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Respiratory-associated deaths in people with intellectual disabilities: a systematic review and meta-analysis

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Title: "Respiratory-associated deaths in people with intellectual disabilities: a systematic review and meta-analysis"

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ABSTRACT

Objective To review and synthesise evidence on rates of respiratory-associated deaths and associated risk factors in the ID population.

Design Systematic review with meta-analysis

Data sources MEDLINE, CINAHL, ISI Web of Science, and PsychINFO were searched for studies published between January 1985 to April 2020 and examined study and outcome quality. Reference lists and Google Scholar were also hand searched.

Results We identified 2,063 studies, 17 were included in the narrative synthesis and 10 in the meta-analysis. Data from 90,302 people with ID and 27,394 deaths were extracted. Significantly higher rates of respiratory-associated deaths were found among people with ID (SMR 10·86 (95% CI 5·32, 22·18, p<0·001), lesser rates for adults (SMR 6·53 (95% CI 4·29,9·96, p<0·001); and relatively high rates from pneumonia 26·65 (95% CI 5·63, 126·24, p<0·001). The overall statistical heterogeneity was I^2= 99·0%.

Conclusion Premature deaths due to respiratory disorders are potentially avoidable with improved public health initiatives and equitable access to quality health care. Further research should focus on developing prognostic guidance and validated tools for clinical practice to mitigate risks of respiratory-associated deaths.

PROSPERO registration number CRD42020180479

Article summary

Strengths and limitations of this study

- The meta-analysis included mortality ratios from ten observational studies covering 1,844 respiratory deaths in people with intellectual disabilities.
- A rigorous and systematic analysis process was undertaken which minimised the risk of bias, errors and omissions.
- Meta-regression was not performed on predictors or factors reported in studies which increase SMRs for respiratory deaths

Introduction

People with intellectual disabilities account for approximately 1-3% of the global population.[1,2] The World Health Organisation (1992)[3] defines intellectual disabilities as impairments in adaptive functioning, social functioning, and intellectual functioning, (IQ<70) requiring a need for daily support, with the onset in the developmental phase (<18 years). Life

expectancy and mortality rates are important indicators of health inequality.[4] People with intellectual disabilities die up to 20 years earlier than the general population.[5-8] Respiratory disorders are a leading cause of death among people with intellectual disabilities.[6,9] The range of standardised mortality ratios (SMRs) due to respiratory disorders for people with intellectual disabilities are very high in some studies,[10-12] and much lower in others.[13-15] This systematic review and meta-analysis aims to investigate and quantify the risk of, and factors associated with, respiratory-associated deaths in people with intellectual disabilities.

Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16] This review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42020180479).

Eligibility

This systematic review included studies with individuals with intellectual disabilities and a comparison group of individuals in the general population, with respiratory disorders included as a separate cause of death. For studies that included multiple disabilities, at least 70% of participants had to have intellectual disabilities, if results were not reported separately. Studies also had to be full-text, peer-reviewed, and published in English. To be included in the meta-analysis, studies had to report SMRs with 95% confidence intervals for respiratory associated deaths or provide sufficient data to calculate SMRs. Studies were excluded if they focused on specific etiologies of intellectual disabilities, such as Down syndrome, were excluded as these are associated with a different health and mortality profiles compared to other people with intellectual disabilities. Studies focused on post-operative and post-treatment deaths were excluded as these are not representative of the wider population with intellectual disabilities. Studies with small samples (<20 participants) or case series designs were also excluded as these papers are less representative.

Search strategy and selection criteria

We searched Embase, ISI Web of Science (all databases), CINAHL, and PsycINFO from 1st January 1985 to the 27th of April 2020, using comprehensive terms related to 'intellectual disabilities', 'mortality', and 'respiratory disease' (full search strategy in Appendix 1). In addition, a manual bibliography and citation search of included studies was conducted using

Google Scholar and key researchers in the field of mortality in individuals with intellectual disabilities were emailed to identify any additional relevant papers. The aforementioned eligibility criteria was used. After duplicates were removed, all records were imported into Covidence software (www.covidence.org) for title and abstract and full text screening. All titles, abstracts (CM & AMcG) and full-texts (CM, AMcG, ER) were double-screened with inter-rater reliability (Cohen's kappa) of $\kappa = \cdot 57$ and $\kappa = \cdot 58$, respectively.

Data Extraction

Data extraction was conducted using a structured database created in Excel. Five researchers (GS, LHM, DK, KD, AMcG) each extracted data from 25% of the included studies and, to check reliability, one other researcher (CM) independently extracted data from 20% of included studies. Extracted data were compared in meetings and discrepancies resolved through consensus discussion. Researchers did not extract data on included papers where they were a listed author.

Assessment of study and outcome quality

Study quality was appraised using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields.[17] Quality ratings were calculated in percentage form using the standard method[17] and categorised as weak (<55%), moderate (55-75%), or strong (>75%) quality. Each paper had quality appraisals completed by two researchers, who then agreed a consensus score for each item (Table 1).[17] Researchers did not evaluate quality of papers where they were a listed author. Risk of bias score was not used to exclude any studies from either the systematic review or meta-analysis. We evaluated the quality of our own systematic review using the Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist.[18]

***Table 1*: Characteristics of studies reporting mortality rates for respiratory disorders and pneumonia in people with intellectual disabilities**

Author	Country	Study design, setting and follow up	Data sources	ID sample (N, % female, age, level of ID)	Deaths in ID sample (N, % female, age at time of death, level of ID)	Comparison sample (N, % female, age,) and deaths (n, % female, age)	Respiratory disorder definition	Quality Percentage (assessment)
Brameld et al (2018)[26]	Australia	Retrospective matched cohort study of adults 20 years old and over. Follow up 2009-2013	Intellectual Disability Exploring Answers (IDEA) Database. Death certificate data	Total sample characteristics not available	N= 591; 43·8% female; mean age* and level of ID not available	Total sample characteristics not available. Number of deaths= 62, 917; 47·4% female; mean age not available	ICD 10-chapter codes for respiratory disorders.	95·45% (strong)
Cooper et al (2020)[28]	UK	Population-based cohort study. Follow up 2001-2018	Primary care records and health check data; Death certificate data. Comparison data from Health Board statistics	N= 962; 45·4% female; mean age= 44·1 years (range 16-83); ID Mild=382 (39·7%), Moderate=236 (24·5%), Severe=180 (18·7%), Profound=163 (17·0%)	N= 294/961 (30·6%); 47·5% female; mean age= 52·4 (SD 13·6)	Not available	ICD 10-chapter codes for respiratory disorders.	86·36% (strong)
Dupont et al. (1987)[40]	Denmark	Population- based cohort study of adults with mild ID. Follow up 1976-1984	Danish National Service for the Mentally Retarded. Death certificate data.	N = 7134; gender, age and level of ID not available	N=446; 37·9% females; age and level of ID not available	Not available	Not described	40·90% (weak)
Durvasula et al (2002)[37]	Australia	Population-based cohort study of children and adults. Follow up 1989 - 1999	ID prevalence study. Death certificate data, medical records and post-mortem data. Australian Bureau of Statistics	N = 693; 44·6% female; mean age= N/A; ID 40% mild, 35% moderate, 25% severe/profound	N=40 (6%); 45% female; median age= 32 (range 10-59); level of ID not available	N= 125,848; 51% female; mean age not available. Number of deaths= 2154; 37·8% female; mean age not available	Not described	90·91% (strong)
Forsgren et al (1996)[15]	Sweden	Population-based cohort study of adults with ID. Follow up 1986 – 1992	Board for Provision and Services to the Mentally Retarded. Death certificate data	N = 1,478; 44·5% female; age and level of ID not available	N= 247; 42·1% female; Median age= 64 years (IQR 52-75 years); ID 39·7% Mild, 31·2%, Moderate, 21·5% Severe 7·7% Profound	Not available	ICD 9-chapter codes for respiratory disorders.	81·82% (strong)

			from Swedish National Bureau of Statistics					
Glover et al (2017)[8]	UK	Population-based case control study in primary care. Follow up 2010-2014	Primary care records (CPRD). Death certificate data	Total sample characteristics not available	N = 664 deaths; 44·1% female	Total sample characteristics not available. N of deaths= 97, 379; 52·3% female; mean age not available	ICD 10-chapter codes for respiratory disorders.	81·82% (strong)
Heslop et al (2014)[5]	UK	Population based audit of deaths of children and adults with intellectual disabilities aged 4 and over. Audit period 2010-2012	Medical records Death certificate data from UK Office of National Statistics	Total sample characteristics not available	N=247; 42·1% female; median age= 64 years (IQR 52-75 years); ID 39·7% mild, 31.2% moderate, 21·5% severe, 7·7% profound	Total sample characteristics not available. Number of deaths= 480, 467; 51·6% female; median age not available		81·82% (strong)
Hollins et al (1998)[11]	UK	Cohort study of adults on an ID register. Follow up 1982-1990	Learning disability register. Death certificate data.	N = 2,026; gender, age and ID level not available	N= 268 deaths; gender and age not available; 51·5% mild-moderate, 48·5% severe-profound	Not available	Not described	81·82% (strong)
Hosking et al (2016)[24]	UK	Population-based case control study in primary care. Follow up 2009-2013	Primary care records (Clinical Practice Research Data linkage; CPRD). Death certificate data	N = 16,666; 58.1% female; mean age 39.9 (SD 16.2). 19.6% of sample had high support needs.	N=656 (3·9%); 55·6% female; age and level of ID not available	N= 113, 562; 58·1% female; mean age not available. Number of deaths= 1358 (1·2%); 60·4% female; mean age not available	ICD 10-chapter codes for respiratory disorders.	90·91% (strong)
Janicki et al (1999)[22]	USA	Cohort of adults with intellectual disabilities 40 years old and over. Follow up 1984-1993	Data from state agency with responsibility for reviewing deaths of disabled persons. Health department data.	Total sample characteristics not available.	N= 2752, 48·1% female; mean age- 65·1; ID 18%, 68% Moderate – profound (68%), 4% unspecified, 10% unknown	Total sample characteristics not available. Number of deaths= 149, 980; gender not available, mean age= 70·0	ICD 9-chapter codes for respiratory disorders.	77·27% (strong)
Ng et al (2017)[12]	Sweden	Population-based case control study of adults with ID 55 years old and over. Follow up 2002-2015	National database of hospital admissions and outpatient care. National disability register. Swedish	N = 15, 289; 45.5% females; mean age not available; level of ID not available	N= 4728; 44·9% female; age and ID level not available	N= 74, 445; 45·5% females; mean age not available. Number of deaths= 8364	ICD 10-chapter codes for respiratory disorders.	95·45% (strong)

			National Cause of Death register					
Oppewal et al (2018)[27]	Netherlands	Cohort study of adults with ID 50 years old and over living in three care organisations. Follow up Nov 2013-March 2018	Medical case notes of participants with ID who died during study period. Cause specific mortality statistics for 50+ population in the Netherlands	N = 1050; 48·7% female; mean age= 61·6 (SD 8·0, range 50-94); ID level= 2·9% borderline, 21·2% mild, 48·2% moderate, 16·4% severe, 8·7% profound;	N=207 deaths (19·7%) but only 159 with cause of death available. 60·7% female; mean age not available; ID level= 5·7% borderline, 18·9% mild, 54·7% moderate, 13·2% severe, 7·5% profound;	Not available	ICD 10-chapter codes for respiratory disorders.	50·0% (weak)
Patja et al (2001)[14]	Finland	Population based, nationwide cohort study. Follow up 1963-1997	Original 1962 population-based study (Amnell et al. 1964). Death certificate data	N = 2,369, gender, age and level of ID not available	1111 deaths with death certificates available for 1,095- 51·0% female, mean age= 57·7; ID 40·3% mild, 29·4% moderate, 11·5% severe, 18·0% profound, 0·7% unknown	Not available	ICD 9-chapter codes for respiratory disorders.	81·82% (strong)
Raitasuo et al (1997)[13]	Finland	Cohort study of adults living in an institution. Follow up 1972-1993	Medical case notes and death certificate data. General population mortality statistics for population in Finland.	N ≈ 2000; gender, age and level of ID not available	216 deaths- 42·6% female; mean age 26·7 (1-86 years); ID level 2·0% borderline, 15·0% mild, 18·0% moderate, 20·0% severe, 45.0% profound, 20·0% unknown	Not available	ICD 9-chapter codes for respiratory disorders.	54·55% (weak)
Smith et al (2020)[10]	UK	Nationwide, population based cohort study of children aged 4-19. Follow up 2008-2015.	Scottish pupils census: Death certificates data	N= 18, 278; 35% female; mean age not available	N= 106; mean age= 14·3 (95% CI 13·4 to 15·1); level of ID not available	N= 777,912; 50% female; mean age not available. number of deaths= 458; mean age= 16·1 years (95% CI 15·8 to 16·5)	ICD 10-chapter codes for respiratory disorders.	100% (strong)
Trollor et al (2017)[25]	Australia	Population based cohort study of adults 20 years old and above registered with	Disability Services Minimal Dataset. Australian Bureau	N= 19,362; 44% female, mean age= 37 (range 27-48); ID not available	N= 732 (4%); 41% female; median age = 54 (42–64), level of ID not available	Total sample characteristics not available. Number of deaths= 305, 050; 49%	ICD 10-chapter codes for respiratory disorders.	95·45% (strong)

		disability services. Follow up 2005-2011	of Statistics. Death records			female; median age= 81 (70–92).		
Tyrer and McGrother (2009)[23]	UK	Population-based cohort study of individuals with moderate-profound ID on a register. Follow up 1993-2006	Leicestershire learning disability register. Death certificate data. National Statistics 1993-2006.	N = 2,995; 41·9% female; Age and level of ID not available	N=503; gender, age and level of ID not available	Total sample characteristics not available. Number of deaths≈126, 000	ICD 9 and ICD 10-chapter codes for respiratory disorders.	72·73% (moderate)

*Individuals in the ID cohort died at a significantly younger age than the comparison cohort

Summary of outcomes and statistical analysis

Findings of all included studies were combined in a narrative synthesis. The primary goal of the meta-analysis was to investigate if the SMRs of respiratory-associated deaths differ for individuals with and without intellectual disabilities. Meta-analysis was undertaken using RevMan. Included studies reported either:

- a SMR or hazard ratio (HR)

OR

- the observed number of deaths or expected deaths necessary to calculate a SMR. These were calculated using STATA (version 14) by dividing the observed number of deaths in a cohort study group by the expected mortality based on age and gender-specific death rates in the general population comparison group.

Random effects meta-analysis (inverse of the variance method) was used to calculate the weighted mean all cause SMR across studies. As the SMR is a ratio, log transformation was needed to maintain symmetry in the analysis.[19] All values were transformed to log values for computations and back transformed for presentation of the results. Weighted mean log-SMRs and their 95% confidence intervals were reported separately for individuals with and without intellectual disabilities with the Q value and associated p value being used to assess the statistical significance of any difference in means. The magnitude of the difference and associated confidence interval (CI) were also be reported. Where data permitted, further subgroup analyses were conducted to examine sources of heterogeneity. Potential factors for consideration included sex, age group, level of intellectual disabilities, socio-economic status and ethnicity. Random effects models were used for subgroup analyses.

The Chi-squared statistic I^2 was chosen to measure level of heterogeneity across the studies, as it allows for interpretation of results regardless of the number of studies included in the meta-analysis, the type of outcome data, or effect measurement.[20] Heterogeneity was interpreted as not observed when I^2=0%, low when I^2=25%, medium when I^2=50%, and high when I^2=75%.[20] Random effects models were selected for this analysis due to the different populations and measures in the included studies.

Sensitivity analysis

Sensitivity analysis was used to assess the impact of risk of bias for each study on the weighted mean SMR. Data were removed one-by-one from the meta-analysis for each study, beginning with the lowest ranked papers, to determine their effect and re-estimate the weighted mean

SMR. Cumulative analysis, starting with larger studies and sequentially adding smaller studies, was used to investigate how the weighted mean SMR estimate changes as small studies are added.[21]

Patient and public involvement

No patient and public involved.

Results

Figure 1 summarises the systematic search, selection and reasons for exclusion. All 17 studies were included in the narrative synthesis and 10 were included in the meta-analysis. A full list of studies excluded from full-text screening is available in Appendix 3.

[Insert Figure 1: PRISMA flow diagram of systematic search and selection]

Table 1 illustrates the characteristics of studies reporting mortality rates for respiratory disorders and pneumonia in people with intellectual disabilities and table 2 presents all-cause mortality and deaths from respiratory disorders in people with intellectual disabilities.

Table 2: **All-cause mortality and deaths from respiratory disorders in people with intellectual disabilities**

Author	All-cause mortality	Deaths from respiratory disorders	Between group comparison of deaths from respiratory disorders	Deaths from individual respiratory disorders	Between group comparison of deaths from individual respiratory disorders	Variables associated with risk of death from respiratory disorders
Brameld et al (2018)[26]	591 had ID /63,508 out of all deaths (0·93%)	62/591 (10·5%) deaths	Not available	Emergency Department presentations in the last year of life: Influenza and pneumonia RR=2·6 (95% CI 2·0-3·4 p<0·001) Chronic obstructive pulmonary disease (COPD) RR=0·8 (95%CI 0·5-1·6, p=0·596) Asthma RR=4.7 (95%CI 2·1-10·4, p<0·001) Ear, nose and throat infections RR=1·9 (95%CI 0·8-4.0, p=0·122) Pneumonitis due to solids/liquids RR=17·9 (95%CI 11·3-28·3 p<0·001) Hospital admissions in the last year of life: Influenza and pneumonia RR=2·3 (1·0-5·3, p=0·044) COPD RR=1·4 (95%CI 0·9-2·4, p=0·164) Asthma RR=4·6 (95%CI 1·4-15·0, p=0·011) Ear, nose and throat infections RR=0·0 (95%CI 0·0-., p=0·972) Pneumonitis due to solids/liquids RR=17·6 (95%CI 11·7-26·5, p<0·001)	Decedents with intellectual disability had increased odds of dying of (relative odds of having condition listed as underlying cause of death), adjusted for comorbidity: Influenza/pneumonia (OR=5·3, 95% CI 2·4-11·8) Pneumonitis due to solids or liquids (OR=9·9, 95% CI 5·1-19·3) Asthma (OR=2·3, 95% CI 1·0=5·2) (not significant) No difference for COPD as cause of death	Decedents with intellectual disability had increased A&E attendance but received less hospital-based specialist palliative care. For those in hospitals, they were more likely to have hospital stays involving intensive care and ventilator support.

Cooper et al (2020)[28]	294/ 961 (30·6%) deaths **SMR = 2·24 (95% CI; 1·98, 2·49)**	Underlying cause of death: 57/ 262 (21.8%) deaths **SMR= 6·78 (95% CI; 5·02, 8·54)**	Underlying cause of death: Down syndrome: 8/ 57 (14·0%) deaths Without Down syndrome: 49/ 205 (23·9%) deaths	All-contributing factors in death: Respiratory infection = 27·1% deaths Aspiration/ reflux/ choking = 19·8% deaths	Underlying cause of death: Down syndrome: Aspiration/ reflux/ choking = <5/ 57 deaths Respiratory infection = <5/ 57 deaths Other respiratory conditions = <5/ 57 deaths Without Down syndrome: Aspiration/ reflux/ choking = 22/ 205 (10·8%) deaths Respiratory infection = 21/ 205 (10·3%) deaths Other respiratory conditions = 9/ 205 (4·4%) deaths All-contributing factors in death: Down syndrome: Respiratory infection = 22/ 57 (38·6%) deaths Aspiration/ reflux/ choking = 11/ 57 (19·3%) deaths Other respiratory conditions = <5/ 57 deaths Without Down syndrome: Respiratory infection = 49/ 205 (23·9%) deaths Aspiration/ reflux/ choking = 41/ 205 (20·2%) deaths Other respiratory conditions = 31/ 205 (15·1%) deaths	Not available

Dupont et al (1987)[40]	N=446 deaths / 7134 (5·9%) people with mild ID N=277 males N=169 females	Respiratory deaths common cause of death in people with ID (all ages) Tests of significance only; respiratory deaths were more common for males with ID (all ages), and females aged 35-64, versus population of Denmark 1977	Not available	Not available	Not available	Not available
Durvasula (2002)[30]	40/693 (6%) deaths	14/40 (35%) deaths	For people under 40, respiratory and external deaths were most common, for people over 40, cancer and respiratory deaths were most common Age: 7/14 deaths in under 25-year-olds and 6/14 deaths in 40+ year olds Sex: 11/14 deaths in males Conditions: 2/14 had Down syndrome & dementia, 1/14 had myelodysplastic syndrome, 1x Battens disease	Not available	Not available	Age, gender, Down syndrome, myelodysplastic syndrome
Forsgren et al (1996)[15]	N=124 / 1478 (8·4%) people with ID (all ages), over 9,992 person-years	N=13 /124 (10%) deaths were respiratory disease for people with ID vs n=3·9 expected,	Respiratory disease was common cause of death for people with ID and epilepsy but SMR was not possible due to small sample size	Pneumonia was most common cause of death, but rarely reported as underlying cause Pneumonia was most common cause of death in	Not available	Epilepsy (active seizures)

	SMR 2.0 (95% CI 1·7, 2·3) Males 1.6 (95% CI 1·2, 2·0), Females 2·6 (95% CI 2·0, 3·3) *Additional: SMRs for severity of ID, epilepsy and cerebral palsy are available in appendix*	**SMR 3·3 (95% CI 2·0, 5·5)**		people with both epilepsy and ID		
Glover et al (2017)[8]	N=664 deaths for people with ID (all ages) over 59,279.7 person-years Crude rate 11·2 (10·4, 12·1) per 1000 person-years **SMR 3·18 (2·94, 3·43) Women 3·40 (3·02, 3·81) Men 3·03 (2·73, 3·35)**	N=114 deaths from respiratory causes for people with ID vs 23·3 expected **SMR 4·9 (4·0, 5·9)**	Not available	N=57 / 114 (50%) of respiratory deaths (and 8·6% of all deaths) were from influenza and pneumonia, vs expected 7·4 deaths **SMR 7·7 (5·8, 9·9)** Vast majority of pneumonia were unspecified (organism) n=24 / 114 (21%) respiratory deaths (3·6% of all deaths) were due to pneumonitis due to solids / liquids vs expected 1.1 deaths **SMR 21·8 (13·9, 32·4)** N=12 (1·8%) of all deaths were due to respiratory and intrathoracic cancers vs expected 16.6 deaths **SMR 0·7, 95% CI 0·4–1·3).**	Not available	Not available

Heslop et al (2014)[6]	N= 247 deaths in people with ID aged 4+ Rate of death 16·2 per 1000 person years Median age of death: 64 (52, 75). *Additional; all-cause mortality for sex, ID severity, amenable mortality, patient care, & accommodation available in appendix*	n=37 (15%) deaths had underlying cause due to respiratory diseases, vs 14·0% England & Wales deaths (p=0·66)	Not available	Not available	Not available	Reduced smoking in ID group p=0·02
Hollins et al (1998)[11]	270/2,026 (13·3%) deaths 116/1,081 (10·7%) deaths on Wandsworth register 154/945 (16·3%) deaths on Kensington register	Not available	Not available	Bronchopneumonia: N=56 (48%) (Wandsworth) N=69 (45%) (Kensingston) COPD Emphysema: N=1 (Wandsworth) N=1 (Kensingston) Asphyxia: N=4 (Wandsworth) N=1 (Kensingston) Respiratory other: N=4 (Wandsworth) N=4 (Kensingston) 52% of all deaths had a diagnosis of pneumonia	Not available	Not available

Hosking et al (2016)[24]	656/ 16666 (3·9%) deaths **HR = 3·62 (95% CI; 3·33, 3·93)**	123/ 16666 (18·8%, rate= 24·8) deaths **HR = 6·68 (95% CI; 5·38, 8·29)**	Down syndrome = 24/ 1793 (20·3%) deaths. General population: 135/ 113562 (rate= 3·9) deaths.	Pneumonia; n = 67/ 16666 (rate = 13·5) Aspiration pneumonitis; n = 21/ 16666 (rate = 4·2)	General population: Pneumonia; 39/ 113562 (rate = 1.1) Aspiration pneumonitis; n = 6/ 113562 (rate = 0.2)	Not available
Janicki et al (1999)[22]	2,752 deaths in the group aged 40+/4,183 all-age deaths (66%)	40+ year olds: N=548 (20%), rate: 201 per 100,000	Increasing by age decade: aged 40s: 343 per 100,000 (16% of those who died) aged 50s: 793 per 100,000 (20%) aged 60s 1660 per 100,000 (25%) aged 70+: 3441 per 100,000 Males with ID rate of death: 257 per 100,000 Females with ID rate of death: 331 per 100,000 Respiratory causes did not vary over the 10-year study period. Deaths due to respiratory diseases increased, with increasing age. Gender: breathing obstructions were more prevalent among males. Gender x age: respiratory disease was increased in the oldest groups, for males particularly while respiratory disease remained static as a cause of death for females across ages.	Breathing obstructions – 2·7% average deaths per year across 10 years, N=75, rate=27·5 per 100,000 Respiratory disease types: pneumonia was the most prevalent type of respiratory cause of death, with 43% of respiratory disease deaths in ID group	Not available	Age, gender
Ng et al. (2017)[12]	4,738/15,289 deaths in	807/4,738 (17%) respiratory	ID rate: 423 per 100,000 DS rate: 3,187 per 1,000	ID group (excludes DS)	Not available	Not available

	people aged 55+ (31%)	deaths for those with ID **HR =12·5 (10·9, 14·2)**		Pneumonitis due to solids and liquids: 10%, rate 25 per 100,000 Pneumonia: 50%, rate 129 per 100,000 Other chronic obstructive pulmonary disease: 20%, 49 per 100,000 DS group Pneumonitis due to solids and liquids 31·4%, 181 per 100,000 Pneumonia 20%, 113 per 100,000 Asthma 8%, 45 per 100,000 Bronchitis 8%, 45 per 100,000 Other respiratory disorders 8%, 45 per 100,000		
Oppewal et al (2018)[27]	207/1050 ID=19·7%; 54/ 149 DS=26·1%	69/159 ID=44.3%; 33/45 DS only=73·3%; 36/114 ID with no DS=31·6% Respiratory causes were the top primary causes of ID deaths. Respiratory causes were the top primary cause of DS deaths. General 50+ population, the three largest	5-year age bands: 50-54 ID=100% GP=3·3%; 55-59 ID=26·5% GP=4·7%; 60-64 ID=51·4% GP=6·0%; 65-69 ID=30·4% GP=6·7%; 70-74 ID=23·8% GP=8·6%; 75-79 ID=12·5% GP=9·4%; 80-84 ID=26·3% GP=9·4%; 85-90 ID=(0) GP=9·9%; 90-95 ID=40% GP=10·4%; 95+ ID=100% GP=10·9%	Pneumonia ID=80·4%; Chronic obstructive pulmonary diseases ID=17·6%	Not available	Not available

		groups of primary causes of death were neoplasms (31%), circulatory diseases (28%) and respiratory diseases (9%). No SMR available.				
Patja et al (2001)[14]	1111/ 2369 ID =46·9%	Immediate cause 322/1093 ID=29%; Primary cause 241/1095 ID=22% Respiratory diseases second largest cause of ID death **SMR=3·76 (CI 3·31 to 4·27)**	Male: age 2-19 **SMR=5·8 (4·4 – 15·6);** age 20-39 **SMR=5·4 (2·9 – 8·0);** age 40-59 **SMR=5·5 (3·5-7·5);** age 60+ **SMR=2·7 (2·7 – 4·8)** Female: age 2-19 **SMR=4·3 (0·3 – 4·7);** age 20-39 **SMR=3·2 (1·1 – 5·1);** age 40-59 **SMR=6·2 (4·1 – 8·2);** age 60+ **SMR=3·3 (1·7 – 3·0)**	Pneumonia ID=83%; Chronic obstructive pulmonary disease ID=11%.	Pneumonia deaths (%): Profound ID=29%; Severe ID=13%; Moderate ID=33%; Mild ID=25%. Risk ratios compared to general population: Mild ID 2.6 times higher; Profound ID 5.8 times higher. ID men higher risk than women in younger age groups (< 39 years), but at lower risk from 60 years of age onwards.	Age, gender (all respiratory) ID severity (with pneumonia)
Raitauso et al (1997)[13]	216 deaths	Immediate cause of death 97/216 ID=45% Primary cause 14/216 ID= 6%. Respiratory diseases were	age 0-14 SMR=0·48; age 15-44 SMR=3·46; age 45-74 SMR=2·35; age 75 SMR=0	Bronchopneumonia (immediate cause) ID=43% Five patients had died of pneumonia caused by aspiration. In one case fatal pneumonia had been caused by a fistula between the bronchus and the pleura. Besides pneumonia, two	Not available	Age (all respiratory)

		the dominant causes of ID death. **SMR=2·15 (CI 1·18 – 3·61)**		patients had acute laryngitis and one patient had hyperplasia of the lymph nodes of the lungs as the immediate cause of death. The latter had trisomy of chromosome 13 (Patau's syndrome) as the basic disorder.		
Smith et al (2020)[10]	N = 106 (0·6%) deaths **SMR = 11·6 (95% CI; 9·6, 14·0)**	Underlying cause of death: N = 8/ 106 (8%) deaths All-contributing factors in death: **n = 55. CMR = 81·7 (95% CI; 62·7, 106·4) deaths** **SMR = 55·3 (95% CI; 42·5, 72·1)**	Underlying cause of death: General population: 17/ 458 (4%) deaths All-contributing factors in death: General population: n = 51. **CMR = 1·4 (95% CI; 1·1, 1·8) deaths**	Underlying cause of death: Pneumonia including influenza; <5/ 106 All-contributing factors in death: Pneumonia= 27/ 106 (25·5%) deaths Respiratory failure; 17/ 106 (16·0%) deaths Respiratory disorders = 15/ 106 (14·2%) deaths Pneumonitis associated with food and vomit = 9/ 106 (8·5%) deaths	General populations: All-contributing factors in death: Pneumonia = 21/ 458 (4·6%) deaths	Not available
Trollor et al (2017)[25]	732 / 19362 ID=4% **SMR=1·3 (1·2 to 1·5)**	632/732 ID=86·3% had cause of death information 78 ID=12% 4th top cause using the ID ABI conversion 130 ID=20% 1st top using the ID revised version	Not available	Not available	Not available	Not available

		16 ID=3% of respiratory deaths were considered avoidable. 26242 GP=9% 3rd top underling cause				
Tyrer & McGrother (2009)[23]	503/ 2995 (17%) deaths **SMR=2·77 (95% CI 2·53, 3·03).**	**SMR=5·46 (95% CI 4·58, 6·46)**	Not available	Bronchopneumonia; **SMR=6·47 (95% CI 5·00 8·23), O=66, E=10·2.** Other respiratory; **SMR= 4·64 (CI 3·58 to 5·91). O=65, E=14·0.**	Male; **SMR=2·28 (95% CI; 2·02-2·56) O=278, E=121·8.** Female; **SMR=3·24 (95% CI; 2·83-3·69). O=225, E=69·4.**	Gender

*only where adjusted specifically for respiratory mortality
SMR=standardised mortality ratio/ CI=confidence interval/ RR=rate ratio/ HR=hazard ratio/CMF=comparative mortality figure/ OR=odds ratio/ O=observed deaths/ E=expected death

Study characteristics

Key features of all studies identified for inclusion in the review were tabulated (Table 1). These were cohort studies (n=12), case control studies (n=4) and one population-based audit of deaths in adults and children. These studies report data on 90,302 people with intellectual disabilities and 27,394 deaths. The average study size was 9,250 people. These studies were from the Netherlands (n = 1), Finland (n = 2), Australia (n = 3), the United Kingdom (n = 7), the United States of America (n = 1), Sweden (n = 2) and Denmark (n = 1).

