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.

Method
This review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42015020896).
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.7 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;30–35 3 on sensory impairments (not sensory sensitivities; 1 on peripheral hearing loss;36 1 on visual impairment,37 and 1 on visual or hearing impairment38 ); 3 on epilepsy;39–41 3 on oral health;42–44 1 on asthma35 and 1 on allergic asthma;45 1 each on diabetes,46 gastro-intestinal conditions,47–49 atopic dermatitis,49 autoimmune disease,50–52 obesity,53–55 incontinence;56 and 1 review on 5 conditions – immunological, gastro-intestinal, incontinence, epilepsy and hypospadias.57 Fifteen studies were on children and young people;11,13,14,16–27 8 were on children, young people and adults;7,9,12,13,28–30 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.
Sleep problems are more common in people with ASD than other people, with some of this attributable to co-occurring intellectual disabilities. There are some inconsistencies in findings, for example regarding any differences in sleep quality and sleep efficiency. 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, or excluded these.

Epilepsy is common. The reviews did not report a comparison with the general population (with the exception of one, which included only a single study on epilepsy), 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. Epilepsy is more common in females with ASD than males with ASD. Self-inflicted oral soft tissue injury is more common in people with ASD than the general population. 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.

Findings on peripheral hearing loss are inconsistent. Among people with hearing impairment, the relative risk of ASD was high. Refractive errors are common but no different to the general population, whereas strabismus may be higher than for the general population. Among people with visual impairment, the relative risk of ASD was very high. 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. Hernia was the only gastrointestinal condition reported to be more common in one of the studies. 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. 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. Conversely to the conditions above, which appear to be more common in people with ASD, asthma probably is not, and in

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**Fig. 1** Study selection process.
### Table 1: Systematic reviews and meta-analyses on epilepsy in ASD

| Topic and authors | Method, included studies, quality assessment | Population type | Findings |
|------------------|---------------------------------------------|-----------------|----------|
| | | | Mean age range or age 2 years to 41 years, 7 months to 16 years, 21 years, 41 years 7 months | ASD with intellectual disabilities |
| | | | n = 15,418 with ASD (range 16–41 years), n = 2,072 with ASD and epilepsy (range 13–111 months) | ASD with intellectual disabilities |
| | | | n = 2,072 with ASD and epilepsy | ASD with intellectual disabilities |
| | | | n = 212 with ASD and epilepsy | ASD with intellectual disabilities |
| | | | n = 12,188 with ASD and epilepsy | ASD with intellectual disabilities |
| | | | n = 1,518 with ASD and epilepsy | ASD with intellectual disabilities |
| | | | n = 303 with ASD and epilepsy | ASD with intellectual disabilities |
| | | | n = 39,133,111 months | ASD with intellectual disabilities |

**Method, included studies, quality assessment**
- Woolfenden et al 2016
- Woodruff et al 2017
- Werner et al 2018
- Strayer et al 2017

**Participants, n**
- ASD, autism spectrum disorder.

**Discussion**

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.

