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Review

# Umbrella systematic review of systematic reviews and meta-analyses on comorbid physical conditions in people with autism spectrum disorder

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**Background**

Comorbid physical conditions may be more common in people with autism spectrum disorder (ASD) than other people.

**Aims**

To identify what is and what is not known about comorbid physical conditions in people with ASD.

**Method**

We undertook an umbrella systematic review of systematic reviews and meta-analyses on comorbid physical conditions in people with ASD. Five databases were searched. There were strict inclusion/exclusion criteria. We undertook double reviewing for eligibility, systematic data extraction and quality assessment. Prospective PROSPERO registration: CRD42015020896.

**Results**

In total, 24 of 5552 retrieved articles were included, 15 on children, 1 on adults, and 8 both on children and adults. Although the quality of included reviews was good, most reported several limitations in the studies they included and considerable heterogeneity. Comorbid physical conditions are common, and some are more prevalent than in the general population: sleep problems, epilepsy, sensory impairments, atopy, autoimmune disorders and obesity. Asthma is not. However, there are substantial gaps in the evidence base. Fewer studies have been undertaken on other conditions and some findings are inconsistent.

**Conclusions**

Comorbid physical conditions occur more commonly in people with ASD, but the evidence base is slim and more research is needed. Some comorbidities compound care if clinicians are unaware, for example sensory impairments, given the communication needs of people with ASD. Others, such as obesity, can lead to an array of other conditions, disadvantages and early mortality. It is essential that potentially modifiable physical conditions are identified to ensure people with ASD achieve their best outcomes. Heightening clinicians' awareness is important to aid in assessments and differential diagnoses, and to improve healthcare.

**Keywords**

Autism spectrum disorders; systematic review; comorbidity; physical conditions; health.



## Background

In recent years there has been a growing awareness of the comorbidity experienced by people with autism spectrum disorder (ASD), particularly regarding psychiatric conditions. (Throughout this report we used the term 'comorbid/ity', which we consider to be synonymous with the alternative terms of 'co-occurring', or 'coexisting.) An umbrella review of psychiatric conditions in people with ASD published in 2020 found a very high burden of comorbidity across several conditions, reported in 26 systematic reviews and meta-analyses.[1] Physical conditions in people with ASD have received lesser research attention. An article in 2011 reported an urgent need for research in this area because of limited literature but probably greater comorbidity than in other people.[2]

Two reviews in 2013 commented that research into comorbidity in people with ASD was of recent origin, and much more was needed.[3,4] A scope of the literature in 2018 reported that people with ASD have high rates of physical comorbidity, but findings were based on few studies.[5] Since then, further studies and systematic reviews have been published, although this field of research is still relatively underdeveloped. Comorbid physical conditions can significantly affect quality of life, so it is important that practitioners and carers are aware of commonly occurring conditions to raise their index of suspicion and address differential diagnosis, thus resulting in earlier detection and, therefore, treatment, care and better outcomes.

## Aims

The aim of our study was to identify what is and what is not known about comorbid physical conditions in people with ASD, through undertaking an umbrella systematic review of systematic reviews and meta-analyses (as these synthesise existing studies, resulting in a pooling of knowledge that is more exhaustive than that contained in single studies).[6] Our aims were designed to be of clinical relevance, not to delineate aetiology. The specific research questions were:

(a) How common are comorbid physical conditions in people with ASD?
(b) Are specific comorbid physical conditions more prevalent in people with ASD than in the general population?
(c) Are there gaps in the evidence base on comorbid physical conditions in people with ASD?

## Method

This review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42015020896).



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### Literature sources

A systematic search strategy was used to identify existing systematic reviews and meta-analyses relating to comorbid physical conditions in people with ASD. The search was conducted through five databases: PsycINFO, CINAHL, Medline, Embase and Cochrane databases. The search was performed on the 21 August 2019. No time limits were applied; all years of literature were searched. The search was limited to publications in English.

### Search terms

A combination of the following search terms was used for PsycINFO, CINAHL, Medline and Embase databases:

(a) 1. 'autis*' AND 'systematic review'
(b) 2. 'autis*' AND 'meta-analysis'
(c) 3. 'pervasive developmental disorder' AND 'systematic review'
(d) 4. 'pervasive developmental disorder' AND 'meta-analysis'
(e) 5. 'Asperger*' AND 'systematic review'
(f) 6. 'Asperger*' AND 'meta-analysis'
(g) 7. 'ASD' AND 'systematic review'
(h) 8. 'ASD' AND 'meta-analysis'
(i) 9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8

### Inclusion criteria

(a) ASD.
(b) All ages.
(c) Comorbid physical condition(s).
(d) Systematic review or meta-analysis of peer-reviewed research.
(e) For reviews which include people both with and without ASD, results for people with ASD are presented separately, and/or >50% of the total sample have ASD.
(f) English language.

### Exclusion criteria

(a) Non-human studies.
(b) Brain-imaging studies.
(c) Genetic studies on syndromes.
(d) Studies on symptoms of ASD.
(e) Treatment studies of comorbid physical conditions.
(f) Reviews assessed as low quality using a quality assessment tool.