Definition of respiratory disorder

Thirteen out of 17 (76%) studies defined the respiratory disorder using ICD 9 -chapter codes[13-15,22,23] and ICD 10 – chapter codes for respiratory disorders.[8,10,12,23-26] The remaining four studies included in the systematic review did not define respiratory disorders according to an operational system.

Individual respiratory disorders

Thirteen papers reported on deaths from individual respiratory disorders.[8,10-15,22-24,26-28] Pneumonia was reported as a cause of death in 12 studies.[8,10-15,22,23,26,27], five studies reported deaths from pneumonitis related to aspiration[8,10,12,14,24], five studies reported on chronic obstructive pulmonary disease (COPD)[11,12,14,26,27], one study reported on asthma[31] and one reported respiratory cancer deaths.[8]

Evidence synthesis

Respiratory-associated mortality

Five papers reported that respiratory disorders were the dominant cause of death in people with intellectual disabilities.[11,13,27,28,30] A further three studies found that deaths from respiratory disorders were the second most common cause of death.[12,14,24] Respiratory-associated deaths were in the top five main causes of deaths for a further four papers.[9,10,22,25] Comparative results (intellectual disabilities vs general population) for deaths due to respiratory disorders were reported in 10/17 (59%) of the studies.[5,8-10,12,22,24-26] In the majority of these studies rates of death from respiratory disorders were higher for people with intellectual disabilities than for people in the general population. However, Troller et al. (2017)[25] reported that respiratory-associated deaths in the general population were (9%) similar to the population with intellectual disabilities (12%). Hollins et

al. (1998)[11] also reported that respiratory disorders were the most commonly cited cause of death for both groups.

Individual respiratory disorders and mortality

Pneumonia was reported as the most common cause of respiratory death in people with intellectual disabilities.[8,10-15,22-24,26,27] Contributors to pneumonia deaths included influenza and injury from inhalation and aspiration events.[10,14] Pneumonitis featured as an underlying or contributing cause for between eight and 21% of respiratory-associated deaths in people with intellectual disabilities.[8,10,12] Crude comparison data showed people with intellectual disabilities were much more likely (between 10 and 20 times) to die from pneumonitis.[24,26] COPD was found to be a common cause of death in two studies focussing on older adults.[12,27]

Factors contributing to respiratory-associated deaths experienced by people with intellectual disabilities

Only four out of 17 (23.5%) papers directly reported on factors associated with the risk of respiratory-associated deaths[14,22,23,30] (see Table 2). Sex was identified as a significant factor in respiratory deaths in all four studies; however, the results were not consistent across all studies.[14,22,23,30] Level of intellectual disabilities was only reported as associated with respiratory related deaths in one study with 35 year follow up.[14] This study found that, when compared to the general population, the risk of respiratory related deaths was 2.6 times higher for people with mild intellectual disabilities and 5.8 times higher for people with profound and multiple intellectual disabilities.

Respiratory deaths amongst children and young people with intellectual disabilities were reported in five studies and found to be a common cause of death across all studies.[10,13,15,29,30] In studies comparing children and young people to a comparison group results were limited by small samples. Raitasuo et al. (1997) reported only one death.[13] Patja et al. (2001) reported higher SMR for males aged 2-19 years but not females.[20] Smith et al. reported 8% deaths had respiratory disease as the underlying cause but the SMR for underlying cause was not reported.[10]

Meta-analytical outcomes

Ten studies[8,10-15,23,24,28] reported the necessary data and were included in the meta-analysis of respiratory mortality of people with intellectual disabilities and the general population. As Hollins (1998) reported the SMR of two separate cohorts, these are displayed separately in the relevant forest plots.[11] The pooled SMRs for respiratory mortality between people with intellectual disabilities and the general population was 10·86 (95% CI 5·32, 22·18). The results indicate that respiratory mortality occurs ten times more frequently in the intellectual disabilities group than in the general population group, after adjustment (at the study level) for age and sex differences. There was evidence of considerable statistical heterogeneity between studies in the meta-analyses, with I^2= 99·0%. Results are displayed in Figure 2.

Insert Figure 2: Forest plot of respiratory associated mortality

As some studies focussed on adults only, while others included people of all ages, a sub-analysis was conducted of studies which reported data on an adult only population. The results of this sub-analysis are displayed in Figure 3. The pooled SMR reduced slightly from 10·86 (95% CI 5·32,22·18) to 6.53 (95% CI 4·29,9·96), after one study with a sample of primarily children was excluded.[10] Studies which included both adults and children in their sample[8,11-15] were next removed one at a time. First, both cohorts from Hollins (1998) were removed and the pooled SMR was reduced by around half, from 9·15 to 4·80[11]. The further removal of studies by Glover (2017)[8], Patja (2001)[14] and Raitasuo (1997)[13] resulted in a final pooled SMR for adults of 5·85 (95% CI 4·73,7·22, p<0·001). Heterogeneity between studies was also reduced from I^2=99% to I^2= 56% by the exclusion of samples which included children.

Insert figure 3: Forest plot for adults only

A sub-analysis was conducted of studies which reported an SMR for pneumonia.[8,11,23] The pooled SMR for pneumonia mortality for people with intellectual disabilities compared to the general population was 26·65 (95% CI 5·63, 126·24, p<0·001). These results, displayed in Figure 4, indicate that pneumonia related mortality occurs much more frequently in people with intellectual disabilities than in the general population group. Evidence of considerable statistical heterogeneity between studies was also present in this sub-analysis with I^2= 99.0%. SMRs were recalculated excluding the only study to include an adult only sample, Tyrer & McGrother (2009)[23] resulting in a substantial increase in pooled SMR (95% CI from 26·65 to 42·70).

Insert figure 4: Forest plot for pneumonia related mortality

Sensitivity analysis

Sensitivity analysis in relation to quality assessment was run for the ten studies included in the meta-analysis (Appendix 2). Studies which were rated as weak[13] or moderate[23] were removed from the analysis. The pooled SMR for mortality ratios changed slightly as Raitasuo (1997)[13] (from 10·81 to 12·67)[27] and then Tyrer and McGrother (2009) (from 12·67 to 13·94)[23] were removed from the analysis. As the change in SMR was small, this suggests that inclusion of weaker studies did not significantly change the results.

Discussion

This systematic review and meta-analysis highlights that people with intellectual disabilities experience excess respiratory-associated deaths, with a respiratory mortality ten times greater than for the general population. Respiratory mortality was more prevalent among studies which include children, and pneumonia was a major contributor to the higher respiratory mortality reported in this study. Clinical guidelines have contributed to a reduction in mortality from community-acquired pneumonia.[31] We believe the evidence presented here highlights the need for clinical guideline development groups to make recommendations on reducing the risks of premature death due to community-acquired pneumonia amongst people with intellectual disabilities. Vaccination programmes for influenza can help to reduce respiratory mortality in children[32] and adults.[33] Although there is a relatively low uptake of influenza vaccine amongst people with intellectual disabilities, annual health-checks for people with intellectual disabilities have been reported to increase uptake of influenza immunisation.[34] People with intellectual disabilities should be identified as a high-risk group and immunisation providers should prioritise the improvement of vaccine uptake, for example through the roll-out of health checks. People with intellectual disabilities are at increased risk of recurrent chest infections which are secondary to dysphagia[35,36] with a high proportion of aspiration pneumonia-related deaths occurring among individuals with severe and profound intellectual disabilities.[5,22,35,37,38] Increased recognition of the link between dysphagia and respiratory disorders among caregivers and practitioners is critical to ensuring the early identification of individuals with respiratory disorders.

The higher risk of death from respiratory disorders, such as pneumonia, for people with intellectual disabilities is a significant concern in relation to the rapidly developing COVID-19

pandemic. Urgent action to disaggregate data on deaths from COVID-19 for people with intellectual disabilities and to investigate factors associated with COVID-19 related mortality for people with intellectual disabilities is vital to ensure that clinical guidelines are based on consideration of the specific risks faced by people with intellectual disabilities. Research is urgently required to investigate the risk factors associated with COVID-19 for people with intellectual disabilities to ensure carers and clinicians have access to the best evidence to reduce the risk of infection in those most vulnerable and to inform the clinical management of those who contract COVID-19. Carers and clinical staff must be given training to ensure they understand the human rights and health care needs of people with intellectual disabilities to ensure that existing stark disparities in the health of people with intellectual disabilities are not widened during this crisis.

Interventions should focus on the pediatric age group. Among the studies included in this meta-analysis we found a relationship between inclusion of children and SMRs from respiratory causes, with those studies including children reporting higher SMRs. This is consistent with studies that have reported higher SMRs in children compared with adults in epilepsy[15] and cerebral palsy.[39] Overall, mortality in childhood is very low relative to adulthood, and in the pediatric age group chronic disabling conditions such as intellectual disability, epilepsy and cerebral palsy all have a marked impact on SMR. Co-morbidity with epilepsy and cerebral palsy are likely to be significant modifiers of the relationship between intellectual disability and respiratory mortality. Children with more severe intellectual disability are more likely to have epilepsy and cerebral palsy, both of which are independent risk factors for respiratory mortality.

Study strengths and limitations

Our study has several strengths. The meta-analysis included mortality ratios from ten observational studies covering 1,844 respiratory deaths in people with intellectual disabilities, which has improved the power and precision to answer this important research question. A rigorous and systematic analysis process was undertaken, and we minimised the risk of bias, errors and omissions by having two or more reviewers conduct comprehensive searches, assess study quality and extract descriptive data. While heterogeneity was found, due to methodological and clinical diversity including study design, age and study nationality, this is common in meta-analyses and statistical heterogeneity was inevitable.[20] Most of the research was conducted in Western countries, thus limiting the extent to which the findings may generalise to non-Western countries. Furthermore, ethnicity was not reported widely which

prevented further analysis. There was variation among studies on how mortality was examined and how deaths were reported. We were not able to perform meta-regression on predictors or factors reported in studies which increase SMRs for respiratory deaths (age, sex, place of death, or severity of intellectual disabilities). Improved reporting of these in studies of general mortality also would benefit future research.

These findings signify the urgent need to develop and implement evidence-informed strategies to reduce premature mortality among people with intellectual disabilities. Respiratory disorders are a major cause of death for people with intellectual disabilities, many of which are avoidable with improved public health initiatives and access to good quality health and social care. However, further research is required to understand both the multifactorial causes of this heightened risk as well as the most effective approaches for the multi-professional clinical management of these risks.

Contributors: MT, CM, AM, ER, LHM, DK, KD, GSS, AH & FB had full access to all the data, contributed to the systematic review and meta-analysis of studies, interpretation of results and the manuscript. JS and BJ helped interpret the result of the study and contributed to the manuscript. MT is study guarantor. All authors reviewed the final manuscript and agreed to be accountable for all aspects of the work and approved the final manuscript for submission. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests None declared.

Patient consent for publication Not required

Ethics Not required as this systematic review and meta-analysis was based on published data

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Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure captions

Figure 1: PRISMA flow diagram of systematic search and selection. A total of 2286 records were retrieved through a search of Embase, ISI Web of Science (all databases), CINAHL, and PsycINFO with an additional 9 records identified through other sources. After removing 241 duplicates, 2025 records were excluded due to ineligible types., the remaining 29 were retrieved as full-texts. From these 17 were included in the narrative review and 10 included in the meta-analysis.

Figure 2: Forest plot of respiratory associated mortality. The pooled SMRs for respiratory mortality between people with intellectual disabilities and the general population was 10·86 (95% CI 5·32, 22·18). There was considerable statistical heterogeneity between studies in the meta-analyses, with I^2= 99·0%.

Figure 3: Forest plot for adults only. The pooled SMR for adults only was 5·85 (95% CI 4·73,7·22, p<0·001). Heterogeneity between studies was also reduced from I^2=99% to I^2= 56% by the exclusion of samples which included children.

Figure 4: Forest plot for pneumonia related mortality. The pooled SMR for pneumonia mortality for people with intellectual disabilities compared to the general population was 26·65 (95% CI 5·63, 126·24, p<0·001). Evidence of considerable statistical heterogeneity between studies was also present in this sub-analysis with I^2= 99.0%.

References

1 Harris JC. Intellectual disability: Understanding its development, causes, classification, evaluation, and treatment. Oxford: Oxford University Press, 2006.

2 Maulik PK, Mascarenhas MN, Mathers CD, Dua T, Saxena S. Prevalence of intellectual disability: a meta-analysis of population-based studies. *Res Dev Disabil* 2011; **32(2):** 419-36

3 Organisation W. The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines. Geneva: World Health Organisation, 1992.

4 World Health Organization. World health statistics 2015. Geneva: World Health Organization, 2015.

5 Heslop P, Blair P, Fleming P, Hoghton M, Marriott A, Russ L. Confidential Inquiry into premature deaths of people with learning disabilities (CIPOLD) Final Report http://www.bristol.ac.uk/cipold/fullfinalreport.pdf (2013) (accessed June 25, 2020).

6 Heslop P, Blair PS, Fleming P, Hoghton M, Marriott A, Russ L. The Confidential Inquiry into premature deaths of people with intellectual disabilities in the UK: a population-based study. *Lancet* 2014; **383(9920):** 889-95.

7 O'Leary L, Cooper SA, Hughes-McCormack L. Early death and causes of death of people with intellectual disabilities: a systematic review. *J Appl Res Intellect Disabil* 2018; **31(3):** 325-42.

8 Glover G, Williams R, Heslop P, Oyinlola J, Grey J. Mortality in people with intellectual disabilities in England. *J Intellect Disabil Res* 2017; **61(1):** 62-74.

9 Tyrer F, Smith LK, McGrother CW. Mortality in adults with moderate to profound intellectual disability: a population-based study. *J Intellect Disabil Res* 2007; **51(7):** 520-7.

10 Smith GS, Fleming M, Kinnear D, Henderson A, Pell JP, Melville C, Cooper S-A. Rates and causes of mortality among children and young people with and without intellectual disabilities in Scotland: a record linkage cohort study of 796,190 schoolchildren. *BMJ Open* 2020 (Accepted for Publication) DOI:10.1136/bmjopen-2019-034077.

11 Hollins S, Attard MT, Fraunhofer Nv, McGuigan S, Sedgwick. Mortality in people with learning disability: risks, causes, and death certification findings in London. *Dev Med Child Neurol* 1998; **40(1):** 50-6.

12 Ng N, Wallén EF, Ahlström G. Mortality patterns and risk among older men and women with intellectual disability: a Swedish national retrospective cohort study. *BMC Geriatr* 2017; **17(1):** 269.

13 Raitasuo J, Mölsä P, Raitasuo S, Mattila K. Deaths among the intellectually disabled: A retrospective study. *J Appl Res Intellect Disabil* 1997; **10(4):** 280-8.

14 Patja K, Mölsä P, Iivanainen M. Cause-specific mortality of people with intellectual disability in a population-based, 35-year follow-up study. *J Intellect Disabil Res* 2001; **45(1):** 30-40.

15 Forsgren L, Edvinsson SO, Nyström L, Blomquist HK. Influence of epilepsy on mortality in mental retardation: an epidemiologic study. *Epilepsia* 1996; **37(10):** 956-63.

16 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8(5):** 336-41.

17 Kmet LM, Cook LS, Lee RC. Standard quality assessment criteria for evaluating primary research papers from a variety of fields. HTA Initiative #13. Edmonton: Alberta Heritage Foundation for Medical Research, 2004.

18 Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). *PLoS One* 2007; **2(12)**: e1350. DOI:10.1371/journal.pone.0001350.

19 Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Res Synth Methods* 2017; **8(1):** 5-18.

20 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327(7414):** 557-60.

21 Borenstein M. Common mistakes in meta-analysis and how to avoid them. New Jersey: Biostat. Inc, 2019: 388.

22 Janicki MP, Dalton AJ, Henderson CM, Davidson PW. Mortality and morbidity among older adults with intellectual disability: health services considerations. *Disabil Rehabil* 1999; **21(5-6):** 284-94.

23 Tyrer F, McGrother C. Cause-specific mortality and death certificate reporting in adults with moderate to profound intellectual disability. *J Intellect Disabil Res* 2009; **53(11):** 898-904.

24 Hosking FJ, Carey IM, Shah SM, Harris T, DeWilde S, Beighton C, et al. Mortality among adults with intellectual disability in England: comparisons with the general population. *Am J Public Health* 2016; **106(8):** 1483-90.

25 Trollor J, Srasuebkul P, Xu H, Howlett S. Cause of death and potentially avoidable deaths in Australian adults with intellectual disability using retrospective linked data. *BMJ Open* 2017; **7(2):** e013489. DOI:10.1136/bmjopen-2016-013489.

26 Brameld K, Spilsbury K, Rosenwax L, Leonard H, Semmens J. Use of health services in the last year of life and cause of death in people with intellectual disability: a retrospective matched cohort study. *BMJ Open* 2018; 8(2):e020268. DOI:10.1136/bmjopen-2017-020268.

27 Oppewal A, Schoufour JD, van der Maarl HJ, Evenhuis HM, Hilgenkamp TI, Festen DA. Causes of mortality in older people with intellectual disability: results from the HA-ID study. *Am J Intellect Dev Disabil* 2018; **123(1):** 61-71.

28 Cooper S-A, Allan L, Greenlaw N, McSkimming, P, Jasilek A, Henderson et al. Rates, causes, place and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage. *BMJ Open* 2020 (Accepted for Publication).

29 Patja K, Iivanainen M, Vesala H, Oksanen H, Ruoppila I. Life expectancy of people with intellectual disability: a 35-year follow-up study. *J Intellect Disabil Res* 2000; **44(5):** 591-9.

30 Durvasula S, Beange H, Baker W. Mortality of people with intellectual disability in northern Sydney. *J Intellect Dev Disabil* 2002; **27(4):** 255-64.

31 Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC et al. Infectious Diseases Society of America/ American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; **44 (Suppl 2):** S27-72.

32 Flannery B, Reynolds SB, Blanton L, Santibanez TA, O'Halloran A, Lu PJ, et al. Influenza vaccine effectiveness against pediatric deaths: 2010–2014. *Pediatrics* 2017; **139(5):** e20164244. DOI:10.1542/peds.2016-4244

33 Backer JA, Wallinga J, Meijer A, Donker GA, Van der Hoek W, Van Boven M. The impact of influenza vaccination on infection, hospitalisation and mortality in the Netherlands between 2003 and 2015. *Epidemics* 2019 Mar 1;26:77-85.

34 Robertson J, Hatton C, Emerson E, Baines S. The impact of health checks for people with intellectual disabilities: an updated systematic review of evidence. *Res Dev Disabil* 2014; **35(10):** 2450-62.

35 Chadwick DD, Jolliffe J. A descriptive investigation of dysphagia in adults with intellectual disabilities. *J Intellect Disabil Res* 2009; **53(1):** 29-43.

36 Robertson J, Chadwick D, Baines S, Emerson E, Hatton C. Prevalence of dysphagia in people with intellectual disability: a systematic review. *Intellect Dev Disabil* 2017; **55(6):** 377-91.

37 Durvasula, S, Beange H, Baker, W. Mortality of people with intellectual disability in northern Sydney. *J Intellect Dev Disabil* 2002; **27(4):** 255-264. DOI:10.1080/1366825021000029311

38 Glover G, Ayub M. How people with learning disabilities die. Improving Health and Lives Learning Disabilities Observatory. Durham, 2010.

39 Blair E, Langdon K, McIntyre S, Lawrence D, Watson L. Survival and mortality in cerebral palsy: observations to the sixth decade from a data linkage study of a total population register and National Death Index. *BMC Neurol* 2019; **19(1):** 111

Appendix 1: Search strategy

Embase- Ovid, 2016-

Search Terms	
1.	developmental disorder/ or intellectual impairment/ or developmental disabilities/ or intellectual disability/ or mentally disabled persons/ or intellectual development disorder/ or "intellectual development disorder (attitudes toward)"/
2.	((intellect$ adj3 (deficien$ or difficult$ or disab$ or disorder$ or impair$ or handicap$ or incapacit$ or handicap$ or sub?average or sub?norm$)) or (low$2 adj2 intellect$)).tw.
3.	(learning adj3 (deficien$ or difficult$ or disab$ or disorder$ or handicap$ or impair$ or incapacit$ or handicap$ or sub?average or sub?norm$)).tw.
4.	(mental$ adj3 (deficien$ or disab$ or handicap$ or impair$ or handicap$ or incapacit$ or retard$ or sub?average or sub?norm$)).tw.
5.	((subaverage or sub$1 average or subnormal or sub$1 normal$) adj3 (cognit$ or intel$)).tw.
6.	((development$ or neurodevelopment$) adj disab$).tw.
7.	(education$ adj5 sub?norm$).tw.
8.	(cretin$ or feeble minded$ or imbecil$ or moron$).tw.
9.	Or/ 1-9
10.	cause of death/ OR mortality/ OR fatal outcome/ OR death/ OR hospital mortality/ OR mortality.ti,ab OR fatal.ti,ab OR death.ti,ab
11.	asthma/ OR asthma.ti,ab OR bronchial asthma.ti,ab OR asthma, bronchial.ti,ab OR pneumonia/ OR pneumonia.ti,ab OR lobar pneumonia.ti,ab OR lobar pneumonia.ti,ab OR pneumonia, lobar.ti,ab OR bacterial pneumonia/ OR pneumonia, bacterial.ti,ab OR viral pneumonia/ OR pneumonia, viral.ti,ab OR viral pneumonia.ti,ab OR bronchopneumonia/ OR bronchopneumonia.ti,ab OR bronchial pneumonia.ti,ab OR pneumonia, bronchial.ti,ab OR lung disease/ OR disease, lung.ti,ab OR pulmonary disease.ti,ab OR disease, pulmonary.ti,ab OR respiratory disease.ti,ab OR disease, respiratory.ti,ab OR chronic obstructive lung disease/ OR lung disease, obstructive.ti,ab OR obstructive lung disease.ti,ab OR obstructive lung diseases.ti,ab OR obstructive pulmonary diseases.ti,ab OR aspiration pneumonia/ OR aspiration pneumonia.ti,ab OR bronchiectasis/ OR bronchiectasis.ti,ab OR respiratory failure/ OR respiratory failure.ti,ab OR interstitial pneumonia/ Or interstitial pneumonia.ti,ab
12.	9 and 10 and 11

Cinahl and APA PsychINFO - Ebscohost, 2016-

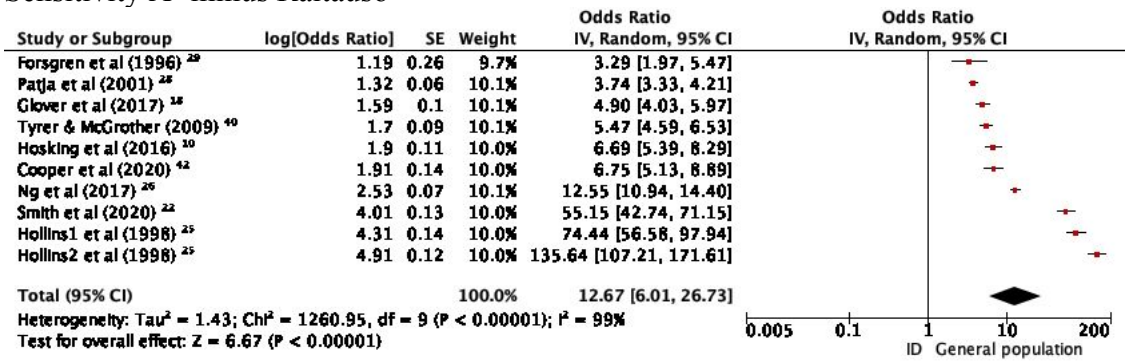
Search Terms	
1.	MH Intellectual disability
2.	(MH "Mentally Disabled Persons")
3.	TX (intellectual* N3 (disab* or disorder* or handicap* or impair* or deficien* or subnorm*))
4.	TX (learning N3 (disab* or disorder* or impair* or difficllt*))
5.	TX (development* N3 (disab* or disorder* or handicap* or impair* or delay*))
6.	TX (Mental* N3 (disab* or disorder* or handicap* or impair* or deficien* or subnorm* or retard*))
7.	((development$ or neurodevelopment$) N disab$).tw.
8.	(education$ N5 su?bnorm$).tw.
9.	(cretin$ or feeble minded$ or imbecil$ or moron$).tw.
10.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
11.	cause of death/
12.	mortality/
13.	fatal outcome/
14.	death/
15.	hospital mortality/
16.	mortality.ti.ab
17.	fatal.ti.ab
18.	death.ti.ab
19.	Or/ 11-18
20.	"pulmonary disease" or "airway disease" or "broncho-pulmonary disease" or "respiratory disease" or "lung disease" or "lung disorder" or "pulmonary disorder" or "respiratory disorder" or "pneumonia" or "bronchopneumonia" or "lung infection" or pulmonary infection" or respiratory infection" or "asthma" or "chronic obstructive pulmonary disease" or "aspiration pneumonia" or "bronchiectasis" or "respiratory failure"
21.	10 and 19 and 20

