Prevalence of Autism Spectrum Disorder (ASD) in all Individuals Diagnosed with Down Syndrome (DS): A Systematic Review and Meta-analysis Protocol

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Protocol

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Abstract

BACKGROUND

Traditionally, autism spectrum disorder in people with Down syndrome was believed to be uncommon. This misconception is rooted in the challenges that a dual diagnosis poses. In fact, evidence indicates that children with Down syndrome are at risk for autism spectrum disorder with a potentially higher prevalence than the typically developing population. The purpose of this review is to determine the reported prevalence rate of autism spectrum disorder in all individuals with Down syndrome in comparison to the prevalence rate of autism spectrum disorder in the typical population when specific diagnostic tools are used.

METHODS

We will conduct a systematic review of the prevalence and incidence data and perform a meta-analysis on these results. This study will consider all studies that reported on children and adults with an existing diagnosis of Down syndrome and diagnosed by the standardized assessments for autism spectrum disorder. We will also consider the diagnoses made by team assessment (psychologist, psychiatrist & developmental pediatrician), according to DSM-III, DSM-IV or DSM-V criteria for diagnosing autism spectrum disorder or if they use autism spectrum disorder screeners. Studies will be considered from all countries that have data reporting prevalence on this topic. We will not apply language restrictions, attempting to translate studies that are not in English. We will search five databases (MEDLINE, Embase, PsychINFO, Scopus, and CINAHL). Two reviewers will conduct all screening and data extraction independently. The articles will be categorized according to key findings and a critical appraisal performed.

DISCUSSION

The results of this review will bring increased awareness of the presence of autism spectrum disorder in individuals with Down syndrome. In doing so, this may facilitate a recommendation for screening and diagnosis for autism spectrum disorder in all individuals with Down syndrome. Based on the research demonstrating the benefits of early identification and intervention on the outcomes of children with autism, we anticipate similar benefits in this population. This will guide the allocation of resources and direct future research.

SYSTEMATIC REVIEW REGISTRATION

We registerd the review title prospectively on PROSPERO on November 8, 2021. Registration number: CRD42020213282

Background

Autism spectrum disorder (ASD) is a developmental disorder characterized by restrictions in communication and behaviour (1). The prevalence of ASD worldwide is reported to be 1 in 60 children (2). The Centres for Disease Control (CDC) reported in 2020 that approximately 1 in 54 children in the United States is diagnosed with ASD (3). In Canada, the National Autism Spectrum Disorder Surveillance System reported a prevalence of 1:66 in a 2018 report (4). Children with a diagnosis of ASD do not uniformly express the same combination of symptoms or symptom severity; hence, the terminology of a spectrum is utilized. Autism spectrum disorder can coexist in a child with a genetic syndrome and those with an intellectual disability (ID) (5).

Amongst live births, Down syndrome (DS) is the most common chromosomal abnormality, with an incidence of about 1 in 700 births (6). The leading etiology of ID from a chromosomal origin is DS (7). It is associated with a cluster of potential developmental and medical co-morbidities, with each individual expressing differing patterns of presentation. Traditionally, it was thought that ASD in people with DS was uncommon (8). The misconception regarding the rarity of the coexistence of ASD and DS is rooted in the challenges that dual diagnosis poses and potentially results in the underdetection of ASD in the population with DS. The medical complexity of DS may in and of itself increase the chances of an ASD diagnosis in this population (9, 10).

Inconsistencies that hamper identification despite increasing awareness include overlapping symptoms, diagnostic overshadowing and a lack of validated tools for this specific populations. We will explore these topics below.

Overlapping symptoms in a dual diagnosis of ASD and DS reflects that individually each diagnosis may impact communication and social skills. Individuals with DS have strong social motivation but may exhibit significant difficulties with expressive

communication and social skills (11, 12). They may experience challenges maintaining appropriate physical boundaries or understanding the nuances and pragmatics of social communication due to ID or possibly due to a secondary diagnosis of ASD (13). Compounding this is the known delay in skill acquisition experienced by individuals with DS. This may make secondary identification of ASD challenging as delays may relate to the delay of DS or be further exacerbated by ASD. For children with DS, cognitive development generally begins fairly typically but then slows in keeping with delayed brain myelination after the first 24 months (14, 15). Learning, however, generally continues into adolescence and adulthood for individuals with DS (16, 17). Beyond the cognitive and social pattern overlap, there is behavioral overlap in the presence of stereotypy (18). Individuals with DS are known to engage in stereotypic behaviours more frequently than in the general population, and stereotypy is a defining characteristic of ASD. The nuance of when a person with DS engages in stereotyped behaviours (all of the time or only when they are not interacting with others) can be missed by someone unfamiliar with the frequency of stereotyped behaviours in the DS population.

Second, diagnostic overshadowing refers to the idea that all symptoms are attributed to one condition, rather than appreciating that coexisting diagnoses can occur in those with a genetic syndrome and/or ID (19). In this case, behaviours from a specific diagnosis (such as ASD) are attributed to another (such as ID) without considering an alternative etiology (for example, a secondary diagnosis of ASD) (20).

Third, there is a lack of validated screening and assessment measures, no identified cut-off scores nor criteria for diagnosing ASD in a population that already has increased challenges with social communication and stereotyped behaviours. The normative population for current standard screening and diagnostic tools is a population that does not have an underlying genetic condition, which poses numerous questions. A 2018 Cochrane review looked at diagnostic tools for ASD in typically developing children and found that the Autism Diagnostic Observational Schedule (ADOS) (21) was the best tool to identify children with ASD. The Childhood Autism Rating Scale (CARS) (11, 12) and Autism Diagnostic Interview-Revised (ADI-R) (11, 12) were better for not falsely diagnosing ASD (11). Metcalfe et al., in 2020, conducted a systematic review of eight ASD screening tools (22). They applied these tools initially developed for a typically developing population and looked at efficacy for use in people with ID. They concluded that while there is potential for adapting these tools in a population with ID, the reliability of the tools needs more research.

