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All-cause and cause-specific mortality in people with autism spectrum disorder: A systematic review

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ABSTRACT

Background: The aim of this systematic review was to synthesise the current literature on all-cause and cause-specific mortality in individuals with autism spectrum disorders (ASD) to identify whether they experience an increased risk of mortality compared to the general population and to establish which specific causes of death are most prevalent in people with ASD.
Method: Medline, Embase, CINAHL and PsycINFO databases were searched. The review was registered with PROSPERO (CRD42021219582).
Results: 26 of the 8505 retrieved papers were included. 25 studies reported an increased risk of mortality for people with ASD. Out of 21 studies reporting the relevant statistics, 15 found autistic individuals to have at least a two times higher risk of dying when compared to the general population. 11 studies suggested that females with ASD were at an even greater risk of death when compared to their male counterparts. The most common causes of deaths were from external causes (particularly suicide) and neurological disorders.
Conclusions: Recognising the increased mortality experienced by people with ASD is an important factor in how clinicians, support workers and healthcare systems in general should plan and approach care for this population. Although a significant portion of deaths in this group occurs due to intentional or unintentional external causes, the reviewed literature also indicates that many people with ASD die from underlying health conditions. As the increased mortality risk seems to be partially mediated by the co-occurrence of other conditions, it is of great importance to provide an increased level of support and care for this population.

1. Introduction

Autism spectrum disorders (ASD) account for an umbrella of neurodevelopmental conditions characterised by a range of clinical presentations (American Psychiatric Association APA, 2013). People with ASD can face extreme adversity throughout their lives. Alongside an overall reduced quality of life for people with ASD (Van Heijst & Geurts, 2015), this group is at a greater risk of a range of medical and psychiatric conditions when compared to controls (Croen et al., 2015). People with ASD have a significantly increased risk of developing major psychiatric disorders such as depression, anxiety, schizophrenia and suicide attempts (Hossain et al., 2020). A recent umbrella systematic review of co-morbid physical conditions in people with ASD found that sleep problems, epilepsy, sensory

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impairments, atopy, autoimmune disorders and obesity were particularly more prevalent amongst people with ASD compared with the general population (Rydzewska et al., 2021). One study found that adults with ASD had a considerably higher prevalence of seizure disorders when compared to the general population (11.2 % vs 1.4 %) (Fortuna et al., 2016). Additionally, people with ASD are more likely to be obese, report limited physical activity and are often prescribed multiple psychotropic medications, all of which have been reported to increase mortality in this population (Esbensen et al., 2009; Ho et al., 1997). A recent study assessing health problems of decedents with ASD compared to matched decedent controls found that people with ASD died, on average, 20 years younger and had higher rates of most health conditions (Bishop-Fitzpatrick et al., 2018).

A systematic review and meta-analysis focusing on all-cause mortality in people with ASD found a pooled SMR of 2.8 (95 % CI 1.8–4.2) for people with ASD, with a significantly higher SMR for females compared to males (7.2 vs 2.1) (Woolfenden et al., 2012). Recent systematic review and meta-analysis on mortality in people with ASD or attention-deficit/hyperactivity disorder synthesised more current research in the field but did not report findings from all available studies on mortality in ASD populations and did not provide a detailed breakdown of all available data on cause-specific mortality for individual papers included in the review (Catalá-López et al., 2022). Additionally, the aforementioned systematic review included results published only until the beginning of 2020, with several new papers having been published since. The aim of our review was to collate and synthesise all available papers on all-cause mortality in ASD populations, including most recent evidence. Additionally, our systematic review also aimed to synthesise and present in detail evidence available on specific causes of death in the ASD population, including providing a breakdown of mortality rates using the ICD-10 classification.

2. Methods

The PRISMA 2020 checklist was used to report findings from the systematic review (Page et al., 2021). Additionally, the review was registered with the International Prospective Register of Systematic Reviews PROSPERO (registration number: CRD42021219582).

2.1. Search strategy

Four online databases were used to garner search results: MEDLINE, EMBASE, CINAHL and PsycINFO. There were no time limiters applied to the search and all four databases were searched from the inception date of each database up until the day the search was run (the 16th of June 2022). Bibliographies of papers the data were extracted from were also assessed to identify any additional papers outwith the results gathered from the database searches. Box 1 includes example search terms used for the search. The full search strategy can be found in the supplementary material on PROSPERO (CRD42021219582).

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

1. autism spectrum disorders (e.g., autism, Asperger's syndrome, pervasive developmental disorder-not otherwise specified)
2. all ages
3. all ethnicities
4. mortality and/or cause-specific mortality investigated as a primary outcome
5. peer-reviewed observational studies such as cohort, case-control or cross-sectional studies
6. where studies only partially focused on mortality in people with ASD, the mortality data had to be presented separately or the sample with ASD had to constitute at least 30 % of the total sample
7. papers had to report at least one of the following: relevant standardised mortality ratio (or other inferential statistic), number/proportion of deaths or cause of death
8. English language

Box 1
Example search strategy.

MEDLINE/ EMBASE databases – via OVID (searched 16/06/2022)
(autism/ OR autis*.mp. OR Asperger syndrome/ OR Asperger*.mp.) AND (Mortality/ OR Mortal*.mp. OR Death/ OR dying*.mp. OR death*.mp.)
CINAHL/ PsycINFO databases- via EBSCO (searched 16/06/2022)
(TX autis* OR TI autis* OR AB autis* OR TX Asperger* OR TI Asperger* OR AB Asperger*) AND (TX mortal* OR TI mortal* OR AB mortal* OR TX death OR TI death OR AB death OR TX dying OR TI dying OR AB dying)

2.2.2. Exclusion criteria

1. non-human studies
2. qualitative studies
3. studies on Rett syndrome, which has been removed from the DSM-5 criteria as a sub-diagnosis of ASD (APA, 2013)
4. grey literature

2.3. Study selection

The titles and abstracts of the studies retrieved from the search were compiled into EndNote v. X9, read by the first reviewer (LF) and compared with the inclusion/exclusion criteria for eligibility. A random 10 % of these were evaluated by the second reviewer (MM) for quality control. Any discrepancies were resolved through discussion with the third reviewer (ER) and were on the side of over-inclusion at this stage. The full texts of potentially eligible studies were then retrieved and assessed for eligibility by the first reviewer (LF), who subsequently extracted relevant data from the selected papers.

2.4. Outcomes

The main outcome of this systematic review was all-cause mortality of individuals with an ASD diagnosis or associated sub-