### Procedures

Papers were selected if they met the predefined inclusion criteria. Papers were initially screened for suitability based on their title and abstract, and then candidate papers were read in full. A second reviewer also read a random 10% of titles and abstracts to ensure the selection approach was systematic. Any discrepancies were planned to be resolved through discussion. Two authors then read the full text of the potentially eligible studies to assess their eligibility. Using a structured database, data were then extracted from the selected review papers on the number and type of studies included in the review, size of studies, population types, definition of ASD, study designs, comparison groups, co-occurring physical conditions included and their definitions, findings and the quality of the review. Additional hand searches were performed to check for relevant reviews or meta-analyses in the references cited in the selected articles.

The Joanna Briggs Institute checklist for systematic reviews and research synthesis was used to assess quality.[6] It includes 11 items on: explicit statement of the research question, use of inclusion criteria, appropriateness of search strategy, adequacy of the sources and resources to search, criteria for appraising studies, double assessment, methods to minimise errors in data extraction, appropriateness of methods to combine studies, assessment of publication bias, whether policy and/or practice recommendations are supported by the data, and whether directions for new research are appropriate. We categorised studies as low, medium, or high quality if they received a score of 0–5, 6–8 and 9–11, respectively. Reviews that were of low quality on this measure were then excluded. The authors discussed together the quality assessment findings to reach agreement.

## Results

Figure 1 summarises the number of reviews included/excluded at each stage. The search returned 5552 records, of which 223 papers were identified to be read in full. There were no disagreements between the first and second reviewer.

The 223 papers were carefully read and classified as either meeting or not meeting inclusion criteria. This resulted in 27 articles selected for data extraction. In general, the quality of the reviews was good. Sixteen studies were assessed as high quality, 8 as medium and 3 were assessed as low quality and excluded from the umbrella review, resulting in 24 studies being the final number selected for inclusion in the review.[7–30] The most commonly noted omissions related to quality assessment, publication bias and methods used to minimise errors in data extraction. The 24 reviews included 12 meta-analyses and 12 systematic reviews without meta-analysis. The reviews are summarised in Tables 1–4.

Of the 24 included reviews, 6 were on sleep;[10–15] 3 on sensory impairments (not sensory sensitivities; 1 on peripheral hearing loss,[18] 1 on visual impairment,[19] and 1 on visual or hearing impairment[20]); 3 on epilepsy;[7–9] 3 on oral health;[21–23] 1 on asthma[26] and 1 on allergic asthma;[27] 1 each on diabetes,[16] gastro-intestinal conditions,[17] atopic dermatitis,[24] autoimmune disease,[25] obesity,[28] incontinence;[29] and 1 review on 5 conditions – immunological, gastro-intestinal, incontinence, epilepsy and hypospadias.[30] Fifteen studies were on children and young people,[11,13,14,16–27] 8 were on children, young people and adults,[7–9,12,15,28–30] and 1 study was on adults only.[10]

Although the quality of the included reviews was good, most, in their own quality assessments, reported several limitations in the papers they included, and also considerable heterogeneity that precluded meta-analysis for several of the reviews. Studies drew their samples from a range of settings, including several reliant on clinical populations, making comparisons difficult. There were also inconsistent findings reported between studies in some of the reviews, hence there is uncertainty in some of the conclusions that can be drawn. Additionally, as Tables 1–4 show, prevalences with confidence intervals, and odds ratios in comparison with the general population were often not reported nor possible to synthesise. Recognising these limitations, our results suggest that answers to our research questions are as follows.

### How common are comorbid physical conditions in people with ASD?

Comorbid physical conditions are common in people with ASD. None of the studies enabled us to say how common physical comorbidities are overall, as the reviews studied specific conditions, or in one review five types of conditions (i.e. a limited number of conditions). We did not identify any systematic reviews on overall comorbidity or multimorbidity in people with ASD.

### Are specific comorbid physical conditions more prevalent in people with ASD than in the general population?

Some specific comorbid physical conditions are more prevalent in people with ASD than in the general population.



