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

Journal:	BMJ Open
Manuscript ID	bmjopen-2020-043658
Article Type:	Original research
Date Submitted by the Author:	11-Aug-2020
Complete List of Authors:	Truesdale, Maria; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Melville, Craig; Glasgow University, Institute of Health and Wellbeing Barlow, Fiona; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Dunn, Kirsty; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Henderson, Angela; University of Glasgow, Institute of Health and Wellbeing Hughes-McCormack, Laura; University of Glasgow, Institute of Health and Wellbeing McGarty, Arlene; University of Glasgow College of Medical Veterinary ar Life Sciences, Mental Health and Wellbeing Rydzewska, Ewelina; University of Glasgow Smith, Gillian; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Rydzewska, Ewelina; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Symonds, Joseph; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Symonds, Joseph; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Jani, Bhautesh; University of Glasgow College of Medical Veterinary and Life Sciences Kinnear, Deborah; University of Glasgow, Institute of Health and Wellbeing
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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Wordcount: 3504

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

 $4 \cdot 29, 9 \cdot 96, p < 0 \cdot 001$ ); and relatively high rates from pneumonia  $26 \cdot 65$  (95% CI  $5 \cdot 63, 126 \cdot 24, p < 0 \cdot 001$ ). The overall statistical heterogeneity was I<sup>2</sup>= 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 1<sup>st</sup> January 1985 to the 27<sup>th</sup> 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  $\kappa = .57$  and  $\kappa = .58$ , 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]

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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 0al (2018) <sup>26</sup> 1 2 3 4	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)
<sup>5</sup> Cooper et al <sup>6</sup> (2020) <sup>28</sup> 7 8 9 0 1	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)
2Dupont et al. 3(1987) <sup>40</sup> 4	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 $(2002)^{37}$	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) <sup>15</sup> 7 3	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)

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2 3 4 5			from Swedish National Bureau of Statistics					
<ul> <li>Glover et al</li> <li>(2017)<sup>8</sup></li> <li>9</li> <li>10</li> </ul>	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; $44 \cdot 1\%$ 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)
11Heslop et al 12(2014) <sup>5</sup> 13 14 15 16 17 18	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)
19Hollins et al 20 <sup>(1998)<sup>11</sup></sup> 21	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)
22 23Hosking et 24 25 26 27	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)
28Janicki et al 29(1999) <sup>22</sup> 30 31 32 33 34	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)
35Ng et al 36(2017) <sup>12</sup> 37 38 39 40	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)
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			National Cause of Death register					
Oppewal et al (2018) <sup>27</sup> 0 1 2 3 4	Netherla nds	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)
<sup>5</sup> Patja et al <sup>6</sup> (2001) <sup>14</sup> 7 8 9 9 0 1	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)
2Raitasuo et 3al (1997) <sup>13</sup> 4 5 5 7 8 9	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)
<sub>0</sub> Smith et al 1(2020) <sup>10</sup> 2 3 4	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= $16 \cdot 1$ years (95% CI $15 \cdot 8$ to $16 \cdot 5$ )	ICD 10- chapter codes for respiratory disorders.	100% (strong)
5 Trollor et al 6(2017) <sup>25</sup> 8 9 0	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)

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3 4 5		disability services. Follow up 2005-2011	of Statistics. Death records			female; median age= 81 (70–92).		
6 Tyrer and 7 McGrother 8 (2009) <sup>23</sup> 9 10 11 12	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)
13	ndividuals i		a significantly young	er age than the comparison co	short			
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#### 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<sup>2</sup> 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 metaanalysis, the type of outcome data, or effect measurement.[20] Heterogeneity was interpreted as not observed when I<sup>2</sup>=0%, low when I<sup>2</sup>=25%, medium when I<sup>2</sup>=50%, and high when I<sup>2</sup>=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.

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5 Author 6 7 8	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
<ul> <li>9 Brameld et</li> <li>10al (2018)<sup>26</sup></li> <li>11</li> <li>12</li> <li>13</li> <li>14</li> <li>15</li> <li>16</li> <li>17</li> <li>18</li> <li>19</li> <li>20</li> <li>21</li> <li>22</li> <li>23</li> <li>24</li> <li>25</li> <li>26</li> <li>27</li> <li>28</li> <li>29</li> <li>30</li> <li>31</li> <li>32</li> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> </ul>	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) <sup>28</sup>	294/961 (30·6%)	Underlying cause of death:	Underlying cause of death: Down syndrome: 8/ 57	All-contributing factors in death:	Underlying cause of death: Down syndrome:	Not available
	deaths	57/262 (21.8%)	(14.0%) deaths		Aspiration/ reflux/ choking =	
	$\mathbf{SMR} = 2 \cdot 24$	deaths	Without Down syndrome:	Respiratory infection =	<5/ 57 deaths	
	(95% CI;	SMR = 6.78	49/205 (23·9%) deaths	27.1% deaths	Respiratory infection = $<5/57$	
	1.98, 2.49)	(95% CI; 5·02,		Aspiration/ reflux/ choking	deaths	
		8.54)		= 19.8% deaths	Other respiratory conditions = $(5/57)$ depths	
)					<5/ 57 deaths	
0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0			K	= 19.8% deaths	Without Down syndrome:	
3					Aspiration/ reflux/ choking =	
4					22/205 (10.8%) deaths	
<u>с</u>					Respiratory infection = $21/205$	
0 7				0	(10.3%) deaths	
/ 0					Other respiratory conditions =	
0					9/205 (4·4%) deaths	
9						
1					All-contributing factors in	
1					death:	
2						
4					Down syndrome:	
5					Respiratory infection = $22/57$	
6					(38.6%) deaths Aspiration/ reflux/ choking =	
7					11/57 (19.3%) deaths	
8					Other respiratory conditions =	
9					<pre></pre> <pre>&lt;</pre>	
0						
1					Without Down syndrome:	
2						
3					Respiratory infection = $49/205$	
4					(23.9%) deaths	
5					Aspiration/ reflux/ choking =	
6					41/205 (20.2%) deaths	
7					Other respiratory conditions =	
8					31/205 (15.1%) deaths	

1						
2 3 Dupont et al 4 (1987) <sup>40</sup> 5 6 7 8 9 10 11 12 13 14 15 16 17 18 10	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
19 20(2002) <sup>30</sup> 21 22 23 24 25 26 27 28 29 30 31 32 33	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
34Forsgren et 35al (1996) <sup>15</sup> 36 37 38 39 40	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)
41 42				13		
42 43			Fermania			
			For peer review or	nly - http://bmjopen.bmj.com/s	site/about/guidelines.xhtml	

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 Glover et al 20 (2017) <sup>8</sup> 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38	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 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)	SMR 3·3 (95% CI 2·0, 5·5) N=114 deaths from respiratory causes for people with ID vs 23·3 expected SMR 4·9 (4·0, 5·9)	Not available	people with both epilepsy and ID N=57 / 114 (50%) of respiratory deaths (and 8·6% of all deaths) were from influenza and pneumonia, vs expected 7·4 deaths <b>SMR 7·7 (5·8, 9·9</b> ) 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 <b>SMR 21·8 (13·9, 32·4)</b> N=12 (1·8%) of all deaths were due to respiratory and intrathoracic cancers vs expected 16.6 deaths	Not available	Not available
33 34 35 36 37 38	3·40 (3·02, 3·81) Men 3·03			were due to respiratory and intrathoracic cancers vs		
39 40 41 42				14		