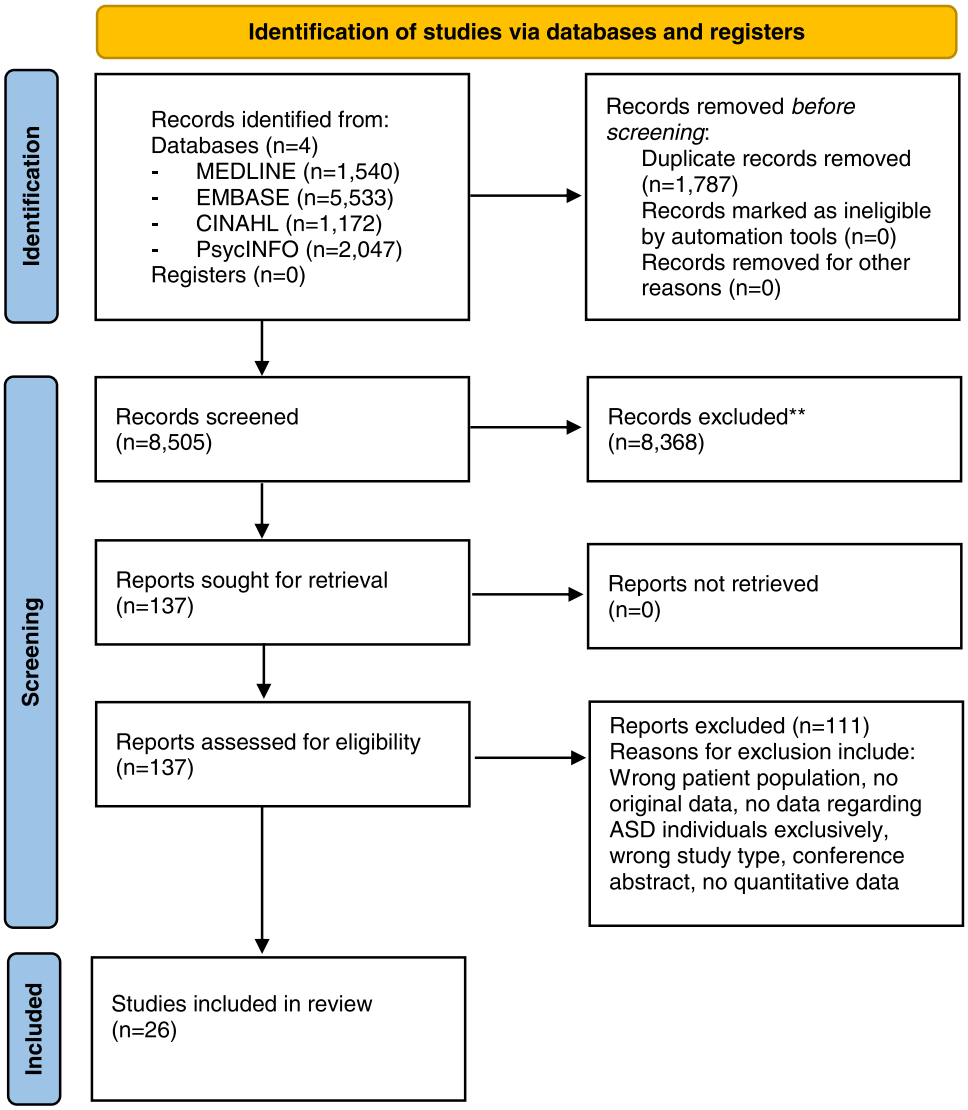

Fig. 1. Study selection process.

Table 1
Study characteristics.

Author and date of publication	ASD sample size	Comparison group size	Study location	Participant recruitment method	Age of participants	Study design	Risk of bias
Studies on All-Cause mortality							
Akobirshoev et al. (2020)	n = 34,237	n = 102,711	USA	Database analysis of hospital discharge data of approximately 8 million patients from approximately 1000 hospitals Control=matched control	18 years or older	Retrospective matched case-control study	A
Bilder et al. (2013)	n = 305 Female= 77 Male= 228 ASD only= 111 ASD with ID= 194	Not reported	USA	Voluntary inclusion through extensive media campaign Control=population controls	3 – 25 years old	Retrospective cohort study	C3.1
1. Billstedt et al. (2005) (data from 2001 to 2003) 2. Gillberg et al. (2010) (data from 2008)	n = 120	No control	Sweden	Screening of population records	1. 17–40 years old 2. 23–46 years old	Prospective population-based follow-up study	1. C3.5 2. C4.1
Bourke et al. (2017)	n = 10,593 of all children with intellectual disabilities; number of children with intellectual disabilities and autism not reported	Not reported	Australia	Western Australian intellectual disability exploring answers database Control=Children without intellectual disabilities	1–25 years old	Retrospective cohort study	B2
DaWalt et al. (2019)	n = 406 ASD only= 122 ASD with ID= 284	No control	USA	Informational packets distributed to families and invited for voluntary inclusion	10 years or older	Retrospective cohort study	C1.2
Guan and Li (2017)	Not reported	Not reported	USA	Screening of cause of death data files in the National Vital Statistics System Control=Matched control from general population of the USA	All ages	Retrospective cohort study	C3
Hirvikoski et al. (2016)	n = 27,122 ASD only= 20,882 ASD with ID= 6240 ASD Females overall= 8429 ASD males overall= 18,693	n = 2672,185	Sweden	Screening of nationwide Swedish population-based register Control=matched control group	All ages	Matched case cohort study	A
Hosking et al. (2016)	ASD only= 10,374 ASD with ID= 1532	n = 103,188	UK	Screening of data from 343 general practises in England between 2009 and 2013 Control= Matched control from general population of England without ID or ASD	18–84 years old	Retrospective matched cohort study	B1
Huang et al. (2021)	n = 6599	n = 26,396	Taiwan	Screening of data from the Taiwan National Health Insurance Research Database	All ages	Retrospective population based cohort study	A
Hwang et al. (2019)	ASD overall= 35,929 ASD only= 19,823 ASD with ID= 16,106 ASD Females overall= 7374	n = 77,967,924	Australia	Screening of datasets Control= Matched control from general population of New South Wales	5–64 years old	Retrospective matched cohort study	A

(*continued on next page*)

Table 1 (*continued*)

Author and date of publication	ASD sample size	Comparison group size	Study location	Participant recruitment method	Age of participants	Study design	Risk of bias
1. Isager et al. (1999) (data from 1993) 2. Mouridsen et al. (2008) (data from 2006)	ASD Males overall= 28,555 n = 314	No control	Denmark	Voluntary inclusion of Inpatients at psychiatric clinics	14–48 years old	Longitudinal follow up study	1. C1.3 2. B1
Jokiranta-Olkoniemi et al. (2020)	n = 4695	n = 18,450	Finland	Screening of Finish hospital discharge register	10–28 years old	Longitudinal matched cohort study	A
Kim et al. (2021)	n = 32,878	Not reported	South Korea	Screening of the National Health insurance databank of Korea of children born between 2007 and 2014	0–7 years old	Retrospective cohort study	A
Lunsky et al. (2022)	n = 10,646	n-42,607	Canada	Screening of linked administrative health and social services in Ontario	19–65 years old	Longitudinal matched cohort study	A
Pickett et al. (2011) (Data from 2 different years, 2007 and 2009)	2007 = 34,724 2009 = 47,376	No control	USA	Analysis of California State Department of Developmental Services	All ages	Retrospective snapshot study	C2.1
Pickett et al. (2006)	n = 13,111	Not reported	USA	Screening of California Department of Developmental Services Database. Data from 1998 to 2002. Control=Matched control from general population of the USA	All ages	Longitudinal matched cohort study	A
Schendel et al. (2016)	n = 20,492 Females= 4590 Males= 15,902	n = 1,892,412	Denmark	Screening of Danish Civil Registration Service and Medical Birth Register	Children born from 1980 to 2010 in Denmark and followed up until 2013	Longitudinal population-based cohort study	A
Shavelle and Strauss, 1998	n = 11,347	Not reported	USA	Screening of California Department of Developmental Services Database. Data from 1980 to 1996 Control=Matched control from general population of the USA	All ages	Longitudinal matched cohort study	A
Shavelle et al. (2001)	n = 13,111	Not reported	USA	Screening of California Department of Developmental Services Database data from 1983 to 1997 Control=Matched control from general population of the USA	All ages	Longitudinal matched cohort study	A
Smith et al. (2021)	n = 9754	n = 777,912	UK	Database linkage of Scotland's annual pupil census and the national records of Scotland deaths register Control= Scotland's annual pupils census	5–24 years old	Matched cohort study	C1
Yoo et al. (2022)	n = 35,529	Not reported	South Korea	Screening of the National Health insurance databank of Korea of children born between 2002 and 2012	0–8 years old	Retrospective cohort study	A
Studies on Cause-specific mortality							

(*continued on next page*)

Table 1 (*continued*)