To add to the above complexities of a diagnosis of ASD in DS, there is some evidence that behavioural patterns for expression of ASD symptoms in children with DS may not present the same pattern as that observed in children (23) without DS who develop ASD.

As a result of these factors affecting the identification of autism in DS, there is significant variability amongst studies demonstrating ASD in the population of individuals with DS. Overall, there appears to be more identification in recent years, but the prevalence ranges from initially as low as 5% to as high as 42% (24–29) (Graph 1). A 2010 study by DiGuiseppi et al. demonstrated that ASD in individuals with DS is 10-25 times more common than in the ‘typical’ population (27). This shifting prevalence may relate to increasing awareness that ASD is not a possible developmental co-morbidity in people with DS, but also reflects the current challenges in diagnosing as well.

The age of detection of ASD in children with DS is also varied. In 2001, Rasmussen documented the age at diagnosis of ASD in children with DS as 14.4 years (standard deviation (SD) 7.4 years) with a range of 4 to 33 years (9). Earlier recognition of symptoms may translate into an earlier age of diagnosis.

Our literature search for reviews on the prevalence of ASD diagnosed with DS revealed a limited selection presented in Table 1 below.

Table 1
Reviews of the prevalence of ASD in DS

Article	Date of publication	Country	Type of studies included	Population (general characteristics)	Key findings	Tools used	Prevalence	Limitations
Richards et al. (30)	2015	United Kingdom		1084 patients Mean age: variable from 2.0 to 169.1 months % with ID not reported in 8 studies. Varying between 49.5 to 100% for the remaining studies Search dates: between 1967 to March week 4, 2014	168 papers looking at ASD diagnosed in 16 syndromes 10 studies were included in the meta-analysis related to DS widely varying methods and quality of data DS diagnosis was verified either by cytogenetics or chromosomal except for 8.5% of the sample who had clinical features consistent with DS	14 ASD measures were reported for 11 studies ADI-R (11, 12) and SCQ (31) were used 3 times each DSM-IV (11, 12) and HBSS (32) were used 2 times each Each of the others used once: ASQ (11, 12), M-CHAT (33), ADOS-G (11), ASS-Q (34), CARS (11, 12), ICD-10 (35), A-PL-ADOS (36), ADDC, DSM-III (11, 12), History questions 1 study did not report the tool used	16.0% (determined by both random-effects and quality-effects pooled prevalence)	Data limited to 2014 or before

Article	Date of publication	Country	Type of studies included	Population (general characteristics)	Key findings	Tools used	Prevalence	Limitations
Reilly (10)	2009	Ireland	Mainly case reports	All ages % with disability not reported Search dates: not detailed	Methodology not detailed DS subgroup in ASD is substantial and likely to need different approaches for supports and interventions	Tools, not all detailed but included: HBSS (32), ASS-Q (34), CARS (11, 12) & ICD-10 (35), ASQ (11, 12), ADOS-G (11), A-PL-ADOS (36), ADI-R (11, 12), DSM-III (11, 12), DSM-II-R (11, 12), expert opinion with DSM-IV-TR (11, 12)	No percentage given as a range overall	No meta-analysis Data period not delineated This was more of a narrative review of the findings

Note. ADDC= Autistic Disorders Diagnostic Checklist, ADI-R= Autism Diagnostic Interview-Revised, ADOS-G= Autism Diagnostic Observation Schedule – Generic, A-PL-ADOS= Pre-linguistic ADOS, ASD=Autism spectrum disorder, ASQ=Autism Screening Questionnaire, ASS-Q= Asperger Syndrome Screening Questionnaire, CARS= Childhood Autism Rating Scale, DS=Down syndrome, DSM= Diagnostic and Statistical Manual of Mental Disorders, HBSS= Handicaps, Behaviours and Skills Schedule, ICD-10=International Classification of Diseases-10, ID=Intellectual disability, M-CHAT= Modified Checklist for Autism in Toddlers – Revised, SCQ=Social Communication Questionnaire

An older narrative review by Reilly in 2008 looked at several studies that reported on the dual diagnosis of DS-ASD. The author did not perform a meta-analysis of the results for prevalence (10). In this review, studies that used both screening and diagnostic tools resulted in prevalence rates between 1 and 11%. In a 2015 systematic review, Richards et al. performed a meta-analysis on the ASD phenomenology in a range of genetic syndromes, including DS (30). They identified 10 studies related to the prevalence of ASD in DS and reported a pooled prevalence of 16.0%. This study was limited to data up to 2014, which was more than five years ago.

Since 2014, more studies have been published that examine the rates of ASD in the population of children with DS and the neurodevelopmental phenotype of individuals with the dual diagnosis of DS-ASD compared to those with DS or ASD alone (37–41). The growing recognition of the dual diagnosis evident in these studies could significantly impact the direction of the research effort for this group. Therefore, an updated review of the literature on this topic is strongly needed.

Earlier identification of autism spectrum disorder is associated with greater intervention efficacy (38–42). This is essential as ASD is associated with substantial lifetime costs to individuals, their families, and the community. Horlin et al. revealed in their Australian study that the median family cost of ASD was A34 900$ (26900$ USD) per annum (42). An extra 1400$ (1080$ USD) per family per annum was incurred for each additional symptom reported. Delays in diagnosis were associated with a modest increase in the number of ASD symptoms, which indirectly impacts the cost of ASD.

Early identification and implementation of management for those with a dual diagnosis of DS and ASD may improve outcomes for the individual and family (43)(44–48). Parental reports of the greater challenges in dealing with the symptoms of ASD versus that of DS itself underscores the need for further amalgamation of the pieces of the dual diagnosis of DS-ASD (49). In light of these factors impacting the identification of clear prevalence rates of ASD in DS, a systematic review of the literature is necessary to

evaluate the most accurate estimate of prevalence rates currently and determine what approaches for diagnosing ASD in DS can be utilized. This will elucidate what additional research needs to be done in order to determine more accurate estimates of prevalence and facilitate earlier and appropriate management for better quality of life.