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1 2						
<ul> <li>Heslop et al</li> <li>(2014)<sup>6</sup></li> <li>(</li></ul>	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, & accommodat ion 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 Bronchopneumonia: N=56	Not available	Reduced smoking in ID group p=0.02
25Hollins et al 26(1998) <sup>11</sup> 27 28 29 30 31 32 33 34 35 36 37 38 39 40	$\begin{array}{c} 270/2,026\\ (13\cdot3\%)\\ \text{deaths}\\ 116/1,081\\ (10\cdot7\%)\\ \text{deaths on}\\ \text{Wandsworth}\\ \text{register}\\ 154/945\\ (16\cdot3\%)\\ \text{deaths on}\\ \text{Kensington}\\ \text{register} \end{array}$	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

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1 2 3 Hosking et 4 al (2016) <sup>24</sup> 5 6 7 8	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
<ul> <li>Janicki et al</li> <li>10(1999)<sup>22</sup></li> <li>11</li> <li>12</li> <li>13</li> <li>14</li> <li>15</li> <li>16</li> <li>17</li> <li>18</li> <li>19</li> <li>20</li> <li>21</li> <li>22</li> <li>23</li> <li>24</li> <li>25</li> <li>26</li> <li>27</li> <li>28</li> <li>29</li> <li>30</li> <li>31</li> <li>32</li> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38Ng et al.</li> </ul>	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.		Not available	
38Ng et al. 39(2017) <sup>12</sup>	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
41 42				16		

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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	(a) with ID HR =12.5 (10.9, 14.2) (10.9,	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%	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 Pneumonia ID=80·4%; Chronic obstructive pulmonary diseases ID=17·6%	Not available	Not available
31 32 33 34 35 36 37 38 39 40 41	deaths. Respiratory	GP=9·9%; 90-95 ID=40% GP=10·4%; 95+ ID=100%			

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1 2 3 4 5 6 7 8 9 10 11 12 13 $14^{Patja et al}$ 15 $(2001)^{14}$ 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	1111/2369 ID =46·9%	groups of primary causes of death were neoplasms (31%), circulatory diseases (28%) and respiratory diseases (9%). No SMR available. 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= $5\cdot8$ ( $4\cdot4-15\cdot6$ ); age 20-39 SMR= $5\cdot4$ ( $2\cdot9-8\cdot0$ ); age 40-59 SMR= $5\cdot5$ ( $3\cdot5-7\cdot5$ ); age 60+ SMR= $2\cdot7$ ( $2\cdot7-4\cdot8$ ) Female: age 2-19 SMR= $4\cdot3$ ( $0\cdot3-4\cdot7$ ); age 20-39 SMR= $3\cdot2$ ( $1\cdot1-5\cdot1$ ); age 40-59 SMR= $6\cdot2$ ( $4\cdot1-8\cdot2$ ); age 60+ SMR= $3\cdot3$ ( $1\cdot7-3\cdot0$ )	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)
32Raitauso et 33al (1997) <sup>13</sup> 34 35 36 37 38 39	216 deaths	Immediate cause of death 97/216 ID=45% Primary cause 14/216 ID=6%.	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	Not available	Age (all respiratory)
38 39 40 41 42		Respiratory diseases were		by a fistula between the bronchus and the pleura. Besides pneumonia, two 18		

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1 2 3 4 5 6 7 8 9 10 11 12Smith et al 13(2020) <sup>10</sup> 14 15 16 17 18 19 20 21 22 23 24 25	N = 106 (0.6%) deaths SMR = 11.6 (95% CI; 9.6, 14.0)	the dominant causes of ID death. SMR= $2\cdot15$ (CI $1\cdot18 - 3\cdot61$ ) 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,	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	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. Underlying cause of death: Pneumonia including influenza; $<5/106$ All-contributing factors in death: Pneumonia= 27/106 ( $25 \cdot 5\%$ ) deaths Respiratory failure; 17/106 ( $16 \cdot 0\%$ ) deaths Respiratory disorders = 15/ 106 ( $14 \cdot 2\%$ ) deaths Pneumonitis associated with	General populations: All-contributing factors in death: Pneumonia = 21/ 458 (4.6%) deaths	Not available
23 24 25 26Trollor et al 27(2017) <sup>25</sup> 28 29 30 31 32 33 34 35 36 37 38 39	732 / 19362 ID=4% SMR=1·3 (1·2 to 1·5)	<ul> <li>(95% CI; 42'5, 72'1)</li> <li>632/732 ID=86'3% had cause of death information</li> <li>78 ID=12% 4<sup>th</sup> top cause using the ID ABI conversion</li> <li>130 ID=20% 1st top using the ID revised version</li> </ul>	Not available	Friedmontus associated with food and vomit = $9/106$ ( $8 \cdot 5\%$ ) deaths Not available	Not available	Not available
40 41 42 43			For peer review of	19 nly - http://bmjopen.bmj.com/s	site/about/guidelines.xhtml	

1						
2 3 4 5 6 7 8 9 10 11		16 ID=3% of respiratory deaths were considered avoidable. 26242 GP=9% 3rd top underling cause				
12Tyrer & 13McGrother 14(2009) <sup>23</sup> 15 16 1 <del>7</del>	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
	IR=standardised		espiratory mortality =confidence interval/ RR=rate	ratio/ HR=hazard ratio/CMF=c	comparative mortality figure/ OR=oc	lds ratio/ O=observed deaths/ E=expected
26 27 28 29 30 31 32 33					comparative mortality figure/ OR=oc	
34 35 36 37 38 39 40						
41 42 43 44 45 46			For peer review of	20 nly - http://bmjopen.bmj.com/	/site/about/guidelines.xhtml	

### **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<sup>31</sup> 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 metaanalysis 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<sup>2</sup>= 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 pneumoniarelated 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

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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 are not widened during this crisis.

Interventions should focus on the pediatric age group. Among the studies included in this metaanalysis 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

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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.

**Funding** The Scottish Government (HSCD 169698)

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<sup>2</sup>= 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<sup>2</sup>=99% to I<sup>2</sup>= 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<sup>2</sup>= 99.0%.

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## **Appendix 1: Search strategy**

## Embase- Ovid, 2016-

Sear	rch 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 lung 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 pulmonary disease.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 bronchiectasis/ OR
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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 disease\* or aspiration pneumoni\* or bronchiecstasi

# Appendix 2: Sensitivity analysis A and B

Sensitivity A- minus Raitauso

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI		· · · · · · · · · · · · · · · · · · ·	dds Ratio 1dom, 95% Cl	
Forsgren et al (1996) 29	1.19	0.26	9.7%	3.29 [1.97, 5.47]			1	
Patja et al (2001) 28	1.32	0.06	10.1%	3.74 [3.33, 4.21]				
Glover et al (2017) 18	1.59	0.1	10.1%	4.90 [4.03, 5.97]			+	
Tyrer & McGrother (2009) 40	1.7	0.09	10.1%	5.47 [4.59, 6.53]			+	
Hosking et al (2016) 10	1.9	0.11	10.0%	6.69 [5.39, 8.29]			-	
Cooper et al (2020) 42	1.91	0.14	10.0%	6.75 [5.13, 8.89]			+	
Ng et al (2017) 26	2.53	0.07	10.1%	12.55 [10.94, 14.40]			+	
Smith et al (2020) 22	4.01	0.13	10.0%	55.15 [42.74, 71.15]			+	1
Hollins1 et al (1998) 25	4.31	0.14	10.0%	74.44 [56.58, 97.94]			-	-
Hollins2 et al (1998) <sup>25</sup>	4.91	0.12	10.0%	135.64 [107.21, 171.61]				+
Total (95% CI)			100.0%	12.67 [6.01, 26.73]			•	
Heterogeneity: $Tau^2 = 1.43$ ; ( Test for overall effect: $Z = 6.6$		= 9 (P	< 0.000	01);	0.005	0.1	1 10 ID General population	200