Author and date of publication	ASD sample size	Comparison group size	Study location	Participant recruitment method	Age of participants	Study design	Risk of bias
Author and date of publication	**Sample size**	**Comparison group**	**Study location**	**Participant recruitment method**	**Age of participants**	**Study design**	**Risk of bias**
Akobirshoev et al. (2020)	n = 34,237	n = 102,711	USA	Database analysis of hospital discharge data of approximately 8 million patients from approximately 1000 hospitals Control=matched control	18 years or older	Retrospective matched case-control study	A
Bilder et al. (2013)	n = 305	Not reported	USA	Voluntary inclusion through extensive media campaign Control=population controls	3 – 25 years old	Retrospective cohort study	C3.1
1. Billstedt et al. (2005) (data from 2001 to 2003) 2. Gillberg et al. (2010) (data from 2008)	n = 120 Females= 35 Males= 85	No control	Sweden	Screening of population records	1. 13–22 years old 2. 23–46 years old	Prospective population-based follow-up study	1. C3.5 2. C4.1
Cassidy et al. (2022)	n = 40	n = 332	UK	Screening of coroner inquests for deaths from suicide for evidence of autism or autistic traits	All ages	Retrospective cohort study	C1
DaWalt et al. (2019)	n = 406	No control	USA	Informational packets distributed to families and invited for voluntary inclusion	10 years or older	Retrospective cohort study	C1.2
Guan and Li (2017)	Not reported	Not reported	USA	Screening of cause of death data files in the National Vital Statistics System Control=Matched control from general population of the USA	All ages	Retrospective cohort study	C3
Hirvikoski et al. (2016)	n = 27,122 Females= 8429 Males= 18,693 ASD with ID= 6240 (Females=2032, Males= 4208) ASD only= 20,882 (Females=6397 Males=14,485	n = 2672,185 Female n = 840962 Male n = 1831223	Sweden	Screening of nationwide Swedish population-based register Control=matched control group	All ages	Matched case cohort study	A
Huang et al. (2021)	n = 6599	n = 26,396	Taiwan	Screening of data from the Taiwan National Health Insurance Research Database	All ages	Retrospective population based cohort study	A
Hwang et al. (2019)	ASD overall=35,929 ASD only=19,823 ASD with ID=16,106 ASD Females overall=7374 ASD Males overall=28,555	n=77,967,924	Australia	Screening of datasets Control=Matched control from general population of New South Wales	5–64 years old	Retrospective matched cohort study	A
1. Isager et al. (1999) (data from 1993) 2. Mouridsen et al. (2008) (data from 2006)	n = 341 Females= 85 Males= 256	No control	Denmark	Voluntary inclusion of Inpatients at psychiatric clinics	14–48 years old	Long term follows up study	1. C1.3 2. B1
Jokiranta-Olkoniemi et al. (2020)	n = 4695	n = 18,450	Finland	Screening of finish hospital discharge register	10–28 years old	Longitudinal matched cohort study	A

(*continued on next page*)

Table 1 (*continued*)

Author and date of publication	ASD sample size	Comparison group size	Study location	Participant recruitment method	Age of participants	Study design	Risk of bias
Lunsky et al. (2022)	n = 10,646	n-42,607	Canada	Screening of linked administrative health and social services in Ontario	19–65 years old	Longitudinal matched cohort study	A
Kirby et al. (2019)	n = 16,904	Not reported	USA	Screening of Utah state-wide autism surveillance data and state-wide suicide data Control=population of Utah	5–89 years old	Retrospective cohort study	C1.1
Kõlves et al. (2021)	n = 35,020	n = 6524246	Denmark	Screening of nationwide register	10 years or older	Retrospective cohort study	A
Pickett et al. (2011)	2007 = 34,724 2009 = 47,376	No control	USA	Analysis of California State Department of Developmental Services	All ages	Retrospective cohort study	C2.1
Schendel et al. (2016)	n = 20,492	n = 189,412	Denmark	Screening of Danish Civil Registration Service and Medical Birth Register	Children born from 1980 to 2010 in Denmark and followed up in 2013	Longitudinal population-based cohort study	A
Shavelle et al. (2001)	n = 13,111	Not reported	USA	Screening of California Department of Developmental Services Database data from 1983 to 1997 Control=Matched control from general population of the USA	All ages	Longitudinal matched cohort study	A

List of abbreviations: ASD=autism spectrum disorders

diagnosis (e.g., Asperger's syndrome, pervasive developmental disorder-not otherwise specified). The secondary outcome was concerned with the specific causes of deaths in people with ASD.

2.5. Risk of bias assessment

The first reviewer (LF) conducted a quality assessment of all relevant papers. The second (MM) and third (ER) reviewer each assessed 50 % of the included papers. Any disagreements were resolved through discussions between reviewers. The Critical Appraisal Skills Programme (CASP) 12-item checklist for cohort studies was used to assess and rate papers for their quality (CASP, 2020). Each of the 12 items on the checklist was given one of three ratings: 'Yes' (low risk of bias), 'Can't tell' (unknown risk of bias), or 'No' (high risk of bias).

A score was then generated by summating the number of CASP items for each study by using the following classification (Mathie et al., 2017):

- Rating A= low risk of bias for all 12 items.
- Rating Bx= uncertain risk of bias for x items, low risk of bias in all other items.
- Rating Cy,x = high risk of bias in y items, uncertain risk of bias in x items, low risk of bias in all other items.

2.6. Interrater reliability

Interrater reliability was assessed at two stages in the review: title and abstract eligibility and quality assessment. Cohen's Kappa coefficient was used to assess interrater agreement at the title and abstract stage of the review, as two reviewers were involved in this stage. Fleiss' Kappa statistic was used to assess interrater agreement at the stage of quality assessment of the papers as there were three reviewers involved in this stage. Both Kappa coefficients were calculated using SPSS v. 28. At the title and abstract review stage, the Cohen's kappa score was 0.89 which was deemed as near perfect agreement. At the quality assessment stage, the Fleiss' kappa score was 1.0, which was deemed as perfect agreement.

3. Results

3.1. Search results

The initial search identified a total of 10,292 references across the four databases. After removing 1787 duplicates, 8368/8505 unique records were then excluded based on title and abstract review. The remaining 137 papers were read in full. 26 of these papers

Table 2
Findings on all-cause mortality.

Author and date of publication	ASD n of deaths (%)	Control group n of deaths (%)	Odds ratio (OR), Hazard ratio (HR), Comparative mortality figure (CMF), Standardised mortality ratio (SMR), Proportionate mortality ratio (PMR)
Akobirshoev et al. (2020)	n = 462 (1.35 %)	n = 967 (0.95 %)	Unadjusted OR= 1.44 (95 %CI 1.29–1.61) Adjusted OR= 1.51 (95 %CI 1.33–1.72) (Adjusted for age, race/ethnicity, type of health insurance, median household income for patients' zip code, number of Elixhauser medical comorbidities, hospital bed size, and region of the hospital)
Bilder et al. (2013)	n = 29 (9.5 %) ASD with ID= 27/29 (93 %) Female n = 9 (7 = IQ≤69, 2 = IQ≥70) Male n = 20 (All IQ≤69)	Not reported	Overalll: HR Without covariates= 9.91 (95 %CI 5.70–17.22) Overall: HR With covariates= 11.59 (95 %CI 6.24–21.53) (Covariates included: maternal age, birth weight, gestational age, age at mother's death, age at father's death) Female: HR without covariates= 20.71 (95 %CI 6.20–69.20) Females: HR with covariates= 30.14 (95 %CI 6.31–143.87) (Covariates included: maternal age, birth weight, gestational age, age at mother's death, age at father's death) Male: HR without covariates= 7.92 (95 %CI 4.17–15.03) Male: HR with covariates= 9.91 (95 %CI 4.77–20.60) (Covariates included: maternal age, birth weight, gestational age, age at mother's death, age at father's death)
1. Billstedt et al. (2005) (data from 2001 to 2003) 2. Gillberg et al. (2010) (data from 2008)	1. n = 6 (5 %) 2. n = 9 (7.5 %) (Males= 3, Females=6)	Not reported	1. Not reported 2. SMR= 5.6 (95 %CI 2.5–10.5)
Bourke et al. (2017)	Not reported	Not reported	HR= 2.1 * (95 %CI 1.0–4.2)
DaWalt et al. (2019)	ASD only= 5 ASD with ID= 21	Not reported	HR ASD only= Not reported HR ASD with ID Model 1 = 1.262 (95 %CI 0.46–3.43) (Adjusted for age) HR ASD with ID Model 2 = 1.211 (95 %CI 0.44–3.33) (Adjusted for health status) HR ASD with ID Model 3 = 0.616 (95 %CI 0.19–2.01) (Adjusted for age and health status)
Guan and Li (2017)	n = 986 (No sample size given) (All other causes excluding injury)	Not reported	PMR= 0.82 (95 %CI 0.77–0.87)
Hirvikoski et al. (2016)	n = 706 (2.6 %) ASD with ID= 169 (2.7 %) Females= 61 (3 %) Males= 108 (2.6 %) ASD only= 537 (2.57 %) Females= 235 (3.6 %) Males= 302 (2.08 %)	n = 24,358 (0.91 %)	Overall OR= 2.56 (95 %CI 2.38–2.76) Overall Low functioning ASD OR= 5.78 (95 %CI 4.94–6.75) Low functioning Females OR= 8.52 (95 %CI 6.55–11.08) Low functioning Males OR= 4.88 (95 %CI 4.02–5.93) Overall High functioning ASD OR= 2.18 (95 %CI 2.00–2.38) High functioning Females OR= 1.88 (95 %CI 1.65–2.14) High functioning Males OR= 2.49 (95 %CI 2.22–2.80)
Hosking et al. (2016)	ASD only= 44 (0.44 %) ASD with ID= 15 (0.98 %)	No ID or ASD= 1 314 (1.27 %)	ASD only: Not reported Unadjusted ASD with ID: HR= 2.39 (95 %CI 1.45–3.96) Adjusted ASD with ID: HR= 2.22 (95 %CI 1.01–4.86) (Adjusted for comorbidity, smoking, and deprivation)
Huang et al. (2021)	n = 119 (1.8 %)	n = 301 (1.1 %)	HR= 2.42 (1.89–2.78)
Hwang et al. (2019)	ASD only= 62 (0.3 %) ASD with ID= 182 (1.1 %) ASD overall= 244 (0.7 %) ASD females overall= 74 ASD males overall= 170	n = 120020 (No sample size data)	ASD only: CMR= 1.61 (95 %CI 1.17–2.21) ASD with ID: CMR= 2.26 (95 %CI 1.74–2.94) ASD overall: CMR= 2.26 (95 % C I1.74–2.94) ASD Females overall: Unadjusted HR= 1.64 (95 %CI 1.25–3.26) ASD Females overall: Adjusted HR= 1.06 (95 %CI 0.80–140) (Adjusted for Age, Rurality, socioeconomic status, presence of ID, epilepsy, mental health and medical conditions) ASD Males overall: Unadjusted HR = Not reported ASD Males overall: Adjusted HR= Not reported
1. Isager et al. (1999) (data from 1993) 2. Mouridsen et al. (2008) (data from 2006)	1. n = 12 (3.5 %) 2. n = 26 (7.6 %) (Females= 8, Males= 18)	Not reported	1. SMR= 1.9 (95 %CI 1.0–3.4) 2. Overall SMR: 0–15 years after diagnosis= 2.40 (95 %CI 0.97–4.95) Overall SMR: 15–30 years after diagnosis= 1.65 (95 %CI 0.71–3.25) Overall SMR: 30–45 years after diagnosis= 1.92 (95 %CI 0.96–3.43) Overall SMR: 0–45 years after diagnosis= 1.93 (95 %CI 1.26–2.82) Female SMR: 0–15 years after diagnosis= 5.22 (95 %CI 0.63–18.9) Female SMR: 15–30 years after diagnosis= 3.17 (95 %CI 0.38–11.4)