Web of Science (All databases, including MEDLINE) 2016-current

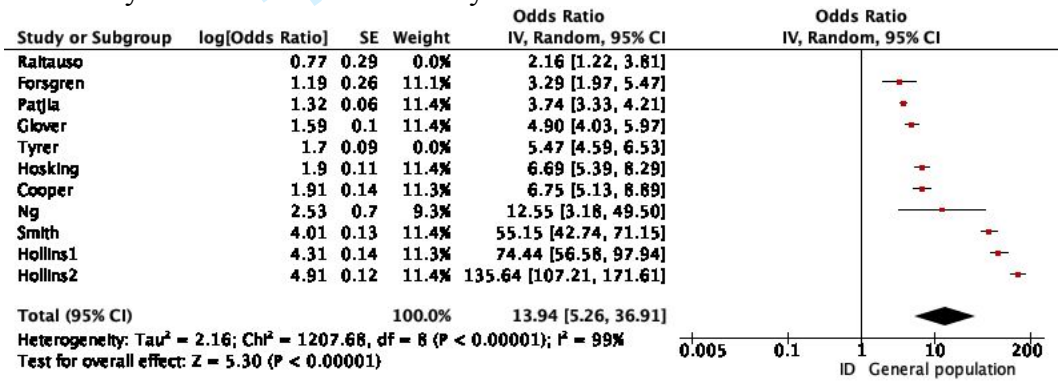
TS= mortality OR death OR cause of death OR cause of mortality OR dead OR died
AND
TS= intellectual disab* or intellectual impair* or developmental disab* or learning disab* or mental retard* or mental handicap*
AND
TS=asthma* or bronchial asthma or pneumoni* or lobar pneumoni* or lobar pneumoni* or bacterial pneumoni* or viral pneumoni* or bronchopneumonia* or bronchial pneumoni* or lung disease* or lung disorder* or lung infect* or pulmonary disease* or pulmonary disorder or pulmonary infect* or respiratory disease* or respiratory disorder or respiratory infect* or obstructive lung disease* or obstructive pulmonary disease* or aspiration pneumoni* or bronchiecstasi

Appendix 2: Sensitivity analysis A and B

Sensitivity A- minus Raitauso



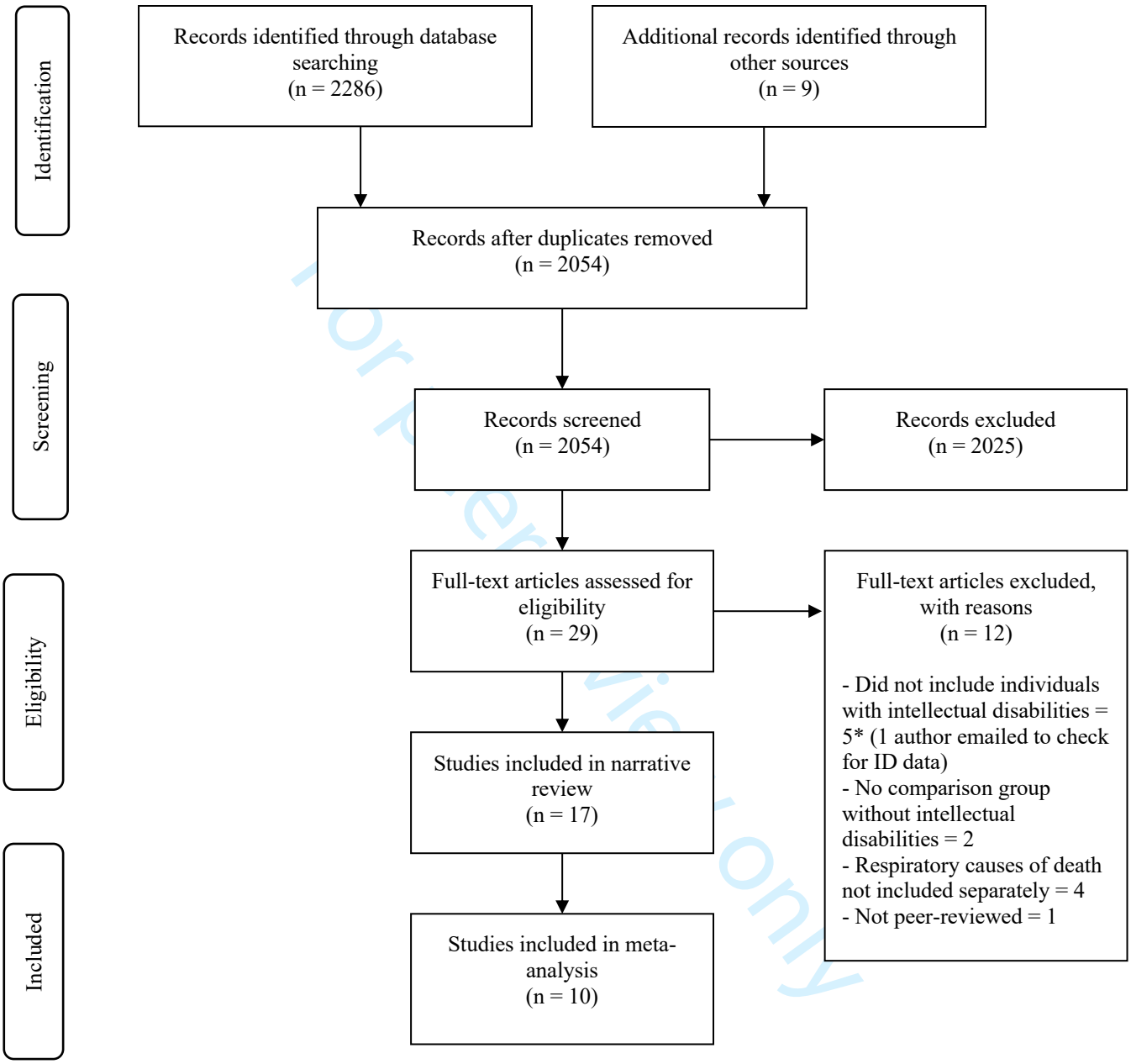
Sensitivity B- minus Raitauso and Tyrer



Appendix 3: Excluded papers – References and reasons for exclusion

	Reference	Reason
1	Bilder D, Botts EL, Smith KR, Pimentel R, Farley M, Viskochil J. Excess mortality and causes of death in autism spectrum disorders: A follow up of the 1980s Utah/ UCLA autism epidemiologic study. *J Autism Dev Disord* 2013; **43(5):** 1196-1204	Did not include individuals with intellectual disabilities.
2	Decoufle P, Autry A. Increased mortality in children and adolescents with developmental disabilities. *Paediatr Perinat Epidemiol* 2002; **16(4):** 375-382	No general population comparison group.
3	Florio T, Trollor J. Mortality among a cohort of persons with an intellectual disability in New South Wales, Australia. *J Appl Res Intellect Disabil* 2015; ***28*(5):** 383-393.	Respiratory causes of death not included separately.
4	Glover G, Ayub M. How people with learning disabilities die. Improving Health and Lives Learning Disabilities Observatory. Durham, 2010.	Not peer-reviewed.

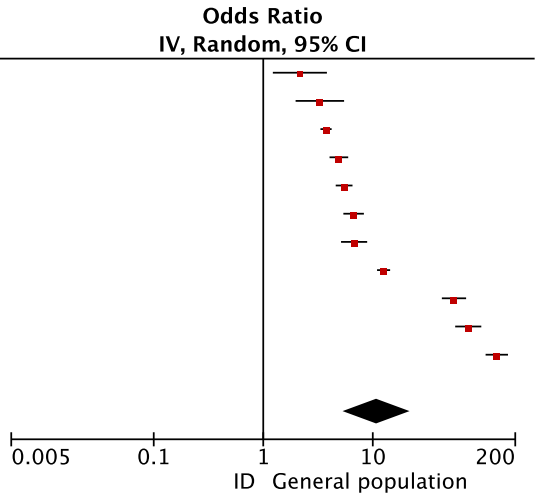
5	Jahan I, Karim T, Das MC, Muhit M, McIntyre S, Smithers-Sheedy H, et al. Mortality in children with cerebral palsy in rural Bangladesh: a population-based surveillance study. *Dev Med Child Neurol* 2019; **61(11):** 1336-1343	Did not include individuals with intellectual disabilities.
6	McCarron M, Carroll R, Kelly C, McCallion P. Mortality rates in the general Irish population compared to those with an intellectual disability from 2003 to 2012. *J Appl Res Intellect Disabil* 2015; ***28*(5):** 406-413.	Respiratory causes of death not included separately.
7	Perez CM, Ball SL, Wagner AP, Clare ICH, Holland AJ, Redley M. The incidence of healthcare use, ill health and mortality in adults with intellectual disabilities and mealtime support needs. *J Intellect Disabil Res* 2015; **59(7):** 638-652	No general population comparison group.
8	Reid, SM, Carlin JB, Reddihough DS. Survival of individuals with cerebral palsy born in Victoria, Australia, between 1970 and 2004. *Dev Med Child Neurol* 2012; **54(4):** 353-360	Did not include individuals with intellectual disabilities.
9	Shavelle, Robert M.; Strauss, David J.; Pickett, Jane Causes of death in autism. *J Autism Dev Disord* 2001; **31(6):** 569-576	Did not include individuals with intellectual disabilities.
10	Similä S, Von Wendt L, Rantakallio P. Mortality of mentally retarded children to 17 years of age assessed in a prospective one-year birth cohort. *J Ment Defic Res* 1986; **30:** 401-5	Respiratory causes of death not included separately.
11	Stankiewicz E, Ouellette-Kuntz H, McIsaac M, Shooshtari S, Balogh R. Patterns of mortality among adults with intellectual and developmental disabilities in Ontario. *Can J Public Health* 2018; **109(5-6):** 866-872	<70%* of participants had intellectual disabilities. *We emailed this author to check if >70% of sample had ID – they replied but didn't have the data to check, so it was excluded.
12	Tyrer F, Smith LK, McGrother CW. Mortality in adults with moderate to profound intellectual disability: a population-based study. *J Intellect Disabil Res*, 2007; ***51*(7):** 520-527.	Respiratory causes of death not included separately.

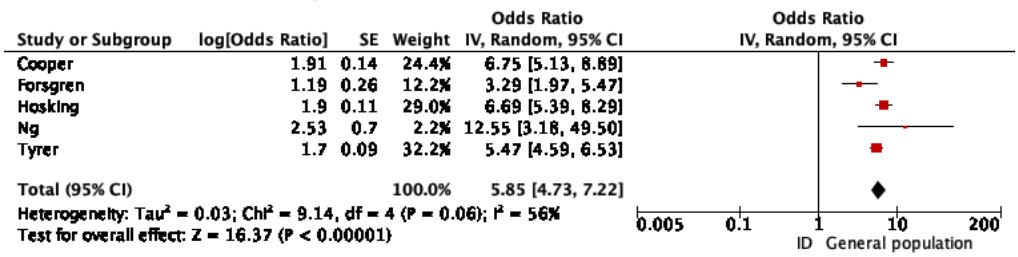


Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Raitauso et al (1997) [27]	0.77	0.29	8.7%	2.16 [1.22, 3.81]
Forsgren et al (1996) [29]	1.19	0.26	8.8%	3.29 [1.97, 5.47]
Patja et al (2001) [28]	1.32	0.06	9.2%	3.74 [3.33, 4.21]
Glover et al (2017) [18]	1.59	0.1	9.2%	4.90 [4.03, 5.97]
Tyrer & McGrother (2009) [40]	1.7	0.09	9.2%	5.47 [4.59, 6.53]
Hosking et al (2016) [10]	1.9	0.11	9.2%	6.69 [5.39, 8.29]
Cooper et al (2020) [42]	1.91	0.14	9.1%	6.75 [5.13, 8.89]
Ng et al (2017) [26]	2.53	0.07	9.2%	12.55 [10.94, 14.40]
Smith et al (2020) [22]	4.01	0.13	9.1%	55.15 [42.74, 71.15]
Hollins1 et al (1998) [25]	4.31	0.14	9.1%	74.44 [56.58, 97.94]
Hollins2 et al (1998) [25]	4.91	0.12	9.1%	135.64 [107.21, 171.61]
Total (95% CI)			**100.0%**	**10.86 [5.32, 22.18]**

Heterogeneity: $Tau^2 = 1.44$; $Chi^2 = 1286.60$, df = 10 ($P < 0.00001$); $I^2 = 99\%$

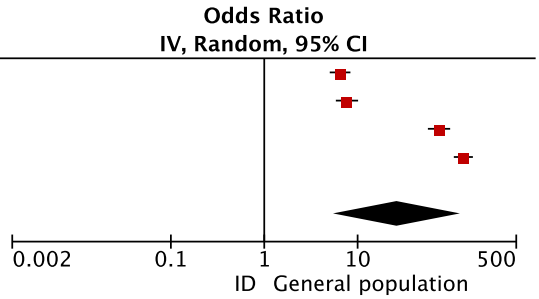
Test for overall effect: $Z = 6.54$ ($P < 0.00001$)





Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Tyrer & McGrother (2009) [40]	1.87	0.13	25.0%	6.49 [5.03, 8.37]
Glover et al (2017) [18]	2.04	0.14	25.0%	7.69 [5.85, 10.12]
Hollins1 et al (1998) [25]	4.31	0.14	25.0%	74.44 [56.58, 97.94]
Hollins2 et al (1998) [25]	4.91	0.12	25.0%	135.64 [107.21, 171.61]
Total (95% CI)			**100.0%**	**26.65 [5.63, 126.24]**

Heterogeneity: $Tau^2 = 2.50$; $Chi^2 = 433.15$, df = 3 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 4.14$ ($P < 0.0001$)



PRISMA-A checklist

Subjects	PRISMA for Acupuncture
Title	
Title	1* Identify the report as a systematic review, meta-analysis, or both; if applicable, state the specific type of acupuncture treatment, such as manual acupuncture or electroacupuncture.
Abstract	
Structured summary	2† Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results limitations; conclusions and implications of key findings; systematic review registration number.
Introduction	
Rationale	3* Describe the rationale for what is already known about acupuncture for the target condition in the background; if applicable, state what is already known about the specific types of acupuncture to be studied, and describe whether there is any difference of the effects among different types of acupuncture.
Objectives	4† Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)
Methods	
Protocol and registration	5† Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and, if available, provide registration information including registration number.
Eligibility criteria	6† Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. 6a.1‡ Describe the diagnostic criteria of the target condition in Western medicine. 6a.2‡ If applicable, describe the diagnostic criteria in terms of Traditional Medicine, such as Traditional Chinese Medicine. 6b‡ Describe the types of acupuncture to be included, such as traditional acupuncture, electroacupuncture, or fire acupuncture.

	6c‡ If applicable, report measures for therapeutic effects using the terminology of either traditional medicine (e.g. syndrome score for syndrome remission) or Western medicine (e.g. pain intensity).
Information sources	7* Describe all sources of information (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search, and report the date of the last search. If applicable, report the databases or complementary search methods for acupuncture or traditional medicine.
Search	8* Present full electronic search strategy for at least one commonly used database (e.g. MEDLINE), including any limits used, such that it could be repeated. If applicable, include the full search strategy for at least a Western and a traditional medicine database for each systematic review where both were used.
Study selection	9† State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10† Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11* List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made; describe data items about details of acupuncture interventions and controls (**e.g.,** sham acupuncture) referring to TIDieR when applicable.
Risk of bias in individual studies	12† Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13† State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14† Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15† Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16† Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
Results	

Study selection	17† Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18* For each study, present characteristics that were extracted (e.g., study size, PICOS, follow-up period) and provide the citations of the included studies. Summarize details of the acupuncture intervention for each study in a table referring to TIDieR**.** 18a‡ Describe details of "De-qi" after acupuncture reported in the included studies.
Risk of bias within studies	19† Present data on risk of bias of each study and, if available, any outcome-level assessment(see item 12).
Results of individual studies	20† For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21† Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22† Present results of any assessment of risk of bias across studies (see item 15).
Additional analysis	23† Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).
Discussion	
Summary of evidence	24† Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25† Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26† Provide a general interpretation of the results in the context of other evidence, and implications for future research.
Funding	
Funding	27† Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

Note: * modified original item † unmodified item from PRISMA ‡ new extended item

BMJ Open

Respiratory-associated deaths in people with intellectual disabilities: a systematic review and meta-analysis

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Manuscript ID	bmjopen-2020-043658.R1
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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Respiratory medicine
Keywords:	RESPIRATORY MEDICINE (see Thoracic Medicine), PUBLIC HEALTH, Respiratory infections < THORACIC MEDICINE

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Title: "Respiratory-associated deaths in people with intellectual disabilities: a systematic review and meta-analysis"

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Keywords: Respiratory disease, mortality, intellectual disability, systematic review, meta-analysis

Wordcount: 3850

ABSTRACT

Objective To review and synthesise evidence on rates of respiratory-associated deaths and associated risk factors in the intellectual disability population.

Design Systematic review with meta-analysis

Data sources Embase, CINAHL, ISI Web of Science (all databases including Medline), and PsychINFO were searched for studies published between January 1985 to April 2020 and examined study and outcome quality. Reference lists and Google Scholar were also hand searched.

Results We identified 2,063 studies, 17 were included in the narrative synthesis and 10 studies (11 cohorts) in the meta-analysis. Data from 90,302 people with ID and 13,808 deaths from all causes in people with ID were extracted. Significantly higher rates of respiratory-associated deaths were found among people with ID (SMR 10·86 (95% CI 5·32, 22·18, p<0·001) compared to those in the general population, lesser rates for adults with intellectual disabilities (SMR 6·53 (95% CI 4·29,9·96, p<0·001); and relatively high rates from pneumonia 26·65 (95% CI 5·63, 126·24, p<0·001). The overall statistical heterogeneity was I^2= 99·0%.

Conclusion Premature deaths due to respiratory disorders are potentially avoidable with improved public health initiatives and equitable access to quality health care. Further research should focus on developing prognostic guidance and validated tools for clinical practice to mitigate risks of respiratory-associated deaths.

PROSPERO registration number CRD42020180479

Article summary

Strengths and limitations of this study

- To our knowledge this is the first systematic review and meta-analysis on respiratory-associated deaths among people with intellectual disabilities.
- Included studies were limited by sample size
- There was no sufficient data and results provided by studies to investigate predictors or factors associated with respiratory-related deaths; meta-regression or stratification was not possible
- The meta-analysis included mortality ratios from ten observational studies covering 90,302 people with intellectual disabilities and 13,808 deaths from all causes in people with intellectual disabilities.

- A rigorous and systematic analysis process was undertaken which minimised the risk of bias, errors and omissions.

Introduction

People with intellectual disabilities account for approximately 1-3% of the global population.[1,2] The World Health Organisation (1992)[3] defines intellectual disabilities as impairments in adaptive functioning, social functioning, and intellectual functioning, (IQ<70) requiring a need for daily support, with the onset in the developmental phase (<18 years). Whilst some heterogeneity is to be expected in the definition of intellectual disabilities across studies drawing on administrative datasets, the WHO definition can be applied to all studies included in this review. Life expectancy and mortality rates are important indicators of health inequality.[4] People with intellectual disabilities die up to 20 years earlier than the general population.[5-8] Respiratory disorders are a leading cause of death among people with intellectual disabilities.[6,9] The range of standardised mortality ratios (SMRs) due to respiratory disorders for people with intellectual disabilities are very high in some studies,[10-12] and much lower in others.[13-15]. Despite this, standardised mortality ratios (SMRs) due to respiratory disorders for people with intellectual disabilities differ widely across studies. While SMRs are very high in some studies [10-12], the populations with intellectual disabilities are younger (4-19 years) or older (55+ years) on average, or the age of the population is not available/reported. Moreover, in studies with very low SMRs [13-15], age (or level of intellectual disabilities) is not reported. This systematic review and meta-analysis aims to investigate and quantify the risk of, and factors associated with, respiratory-associated deaths in people with intellectual disabilities.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed.[16] This review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42020180479).

Eligibility

This systematic review included studies which analysed and presented data on people who were ascertained as having intellectual disabilities and a comparison group of individuals in the general population, with respiratory disorders included as a separate cause of death. For studies

that included multiple disabilities, at least 70% of participants had to have intellectual disabilities, if results were not reported separately. Studies also had to be full-text, peer-reviewed, and published in English. To be included in the meta-analysis, studies had to report SMRs with 95% confidence intervals for respiratory associated deaths based on external comparison group or to have presented data allowing such outcomes to be derived. Studies were excluded if they focused on specific etiologies of intellectual disabilities, such as Down syndrome, as these are associated with a different health and mortality profiles compared to other people with intellectual disabilities. Studies were excluded if the full paper was not available in English. Studies focused on post-operative and post-treatment deaths were excluded as these are not representative of the wider population with intellectual disabilities. Studies with small samples (<20 participants) or case series designs were also excluded as these papers are less representative.

Search strategy and selection criteria

We searched Ovid Embase, ISI Web of Science (all databases), CINAHL, and PsycINFO from 1st January 1985 to the 27th of April 2020, using comprehensive terms related to 'intellectual disabilities', 'mortality', and 'respiratory disease' (full search strategy in Appendix 1). In addition, a manual bibliography and citation search of included studies was conducted using Google Scholar and key researchers in the field of mortality in individuals with intellectual disabilities were emailed to identify any additional relevant papers. The aforementioned eligibility criteria were used. After duplicates were removed, all records were imported into Covidence software (www.covidence.org) for title and abstract and full text screening. All titles, abstracts (CM & AMcG) and full-texts (CM, AMcG, ER) were double-screened with inter-rater reliability (Cohen's kappa) of $\kappa = \cdot 57$ and $\kappa = \cdot 58$, respectively.

Data Extraction

Data extraction was conducted using a structured database created in Excel. Five researchers (GS, LHM, DK, KD, AMcG) each extracted data from 25% of the included studies and, to check reliability, one other researcher (CM) independently extracted data from 20% of included studies. Extracted data were compared in meetings and discrepancies resolved through consensus discussion. Researchers did not extract data on included papers where they were a listed author.

Assessment of study and outcome quality

Study quality was appraised using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields.[17] Quality ratings were calculated in percentage form using the standard method[17] and categorised as weak (<55%), moderate (55-75%), or strong (>75%) quality. Each paper had quality appraisals completed by two researchers, who then agreed a consensus score for each item (Table 1).[17] Researchers did not evaluate quality of papers where they were a listed author. Risk of bias score was not used to exclude any studies from either the systematic review or meta-analysis. We evaluated the quality of our own systematic review using the Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist.[18]

***Table 1*: Characteristics of studies reporting mortality rates for respiratory disorders and pneumonia in people with intellectual disabilities**

Author	Country	Study design, setting and follow up	Data sources	ID sample (N, % female, age, level of ID)	Deaths in ID sample (N, % female, age at time of death, level of ID)	Comparison sample (N, % female, age,) and deaths (n, % female, age)	Respiratory disorder definition (e.g. ICD codes or other definitions)	Quality Percentage (assessment)
Brameld et al (2018)[26]	Australia	Retrospective matched cohort study of adults 20 years old and over. Follow up 2009-2013	Intellectual Disability Exploring Answers (IDEA) Database. Death certificate data	Total sample characteristics not available	N= 591; 43·8% female; mean age* and level of ID not available	Total sample characteristics not available. Number of deaths= 62, 917; 47·4% female; mean age not available	ICD 10-chapter codes for respiratory disorders.	95·45% (strong)
Cooper et al (2020)[28]	UK	Population-based cohort study. Follow up 2001-2018	Primary care records and health check data; Death certificate data. Comparison data from Health Board statistics	N= 962; 45·4% female; mean age= 44·1 years (range 16-83); ID Mild=382 (39·7%), Moderate=236 (24·5%), Severe=180 (18·7%), Profound=163 (17·0%)	N= 294/961 (30·6%); 47·5% female; mean age= 52·4 (SD 13·6)	Not available	ICD 10-chapter codes for respiratory disorders.	86·36% (strong)
Dupont et al. (1987)[40]	Denmark	Population- based cohort study of adults with mild ID. Follow up 1976-1984	Danish National Service for the Mentally Retarded. Death certificate data.	N = 7134; gender, age and level of ID not available	N=446; 37·9% females; age and level of ID not available	Not available	Not described	40·90% (weak)
Durvasula et al (2002)[37]	Australia	Population-based cohort study of children and adults. Follow up 1989 - 1999	ID prevalence study. Death certificate data, medical records and post-mortem data. Australian Bureau of Statistics	N = 693; 44·6% female; mean age= N/A; ID 40% mild, 35% moderate, 25% severe/profound	N=40 (6%); 45% female; median age= 32 (range 10-59); level of ID not available	N= 125,848; 51% female; mean age not available. Number of deaths= 2154; 37·8% female; mean age not available	Not described	90·91% (strong)
Forsgren et al (1996)[15]	Sweden	Population-based cohort study of adults with ID.	Board for Provision and Services to the Mentally	N = 1,478; 44·5% female; age and level of ID not available	N= 247; 42·1% female; Median age= 64 years (IQR 52-75 years); ID 39·7% Mild,	Not available	ICD 9-chapter codes for respiratory disorders.	81·82% (strong)