Methods/ Design

OBJECTIVES

The primary question for this review is: What is the reported prevalence rate of ASD in all individuals with DS compared to the prevalence rate of ASD in the typical population when diagnostic tools are used?

The secondary research questions for this review are:

- What is the reported mean age of diagnosis of ASD in DS?

- What are the primary distinguishing characteristics of ASD in DS?

- Do medical co-morbidities affect the prevalence rate of ASD in DS?

ELIGIBILITY CRITERIA

This study will consider studies that reported on children, adolescents, and adults with an existing diagnosis of DS and diagnosed by the standard assessments used for DS (clinical and genetic testing) and ASD.

We will use the Condition, Context and Population (CoCoPop) as per the format in Joanna Briggs Institute (JBI) (50). The JBI format was chosen as their methodology has specific formal guidance for reviews of prevalence and includes a critical appraisal tool specific for prevalence studies. This will facilitate an analysis specific to the type of evidence for prevalence and potentially provide stronger conclusions of the data (51). The criteria for each of these is detailed in the text below and further in Tables 2 and 3

Condition

This review will consider studies that report on the prevalence and/or incidence of ASD in the DS population. Prevalence is defined as “The fraction or proportion of the population that has the condition (i.e., cases)” (52). Incidence is defined as the rate of new events in a group of people of fixed size, all of which are observed over time (52).

Context

This review will consider studies that reported on children, adolescents, and adults with an existing diagnosis of DS and diagnosed by the standard assessments used for DS (clinical and genetic testing) and ASD. We will also consider the diagnoses made by team assessment by (psychologist, psychiatrist & developmental pediatrician), when it is based on DSM-III, DSM-IV or DSM-V criteria for the diagnosis of ASD or if they use ASD screeners. Studies will be considered from all countries that have data reporting prevalence on this topic. We will not apply language restrictions, and studies published in languages other than English will be considered for translation.

Participants

Table 2

Participants Inclusion and Exclusion Criteria

Inclusion	Exclusion
Original studies in which researchers report on the prevalence of ASD in individuals with DS were included. Studies in which data allowed for the calculation of prevalence were also included.	Studies in which information regarding the number of individuals with DS and ASD, the total number of individuals with DS tested, and tools used to diagnose ASD were not available were excluded.
Studies in which researchers described the prevalence of ASD in the general population were included if specific information on the DS population was available (i.e., the number of individuals with DS and ASD, total number of individuals with DS tested, and tool used). The studies could have been published in peer-reviewed journals or presented as conference abstracts.	Studies using ASD screening tools only will be excluded if no team assessment (psychologist, psychiatrist & developmental pediatrician) was done after the screening tool.
The diagnosis of ASD should have been based on diagnostic tests rather than screening tools.	Multiple publications from the same cohort will be excluded unless any additional information was available.
Studies in all languages from all countries internationally will be considered.	Animal studies will be excluded.

Note. ASD = Autism spectrum disorder, DS = Down syndrome

Table 3

Tools Inclusion and Exclusion criteria

ASD Inclusion tools		ASD Exclusion tools	
Tools that will be considered	**Inclusion tools - Brief description**	**Tools that will be excluded if used in isolation (no team assessment done)**	**Exclusion tools - Brief description**
The Autism Diagnostic Observational Schedule (ADOS™-2)	A semi-structured, standardized assessment scoring activities or social presses on a 4-point scale (21)	**Modified Checklist for Autism in Toddlers, Revised with Follow-Up (M-CHAT-R/F)**	A modified checklist for toddlers with a parent-completed questionnaire screening for autism in the general population (33)
The Autism Diagnostic Interview-Revised (ADI-R)	A semi-structured, investigator-based interview for caregivers of children and adults for whom autism or pervasive developmental disorders are possible diagnoses between the mental ages from 18 months into adulthood (11, 12)	**Screening Tool for Autism in Toddlers and Young Children (STAT)**	An interactive screening tool for suspected autism in children 24 to 36 months. It consists of 12 activities assessing play, requesting, directing attention and motor initiation (53)
The Development and Well-being Assessment	A package of questionnaires, interviews, and rating techniques designed to generate ICD-10 and DSM-IV psychiatric diagnoses on five to 16-year-old patients. Interviewers administer a structured interview to parents about psychiatric symptoms and their resultant impact. Teachers complete a brief questionnaire covering the main conduct, emotional, and hyperactivity symptoms and any resultant impairment. A computer program uses this information to predict likely diagnoses. Finally, clinicians use this to allocate a diagnosis (11, 12)	**Communication and Symbolic Behavior Scales Developmental Profile (CSBS-DP)**	A standardized screening tool for communication and symbolic abilities between 6 to 24-month levels. It consists of an Infant-Toddler Checklist and a parent-completed screening tool (54)
The Childhood Autism Rating Scale (CARS)	A clinical scale for the trained clinician to rate items that are indicative of ASD after direct observation and to determine the symptom severity through quantifiable ratings, between the ages of 2 years to late adulthood (11, 12)	**The Social Communication Questionnaire (SCQ)**	A parent-report screen used in children 4 years (31)
Gilliam Autism Rating Scale –	A parent or teacher-based tool assists in the identification and diagnosis of autism between the ages of 3 to 22 years (11, 12)	**Parents' Evaluation of Developmental Status (PEDS)**	A general developmental screening tool that uses a parent-interview form (55)