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Table 2 (*continued*)

Author and date of publication	ASD n of deaths (%)	Control group n of deaths (%)	Odds ratio (OR), Hazard ratio (HR), Comparative mortality figure (CMF), Standardised mortality ratio (SMR), Proportionate mortality ratio (PMR)
			Female SMR: 30–45 years after diagnosis= 4.08 (95 %CI 1.11–10.4) Female SMR: 0–45 years after diagnosis= 4.01 (95 %CI 1.73–7.90) Male SMR: 0–15 years after diagnosis= 1.98 (95 %CI 0.64–4.61) Male SMR: 15–30 years after diagnosis= 1.42 (95 %CI 0.52–3.10) Male SMR: 30–45 years after diagnosis= 1.47 (95 %CI 0.59–3.04) Male SMR: 0–45 years after diagnosis= 1.57 (95 %CI 0.93–2.48)
Jokiranta-Olkoniemi et al. (2020)	n = 53 (1.1 %)	n = 76 (0.4 %)	Unadjusted HR= 2.8 (95 %CI 2.0–3.9) Adjusted HR= 1.7 (95 %CI 1.2–2.6) (Adjusted for comorbid psychiatric disorder(s))
Kim et al. (2021)	Not reported	Not reported	Adjusted HR(Total)= 2.6 (95 %CI 2.3–3.0) (Adjusted for sex, income, area of residence, and year of birth) Adjusted HR(female)= 4.8 (95 %CI 3.9–5.8)(Adjusted for sex, income, area of residence, and year of birth) Adjusted HR(male)= 1.9 (95 %CI 1.6–2.2)(Adjusted for sex, income, area of residence, and year of birth)
Lunsky et al. (2022)	n = 259 (2.43 %)	n = 330 (0.78 %)	Male Adjusted RR= 3.31 (95 %CI 2.58–3.79) (Adjusted for sex, age and neighbourhood income) Female Adjusted RR= 3.12 (95 %CI 2.35–4.13) (Adjusted for sex, age and neighbourhood income)
Pickett et al. (2006)	n = 78 (N/A)	Not reported	SMR= 2.6
Pickett et al. (2011)	2007: Autism only= 23** (0.07 %) 2009: Autism only= 37** (0.08 %)	Not reported	Not reported
Schendel et al. (2016)	n = 68 (0.33 %) Females= 14 Males= 54	n = 7168 (Not reported)	Unadjusted HR= 2.2 (95 %CI 1.8–2.8) Adjusted HR= 2.0 (95 %CI 1.5–2.8) (Adjusted for sex, birth weight, gestational age, and parental age) Females: Unadjusted HR= 3.5 (95 %CI 2.1–5.9), Adjusted HR= 3.5 (95 % CI 1.7–7.0) Males: Unadjusted HR= 1.7 (95 % CI 1.3–2.2), Adjusted HR= 1.8 (95 % CI 1.2–2.6)
Shavelle and Strauss, 1998	Female n = 166 Male n = 82	Not reported	Female MR= 167 % (95 % CI 145 %–192 %) Male MR= 490 % (95 % CI 384 %–596 %)
Shavelle et al. (2001)	Overall n = 202 (1.5 %) No or mild Intellectual disability with comorbid ASD: n = 49 (0.38 %) Moderate, severe or profound Intellectual disability with comorbid ASD: n = 153 (1.2 %)	Not reported	SMR Overall = 2.4 SMR Males= 1.7 SMR Female= 5.5
Smith et al. (2021)	n = 6 (0.06 %)	n = 458 (0.058 %)	SMR= 1.1 (95 %CI0.4–1.9)
Yoo et al. (2022)	Not reported	Not reported	Adjusted HR(Total)= 2.34 (95 %CI 2.06–2.65) (Adjusted for sex, income, area of residence, and year of birth) Adjusted HR(female)= 4.22 (95 %CI 3.47–5.14)(Adjusted for sex, income, area of residence, and year of birth) Adjusted HR(male)= 1.77 (95 %CI 1.51–2.09)(Adjusted for sex, income, area of residence, and year of birth)

List of abbreviations: ASD=autism spectrum disorders; CI=Confidence interval; HR=Hazard ratio; OR=odds ratio; PRM=proportionate mortality ratio; RR=Relative risk; SMR= standardised mortality ratio

* HR for individuals with autism and comorbid intellectual disability

** Mortality data on the population with autism and comorbid epilepsy were not extracted

*** Data are split into subgroups by year of diagnosis

met the inclusion criteria and were subsequently included in this systematic review. Fig. 1 summarises the inclusion and exclusion of records at different stages in the review (Page et al., 2021).

3.2. Study characteristics

Six papers included in the previous systematic review on all-cause mortality in ASD (Woolfenden et al., 2012) were also identified and incorporated in this systematic review. In addition, we have identified 20 other studies not reported on by Woolfenden et al. (2012) with 17 of these papers having been published since 2016.

Of the 26 papers, nine were conducted in the US, four in Denmark, three in Sweden, three in the UK, two in Australia, two in South

Korea and one in Finland, Canada and Taiwan. All included studies are from high income countries and lie within the top 20 countries for average annual income, with the exception of South Korea and Taiwan (OECD, 2016). The sample sizes ranged from 40 to 47,367 individuals with a diagnosis of ASD. One paper did not have a sample size available (Guan and Li, 2017).