		Follow up 1986 – 1992	Retarded. Death certificate data from Swedish National Bureau of Statistics		31·2%, Moderate, 21·5% Severe 7·7% Profound			
Glover et al (2017)[8]	UK	Population-based case control study in primary care. Follow up 2010-2014	Primary care records (CPRD). Death certificate data	Total sample characteristics not available	N = 664 deaths; 44·1% female	Total sample characteristics not available. N of deaths= 97, 379; 52·3% female; mean age not available	ICD 10-chapter codes for respiratory disorders.	81·82% (strong)
Heslop et al (2014)[5]	UK	Population based audit of deaths of children and adults with intellectual disabilities aged 4 and over. Audit period 2010-2012	Medical records Death certificate data from UK Office of National Statistics	Total sample characteristics not available	N=247; 42·1% female; median age= 64 years (IQR 52-75 years); ID 39·7% mild, 31.2% moderate, 21·5% severe, 7·7% profound	Total sample characteristics not available. Number of deaths= 480, 467; 51·6% female; median age not available		81·82% (strong)
Hollins et al (1998)[11]	UK	Cohort study of adults on an ID register. Follow up 1982-1990	Learning disability register. Death certificate data.	N = 2,026; gender, age and ID level not available	N= 268 deaths; gender and age not available; 51·5% mild-moderate, 48·5% severe-profound	Not available	Not described	81·82% (strong)
Hosking et al (2016)[24]	UK	Population-based case control study in primary care. Follow up 2009-2013	Primary care records (Clinical Practice Research Data linkage; CPRD). Death certificate data	N = 16,666; 58.1% female; mean age 39.9 (SD 16.2). 19.6% of sample had high support needs.	N=656 (3·9%); 55·6% female; age and level of ID not available	N= 113, 562; 58·1% female; mean age not available. Number of deaths= 1358 (1·2%); 60·4% female; mean age not available	ICD 10-chapter codes for respiratory disorders.	90·91% (strong)
Janicki et al (1999)[22]	USA	Cohort of adults with intellectual disabilities 40 years old and over. Follow up 1984-1993	Data from state agency with responsibility for reviewing deaths of disabled persons. Health department data.	Total sample characteristics not available.	N= 2752, 48·1% female; mean age- 65·1; ID 18%, 68% Moderate – profound (68%), 4% unspecified, 10% unknown	Total sample characteristics not available. Number of deaths= 149, 980; gender not available, mean age= 70·0	ICD 9-chapter codes for respiratory disorders.	77·27% (strong)
Ng et al (2017)[12]	Sweden	Population-based case control study of adults with ID 55 years old and	National database of hospital admissions and outpatient care.	N = 15, 289; 45.5% females; mean age not available; level of ID not available	N= 4728; 44·9% female; age and ID level not available	N= 74, 445; 45·5% females; mean age not available. Number of deaths= 8364	ICD 10-chapter codes for respiratory disorders.	95·45% (strong)

		over. Follow up 2002-2015	National disability register. Swedish National Cause of Death register					
Oppewal et al (2018)[27]	Netherlands	Cohort study of adults with ID 50 years old and over living in three care organisations. Follow up Nov 2013-March 2018	Medical case notes of participants with ID who died during study period. Cause specific mortality statistics for 50+ population in the Netherlands	N = 1050; 48·7% female; mean age= 61·6 (SD 8·0, range 50-94); ID level= 2·9% borderline, 21·2% mild, 48·2% moderate, 16·4% severe, 8·7% profound;	N=207 deaths (19·7%) but only 159 with cause of death available. 60·7% female; mean age not available; ID level= 5·7% borderline, 18·9% mild, 54·7% moderate, 13·2% severe, 7·5% profound;	Not available	ICD 10-chapter codes for respiratory disorders.	50·0% (weak)
Patja et al (2001)[14]	Finland	Population based, nationwide cohort study. Follow up 1963-1997	Original 1962 population-based study (Amnell et al. 1964). Death certificate data	N = 2,369, gender, age and level of ID not available	1111 deaths with death certificates available for 1,095- 51·0% female, mean age= 57·7; ID 40·3% mild, 29·4% moderate, 11·5% severe, 18·0% profound, 0·7% unknown	Not available	ICD 9-chapter codes for respiratory disorders.	81·82% (strong)
Raitasuo et al (1997)[13]	Finland	Cohort study of adults living in an institution. Follow up 1972-1993	Medical case notes and death certificate data. General population mortality statistics for population in Finland.	N ≈ 2000; gender, age and level of ID not available	216 deaths- 42·6% female; mean age 26·7 (1-86 years); ID level 2·0% borderline, 15·0% mild, 18·0% moderate, 20·0% severe, 45.0% profound, 20·0% unknown	Not available	ICD 9-chapter codes for respiratory disorders.	54·55% (weak)
Smith et al (2020)[10]	UK	Nationwide, population based cohort study of children aged 4-19. Follow up 2008-2015.	Scottish pupils census: Death certificates data	N= 18, 278; 35% female; mean age not available	N= 106; mean age= 14·3 (95% CI 13·4 to 15·1); level of ID not available	N= 777,912; 50% female; mean age not available. number of deaths= 458; mean age= 16·1 years (95% CI 15·8 to 16·5)	ICD 10-chapter codes for respiratory disorders.	100% (strong)
Trollor et al (2017)[25]	Australia	Population based cohort study of adults 20 years old and above	Disability Services Minimal Dataset. Australian Bureau	N= 19,362; 44% female, mean age= 37 (range 27-48); ID not available	N= 732 (4%); 41% female; median age = 54 (42–64), level of ID not available	Total sample characteristics not available. Number of deaths= 305, 050; 49%	ICD 10-chapter codes for respiratory disorders.	95·45% (strong)

		registered with disability services. Follow up 2005-2011	of Statistics. Death records			female; median age= 81 (70–92).		
Tyrer and McGrother (2009)[23]	UK	Population-based cohort study of individuals with moderate-profound ID on a register. Follow up 1993-2006	Leicestershire learning disability register. Death certificate data. National Statistics 1993-2006.	N = 2,995; 41·9% female; Age and level of ID not available	N=503; gender, age and level of ID not available	Total sample characteristics not available. Number of deaths≈126, 000	ICD 9 and ICD 10-chapter codes for respiratory disorders.	72·73% (moderate)

*Individuals in the ID cohort died at a significantly younger age than the comparison cohort

Summary of outcomes and statistical analysis

Findings of all included studies were combined in a narrative synthesis. The primary goal of the meta-analysis was to investigate if the SMRs of respiratory-associated deaths differ for individuals with and without intellectual disabilities. If SMRs were reported by specific respiratory causes, sex, age group, level of intellectual disability, socio-economic status or ethnicity, these were collected and presented for potential analysis (see table 2). Random effects meta-analysis was undertaken using RevMan. Included studies reported either:

- a SMR or hazard ratio (HR)

OR

- the observed number of deaths or expected deaths necessary to calculate a SMR. These were calculated using STATA (version 14) by dividing the observed number of deaths in a cohort study group by the expected mortality based on age and gender-specific death rates in the general population comparison group.

Random effects models were selected for all meta-analyses due to the different populations and measures in the included studies. Inverse of the variance method was used to calculate the weighted mean respiratory mortality log-SMR across studies, as well as for subgroup meta-analyses. As the SMR is a ratio, log transformation was needed to maintain symmetry in the analysis.[19] SMRs and HRs from each study were transformed to log values for computations and back transformed for presentation of the results. Weighted mean log-SMRs and their 95% confidence intervals were reported separately for individuals with and without intellectual disabilities. The magnitude of the back transformed ration and associated confidence interval (CI) were also reported. Where data permitted, further subgroup analyses were conducted to examine sources of heterogeneity. Where more than two studies reported sub-group level data, or cause-specific results of causes of respiratory deaths (e.g. pneumonia) random effects models were considered for subgroup meta-analyses.

For the random effects meta-analysis, heterogeneity was expected in the pooled result. Therefore, the Chi-squared statistic I^2 was chosen to measure level of heterogeneity across the studies, as it allows for interpretation of results regardless of the number of studies included in the meta-analysis, the type of outcome data, or effect measurement.[20] Heterogeneity was interpreted as not observed when I^2=0%, low when I^2=25%, medium when I^2=50%, and high when I^2=75%.[20]

Sensitivity analysis

Sensitivity analysis was used to assess the impact of risk of bias for each study on the weighted mean SMR. Data were removed one-by-one from the meta-analysis for each study, beginning with the lowest ranked papers, to determine their effect and re-estimate the weighted mean SMR. Cumulative analysis, starting with larger studies and sequentially adding smaller studies, was used to investigate how the weighted mean SMR estimate changes as small studies are added.[21]

Patient and public involvement

No patient and public involved.

Results

Figure 1 summarises the systematic search, selection and reasons for exclusion. All 17 studies were included in the narrative synthesis and 10 were included in the meta-analysis (studies with relevant SMRs n=8 and HR n=2). A full list of studies excluded from full-text screening is available in Appendix 2.

[Insert Figure 1: PRISMA flow diagram of systematic search and selection]

Table 1 illustrates the characteristics of studies reporting mortality rates for respiratory disorders and pneumonia in people with intellectual disabilities and table 2 presents all-cause mortality and deaths from respiratory disorders in people with intellectual disabilities.

Table 2: **All-cause mortality and deaths from respiratory disorders in people with intellectual disabilities**

Author	All-cause mortality	Deaths from respiratory disorders	Between group comparison of deaths from respiratory disorders	Deaths from individual respiratory disorders	Between group comparison of deaths from individual respiratory disorders	Variables associated with risk of death from respiratory disorders
Brameld et al (2018)[26]	591 had ID /63,508 out of all deaths (0·93%)	62/591 (10·5%) deaths	Not available	Emergency Department presentations in the last year of life: Influenza and pneumonia RR=2·6 (95% CI 2·0-3·4 p<0·001) Chronic obstructive pulmonary disease (COPD) RR=0·8 (95%CI 0·5-1·6, p=0·596) Asthma RR=4.7 (95%CI 2·1-10·4, p<0·001) Ear, nose and throat infections RR=1·9 (95%CI 0·8-4.0, p=0·122) Pneumonitis due to solids/liquids RR=17·9 (95%CI 11·3-28·3 p<0·001) Hospital admissions in the last year of life: Influenza and pneumonia RR=2·3 (1·0-5·3, p=0·044) COPD RR=1·4 (95%CI 0·9-2·4, p=0·164) Asthma RR=4·6 (95%CI 1·4-15·0, p=0·011) Ear, nose and throat infections RR=0·0 (95%CI 0·0-., p=0·972) Pneumonitis due to solids/liquids RR=17·6 (95%CI 11·7-26·5, p<0·001)	Decedents with intellectual disability had increased odds of dying of (relative odds of having condition listed as underlying cause of death), adjusted for comorbidity: Influenza/pneumonia (OR=5·3, 95% CI 2·4-11·8) Pneumonitis due to solids or liquids (OR=9·9, 95% CI 5·1-19·3) Asthma (OR=2·3, 95% CI 1·0=5·2) (not significant) No difference for COPD as cause of death	Decedents with intellectual disability had increased A&E attendance but received less hospital-based specialist palliative care. For those in hospitals, they were more likely to have hospital stays involving intensive care and ventilator support.

Cooper et al (2020)[28]	294/ 961 (30·6%) deaths **SMR = 2·24 (95% CI; 1·98, 2·49)**	Underlying cause of death: 57/ 262 (21.8%) deaths **SMR= 6·78 (95% CI; 5·02, 8·54)** **(adjusted for age and sex)**	Underlying cause of death: Down syndrome: 8/ 57 (14·0%) deaths Without Down syndrome: 49/ 205 (23·9%) deaths	All-contributing factors in death: Respiratory infection = 27·1% deaths Aspiration/ reflux/ choking = 19·8% deaths	Underlying cause of death: Down syndrome: Aspiration/ reflux/ choking = <5/ 57 deaths Respiratory infection = <5/ 57 deaths Other respiratory conditions = <5/ 57 deaths Without Down syndrome: Aspiration/ reflux/ choking = 22/ 205 (10·8%) deaths Respiratory infection = 21/ 205 (10·3%) deaths Other respiratory conditions = 9/ 205 (4·4%) deaths All-contributing factors in death: Down syndrome: Respiratory infection = 22/ 57 (38·6%) deaths Aspiration/ reflux/ choking = 11/ 57 (19·3%) deaths Other respiratory conditions = <5/ 57 deaths Without Down syndrome: Respiratory infection = 49/ 205 (23·9%) deaths Aspiration/ reflux/ choking = 41/ 205 (20·2%) deaths Other respiratory conditions = 31/ 205 (15·1%) deaths	Not available

Dupont et al (1987)[40]	N=446 deaths / 7134 (5·9%) people with mild ID N=277 males N=169 females	Respiratory deaths common cause of death in people with ID (all ages) Tests of significance only; respiratory deaths were more common for males with ID (all ages), and females aged 35-64, versus population of Denmark 1977	Not available	Not available	Not available	Not available
Durvasula (2002)[29]	40/693 (6%) deaths	14/40 (35%) deaths	For people under 40, respiratory and external deaths were most common, for people over 40, cancer and respiratory deaths were most common Age: 7/14 deaths in under 25-year-olds and 6/14 deaths in 40+ year olds Sex: 11/14 deaths in males Conditions: 2/14 had Down syndrome & dementia, 1/14 had myelodysplastic syndrome, 1x Battens disease	Not available	Not available	Age, gender, Down syndrome, myelodysplastic syndrome
Forsgren et al (1996)[15]	N=124 / 1478 (8·4%) people with ID (all ages), over 9,992 person-years	N=13 /124 (10%) deaths were respiratory disease for people with ID vs n=3·9 expected,	Respiratory disease was common cause of death for people with ID and epilepsy but SMR was not possible due to small sample size	Pneumonia was most common cause of death, but rarely reported as underlying cause Pneumonia was most common cause of death in	Not available	Epilepsy (active seizures)

	SMR 2.0 (95% CI 1·7, 2·3) Males 1.6 (95% CI 1·2, 2·0), Females 2·6 (95% CI 2·0, 3·3) *Additional: SMRs for severity of ID, epilepsy and cerebral palsy are available in appendix*	**SMR 3·3 (95% CI 2·0, 5·5)** (adjusted for age and sex)		people with both epilepsy and ID		
Glover et al (2017)[8]	N=664 deaths for people with ID (all ages) over 59,279.7 person-years Crude rate 11·2 (10·4, 12·1) per 1000 person-years **SMR 3·18 (2·94, 3·43) Women 3·40 (3·02, 3·81) Men 3·03 (2·73, 3·35)**	N=114 deaths from respiratory causes for people with ID vs 23·3 expected **SMR 4·9 (4·0, 5·9)** (adjusted for age and sex)	Not available	N=57 / 114 (50%) of respiratory deaths (and 8·6% of all deaths) were from influenza and pneumonia, vs expected 7·4 deaths **SMR 7·7 (5·8, 9·9)** Vast majority of pneumonia were unspecified (organism) n=24 / 114 (21%) respiratory deaths (3·6% of all deaths) were due to pneumonitis due to solids / liquids vs expected 1.1 deaths **SMR 21·8 (13·9, 32·4)** N=12 (1·8%) of all deaths were due to respiratory and intrathoracic cancers vs expected 16.6 deaths **SMR 0·7, 95% CI 0·4–1·3).**	Not available	Not available

Heslop et al (2014)[6]	N= 247 deaths in people with ID aged 4+ Rate of death 16·2 per 1000 person years Median age of death: 64 (52, 75). *Additional; all-cause mortality for sex, ID severity, amenable mortality, patient care, & accommodation available in appendix*	n=37 (15%) deaths had underlying cause due to respiratory diseases, vs 14·0% England & Wales deaths (p=0·66)	Not available	Not available	Not available	Reduced smoking in ID group p=0·02
Hollins et al (1998)[11]	270/2,026 (13·3%) deaths 116/1,081 (10·7%) deaths on Wandsworth register 154/945 (16·3%) deaths on Kensington register	Not available	Not available	Bronchopneumonia: N=56 (48%) (Wandsworth) N=69 (45%) (Kensingston) COPD Emphysema: N=1 (Wandsworth) N=1 (Kensingston) Asphyxia: N=4 (Wandsworth) N=1 (Kensingston) Respiratory other: N=4 (Wandsworth) N=4 (Kensingston) 52% of all deaths had a diagnosis of pneumonia	Not available	Not available

Hosking et al (2016)[24]	656/ 16666 (3·9%) deaths **HR = 3·62 (95% CI; 3·33, 3·93)**	123/ 16666 (18·8%, rate= 24·8) deaths **HR = 6·68 (95% CI; 5·38, 8·29)** **(adjusted for age, sex and general practice)**	Down syndrome = 24/ 1793 (20·3%) deaths. General population: 135/ 113562 (rate= 3·9) deaths.	Pneumonia; n = 67/ 16666 (rate = 13·5) Aspiration pneumonitis; n = 21/ 16666 (rate = 4·2)	General population: Pneumonia; 39/ 113562 (rate = 1.1) Aspiration pneumonitis; n = 6/ 113562 (rate = 0.2)	Not available
Janicki et al (1999)[22]	2,752 deaths in the group aged 40+/4,183 all-age deaths (66%)	40+ year olds: N=548 (20%), rate: 201 per 100,000	Increasing by age decade: aged 40s: 343 per 100,000 (16% of those who died) aged 50s: 793 per 100,000 (20%) aged 60s 1660 per 100,000 (25%) aged 70+: 3441 per 100,000 Males with ID rate of death: 257 per 100,000 Females with ID rate of death: 331 per 100,000 Respiratory causes did not vary over the 10-year study period. Deaths due to respiratory diseases increased, with increasing age. Gender: breathing obstructions were more prevalent among males. Gender x age: respiratory disease was increased in the oldest groups, for males particularly while respiratory disease remained static as a cause	Breathing obstructions – 2·7% average deaths per year across 10 years, N=75, rate=27·5 per 100,000 Respiratory disease types: pneumonia was the most prevalent type of respiratory cause of death, with 43% of respiratory disease deaths in ID group	Not available	Age, gender

			of death for females across ages.			
Ng et al. (2017)[12]	4,738/15,289 deaths in people aged 55+ (31%)	807/4,738 (17%) respiratory deaths for those with ID **HR =12·5 (10·9, 14·2)** **(adjusted for sex, year of birth and year of access to services)**	ID rate: 423 per 100,000 DS rate: 3,187 per 1,000	ID group (excludes DS) Pneumonitis due to solids and liquids: 10%, rate 25 per 100,000 Pneumonia: 50%, rate 129 per 100,000 Other chronic obstructive pulmonary disease: 20%, 49 per 100,000 DS group Pneumonitis due to solids and liquids 31·4%, 181 per 100,000 Pneumonia 20%, 113 per 100,000 Asthma 8%, 45 per 100,000 Bronchitis 8%, 45 per 100,000 Other respiratory disorders 8%, 45 per 100,000	Not available	Not available
Oppewal et al (2018)[27]	207/1050 ID=19·7%; 54/ 149 DS=26·1%	69/159 ID=44.3%; 33/45 DS only=73·3%; 36/114 ID with no DS=31·6% Respiratory causes were the top primary causes of ID deaths. Respiratory causes were the top primary	5-year age bands: 50-54 ID=100% GP=3·3%; 55-59 ID=26·5% GP=4·7%; 60-64 ID=51·4% GP=6·0%; 65-69 ID=30·4% GP=6·7%; 70-74 ID=23·8% GP=8·6%; 75-79 ID=12·5% GP=9·4%; 80-84 ID=26·3% GP=9·4%; 85-90 ID=(0) GP=9·9%; 90-95 ID=40% GP=10·4%; 95+ ID=100% GP=10·9%	Pneumonia ID=80·4%; Chronic obstructive pulmonary diseases ID=17·6%	Not available	Not available

		cause of DS deaths. General 50+ population, the three largest groups of primary causes of death were neoplasms (31%), circulatory diseases (28%) and respiratory diseases (9%). No SMR available.				
Patja et al (2001)[14]	1111/ 2369 ID =46·9%	Immediate cause 322/1093 ID=29%; Primary cause 241/1095 ID=22% Respiratory diseases second largest cause of ID death **SMR=3·76 (CI 3·31 to 4·27)*** **(adjusted for age and sex)**	Male: age 2-19 **SMR=5·8 (4·4 – 15·6);** age 20-39 **SMR=5·4 (2·9 – 8·0);** age 40-59 **SMR=5·5 (3·5-7·5);** age 60+ **SMR=2·7 (2·7 – 4·8)** Female: age 2-19 **SMR=4·3 (0·3 – 4·7);** age 20-39 **SMR=3·2 (1·1 – 5·1);** age 40-59 **SMR=6·2 (4·1 – 8·2);** age 60+ **SMR=3·3 (1·7 – 3·0)**	Pneumonia ID=83%; Chronic obstructive pulmonary disease ID=11%.	Pneumonia deaths (%): Profound ID=29%; Severe ID=13%; Moderate ID=33%; Mild ID=25%. Risk ratios compared to general population: Mild ID 2.6 times higher; Profound ID 5.8 times higher. ID men higher risk than women in younger age groups (< 39 years), but at lower risk from 60 years of age onwards.	Age, gender (all respiratory) ID severity (with pneumonia)
Raitauso et al (1997)[13]	216 deaths	Immediate cause of death 97/216 ID=45%	age 0-14 SMR=0·48; age 15-44 SMR=3·46; age 45-74 SMR=2·35; age 75 SMR=0	Bronchopneumonia (immediate cause) ID=43% Five patients had died of pneumonia caused by	Not available	Age (all respiratory)

		Primary cause 14/216 ID= 6%. Respiratory diseases were the dominant causes of ID death. **SMR=2·15 (CI 1·18 – 3·61)** **(adjusted for age, and year of death)**		aspiration. In one case fatal pneumonia had been caused by a fistula between the bronchus and the pleura. Besides pneumonia, two patients had acute laryngitis and one patient had hyperplasia of the lymph nodes of the lungs as the immediate cause of death. The latter had trisomy of chromosome 13 (Patau's syndrome) as the basic disorder.		
Smith et al (2020)[10]	N = 106 (0·6%) deaths **SMR = 11·6 (95% CI; 9·6, 14·0)**	Underlying cause of death: N = 8/ 106 (8%) deaths All-contributing factors in death: **n = 55. CMR = 81·7 (95% CI; 62·7, 106·4) deaths** **SMR = 55·3 (95% CI; 42·5, 72·1)** **(adjusted for age and sex)**	Underlying cause of death: General population: 17/ 458 (4%) deaths All-contributing factors in death: General population: n = 51. **CMR = 1·4 (95% CI; 1·1, 1·8) deaths**	Underlying cause of death: Pneumonia including influenza; <5/ 106 All-contributing factors in death: Pneumonia= 27/ 106 (25·5%) deaths Respiratory failure; 17/ 106 (16·0%) deaths Respiratory disorders = 15/ 106 (14·2%) deaths Pneumonitis associated with food and vomit = 9/ 106 (8·5%) deaths	General populations: All-contributing factors in death: Pneumonia = 21/ 458 (4·6%) deaths	Not available
Trollor et al (2017)[25]	732 / 19362 ID=4% **SMR=1·3 (1·2 to 1·5)**	632/732 ID=86·3% had cause of death information 78 ID=12% 4th top cause using the ID ABI conversion	Not available	Not available	Not available	Not available

		130 ID=20% 1st top using the ID revised version 16 ID=3% of respiratory deaths were considered avoidable. 26242 GP=9% 3rd top underling cause				
Tyrer & McGrother (2009)[23]	503/ 2995 (17%) deaths **SMR=2·77 (95% CI 2·53, 3·03).**	**SMR=5·46 (95% CI 4·58, 6·46) (adjusted for age and sex)**	Not available	Bronchopneumonia; **SMR=6·47 (95% CI 5·00 8·23), O=66, E=10·2.** Other respiratory; **SMR= 4·64 (CI 3·58 to 5·91). O=65, E=14·0.**	Male; **SMR=2·28 (95% CI; 2·02-2·56) O=278, E=121·8.** Female; **SMR=3·24 (95% CI; 2·83-3·69). O=225, E=69·4.**	Gender

*only where adjusted specifically for respiratory mortality

SMR=standardised mortality ratio/ CI=confidence interval/ RR=rate ratio/ HR=hazard ratio/CMF=comparative mortality figure/ OR=odds ratio/ O=observed deaths/ E=expected death* calculated by authors using data from the study

Study characteristics

Key features of all studies identified for inclusion in the review were tabulated (Table 1). These were cohort studies (n=12), case control studies (n=4) and one population-based audit of deaths in adults and children. These studies report data on 90,302 people with intellectual disabilities and 27,394 deaths. The average study size was 9,250 people. These studies were from the Netherlands (n = 1), Finland (n = 2), Australia (n = 3), the United Kingdom (n = 7), the United States of America (n = 1), Sweden (n = 2) and Denmark (n = 1).

Definition of respiratory disorder

Thirteen out of 17 (76%) studies defined the respiratory disorder using ICD 9 -chapter codes[13-15,22,23] and ICD 10 – chapter codes for respiratory disorders.[8,10,12,23-26] The remaining four studies included in the systematic review did not define respiratory disorders.

Causes of death from respiratory disorders

Thirteen papers reported on cause of deaths from respiratory disorders.[8,10-15,22-24,26-28] Pneumonia was reported as a cause of death in 12 studies.[8,10-15,22,23,26,27], five studies reported deaths from pneumonitis related to aspiration[8,10,12,14,24], five studies reported on chronic obstructive pulmonary disease (COPD)[11,12,14,26,27], one study reported on asthma[31] and one reported respiratory cancer deaths.[8]

Evidence synthesis

Respiratory-associated mortality

Five papers reported that respiratory disorders were the dominant cause of death in people with intellectual disabilities.[11,13,27,28,29] A further three studies found that deaths from respiratory disorders were the second most common cause of death.[12,14,24] Respiratory-associated deaths were in the top five main causes of deaths for a further four papers.[9,10,22,25] Comparative results (intellectual disabilities vs general population) for deaths due to respiratory disorders were reported in 10/17 (59%) of the studies.[5,8-10,12,22,24-26] In the majority of these studies rates of death from respiratory disorders were higher for people with intellectual disabilities than for people in the general population. However, Troller et al. (2017)[25] reported that respiratory-associated deaths in the general population were (9%) similar to the population with intellectual disabilities (12%). Hollins et al. (1998)[11] also reported that respiratory disorders were the most commonly cited cause of death for both groups.

Individual respiratory disorders and mortality

Pneumonia was reported as the most common cause of respiratory death in people with intellectual disabilities.[8,10-15,22-24,26,27] Contributors to pneumonia deaths included influenza and injury from inhalation and aspiration events.[10,14] Pneumonitis featured as an underlying or contributing cause for between eight and 21% of respiratory-associated deaths in people with intellectual disabilities.[8,10,12] Crude comparison data showed people with intellectual disabilities were much more likely (between 10 and 20 times) to die from pneumonitis.[24,26] COPD was found to be a common cause of death in two studies focussing on older adults.[12,27]

Factors associated with respiratory-associated deaths experienced by people with intellectual disabilities

Only four out of 17 (23.5%) papers directly reported on factors associated with the risk of respiratory-associated deaths[14,22,23,29] (see Table 2). Two reported SMRs separately for males and females[14,23], while two reported proportions of respiratory deaths between males and females. None directly compared males versus females or reported tests of significance. While one study reported higher respiratory SMS among females[23], another study reported separate SMRs for different age-bands which varied widely[14]. Group-level analysis was not possible. Level of intellectual disabilities was only reported as associated with respiratory related deaths in one study with 35 year follow up using relative risk but failed to report confidence or p-values.[14] This study found that, when compared to the general population, the relative risk of respiratory related deaths was 2.6 times higher for people with mild intellectual disabilities and 5.8 times higher for people with profound and multiple intellectual disabilities.

Respiratory mortality among children and young people

Respiratory deaths amongst children and young people with intellectual disabilities were reported in five studies and found to be a common cause of death across all studies.[10,13,15,29,30] Four studies included comparison with the general population for respiratory causes of death, while one included the national population without intellectual disabilities[10]. All analyses were limited by the small numbers of death. Raitasuo et al. (1997) reported only one death.[13] Patja et al. (2001) reported higher SMR for males aged 2-19 years but not females.[30] Smith et al. reported 8% deaths had respiratory disease as the underlying cause but the SMR for underlying cause was not reported.[10]

Meta-analytical outcomes

Ten studies[8,10-15,23,24,28] reported the necessary data to calculate (SMR, hazard ratio, or data necessary to calculate these) and were included in the meta-analysis of respiratory mortality of people with intellectual disabilities and the general population. As Hollins (1998) reported the SMR of two separate cohorts, these are displayed separately in the relevant forest plots.[11] The pooled SMRs for respiratory mortality between people with intellectual disabilities and the general population was 10·86 (95% CI 5·32, 22·18). The results indicate that respiratory mortality occurs ten times more frequently in the intellectual disabilities group than in the general population group. At the individual study level, this was adjusted for age (all studies) and for sex in all studies except two[11,13], where this was not clear. There was evidence of considerable statistical heterogeneity between studies in the meta-analyses, with I^2= 99·0%. Results are displayed in Figure 2.