Second Edition (GARS-2)			
Developmental Dimensional and Diagnostic Interview (3di)	A parental interview using a computerized format (11, 12)	**The Parent's Observations of Social Interactions (POSI)**	A parent-report screening instrument for ASD in children 16 to 35 months (56)
Diagnostic Interview for Social and Communication Disorder (DISCO)	A semi-structured interview with a person who knows the individual, preferably from birth it focuses on patterns of behaviour over time (11, 12)	**Ages and Stages Questionnaires (ASQ)**	A general developmental screening tool (57). Not specific ASD screening
Team assessment (psychologist, psychiatrist, and developmental pediatrician)	Done in accordance with according to DSM-IV or DSM-V criteria for the diagnosis of ASD (11, 12)	**The Developmental Behaviour Checklist-Autism Screening Algorithm (DBC-ASA)**	A parent-report tool to assess behavioural and emotional disturbance in 4- to 18-year-old individuals with intellectual disability (58)
		Developmental Behavior Checklist-Early Screen (DBC-ES)	A screen for autism in developmentally delayed children 18 to 48 months of age (59)
		Rapid Interactive Screening Test for Autism in Toddlers (RITA-T)	An interactive clinical tool for children 18 – 36 months (60)
		Social Responsiveness Scale (SRS)	A 65-item rating scale can be used as a screener in clinical or educational settings, an aid to clinical diagnosis, or a measure of response to intervention. Completed by a parent or teacher in just 15 to 20 minutes, the SRS provides a clear picture of a child's social impairments, assessing social awareness, social

	information processing, capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupations and traits. It is appropriate for use with children from 4 to 18 years of age (61)

Note. 3di, Developmental Dimensional and Diagnostic Interview; ADDC, Autistic Disorders Diagnostic Checklist; ADI-R, Autism Diagnostic Interview – Revised; ADOS-G, Autism Diagnostic Observation Schedule – Generic; A-PL-ADOS, Pre-linguistic ADOS; ASD, Autism spectrum disorder; ASQ, Autism Screening Questionnaire; ASS-Q, Asperger Syndrome Screening Questionnaire; CARS, Childhood Autism Rating Scale; CSBS-DPDS, Communication and Symbolic Behavior Scales Developmental Profile; DBC-ASA, Developmental Behaviour Checklist-Autism Screening Algorithm; DBC-ES, Developmental Behavior Checklist-Early Screen; DISCO, Diagnostic Interview for Social and Communication Disorder; Down syndrome; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSMIG, Down Syndrome Medical Interest Group; GARS-2, Gilliam Autism Rating Scale – Second Edition; HBS, Handicaps, Behaviours and Skills Schedule; ICD-10, International Classification of Diseases-10; ID, Intellectual disability; M-CHAT, Modified Checklist for Autism in Toddlers – Revised; POSI, Parent's Observations of Social Interactions; PCC, Population, Concept, Context; PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols (PRISMA-P) guidelines; RITA-T, Rapid Interactive Screening Test for Autism in Toddlers; SCQ, Social Communication Questionnaire; STAT, Screening Tool for Autism in Toddlers and Young Children.

STUDY DESIGN

This prevalence study will be conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of prevalence and incidence (50).

The review will consider observational and descriptive study designs as these designs will have the anticipated information on prevalence (50). These will include prospective and retrospective cohort studies, case-control studies, cross-sectional studies, case series and case reports of any design from all countries. In addition, primary studies identified in published systematic reviews that meet the inclusion criteria will be considered. Text and opinion papers will also be considered for inclusion in this systematic review to capture all available data if they meet our selection criteria. Registry and census data will also be included.

This wide range of studies was chosen as a starting point in order to capture data comprehensively. Studies that do not meet the full inclusion criteria for the diagnosis itself may contain relevant information; for example, the mean age of presentation of symptoms consistent with ASD may be included. These excluded studies will be presented in a table with reasons for their exclusion.

Animal studies will not be included. Studies published from at least 1947 will be included as this is around the time when ASD was first described in the literature. The reference lists of articles will be scanned.

Experts in the developmental pediatric field and experts in Down syndrome will be consulted to identify studies relevant to our topic. Abstracts of conference proceedings, such as the Down Syndrome Medical Interest Group (DSMIG), will be searched.

Articles in any language will be considered if they can be translated into English. If the translation is not possible, they will be excluded but listed in a table in the appendix.

METHODS

Search strategy

The search strategy will aim to locate both published and unpublished studies. It will be phased, firstly in Ovid Medline, using a combination of index terms and keywords around Down syndrome, Trisomy 21, AND [autism. mp. or exp Autistic Disorder/ OR exp Asperger Syndrome/ or exp Autistic Disorder/ or exp Child Development Disorders, Pervasive/ or pervasive developmental disorder. mp. Or exp Developmental Disabilities/]. An initial limited search of Ovid Medline, Embase and PsychINFO was undertaken to identify articles on the topic (Appendix I). There were no previous similar reviews. The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles from this limited search will then be used to develop a more refined full search strategy in the second phase for MEDLINE, Embase, PsychINFO, Scopus and CINAHL. The search strategy, including all identified keywords and index terms, will be adapted for each included information source.

Study selection

EndNote X9 will be used for citation collation. Duplicates will be removed manually. Covidence will be used for screening by two independent reviewers. Disagreements will be resolved through a third reviewer.

Data extraction and analysis

Two reviewers (RB and JS) independently will screen the titles and abstracts of all the potentially relevant studies. At this stage, the search will purposely be broad to allow for the inclusion of all potentially relevant studies. Publications meeting the inclusion criteria will have a full-text review to validate their eligibility. Each article will be assessed independently by (RB and JS). A third author (PC) will review all studies that met the inclusion criteria at this stage will be reviewed by a third author (PC) to ensure appropriateness for inclusion in the final analysis. Disagreements of eligibility will be reconciled by discussion and review with the rest of the authors to ensure appropriateness for inclusion in the final analysis. The extraction will be done after full-text screening using a data extraction tool developed by the reviewers.

A standardized data abstraction form will be used to enter the study-related variables (Appendix II). The data extracted from the identified studies will include specific details about the population, concept and context. Two tables will be generated with the first table having information on the key characteristics of each study, including author, year of publication, geographical setting, type of study, demographics of the participants, the period over which the study was conducted, the method of identification or diagnosis of ASD, age at which participants were assessed and the tools used for diagnosis in the studies (Table 4, Appendix II). The second table will have information on the key findings such as the age at which ASD was diagnosed, the prevalence of ASD based on diagnostic tools and limitations of the studies (Table 5, Appendix II).