Of the 26 papers, four used voluntary inclusion to recruit participants (Bilder et al., 2013; DaWalt et al., 2019; Isager et al., 1999; Mouridsen et al., 2008), with the rest of the studies using database screening to gather and evaluate data. Two Danish studies used a cohort of ASD patients born between 1960 and 1984 to first evaluate the group's mortality up until 1993 (Isager et al., 1999) and subsequently up until 2006 (Mouridsen et al., 2008). Two Swedish studies used a cohort born between 1962 and 1984 to first assess mortality in 2000 (Billstedt et al., 2005) and subsequently in 2008 (Gillberg et al., 2010). One other study screened the California Developmental Disabilities Services Database in 2007 and 2009 and presented findings for both years (Pickett et al., 2011). Another study, using the same database, identified mortality rates between 1983 and 1997 (Shavelle et al., 2001) and then provided new updated data for the years 1998–2005 via a letter to the editor (Pickett et al., 2006). Both South Korean studies used the same database, one screened births between 2002 and 2012 (Yoo et al., 2022) and the second births between 2007 and 2014 (Kim et al., 2021). A paper focusing on ASD patients with substance use disorders reported a number of deaths for this group but it is unclear as to whether this was their cause of death (Huang et al., 2021). These deaths have been added to Table 3 under the subheading 'Other'.

Of the 17 papers that stated an age range, the youngest participants were 1 year old (Bourke et al., 2017) and the oldest were 89 (Kirby et al., 2019). Most of the studies focused on adult mortality and only three studies reported exclusively on children (Kim et al., 2021; Schendel et al., 2016; Yoo et al., 2022). Eight papers included individuals of all ages (Cassidy et al., 2022; Guan and Li, 2017; Hirvikoski et al., 2016; Huang et al., 2021; Pickett et al., 2011; Pickett et al., 2006; Shavelle and Strauss, 1998; Shavelle et al., 2001). Details of all the study characteristics for the included papers are presented in Table 1.

3.3. All-cause mortality

23 of the 26 papers in this systematic review included data on all-cause mortality. Across all 23 studies regarding all-cause mortality, >3600 deaths were reported. The highest number of deaths was reported for an ASD population of all ages and included 986 deaths based on hospital mortality records in the US from 1999 to 2014 (Guan and Li, 2017). The highest reported percentage of deaths by sample size was 9.5 % (29 deaths/305 in children and young people aged 3–25 years old) (Bilder et al., 2013). Out of those 29 deaths, 27 occurred among people with ASD and co-occurring intellectual disabilities (Bilder et al., 2013). The lowest number of deaths reported was six which was found in two independent papers with a sample size of 120 of adults (Billstedt et al., 2005) and 9,754 of children and young people (Smith et al., 2021) respectively. The lowest reported percentage of deaths by sample size was 0.06 % (6 deaths/9,754 participants) in children and young people aged 5–24 years old (Smith et al., 2021).

Five different inferential statistics were used to evaluate all-cause mortality in 21 papers, with two papers not reporting any (Billstedt et al., 2005; Pickett et al., 2011). Standardised mortality ratios and hazard ratios were most commonly reported. The highest standardised mortality ratio was 5.6 (95 % Confidence interval (CI) 2.5–10.5) in a study of adults (Gillberg et al., 2010), with the lowest being 1.1 (95 %CI 0.4–1.9) for children and young people aged 5–24 years old (Smith et al., 2021). The highest hazard ratio was reported for children and young people aged 3–25 years old at 11.59 (95 %CI 6.24–21.53) when adjusting for confounding factors such as maternal age, birth weight and gestational age and 9.91 (95 %CI 5.70–17.22) without adjustment (Bilder et al., 2013). The lowest unadjusted hazard ratio was 2.1 (95 %CI 1.0–4.2) and was found in autistic children and young people aged 1–25 years old with co-occurring intellectual disabilities (Bourke et al., 2017). The lowest adjusted hazard ratio was reported at 1.51 for adults 18 years or older when adjusted for a number of variables such as age, race/ethnicity, type of health insurance and median household income (Akobirshoev et al., 2020). Findings on all-cause mortality rates can be found in Table 2.

3.4. Cause-specific mortality

19 papers included data on cause-specific mortality. The most commonly reported cause of death was from external causes (suicides, accidents, asphyxiation, drowning etc.), with 8 papers reporting specifically on suicide and 14 papers reporting deaths from other external causes. Twelve papers included data on deaths caused by diseases of the nervous system, with epilepsy being the most common cause of death within this category. One of the papers presented data for 14 categories of causes as per the ICD-10 classification in an autistic population of all ages (Hirvikoski et al., 2016). In this study, the circulatory system conditions were the most common cause of death (Hirvikoski et al., 2016). When comparing individuals with and without co-occurring intellectual disabilities, the group with ASD and intellectual disability had a particularly high risk of mortality from mental and behavioural disorders, conditions of nervous and respiratory systems and congenital malformations whilst the autistic individuals without intellectual disability had a higher risk of mortality from suicide (Hirvikoski et al., 2016). Two papers, one on adults and one on children and young people, could not report the exact number of deaths for some causes, as the low number of deaths would breach patient confidentiality (Akobirshoev et al., 2020; Smith et al., 2021).

The highest hazard ratio was reported for the external causes, more specifically intentional self-harm in children and young people, at 4.6 (95 %CI 2.7–8.0), with a higher proportion of deaths occurring in individuals with mental/behavioural co-morbidities, including but not exclusive to intellectual disabilities (Schendel et al., 2016). The highest SMR reported was regarding asphyxiation of individuals of all ages with ASD and co-occurring moderate, severe or profound intellectual disabilities at 51.4 (no CI reported) (Shavelle et al., 2001). The highest proportionate mortality ratio was reported for deaths at any age caused by drowning at 39.89 (95 %CI 31.34–50.06) but the study did not compare mortality rates for people with ASD with or without co-occurring intellectual disabilities (Guan and Li, 2017). The highest odds ratio reported was at 19.10 (95 %CI 11.94–30.55) for deaths at any age caused by congenital

malformations for all people with ASD in study but the odds ratio was particularly high for the group with co-occurring intellectual disabilities when compared to the group with ASD only (38.75 vs. 10.38) (Hirvikoski et al., 2016).

Two papers reported odds ratios for several different cause of death, so a comparison of odds ratios was possible (Akobirshoev et al., 2020; Hirvikoski et al., 2016). For deaths due to all diseases of the nervous system (7.49, 95 %CI 5.78–9.72) (Hirvikoski et al., 2016) and for deaths due to diseases of the nervous system excluding paralysis (5.21, 95 %CI 3.98–6.80) (Akobirshoev et al., 2020) was reported. Findings on cause-specific mortality in people with ASD can be found in Table 3.

3.5. Quality assessment and risk of bias

The overall quality of the papers was high, with a low risk of bias found in the majority of items for each paper as per the cohort study CASP checklist (CASP, 2020). 13 of the 26 papers had an overall low risk of bias or 'A′ rating as per the rating scale described in the methodology section. Three papers had an overall unknown risk of bias ('B′ rating) and further 10 had a high risk of bias ('C′ rating). Of the papers with a high risk of bias, the majority only had one or two components of the checklist rated as such. Five of the papers were classed as having a high risk of bias due to the study not identifying the important confounding factors (e.g., co-morbidities, age or gender) and/or not taking them into account in terms of design or analysis (Bilder et al., 2013; Billstedt et al., 2005; Gillberg et al., 2010; Guan and Li, 2017; Pickett et al., 2011). Three papers had a high risk of bias due to the recruitment methods utilised in the studies, as the authors included their own patients in the respective studies; hence, drawing on highly selective, clinical samples and decreasing the comparability of the findings to other papers (Bilder et al., 2013; Billstedt et al., 2005; Gillberg et al., 2010). Some studies only evaluated data from one particular year (e.g., Isager et al., 1999; Mouridsen et al., 2008; Pickett et al., 2011). Therefore, data from these studies may not be a true representation of the mortality risk over a longer time period. Several studies were reliant on database screening of inpatient care to assess the mortality of people with ASD, making comparisons with other non-clinical studies difficult (Akobirshoev et al., 2020; Guan and Li, 2017; Pickett et al., 2011). The quality assessment scores for each study can be found in Table 1.

4. Discussion

4.1. Principle findings and interpretation

The reviewed evidence shows that people with ASD experience an increased risk of mortality when compared to the general population. Regarding all-cause mortality, in all but one study on children and young people (Smith et al., 2021) the data indicated that people with ASD had a significantly higher mortality than the general population. Of the reviewed studies, one paper with a large sample size (n = 27,122) found people with ASD of all ages to be 2.5 times more likely to die than non-autistic controls (OR=2.56, 95 % CI 2.38–2.76) (Hirvikoski et al., 2016). Of the 21 studies that reported inferential statistics on all-cause mortality (e.g., OR, SMR, HR), 15 found people with ASD to have at least a two times higher risk of dying when compared to the general population. After adjusting for confounding factors such as mothers' age at subjects' birth and birth weight, one study on children and young people found a 12 times higher likelihood of death amongst the ASD population (HR=11.59, 95 % CI 6.24–21.53) (Bilder et al., 2013).