Insert Figure 2: Forest plot of respiratory associated mortality

As five studies (12, 15, 23, 24, 28) focussed on adults only, one study (10) focussed on children only, and six (8, 11-15) included people of all ages, a sub-analysis was conducted of studies which reported data on an adult only population. The results of this sub-analysis are displayed in Figure 3. The pooled SMR reduced slightly from 10·86 (95% CI 5·32,22·18) to 6.53 (95% CI 4·29,9·96), after one study with a sample of primarily children was excluded.[10] Studies which included both adults and children in their sample[8,11-15] were next removed one at a time. First, both cohorts from Hollins (1998) were removed and the pooled SMR was reduced by around half, from 9·15 to 4·80[11]. The further removal of studies by Glover (2017)[8], Patja (2001)[14] and Raitasuo (1997)[13] resulted in a final pooled SMR for adults of 5·85 (95% CI 4·73,7·22, p<0·001). Heterogeneity between studies was also reduced from I^2=99% to I^2= 56% by the exclusion of samples which included children.

Insert figure 3: Forest plot for adults only

A sub-analysis was conducted of studies which reported an SMR for pneumonia.[8,11,23] The pooled SMR for pneumonia mortality for people with intellectual disabilities compared to the general population was 26·65 (95% CI 5·63, 126·24, p<0·001). These results, displayed in Figure 4, indicate that pneumonia related mortality occurs much more frequently in people with intellectual disabilities than in the general population group. Evidence of considerable statistical

heterogeneity between studies was also present in this sub-analysis with I^2= 99.0%. SMRs were recalculated excluding the only study to include an adult only sample, Tyrer & McGrother (2009)[23] resulting in a substantial increase in pooled SMR (95% CI from 26·65 to 42·70).

Insert figure 4: Forest plot for pneumonia related mortality

Sensitivity analysis

Sensitivity analysis in relation to quality assessment was run for the ten studies included in the meta-analysis (Appendix 3). Studies which were rated as weak[13] or moderate[23] were removed from the analysis. The pooled SMR for mortality ratios changed slightly as Raitasuo (1997)[13] (from 10·81 to 12·67)[27] and then Tyrer and McGrother (2009) (from 12·67 to 13·94)[23] were removed from the analysis. As the change in SMR was small, this suggests that inclusion of weaker studies did not significantly change the results.

Discussion

This systematic review and meta-analysis highlights that people with intellectual disabilities experience excess respiratory-associated deaths, with a respiratory mortality ten times greater than for the general population. Respiratory mortality was more prevalent among studies which include children, and pneumonia was a major contributor to the higher respiratory mortality reported in this study. Clinical guidelines have contributed to a reduction in mortality from community-acquired pneumonia.[31] We believe the evidence presented here highlights the need for clinical guideline development groups to make recommendations on reducing the risks of premature death due to community-acquired pneumonia amongst people with intellectual disabilities. Vaccination programmes for influenza can help to reduce respiratory mortality in children[32] and adults.[33] Although there is a relatively low uptake of influenza vaccine amongst people with intellectual disabilities, annual health-checks for people with intellectual disabilities have been reported to increase uptake of influenza immunisation.[34] People with intellectual disabilities should be identified as a high-risk group and immunisation providers should prioritise the improvement of vaccine uptake, for example through the roll-out of health checks. People with intellectual disabilities are at increased risk of recurrent chest infections which are secondary to dysphagia[35,36] with a high proportion of aspiration pneumonia-related deaths occurring among individuals with severe and profound intellectual disabilities.[5,22,35,37,38] Increased recognition of the link between dysphagia and respiratory

disorders among caregivers and practitioners is critical to ensuring the early identification of individuals with respiratory disorders.

The higher risk of death from respiratory disorders, such as pneumonia, for people with intellectual disabilities is a significant concern in relation to the rapidly developing COVID-19 pandemic[39,40]. Urgent action to disaggregate data on deaths from COVID-19 for people with intellectual disabilities and to investigate factors associated with COVID-19 related mortality for people with intellectual disabilities is vital to ensure that clinical guidelines are based on consideration of the specific risks faced by people with intellectual disabilities. Research is urgently required to investigate the risk factors associated with COVID-19 for people with intellectual disabilities to ensure carers and clinicians have access to the best evidence to reduce the risk of infection in those most vulnerable and to inform the clinical management of those who contract COVID-19. Carers and clinical staff must be given training to ensure they understand the human rights and health care needs of people with intellectual disabilities to ensure that existing stark disparities in the health of people with intellectual disabilities are not widened during this crisis.

Interventions should focus on the pediatric age group. Among the studies included in this meta-analysis we found a relationship between inclusion of children and SMRs from respiratory causes, with those studies including children reporting higher SMRs. This is consistent with studies that have reported higher SMRs in children compared with adults in epilepsy[15] and cerebral palsy.[41] Overall, mortality in childhood is very low relative to adulthood, and in the pediatric age group chronic disabling conditions such as intellectual disability, epilepsy and cerebral palsy all have a marked impact on SMR. Co-morbidity with epilepsy and cerebral palsy are likely to be significant modifiers of the relationship between intellectual disability and respiratory mortality. Children with more severe intellectual disability are more likely to have epilepsy and cerebral palsy, both of which are independent risk factors for respiratory mortality.

Study strengths and limitations

Our study has several strengths. The meta-analysis included mortality ratios from ten observational studies covering 1,844 respiratory deaths in people with intellectual disabilities, which has improved the power and precision to answer this important research question. A rigorous and systematic analysis process was undertaken, and we minimised the risk of bias, errors and omissions by having two or more reviewers conduct comprehensive searches, assess

study quality and extract descriptive data. Due to the low prevalence (~1%) of intellectual disabilities among the general population, low sample size was a considerable limitation, relative to other patient groups. However, our meta-analysis included two national [10,12], and five regional intellectual populations in their respective countries [11,15,23,28]. While heterogeneity was found, due to methodological and clinical diversity including study design, age and study nationality, this is common in meta-analyses and statistical heterogeneity was inevitable.[20] We have not included assessment of non-reporting or publication bias. Most of the research was conducted in Western countries, thus limiting the extent to which the findings may generalise to non-Western countries. Furthermore, ethnicity was not reported widely which prevented further analysis. There was variation among studies on how mortality was examined and how deaths were reported. There is a general lack of evidence on factors associated with the increased risk of respiratory related deaths in people with intellectual disabilities. As a consequence, we were not able to perform meta-regression on predictors or factors reported in studies which increase SMRs for respiratory deaths (age, sex, place of death, or severity of intellectual disabilities). This should be a priority for future research in order to inform the development of targeted interventions to prevent respiratory related deaths. Although the meta-analysis enables synthesis of data from a large sample, many of the individual studies reported on small samples and are at increased risk of bias. It is encouraging that there have been several larger studies in recent years and future research should focus on reporting respiratory mortality in representative, population-based samples. Furthermore, the majority of the studies included for review relied on death certificate data. One the most reported causes on the death certificate of people with intellectual disabilities is the intellectual disability itself. Given that this problem only exists within this population, true causes of death remain under-estimated.[42,43] As reporting has improved over the years, and many counties implemented automated coding systems, it is likely that older paper have more bias than more recent studies.

These findings signify the urgent need to develop and implement evidence-informed strategies to reduce premature mortality among people with intellectual disabilities. Respiratory disorders are a major cause of death for people with intellectual disabilities, many of which are avoidable with improved public health initiatives and access to good quality health and social care. However, further research is required to understand both the multifactorial causes of this heightened risk as well as the most effective approaches for the multi-professional clinical management of these risks.

Contributors: MT, CM, AM, ER, LHM, DK, KD, GSS, AH & FB had full access to all the data, contributed to the systematic review and meta-analysis of studies, interpretation of results and the manuscript. JS and BJ helped interpret the result of the study and contributed to the manuscript. MT is study guarantor. All authors reviewed the final manuscript and agreed to be accountable for all aspects of the work and approved the final manuscript for submission. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests None declared.

Patient consent for publication Not required

Ethics Not required as this systematic review and meta-analysis was based on published data

Provenance and peer review: Not commissioned; externally peer reviewed

Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure captions

Figure 1: PRISMA flow diagram of systematic search and selection. A total of 2286 records were retrieved through a search of Embase, ISI Web of Science (all databases), CINAHL, and PsycINFO with an additional 9 records identified through other sources. After removing 241 duplicates, 2025 records were excluded due to ineligible types., the remaining 29 were retrieved as full-texts. From these 17 were included in the narrative review and 10 included in the meta-analysis.

Figure 2: Forest plot of respiratory associated mortality. The pooled SMRs for respiratory mortality between people with intellectual disabilities and the general population was 10·86 (95% CI 5·32, 22·18). There was considerable statistical heterogeneity between studies in the meta-analyses, with I^2= 99·0%.

Figure 3: Forest plot for adults only. The pooled SMR for adults only was 5·85 (95% CI 4·73,7·22, p<0·001). Heterogeneity between studies was also reduced from I^2=99% to I^2= 56% by the exclusion of samples which included children.

Figure 4: Forest plot for pneumonia related mortality. The pooled SMR for pneumonia mortality for people with intellectual disabilities compared to the general population was 26·65 (95% CI 5·63, 126·24, p<0·001). Evidence of considerable statistical heterogeneity between studies was also present in this sub-analysis with I^2= 99.0%.

References

1 Harris JC. Intellectual disability: Understanding its development, causes, classification, evaluation, and treatment. Oxford: Oxford University Press, 2006.

2 Maulik PK, Mascarenhas MN, Mathers CD, Dua T, Saxena S. Prevalence of intellectual disability: a meta-analysis of population-based studies. *Res Dev Disabil* 2011; **32(2):** 419-36

3 Organisation W. The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines. Geneva: World Health Organisation, 1992.

4 World Health Organization. World health statistics 2015. Geneva: World Health Organization, 2015.

5 Heslop P, Blair P, Fleming P, Hoghton M, Marriott A, Russ L. Confidential Inquiry into premature deaths of people with learning disabilities (CIPOLD) Final Report http://www.bristol.ac.uk/cipold/fullfinalreport.pdf (2013) (accessed June 25, 2020).

6 Heslop P, Blair PS, Fleming P, Hoghton M, Marriott A, Russ L. The Confidential Inquiry into premature deaths of people with intellectual disabilities in the UK: a population-based study. *Lancet* 2014; **383(9920):** 889-95.

7 O'Leary L, Cooper SA, Hughes-McCormack L. Early death and causes of death of people with intellectual disabilities: a systematic review. *J Appl Res Intellect Disabil* 2018; **31(3):** 325-42.

8 Glover G, Williams R, Heslop P, Oyinlola J, Grey J. Mortality in people with intellectual disabilities in England. *J Intellect Disabil Res* 2017; **61(1):** 62-74.

9 Tyrer F, Smith LK, McGrother CW. Mortality in adults with moderate to profound intellectual disability: a population-based study. *J Intellect Disabil Res* 2007; **51(7):** 520-7.

10 Smith GS, Fleming M, Kinnear D, Henderson A, Pell JP, Melville C, Cooper S-A. Rates and causes of mortality among children and young people with and without intellectual disabilities in Scotland: a record linkage cohort study of 796,190 schoolchildren. *BMJ Open* 2020 (Accepted for Publication) DOI:10.1136/bmjopen-2019-034077.

11 Hollins S, Attard MT, Fraunhofer Nv, McGuigan S, Sedgwick. Mortality in people with learning disability: risks, causes, and death certification findings in London. *Dev Med Child Neurol* 1998; **40(1):** 50-6.

12 Ng N, Wallén EF, Ahlström G. Mortality patterns and risk among older men and women with intellectual disability: a Swedish national retrospective cohort study. *BMC Geriatr* 2017; **17(1):** 269.

13 Raitasuo J, Mölsä P, Raitasuo S, Mattila K. Deaths among the intellectually disabled: A retrospective study. *J Appl Res Intellect Disabil* 1997; **10(4):** 280-8.

14 Patja K, Mölsä P, Iivanainen M. Cause-specific mortality of people with intellectual disability in a population-based, 35-year follow-up study. *J Intellect Disabil Res* 2001; **45(1):** 30-40.

15 Forsgren L, Edvinsson SO, Nyström L, Blomquist HK. Influence of epilepsy on mortality in mental retardation: an epidemiologic study. *Epilepsia* 1996; **37(10):** 956-63.

16 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8(5):** 336-41.

17 Kmet LM, Cook LS, Lee RC. Standard quality assessment criteria for evaluating primary research papers from a variety of fields. HTA Initiative #13. Edmonton: Alberta Heritage Foundation for Medical Research, 2004.

18 Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). *PLoS One* 2007; **2(12)**: e1350. DOI:10.1371/journal.pone.0001350.

19 Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Res Synth Methods* 2017; **8(1):** 5-18.

20 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327(7414):** 557-60.

21 Borenstein M. Common mistakes in meta-analysis and how to avoid them. New Jersey: Biostat. Inc, 2019: 388.

22 Janicki MP, Dalton AJ, Henderson CM, Davidson PW. Mortality and morbidity among older adults with intellectual disability: health services considerations. *Disabil Rehabil* 1999; **21(5-6):** 284-94.

23 Tyrer F, McGrother C. Cause-specific mortality and death certificate reporting in adults with moderate to profound intellectual disability. *J Intellect Disabil Res* 2009; **53(11):** 898-904.

24 Hosking FJ, Carey IM, Shah SM, Harris T, DeWilde S, Beighton C, et al. Mortality among adults with intellectual disability in England: comparisons with the general population. *Am J Public Health* 2016; **106(8):** 1483-90.

25 Trollor J, Srasuebkul P, Xu H, Howlett S. Cause of death and potentially avoidable deaths in Australian adults with intellectual disability using retrospective linked data. *BMJ Open* 2017; **7(2):** e013489. DOI:10.1136/bmjopen-2016-013489.

26 Brameld K, Spilsbury K, Rosenwax L, Leonard H, Semmens J. Use of health services in the last year of life and cause of death in people with intellectual disability: a retrospective matched cohort study. *BMJ Open* 2018; 8(2):e020268. DOI:10.1136/bmjopen-2017-020268.

27 Oppewal A, Schoufour JD, van der Maarl HJ, Evenhuis HM, Hilgenkamp TI, Festen DA. Causes of mortality in older people with intellectual disability: results from the HA-ID study. *Am J Intellect Dev Disabil* 2018; **123(1):** 61-71.

28 Cooper S-A, Allan L, Greenlaw N, McSkimming, P, Jasilek A, Henderson et al. Rates, causes, place and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage. *BMJ Open* 2020 (Accepted for Publication).

29 Durvasula S, Beange H, Baker W. Mortality of people with intellectual disability in northern Sydney. *J Intellect Dev Disabil* 2002; **27(4):** 255-64.

30 Patja K, Iivanainen M, Vesala H, Oksanen H, Ruoppila I. Life expectancy of people with intellectual disability: a 35-year follow-up study. *J Intellect Disabil Res* 2000; **44(5):** 591-9.

31 Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC et al. Infectious Diseases Society of America/ American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; **44 (Suppl 2):** S27-72.

32 Flannery B, Reynolds SB, Blanton L, Santibanez TA, O'Halloran A, Lu PJ, et al. Influenza vaccine effectiveness against pediatric deaths: 2010–2014. *Pediatrics* 2017; **139(5):** e20164244. DOI:10.1542/peds.2016-4244

33 Backer JA, Wallinga J, Meijer A, Donker GA, Van der Hoek W, Van Boven M. The impact of influenza vaccination on infection, hospitalisation and mortality in the Netherlands between 2003 and 2015. *Epidemics* 2019 Mar 1;26:77-85.

34 Robertson J, Hatton C, Emerson E, Baines S. The impact of health checks for people with intellectual disabilities: an updated systematic review of evidence. *Res Dev Disabil* 2014; **35(10):** 2450-62.

35 Chadwick DD, Jolliffe J. A descriptive investigation of dysphagia in adults with intellectual disabilities. *J Intellect Disabil Res* 2009; **53(1):** 29-43.

36 Robertson J, Chadwick D, Baines S, Emerson E, Hatton C. Prevalence of dysphagia in people with intellectual disability: a systematic review. *Intellect Dev Disabil* 2017; **55(6):** 377-91.

37 Durvasula, S, Beange H, Baker, W. Mortality of people with intellectual disability in northern Sydney. *J Intellect Dev Disabil* 2002; **27(4):** 255-264. DOI:10.1080/1366825021000029311

38 Glover G, Ayub M. How people with learning disabilities die. Improving Health and Lives Learning Disabilities Observatory. Durham, 2010.

39 Landes SD, Turk MA, Formica MK, McDonald KE, Stevens JD. COVID_19 outcomes among people with intellectual and developmental disability living in residential group homes in New York State. Disability and Health Journal, 2020 Oct 1;13(4): 100969

40 Cuypers M, Schalk BW, Koks-Leensen MC, Nägele ME, Bakker-van Gijssel EJ, Naaldenberg J, Leusink GL. Mortality of people with intellectual disabilities during the 2017/2018 influenza epidemic in the Netherlands: potential implications for the COVID-19 pandemic. Journal of Intellectual Disability Research. 2020 May 26.

41 Blair E, Langdon K, McIntyre S, Lawrence D, Watson L. Survival and mortality in cerebral palsy: observations to the sixth decade from a data linkage study of a total population register and National Death Index. *BMC Neurol* 2019; **19(1):** 111

42 Landes SD, Peek CW. Death by mental retardation? The influence of ambiguity on death certificate coding error for adults with intellectual disability. Journal of Intellectual Disability Research. 2013 Dec;57(12):1183-90.

43 Dunwoodie Stirton F, Heslop P. Medical certificates of cause of death for people with intellectual disabilities: a systematic literature review. Journal of Applied Research in Intellectual Disabilities. 2018 Sep;31(5):659-68.

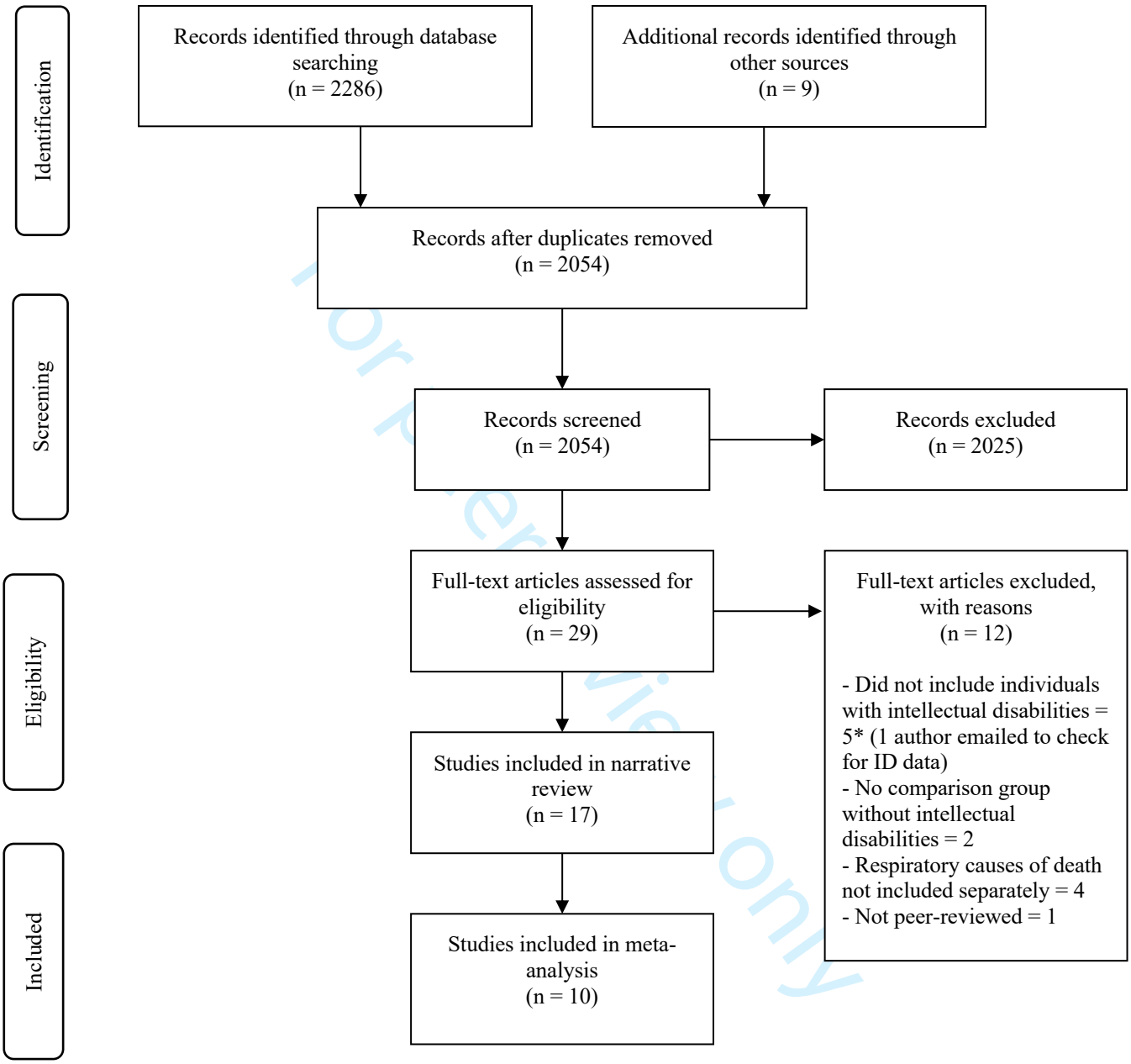


Figure 2: Forest plot of respiratory associated mortality

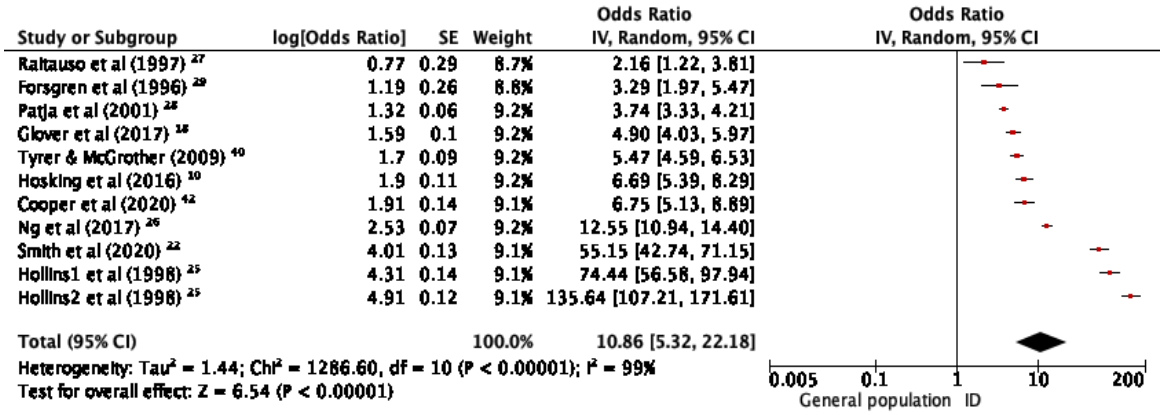


Figure 3: Forest plot for adults only

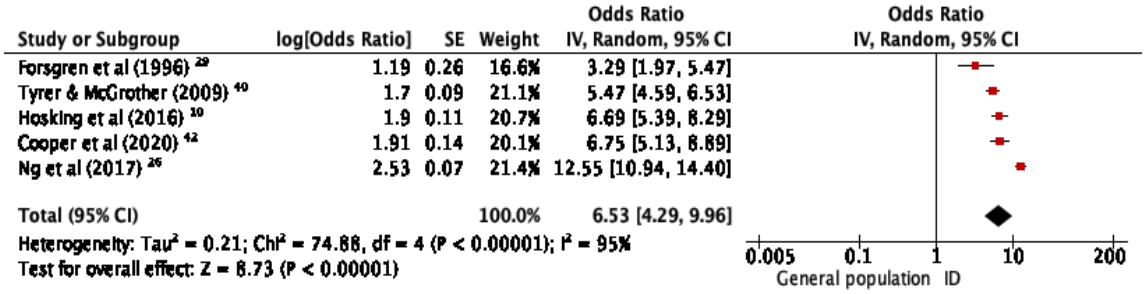
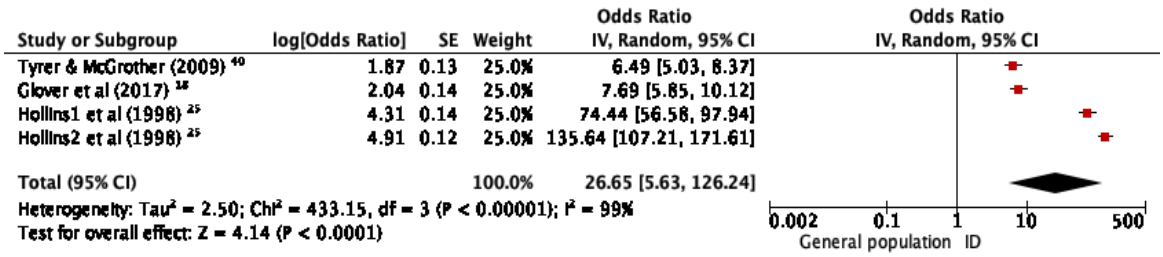


Figure 4: Forest plot for pneumonia related mortality



Appendix 1: Search strategy

Embase- Ovid, 2016-

Search Terms	
1.	developmental disorder/ or intellectual impairment/ or developmental disabilities/ or intellectual disability/ or mentally disabled persons/ or intellectual development disorder/ or "intellectual development disorder (attitudes toward)"/
2.	((intellect$ adj3 (deficien$ or difficult$ or disab$ or disorder$ or impair$ or handicap$ or incapacit$ or handicap$ or sub?average or sub?norm$)) or (low$2 adj2 intellect$)).tw.
3.	(learning adj3 (deficien$ or difficult$ or disab$ or disorder$ or handicap$ or impair$ or incapacit$ or handicap$ or sub?average or sub?norm$)).tw.
4.	(mental$ adj3 (deficien$ or disab$ or handicap$ or impair$ or handicap$ or incapacit$ or retard$ or sub?average or sub?norm$)).tw.
5.	((subaverage or sub$1 average or subnormal or sub$1 normal$) adj3 (cognit$ or intel$)).tw.
6.	((development$ or neurodevelopment$) adj disab$).tw.
7.	(education$ adj5 sub?norm$).tw.
8.	(cretin$ or feeble minded$ or imbecil$ or moron$).tw.
9.	Or/ 1-9
10.	cause of death/ OR mortality/ OR fatal outcome/ OR death/ OR hospital mortality/ OR mortality.ti,ab OR fatal.ti,ab OR death.ti,ab
11.	asthma/ OR asthma.ti,ab OR bronchial asthma.ti,ab OR asthma, bronchial.ti,ab OR pneumonia/ OR pneumonia.ti,ab OR lobar pneumonia.ti,ab OR lobar pneumonia.ti,ab OR pneumonia, lobar.ti,ab OR bacterial pneumonia/ OR pneumonia, bacterial.ti,ab OR viral pneumonia/ OR pneumonia, viral.ti,ab OR viral pneumonia.ti,ab OR bronchopneumonia/ OR bronchopneumonia.ti,ab OR bronchial pneumonia.ti,ab OR pneumonia, bronchial.ti,ab OR lung disease/ OR disease, lung.ti,ab OR pulmonary disease.ti,ab OR disease, pulmonary.ti,ab OR respiratory disease.ti,ab OR disease, respiratory.ti,ab OR chronic obstructive lung disease/ OR lung disease, obstructive.ti,ab OR obstructive lung disease.ti,ab OR obstructive lung diseases.ti,ab OR obstructive pulmonary diseases.ti,ab OR aspiration pneumonia/ OR aspiration pneumonia.ti,ab OR bronchiectasis/ OR bronchiectasis.ti,ab OR respiratory failure/ OR respiratory failure.ti,ab OR interstitial pneumonia/ Or interstitial pneumonia.ti,ab
12.	9 and 10 and 11