# Sensitivity B- minus Raitauso and Tyrer

•				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Raitauso	0.77	0.29	0.0%	2.16 [1.22, 3.81]	
Forsgren	1.19	0.26	11.1%	3.29 [1.97, 5.47]	
Patjia	1.32	0.06	11.4%	3.74 [3.33, 4.21]	•
Glover	1.59	0.1	11.4%	4.90 [4.03, 5.97]	-
Tyrer	1.7	0.09	0.0%	5.47 [4.59, 6.53]	
Hosking	1.9	0.11	11.4%	6.69 [5.39, 8.29]	+
Cooper	1.91	0.14	11.3%	6.75 [5.13, 8.89]	-
Ng	2.53	0.7	9.3%	12.55 [3.18, 49.50]	
Smith	4.01	0.13	11.4%	55.15 [42.74, 71.15]	+
Hollins1	4.31	0.14	11.3%	74.44 [56.58, 97.94]	-
Hollins2	4.91	0.12	11.4%	135.64 [107.21, 171.61]	*
Total (95% CI)			100.0%	13.94 [5.26, 36.91]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				< 0.00001); i <sup>2</sup> = 99%	0.005 0.1 1 10 200 ID General population
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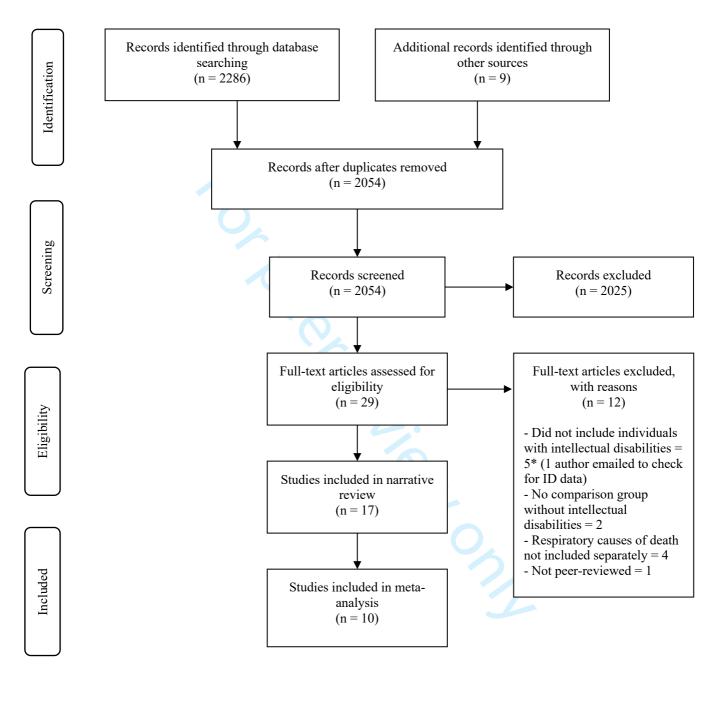
# Appendix 3: Excluded papers – References and reasons for exclusion

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

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

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22					Odds Ratio	Odd	s Ratio
23	Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI		om, 95% Cl
24	Raitauso et al (1997) <sup>27</sup>	0.77		8.7%	2.16 [1.22, 3.81]		
25	Forsgren et al (1996) <sup>29</sup>	1.19	0.26	8.8%	3.29 [1.97, 5.47]		<b>  →</b>
26	Patja et al (2001) 28	1.32	0.06	9.2%	3.74 [3.33, 4.21]		•
27	Glover et al (2017) <sup>18</sup>	1.59	0.1	9.2%	4.90 [4.03, 5.97]		-
28	Tyrer & McGrother (2009) <sup>40</sup>	1.7	0.09	9.2%	5.47 [4.59, 6.53]		-
	Hosking et al (2016) <sup>10</sup>		0.11	9.2%	6.69 [5.39, 8.29]		-
29	Cooper et al (2020) <sup>42</sup>	1.91	0.14	9.1%	6.75 [5.13, 8.89]		-
30	Ng et al (2017) <sup>26</sup>	2.53		9.2%	12.55 [10.94, 14.40]		-
31	Smith et al (2020) <sup>22</sup>	4.01		9.1%	55.15 [42.74, 71.15]		-
32	Hollins1 et al (1998) <sup>25</sup>	4.31		9.1%	74.44 [56.58, 97.94]		-
33	Hollins2 et al (1998) <sup>25</sup>	4.91	0.12	9.1%	135.64 [107.21, 171.61]		· ·
34				100.00/			
35	Total (95% CI)	21.12 1222 22 12		100.0%	10.86 [5.32, 22.18]		
36	Heterogeneity: $Tau^2 = 1.44$ ; C		= 10 (I	P < 0.000	01); $I^2 = 99\%$	0.005 0.1	1 10 2
37	Test for overall effect: $Z = 6.5$	54 (P < 0.00001)				IC	General population
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Study or Subgroup         log[Odds Ratio]         SE         Weight IV, Random, 95% CI         IV, Random, 95% CI           Cooper         1.31         0.14         24.4%         6.75         5.81         1.7           Forsgren         1.39         0.26         12.2%         3.28         1.97         5.47           Higking         1.39         0.11         20.66         12.68         6.83         8.29           Ng         2.53         0.7         2.2%         12.59         3.68         9.53           Ng         2.53         0.7         2.2%         5.47         4.65         9.63           Ng         2.53         0.7         2.2%         5.47         1.63         5.83           Ng         2.53         0.7         2.2%         5.47         1.63         5.33           Total (95% CI)         1.00.0%         5.85         1.73         7.22         4           Heitrogrendty, Tau' = 0.03; Ch' = 9.1.4, d' = 4.0°         0.00; t' = 5.6N         0.005         0.1         1         10         Ceneral population           Test for overall effect Z = 16.37 (P < 0.00001)         0.00001)         0.005         0.1         1         0.005         0.1         1         0.005 <th></th> <th></th> <th>BMJ Open</th> <th></th>			BMJ Open	
Study or Subgroup         log[Odds Ratio]         SE         Weight         IV, Random, 95% CI         IV, Random, 95% CI           Cooper         1.91         0.14         24.4%         6.75         [5.13, 8.69]				
Study or Subgroup         log[Odds Ratio]         SE         Weight         IV, Random, 95% CI         IV, Random, 95% CI           Cooper         1.91         0.14         24.4%         6.75         [5.13, 8.69]				
Study or Subgroup         log[Odds Ratio]         SE         Weight         IV, Random, 95% CI         IV, Random, 95% CI           Cooper         1.91         0.14         24.4%         6.75         [5.13, 8.69]				
Study or Subgroup         log[Odds Ratio]         SE         Weight         IV, Random, 95% CI         IV, Random, 95% CI           Cooper         1.91         0.14         24.4%         6.75         [5.13, 8.69]				
Study or Subgroup         log[Odds Ratio]         SE         Weight         IV, Random, 95% CI         IV, Random, 95% CI           Cooper         1.91         0.14         24.4%         6.75         [5.13, 8.69]				
Study or Subgroup         log[Odds Ratio]         SE         Weight         IV, Random, 95% CI         IV, Random, 95% CI           Cooper         1.91         0.14         24.4%         6.75         [5.13, 8.69]				
Study or Subgroup         log[Odds Ratio]         SE         Weight         IV, Random, 95% CI         IV, Random, 95% CI           Cooper         1.91         0.14         24.4%         6.75         [5.13, 8.69]				
Study or Subgroup         log[Odds Ratio]         SE         Weight         IV, Random, 95% CI         IV, Random, 95% CI           Cooper         1.91         0.14         24.4%         6.75         [5.13, 8.69]				
Forsgren       1.19       0.26       12.2%       3.29       [1.97, 5.47]         Hosking       1.9       0.11       29.0%       6.69       [5.39, 8.29]         Ng       2.53       0.7       2.2%       12.55       [3.18, 49.50]         Tyrer       1.7       0.09       32.2%       5.47       [4.59, 6.53]         Total (95% Cl)       100.0%       5.85       [4.73, 7.22]       +         Heterogeneity: Tau <sup>2</sup> = 0.03; Ch <sup>2</sup> = 9.14, df = 4 (P = 0.06); l <sup>2</sup> = 56%       0.005       0.1       1       10         Test for overall effect: Z = 16.37 (P < 0.00001)		og[Odds Ratio]   SE Weight IV, Rando	m, 95% CI IV	/, Random, 95% Cl
Total (95% CI) 100.0% 5.85 [4.73, 7.22] Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 9.14, df = 4 (P = 0.06); i <sup>2</sup> = 56% 0.005 0.1 1 10 2 Test for overall effect: Z = 16.37 (P < 0.00001) ID General population	Forsgren Hosking Ng	1.19 0.26 12.2% 3.29 [1 1.9 0.11 29.0% 6.69 [5 2.53 0.7 2.2% 12.55 [3.3	97, 5.47] 39, 8.29] 18, 49.50]	•
Test for overall effect: Z = 16.37 (P < 0.00001)	Total (95% CI)	100.0% 5.85 [4	4.73, 7.22]	•
	Test for overall effect: Z	= 16.37 (P < 0.00001)	0.005 0.1	1 10 ID General population