Moreover, although males are diagnosed with ASD at a much greater rate than females, 11 of the included studies suggest that females with ASD are at an even greater risk of death when compared to their male counterparts (Bilder et al., 2013; Gillberg et al., 2010; Hirvikoski et al., 2016; Hwang et al., 2019; Kim et al., 2021; Lunsky et al., 2022; Mouridsen et al., 2008; Schendel et al., 2016; Shavelle and Strauss, 1998; Shavelle et al., 2001; Yoo et al., 2022). In large sample sizes of children, reported hazard ratios for all-cause mortality were more than two times higher for girls than for boys with ASD when adjusting for sex, income, area of residence and year of birth (e.g., Kim et al., 2021; Yoo et al., 2022). In large samples of all ages, the trends were similar (e.g., Shavelle et al., 2001; Schendel et al., 2016). However, one study comparing mortality between men and women with and without co-occurring intellectual disabilities reported that mortality was higher for women only in the group with co-occurring intellectual disabilities (females: OR=8.52 vs. males: OR=4.88) (Hirvikoski et al., 2016). In the group with autism only, mortality was higher for men but differences in odds ratios were significantly less pronounced (females: OR=1.88 vs. males: OR=2.49), suggesting that the impact of co-occurring intellectual disabilities on mortality in ASD is greater than the impact of gender and that co-occurring intellectual disability may be one of the most important risk factors in premature mortality, having a large effect on both all-cause mortality and potentially some specific causes of death in the population with ASD.

Five studies reported increased premature mortality amongst people with ASD and a co-occurring intellectual disability when compared to people with ASD without an intellectual disability (Bilder et al., 2013; DaWalt et al., 2019; Hirvikoski et al., 2016; Hwang et al., 2019; Shavelle et al., 2001). Within these studies, a significant proportion of all reported deaths occurred in individuals with co-occurring intellectual disabilities. In one paper on children and young people, 27/29 (93 %) of deaths were recorded for individuals with co-occurring intellectual disabilities (Bilder et al., 2013). Similarly, in a study of adolescents and adults, 21/26 (80.8 %) deaths were recorded for individuals with co-occurring intellectual disabilities (DaWalt et al., 2019). One paper on people with ASD of all ages reported an overall mortality odds ratio of 5.78 (95CI % 4.94–6.75) for individuals with co-occurring intellectual disabilities compared to 2.18 (95 %CI 2.00–2.38) for individuals with autism only. Additionally, the rates were significantly higher for women with co-occurring intellectual disabilities compared to women with autism only (8.52 vs. 1.88 respectively). For men, co-occurring intellectual disabilities had a mortality odds ratio of 4.88 compared to 2.49 in a group of men with autism only (Hirvikoski et al., 2016).

The reviewed literature also suggests that people with ASD have a higher risk of dying from certain causes compared to the general population. Diseases of the nervous system, external causes such as suicide, particularly in populations without co-occurring

Table 3
Findings on cause-specific mortality.

Author and date of publication	Number of all deaths in ASD sample	Deaths due to specific cause in ASD sample	Deaths due to specific cause in control group	Odds Ratio (OR), Hazard ratios (HR), Standardised mortality ratio (SMR), Proportionate mortality ratio (PMR), Relative Risk (RR)
Cause of death: Infection				
Bilder et al. (2013)	n = 29	Staphylococcus septicaemia= 1	Not reported	Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 5 ASD with ID=N/A, ASD only=N/A	Unspecified= 245	OR= 1.83 (95 %CI 0.75–4.30) ASD with ID OR=N/A ASD only OR=N/A
Mouridsen et al. (2008)**	n = 26	Septicaemia= 1	No control	Not reported
Cause of death: Neoplasm				
Bilder et al. (2013)	n = 29	Acute lymphocytic leukaemia= 1 Benign neoplasm= 1	Not reported	Not reported
Billstedt et al. (2005)*	n = 6	Cerebral malignancy= 1	No control	Not reported
DaWalt et al. (2019)	n = 26	Unspecified= 5	No control	Not reported
Gillberg et al. (2010)*	n = 9	Cerebral malignancy= 1	No control	Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 88 ASD with ID= 14 ASD only= 74	Unspecified= 4493	OR= 1.80 (95 %CI 1.46–2.23) ASD with ID OR = 2.12 (95 % CI 1.25–3.61) ASD only OR = 1.75 (95 % CI 1.39–2.21)
Hwang et al. (2019)	n = 244	Unspecified= 31	Not reported	Not reported
Lunsky et al. (2022)	n = 259	Unspecified(male)= 24 Unspecified(female)= 23	Unspecified(male)= 47 Unspecified(female)= 40	Not reported
Mouridsen et al. (2008)**	n = 26	Lymphoma= 1 Pulmonary neoplasm= 1	No control	Not reported
Shavelle et al. (2001)	n = 202	Unspecified= 21	Not reported	No or mild Intellectual disability with comorbid ASD: SMR= 1.9 Moderate, severe or profound Intellectual disability with comorbid ASD: SMR= 2.9
Cause of death: Endocrine system				
Akobirshoev et al. (2020)	n = 462	Hypothyroidism= 61 Obesity= 35	Hypothyroidism= 41 Obesity= 47	Hypothyroidism: OR= 4.47 (95 %CI 3.01–6.64) Obesity: OR= 2.24 (95 %CI 1.44–3.46)
Bilder et al. (2013)	n = 29	Unspecified= 1	Not reported	Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 19 ASD with ID= 5 ASD only= 14	Unspecified= 474	OR= 8.89 (95 %CI 3.52–22.41) ASD with ID OR = 8.89 (95 % CI 3.52–22.41) ASD only OR = 3.07 (95 % CI 1.80–5.23)
Cause of death: Mental and Behavioural disorders				
Akobirshoev et al. (2020)	n = 462	Psychoses= 54	Psychoses= 24	Psychoses: OR= 6.76 (95 %CI 4.18–10.93)
Bilder et al. (2013)	n = 29	Intellectual disability not otherwise specified= 1	Not reported	Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 30 ASD with ID= 14 ASD only= 16	Unspecified= 925	OR= 2.80 (95 %CI 1.94–4.03) ASD with ID OR = 21.81 (95 % CI 12.20–39.00) ASD only OR = 1.58 (95 % CI 0.96–2.59)
Cause of death: Nervous system				
Akobirshoev et al. (2020)	n = 462	Other neurological disorders= 147 Paralysis= 52	Other neurological disorders= 85 Paralysis= 53	Other neurological disorders: OR= 5.21 (95 %CI 3.98–6.80) Paralysis: OR= 2.95 (95 %CI 2.01–4.32)
Bilder et al. (2013)	n = 29	Convulsions= 1 Seizures= 5 Unspecified= 2	Not reported	Not reported
Billstedt et al. (2005)*	n = 6	SUDEP= 2	No control	Not reported
DaWalt et al. (2019)	n = 26	Seizures= 3	No control	Not reported
Gillberg et al. (2010)*	n = 9	Cerebral infection= 1 SUDEP= 3	No control	Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 62 ASD with ID= 32 ASD only= 30	Unspecified= 737	OR= 7.49 (95 %CI 5.78–9.72) ASD with ID OR = 40.56 (95 % CI 26.82–61.33) ASD only OR = 3.98 (95 % CI 2.76–5.74)

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Table 3 (*continued*)