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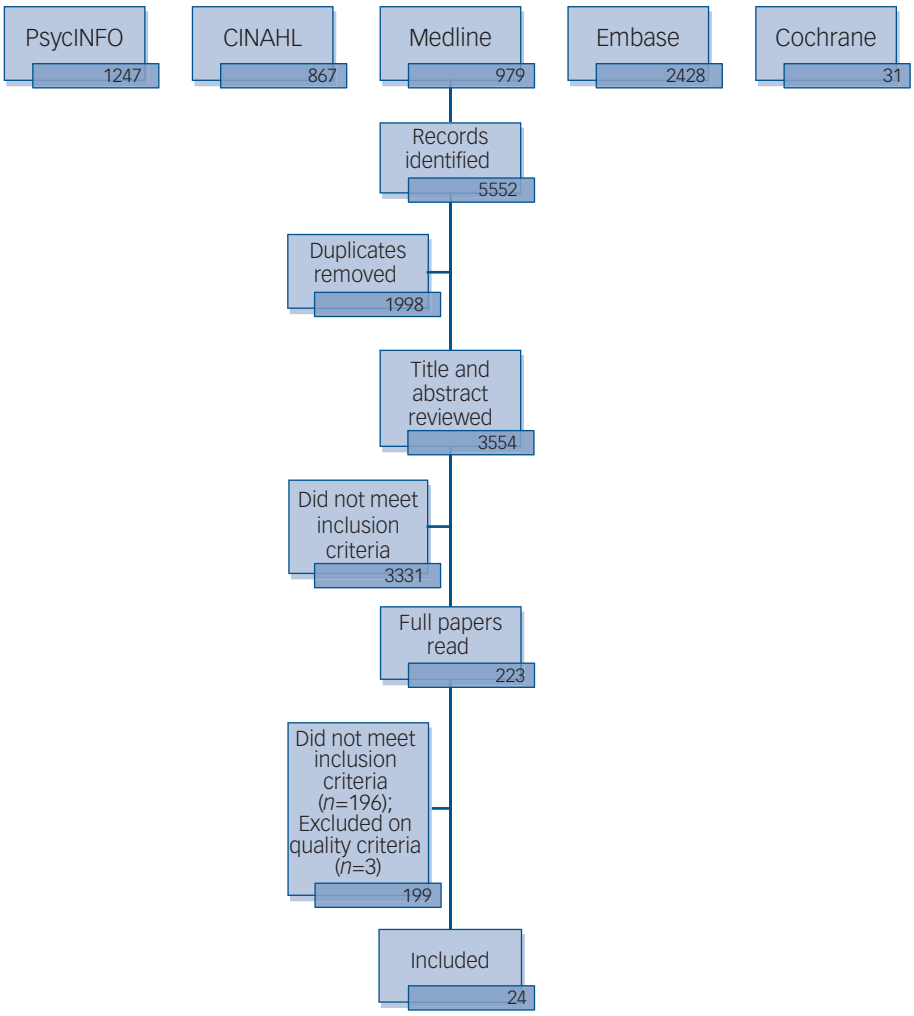


**Fig. 1** Study selection process.

(a) Sleep problems are more common in people with ASD than other people, with some of this attributable to co-occurring intellectual disabilities.[10–15] There are some inconsistencies in findings, for example regarding any differences in sleep quality and sleep efficiency.[10,14,15] The sleep studies included objective measures of sleep in people with ASD, and additionally most also considered sleep in relation to some or all of physical, psychiatric, behavioural, other neurodevelopmental, and intellectual abilities/conditions, and medication,[10–14] or excluded these.[15]

(b) Epilepsy is common.[7–9,30] The reviews did not report a comparison with the general population (with the exception of one, which included only a single study on epilepsy),[30] but the estimated pooled prevalences are higher than those previously reported in the general population. Prevalence varies depending upon co-occurring intellectual disabilities, age and aetiology of epilepsy.[7–9] Epilepsy is more common in females with ASD than males with ASD.[9]

(c) Self-inflicted oral soft tissue injury is more common in people with ASD than the general population.[21] Dental caries are common, but results are inconsistent as to whether they are more common than in the general population, and on comparisons of dental treatment for caries.[21–23]

(d) Findings on peripheral hearing loss are inconsistent.[18] Among people with hearing impairment, the relative risk of ASD was high.[20]

(e) Refractive errors are common but no different to the general population, whereas strabismus may be higher than for the general population.[19] Among people with visual impairment, the relative risk of ASD was very high.[20]

(f) Diarrhoea, constipation, and abdominal pain appear to be reported more for children with ASD than for their siblings or general population, although there is some inconsistency.[17,30] Hernia was the only gastrointestinal condition reported to be more common in one of the studies.[30]

(g) Rates of ASD are higher in people with atopic dermatitis, and people with atopic dermatitis plus allergic rhinitis, than in people who do not have these conditions. Autoimmune disease is also more common than in the general population.[24,30] Additionally, parents with autoimmune disorders (hypothyroidism, type 1 diabetes, rheumatoid arthritis, psoriasis) are at higher risk of their children having ASD, alluding to an association between these conditions and ASD.[25]

(h) Obesity is more common in people with ASD than in the general population.[28]

(i) Incontinence is more common in people with ASD than in the general population.[29,30]

(j) Hypospadias might be more common in males with ASD, but the finding relates to only one study.[30]

Conversely to the conditions above, which appear to be more common in people with ASD, asthma probably is not,[26] and in