Cinahl and APA PsychINFO - Ebscohost, 2016-

Search Terms	
1.	MH Intellectual disability
2.	(MH "Mentally Disabled Persons")
3.	TX (intellectual* N3 (disab* or disorder* or handicap* or impair* or deficien* or subnorm*))
4.	TX (learning N3 (disab* or disorder* or impair* or difficllt*))
5.	TX (development* N3 (disab* or disorder* or handicap* or impair* or delay*))
6.	TX (Mental* N3 (disab* or disorder* or handicap* or impair* or deficien* or subnorm* or retard*))
7.	((development$ or neurodevelopment$) N disab$).tw.
8.	(education$ N5 su?bnorm$).tw.
9.	(cretin$ or feeble minded$ or imbecil$ or moron$).tw.
10.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
11.	cause of death/
12.	mortality/
13.	fatal outcome/
14.	death/
15.	hospital mortality/
16.	mortality.ti.ab
17.	fatal.ti.ab
18.	death.ti.ab
19.	Or/ 11-18
20.	"pulmonary disease" or "airway disease" or "broncho-pulmonary disease" or "respiratory disease" or "lung disease" or "lung disorder" or "pulmonary disorder" or "respiratory disorder" or "pneumonia" or "bronchopneumonia" or "lung infection" or pulmonary infection" or respiratory infection" or "asthma" or "chronic obstructive pulmonary disease" or "aspiration pneumonia" or "bronchiectasis" or "respiratory failure"
21.	10 and 19 and 20

Web of Science (All databases, including MEDLINE) 2016-current

TS= mortality OR death OR cause of death OR cause of mortality OR dead OR died
AND
TS= intellectual disab* or intellectual impair* or developmental disab* or learning disab* or mental retard* or mental handicap*
AND
TS=asthma* or bronchial asthma or pneumoni* or lobar pneumoni* or lobar pneumoni* or bacterial pneumoni* or viral pneumoni* or bronchopneumonia* or bronchial pneumoni* or lung disease* or lung disorder* or lung infect* or pulmonary disease* or pulmonary disorder or pulmonary infect* or respiratory disease* or respiratory disorder or respiratory infect* or obstructive lung disease* or obstructive pulmonary disease* or aspiration pneumoni* or bronchiecstasi

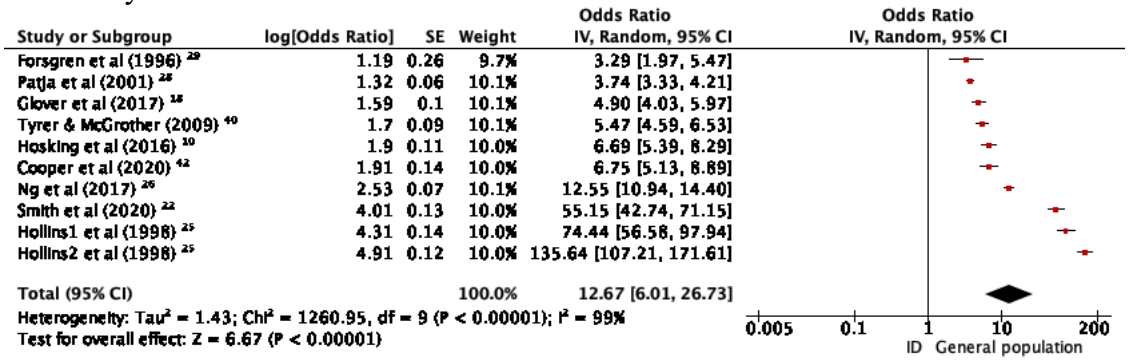
Appendix 2: Excluded papers – References and reasons for exclusion

	Reference	Reason
1	Bilder D, Botts EL, Smith KR, Pimentel R, Farley M, Viskochil J. Excess mortality and causes of death in autism spectrum disorders: A follow up of the 1980s Utah/ UCLA autism epidemiologic study. *J Autism Dev Disord* 2013; **43(5):** 1196-1204	Did not include individuals with intellectual disabilities.
2	Decoufle P, Autry A. Increased mortality in children and adolescents with developmental disabilities. *Paediatr Perinat Epidemiol* 2002; **16(4):** 375-382	No general population comparison group.
3	Florio T, Trollor J. Mortality among a cohort of persons with an intellectual disability in New South Wales, Australia. *J Appl Res Intellect Disabil* 2015; ***28*(5):** 383-393.	Respiratory causes of death not included separately.
4	Glover G, Ayub M. How people with learning disabilities die. Improving Health and Lives Learning Disabilities Observatory. Durham, 2010.	Not peer-reviewed.
5	Jahan I, Karim T, Das MC, Muhit M, McIntyre S, Smithers-Sheedy H, et al. Mortality in children with cerebral palsy in rural Bangladesh: a population-based surveillance study. *Dev Med Child Neurol* 2019; **61(11):** 1336-1343	Did not include individuals with intellectual disabilities.
6	McCarron M, Carroll R, Kelly C, McCallion P. Mortality rates in the general Irish population compared to those with an intellectual disability from 2003 to 2012. *J Appl Res Intellect Disabil* 2015; ***28*(5):** 406-413.	Respiratory causes of death not included separately.
7	Perez CM, Ball SL, Wagner AP, Clare ICH, Holland AJ, Redley M. The incidence of healthcare use, ill health and mortality in adults with intellectual disabilities and mealtime support needs. *J Intellect Disabil Res* 2015; **59(7):** 638-652	No general population comparison group.
8	Reid, SM, Carlin JB, Reddihough DS. Survival of individuals with cerebral palsy born in Victoria, Australia, between 1970 and 2004. *Dev Med Child Neurol* 2012; **54(4):** 353-360	Did not include individuals with intellectual disabilities.
9	Shavelle, Robert M.; Strauss, David J.; Pickett, Jane Causes of death in autism. *J Autism Dev Disord* 2001; **31(6):** 569-576	Did not include individuals with intellectual disabilities.
10	Similä S, Von Wendt L, Rantakallio P. Mortality of mentally retarded children to 17 years of age assessed in a prospective one-year birth cohort. *J Ment Defic Res* 1986; **30:** 401-5	Respiratory causes of death not included separately.

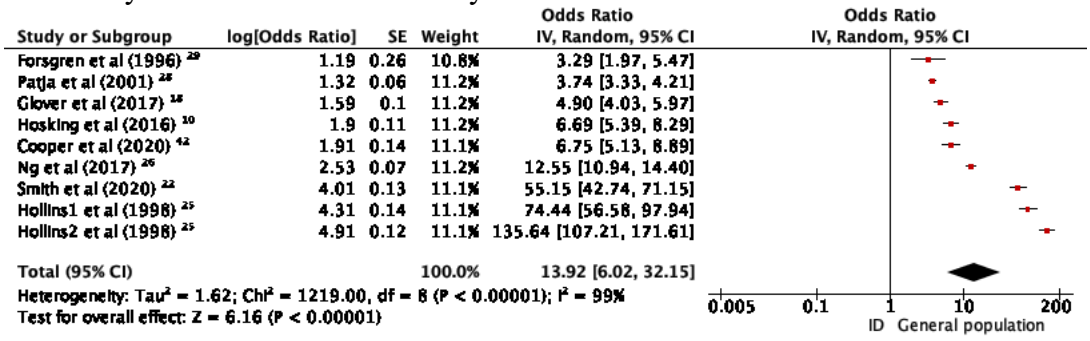
11	Stankiewicz E, Ouellette-Kuntz H, McIsaac M, Shooshtari S, Balogh R. Patterns of mortality among adults with intellectual and developmental disabilities in Ontario. *Can J Public Health* 2018; **109(5-6):** 866-872	<70%* of participants had intellectual disabilities. *We emailed this author to check if >70% of sample had ID – they replied but didn't have the data to check, so it was excluded.
12	Tyrer F, Smith LK, McGrother CW. Mortality in adults with moderate to profound intellectual disability: a population-based study. *J Intellect Disabil Res*, 2007; ***51*(7):** 520-527.	Respiratory causes of death not included separately.

Appendix 3: Sensitivity analysis A and B

Sensitivity A- minus Raitasuo



Sensitivity B- minus Raitasuo and Tyrer



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4/5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 and Appx 1 pgs 35-36
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12, 39
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	25,26 Appx.3 pg 40-42
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	25
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	26
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	26
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	27
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	29

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Respiratory-associated deaths in people with intellectual disabilities: a systematic review and meta-analysis

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Title: "Respiratory-associated deaths in people with intellectual disabilities: a systematic review and meta-analysis"

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ABSTRACT

Objective To review and synthesise evidence on rates of respiratory-associated deaths and associated risk factors in the intellectual disability population.

Design Systematic review with meta-analysis

Data sources Embase, CINAHL, ISI Web of Science (all databases including Medline), and PsychINFO were searched for studies published between January 1985 to April 2020 and examined study and outcome quality. Reference lists and Google Scholar were also hand searched.

Results We identified 2,063 studies, 17 were included in the narrative synthesis and 10 studies (11 cohorts) in the meta-analysis. Data from 90,302 people with ID and 13,808 deaths from all causes in people with ID were extracted. Significantly higher rates of respiratory-associated deaths were found among people with ID (SMR 10·86 (95% CI 5·32, 22·18, p<0·001) compared to those in the general population, lesser rates for adults with intellectual disabilities (SMR 6·53 (95% CI 4·29,9·96, p<0·001); and relatively high rates from pneumonia 26·65 (95% CI 5·63, 126·24, p<0·001). The overall statistical heterogeneity was I^2= 99·0%.

Conclusion Premature deaths due to respiratory disorders are potentially avoidable with improved public health initiatives and equitable access to quality health care. Further research should focus on developing prognostic guidance and validated tools for clinical practice to mitigate risks of respiratory-associated deaths.

PROSPERO registration number CRD42020180479

Article summary

Strengths and limitations of this study

- To our knowledge this is the first systematic review and meta-analysis on respiratory-associated deaths among people with intellectual disabilities.
- Included studies were limited by sample size
- There was no sufficient data and results provided by studies to investigate predictors or factors associated with respiratory-related deaths; meta-regression or stratification was not possible
- The meta-analysis included mortality ratios from ten observational studies covering 90,302 people with intellectual disabilities and 13,808 deaths from all causes in people with intellectual disabilities.

- A rigorous and systematic analysis process was undertaken which minimised the risk of bias, errors and omissions.

Introduction

People with intellectual disabilities account for approximately 1-3% of the global population.[1,2] The World Health Organisation (1992)[3] defines intellectual disabilities as impairments in adaptive functioning, social functioning, and intellectual functioning, (IQ<70) requiring a need for daily support, with the onset in the developmental phase (<18 years). Whilst some heterogeneity is to be expected in the definition of intellectual disabilities across studies drawing on administrative datasets, the WHO definition can be applied to all studies included in this review. Life expectancy and mortality rates are important indicators of health inequality.[4] People with intellectual disabilities die up to 20 years earlier than the general population.[5-8] Respiratory disorders are a leading cause of death among people with intellectual disabilities.[6,9] The range of standardised mortality ratios (SMRs) due to respiratory disorders for people with intellectual disabilities are very high in some studies,[10-12] and much lower in others.[13-15]. Despite this, standardised mortality ratios (SMRs) due to respiratory disorders for people with intellectual disabilities differ widely across studies. Respiratory cause of mortality in people with intellectual disabilities has not been systematically examined. Previous studies have focused on either children and young people(4-19 years)[10] or older adults (55+years) on average[12]. This systematic review and meta-analysis aims to investigate and quantify the risk of, and factors associated with, respiratory-associated deaths in people with intellectual disabilities.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed.[16] This review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42020180479).

Eligibility

This systematic review included studies which analysed and presented data on people who were ascertained as having intellectual disabilities and a comparison group of individuals in the general population, with respiratory disorders included as a separate cause of death. For studies that included multiple disabilities, at least 70% of participants had to have intellectual

disabilities, if results were not reported separately. Studies also had to be full-text, peer-reviewed, and published in English. To be included in the meta-analysis, studies had to report SMRs with 95% confidence intervals for respiratory associated deaths based on external comparison group or to have presented data allowing such outcomes to be derived. Studies were excluded if they focused on specific etiologies of intellectual disabilities, such as Down syndrome, as these are associated with a different health and mortality profiles compared to other people with intellectual disabilities. Studies were excluded if the full paper was not available in English. Studies focused on post-operative and post-treatment deaths were excluded as these are not representative of the wider population with intellectual disabilities. Studies with small samples (<20 participants) or case series designs were also excluded as these papers are less representative.

Search strategy and selection criteria

We searched Ovid Embase, ISI Web of Science (all databases), CINAHL, and PsycINFO from 1st January 1985 to the 27th of April 2020, using comprehensive terms related to 'intellectual disabilities', 'mortality', and 'respiratory disease' (full search strategy in Appendix 1). In addition, a manual bibliography and citation search of included studies was conducted using Google Scholar and key researchers in the field of mortality in individuals with intellectual disabilities were emailed to identify any additional relevant papers. The aforementioned eligibility criteria were used. After duplicates were removed, all records were imported into Covidence software (www.covidence.org) for title and abstract and full text screening. All titles, abstracts (CM & AMcG) and full-texts (CM, AMcG, ER) were double-screened with inter-rater reliability (Cohen's kappa) of $\kappa = \cdot 57$ and $\kappa = \cdot 58$, respectively.

Data Extraction

Data extraction was conducted using a structured database created in Excel. Five researchers (GS, LHM, DK, KD, AMcG) each extracted data from 25% of the included studies and, to check reliability, one other researcher (CM) independently extracted data from 20% of included studies. Extracted data were compared in meetings and discrepancies resolved through consensus discussion. Researchers did not extract data on included papers where they were a listed author.

Assessment of study and outcome quality

Study quality was appraised using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields.[17] Quality ratings were calculated in percentage form using the standard method[17] and categorised as weak (<55%), moderate (55-75%), or strong (>75%) quality. Each paper had quality appraisals completed by two researchers, who then agreed a consensus score for each item (Table 1).[17] Researchers did not evaluate quality of papers where they were a listed author. Risk of bias score was not used to exclude any studies from either the systematic review or meta-analysis. We evaluated the quality of our own systematic review using the Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist.[18]

***Table 1*: Characteristics of studies reporting mortality rates for respiratory disorders and pneumonia in people with intellectual disabilities**

Author	Country	Study design, setting and follow up	Data sources	ID sample (N, % female, age, level of ID)	Deaths in ID sample (N, % female, age at time of death, level of ID)	Comparison sample (N, % female, age,) and deaths (n, % female, age)	Respiratory disorder definition (e.g. ICD codes or other definitions)	Quality Percentage (assessment)
Brameld et al (2018)[26]	Australia	Retrospective matched cohort study of adults 20 years old and over. Follow up 2009-2013	Intellectual Disability Exploring Answers (IDEA) Database. Death certificate data	Total sample characteristics not available	N= 591; 43·8% female; mean age* and level of ID not available	Total sample characteristics not available. Number of deaths= 62, 917; 47·4% female; mean age not available	ICD 10-chapter codes for respiratory disorders.	95·45% (strong)
Cooper et al (2020)[28]	UK	Population-based cohort study. Follow up 2001-2018	Primary care records and health check data; Death certificate data. Comparison data from Health Board statistics	N= 962; 45·4% female; mean age= 44·1 years (range 16-83); ID Mild=382 (39·7%), Moderate=236 (24·5%), Severe=180 (18·7%), Profound=163 (17·0%)	N= 294/961 (30·6%); 47·5% female; mean age= 52·4 (SD 13·6)	Not available	ICD 10-chapter codes for respiratory disorders.	86·36% (strong)
Dupont et al. (1987)[40]	Denmark	Population- based cohort study of adults with mild ID. Follow up 1976-1984	Danish National Service for the Mentally Retarded. Death certificate data.	N = 7134; gender, age and level of ID not available	N=446; 37·9% females; age and level of ID not available	Not available	Not described	40·90% (weak)
Durvasula et al (2002)[37]	Australia	Population-based cohort study of children and adults. Follow up 1989 - 1999	ID prevalence study. Death certificate data, medical records and post-mortem data. Australian Bureau of Statistics	N = 693; 44·6% female; mean age= N/A; ID 40% mild, 35% moderate, 25% severe/profound	N=40 (6%); 45% female; median age= 32 (range 10-59); level of ID not available	N= 125,848; 51% female; mean age not available. Number of deaths= 2154; 37·8% female; mean age not available	Not described	90·91% (strong)
Forsgren et al (1996)[15]	Sweden	Population-based cohort study of adults with ID.	Board for Provision and Services to the Mentally	N = 1,478; 44·5% female; age and level of ID not available	N= 247; 42·1% female; Median age= 64 years (IQR 52-75 years); ID 39·7% Mild,	Not available	ICD 9-chapter codes for respiratory disorders.	81·82% (strong)

		Follow up 1986 – 1992	Retarded. Death certificate data from Swedish National Bureau of Statistics		31·2%, Moderate, 21·5% Severe 7·7% Profound			
Glover et al (2017)[8]	UK	Population-based case control study in primary care. Follow up 2010-2014	Primary care records (CPRD). Death certificate data	Total sample characteristics not available	N = 664 deaths; 44·1% female	Total sample characteristics not available. N of deaths= 97, 379; 52·3% female; mean age not available	ICD 10-chapter codes for respiratory disorders.	81·82% (strong)
Heslop et al (2014)[5]	UK	Population based audit of deaths of children and adults with intellectual disabilities aged 4 and over. Audit period 2010-2012	Medical records Death certificate data from UK Office of National Statistics	Total sample characteristics not available	N=247; 42·1% female; median age= 64 years (IQR 52-75 years); ID 39·7% mild, 31.2% moderate, 21·5% severe, 7·7% profound	Total sample characteristics not available. Number of deaths= 480, 467; 51·6% female; median age not available		81·82% (strong)
Hollins et al (1998)[11]	UK	Cohort study of adults on an ID register. Follow up 1982-1990	Learning disability register. Death certificate data.	N = 2,026; gender, age and ID level not available	N= 268 deaths; gender and age not available; 51·5% mild-moderate, 48·5% severe-profound	Not available	Not described	81·82% (strong)
Hosking et al (2016)[24]	UK	Population-based case control study in primary care. Follow up 2009-2013	Primary care records (Clinical Practice Research Data linkage; CPRD). Death certificate data	N = 16,666; 58.1% female; mean age 39.9 (SD 16.2). 19.6% of sample had high support needs.	N=656 (3·9%); 55·6% female; age and level of ID not available	N= 113, 562; 58·1% female; mean age not available. Number of deaths= 1358 (1·2%); 60·4% female; mean age not available	ICD 10-chapter codes for respiratory disorders.	90·91% (strong)
Janicki et al (1999)[22]	USA	Cohort of adults with intellectual disabilities 40 years old and over. Follow up 1984-1993	Data from state agency with responsibility for reviewing deaths of disabled persons. Health department data.	Total sample characteristics not available.	N= 2752, 48·1% female; mean age- 65·1; ID 18%, 68% Moderate – profound (68%), 4% unspecified, 10% unknown	Total sample characteristics not available. Number of deaths= 149, 980; gender not available, mean age= 70·0	ICD 9-chapter codes for respiratory disorders.	77·27% (strong)
Ng et al (2017)[12]	Sweden	Population-based case control study of adults with ID 55 years old and	National database of hospital admissions and outpatient care.	N = 15, 289; 45.5% females; mean age not available; level of ID not available	N= 4728; 44·9% female; age and ID level not available	N= 74, 445; 45·5% females; mean age not available. Number of deaths= 8364	ICD 10-chapter codes for respiratory disorders.	95·45% (strong)

		over. Follow up 2002-2015	National disability register. Swedish National Cause of Death register					
Oppewal et al (2018)[27]	Netherlands	Cohort study of adults with ID 50 years old and over living in three care organisations. Follow up Nov 2013-March 2018	Medical case notes of participants with ID who died during study period. Cause specific mortality statistics for 50+ population in the Netherlands	N = 1050; 48·7% female; mean age= 61·6 (SD 8·0, range 50-94); ID level= 2·9% borderline, 21·2% mild, 48·2% moderate, 16·4% severe, 8·7% profound;	N=207 deaths (19·7%) but only 159 with cause of death available. 60·7% female; mean age not available; ID level= 5·7% borderline, 18·9% mild, 54·7% moderate, 13·2% severe, 7·5% profound;	Not available	ICD 10-chapter codes for respiratory disorders.	50·0% (weak)
Patja et al (2001)[14]	Finland	Population based, nationwide cohort study. Follow up 1963-1997	Original 1962 population-based study (Amnell et al. 1964). Death certificate data	N = 2,369, gender, age and level of ID not available	1111 deaths with death certificates available for 1,095- 51·0% female, mean age= 57·7; ID 40·3% mild, 29·4% moderate, 11·5% severe, 18·0% profound, 0·7% unknown	Not available	ICD 9-chapter codes for respiratory disorders.	81·82% (strong)
Raitasuo et al (1997)[13]	Finland	Cohort study of adults living in an institution. Follow up 1972-1993	Medical case notes and death certificate data. General population mortality statistics for population in Finland.	N ≈ 2000; gender, age and level of ID not available	216 deaths- 42·6% female; mean age 26·7 (1-86 years); ID level 2·0% borderline, 15·0% mild, 18·0% moderate, 20·0% severe, 45.0% profound, 20·0% unknown	Not available	ICD 9-chapter codes for respiratory disorders.	54·55% (weak)
Smith et al (2020)[10]	UK	Nationwide, population based cohort study of children aged 4-19. Follow up 2008-2015.	Scottish pupils census: Death certificates data	N= 18, 278; 35% female; mean age not available	N= 106; mean age= 14·3 (95% CI 13·4 to 15·1); level of ID not available	N= 777,912; 50% female; mean age not available. number of deaths= 458; mean age= 16·1 years (95% CI 15·8 to 16·5)	ICD 10-chapter codes for respiratory disorders.	100% (strong)
Trollor et al (2017)[25]	Australia	Population based cohort study of adults 20 years old and above	Disability Services Minimal Dataset. Australian Bureau	N= 19,362; 44% female, mean age= 37 (range 27-48); ID not available	N= 732 (4%); 41% female; median age = 54 (42–64), level of ID not available	Total sample characteristics not available. Number of deaths= 305, 050; 49%	ICD 10-chapter codes for respiratory disorders.	95·45% (strong)

		registered with disability services. Follow up 2005-2011	of Statistics. Death records			female; median age= 81 (70–92).		
Tyrer and McGrother (2009)[23]	UK	Population-based cohort study of individuals with moderate-profound ID on a register. Follow up 1993-2006	Leicestershire learning disability register. Death certificate data. National Statistics 1993-2006.	N = 2,995; 41·9% female; Age and level of ID not available	N=503; gender, age and level of ID not available	Total sample characteristics not available. Number of deaths≈126, 000	ICD 9 and ICD 10-chapter codes for respiratory disorders.	72·73% (moderate)

*Individuals in the ID cohort died at a significantly younger age than the comparison cohort

Summary of outcomes and statistical analysis

Findings of all included studies were combined in a narrative synthesis. The primary goal of the meta-analysis was to investigate if the SMRs of respiratory-associated deaths differ for individuals with and without intellectual disabilities. If SMRs were reported by specific respiratory causes, sex, age group, level of intellectual disability, socio-economic status or ethnicity, these were collected and presented for potential analysis (see table 2). Random effects meta-analysis was undertaken using RevMan. Included studies reported either:

- a SMR or hazard ratio (HR)

OR

- the observed number of deaths or expected deaths necessary to calculate a SMR. These were calculated using STATA (version 14) by dividing the observed number of deaths in a cohort study group by the expected mortality based on age and gender-specific death rates in the general population comparison group.

Random effects models were selected for all meta-analyses due to the different populations and measures in the included studies. Inverse of the variance method was used to calculate the weighted mean respiratory mortality log-SMR across studies, as well as for subgroup meta-analyses. As the SMR is a ratio, log transformation was needed to maintain symmetry in the analysis.[19] SMRs and HRs from each study were transformed to log values for computations and back transformed for presentation of the results. Weighted mean log-SMRs and their 95% confidence intervals were reported separately for individuals with and without intellectual disabilities. The magnitude of the back transformed ratio and associated confidence interval (CI) were also reported. Where data permitted, further subgroup analyses were conducted to examine sources of heterogeneity. Where more than two studies reported sub-group level data, or cause-specific results of causes of respiratory deaths (e.g. pneumonia) random effects models were considered for subgroup meta-analyses.

For the random effects meta-analysis, heterogeneity was expected in the pooled result. Therefore, the Chi-squared statistic I^2 was chosen to measure level of heterogeneity across the studies, as it allows for interpretation of results regardless of the number of studies included in the meta-analysis, the type of outcome data, or effect measurement.[20] Heterogeneity was interpreted as not observed when I^2=0%, low when I^2=25%, medium when I^2=50%, and high when I^2=75%.[20]

Sensitivity analysis

Sensitivity analysis was used to assess the impact of risk of bias for each study on the weighted mean SMR. Data were removed one-by-one from the meta-analysis for each study, beginning with the lowest ranked papers, to determine their effect and re-estimate the weighted mean SMR. Cumulative analysis, starting with larger studies and sequentially adding smaller studies, was used to investigate how the weighted mean SMR estimate changes as small studies are added.[21]

Patient and public involvement

No patient and public involved.

Results

Figure 1 summarises the systematic search, selection and reasons for exclusion. All 17 studies were included in the narrative synthesis and 10 were included in the meta-analysis (studies with relevant SMRs n=8 and HR n=2). A full list of studies excluded from full-text screening is available in Appendix 2.

[Insert Figure 1: PRISMA flow diagram of systematic search and selection]

Table 1 illustrates the characteristics of studies reporting mortality rates for respiratory disorders and pneumonia in people with intellectual disabilities and table 2 presents all-cause mortality and deaths from respiratory disorders in people with intellectual disabilities.

Table 2: **All-cause mortality and deaths from respiratory disorders in people with intellectual disabilities**

Author	All-cause mortality	Deaths from respiratory disorders	Between group comparison of deaths from respiratory disorders	Deaths from individual respiratory disorders	Between group comparison of deaths from individual respiratory disorders	Variables associated with risk of death from respiratory disorders
Brameld et al (2018)[26]	591 had ID /63,508 out of all deaths (0·93%)	62/591 (10·5%) deaths	Not available	Emergency Department presentations in the last year of life: Influenza and pneumonia RR=2·6 (95% CI 2·0-3·4 p<0·001) Chronic obstructive pulmonary disease (COPD) RR=0·8 (95%CI 0·5-1·6, p=0·596) Asthma RR=4.7 (95%CI 2·1-10·4, p<0·001) Ear, nose and throat infections RR=1·9 (95%CI 0·8-4.0, p=0·122) Pneumonitis due to solids/liquids RR=17·9 (95%CI 11·3-28·3 p<0·001) Hospital admissions in the last year of life: Influenza and pneumonia RR=2·3 (1·0-5·3, p=0·044) COPD RR=1·4 (95%CI 0·9-2·4, p=0·164) Asthma RR=4·6 (95%CI 1·4-15·0, p=0·011) Ear, nose and throat infections RR=0·0 (95%CI 0·0-., p=0·972) Pneumonitis due to solids/liquids RR=17·6 (95%CI 11·7-26·5, p<0·001)	Decedents with intellectual disability had increased odds of dying of (relative odds of having condition listed as underlying cause of death), adjusted for comorbidity: Influenza/pneumonia (OR=5·3, 95% CI 2·4-11·8) Pneumonitis due to solids or liquids (OR=9·9, 95% CI 5·1-19·3) Asthma (OR=2·3, 95% CI 1·0=5·2) (not significant) No difference for COPD as cause of death	Decedents with intellectual disability had increased A&E attendance but received less hospital-based specialist palliative care. For those in hospitals, they were more likely to have hospital stays involving intensive care and ventilator support.