Author and date of publication	Number of all deaths in ASD sample	Deaths due to specific cause in ASD sample	Deaths due to specific cause in control group	Odds Ratio (OR), Hazard ratios (HR), Standardised mortality ratio (SMR), Proportionate mortality ratio (PMR), Relative Risk (RR)
Hwang et al. (2019)	n = 244	Nervous system and sense organ disorders= 33	Not reported	Not reported
Isager et al. (1999)**	n = 12	Epileptic attack= 2 Meningitis= 1	No control	Not reported
Lunsky et al. (2022)	n = 259	Unspecified(male)= 20 Unspecified(female)= 9	Unspecified(male)=Not reported Unspecified(female)= 8	Not reported
Mouridsen et al. (2008)**	n = 26	Epileptic attack= 4 Meningitis= 1	No control	Not reported
Schendel et al. (2016)	n = 68	Neurologic= 7	Not reported	HR= 4.1 (95 %CI 2.0–8.8)
Shavelle et al. (2001)	n = 202	Seizures= 15 Unspecified= 10	Not reported	No or mild Intellectual disability with comorbid ASD: Seizures: SMR= 22.6 Unspecified: SMR= 4.6 Moderate, severe or profound Intellectual disability Seizures: SMR= 36.9 Unspecified: SMR= 6.2
Cause of death: Circulatory system				
Akobirshoev et al. (2020)	n = 462	Valvular disease= 16	Valvular disease= 26	Valvular disease: OR= 1.85 (95 %CI 0.99–3.44)
Bilder et al. (2013)	n = 29	Arrythmia= 1 Congestive heart failure= 1 Mitral regurgitation= 1	Not reported	Not reported
DaWalt et al. (2019)	n = 26	Cardiac arrest= 5	No control	Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 157 ASD with ID= 24 ASD only= 133	Unspecified= 8820	OR= 1.49 (95 %CI 1.27–1.75) ASD with ID OR = 4.61 (95 % CI 3.06–6.95) ASD only OR = 1.33 (95 % CI 1.12–1.58)
Lunsky et al. (2022)	n = 259	Unspecified(male)= 22 Unspecified(female)= 18	Unspecified(male)= 33 Unspecified(female)= 15	Not reported
Mouridsen et al. (2008)**	n = 26	Acute ischaemic heart disease= 1 Cardiac incompensation= 1 Cardiomyopathy= 1 Myocardial infarction= 2	No control	Not reported
Shavelle et al. (2001)	n = 202	Unspecified= 22	Not reported	No or mild Intellectual disability with comorbid ASD: SMR= 2.3 Moderate, severe or profound Intellectual disability: SMR= 3.8
Cause of death: Respiratory system				
Bilder et al. (2013)	n = 29	Pneumonia= 3	Not reported	Not reported
DaWalt et al. (2019)	n = 26	Respiratory failure or pneumonia= 3 (data not separated in paper)	No control	Not reported
Gillberg et al. (2010)*	n = 9	Pneumonia= 1	No control	Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall = 45 ASD with ID= 10 ASD only= 35	Unspecified= 1351	OR= 2.68 (95 %CI 1.99–3.62) ASD with ID OR = 13.92 (95 % CI 7.04–27.50) ASD only OR = 2.17 (95 % CI 1.55–3.05)
Isager et al. (1999)**	n = 12	Pneumonia= 2	No control	Not reported
Lunsky et al. (2022)	n = 259	Unspecified(male)=Not reported Unspecified(female)= 7	Unspecified(male)= 13 Unspecified(female)= 10	Not reported
Mouridsen et al. (2008)**	n = 26	Pneuonia= 4	No control	Not reported
Shavelle et al. (2001)	n = 202	Unspecified= 13 (primarily pneumonia)	Not reported	No or mild Intellectual disability with comorbid ASD: SMR= 1.3 Moderate, severe or profound Intellectual disability: SMR= 10.8
Cause of death: Digestive system				
Bilder et al. (2013)	n = 29	Pancreatitis= 1 Unspecified= 1	Not reported	Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 27 ASD with ID= 8 ASD only= 19	Unspecified= 733	OR= 3.31 (95 %CI 2.25–4.87) ASD with ID OR = 9.13 (95 % CI 4.42–18.87) ASD only OR = 2.61 (95 % CI 1.65–4.12)

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Table 3 (*continued*)

Author and date of publication	Number of all deaths in ASD sample	Deaths due to specific cause in ASD sample	Deaths due to specific cause in control group	Odds Ratio (OR), Hazard ratios (HR), Standardised mortality ratio (SMR), Proportionate mortality ratio (PMR), Relative Risk (RR)
Lunsky et al. (2022)	n = 259	Unspecified(male)= 13 Unspecified(female)=Not reported	Unspecified(male)= 9 Unspecified(female)=Not reported	Not reported
Mouridsen et al. (2008)**	n = 26	Appendicitis= 1	No control	Not reported
Shavelle et al. (2001)	n = 202	Unspecified= 13	Not reported	No or mild Intellectual disability: SMR= 1.2 Moderate, severe or profound Intellectual disability: SMR= 7.5
Cause of death: Genitourinary system				
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 12 ASD with ID=N/A ASD only=N/A	Unspecified= 253	OR= 3.82 (95 %CI 2.13–6.84) ASD with ID OR = N/A ASD only OR = N/A
Isager et al. (1999)**	n = 12	Urethral bleeding= 1	No control	Not reported
Cause of death: Congenital malformations				
Bilder et al. (2013)	n = 29	Congenital abnormal heart= 1 Microcephaly= 1 Trisomy 8 = 1	Not reported	Not reported
Billstedt et al. (2005)*	n = 6	Heart malformation= 1	No control	Not reported
Gillberg et al. (2010)*	n = 9	Heart malformation= 1	No control	Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 21 ASD with ID= 13 ASD only= 8	Unspecified= 106	OR= 19.10 (95 %CI 11.94–30.55) ASD with ID OR = 38.75 (95 %CI 20.39–73.64) ASD only OR = 10.38 (95 %CI 4.98–21.61)
Shavelle et al. (2001)	n = 202	Unspecified= 16	Not reported	No or mild Intellectual disability: SMR= 2.0 Moderate, severe or profound Intellectual disability: SMR= 9.4
Cause of death: Symptoms, Signs and abnormal findings, other				
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 14 ASD with ID=N/A ASD only=N/A	Unspecified= 618	OR= 1.81 (95 %CI 1.06–3.08) ASD with ID OR = N/A ASD only OR = N/A
Cause of death: External causes - Suicide				
Cassidy et al. (2022)	n = 40	Suicide = 37 Self harm = 3	Suicide= 273 Self harm= 59	Suicide: OR= 11.08 (95 % CI 3.92–31.31) Self harm: Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 83 ASD with ID= 7 ASD only= 76	Unspecified= 1094	OR= 7.55 (95 %CI 6.04–9.44) ASD with ID OR = 2.41 (95 % CI 1.14–5.11) ASD only OR = 9.40 (95 %CI 7.43–11.90)
Isager et al. (1999)**	n = 12	Jump= 1 Overdose= 1	No control	Not reported
Jokiranta-Olkoniemi et al. (2020)	n = 53	Suicide= 12	Suicide= 23	Suicide: HR= 2.1 (95 %CI 1.02–4.1)
Kirby et al. (2019)	n = 49	Violent* ** =36 Nonviolent* ** *= 13		1998–2002: RR= 0.46 (95 %CI 0.11–1.83) 2003–2007: RR= 0.66 (95 %CI 0.28–1.59) 2008–2011: RR= 0.95 (95 %CI 0.56–1.61) 2013–2017: RR= 1.56 (95 %CI 1.08–2.26)
Kölves et al. (2021)	n = 53	Suicide= 53	Suicide= 14,144	IRR 1.68 aIRR 3.75 (95 % CI 2.85–4.92) (adjusted for age, sex and period)
Mouridsen et al. (2008)**	n = 26	Jump= 1 Overdose= 1	No control	Not reported
Pickett et al. (2011)	n = 23	Suicide= 1	No control	Not reported
Cause of death: External causes – Other external causes				
Bilder et al. (2013)	n = 29	Poisoning= 2 Superficial injury to trunk= 1	Not reported	Not reported
Billstedt et al. (2005)*	n = 6	Accident= 1	No control	Not reported
DaWalt et al. (2019)	n = 26	Choking on food= 2 Medication side effects= 2 Poisoning= 1	No control	Not reported

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Table 3 (*continued*)