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**Table 1** Systematic reviews and meta-analyses on epilepsy in ASD

| Topic and authors | Method, included studies, quality assessment | Participants, *n* | Population type | Comparison groups | Findings |
|---|---|---|---|---|---|
| Epilepsy (Woolfenden et al 2012)[7] | Systematic review<br>16 studies<br>Medium | *n* = 15 418 with ASD (range 39–13 111; median 100) | Mean age range 2 years 7 months to 16 years 11 months<br>Clinical samples with ASD | – | 1.8% aged <12 years with ASD without intellectual disabilities had epilepsy; 8.9% aged >12 years with ASD without intellectual disabilities had epilepsy; 6.1% aged <12 years with ASD with intellectual disabilities had epilepsy; 23.7% aged >12 years with ASD with intellectual disabilities had epilepsy<br>Quality findings: non-representative samples |
| Epilepsy (Amiet et al 2008)[8] | Meta-analysis<br>23 studies; 10/23 also report on intellectual disabilities<br>Medium | *n* = 3236 with ASD (range 16–1090; median 77)<br>*n* = 2112 with ASD and intellectual disabilities | All ages | ASD with intellectual disabilities | 21.4% epilepsy in ASD with intellectual disabilities (*n* = 1485); 8% epilepsy in ASD without intellectual disabilities (*n* = 627); 34.5% epilepsy in ASD females and 18.5% in ASD males; 2:1 male:female ratio of ASD with epilepsy; 3.5:1 male:female ratio of ASD without epilepsy<br>Quality findings: heterogeneous definition of ASD and epilepsy |
| Epilepsy (Strasser et al 2017)[9] | Systematic review<br>19 studies<br>Medium | *n* range 13–85 201 with epilepsy | Mean age 2 years 6 months to 41 years 7 months<br>Cross-sectional studies, cohort studies | – | Pooled ASD prevalence of 6.3% in epilepsy; 4.7% for general epilepsy, 19.9% for infantile spasms, 41.9% for focal seizures, 47.4% for Dravet syndrome. Risk for ASD in epilepsy 13.2 times greater in populations under 18 years than those over 18 years. Main risk factors for ASD in epilepsy were intellectual disabilities, female gender, age group, and aetiology of epilepsy<br>Quality findings: non-representative samples, heterogeneity, high or unspecified exclusions, lack of baseline characteristics, lack of information on ASD diagnosis, not reporting/taking account of other confounders, for example intellectual disabilities |

ASD, autism spectrum disorder.

antipsychotic-exposed youth, incidence of type 2 diabetes was less common than in those without ASD.[16]

### Are there gaps in the evidence base on comorbid physical conditions in people with ASD?

There are substantial gaps in the evidence base on comorbid physical conditions in people with ASD. There is good evidence that sleep problems, epilepsy, sensory impairments, atopy, autoimmune conditions and obesity are common, more so than in the general population, despite some inconsistencies in findings. However, it is harder to draw conclusions on other conditions, because of fewer studies having been undertaken, and inconsistency in their findings. The results point to considerable comorbidity in several areas, but further research is needed. There were no systematic reviews that met our criteria in some areas, such as cardiovascular conditions, cancers, neurological conditions apart from epilepsy, and musculoskeletal conditions.

## Discussion

### Principal findings and interpretation

Our study has demonstrated that comorbid physical conditions are common in people with ASD. The study is important as its design enabled coverage of a wide range of physical conditions. There is evidence to suggest that people with ASD experience health inequalities compared with the general population, including higher rates of sleep problems, epilepsy, sensory impairments, atopy, autoimmune disorders and obesity, and probably also other conditions that have been studied to a lesser extent. However, evidence is limited regarding other conditions, and has inconsistencies in findings and methodological differences. There are also few studies on some conditions. As far as our umbrella review identified, some areas have not been systematically reviewed at all, such as cardiovascular conditions, cancers, neurological conditions apart from epilepsy and musculoskeletal conditions. We therefore conclude that comorbidity is common in people with ASD, but there remain considerable gaps in the evidence base. Information about the comorbid physical health of people with ASD is important in order to heighten awareness for clinicians to aid in their assessments and differential diagnoses, especially because of the added complexity of such assessments with people with ASD given their communication needs.

While we identified a number of systematic reviews and meta-analyses on comorbid physical conditions in people with ASD, and the quality of the reviews was good, they highlighted that the quality of many of the individual studies they included was limited. This included studies of small or highly selected samples, and with no power considerations. Detailed information on the samples' recruitment was often not comprehensive or was lacking. In some cases, inconsistent results were reported as a result of varying study designs, different source populations and participant characteristics, as well as small samples. Some studies had unclear statistical methods or inclusion criteria. Some studies did not discuss how ASD and its comorbid physical conditions were assessed and operationalised. Reported prevalence rates varied considerably between studies because of different methodological designs and limitations.

Our umbrella systematic review does not include single studies that have not previously been subject to a systematic review. This does not devalue such studies, but highlights