Cooper et al (2020)[28]	294/ 961 (30·6%) deaths **SMR = 2·24 (95% CI; 1·98, 2·49)**	Underlying cause of death: 57/ 262 (21.8%) deaths **SMR= 6·78 (95% CI; 5·02, 8·54)** **(adjusted for age and sex)**	Underlying cause of death: Down syndrome: 8/ 57 (14·0%) deaths Without Down syndrome: 49/ 205 (23·9%) deaths	All-contributing factors in death: Respiratory infection = 27·1% deaths Aspiration/ reflux/ choking = 19·8% deaths	Underlying cause of death: Down syndrome: Aspiration/ reflux/ choking = <5/ 57 deaths Respiratory infection = <5/ 57 deaths Other respiratory conditions = <5/ 57 deaths Without Down syndrome: Aspiration/ reflux/ choking = 22/ 205 (10·8%) deaths Respiratory infection = 21/ 205 (10·3%) deaths Other respiratory conditions = 9/ 205 (4·4%) deaths All-contributing factors in death: Down syndrome: Respiratory infection = 22/ 57 (38·6%) deaths Aspiration/ reflux/ choking = 11/ 57 (19·3%) deaths Other respiratory conditions = <5/ 57 deaths Without Down syndrome: Respiratory infection = 49/ 205 (23·9%) deaths Aspiration/ reflux/ choking = 41/ 205 (20·2%) deaths Other respiratory conditions = 31/ 205 (15·1%) deaths	Not available

Dupont et al (1987)[40]	N=446 deaths / 7134 (5·9%) people with mild ID N=277 males N=169 females	Respiratory deaths common cause of death in people with ID (all ages) Tests of significance only; respiratory deaths were more common for males with ID (all ages), and females aged 35-64, versus population of Denmark 1977	Not available	Not available	Not available	Not available
Durvasula (2002)[29]	40/693 (6%) deaths	14/40 (35%) deaths	For people under 40, respiratory and external deaths were most common, for people over 40, cancer and respiratory deaths were most common Age: 7/14 deaths in under 25-year-olds and 6/14 deaths in 40+ year olds Sex: 11/14 deaths in males Conditions: 2/14 had Down syndrome & dementia, 1/14 had myelodysplastic syndrome, 1x Battens disease	Not available	Not available	Age, gender, Down syndrome, myelodysplastic syndrome
Forsgren et al (1996)[15]	N=124 / 1478 (8·4%) people with ID (all ages), over 9,992 person-years	N=13 /124 (10%) deaths were respiratory disease for people with ID vs n=3·9 expected,	Respiratory disease was common cause of death for people with ID and epilepsy but SMR was not possible due to small sample size	Pneumonia was most common cause of death, but rarely reported as underlying cause Pneumonia was most common cause of death in	Not available	Epilepsy (active seizures)

	SMR 2.0 (95% CI 1·7, 2·3) Males 1.6 (95% CI 1·2, 2·0), Females 2·6 (95% CI 2·0, 3·3) *Additional: SMRs for severity of ID, epilepsy and cerebral palsy are available in appendix*	**SMR 3·3 (95% CI 2·0, 5·5)** (adjusted for age and sex)		people with both epilepsy and ID		
Glover et al (2017)[8]	N=664 deaths for people with ID (all ages) over 59,279.7 person-years Crude rate 11·2 (10·4, 12·1) per 1000 person-years **SMR 3·18 (2·94, 3·43) Women 3·40 (3·02, 3·81) Men 3·03 (2·73, 3·35)**	N=114 deaths from respiratory causes for people with ID vs 23·3 expected **SMR 4·9 (4·0, 5·9)** (adjusted for age and sex)	Not available	N=57 / 114 (50%) of respiratory deaths (and 8·6% of all deaths) were from influenza and pneumonia, vs expected 7·4 deaths **SMR 7·7 (5·8, 9·9)** Vast majority of pneumonia were unspecified (organism) n=24 / 114 (21%) respiratory deaths (3·6% of all deaths) were due to pneumonitis due to solids / liquids vs expected 1.1 deaths **SMR 21·8 (13·9, 32·4)** N=12 (1·8%) of all deaths were due to respiratory and intrathoracic cancers vs expected 16.6 deaths **SMR 0·7, 95% CI 0·4–1·3).**	Not available	Not available

Heslop et al (2014)[6]	N= 247 deaths in people with ID aged 4+ Rate of death 16·2 per 1000 person years Median age of death: 64 (52, 75). *Additional; all-cause mortality for sex, ID severity, amenable mortality, patient care, & accommodation available in appendix*	n=37 (15%) deaths had underlying cause due to respiratory diseases, vs 14·0% England & Wales deaths (p=0·66)	Not available	Not available	Not available	Reduced smoking in ID group p=0·02
Hollins et al (1998)[11]	270/2,026 (13·3%) deaths 116/1,081 (10·7%) deaths on Wandsworth register 154/945 (16·3%) deaths on Kensington register	Not available	Not available	Bronchopneumonia: N=56 (48%) (Wandsworth) N=69 (45%) (Kensingston) COPD Emphysema: N=1 (Wandsworth) N=1 (Kensingston) Asphyxia: N=4 (Wandsworth) N=1 (Kensingston) Respiratory other: N=4 (Wandsworth) N=4 (Kensingston) 52% of all deaths had a diagnosis of pneumonia	Not available	Not available

Hosking et al (2016)[24]	656/ 16666 (3·9%) deaths **HR = 3·62 (95% CI; 3·33, 3·93)**	123/ 16666 (18·8%, rate= 24·8) deaths **HR = 6·68 (95% CI; 5·38, 8·29)** **(adjusted for age, sex and general practice)**	Down syndrome = 24/ 1793 (20·3%) deaths. General population: 135/ 113562 (rate= 3·9) deaths.	Pneumonia; n = 67/ 16666 (rate = 13·5) Aspiration pneumonitis; n = 21/ 16666 (rate = 4·2)	General population: Pneumonia; 39/ 113562 (rate = 1.1) Aspiration pneumonitis; n = 6/ 113562 (rate = 0.2)	Not available
Janicki et al (1999)[22]	2,752 deaths in the group aged 40+/4,183 all-age deaths (66%)	40+ year olds: N=548 (20%), rate: 201 per 100,000	Increasing by age decade: aged 40s: 343 per 100,000 (16% of those who died) aged 50s: 793 per 100,000 (20%) aged 60s 1660 per 100,000 (25%) aged 70+: 3441 per 100,000 Males with ID rate of death: 257 per 100,000 Females with ID rate of death: 331 per 100,000 Respiratory causes did not vary over the 10-year study period. Deaths due to respiratory diseases increased, with increasing age. Gender: breathing obstructions were more prevalent among males. Gender x age: respiratory disease was increased in the oldest groups, for males particularly while respiratory disease remained static as a cause	Breathing obstructions – 2·7% average deaths per year across 10 years, N=75, rate=27·5 per 100,000 Respiratory disease types: pneumonia was the most prevalent type of respiratory cause of death, with 43% of respiratory disease deaths in ID group	Not available	Age, gender

			of death for females across ages.			
Ng et al. (2017)[12]	4,738/15,289 deaths in people aged 55+ (31%)	807/4,738 (17%) respiratory deaths for those with ID **HR =12·5 (10·9, 14·2)** **(adjusted for sex, year of birth and year of access to services)**	ID rate: 423 per 100,000 DS rate: 3,187 per 1,000	ID group (excludes DS) Pneumonitis due to solids and liquids: 10%, rate 25 per 100,000 Pneumonia: 50%, rate 129 per 100,000 Other chronic obstructive pulmonary disease: 20%, 49 per 100,000 DS group Pneumonitis due to solids and liquids 31·4%, 181 per 100,000 Pneumonia 20%, 113 per 100,000 Asthma 8%, 45 per 100,000 Bronchitis 8%, 45 per 100,000 Other respiratory disorders 8%, 45 per 100,000	Not available	Not available
Oppewal et al (2018)[27]	207/1050 ID=19·7%; 54/ 149 DS=26·1%	69/159 ID=44.3%; 33/45 DS only=73·3%; 36/114 ID with no DS=31·6% Respiratory causes were the top primary causes of ID deaths. Respiratory causes were the top primary	5-year age bands: 50-54 ID=100% GP=3·3%; 55-59 ID=26·5% GP=4·7%; 60-64 ID=51·4% GP=6·0%; 65-69 ID=30·4% GP=6·7%; 70-74 ID=23·8% GP=8·6%; 75-79 ID=12·5% GP=9·4%; 80-84 ID=26·3% GP=9·4%; 85-90 ID=(0) GP=9·9%; 90-95 ID=40% GP=10·4%; 95+ ID=100% GP=10·9%	Pneumonia ID=80·4%; Chronic obstructive pulmonary diseases ID=17·6%	Not available	Not available

		cause of DS deaths. General 50+ population, the three largest groups of primary causes of death were neoplasms (31%), circulatory diseases (28%) and respiratory diseases (9%). No SMR available.				
Patja et al (2001)[14]	1111/ 2369 ID =46·9%	Immediate cause 322/1093 ID=29%; Primary cause 241/1095 ID=22% Respiratory diseases second largest cause of ID death **SMR=3·76 (CI 3·31 to 4·27)*** **(adjusted for age and sex)**	Male: age 2-19 **SMR=5·8 (4·4 – 15·6);** age 20-39 **SMR=5·4 (2·9 – 8·0);** age 40-59 **SMR=5·5 (3·5-7·5);** age 60+ **SMR=2·7 (2·7 – 4·8)** Female: age 2-19 **SMR=4·3 (0·3 – 4·7);** age 20-39 **SMR=3·2 (1·1 – 5·1);** age 40-59 **SMR=6·2 (4·1 – 8·2);** age 60+ **SMR=3·3 (1·7 – 3·0)**	Pneumonia ID=83%; Chronic obstructive pulmonary disease ID=11%.	Pneumonia deaths (%): Profound ID=29%; Severe ID=13%; Moderate ID=33%; Mild ID=25%. Risk ratios compared to general population: Mild ID 2.6 times higher; Profound ID 5.8 times higher. ID men higher risk than women in younger age groups (< 39 years), but at lower risk from 60 years of age onwards.	Age, gender (all respiratory) ID severity (with pneumonia)
Raitauso et al (1997)[13]	216 deaths	Immediate cause of death 97/216 ID=45%	age 0-14 SMR=0·48; age 15-44 SMR=3·46; age 45-74 SMR=2·35; age 75 SMR=0	Bronchopneumonia (immediate cause) ID=43% Five patients had died of pneumonia caused by	Not available	Age (all respiratory)

		Primary cause 14/216 ID= 6%. Respiratory diseases were the dominant causes of ID death. **SMR=2·15 (CI 1·18 – 3·61)** **(adjusted for age, and year of death)**		aspiration. In one case fatal pneumonia had been caused by a fistula between the bronchus and the pleura. Besides pneumonia, two patients had acute laryngitis and one patient had hyperplasia of the lymph nodes of the lungs as the immediate cause of death. The latter had trisomy of chromosome 13 (Patau's syndrome) as the basic disorder.		
Smith et al (2020)[10]	N = 106 (0·6%) deaths **SMR = 11·6 (95% CI; 9·6, 14·0)**	Underlying cause of death: N = 8/ 106 (8%) deaths All-contributing factors in death: **n = 55. CMR = 81·7 (95% CI; 62·7, 106·4) deaths** **SMR = 55·3 (95% CI; 42·5, 72·1)** **(adjusted for age and sex)**	Underlying cause of death: General population: 17/ 458 (4%) deaths All-contributing factors in death: General population: n = 51. **CMR = 1·4 (95% CI; 1·1, 1·8) deaths**	Underlying cause of death: Pneumonia including influenza; <5/ 106 All-contributing factors in death: Pneumonia= 27/ 106 (25·5%) deaths Respiratory failure; 17/ 106 (16·0%) deaths Respiratory disorders = 15/ 106 (14·2%) deaths Pneumonitis associated with food and vomit = 9/ 106 (8·5%) deaths	General populations: All-contributing factors in death: Pneumonia = 21/ 458 (4·6%) deaths	Not available
Trollor et al (2017)[25]	732 / 19362 ID=4% **SMR=1·3 (1·2 to 1·5)**	632/732 ID=86·3% had cause of death information 78 ID=12% 4th top cause using the ID ABI conversion	Not available	Not available	Not available	Not available

		130 ID=20% 1st top using the ID revised version 16 ID=3% of respiratory deaths were considered avoidable. 26242 GP=9% 3rd top underling cause				
Tyrer & McGrother (2009)[23]	503/ 2995 (17%) deaths **SMR=2·77 (95% CI 2·53, 3·03).**	**SMR=5·46 (95% CI 4·58, 6·46) (adjusted for age and sex)**	Not available	Bronchopneumonia; **SMR=6·47 (95% CI 5·00 8·23), O=66, E=10·2.** Other respiratory; **SMR= 4·64 (CI 3·58 to 5·91). O=65, E=14·0.**	Male; **SMR=2·28 (95% CI; 2·02-2·56) O=278, E=121·8.** Female; **SMR=3·24 (95% CI; 2·83-3·69). O=225, E=69·4.**	Gender

*only where adjusted specifically for respiratory mortality

SMR=standardised mortality ratio/ CI=confidence interval/ RR=rate ratio/ HR=hazard ratio/CMF=comparative mortality figure/ OR=odds ratio/ O=observed deaths/ E=expected death* calculated by authors using data from the study

Study characteristics

Key features of all studies identified for inclusion in the review were tabulated (Table 1). These were cohort studies (n=12), case control studies (n=4) and one population-based audit of deaths in adults and children. These studies report data on 90,302 people with intellectual disabilities and 27,394 deaths. The average study size was 9,250 people. These studies were from the Netherlands (n = 1), Finland (n = 2), Australia (n = 3), the United Kingdom (n = 7), the United States of America (n = 1), Sweden (n = 2) and Denmark (n = 1).

Definition of respiratory disorder

Thirteen out of 17 (76%) studies defined the respiratory disorder using ICD 9 -chapter codes[13-15,22,23] and ICD 10 – chapter codes for respiratory disorders.[8,10,12,23-26] The remaining four studies included in the systematic review did not define respiratory disorders.

Causes of death from respiratory disorders

Thirteen papers reported on cause of deaths from respiratory disorders.[8,10-15,22-24,26-28] Pneumonia was reported as a cause of death in 12 studies.[8,10-15,22,23,26,27], five studies reported deaths from pneumonitis related to aspiration[8,10,12,14,24], five studies reported on chronic obstructive pulmonary disease (COPD)[11,12,14,26,27], one study reported on asthma[31] and one reported respiratory cancer deaths.[8]

Evidence synthesis

Respiratory-associated mortality

Five papers reported that respiratory disorders were the dominant cause of death in people with intellectual disabilities.[11,13,27,28,29] A further three studies found that deaths from respiratory disorders were the second most common cause of death.[12,14,24] Respiratory-associated deaths were in the top five main causes of deaths for a further four papers.[9,10,22,25] Comparative results (intellectual disabilities vs general population) for deaths due to respiratory disorders were reported in 10/17 (59%) of the studies.[5,8-10,12,22,24-26] In the majority of these studies rates of death from respiratory disorders were higher for people with intellectual disabilities than for people in the general population. However, Troller et al. (2017)[25] reported that respiratory-associated deaths in the general population were (9%) similar to the population with intellectual disabilities (12%). Hollins et al. (1998)[11] also reported that respiratory disorders were the most commonly cited cause of death for both groups.

Individual respiratory disorders and mortality

Pneumonia was reported as the most common cause of respiratory death in people with intellectual disabilities.[8,10-15,22-24,26,27] Contributors to pneumonia deaths included influenza and injury from inhalation and aspiration events.[10,14] Pneumonitis featured as an underlying or contributing cause for between eight and 21% of respiratory-associated deaths in people with intellectual disabilities.[8,10,12] Crude comparison data showed people with intellectual disabilities were much more likely (between 10 and 20 times) to die from pneumonitis.[24,26] COPD was found to be a common cause of death in two studies focussing on older adults.[12,27]

Factors associated with respiratory-associated deaths experienced by people with intellectual disabilities

Age, gender and severity of intellectual disability have been found to be associated with risk of respiratory cause of death. Only four out of 17 (23.5%) papers directly reported on factors associated with the risk of respiratory-associated deaths[14,22,23,29] (see Table 2). Two reported SMRs separately for males and females[14,23], while two reported proportions of respiratory deaths between males and females. None directly compared males versus females or reported tests of significance. While one study reported higher respiratory SMRs among females[23], another study reported separate SMRs for different age-bands which varied widely[14]. Group-level analysis was not possible. Level of intellectual disabilities was only reported as associated with respiratory related deaths in one study with 35 year follow up using relative risk but failed to report confidence or p-values.[14] This study found that, when compared to the general population, the relative risk of respiratory related deaths was 2.6 times higher for people with mild intellectual disabilities and 5.8 times higher for people with profound and multiple intellectual disabilities.

Respiratory mortality among children and young people

Respiratory deaths amongst children and young people with intellectual disabilities were reported in five studies and found to be a common cause of death across all studies.[10,13,15,29,30] Four studies included comparison with the general population for respiratory causes of death, while one included the national population without intellectual disabilities[10]. All analyses were limited by the small numbers of death. Raitasuo et al. (1997) reported only one death.[13] Patja et al. (2001) reported higher SMR for males aged 2-19 years

but not females.[30] Smith et al. reported 8% deaths had respiratory disease as the underlying cause but the SMR for underlying cause was not reported.[10]

Meta-analytical outcomes

Ten studies[8,10-15,23,24,28] reported the necessary data to calculate (SMR, hazard ratio, or data necessary to calculate these) and were included in the meta-analysis of respiratory mortality of people with intellectual disabilities and the general population. As Hollins (1998) reported the SMR of two separate cohorts, these are displayed separately in the relevant forest plots.[11] The pooled SMRs for respiratory mortality between people with intellectual disabilities and the general population was 10·86 (95% CI 5·32, 22·18). The results indicate that respiratory mortality occurs ten times more frequently in the intellectual disabilities group than in the general population group. At the individual study level, this was adjusted for age in all studies and for sex in all studies except for two of these studies[11,13], where this was not clear. There was evidence of considerable statistical heterogeneity between studies in the meta-analyses, with I^2= 99·0%. Results are displayed in Figure 2.

Insert Figure 2: Forest plot of respiratory associated mortality

As five studies (12, 15, 23, 24, 28) focussed on adults only, one study (10) focussed on children only, and six (8, 11-15) included people of all ages, a sub-analysis was conducted of studies which reported data on an adult only population. The results of this sub-analysis are displayed in Figure 3. The pooled SMR reduced slightly from 10·86 (95% CI 5·32,22·18) to 6.53 (95% CI 4·29,9·96), after one study with a sample of primarily children was excluded.[10] Studies which included both adults and children in their sample[8,11-15] were next removed one at a time. First, both cohorts from Hollins (1998) were removed and the pooled SMR was reduced by around half, from 9·15 to 4·80[11]. The further removal of studies by Glover (2017)[8], Patja (2001)[14] and Raitasuo (1997)[13] resulted in a final pooled SMR for adults of 5·85 (95% CI 4·73,7·22, p<0·001). Heterogeneity between studies was also reduced from I^2=99% to I^2= 56% by the exclusion of samples which included children.

Insert figure 3: Forest plot for adults only

A sub-analysis was conducted of studies which reported an SMR for pneumonia.[8,11,23] The pooled SMR for pneumonia mortality for people with intellectual disabilities compared to the general population was 26·65 (95% CI 5·63, 126·24, p<0·001). These results, displayed in

Figure 4, indicate that pneumonia related mortality occurs much more frequently in people with intellectual disabilities than in the general population group. Evidence of considerable statistical heterogeneity between studies was also present in this sub-analysis with I^2= 99.0%. SMRs were recalculated excluding the only study to include an adult only sample, Tyrer & McGrother (2009)[23] resulting in a substantial increase in pooled SMR (95% CI from 26·65 to 42·70).

Insert figure 4: Forest plot for pneumonia related mortality

Sensitivity analysis

Sensitivity analysis in relation to quality assessment was run for the ten studies included in the meta-analysis (Appendix 3). Studies which were rated as weak[13] or moderate[23] were removed from the analysis. The pooled SMR for mortality ratios changed slightly as Raitasuo (1997)[13] (from 10·81 to 12·67)[27] and then Tyrer and McGrother (2009) (from 12·67 to 13·94)[23] were removed from the analysis. As the change in SMR was small, this suggests that inclusion of weaker studies did not significantly change the results.

Discussion

This systematic review and meta-analysis highlights that people with intellectual disabilities experience excess respiratory-associated deaths, with a respiratory mortality ten times greater than for the general population. Respiratory mortality was more prevalent among studies which include children, and pneumonia was a major contributor to the higher respiratory mortality reported in this study. Clinical guidelines have contributed to a reduction in mortality from community-acquired pneumonia.[31] We believe the evidence presented here highlights the need for clinical guideline development groups to make recommendations on reducing the risks of premature death due to community-acquired pneumonia amongst people with intellectual disabilities. Vaccination programmes for influenza can help to reduce respiratory mortality in children[32] and adults.[33] Although there is a relatively low uptake of influenza vaccine amongst people with intellectual disabilities, annual health-checks for people with intellectual disabilities have been reported to increase uptake of influenza immunisation.[34] People with intellectual disabilities should be identified as a high-risk group and immunisation providers should prioritise the improvement of vaccine uptake, for example through the roll-out of health checks. People with intellectual disabilities are at increased risk of recurrent chest infections which are secondary to dysphagia[35,36] with a high proportion of aspiration pneumonia-related deaths occurring among individuals with severe and profound intellectual

disabilities.[5,22,35,37,38] Increased recognition of the link between dysphagia and respiratory disorders among caregivers and practitioners is critical to ensuring the early identification of individuals with respiratory disorders.

The higher risk of death from respiratory disorders, such as pneumonia, for people with intellectual disabilities is a significant concern in relation to the rapidly developing COVID-19 pandemic[39,40]. Urgent action to disaggregate data on deaths from COVID-19 for people with intellectual disabilities and to investigate factors associated with COVID-19 related mortality for people with intellectual disabilities is vital to ensure that clinical guidelines are based on consideration of the specific risks faced by people with intellectual disabilities. Research is urgently required to investigate the risk factors associated with COVID-19 for people with intellectual disabilities to ensure carers and clinicians have access to the best evidence to reduce the risk of infection in those most vulnerable and to inform the clinical management of those who contract COVID-19. Carers and clinical staff must be given training to ensure they understand the human rights and health care needs of people with intellectual disabilities to ensure that existing stark disparities in the health of people with intellectual disabilities are not widened during this crisis.

Interventions should focus on the pediatric age group. Among the studies included in this meta-analysis we found a relationship between inclusion of children and SMRs from respiratory causes, with those studies including children reporting higher SMRs. This is consistent with studies that have reported higher SMRs in children compared with adults in epilepsy[15] and cerebral palsy.[41] Overall, mortality in childhood is very low relative to adulthood, and in the pediatric age group chronic disabling conditions such as intellectual disability, epilepsy and cerebral palsy all have a marked impact on SMR. Co-morbidity with epilepsy and cerebral palsy are likely to be significant modifiers of the relationship between intellectual disability and respiratory mortality. Children with more severe intellectual disability are more likely to have epilepsy and cerebral palsy, both of which are independent risk factors for respiratory mortality.

Study strengths and limitations

Our study has several strengths. The meta-analysis included mortality ratios from ten observational studies covering 1,844 respiratory deaths in people with intellectual disabilities, which has improved the power and precision to answer this important research question. A rigorous and systematic analysis process was undertaken, and we minimised the risk of bias,

errors and omissions by having two or more reviewers conduct comprehensive searches, assess study quality and extract descriptive data. Due to the low prevalence (~1%) of intellectual disabilities among the general population, low sample size was a considerable limitation, relative to other patient groups. However, our meta-analysis included two national [10,12], and five regional intellectual populations in their respective countries [11,15,23,28]. While heterogeneity was found, due to methodological and clinical diversity including study design, age and study nationality, this is common in meta-analyses and statistical heterogeneity was inevitable.[20] We have not included assessment of non-reporting or publication bias. Most of the research was conducted in Western countries, thus limiting the extent to which the findings may generalise to non-Western countries. Furthermore, ethnicity was not reported widely which prevented further analysis. There was variation among studies on how mortality was examined and how deaths were reported. There is a general lack of evidence on factors associated with the increased risk of respiratory related deaths in people with intellectual disabilities. As a consequence, we were not able to perform meta-regression on predictors or factors reported in studies which increase SMRs for respiratory deaths (age, sex, place of death, or severity of intellectual disabilities). This should be a priority for future research in order to inform the development of targeted interventions to prevent respiratory related deaths. Although the meta-analysis enables synthesis of data from a large sample, many of the individual studies reported on small samples and are at increased risk of bias. It is encouraging that there have been several larger studies in recent years and future research should focus on reporting respiratory mortality in representative, population-based samples. Furthermore, the majority of the studies included for review relied on death certificate data. One the most reported causes on the death certificate of people with intellectual disabilities is the intellectual disability itself. Given that this problem only exists within this population, true causes of death remain under-estimated.[42,43] As reporting has improved over the years, and many counties implemented automated coding systems, it is likely that older paper have more bias than more recent studies.

These findings signify the urgent need to develop and implement evidence-informed strategies to reduce premature mortality among people with intellectual disabilities. Respiratory disorders are a major cause of death for people with intellectual disabilities, many of which are avoidable with improved public health initiatives and access to good quality health and social care. However, further research is required to understand both the multifactorial causes of this heightened risk as well as the most effective approaches for the multi-professional clinical management of these risks.

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Ethics Not required as this systematic review and meta-analysis was based on published data

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Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure captions

Figure 1: PRISMA flow diagram of systematic search and selection. A total of 2286 records were retrieved through a search of Embase, ISI Web of Science (all databases), CINAHL, and PsycINFO with an additional 9 records identified through other sources. After removing 241 duplicates, 2025 records were excluded due to ineligible types., the remaining 29 were retrieved as full-texts. From these 17 were included in the narrative review and 10 included in the meta-analysis.

Figure 2: Forest plot of respiratory associated mortality. The pooled SMRs for respiratory mortality between people with intellectual disabilities and the general population was 10·86 (95% CI 5·32, 22·18). There was considerable statistical heterogeneity between studies in the meta-analyses, with I^2= 99·0%.

Figure 3: Forest plot for adults only. The pooled SMR for adults only was 5·85 (95% CI 4·73,7·22, p<0·001). Heterogeneity between studies was also reduced from I^2=99% to I^2= 56% by the exclusion of samples which included children.

Figure 4: Forest plot for pneumonia related mortality. The pooled SMR for pneumonia mortality for people with intellectual disabilities compared to the general population was 26·65 (95% CI 5·63, 126·24, p<0·001). Evidence of considerable statistical heterogeneity between studies was also present in this sub-analysis with I^2= 99.0%.

References

1 Harris JC. Intellectual disability: Understanding its development, causes, classification, evaluation, and treatment. Oxford: Oxford University Press, 2006.

2 Maulik PK, Mascarenhas MN, Mathers CD, Dua T, Saxena S. Prevalence of intellectual disability: a meta-analysis of population-based studies. *Res Dev Disabil* 2011; **32(2):** 419-36

3 Organisation W. The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines. Geneva: World Health Organisation, 1992.

4 World Health Organization. World health statistics 2015. Geneva: World Health Organization, 2015.

5 Heslop P, Blair P, Fleming P, Hoghton M, Marriott A, Russ L. Confidential Inquiry into premature deaths of people with learning disabilities (CIPOLD) Final Report http://www.bristol.ac.uk/cipold/fullfinalreport.pdf (2013) (accessed June 25, 2020).

6 Heslop P, Blair PS, Fleming P, Hoghton M, Marriott A, Russ L. The Confidential Inquiry into premature deaths of people with intellectual disabilities in the UK: a population-based study. *Lancet* 2014; **383(9920):** 889-95.