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25					Odds Ratio	Odds Ratio
26	Study or Subgroup	log[Odds Ratio]		Weight	IV, Random, 95% CI	IV, Random, 95% Cl
27 28	Tyrer & McGrother (2009) <sup>40</sup> Glover et al (2017) <sup>18</sup>	1.87 2.04	0.13 0.14	25.0% 25.0%	6.49 [5.03, 8.37] 7.69 [5.85, 10.12]	• • • • • • • • • • • • • • • • • • •
29	Hollins1 et al (1998) <sup>25</sup> Hollins2 et al (1998) <sup>25</sup>	4.31	0.14	25.0%	74.44 [56.58, 97.94]	
30 31		4.91	0.12		135.64 [107.21, 171.61]	-
	Total (95% CI)			100.0%	26.65 [5.63, 126.24]	
32		$Chi^2 - 433.15 df -$	3 (P ~	0.00001	$1^2 - 99\%$	
33	Heterogeneity: $Tau^2 = 2.50$ ; Test for overall effect: $Z = 4$ .	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)	$; I^2 = 99\%$	0.002 0.1 1 10 500 ID General population
33 34	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)	; I <sup>2</sup> = 99%	0.002 0.1 1 10 500 ID General population
33 34 35 36	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)	r; I <sup>2</sup> = 99%	0.002 0.1 1 10 500 ID General population
33 34 35 36 37	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)	r; I <sup>2</sup> = 99%	0.002 0.1 1 10 500 ID General population
33 34 35 36	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
33 34 35 36 37 38 39 40	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> </ul>	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> </ul>	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		0.002 0.1 1 10 500 ID General population
<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> </ul>	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> </ul>	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
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<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> </ul>	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> </ul>	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> <li>52</li> </ul>	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
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<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> <li>52</li> <li>53</li> <li>54</li> <li>55</li> </ul>	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> <li>52</li> <li>53</li> <li>54</li> </ul>	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> <li>52</li> <li>53</li> <li>54</li> <li>55</li> <li>56</li> <li>57</li> <li>58</li> </ul>	Heterogeneity: $Tau^2 = 2.50$ ;	Chi <sup>2</sup> = 433.15, df = 14 (P < 0.0001)	3 (P <	0.00001)		ID General population
<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> <li>52</li> <li>53</li> <li>54</li> <li>55</li> <li>56</li> <li>57</li> </ul>	Heterogeneity: Tau <sup>2</sup> = 2.50; Test for overall effect: Z = 4.	14 (P < 0.0001)				ID General population

	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
Thuc	manual acupuncture or electroacupuncture.
Abstract	
	2 <sup>†</sup> Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and
Structured summary	interventions; study appraisal and synthesis methods; results limitations; conclusions and implications of key findings; systematic review
	registration number.
Introduction	
	3* Describe the rationale for what is already known about acupuncture for the target condition in the background; if applicable, state what
Rationale	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 <sup>†</sup> Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and
•	study design (PICOS)
Methods	
Protocol and registration	5 <sup>†</sup> Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and, if available, provide registration information
i rotocor and registration	including registration number.
	6 <sup>†</sup> Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication
Eligibility criteria	status) used as criteria for eligibility, giving rationale.
	$6a.1^{\ddagger}$ Describe the diagnostic criteria of the target condition in Western medicine.
	6a.2 <sup>‡</sup> If applicable, describe the diagnostic criteria in terms of Traditional Medicine, such as Traditional Chinese Medicine.
	6b <sup>‡</sup> Describe the types of acupuncture to be included, such as traditional acupuncture, electroacupuncture, or fire acupuncture.
	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

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

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2020-043658.R1
Article Type:	Original research
Date Submitted by the Author:	08-Feb-2021
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<b>Primary Subject Heading</b> :	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"

Authors

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Keywords: Respiratory disease, mortality, intellectual disability, systematic review, metaanalysis

Wordcount: 3850

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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 respiratoryassociated 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

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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 1<sup>st</sup> January 1985 to the 27<sup>th</sup> 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  $\kappa = .57$  and  $\kappa = .58$ , 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

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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]

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Author Author A A A A A A A A A A A A A A A A A A A	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)
<sup>1</sup> Brameld et 2 <sub>al</sub> (2018) <sup>26</sup> 3 4 5 6	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)
17Cooper et al 18(2020) <sup>28</sup> 19 20 21 22 23	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)
4Dupont et al. 5(1987) <sup>40</sup> 6 7	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)
9Durvasula et 9Durvasula et 0al (2002) <sup>37</sup> 1 2 3 4 5 6 7 Forsgren et 7 al (1996) <sup>15</sup> 8 9 0	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)
<sup>6</sup> Forsgren et 7al (1996) <sup>15</sup> 8	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)

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		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) <sup>8</sup>	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; $44 \cdot 1\%$ 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) <sup>5</sup>	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)
$(1998)^{11}$	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) <sup>24</sup>	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 $\cdot$ 1% female; mean age not available. Number of deaths= 1358 (1 $\cdot$ 2%); 60 $\cdot$ 4% female; mean age not available	ICD 10- chapter codes for respiratory disorders.	90·91% (strong)
Janicki et al (1999) <sup>22</sup>	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)
7Ng et al 3(2017) <sup>12</sup> 9	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; $45 \cdot 5\%$ females; mean age not available. Number of deaths= 8364	ICD 10- chapter codes for respiratory disorders.	95·45% (strong)