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...
| 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) | Systematic review 3/50 studies reported on ASD High | n = 259 with ASD (range 14–168; median 77) | 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 |
| | | | | | Quality findings: (a) Prevalence – well-conducted with very low risk of bias (b) Associated factors – 1 high quality study, 2 with low risk of bias; no information on ASD diagnosis |
| Sleep problems (Elrod and Hood, 2015) | Meta-analysis 10 studies High | n = 333 with ASD (range 8–68; median 25.5) | Children 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 |
| Sleep problems (Baglioni et al 2016) | Meta-analysis 3 studies on Asperger syndrome 7 studies on autistic disorder High | n = 34 with Asperger syndrome n = 103 with autistic disorder | <18 years with Asperger syndrome in 2 studies; 18–60 years with Asperger syndrome in 1 study | 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. |
| | | | <18 years with autistic disorder in 4 studies; adolescents and adults with autistic disorder in 2 studies | | Quality findings: small sample sizes, and small number of studies |
| Intraindividual variability of sleep/wake patterns (Becker et al 2017) | Systematic review 3/52 studies reported on ASD High | n range 186–194 with ASD | Children 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 a ADHD |
| | | | | | 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 |
| Sleep problems (Diaz-Roman et al 2018) | Meta-analysis 47 studies; subjective measures in 37 studies, objective measures in 15 studies High | n range 75–5430 with ASD for subjective sleep parameters n range 144–312 with ASD for objective sleep parameters | Children and youth ≤20 years Case–control studies | Typically developing controls | Quality findings: heterogeneity, few studies, not primary findings of studies |
| | | | | | 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) |
| | | | | | 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**<br>(Carmassi et al 2019)<sup>15</sup> | Systematic review 103 studies: 12 on circadian sleep dysrhythmity (7 in children, 5 in adults), 74 on sleep disturbances (65 in children, 9 in adults), 17 on melatonin alteration | 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. 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**<br>(Bartolomé-Villar et al 2016)<sup>17</sup> | Systematic review 10 studies | 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. Quality findings: no information on ASD diagnosis. |
| **Oral health**<br>(Da Silver et al 2016)<sup>22</sup> | Meta-analysis 7 studies: 7 on dental caries, 3 on periodontal disease | 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%). 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**<br>(Robertson et al 2019)<sup>23</sup> | Meta-analysis 8/25 studies were on ASD; 2 studies included care index and restorative index | 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. 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.
| Topic and authors | Method, included studies, quality assessment | Participants, n | Population type | Comparison groups | Findings |
|------------------|---------------------------------------------|-----------------|----------------|-----------------|---------|
| **Diabetes when exposed to antipsychotics** *(Galling et al 2016)* | Meta-analysis 13 studies High | n = 185 105 youth exposed to antipsychotics (range 179–107 551; median 5370) | Children and youth 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 ≤ 0.05) Quality findings: no information on ASD diagnosis |
| **Gastrointestinal problems** *(McElhanon et al 2014)* | Meta-analysis 15 studies High | n = 2215 with ASD (range 33–389; median 75) | 0–18 years Studies of children with known gastrointestinal diagnoses were excluded 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) Quality findings: no studies included diagnosis of gastro-intestinal problems, they relied on chart reviews or questionnaires |
| **Peripheral hearing loss** *(Beers et al 2014)* | Systematic review 5 studies Medium | n = 349 with ASD (range 22–199; median 37) | Children and adolescents 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 3.3% in 199 children and adolescents with ASD Quality findings: lack of detail on sample to generalise findings 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%) 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 impairment** *(Butchart et al 2017)* | Systematic review 7 studies Medium | n = 1035 with ASD (range 18–324) | 1–22 years 6 case record reviews from screening studies; 1 screening study of children with ASD and visual impairment | 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 Quality findings: selection bias (clinical populations), ASD diagnosis, unclear reporting, confounding factors, heterogeneity |
| **Visual or hearing impairment** *(Do et al 2017)* | Meta-analysis 15 studies: 8 visual impairment, 5 hearing impairment, 2 both High | Unknown n with visual or hearing impairment | 1–18 years Cross-sectional and case series, and retrospective case-note review | Previously published literature | 1 reported 2.2% with atopic dermatitis had ASD, 0.9% without atopic dermatitis had ASD. 14 studies considered dermatitis with other atopic disorders: dermatitis in 3.8–64.2% with ASD compared with 0.0–15.8% in typically developing; 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 Quality findings: no information on ASD diagnosis |
| **Atopic dermatitis** *(Bilecici et al 2015)* | Systematic review 18 studies High | n = 1 245 225 with atopic dermatitis (range 40–1 000 000; median 1955.5) n with ASD not provided for all studies | 0–2 years Case–control studies, national surveys or population studies | Typically developing and healthy controls | 28% (95% CI 12–48%); hypothyroidism – OR = 1.64 (95% CI 1.19–2.1); type 1 diabetes – OR = 1.49 (95% CI 1.25–1.81); rheumatoid arthritis – OR = 1.51 (95% CI 1.19–1.91); psoriasis – OR = 1.59 (95% CI 1.28–1.97) Quality findings: potential publication bias for all autoimmune conditions combined, and for type 1 diabetes |
| **Autoimmune disease** *(Wu et al 2015)* | Meta-analysis 11 studies High | n range 102–857 014 family members | 3 cohort studies, 6 case–control studies, 2 cross-sectional studies Clinical samples, register data, autism society | Family members | Family history associated with higher risk of autism in children: All autoimmune diseases combined – 28% (95% CI 12–48%); hypothyroidism – OR = 1.64 (95% CI 1.19–2.1); type 1 diabetes – OR = 1.49 (95% CI 1.25–1.81); rheumatoid arthritis – OR = 1.51 (95% CI 1.19–1.91); psoriasis – OR = 1.59 (95% CI 1.28–1.97) Quality findings: potential publication bias for all autoimmune conditions combined, and for type 1 diabetes |

(Continued)
| Topic and authors                        | Method, included studies, quality assessment | Participants, n | Population type                                                                 | Comparison groups | Findings                                                                                                                                 |
|-----------------------------------------|---------------------------------------------|-----------------|---------------------------------------------------------------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Asthma (Zheng et al 2016)               | Meta-analysis 10 studies High               | n = 8809/175 406 with ASD | Children 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) Quality findings: 9 studies high quality, 1 study moderate quality, average Newcastle-Ottawa Scale score = 7/9 |
| Allergic asthma (Tonacci et al 2017)    | Systematic review 18 studies High           | n range 15–14 812 with ASD | Children 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 Quality findings: small sample sizes, many methodological limitations in studies, narrow age range in some, findings uncertain |
| Obesity and overweight (Zheng et al 2017) | Meta-analysis 15 studies (10 objectively measured, 3 parental reports, 2 medical records) 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) 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) Quality findings: findings were robust |
| Incontinence (Niemczyk et al 2018)      | Systematic review 19 studies Medium         | n = 7 033 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 Quality findings: no population-based samples, selected samples, retrospective analyses, missing diagnostic criteria for ASD and for incontinence |
| Medical conditions (Muskens et al 2017) | Systematic review 5 studies on immunological conditions, 5 studies on gastrointestinal problems, 1 study on genitourinary symptoms, 1 study on epilepsy, 1 study on hypospadias High | n range 26–18 812 with ASD | 1–26 years in 11 studies; 0–65 years in 2 studies 7 cross-sectional studies; 6 case–control studies Controls including healthy children, siblings or family | Typically developing controls | 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 diarrhoeal). 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) 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 unaware 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 need 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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Chained and unchained

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 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 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:

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