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**Table 2** Systematic reviews and meta-analyses on sleep in ASD

| Topic and authors | Method, included studies, quality assessment | Participants, *n* | Population type | Comparison groups | Findings |
|---|---|---|---|---|---|
| Sleep problems in intellectual disabilities (van de Wouw et al 2012)[10] | Systematic review<br>3/50 studies reported on ASD<br>High | *n* = 259 with ASD (range 14–168; median 77) | 16–88 years with ASD, all levels of intellectual disabilities<br>Cross-sectional studies | Adults with intellectual disabilities without ASD | 1 study reported 44.7% of intellectual disabilities with ASD experienced sleep problems; 2 studies reported no difference in sleep problems or sleep quality between intellectual disabilities with ASD and intellectual disabilities without ASD; 1 study reported more sleep difficulties in intellectual disabilities with ASD compared with intellectual disabilities without ASD<br>Quality findings:<br>(a) Prevalence – well-conducted with very low risk of bias<br>(b) Associated factors – 1 high quality study, 2 with low risk of bias; no information on ASD diagnosis |
| Sleep problems (Elrod and Hood, 2015)[11] | Meta-analysis<br>10 studies<br>High | *n* = 333 with ASD (range 8–68; median 25.5) | Children<br>Specialty clinics studies | Typically developing controls | 45 min pooled difference in mean total sleep time between ASD with intellectual disabilities and typically developing, but –7.3 min difference between ASD and typically developing when intellectual disabilities were excluded. Increase in difference in mean sleep latency as age increased<br>Sleep efficiency was poorer with psychotropics and age<br>Quality findings: small samples |
| Sleep problems (Baglioni et al 2016)[12] | Meta-analysis<br>3 studies on Asperger syndrome<br>7 studies on autistic disorder<br>High | *n* = 34 with Asperger syndrome<br>*n* = 103 with autistic disorder | <18 years with Asperger syndrome in 2 studies; 18–60 years with Asperger syndrome in 1 study<br><18 years with autistic disorder in 4 studies; adolescents and adults with autistic disorder in 2 studies | Typically developing controls | Diverse sleep alterations found on polysomnography. Sleep continuity disturbance, but not sleep depth was found in Asperger syndrome and autistic disorder. Reduced time in rapid eye movement in autistic disorder but not in Asperger syndrome.<br>Quality findings: small sample sizes, and small number of studies |
| Intraindividual variability of sleep/wake patterns (Becker et al 2017)[13] | Systematic review<br>3/52 studies reported on ASD<br>High | *n* range 186–194 with ASD | Children<br>Cross-sectional, and cohort studies | Typically developing and other developmental disabilities controls | Cross-sectional study: no differences in Intraindividual variability of sleep/wake patterns. No difference when also subdivided into ± ADHD<br>Longitudinal: ASD had greater duration and quality of intraindividual variability of sleep/wake patterns than typically developing children, although within-child variability was greater than between-child variability<br>Quality findings: heterogeneity, few studies, not primary findings of studies |
| Sleep problems (Diaz-Roman et al 2018)[14] | Meta-analysis<br>47 studies; subjective measures in 37 studies, objective measures in 15 studies<br>High | *n* range 75–5430 with ASD for subjective sleep parameters<br>*n* range 144–312 with ASD for objective sleep parameters | Children and youth ≤20 years<br>Case–control studies | Typically developing controls | ASD differed from typically developing controls in 10/14 subjective sleep parameters (sleep questionnaire) and in 7/14 objective sleep parameters (polysomnography, actigraphy, multiple sleep latency test). Including greater bedtime resistance, sleep anxiety, sleep-disordered breathing, parasomnias, and longer sleep latency and higher daytime sleepiness. Less consistency about total sleep time. No difference in subjectively reported sleep quality (although only 3 studies) and sleep efficiency (only 2 studies)<br>Quality findings: average quality score of 5.9/9 on the Newcastle–Ottawa Scale; heterogeneity, publication bias, most not comorbidity free or medication naive |

(*Continued*)

**Table 2** (*Continued*)

| Topic and authors | Method, included studies, quality assessment | Participants, *n* | Population type | Comparison groups | Findings |
|---|---|---|---|---|---|
| Sleep problems (Carmassi et al 2019)[15] | Systematic review<br>103 studies: 12 on circadian sleep dysrhythmicity (7 in children, 5 in adults), 74 on sleep disturbances (65 in children, 9 in adults), 17 on melatonin alteration<br>Medium | Circadian rhythmicity in children *n* range 19–198 with ASD<br>Sleep disturbance in children *n* range 8–2714 with ASD<br>Circadian rhythmicity in adults *n* range 10–41 with ASD<br>Sleep disturbance in adults *n* range 8–36 with ASD<br>Melatonin *n* range 10–398 with ASD | All ages<br>Cohort, cross-sectional or case–control studies | Typically developing controls | Sleep disturbances are frequent in ASD, especially short sleep duration, low sleep quality, low sleep efficiency and circadian sleep desynchronisation such as delayed phases and/or eveningness. Sleep disturbances and circadian sleep alteration have been related to severity of ASD symptoms. Melatonin dysregulation, including delay in melatonin peak and reduction in amplitude may contribute to sleep desynchronisation in ASD<br>Quality findings: heterogeneity of studies including diagnostic criteria, measures, psychiatric comorbidity and psychotropic drugs, small study sizes, not all had control groups |

ASD, autism spectrum disorder.