Excluded studies closely meeting the inclusion criteria will be included in a separate table as they may contain many elements of our inclusion criteria but not present the specific criteria of our interest separately. Further investigation of their data may provide significant results. The authors will be contacted to access additional information and reassess the eligibility of these studies. Excluded studies will be documented with reasons for their exclusion.

As the process evolves, the data extraction form may require modification to ensure all relevant information is included. Additionally, the critical appraisal tool for JBI (62) will help identify differences and similarities between the included studies. The answers to the JBI critical appraisal tool will be detailed in Table 6, Appendix II).

We will use random-effects models for meta-analysis and subgroup analysis. If the I^2 value is less than 50%, a pooled estimate will be generated in the form of a forest plot.

Risk of bias assessment of included studies

The risk of bias will be assessed by two reviewers (RB and JS), using the quality assessment tool for prevalence studies from the Joanna Briggs Institute (Appendix III) using the following criteria: (1) Was the sample frame appropriate to address the target population? (2) Was the study population sampled appropriately? (3) Was the sample size adequate? (4) Were the study subjects and settings described in detail? (5) Was the data analysis conducted with sufficient coverage of the identified sample? (6) Were

valid methods used for identification of the condition? (7) Was the condition measured in a standard, reliable way for all the participants? (8) Was there appropriate statistical analysis? (9) Was the response rate adequate, and if not, was the low response rate managed appropriately? The criteria were rated as either yes, no, not clear, or not applicable. We will use a scoring system to rate the risk of bias. Scores will be assigned as “1” if answered with “Yes” and scored “0” if answered with “no” or “not clear.” Studies will be rated as high, moderate, and low risk of bias when quality is scored 0–3, 4–6, and 7–8 respectively. Cross-checking of the assessments will be done by a third reviewer (PTC), and disagreements will be resolved.When necessary, authors of the included studies will be contacted, requesting additional information from their studies. The answers to this will be detailed in an additional table in the main manuscript (62).

Data synthesis

If the studies are comparable in terms of their PICO elements especially where it relates to the diagnosis of ASD (homogenous), and the heterogeneity is low, then we will pool studies in a quantitative analysis in a meta-analysis. If the studies vary too much in their PICO elements, then we will only describe them narratively and in tables, to aid in data presentation. Stata will be used.

We will use random effects model for the meta-analysis and subgroup analysis. If I^2 value is less than 50%, a pooled estimate will be generated in form of a forest plot. .

Analysis of subgroups or subsets

We will conduct a sensitivity analysis of different types of participants by age, region, decade of study, type of study and medical co-morbidities, especially infantile spasm, obstructive sleep apnea and congenital heart disease, in order to test the robustness of our meta-analytic findings. Moreover, we will conduct a sensitivity analysis of studies categorized as having a high risk of bias (RoB). We will exclude studies on high risk of bias to estimate their impact on the overall pooled prevalence estimates, and how robust our pooled estimates are.

Discussion

A diagnostic dilemma occurs when ASD is present in the face of DS. Determining the contribution of symptoms related to ID and/or ASD remains challenging. Autism spectrum disorder is present in individuals with DS, and early recognition is important in improving functional outcomes in an already neurodevelopmentally complex individual. The best tools for screening and determining a dual diagnosis of DS-ASD are not yet determined in current literature. As such, the true prevalence is unclear. This systematic review will look at the current literature in an attempt to more accurately determine the prevalence of the dual diagnosis of DS-ASD.

The strengths and limitations of our study and the effect of these on the credibility of our results will be detailed. The areas identified for future research in this area will be highlighted.

PROTOCOL AMENDMENTS

Necessary amendments to the protocol will be reported with the results of the review.

WHAT THIS STUDY WILL ADD

This study will examine the scope of the literature with respect to the prevalence of ASD in DS. Assessment of the extent of the knowledge on this topic seems to have not previously been done. Including a critical appraisal of the available relevant literature will facilitate an appreciation of the quality of the existing knowledge in this area. It will, therefore, identify gaps in the research, especially in the early identification of the dual diagnosis of DS-ASD.

Abbreviations

3di, Developmental Dimensional and Diagnostic Interview; ADDC, Autistic Disorders Diagnostic Checklist; ADI-R, Autism Diagnostic Interview – Revised; ADOS-G, Autism Diagnostic Observation Schedule – Generic; A-PL-ADOS, Pre-linguistic ADOS; ASD, Autism spectrum disorder; ASQ, Autism Screening Questionnaire; ASS-Q, Asperger Syndrome Screening Questionnaire; CARS, Childhood Autism Rating Scale; CSBS-DPDS, Communication and Symbolic Behavior Scales Developmental Profile; DBC-ASA, Developmental Behaviour Checklist-Autism Screening Algorithm; DBC-ES, Developmental Behavior Checklist-Early Screen; DISCO, Diagnostic Interview for Social and Communication Disorder; Down syndrome; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSMIG, DS, Down Syndrome; Down Syndrome Medical Interest Group; GARS-2, Gilliam Autism Rating Scale – Second Edition; HBS, Handicaps, Behaviours and Skills Schedule; ICD-10, International Classification of Diseases-10; ID, Intellectual disability; JBI, Joanna Briggs Institute; M-CHAT, Modified Checklist for Autism in Toddlers – Revised; PEDS, Parents' Evaluation of Developmental Status; POSI, Parent's Observations of Social Interactions; PCC, Population, Concept, Context; PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols (PRISMA-P) guidelines; RITA-T, Rapid Interactive Screening Test for Autism in Toddlers; SCQ, Social Communication Questionnaire; SRS, Social Responsiveness Scale; STAT, Screening Tool for Autism in Toddlers and Young Children.

Declarations

Ethics approval and consent to participate

Ethical approval will not be required as this is a systematic review of the literature and will not contain information directly identifying patients or content requiring patient consent.