7 O'Leary L, Cooper SA, Hughes-McCormack L. Early death and causes of death of people with intellectual disabilities: a systematic review. *J Appl Res Intellect Disabil* 2018; **31(3):** 325-42.

8 Glover G, Williams R, Heslop P, Oyinlola J, Grey J. Mortality in people with intellectual disabilities in England. *J Intellect Disabil Res* 2017; **61(1):** 62-74.

9 Tyrer F, Smith LK, McGrother CW. Mortality in adults with moderate to profound intellectual disability: a population-based study. *J Intellect Disabil Res* 2007; **51(7):** 520-7.

10 Smith GS, Fleming M, Kinnear D, Henderson A, Pell JP, Melville C, Cooper S-A. Rates and causes of mortality among children and young people with and without intellectual disabilities in Scotland: a record linkage cohort study of 796,190 schoolchildren. *BMJ Open* 2020 (Accepted for Publication) DOI:10.1136/bmjopen-2019-034077.

11 Hollins S, Attard MT, Fraunhofer Nv, McGuigan S, Sedgwick. Mortality in people with learning disability: risks, causes, and death certification findings in London. *Dev Med Child Neurol* 1998; **40(1):** 50-6.

12 Ng N, Wallén EF, Ahlström G. Mortality patterns and risk among older men and women with intellectual disability: a Swedish national retrospective cohort study. *BMC Geriatr* 2017; **17(1):** 269.

13 Raitasuo J, Mölsä P, Raitasuo S, Mattila K. Deaths among the intellectually disabled: A retrospective study. *J Appl Res Intellect Disabil* 1997; **10(4):** 280-8.

14 Patja K, Mölsä P, Iivanainen M. Cause-specific mortality of people with intellectual disability in a population-based, 35-year follow-up study. *J Intellect Disabil Res* 2001; **45(1):** 30-40.

15 Forsgren L, Edvinsson SO, Nyström L, Blomquist HK. Influence of epilepsy on mortality in mental retardation: an epidemiologic study. *Epilepsia* 1996; **37(10):** 956-63.

16 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8(5):** 336-41.

17 Kmet LM, Cook LS, Lee RC. Standard quality assessment criteria for evaluating primary research papers from a variety of fields. HTA Initiative #13. Edmonton: Alberta Heritage Foundation for Medical Research, 2004.

18 Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). *PLoS One* 2007; **2(12)**: e1350. DOI:10.1371/journal.pone.0001350.

19 Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Res Synth Methods* 2017; **8(1):** 5-18.

20 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327(7414):** 557-60.

21 Borenstein M. Common mistakes in meta-analysis and how to avoid them. New Jersey: Biostat. Inc, 2019: 388.

22 Janicki MP, Dalton AJ, Henderson CM, Davidson PW. Mortality and morbidity among older adults with intellectual disability: health services considerations. *Disabil Rehabil* 1999; **21(5-6):** 284-94.

23 Tyrer F, McGrother C. Cause-specific mortality and death certificate reporting in adults with moderate to profound intellectual disability. *J Intellect Disabil Res* 2009; **53(11):** 898-904.

24 Hosking FJ, Carey IM, Shah SM, Harris T, DeWilde S, Beighton C, et al. Mortality among adults with intellectual disability in England: comparisons with the general population. *Am J Public Health* 2016; **106(8):** 1483-90.

25 Trollor J, Srasuebkul P, Xu H, Howlett S. Cause of death and potentially avoidable deaths in Australian adults with intellectual disability using retrospective linked data. *BMJ Open* 2017; **7(2):** e013489. DOI:10.1136/bmjopen-2016-013489.

26 Brameld K, Spilsbury K, Rosenwax L, Leonard H, Semmens J. Use of health services in the last year of life and cause of death in people with intellectual disability: a retrospective matched cohort study. *BMJ Open* 2018; 8(2):e020268. DOI:10.1136/bmjopen-2017-020268.

27 Oppewal A, Schoufour JD, van der Maarl HJ, Evenhuis HM, Hilgenkamp TI, Festen DA. Causes of mortality in older people with intellectual disability: results from the HA-ID study. *Am J Intellect Dev Disabil* 2018; **123(1):** 61-71.

28 Cooper S-A, Allan L, Greenlaw N, McSkimming, P, Jasilek A, Henderson et al. Rates, causes, place and predictors of mortality in adults with intellectual disabilities with and without Down syndrome: cohort study with record linkage. *BMJ Open* 2020 (Accepted for Publication).

29 Durvasula S, Beange H, Baker W. Mortality of people with intellectual disability in northern Sydney. *J Intellect Dev Disabil* 2002; **27(4):** 255-64.

30 Patja K, Iivanainen M, Vesala H, Oksanen H, Ruoppila I. Life expectancy of people with intellectual disability: a 35-year follow-up study. *J Intellect Disabil Res* 2000; **44(5):** 591-9.

31 Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC et al. Infectious Diseases Society of America/ American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; **44 (Suppl 2):** S27-72.

32 Flannery B, Reynolds SB, Blanton L, Santibanez TA, O'Halloran A, Lu PJ, et al. Influenza vaccine effectiveness against pediatric deaths: 2010–2014. *Pediatrics* 2017; **139(5):** e20164244. DOI:10.1542/peds.2016-4244

33 Backer JA, Wallinga J, Meijer A, Donker GA, Van der Hoek W, Van Boven M. The impact of influenza vaccination on infection, hospitalisation and mortality in the Netherlands between 2003 and 2015. *Epidemics* 2019 Mar 1;26:77-85.

34 Robertson J, Hatton C, Emerson E, Baines S. The impact of health checks for people with intellectual disabilities: an updated systematic review of evidence. *Res Dev Disabil* 2014; **35(10):** 2450-62.

35 Chadwick DD, Jolliffe J. A descriptive investigation of dysphagia in adults with intellectual disabilities. *J Intellect Disabil Res* 2009; **53(1):** 29-43.

36 Robertson J, Chadwick D, Baines S, Emerson E, Hatton C. Prevalence of dysphagia in people with intellectual disability: a systematic review. *Intellect Dev Disabil* 2017; **55(6):** 377-91.

37 Durvasula, S, Beange H, Baker, W. Mortality of people with intellectual disability in northern Sydney. *J Intellect Dev Disabil* 2002; **27(4):** 255-264. DOI:10.1080/1366825021000029311

38 Glover G, Ayub M. How people with learning disabilities die. Improving Health and Lives Learning Disabilities Observatory. Durham, 2010.

39 Landes SD, Turk MA, Formica MK, McDonald KE, Stevens JD. COVID_19 outcomes among people with intellectual and developmental disability living in residential group homes in New York State. Disability and Health Journal, 2020 Oct 1;13(4): 100969

40 Cuypers M, Schalk BW, Koks-Leensen MC, Nägele ME, Bakker-van Gijssel EJ, Naaldenberg J, Leusink GL. Mortality of people with intellectual disabilities during the 2017/2018 influenza epidemic in the Netherlands: potential implications for the COVID-19 pandemic. Journal of Intellectual Disability Research. 2020 May 26.

41 Blair E, Langdon K, McIntyre S, Lawrence D, Watson L. Survival and mortality in cerebral palsy: observations to the sixth decade from a data linkage study of a total population register and National Death Index. *BMC Neurol* 2019; **19(1):** 111

42 Landes SD, Peek CW. Death by mental retardation? The influence of ambiguity on death certificate coding error for adults with intellectual disability. Journal of Intellectual Disability Research. 2013 Dec;57(12):1183-90.

43 Dunwoodie Stirton F, Heslop P. Medical certificates of cause of death for people with intellectual disabilities: a systematic literature review. Journal of Applied Research in Intellectual Disabilities. 2018 Sep;31(5):659-68.

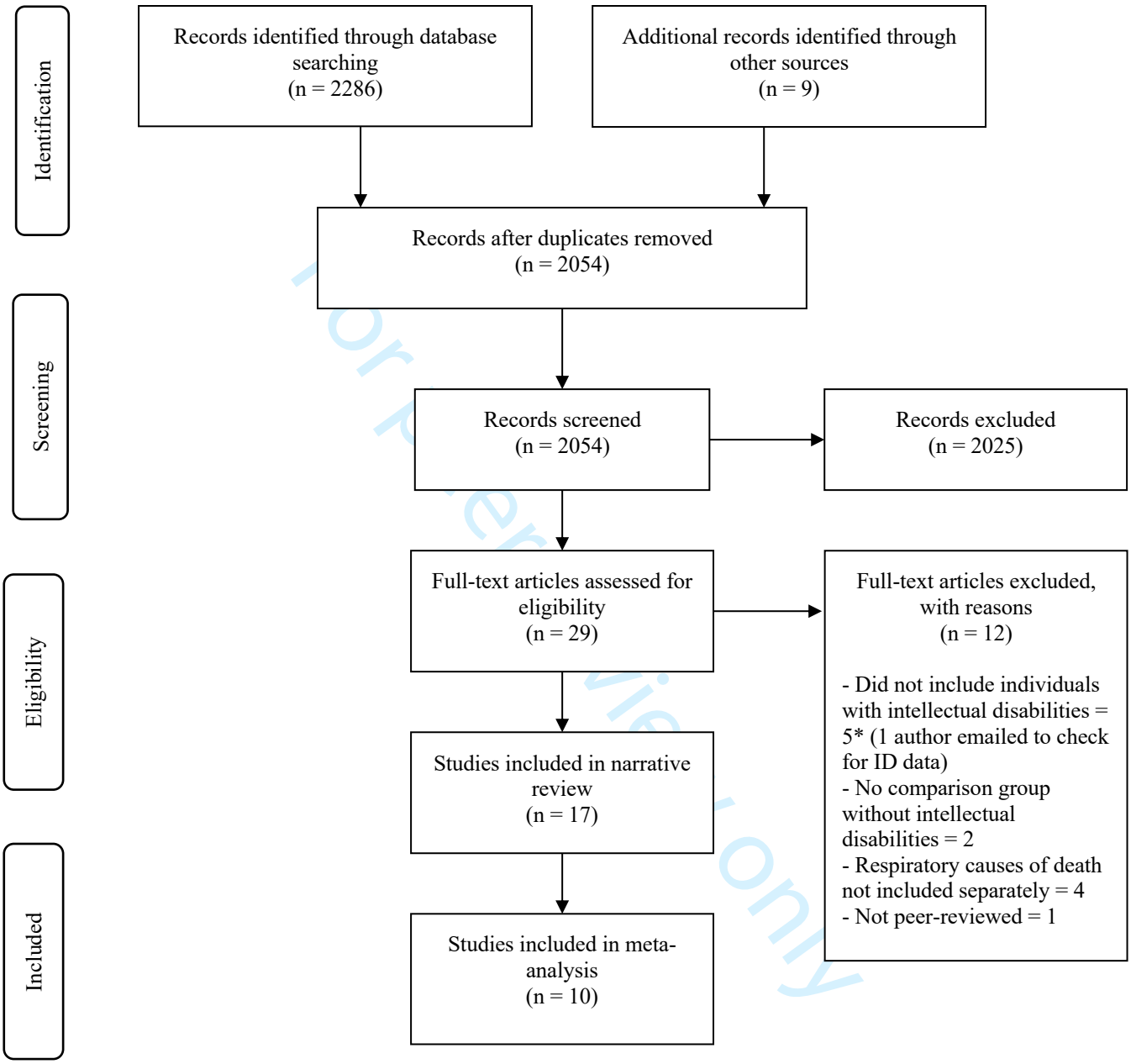


Figure 2: Forest plot of respiratory associated mortality

Study or Subgroup	SMR	SE	Weight	SMR IV, Random, 95% CI
Raitauso et al (1997) [27]	0.77	0.29	8.7%	2.16 [1.22, 3.81]
Forsgren et al (1996) [29]	1.19	0.26	8.8%	3.29 [1.97, 5.47]
Patja et al (2001) [28]	1.32	0.06	9.2%	3.74 [3.33, 4.21]
Glover et al (2017) [18]	1.59	0.1	9.2%	4.90 [4.03, 5.97]
Tyrer & McGrother (2009) [40]	1.7	0.09	9.2%	5.47 [4.59, 6.53]
Hosking et al (2016) [10]	1.9	0.11	9.2%	6.69 [5.39, 8.29]
Cooper et al (2020) [42]	1.91	0.14	9.1%	6.75 [5.13, 8.89]
Ng et al (2017) [26]	2.53	0.07	9.2%	12.55 [10.94, 14.40]
Smith et al (2020) [22]	4.01	0.13	9.1%	55.15 [42.74, 71.15]
Hollins1 et al (1998) [25]	4.31	0.14	9.1%	74.44 [56.58, 97.94]
Hollins2 et al (1998) [25]	4.91	0.12	9.1%	135.64 [107.21, 171.61]
Total (95% CI)			100.0%	10.86 [5.32, 22.18]

Heterogeneity: $Tau^2 = 1.44$; $Chi^2 = 1286.60$, $df = 10$ ($P < 0.00001$); $I^2 = 99\%$

Test for overall effect: $Z = 6.54$ ($P < 0.00001$)

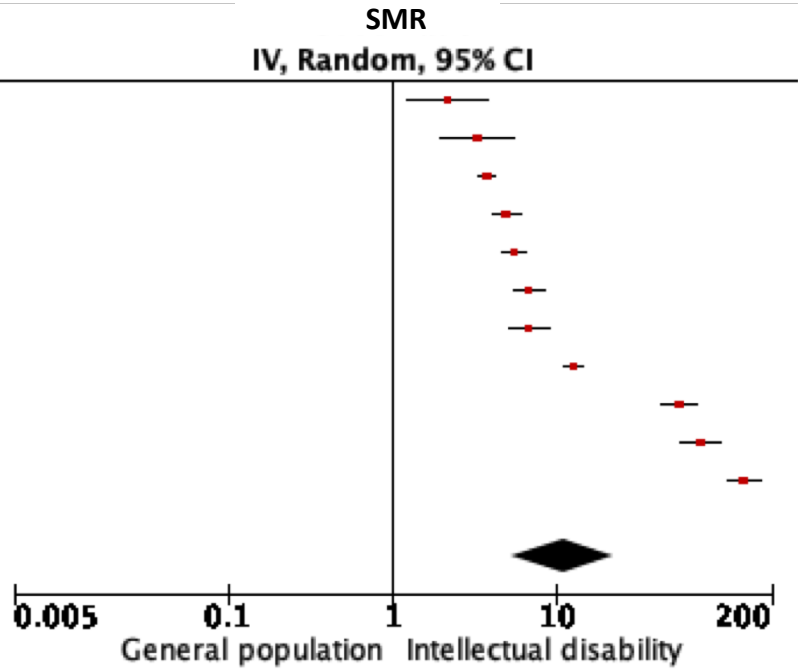


Figure 3: Forest plot for adults only

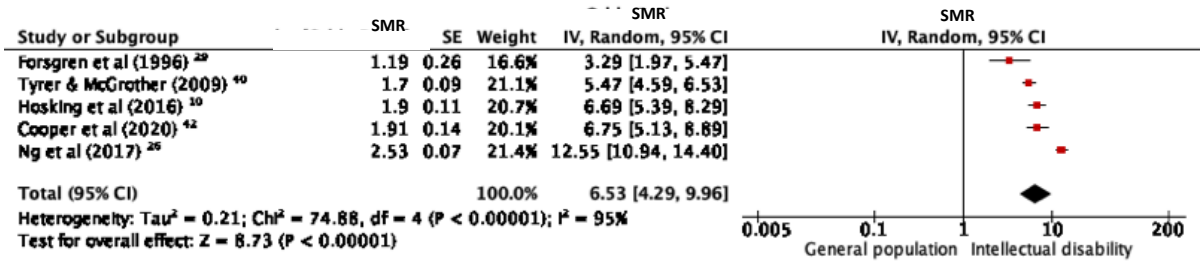
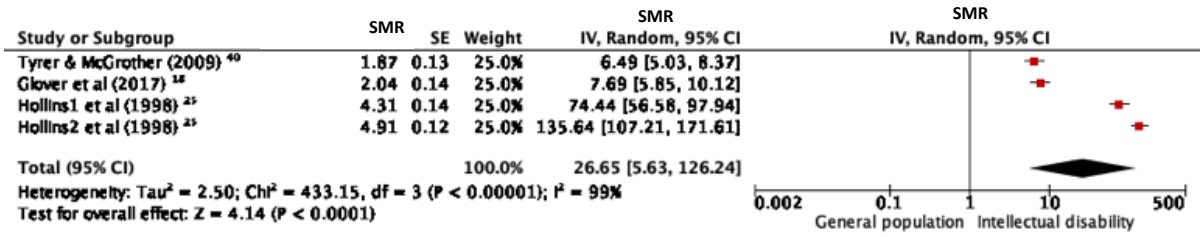


Figure 4: Forest plot pneumonia related mortality



Appendix 1: Search strategy

Embase- Ovid, 2016-

Search Terms	
1.	developmental disorder/ or intellectual impairment/ or developmental disabilities/ or intellectual disability/ or mentally disabled persons/ or intellectual development disorder/ or "intellectual development disorder (attitudes toward)"/
2.	((intellect$ adj3 (deficien$ or difficult$ or disab$ or disorder$ or impair$ or handicap$ or incapacit$ or handicap$ or sub?average or sub?norm$)) or (low$2 adj2 intellect$)).tw.
3.	(learning adj3 (deficien$ or difficult$ or disab$ or disorder$ or handicap$ or impair$ or incapacit$ or handicap$ or sub?average or sub?norm$)).tw.
4.	(mental$ adj3 (deficien$ or disab$ or handicap$ or impair$ or handicap$ or incapacit$ or retard$ or sub?average or sub?norm$)).tw.
5.	((subaverage or sub$1 average or subnormal or sub$1 normal$) adj3 (cognit$ or intel$)).tw.
6.	((development$ or neurodevelopment$) adj disab$).tw.
7.	(education$ adj5 sub?norm$).tw.
8.	(cretin$ or feeble minded$ or imbecil$ or moron$).tw.
9.	Or/ 1-9
10.	cause of death/ OR mortality/ OR fatal outcome/ OR death/ OR hospital mortality/ OR mortality.ti,ab OR fatal.ti,ab OR death.ti,ab
11.	asthma/ OR asthma.ti,ab OR bronchial asthma.ti,ab OR asthma, bronchial.ti,ab OR pneumonia/ OR pneumonia.ti,ab OR lobar pneumonia.ti,ab OR lobar pneumonia.ti,ab OR pneumonia, lobar.ti,ab OR bacterial pneumonia/ OR pneumonia, bacterial.ti,ab OR viral pneumonia/ OR pneumonia, viral.ti,ab OR viral pneumonia.ti,ab OR bronchopneumonia/ OR bronchopneumonia.ti,ab OR bronchial pneumonia.ti,ab OR pneumonia, bronchial.ti,ab OR lung disease/ OR disease, lung.ti,ab OR pulmonary disease.ti,ab OR disease, pulmonary.ti,ab OR respiratory disease.ti,ab OR disease, respiratory.ti,ab OR chronic obstructive lung disease/ OR lung disease, obstructive.ti,ab OR obstructive lung disease.ti,ab OR obstructive lung diseases.ti,ab OR obstructive pulmonary diseases.ti,ab OR aspiration pneumonia/ OR aspiration pneumonia.ti,ab OR bronchiectasis/ OR bronchiectasis.ti,ab OR respiratory failure/ OR respiratory failure.ti,ab OR interstitial pneumonia/ Or interstitial pneumonia.ti,ab
12.	9 and 10 and 11

Cinahl and APA PsychINFO - Ebscohost, 2016-

Search Terms	
1.	MH Intellectual disability
2.	(MH "Mentally Disabled Persons")
3.	TX (intellectual* N3 (disab* or disorder* or handicap* or impair* or deficien* or subnorm*))
4.	TX (learning N3 (disab* or disorder* or impair* or difficllt*))
5.	TX (development* N3 (disab* or disorder* or handicap* or impair* or delay*))
6.	TX (Mental* N3 (disab* or disorder* or handicap* or impair* or deficien* or subnorm* or retard*))
7.	((development$ or neurodevelopment$) N disab$).tw.
8.	(education$ N5 su?bnorm$).tw.
9.	(cretin$ or feeble minded$ or imbecil$ or moron$).tw.
10.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
11.	cause of death/
12.	mortality/
13.	fatal outcome/
14.	death/
15.	hospital mortality/
16.	mortality.ti.ab
17.	fatal.ti.ab
18.	death.ti.ab
19.	Or/ 11-18
20.	"pulmonary disease" or "airway disease" or "broncho-pulmonary disease" or "respiratory disease" or "lung disease" or "lung disorder" or "pulmonary disorder" or "respiratory disorder" or "pneumonia" or "bronchopneumonia" or "lung infection" or pulmonary infection" or respiratory infection" or "asthma" or "chronic obstructive pulmonary disease" or "aspiration pneumonia" or "bronchiectasis" or "respiratory failure"
21.	10 and 19 and 20

Web of Science (All databases, including MEDLINE) 2016-current

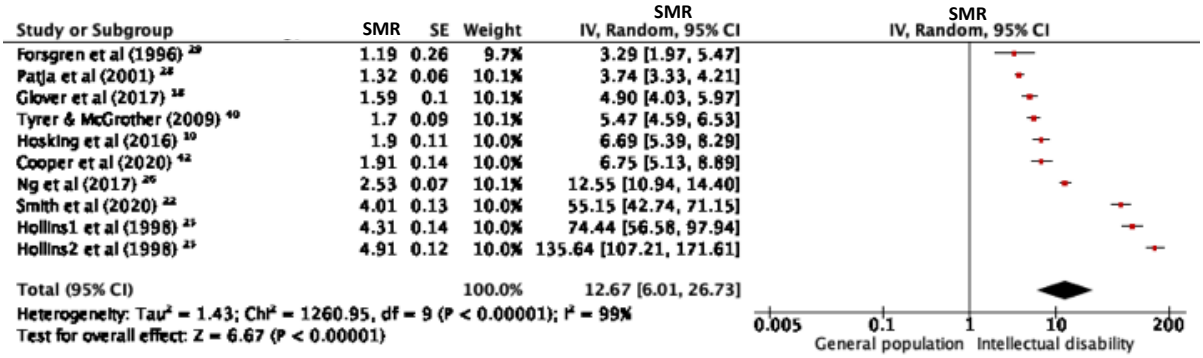
TS= mortality OR death OR cause of death OR cause of mortality OR dead OR died
AND
TS= intellectual disab* or intellectual impair* or developmental disab* or learning disab* or mental retard* or mental handicap*
AND
TS=asthma* or bronchial asthma or pneumoni* or lobar pneumoni* or lobar pneumoni* or bacterial pneumoni* or viral pneumoni* or bronchopneumonia* or bronchial pneumoni* or lung disease* or lung disorder* or lung infect* or pulmonary disease* or pulmonary disorder or pulmonary infect* or respiratory disease* or respiratory disorder or respiratory infect* or obstructive lung disease* or obstructive pulmonary disease* or aspiration pneumoni* or bronchiecstasi

Appendix 2: Excluded papers – References and reasons for exclusion

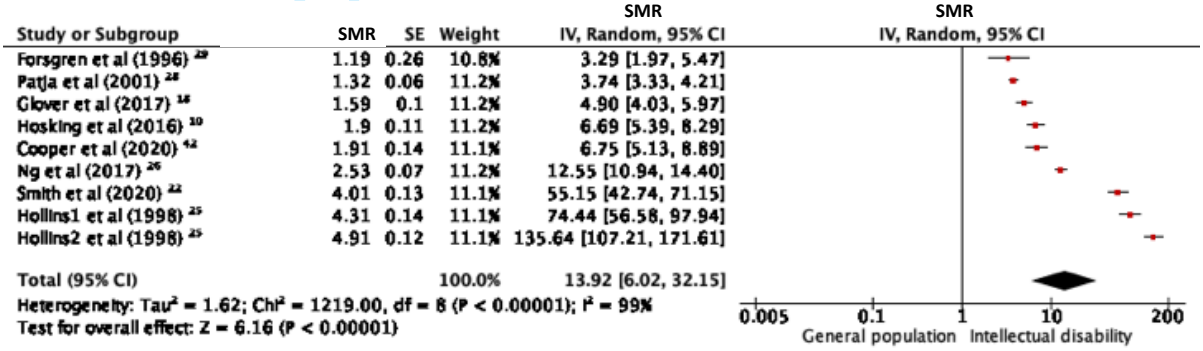
	Reference	Reason
1	Bilder D, Botts EL, Smith KR, Pimentel R, Farley M, Viskochil J. Excess mortality and causes of death in autism spectrum disorders: A follow up of the 1980s Utah/ UCLA autism epidemiologic study. *J Autism Dev Disord* 2013; **43(5):** 1196-1204	Did not include individuals with intellectual disabilities.
2	Decoufle P, Autry A. Increased mortality in children and adolescents with developmental disabilities. *Paediatr Perinat Epidemiol* 2002; **16(4):** 375-382	No general population comparison group.
3	Florio T, Trollor J. Mortality among a cohort of persons with an intellectual disability in New South Wales, Australia. *J Appl Res Intellect Disabil* 2015; ***28*(5):** 383-393.	Respiratory causes of death not included separately.
4	Glover G, Ayub M. How people with learning disabilities die. Improving Health and Lives Learning Disabilities Observatory. Durham, 2010.	Not peer-reviewed.
5	Jahan I, Karim T, Das MC, Muhit M, McIntyre S, Smithers-Sheedy H, et al. Mortality in children with cerebral palsy in rural Bangladesh: a population-based surveillance study. *Dev Med Child Neurol* 2019; **61(11):** 1336-1343	Did not include individuals with intellectual disabilities.
6	McCarron M, Carroll R, Kelly C, McCallion P. Mortality rates in the general Irish population compared to those with an intellectual disability from 2003 to 2012. *J Appl Res Intellect Disabil* 2015; ***28*(5):** 406-413.	Respiratory causes of death not included separately.
7	Perez CM, Ball SL, Wagner AP, Clare ICH, Holland AJ, Redley M. The incidence of healthcare use, ill health and mortality in adults with intellectual disabilities and mealtime support needs. *J Intellect Disabil Res* 2015; **59(7):** 638-652	No general population comparison group.
8	Reid, SM, Carlin JB, Reddihough DS. Survival of individuals with cerebral palsy born in Victoria, Australia, between 1970 and 2004. *Dev Med Child Neurol* 2012; **54(4):** 353-360	Did not include individuals with intellectual disabilities.
9	Shavelle, Robert M.; Strauss, David J.; Pickett, Jane Causes of death in autism. *J Autism Dev Disord* 2001; **31(6):** 569-576	Did not include individuals with intellectual disabilities.
10	Similä S, Von Wendt L, Rantakallio P. Mortality of mentally retarded children to 17 years of age assessed in a prospective one-year birth cohort. *J Ment Defic Res* 1986; **30:** 401-5	Respiratory causes of death not included separately.

11	Stankiewicz E, Ouellette-Kuntz H, McIsaac M, Shooshtari S, Balogh R. Patterns of mortality among adults with intellectual and developmental disabilities in Ontario. *Can J Public Health* 2018; **109(5-6):** 866-872	<70%* of participants had intellectual disabilities. *We emailed this author to check if >70% of sample had ID – they replied but didn't have the data to check, so it was excluded.
12	Tyrer F, Smith LK, McGrother CW. Mortality in adults with moderate to profound intellectual disability: a population-based study. *J Intellect Disabil Res*, 2007; ***51*(7):** 520-527.	Respiratory causes of death not included separately.

Sensitivity A- minus Raitasuo



Sensitivity B- minus Raitasuo and Tyrer



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4/5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 and Appx 1 pgs 35-36
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12, 39
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	25,26 Appx.3 pg 40-42
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	25
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	26
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	26
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	27
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	29

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.