**Table 3** Systematic reviews and meta-analyses on oral health in ASD

| Topic and authors | Method, included studies, quality assessment | Participants, *n* | Population type | Comparison groups | Findings |
|---|---|---|---|---|---|
| Oral health in patients with disabilities (Bartolomé-Villar et al 2016)[21] | Systematic review<br>10 studies<br>High | *n* = 628 with ASD (range 20–135; median 55.5) | 0–18 years<br>Records from oral examination in schools, institutions or clinics; no information for 6 studies | Typically developing controls | Inconclusive findings on dental caries: 1 study reported no findings, 2 reported similar prevalence between ASD and controls, 4 reported lower incidence, and 3 higher incidence. 1 study reported 38.2% with ASD had gingival inflammation. 2 studies reported more self-inflicted injury in soft tissues and self-injurious habits in ASD. 1 study reported 60.0% with ASD needed orthodontic treatment compared with 40.0% typically developing; 1 study reported malocclusion disorders in 60.0% of ASD<br>Quality findings: no information on ASD diagnosis |
| Oral health (Da Silver et al 2016)[22] | Meta-analysis<br>7 studies: 7 on dental caries, 3 on periodontal disease<br>High | *n* range 22–483 with ASD | 2.5–21 years | – | Pooled prevalence of dental caries 60.6% (95% CI 44.0–75.1%); pooled prevalence of periodontal disease 69.4% (95% CI 47.6–85.0%)<br>Quality findings: Newcastle-Ottawa Scale scores were 9–12; 2 were rated high quality and 5 were rated medium quality, so moderate to low risk of bias |
| Dental caries (Robertson et al 2019)[23] | Meta-analysis<br>8/25 studies were on ASD; 2 studies included care index and restorative index<br>High | *n* = 737 with ASD (range 30–135; mean 92) | 3–16 years<br>Clinical examinations | Typically developing and healthy controls | No difference in caries experience; mean DMFT 1.10 *v.* 1.01 in controls. Opposite results on care index and restorative index in 2 studies<br>Quality findings: Newcastle-Ottawa Scale average score across all studies was 5.2 showing a medium to high risk of bias; 1 was high quality, 9 medium quality and 15 were low quality |

ASD, autism spectrum disorder; DMFT, decayed, missing and filled teeth index.

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**Table 4** Systematic reviews and meta-analyses on diabetes, gastro-intestinal problems, hearing, vision, dermatitis, autoimmune disease, asthma, obesity, incontinence, and other conditions in ASD

| Topic and authors | Method, included studies, quality assessment | Participants, *n* | Population type | Comparison groups | Findings |
|---|---|---|---|---|---|
| Diabetes when exposed to antipsychotics (Galling et al 2016)[16] | Meta-analysis<br>13 studies<br>High | *n* = 185 105 youth exposed to antipsychotics (range 179–107 551; median 5370) | Children and youth<br>Database of medical records, prospective cohort and case–control studies | Psychiatric controls unexposed to antipsychotics (7 studies), healthy controls (8), no controls (2) | In antipsychotic exposed youths, ASD was associated with lower incidence of type 2 diabetes mellitus than non-ASD ($P = 0.48$). Greater incidence of type 2 diabetes mellitus was associated with second-generation antipsychotics ($P \leq 0.05$)<br>Quality findings: no information on ASD diagnosis |
| Gastrointestinal problems (McElhanon et al 2014)[17] | Meta-analysis<br>15 studies<br>High | *n* = 2215 with ASD (range 33–589; median 75) | 0–18 years<br>Studies of children with known gastrointestinal diagnoses were excluded<br>Community wide (8 studies), diagnostic clinics (4 studies), other medical settings (3 studies) | Typically developing children or siblings | General gastrointestinal concerns: OR = 4.42 (95% CI 1.90–10.28); diarrhoea: OR = 3.63 (95% CI 1.82–7.23); constipation: OR = 3.86 (95% CI 2.23–6.71); abdominal pain: OR = 2.45 (95% CI 1.19–5.07)<br>Quality findings: no studies included diagnosis of gastro-intestinal problems, they relied on chart reviews or questionnaires |
| Peripheral hearing loss (Beers et al 2014)[18] | Systematic review<br>5 studies<br>Medium | *n* = 349 with ASD (range 22–199; median 37) | Children and adolescents<br>Hearing tests | Typically developing participants in 1 study | Inconsistent findings: 2 studies reported normal peripheral hearing; 2 reported possible increased peripheral hearing loss, but no prevalence estimates; 1 reported prevalence of 3.5% in 199 children and adolescents with ASD<br>Quality findings: lack of detail on sample to generalise findings |
| Visual impairment (Butchart et al 2017)[19] | Systematic review<br>7 studies<br>Medium | *n* = 1035 with ASD (range 18–324) | 1–22 years<br>6 case record reviews from screening studies; 1 screening study of children with ASD and visual impairment | Previously published literature | 22.9–32.7% had refractive errors, similar to rates in the general population (29.5% at 6–7 years and 32.3% at 12–13 years). 8.3% had strabismus, higher than rates in the general population (1.5–5.3%)<br>Quality findings: 6 studies were rated as moderate, and 1 as strong on quality. Weak findings were mostly for confounders and withdrawals. Specific points included chart reviews, lack of detail on sample selection, small sample sizes, no visual acuity testing |
| Visual or hearing impairment (Do et al 2017)[20] | Meta-analysis<br>15 studies: 8 visual impairment, 5 hearing impairment, 2 both<br>High | Unknown *n* with visual or hearing impairment | 1–18 years<br>Cross-sectional and case series, and retrospective case-note review | Previously published literature | 19% (13–25%) of visually impaired had ASD; relative risk of ASD was 31.0 times. 9% (6–12%) of hearing impaired had ASD; relative risk of ASD was 14.1 times<br>Quality findings: selection bias (clinical populations), ASD diagnosis, unclear reporting, confounding factors, heterogeneity |
| Atopic dermatitis (Billeci et al 2015)[24] | Systematic review<br>18 studies<br>High | *n* = 1 245 225 with atopic dermatitis (range 40–1 000 000; median 1955.5)<br>*n* with ASD not provided for all studies | 0–2 years<br>Case–control studies, national surveys or population studies | Typically developing and healthy controls | 1 reported 2.2% with atopic dermatitis had ASD, 0.9% without atopic dermatitis had ASD. 14 studies considered dermatitis with other atopic disorders:<br>dermatitis in 3.8–64.2% with ASD compared with 0.0–15.8% in typically developing;<br>dermatitis + allergic rhinitis in 3.0–13.3% with ASD compared with 0.0–2.5% in typically developing; dermatitis + asthma in 2.5–9.5% with ASD compared with 2.5–4.0% typically developing<br>Quality findings: no information on ASD diagnosis |
| Autoimmune disease (Wu et al 2015)[25] | Meta-analysis<br>11 studies<br>High | *n* range 102–857 014 family members | 3 cohort studies, 6 case–control studies, 2 cross-sectional studies<br>Clinical samples, register data, autism society | Family members | Family history associated with higher risk of autism in children:<br>All autoimmune diseases combined –28% (95% CI 12–48%); hypothyroidism – OR = 1.64 (95% CI 1.19–1.91); type 1 diabetes – OR = 1.49 (95% CI 1.23–1.81); rheumatoid arthritis – OR = 1.51 (95% CI 1.19–1.91); psoriasis – OR = 1.59 (95% CI 1.28–1.97)<br>Quality findings: potential publication bias for all autoimmune conditions combined, and for type 1 diabetes |