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2 3 4 5 6		over. Follow up 2002-2015	National disability register. Swedish National Cause of Death register					
<ul> <li>7 Oppewal et</li> <li>8 al (2018)<sup>27</sup></li> <li>9</li> <li>10</li> <li>11</li> <li>12</li> <li>13</li> <li>14</li> <li>15</li> <li>16</li> </ul>	Netherla nds	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)
17 <sup>P</sup> atja et al 18 <sup>(2001)<sup>14</sup></sup> 19 20 21	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)
22 23Raitasuo et 24al (1997) <sup>13</sup> 25 26 27 28 29 30	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)
3 <sup>1</sup> Smith et al 32(2020) <sup>10</sup> 33 34 35 36	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= $16 \cdot 1$ years (95% CI $15 \cdot 8$ to $16 \cdot 5$ )	ICD 10- chapter codes for respiratory disorders.	100% (strong)
37Trollor et al 38(2017) <sup>25</sup> 39 40	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)

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2 3 4 5 6		registered with disability services. Follow up 2005-2011	of Statistics. Death records			female; median age= 81 (70–92).		
<ul> <li>7 Tyrer and</li> <li>8 McGrother</li> <li>9 (2009)<sup>23</sup></li> <li>10</li> <li>11</li> <li>12</li> <li>13</li> </ul>	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)
14 15 *Ir	ndividuals in	the ID cohort died at	a significantly young	er age than the comparison co	hort			
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# 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.

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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) <sup>26</sup>	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	294/961	Underlying	Underlying cause of death:	All-contributing factors in	Underlying cause of death:	Not available
$(2020)^{28}$	(30.6%)	cause of death:	Down syndrome: 8/ 57	death:	Down syndrome:	
	deaths	57/262 (21.8%)	(14.0%) deaths		Aspiration/ reflux/ choking =	
	$\mathbf{SMR} = 2 \cdot 24$	deaths	Without Down syndrome:	Respiratory infection =	<5/ 57 deaths	
	(95% CI;	SMR = 6.78	49/205 (23·9%) deaths	$27 \cdot 1\%$ deaths	Respiratory infection = $<5/57$	
	1.98, 2.49)	(95% CI; 5·02,		Aspiration/ reflux/ choking	deaths	
<b>^</b>		8.54)		= 19.8% deaths	Other respiratory conditions = $<5/57$ deaths	
) 1		(adjusted for				
ן ר		age and sex)			Without Down syndrome:	
2		uge und sex)			White Down Synatome.	
4				= 19.8% deaths	Aspiration/ reflux/ choking =	
5					22/205 (10.8%) deaths	
6					Respiratory infection = $21/205$	
7					(10.3%) deaths	
8					Other respiratory conditions =	
9					9/ 205 (4·4%) deaths	
0					All contributing factors in	
1					All-contributing factors in death:	
2					death.	
3					Down syndrome:	
4					Respiratory infection = $22/57$	
5					(38.6%) deaths	
6					Aspiration/ reflux/ choking =	
7					11/57 (19.3%) deaths	
8					Other respiratory conditions =	
9					<5/ 57 deaths	
0						
0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 8 9 0 1 2 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 8 9 0 1 1 8 9 0 1 1 8 9 0 1 1 8 9 0 1 1 8 9 0 1 1 8 9 0 1 1 8 9 0 1 1 8 9 0 1 1 8 9 0 1 1 8 9 0 1 1 8 9 0 1 1 2 8 9 0 1 1 8 9 0 1 1 2 8 8 9 0 1 1 2 8 8 9 0 1 1 2 8 8 9 0 1 1 2 8 8 9 0 1 1 2 8 8 9 0 1 1 2 8 8 9 0 1 1 2 8 8 9 0 1 1 2 8 8 9 0 1 1 8 9 0 1 1 2 8 8 9 0 1 1 2 8 8 9 0 1 1 2 8 8 9 0 1 1 8 8 9 0 1 1 2 8 8 9 0 1 1 2 8 8 9 0 1 1 8 9 0 1 1 8 8 9 0 1 1 8 8 9 0 1 1 8 8 9 0 1 1 8 9 9 0 1 1 8 9 9 0 1 1 8 9 9 0 1 1 8 9 9 0 1 1 8 9 9 0 1 1 8 9 9 1 8 9 9 0 1 8 9 9 1 8 8 9 9 0 1 1 8 8 8 8 8 9 9 1 8 8 8 8 9 1 8 8 9 9 1 8 8 8 8					Without Down syndrome:	
2					Respiratory infection = $49/205$	
3					(23.9%) deaths	
4 r					Aspiration/ reflux/ choking =	
5 6					41/205 (20.2%) deaths	
0 7					Other respiratory conditions =	
/ 0					31/205 (15.1%) deaths	

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2 3 Dupont et al 4 (1987) <sup>40</sup> 5 6 7 8 9 10 11 12 13 14 15 16 17 18	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
18 19 20 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34Forseren et	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
34Forsgren et 35al (1996) <sup>15</sup> 36 37 38 39 40	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)
40 41 42 43 44	·	· · /	For peer review or	14 hly - http://bmjopen.bmj.com/s	; ite/about/guidelines.xhtml	·

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	SMR 2.0	SMR 3·3 (95%		people with both epilepsy		
	(95% CI	CI 2.0, 5.5)		and ID		
	1.7, 2.3					
	Males 1.6	(adjusted for				
	(95% CI 1·2,	age and sex)				
	2.0),					
	Females 2.6					
	(95% CI 2·0,					
	3.3)					
	Additional:					
	SMRs for					
	severity of					
	ID, epilepsy					
	and cerebral		Forp			
	palsy are					
	available in					
	appendix					
lover et al	N=664	N=114 deaths	Not available	N=57 / 114 (50%) of	Not available	Not available
$(017)^8$	deaths for	from respiratory		respiratory deaths (and 8.6%		
	people with	causes for		of all deaths) were from		
	ID (all ages)	people with ID		influenza and pneumonia, vs		
	over	vs 23·3		expected 7.4 deaths	<b>&gt;</b> ,	
	59,279.7	expected SMR 4·9 (4·0,		SMR 7.7 (5.8, 9.9) Vast majority of pneumonia		
	person-years Crude rate	5·9)		were unspecified (organism)		
	11.2 (10.4)	5.9)		n=24 / 114 (21%) respiratory		
	$112(104, 12\cdot1)$ per	(adjusted for		deaths $(3.6\% \text{ of all deaths})$		
	1000 person-	age and sex)		were due to pneumonitis due		
	years	"Go und Son)		to solids / liquids vs	en onz	
	SMR 3.18			expected 1.1 deaths		
	(2.94, 3.43)			SMR 21.8 (13.9, 32.4)		
	Women					
	3.40 (3.02,			N=12 ( $1.8\%$ ) of all deaths		
	3.81)			were due to respiratory and		
	Men 3.03			intrathoracic cancers vs		
olover et al 2017) <sup>8</sup>	(2.73, 3.35)			expected 16.6 deaths		
				SMR 0.7, 95% CI 0.4–1.3).		

