to those with children/adolescents (Table 1; eFigures 1 in the Supplements 2 and 3; for lifetime prevalence results, see eTables 3 in the Supplement 1).

3.6. Subgroup analysis results: study design

Regarding the subgroup analysis on the study design (Clin Com *vs* Pop Reg), motor problem (59% *vs* 23%, p = 0.04), organic nutrition disorder (53% *vs* 1%, p < 0.0001), sleep-wake problem (51% *vs* 26%, p = 0.001), ADHD (43% *vs* 25%, p = 0.03), sleep-wake disorder (40% *vs* 12%, p = 0.01), anxiety disorder (38% *vs* 25%, p = 0.01), disruptive impulse control disorder (25% *vs* 9%, p = 0.01), depressive disorder (21% *vs* 8%, p < 0.0001), epilepsy (18% *vs* 12%, p = 0.002), obsessive compulsive disorder (10% *vs* 5%, p < 0.0001), bipolar disorder (9% *vs* 3%, p < 0.0001), Fragile X syndrome (5% *vs* 0%, p < 0.0001), and neurocutaneous disorder (3% *vs* 0%, p = 0.001) showed prevalence estimates from Clin Com studies significantly higher than those from Pop Reg (Table 1, eFigures 1 in the Supplements 2 and 3). The Clin Com point estimates of elimination disorder, tic disorder, disruptive behavior, schizophrenia, GI disorder and problem, ID, overweight/obesity, genetic disorder, food intolerance, and hearing disorder were descriptively higher than Pop Reg estimates, indeed CIs overlapped across study-design subgroups.

On the contrary, for somatic symptom and related disorders (17% *vs* 55%, p = 0.002), affective disorder (35% *vs* 12%, p = 0.01), celiac disease (1% *vs* 10%, p < 0.0001), and metabolic disorder (2% *vs* 9%, p = 0.03), Pop Reg studies were significantly higher than those from Clin Com. For any kind of personality disorder (7%), and substance use disorder (4%), Clin Com and Pop Reg studies presented the same prevalence. The Pop Reg estimates of feeding and eating disorder-point, language disorder, and trauma stress related disorder were descriptively higher than Clin Com estimates (Table 1; eFigures 1 in the Supplements 2 and 3; for lifetime prevalence results, see eTables 3 in the Supplement 1).

4. Discussion

A total of 340 studies including about 590,000 autistic participants have been considered eligible for systematic review and meta-analysis for the prevalence of 38-point prevalence CCs, 27-lifetime, and 3 without distinction between point and lifetime prevalence (ID, Down and Fragile X syndromes) because lifelong conditions. Among the

mental health/psychiatric CCs, the most frequently reported CCs, with their point pooled prevalence estimates, were developmental coordination disorder, sleep-wake problem, ADHD, anxiety disorder, ID (point and lifetime prevalence pooled together), feeding and eating disorder, disruptive behavior, somatic symptom and related disorders, and sleep-wake disorder. Among the neurological and medical CCs, the most frequent overall point prevalence was the following: motor problem, GI problem, overweight/obesity, elimination disorder, organic nutrition disorder, and GI disorder. Prevalence of ADHD, sleep-wake problem, somatic symptom and related disorders, and celiac disease were higher in children/adolescents compared to adults. While, the prevalence of motor problem, GI disorder, depressive disorder, epilepsy, hearing disorder, and neurocutaneous disorder were higher in adults compared to children/adolescents.

Most of the CCs explored in the present meta-analyses were highly prevalent in the autism population, mostly significantly higher than general population prevalence rates reported in representative studies (non-overlapping prevalence estimates/CIs), except for the point prevalence of the depressive disorder in children (Shorey et al., 2022), personality disorder in children (Winsper et al., 2020), somatic symptom disorder (Löwe et al., 2022), trauma stress-related disorder (Kessler et al., 1995), celiac disease in adults (Singh et al., 2018), chromosome abnormalities (Xie et al., 2021), GI problems in adults (Croen et al., 2015), and organic nutrition disorders in children (Awate et al., 1997). However, a direct comparison of prevalence among individuals with autism and the general population is not possible, due to the wide differences in the sample recruitment, age range sample characteristics, and measurement tools.