(*Continued*)

**Table 4** (*Continued*)

| Topic and authors | Method, included studies, quality assessment | Participants, *n* | Population type | Comparison groups | Findings |
|---|---|---|---|---|---|
| Asthma (Zheng et al 2016)[26] | Meta-analysis<br>10 studies<br>High | *n* = 8809/175 406 with ASD | Children<br>Case–control, cohort or cross-sectional studies | Typically developing controls | No association between asthma and ASD: pooled OR = 1.26 (95% CI 0.98–1.61) for prevalence of asthma in ASD. In the case–control studies, pooled OR = 0.98 (95% CI 0.68–1.43)<br>Quality findings: 9 studies high quality, 1 study moderate quality, average Newcastle-Ottawa Scale score = 7/9 |
| Allergic asthma (Tonacci et al 2017)[27] | Systematic review<br>18 studies<br>High | *n* range 15–14 812 with ASD | Children<br>8 case–control studies, 8 nationwide-studies, 2 epidemiological studies | Typically developing controls | A 'slight correlation' found between asthma and ASD in 11/18 studies<br>Quality findings: small sample sizes, many methodological limitations in studies, narrow age range in some, findings uncertain |
| Obesity and overweight (Zheng et al 2017)[28] | Meta-analysis<br>15 studies (10 objectively measured, 3 parental reports, 2 medical records)<br>High | *n* = 1 045 538 with ASD (range 40–986 352) | Mean age 6.6 years (s.d. = 2.1 years) to 74.38 years (s.d. = 22.3 years)<br>11 cross-sectional studies; 4 case–control studies | Typically developing controls | Obesity was higher than controls, OR = 1.84 (95% CI 1.37–2.48); overweight was not higher than controls, OR = 1.07 (95% CI 0.83–1.38)<br>Quality findings: findings were robust |
| Incontinence (Niemczyk et al 2018)[29] | Systematic review<br>19 studies<br>Medium | *n* = 7033 with ASD (range 25–5076 with ASD) | 2–18 years in 16 studies, adults in 1 study, children and adults combined in 1 study | Typically developing controls | Nocturnal enuresis rates were 2–90%, median 22.6% in 13 studies. Daily urinary incontinence rates were 13.3–55% in 4 studies. Faecal incontinence rates were 2–70.6%, median 12% in 11 studies. Incontinence rates were higher than typically developing controls in 4/5 studies<br>Quality findings: no population-based samples, selected samples, retrospective analyses, missing diagnostic criteria for ASD and for incontinence |
| Medical conditions (Muskens et al 2017)[30] | Systematic review<br>5 studies on immunological conditions, 5 studies on gastrointestinal problems, 1 study on genitourinary symptoms, 1 study on epilepsy, 1 study on hypospadias<br>High | *n* range 26–14 812 with ASD | 1–26 years in 11 studies; 0–65 years in 2 studies<br>7 cross-sectional studies; 6 case–control studies | Controls including healthy children, siblings or family | Allergic disease or autoimmune disease was higher than controls with OR = 1.22 (95% CI 1.13–1.31) and OR = 1.36 (95% CI 1.01–1.83) respectively, or no different. Children with atopy had HR = 3.40 for developing autism, there was no difference compared with controls in rates of herpes simplex. 3 studies report gastrointestinal symptoms to be higher than controls (1 specifically reports constipation and chronic diarrhoea). 1 reports no difference, except hernia with OR = 2.6 (95% CI 1.08–6.2). 1 reports no difference. Nocturnal enuresis and urinary incontinence more common than in controls in 1 study. Epilepsy more common than in controls in 1 study (3.9% *v.* 2%). Hypospadias more common than in controls in 1 study with OR = 3.20 (95% CI 2.8–3.8)<br>Quality findings: only studies assessed to be high quality were selected |