Heslop et al	N= 247	n=37 (15%)	Not available	Not available	Not available	Reduced smoking in ID group
$(2014)^6$	deaths in	deaths had				p=0.02
	people with ID aged 4+	underlying cause due to				
	Rate of	respiratory				
	death 16.2	diseases,				
	per 1000	vs 14.0%				
0	person years					
1	Median age	Wales deaths				
	of death: 64	(p=0.66)				
2	(52, 75).	<b>u</b> ,				
2 3 4 5 6 7	Additional;					
5	all-cause					
5	mortality for					
7	sex, ID					
	severity,			$\sim 0$		
9	amenable					
0	mortality,					
1	patient care,					
2	& accommodat					
8 9 0 1 2 3 4	ion available					
4	in appendix					
<b>F</b>	270/2,026	Not available	Not available	Bronchopneumonia: N=56	Not available	Not available
6(1998) <sup>11</sup>	(13.3%)			(48%) (Wandsworth)		
7	deaths			N=69 (45%) (Kensingston)		
8	116/1,081			COPD Emphysema:		
9	(10.7%)			N=1 (Wandsworth)		
0	deaths on			N=1 (Kensingston)	07/	
1	Wandsworth			Asphyxia:		
2	register			N=4 (Wandsworth)		
3	154/945			N=1 (Kensingston)		
1	(16.3%)			Respiratory other:		
5	deaths on			N=4 (Wandsworth)		
б	Kensington			N=4 (Kensingston)		
<sup>5</sup> Hollins et al 6(1998) <sup>11</sup> 7 8 9 0 1 2 3 4 5 5 6 7 8 9 9	register					
8				52% of all deaths had a diagnosis of pneumonia		

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Hosking et al $(2016)^{24}$ (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
12	(adjusted for age, sex and general practice)	<b>K</b>			
4Janicki et al       2,752 deaths         15(1999) <sup>22</sup> in the group         aged       40+/4,183         17       40+/4,183         18       all-age         19       deaths         20       (66%)         21       22         23       24         25       26         27       28         29       30         31       32         33       34         35       36         37       38         39       40	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

3 4 5			of death for females across ages.			
6 Ng et al. 7 (2017) <sup>12</sup> 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24	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
25 <sub>Oppewal et</sub> 26 <sub>al (2018)<sup>27</sup></sub> 27 28 29 30 31 32 33 34 35 36 37 38 39 40	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

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2 3 4		cause of DS				
5 6 7 8 9 10 11 12 13 14 15 16 17 18		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.	Forp			
	111/2369 D =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= $5\cdot8$ ( $4\cdot4 - 15\cdot6$ ); age 20-39 SMR= $5\cdot4$ ( $2\cdot9 - 8\cdot0$ ); age 40-59 SMR= $5\cdot5$ ( $3\cdot5-7\cdot5$ ); age 60+ SMR= $2\cdot7$ ( $2\cdot7 - 4\cdot8$ ) Female: age 2-19 SMR= $4\cdot3$ ( $0\cdot3 - 4\cdot7$ ); age 20-39 SMR= $3\cdot2$ ( $1\cdot1 - 5\cdot1$ ); age 40-59 SMR= $6\cdot2$ ( $4\cdot1 - 8\cdot2$ ); age 60+ SMR= $3\cdot3$ ( $1\cdot7 - 3\cdot0$ )	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)
37Raitauso et 38al (1997) <sup>13</sup> 39 40	16 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)

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 <sup>Smith</sup> et al 19 <sup><math>(2020)^{10}</math></sup> 20 21	N = 106 (0.6%) deaths SMR = 11.6 (95% CI;	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) Underlying cause of death: N = 8/ 106 (8%) deaths All-contributing	Underlying cause of death: General population: 17/ 458 (4%) deaths All-contributing factors in 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. Underlying cause of death: Pneumonia including influenza; <5/ 106 All-contributing factors in death:	General populations: All-contributing factors in death: Pneumonia = 21/ 458 (4.6%) deaths	Not available
20 21 22 23 24 25 26 27 28 29 30 31 32Trollor et al 33(2017) <sup>25</sup> 34 35	732 / 19362 ID=4% SMR=1·3 (1·2 to 1·5)	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) 632/732 ID= $86.3\%$ had cause of death information	General population: n = 51. CMR = 1·4 (95% CI; 1·1, 1·8) deaths	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 Not available	Not available	Not available
34 35 36 37 38 39 40 41		78 ID=12% 4 <sup>th</sup> top cause using the ID ABI conversion		20		



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		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				
yrer &	503/2995	SMR=5·46	Not available	Bronchopneumonia;	Male; SMR=2.28 (95% CI;	Gender
IcGrother	(17%)	(95% CI 4·58,		SMR=6·47 (95% CI 5·00	2·02-2·56) O=278, E=121·8.	
$(2009)^{23}$	deaths	6.46)		8·23), O=66, E=10·2.	Female; SMR=3·24 (95% CI;	
	SMR=2.77	(adjusted for		Other respiratory; SMR=	2·83-3·69). O=225, E=69·4.	
	(95% CI	age and sex)		4.64 (CI 3.58 to 5.91).		
	2.53, 3.03).			O=65, E=14·0.		<u> </u>

 \*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 parative

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<sup>31</sup> 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<sup>2</sup>=99% to I<sup>2</sup>= 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 pneumoniarelated deaths occurring among individuals with severe and profound intellectual disabilities. [5,22,35,37,38] Increased recognition of the link between dysphagia and respiratory

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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 the react of people with intellectual disabilities and 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 metaanalysis 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

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study quality and extract descriptive data. Due to the low prevalence ( $\sim 1\%$ ) 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 metaanalysis 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.

**Funding** This work was supported by The Scottish Government grant number (HSCD 169698)

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<sup>2</sup>= 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<sup>2</sup>=99% to I<sup>2</sup>= 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<sup>2</sup>= 99.0%.

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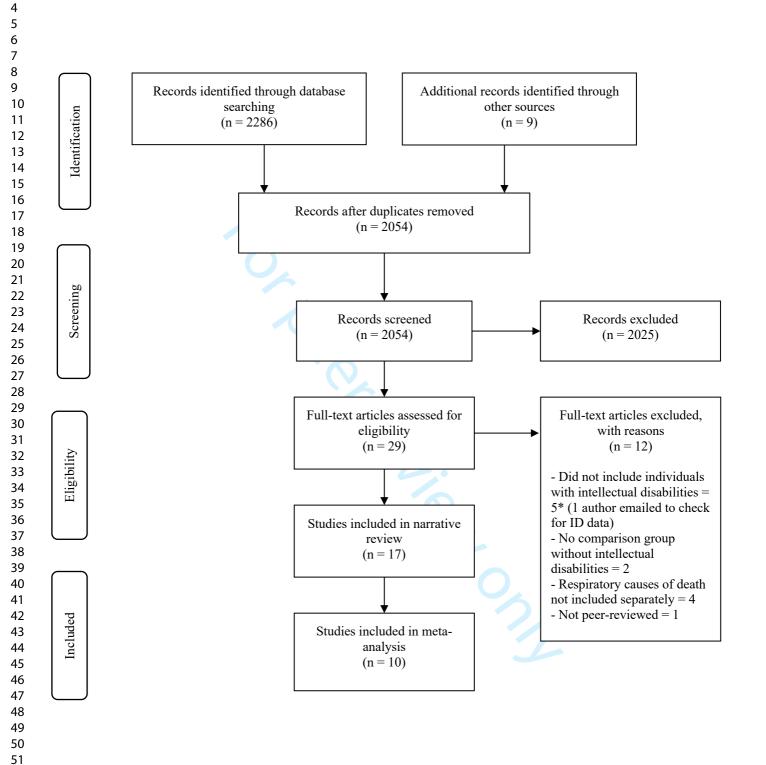
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# Figure 2: Forest plot of respiratory associated mortality