Even if CCs contribute to worsening quality of life from childhood into adulthood, more than half of the studies (59%) have focused on CCs in childhood rather than in adulthood (22%). Studies on autistic adults are still few, however, especially in the context of CCs that can also begin or worsen during adulthood, it is crucial to conduct dedicated studies. For autistic adults, the formulation of a life plan should consider the presence of associated co-occurring conditions to determine the most appropriate opportunities of support. Specifically, when identifying a person's preferences, career paths, autonomy programs, job prospects, and opportunities for social integration, it is crucial to give substantial consideration to the presence of conditions like depression and intellectual disability. In addition, recognizing the varying prevalence of co-occurring conditions in different age groups enables healthcare professionals to customize interventions more effectively. This personalized and tailored approach improves treatment accuracy and promotes positive outcomes. In addition, our data suggest the promotion in clinical practice of the evaluation of the most prevalent co-occurring conditions in the various age groups. Overall, this in-depth analysis may lead to the development of more tailored treatments and of strategies for early identification of these conditions that are so impactful on the quality of life of autistic individuals.

A favorable aspect was that most of the studies assessed CCs at a precise timepoint of people life which preserves from recall biases (Simon and VonKorff, 1995), instead of registering a lifetime prevalence. As Lai and colleagues (Lai et al., 2019) observed for the psychiatric CCs, most of the studies were clinical sample-based and their estimates were generally higher than population/registry-based studies, except for point prevalence of somatic symptom and related disorders, affective disorder, celiac disease, and metabolic disorder. In clinical settings, comprehensive and rigorous diagnostic assessments are often performed to confirm or exclude primary diagnosis and co-occurring conditions. This can lead to higher detection values than population-based studies that may rely on screening or self-reported data.

It should be noted that, although most of the studies indicated the number of females included, only 2% recruited more than a half of females. This can be partially explained by the fact that ASD is a predominant male condition with a 4.2 median male-to-female ratio (Zeidan et al., 2022). Since this gender imbalance, studies that primarily include males may not adequately represent the full spectrum of the condition. This can lead to an underestimation or overestimation of the prevalence of CCs that are less or more frequently observed in males but may be more/less common in females with ASD, influencing research focuses. It is widely recognized that the occurrence of numerous CCs in the general population varies significantly based on gender. Only few studies previously observed substantial differences between autistic males and females in the prevalence rate of CCs (Hsu et al., 2022; May et al., 2016; Supekar et al., 2017), future research should aim to consider the gender distribution in their studies and aim for more balanced representation, leading to a more comprehensive identification of gender-specific factors that may influence CC prevalence. Only the 32% of the studies reported the number of individuals with autism and ID but, almost half of these studies, presented more than 50% of the autistic sample with ID and reported the percentage of autistic people with ID and CC. The high median percentage of autism cases with co-occurring ID (33%) (Zeidan et al., 2022) and high presence of co-occurring symptomatology (Cervantes and Matson, 2015) should encourage researchers to conduct more studies showing possible differences in the prevalence of CCs and their clinical implications in the autistic population with ID. Very few studies (12%) reported the prevalence of autistic people with language disorder in their sample; however, in almost half of these studies, more than 50% of the autistic people presented language disorder, and 77% reported also the percentage of autistic people with language disorder and CC. Exploring the prevalence of CCs holds particular significance, especially for autistic individuals facing challenges such as behavioral issues, language disorders, and intellectual disabilities, which can hinder their ability to verbally express their symptoms and needs. It is crucial that future prevalence studies inform on the language profile of their sample using standardized instruments for its assessment, because it may influence CCs symptoms presentation and consequently diagnosis and treatment. The studies included in the present systematic review generally used standardized instruments to investigate mental health and psychiatric CCs in autism. Noteworthy, only a few tools are targeted to autistic people but are standardized on the general population. Future studies should adapt existing tools to the autistic population or develop new targeted measures, especially in reference to persons with major communication and/or cognitive difficulties. The knowledge of the prevalence of CCs in autism is fundamental to set up health services, especially mental health services, for adequate screening, diagnosis, and management of these conditions in users with autism, as well as support for carers, training for professionals, and interventions to improve psychical and mental health, especially in most vulnerable life periods such as transitional life periods. Due to the higher prevalence of CCs in autism compared to the general population, the appropriate screening, assessments, support, and interventions focused on mental and physical well-being, should be carefully considered in the clinical and therapeutic routine.