Consent for publication

Not applicable

Availability of data and materials

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study. Materials during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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There is no funding for this review.

Authors' contributions

First author: Judy Seesahai (JS). Contributions: Substantial contributions to research design, acquisition, analysis and interpretation of data, and drafting the paper.

Second author: Paige Terrien Church (PC). Contributions: Substantial contributions to research design, analysis and interpretation of data, and reviewing the paper.

Lina Patel (LP). Contributions: Contribution to acquisition, analysis and interpretation of data and involved in revisions to the paper.

Thomas Rotter (TR). Contributions: Substantial contributions to research design and reviewing of the paper.

Elizabeth Asztalos (EA). Contribution: Substantial contributions to research design, analysis and interpretation of data, and reviewing the paper.

Henry Lam (HL). Contribution: librarians that assisted with this research project from the Sunnybrook R. Ian MacDonald Library. Finding full-text articles, the team was not able to find and update the search as needed.

Brian D Belden (BB). Contributions: Contribution to acquisition, analysis and interpretation of data as well as involved in revisions to the paper.

Principal Investigator and Corresponding Author: Rudaina Banihani (RB). Contributions: Substantial contributions to research design, acquisition, analysis and interpretation of data, and drafting the paper.

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References

1. Edition F, Diagnostic and statistical manual of mental disorders. Am Psychiatric Assoc, 2013. 21. 2013.
2. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, et al. Global prevalence of autism and other pervasive developmental disorders. Autism Res. 2012;5(3):160–79.
3. Community Report on Autism. A Snapshot of Autism Spectrum Disorder among 8-year-old Children in Multiple Communities across the United States in 2016. National Center on Birth Defects and Developmental Disabilities, Centres for Disease Control and Prevention, Network AaDDMA; 2020.
4. Marianna Ofner AC, Decou ML, Minh T, Do A, Bienek. Judy Snider, and Anne-Marie Ugnat. In: Autism Spectrum Disorder Among Children and Youth in Canada 2018. Ottawa: Public Health Agency of Canada; March 2018.
5. Moss J, Howlin P. Autism spectrum disorders in genetic syndromes: implications for diagnosis, intervention and understanding the wider autism spectrum disorder population. J Intellect Disabil Res. 2009;53(10):852–73.
6. Mai CT, Isenburg JL, Canfield MA, Meyer RE, Correa A, Alverson CJ, et al. National population-based estimates for major birth defects, 2010–2014. Birth defects research. 2019;111(18):1420–35.
7. Rauch A, Hoyer J, Guth S, Zweier C, Kraus C, Becker C, et al. Diagnostic yield of various genetic approaches in patients with unexplained developmental delay or mental retardation. American Journal of Medical Genetics Part A. 2006;140A(19):2063–74.
8. Capone GT, Grados MA, Kaufmann WE, Bernad-Ripoll S, Jewell A. Down syndrome and comorbid autism-spectrum disorder: Characterization using the aberrant behavior checklist. American Journal of Medical Genetics Part A. 2005;134A(4):373–80.
9. Rasmussen P, Börjesson O, Wentz E, Gillberg C. Autistic disorders in Down syndrome: background factors and clinical correlates. Developmental Medicine Child Neurology. 2001;43(11):750–4.
10. Reilly C. Autism spectrum disorders in Down syndrome: A review. Research in autism spectrum disorders. 2009;3(4):829–39.
11. Randall M, Egberts KJ, Samtani A, Scholten RJPM, Hooft L, Livingstone N, et al. Diagnostic tests for autism spectrum disorder (ASD) in preschool children. Cochrane database of systematic reviews. 2018;2018(7):CD009044-CD.
12. Falkmer T, Anderson K, Falkmer M, Horlin C. Diagnostic procedures in autism spectrum disorders: a systematic literature review. Eur Child Adolesc Psychiatry. 2013;22(6):329–40.
13. Buckley S. Autism and Down syndrome. Down Syndrome News and Update; 2005.