Author and date of publication	Number of all deaths in ASD sample	Deaths due to specific cause in ASD sample	Deaths due to specific cause in control group	Odds Ratio (OR), Hazard ratios (HR), Standardised mortality ratio (SMR), Proportionate mortality ratio (PMR), Relative Risk (RR)
Gillberg et al. (2010)*	n = 9	Accident= 1	No control	Not reported
Guan and Li (2017)	n = 1367	Injury = 381 Comprises of: Asphyxiation= 78 Drowning= 74 Suffocation= 90 Other= 139	Not reported	Injury overall: PMR= 2.93 (95 %CI 2.64–3.24) Asphyxiation: PMR= 13.50 (95 %CI10.68–16.85) Drowning: PMR= 39.89 (95 %CI 31.34–50.06) Suffocation: PMR= 31.93 (95 %CI 25.69–39.24) Other: PMR= 1.05 (95 %CI 0.89–1.24)
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 30 ASD with ID= 6 ASD only= 24	Unspecified= 1696	OR= 1.67 (95 %CI 1.16–2.40) ASD with ID OR = 1.53 (95 % CI 0.69–3.44) ASD only OR = 1.71 (95 % CI 1.14–2.56)
Hwang et al. (2019)	n = 244	Injury and poisoning= 38	Not reported	Not reported
Isager et al. (1999)**	n = 12	Asphyxiation= 2 Drowning= 1 Overdose= 1	No control	Not reported
Jokiranta-Olkoniemi et al. (2020)	n = 53	Accident= 13	Unspecified= 29	HR= 1.8 (95 %CI 0.9–3.3)
Lunsky et al. (2022)	n = 259	Unspecified(male)= 33 Unspecified(female)= 7	Unspecified(male)= 72 Unspecified(female)= 13	Not reported
Mouridsen et al. (2008)**	n = 26	Asphyxiation= 2 Drowning= 1 Overdose= 1	No control	Not reported
Pickett et al. (2011)	n = 23	Accident= 1 Unspecified= 8	No control	Not reported
Schendel et al. (2016)	n = 68	Accident= 15 Intentional self-harm= 13	Missing information	Accident: HR= 1.4 (95 %CI 0.8–2.4) Intentional self-harm: HR= 4.6 (95 %CI 2.7–8.0)
Shavelle et al. (2001)	n = 202	Asphyxiation= 8 Drowning= 11 Unspecified= 30 (mostly motor vehicle accidents)	Not reported	No or mild Intellectual disability with comorbid ASD: Asphyxiation: SMR= 5.7 Drowning: SMR= 3.9 Unspecified: SMR= 1.0 Moderate, severe or profound Intellectual disability: Asphyxiation: SMR= 51.4 Drowning: SMR= 13.7 Unspecified: SMR= 3.8
Cause of death: Other				
Bilder et al. (2013)	n = 29	Unspecified = 3	Not reported	Not reported
Billstedt et al. (2005)*	n = 6	Unspecified = 1	No control	Not reported
DaWalt et al. (2019)	n = 26	Unspecified = 5	No control	Not reported
Gillberg et al. (2010)*	n = 9	Unspecified = 1	No control	Not reported
Hirvikoski et al. (2016)	n = 706	Unspecified: Overall= 15 ASD with ID=N/A ASD only=N/A	Unspecified= 232	OR= 5.84 (95 %CI 3.46–9.86) ASD with ID OR = N/A ASD only OR = N/A
Huang et al. (2021)	n = 6599	Substance use disorder= 3	Substance use disorder= 4	HR= 3.17 (95 % CI 2.69–3.89)
Mouridsen et al. (2008)**	n = 26	Unspecified = 1	No control	Not reported
Pickett et al. (2011)	n = 23	Unspecified= 3	No control	Not reported
Shavelle et al. (2001)	n = 202	Unspecified= 43	Not reported	Not reported

List of abbreviations: ASD=autism spectrum disorders; CI=Confidence interval; HR=Hazard ratio; IRR= Incidence Rate Ratio; MR=Mortality ratio; OR=odds ratio; PRM=proportionate mortality ratio; RR=Relative risk; SMR=standardised mortality ratio; SUDEP=Sudden Unexpected Death in Epilepsy

*Same cohort of patients used

**Same cohort of patients used

***Violent included=firearm/gunshot, hanging or strangulation, and blunt force injury (e.g., jumping from a high point, stepping in front of a train)

****Nonviolent included: poisoning by asphyxiants (e.g., carbon monoxide) and intoxication (e.g., drug overdose)

intellectual disabilities (OR=9.40; Hirvikoski et al., 2016), accidents, drowning and suffocation and diseases of the circulatory system were consistently the leading causes of deaths across the reviewed studies. In comparison, the leading causes of deaths in the general population include the diseases of the circulatory system and neoplasms (Richtich & Roser, 2018).

Epilepsy was identified across seven different papers as causing a particularly high mortality rate amongst the ASD population. One study reported an SMR of 36.9 for ASD patients of all ages with co-occurring moderate, severe or profound intellectual disabilities and epilepsy (Shavelle et al., 2001).

4.2. Strengths and limitations

The strengths of this review include its prospective registration with PROSPERO, comprehensive search strategy including multiple databases, clear inclusion and exclusion criteria and dual screening of study eligibility and quality assessment.

The limitations include the lack of comparability between studies due to the use of different descriptive and/or inferential statistics to assess mortality, which precluded a meaningful meta-analysis of the findings. All papers included in the review had been conducted in high income countries, so the findings may not be applicable to other research and socioeconomic contexts. Additionally, this review is limited by the exclusion of papers not written in English. Data extraction was performed only by the first reviewer (LF) but was undertaken systematically using a structured database.

4.3. Implications for practice

Recognising the increased mortality that people with ASD experience is an important factor in how clinicians, support workers and healthcare systems in general should plan and approach care for this population. Although a significant portion of deaths in this group occurs due to intentional or unintentional external causes, the literature also indicates that many people with ASD die from underlying health conditions. Therefore, as the increased mortality risk seems to be partially mediated by the co-occurrence of other conditions, it is of great importance to provide an increased level of support and care for this population. Other research has highlighted the lack of adequate and appropriate healthcare services for adults with ASD and in particular autistic people without an intellectual disability (Calleja et al., 2020). It is imperative to develop appropriate resources and tools that will assist adults with ASD in accessing healthcare and help ensure that comorbid conditions with an increased prevalence in this population are actively assessed for, diagnosed and treated by the healthcare system. Increased support in the transition from the paediatric healthcare system to the adult equivalent is just one way to tackle this issue.

Nine studies included in this review reported on several deaths with an unspecified cause. The lack of clarity surrounding causes of deaths in the ASD population needs to be addressed in future studies. More autopsies need to be completed to ascertain the true circumstances surrounding the deaths of people with ASD. This will increase the validity of the conclusions that can be gathered about the most common causes of death in the ASD population. Additionally, national patient and death registers could be used to record and monitor clinical diagnoses of ASD and specific causes of death in autistic individuals in countries where these data are not currently readily available to researchers. Existing studies utilising such registers with routinely collected health data to investigate mortality in autism clearly highlight the strengths of such methodological approach, including large study populations with high statistical power and good validity of the registers (e.g., Akobirshoev et al., 2020; Hirvikoski et al., 2016).

4.4. Further research

As the prevalence of ASD continues to increase, it is essential that more research is completed to understand why this population experiences an increased premature mortality risk. Additionally, research focused on building an understanding of the biological mechanisms of different comorbid conditions such as epilepsy and how they specifically link to premature mortality in people with ASD is needed. Understanding these mechanisms can help assess the extent to which premature mortality can be avoided in the autistic populations either through timely and effective healthcare interventions, including secondary prevention and treatment (treatable mortality, previously known as amenable mortality, for example, deaths due to diabetes and respiratory infections) or through public health and primary prevention interventions (preventable mortality, for example, deaths due to obesity or alcohol misuse) (ONS, 2020). The only study of avoidable mortality to date, which included an autistic population of children and young people, cautiously concluded that some deaths in the group with autism could have been avoided through high quality care but did not report rates of avoidable mortality (Smith et al., 2021). Despite including a large cohort of children and young people with and without autism, the study was limited in its statistical power, in that only a small number of deaths occurred in the group with autism. Further investigation of avoidable mortality in autistic individuals on a larger scale is necessary. Given an increased risk of suicide death, further research is also required to assess the link between ASD, co-occurring psychiatric conditions and the possibility of increased suicide attempts or ideation, especially since mental health conditions, and in particular depressive symptoms, are the most frequently reported factors in relation to suicide risk among autistic adults (Mournet et al., 2023).

All the studies in this review came from high income countries and may not be, therefore, a true representation of the overall mortality and causes of deaths in people with ASD in poorer socioeconomic contexts. More quantitative research is needed from a variety of countries and socioeconomic backgrounds to accurately identify the main outcomes in distinct geographical locations.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data availability

This research is a systematic review only and does not include any original data.

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