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7	Study or Subgroup	lag[Odds Batia]	CE Waight	Odds Ratio	Odds Ratio	
8	Study or Subgroup Raitauso et al (1997) 27	log[Odds Ratio] 0.77 0.1	SE Weight 29 8.7%	IV, Random, 95% Cl 2.16 [1.22, 3.81]	IV, Random, 95% CI	
9	Forsgren et al (1996) 29	1.19 0.		3.29 [1.97, 5.47]		
	Patja et al (2001) 28	1.32 0.	06 9.2%	3.74 [3.33, 4.21]	+	
10	Glover et al (2017) 18	1.59 0		4.90 [4.03, 5.97]	-	
11	Tyrer & McGrother (2009) 40 Hosking et al (2016) 10	1.7 0.4 1.9 0.1		5.47 [4.59, 6.53]	-	
12	Cooper et al (2020) 42	1.91 0.1		6.69 [5.39, 8.29] 6.75 [5.13, 8.89]	-	
13	Ng et al (2017) 26	2.53 0.		12.55 [10.94, 14.40]	+	
14	Smith et al (2020) 22	4.01 0.1		55.15 [42.74, 71.15]	-	-
15	Hollins1 et al (1998) <sup>25</sup>	4.31 0.1		74.44 [56.58, 97.94]		-
16	Hollins2 et al (1998) <sup>25</sup>	4.91 0.1	12 9.1%	135.64 [107.21, 171.61]		-
17	Total (95% CI)		100.0%	10.86 [5.32, 22.18]	•	
18	Heterogeneity: Tau <sup>2</sup> = 1.44; Ch		LO (P < 0.000	)01); i <sup>2</sup> = 99%	0.005 0.1 1 10	200
	Test for overall effect: Z = 6.54	(P < 0.00001)			General population ID	200
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# Figure 3: Forest plot for adults only

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6					Odds Ratio		s Ratio	
7	Study or Subgroup Forsgren et al (1996) <sup>29</sup>	log[Odds Ratio] 1.19		Weight 16.6X		IV, Rand	om, 95% Cl	
8	Tyrer & McGrother (2009) <sup>40</sup>		0.09	21.1%				
9	Hosking et al (2016) <sup>10</sup>	1.9	0.11	20.7%	6.69 [5.39, 8.29]		+	
10	Cooper et al (2020) 42		0.14	20.1%	6.75 [5.13, 8.89]		-	
11	Ng et al (2017) 26	2.53	0.07	21.4%	12.55 [10.94, 14.40]			
12	Total (95% CI)			100.0%	6.53 [4.29, 9.96]		•	
13	Heterogeneity: Tau <sup>2</sup> = 0.21; (		(P < (	0.00001	); i² = 95%	0.005 0.1	1 10	200
14	Test for overall effect: $Z = 8.7$	'3 (P < 0.00001)				General population		
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## Figure 4: Forest plot for pneumonia related mortality

Tyrer & McGrother (2009) 40       1.87       0.13       25.0%       6.49 [5.03, 8.37]       +         Sover et al (2017) 35       2.04       0.14       25.0%       7.69 [5.85, 10.12]       +         Solutions 1 et al (1998) 25       4.31       0.14       25.0%       74.44 [56.58, 97.94]       +         Solutions 2 et al (1998) 25       4.91       0.12       25.0%       135.64 [107.21, 171.61]       +         Fotal (95% Cl)       100.0%       26.65 [5.63, 126.24]       -       +	Study or Subgroup	log[Odds Ratio] SE	Odds Ratio Weight IV, Random, 95%	Odds R % CL IV. Random	
leterogenetiv: Tau <sup>2</sup> = 2.50; Ch <sup>2</sup> = 433.15, df = 3 (P < 0.00001); P = 99% est for overall effect: Z = 4.14 (P < 0.0001)	Tyrer & McCrother (2009) <sup>40</sup> Glover et al (2017) <sup>36</sup> Hollins1 et al (1998) <sup>25</sup> Hollins2 et al (1998) <sup>25</sup>	1.87 0.13 2.04 0.14 4.31 0.14	25.0%         6.49 [5.03, 8.           25.0%         7.69 [5.85, 10.           25.0%         74.44 [56.56, 97.	.37] .12] .94]	+ +
	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 2.50; ( Test for overall effect: Z = 4.1	Cht² = 433.15, df = 3 (P <		0.002 0.1 1	10 500 D

# **Appendix 1: Search strategy**

# Embase- Ovid, 2016-

Sear	rch 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\$) 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/ OI						
	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 obstructive						
	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						
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Sear	ch 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 difficIlt*))
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 disease\* or respiratory infect\* or obstructive lung disease\* or obstructive pulmonary disease\* or aspiration pneumoni\* or bronchiecstasi

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

# Appendix 2: Excluded papers – References and reasons for exclusion

3 4	11	Stankiewicz E, Ouellette-Kuntz H, McIsaac M, Shooshtari S, Balogh R.	<70%* of participants had
5 6		Patterns of mortality among adults with intellectual and developmental	intellectual disabilities.
7		disabilities in Ontario. Can J Public Health 2018; 109(5-6): 866-872	*We emailed this author to
8 9			check if >70% of sample had ID
10			– they replied but didn't have
11 12			the data to check, so it was
13			excluded.
14 15	12	Tyrer F, Smith LK, McGrother CW. Mortality in adults with moderate to	Respiratory causes of death not
16		profound intellectual disability: a population-based study. J Intellect	included separately.
17 18		Disabil Res, 2007; 51(7): 520-527.	
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 9 40 41 42 43 44 5 46 47 48 49		Disabil Res, 2007; 51(7): 520-527.	

Odds Ratio

Odds Ratio

# Appendix 3: Sensitivity analysis A and B

Sensitivity A- minus Raitasuo

			Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE Weight	IV, Random, 95% CI	IV, Random, 95% CI
Forsgren et al (1996) 29	1.19 0		3.29 [1.97, 5.47]	
Patja et al (2001) 28	1.32 0		3.74 [3.33, 4.21]	•
Glover et al (2017) 18	1.59	0.1 10.1%	4.90 [4.03, 5.97]	-
Tyrer & McGrother (2009) 40	1.7 0	.09 10.1%	5.47 [4.59, 6.53]	-
Hosking et al (2016) 10	1.9 0		6.69 [5.39, 8.29]	-
Cooper et al (2020) 42	1.91 0		6.75 [5.13, 8.89]	-
Ng et al (2017) 25	2.53 0		12.55 [10.94, 14.40]	-
Smith et al (2020) 22	4.01 0		55.15 [42.74, 71.15]	+
Hollins1 et al (1998) 25	4.31 0		74.44 [56.58, 97.94]	+
Hollins2 et al (1998) 25	4.91 0		135.64 [107.21, 171.61]	
Total (95% CI)		100.0%	12.67 [6.01, 26.73]	•
Heterogeneity: Tau <sup>2</sup> = 1.43; (		9 (P < 0.0000)	)1);	0.005 0.1 1 10 2
Test for overall effect: $Z = 6.6$	i7 (P < 0.00001)			ID General population