Regarding the years of publication, from 2004 to date, more than 10 records per year have been considered eligible for inclusion in the systematic review. This may be due, on one hand, to a greater interest in the field of autism and its mental and physical health; on the other hand, to the fact that prevalence studies have started to be better designed and use validated diagnostic tools. Regarding the sites of publications, most of the studies included were conducted in the US. More research efforts should be dedicated to promoting CCs prevalence studies in countries where these types of studies have never been conducted. Finally, more than half of the reports (56%) omitted information on potential conflicts of interest and 37% did not disclose funding sources, which is critical to promote in order to increase transparency.

4.1. Strengths and limitations

The present systematic review and meta-analysis provide prevalence of psychiatric, neurological, and medical CCs for different autistic group

ages (children/adolescents *vs* adults), study designs (population/registry-based *vs* clinical sample-based), and prevalence types (point *vs* lifetime). Therefore, the stringent inclusion and exclusion criteria allowed to select the highest quality studies, providing valid prevalence estimates.

Despite the relevance of this work, some limitations can be pointed out that should be considered when interpreting the results. First, the heterogeneity among studies can arise from variations in participant characteristics (*e.g.*, age, gender, phenotype, number of CCs and symptoms' severity), differences in study design and execution (*e.g.*, diagnostic criteria, assessment tools, recruitment methods), and variations in methodological quality. Controlling for this heterogeneity remains challenging and may contribute to the wide range of estimated prevalence rates. Future research should be designed to clarify heterogeneity (e. g., exploring CCs in stratified subgroups such as by intellectual/communication abilities, gender, phenotype, genetic or neurological background, illness loads and CCs patterns) (Lai et al., 2019). In addition, some CCs prevalence were measured based on a few studies, limiting the generalizability of findings. Finally, even if the search strategy was developed primary around the general term of CCs, the inclusion of terms indicated by existing guidelines, the DSM5 diagnostic manual, and experts may have facilitated the interception of studies geared toward presenting the prevalence of outlined CCs. In this study, we described all CCs included in the search strategy that could be subjected to a metanalysis process. The remaining ones, along with a group of minor CCs were not described but listed in Supplement. These latest are not listed among the major CCs listed by the scientific community summarized by guidelines, diagnostic manuals, and publications (Lai et al., 2019; Lord et al., 2022). Future works may measure the prevalence of these CCs less explored.

Regarding the limitations of the evidence included in the review, most of the studies (60%) were rated low and moderate (38%) risk of bias, resulting in trustable results. However, the most common weaknesses revealed by the risk of bias assessment concerned the population recruitment lacking random selection, and not being representative of the target population, due the fact that the majority of the studies were clinical sample-based studies. Future studies should seek to recruit large samples with a representation of females, people with ID, and language disorders. Other aspects to be improved, revealed by the risk assessment, concern instruments that measured CCs that have been often not evaluated as valid.

In conclusion, psychiatric, neurological, and medical CCs are common in autism and their prevalence change depending mainly on the age of the autistic person and design of the study measuring the prevalence. Such a high rate of one or more CCs may significantly affect the health status and quality of life of people with autism and their families, representing a notable cost for the health-care systems. It is crucial to gain a comprehensive understanding and precise recognition of CC patterns within the autistic population. These accompanying issues significantly impact the overall prognosis and the level of long-term adjustment and quality of life of individuals with ASD. Therefore, an accurate assessment of the prevalence of various CCs within the autistic population is indispensable for the development of more efficient diagnostic and treatment approaches to better assist individuals and families. The mental and physical health of autistic persons should be promoted by encouraging screening, diagnosis, support, and treatment of CCs at all stages of life. Future research should seek to measure CCs prevalence using study protocols with high-standard quality.

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CRediT authorship contribution statement

MLS, HJS: conception. MLS, MM, FF, AC, LMF, LG, AntC, and MB: design of the work. MM, LG, AC, LMF, AntC, FF, and MB: data acquisition/extraction and interpretation of data. TS, RdA, CdG, and MM: statistical analysis; MM: writing—original draft preparation. MLS and GR: funding acquisition. All authors contributed to the writing—review and editing. They read and agreed to the published version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Declaration of Competing Interest

None.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105436.

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