14. Dunst CJ, Rheingrover RM. STRUCTURAL CHARACTERISTICS OF SENSORIMOTOR, DEVELOPMENT AMONG DOWN'S SYNDROME INFANTS. Journal of intellectual disability research. 1983;27(1):11–22.
15. Koo BKK, Blaser S, Harwood-Nash D, Becker LE, Murphy EG. Magnetic Resonance Imaging Evaluation of Delayed Myelination in Down Syndrome: A Case Report and Review of the Literature. J Child Neurol. 1992;7(4):417–21.
16. Chapman RS, Hesketh LJ, Kistler DJ. Predicting Longitudinal Change in Language Production and Comprehension in Individuals With Down Syndrome: Hierarchical Linear Modeling. Journal of speech language hearing research. 2002;45(5):902–15.
17. Wishart JG. Cognitive abilities in children with Down syndrome: developmental instability and motivational deficits. Prog Clin Biol Res. 1995;393:57–91.
18. Association AP. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition ed. Arlington, VA: American Psychiatric Association Publishing; 2013.
19. Avlund SH, Thomsen PH, Schendel D, Jørgensen M, Carlsen AH, Clausen L. Factors Associated with a Delayed Autism Spectrum Disorder Diagnosis in Children Previously Assessed on Suspicion of Autism. Journal of Autism and Developmental Disorders. 2021.
20. Bradley EA, Hollins S. Chapter 17 - Assessment of Patients with Intellectual Disabilities. p. 235-53.
21. Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord. 2000;30(3):205–23.
22. Metcalfe D, McKenzie K, McCarty K, Murray G. Screening tools for autism spectrum disorder, used with people with an intellectual disability: A systematic review. Research in Autism Spectrum Disorders. 2020;74:101549.
23. Hepburn S, Philofsky A, Fidler DJ, Rogers S. Autism symptoms in toddlers with Down syndrome: a descriptive study. Journal of applied research in intellectual disabilities. 2008;21(1):48–57.
24. Ghaziuddin M, Mountain-Kimchi K. Defining the Intellectual Profile of Asperger Syndrome: Comparison with High-Functioning Autism. J Autism Dev Disord. 2004;34(3):279–84.
25. Lowenthal R, Paula CS, Schwartzman JS, Brunoni D, Mercadante MT. Prevalence of Pervasive Developmental Disorder in Down's Syndrome. J Autism Dev Disord. 2007;37(7):1394–5.
26. Kent L, Evans J, Paul M, Sharp M. Comorbidity of autistic spectrum disorders in children with Down syndrome. Developmental Medicine Child Neurology. 1999;41(3):153–8.
27. Diguiseppi C, Hepburn S, Davis JM, Fidler DJ, Hartway S, Raitano Lee N, et al. Screening for Autism Spectrum Disorders in Children With Down Syndrome: Population Prevalence and Screening Test Characteristics. Journal of developmental behavioral pediatrics. 2010;31(3):181–91.
28. Warner G, Moss J, Smith P, Howlin P. Autism Characteristics and Behavioural Disturbances in ~ 500 Children with Down's Syndrome in England and Wales. Autism Res. 2014;7(4):433–41.
29. Oxelgren UW, Myrelid Å, Annerén G, Ekstam B, Göransson C, Holmbom A, et al. Prevalence of autism and attention-deficit–hyperactivity disorder in Down syndrome: a population-based study. Developmental Medicine Child Neurology. 2017;59(3):276–83.
30. Richards CD, Jones CCP, Groves LB, Moss JP, Oliver CP. Prevalence of autism spectrum disorder phenomenology in genetic disorders: a systematic review and meta-analysis. The Lancet Psychiatry. 2015;2(10):909–16.
31. Snow A. Social Communication Questionnaire. In: Volkmar FR, editor. Encyclopedia of Autism Spectrum Disorders. New York: Springer New York; 2013. pp. 2893–5.
32. de Jonge M, Handicaps. Behavior and Skills Schedule (HBSS). Cham: Springer International Publishing; 2021. pp. 2303–5.
33. Robins DL. Modified Checklist for Autism in Toddlers, Revised with Follow-Up [.
34. Ehlers S, Gillberg C, Wing L. A Screening Questionnaire for Asperger Syndrome and Other High-Functioning Autism Spectrum Disorders in School Age Children. J Autism Dev Disord. 1999;29(2):129–41.
35. Harrigan S. Diagnosing mental disorders: DSM-5 and ICD-10. Diagnostic criteria. San Luis Obispo: Classroom Productions; 2015.

36. Dilavore PC, Lord C, Rutter M. The Pre-Linguistic Autism Diagnostic Observation Schedule. J Autism Dev Disord. 1995;25(4):355–79.
37. Ward R, Sanoudaki E. Bilingualism in children with a dual diagnosis of Down syndrome and Autism Spectrum Disorder. Clin Linguist Phon. 2020:1–27.
38. Versaci TM, Mattie LJ, Imming LJ. Down Syndrome and Autism Spectrum Disorder Dual Diagnosis: Important Considerations for Speech-Language Pathologists. Am J Speech Lang Pathol. 2020:1–13.
39. Kirchner RM, Walton KM. Symptoms of Autism Spectrum Disorder in Children With Down Syndrome and Williams Syndrome. American Journal on Intellectual Developmental Disabilities. 2020;126(1):58–74.
40. Hamner T, Hepburn S, Zhang F, Fidler D, Robinson Rosenberg C, Robins DL, et al. Cognitive Profiles and Autism Symptoms in Comorbid Down Syndrome and Autism Spectrum Disorder. J Dev Behav Pediatr. 2020;41(3):172–9.
41. Hahn LJ, Hamrick LM, Kelleher BL, Roberts JE. Autism Spectrum Disorder-Associated Behaviour in Infants with Down Syndrome. J Health Sci Educ. 2020;4(2).
42. Horlin C, Falkmer M, Parsons R, Albrecht MA, Falkmer T. The cost of autism spectrum disorders. PloS one. 2014;9(9):e106552-e.
43. Zwaigenbaum L, Bauman ML, Fein D, Pierce K, Buie T, Davis PA, et al. Early Screening of Autism Spectrum Disorder: Recommendations for Practice and Research. Pediatrics. 2015;136(Suppl 1(Supplement):41–59.
44. Koegel LK, Koegel RL, Ashbaugh K, Bradshaw J. The importance of early identification and intervention for children with or at risk for autism spectrum disorders. International journal of speech language pathology. 2014;16(1):50–6.
45. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, et al. Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model. PEDIATRICS. 2010;125(1):e17–23.
46. Rogers SJPD, Estes APD, Lord CPD, Vismara LPD, Winter JPD, Fitzpatrick APD, et al. Effects of a Brief Early Start Denver Model (ESDM)–Based Parent Intervention on Toddlers at Risk for Autism Spectrum Disorders: A Randomized Controlled Trial. J Am Acad Child Adolesc Psychiatry. 2012;51(10):1052–65.
47. Zachor DA, Ben Itzchak E. Treatment approach, autism severity and intervention outcomes in young children. Research in autism spectrum disorders. 2010;4(3):425–32.
48. Grzadzinski R, Janvier D, Kim SH. Recent Developments in Treatment Outcome Measures for Young Children With Autism Spectrum Disorder (ASD). Seminars in pediatric neurology. 2020;34:100806-.
49. Susan F. Down Syndrome Resource Foundationn.s. [cited 2021]. Available from: https://www.dsrf.org/blog/putting-the-pieces-together–the-down-syndrome-autism-connection.
50. Munn Zachary MS, Karolina L, Dagmara R, Tufanaru Catalin. Systematic reviews of prevalence and incidence. 2020. In: JBI Manual for Evidence Synthesis, JBI [Internet].
51. Borges Migliavaca C, Stein C, Colpani V, Barker TH, Munn Z, Falavigna M. How are systematic reviews of prevalence conducted? A methodological study. BMC medical research methodology. 2020;20(1):96-.
52. Fletcher GS, Fletcher RH. Clinical epidemiology: the essentials. 6th ed. ed. Philadelphia: Lippincott Williams & Wilkins/Wolters Kluwer; 2021.
53. Stone WL, Coonrod EE, Ousley OY. Brief report: screening tool for autism in two-year-olds (STAT): development and preliminary data. J Autism Dev Disord. 2000;30(6):607–12.
54. Wetherby AM, Brosnan-Maddox S, Peace V, Newton L. Validation of the Infant-Toddler Checklist as a broadband screener for autism spectrum disorders from 9 to 24 months of age. Autism. 2008;12(5):487–511.
55. Glascoe FPRN. Parents' Evaluation of Developmental Status (PEDS)2006 August 26, 2021.
56. Lipkin PH, Macias MM. Promoting Optimal Development: Identifying Infants and Young Children With Developmental Disorders Through Developmental Surveillance and Screening. Pediatrics. 2020;145(1).
57. Singh A, Yeh CJ, Boone Blanchard S. Ages and Stages Questionnaire: a global screening scale. Bol Med Hosp Infant Mex. 2017;74(1):5–12.
58. Brereton AV, Tonge BJ, Mackinnon AJ, Einfeld SL. Screening young people for autism with the developmental behavior checklist. J Am Acad Child Adolesc Psychiatry. 2002;41(11):1369–75.