ASD, autism spectrum disorder; OR, odds ratio; HR, hazard ratio.

where further research endeavours would be useful. Our umbrella approach has the advantage of being suitable to answer the research questions we posed in one report.

## Strengths and limitations

The strengths of this review include its broad reach, the prospective registration of the review protocol, clear inclusion and exclusion criteria, a comprehensive search strategy including searching multiple databases, and duplicate study selection and data extraction, and quality assessment. The review is limited by excluding papers not written in English. Our review was of systematic reviews only; hence, it does not include any physical conditions that have not been subject to systematic review.

## Implications

People with ASD experience more comorbid physical conditions than other people (although we draw no conclusions on shared aetiologies as we did not investigate that). Clinicians require heightened awareness of these high rates of comorbidities in order to improve assessments and diagnoses so that people with ASD can receive the best possible healthcare and support they require. Some of their comorbidities are likely to compound health assessments and interventions if health professionals are unwary of their existence, such as sensory impairments, given the communication needs that people with ASD already experience. Other comorbidities, such as obesity, if not addressed, can lead to an array of other conditions, disadvantages and early death. Given the impact that ASD can have on the individual, it is essential that all other, potentially modifiable health conditions are identified and managed to ensure that people with ASD achieve their best outcomes.

## Future research

Comorbid physical conditions occur more commonly in people with ASD compared with the general population, but the evidence is limited. Given that physical conditions can have substantial bearing on function, and quality of life, further robust research is needed. The prevalence of conditions and their associations needs to be more firmly established, including for physical conditions that have to date received little attention. This would form a basis from which a better understanding of the long-term impact on quality of life could be gained, a start towards improved understanding of causation, and development of interventions to improve health. Further studies are also warranted on physical conditions commonly diagnosed in the general population, such as cancers, cardiovascular disorders and on physical comorbidities in ageing populations, to investigate how they have an impact on people with ASD. This in turn will allow for informed decision-making around healthcare, service commissioning and provision for people with ASD.

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## Data availability

Data sharing is not applicable, as no new data were collected (all referenced studies are in the public domain).

## Author contributions

E.R. and S.-A.C. jointly conceived, designed and conducted the study, interpreted data and wrote the first manuscript. K.D. double rated papers, and contributed to interpretation of data. All authors approved the final version of the manuscript.

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## Declaration of interest

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ICMJE forms are in the supplementary material, available online at https://doi.org/10.1192/bjp.2020.167.

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psychiatry in history

## Chained and unchained[a]

**Stephen Wilson**

Although Philippe Pinel (1745–1826) made significant contributions to nosology and research methodology, he was a clinician at heart and is universally acclaimed today for the humanitarian reforms he introduced in mental healthcare, symbolised by the dramatic act of striking off chains. But Pinel's unchaining was, at first, judiciously implemented and far from indiscriminate. He lived through troubled times where revolutionary fervour in France had given way to the excesses of The Reign of Terror. The Bicêtre Hospital under his direction was (correctly) suspected of harbouring 'Enemies of the Revolution', priests and returned émigrés masquerading as lunatics; but it was also suspected of confining sane prisoners of the Ancien Régime and labelling them mad. According to Pinel:

> 'During a massacre in the prisons, brigands forced their way into the Bicêtre under the pretext of setting free some victims of the ancient tyranny…they went from ward to ward brandishing arms and interrogating detainees, passing over them if madness was obvious. But one of the secluded who was kept in chains, caught their attention with his bitter complaints. Wasn't it odious that he was kept in irons and confused with other madmen? He denied that one could reproach him with the least extravagance; it was, he added the most revolting injustice.'

> 'The sight of those armed men with their confused shouting, faces illuminated with wine vapours, stirred up the patient's rage, who grabbed one of their sabres with a strong arm and began thrusting it from left to right, drawing blood; and if one hadn't been able to master him quickly, he would have avenged the whole of outraged humanity. That barbarous howling horde returned him to his ward and blushingly seemed to give way to the voice of justice and experience.'



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[a] Quotes from Pinel are taken from René Semelaigne, *Les Grands Aliénistes Français,* G.Steinheil, Paris, 1894, translated by myself.



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