59. Gray KM, Tonge BJ. Screening for autism in infants and preschool children with developmental delay. Aust N Z J Psychiatry. 2005;39(5):378–86.
60. Choueiri R, Wagner S. A New Interactive Screening Test for Autism Spectrum Disorders in Toddlers. J Pediatr. 2015;167(2):460–6.
61. Constantino JN, Davis SA, Todd RD, Schindler MK, Gross MM, Brophy SL, et al. Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. J Autism Dev Disord. 2003;33(4):427–33.
62. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc. 2015;13(3):147–53.

Figures

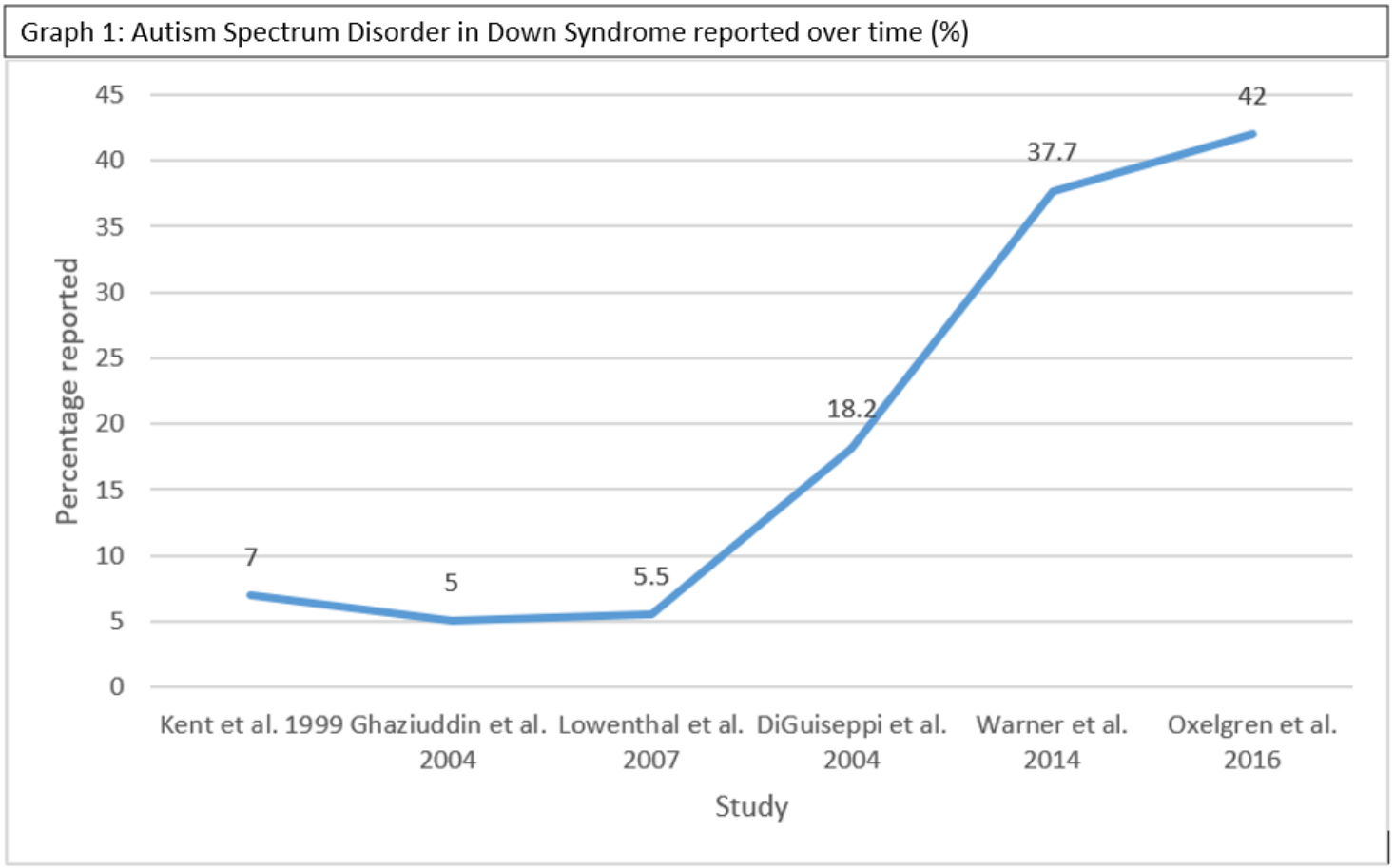

Figure 1

Please See image above for figure legend.

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