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3	Sensitivity B- minus Raitasuo and Tyrer
4	Odds Ratio Odds Ratio
5	Study or Subgroup         log[Odds Ratio]         SE         Weight         IV, Random, 95% CI         IV, Random, 95% CI           Forsgren et al (1996)         29         1.19         0.26         10.8%         3.29         [1.97, 5.47]
6	Patja et al (2001) <sup>28</sup> 1.32 0.06 11.2% 3.74 [3.33, 4.21] -
7	Glover et al (2017)         1.59         0.1         11.2%         4.90         [4.03, 5.97]         +           Hosking et al (2016)         10         1.9         0.11         11.2%         6.69         [5.39, 8.29]         +
8	Hosking et al (2016) <sup>10</sup> 1.9 0.11 11.2% 6.69 [5.39, 8.29] + Cooper et al (2020) <sup>42</sup> 1.91 0.14 11.1% 6.75 [5.13, 8.69] +
9	Ng et al (2017) 26 2.53 0.07 11.2% 12.55 [10.94, 14.40]
10	Smith et al (2020)       4.01       0.13       11.1%       55.15       [42.74, 71.15]          Hollins1 et al (1998)       4.31       0.14       11.1%       74.44       [56.58, 97.94]
11	Hollins2 et al (1998) 25 4.91 0.12 11.1% 135.64 [107.21, 171.61]
12	Total (95% CI) 100.0% 13.92 [6.02, 32.15]
13	Heterogeneity: Tau <sup>2</sup> = 1.62; Ch <sup>2</sup> = 1219.00, df = 8 ( $P < 0.00001$ ); i <sup>2</sup> = 99%
14	Test for overall effect: Z = 6.16 (P < 0.00001) 0.005 0.1 1 10 200 ID General population
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# 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). For peer review only - http://bmjbpen.bmj.com/site/about/guidelines.xhtml	11

4 47 Page 47 of 47



2

# 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 <sup>2</sup> ) for each meta-analysis.	11
		Page 1 of 2	1
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	<u> </u>	·	
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
5		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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# PRISMA 2009 Checklist

.ed Reportin, Bege 2 of 2 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

Journal:	BMJ Open
Manuscript ID	bmjopen-2020-043658.R2
Article Type:	Original research
Date Submitted by the Author:	26-Apr-2021
Complete List of Authors:	Truesdale, Maria; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Melville, Craig; University of Glasgow, Institute of Health and Wellbeing Barlow, Fiona; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Dunn, Kirsty; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Henderson, Angela; University of Glasgow, Institute of Health and Wellbeing Hughes-McCormack, Laura; University of Glasgow, Institute of Health and Wellbeing McGarty, Arlene; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Rydzewska, Ewelina; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Rydzewska, Ewelina; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Rydzewska, Ewelina; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Symonds, Joseph; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Jani, Bhautesh; University of Glasgow College of Medical Veterinary and Life Sciences, Mental Health and Wellbeing Jani, Bhautesh; University of Glasgow College of Medical Veterinary and Life Sciences Kinnear, Deborah; University of Glasgow, Institute of Health and Wellbeing
<b>Primary Subject Heading</b> :	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, metaanalysis

Wordcount: 3893

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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 respiratoryassociated 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 metaanalysis aims to investigate and quantify the risk of, and factors associated with, respiratoryassociated 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

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disabilities, if results were not reported separately. Studies also had to be full-text, peerreviewed, 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 1<sup>st</sup> January 1985 to the 27<sup>th</sup> 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  $\kappa = .57$  and  $\kappa = .58$ , 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

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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]

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Author 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)
11 <mark>Brameld et</mark> 12al (2018) <sup>26</sup> 13 14 15 16	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)
17Cooper et al 18(2020) <sup>28</sup> 19 20 21 22 23	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)
24Dupont et al. 25(1987) <sup>40</sup> 26 27 28	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)
2 2 2 2 3 4 5 5 6 7 6 7 1 2 3 4 5 5 6 7 8 7 1 1 2 3 4 5 5 5 7 8 9 10 10 10 10 10 10 10 10 10 10	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)
<sup>6</sup> Forsgren et <sup>7</sup> al (1996) <sup>15</sup> 8 9	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)

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		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) <sup>8</sup> 0 1 2	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; $44 \cdot 1\%$ 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)
3Heslop et al 4(2014) <sup>5</sup> 5 6 7 8 9	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)
0 Hollins et al 2 <sup>(1998)<sup>11</sup> 3</sup>	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)
4 Hosking et 5al (2016) <sup>24</sup> 6 7 8 9	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)
<sup>D</sup> Janicki et al 1(1999) <sup>22</sup> 2 3 4 5 5	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)
7Ng et al 8(2017) <sup>12</sup> 9 0	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; $45 \cdot 5\%$ females; mean age not available. Number of deaths= 8364	ICD 10- chapter codes for respiratory disorders.	95·45% (strong)

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2 3 4 5 6		over. Follow up 2002-2015	National disability register. Swedish National Cause of Death register					
<ul> <li>7 Oppewal et</li> <li>8 al (2018)<sup>27</sup></li> <li>9</li> <li>10</li> <li>11</li> <li>12</li> <li>13</li> <li>14</li> <li>15</li> <li>16</li> </ul>	Netherla nds	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)
17 <sup>P</sup> atja et al 17 <sup>P</sup> atja et al 18 <sup>(2001)<sup>14</sup> 19 20 21 22</sup>	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)
19 20 21 22 2 <sup>3</sup> Raitasuo et 24 <sub>al</sub> (1997) <sup>13</sup> 25 26 27 28 29 30	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)
3 <sup>1</sup> Smith et al 32(2020) <sup>10</sup> 33 34 35 36	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= $16 \cdot 1$ years (95% CI $15 \cdot 8$ to $16 \cdot 5$ )	ICD 10- chapter codes for respiratory disorders.	100% (strong)
37Trollor et al 38(2017) <sup>25</sup> 39 40	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)

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1									
2 3 4 5 6			registered with disability services. Follow up 2005-2011	of Statistics. Death records			female; median age= 81 (70–92).		
9 1 1 1	Tyrer and McGrother (2009) <sup>23</sup> 0 1 2 3	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)
1 1		dividuals in	the ID cohort died at	a significantly young	er age than the comparison co	hort			
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## 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.

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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) <sup>26</sup>	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.

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Cooper et al	294/961	Underlying	Underlying cause of death:	All-contributing factors in	Underlying cause of death:	Not available
$(2020)^{28}$	(30.6%)	cause of death:	Down syndrome: 8/ 57	death:	Down syndrome:	
	deaths	57/262 (21.8%)	(14.0%) deaths		Aspiration/ reflux/ choking =	
	$SMR = 2 \cdot 24$	deaths	Without Down syndrome:	Respiratory infection =	<5/ 57 deaths	
	(95% CI;	SMR = 6.78	49/205 (23·9%) deaths	27.1% deaths	Respiratory infection = $<5/57$	
	1.98, 2.49)	(95% CI; 5·02,		Aspiration/ reflux/ choking	deaths	
		8.54)		= 19.8% deaths	Other respiratory conditions = $<5/57$ deaths	
0		(adjusted for			<5/ 5/ deaths	
1		age and sex)			Without Down syndrome:	
2		age and sex)			without Down syndrome.	
				= 19.8% deaths	Aspiration/ reflux/ choking =	
-+ 5					22/205 (10.8%) deaths	
5					Respiratory infection = $21/205$	
7					(10.3%) deaths	
, 8					Other respiratory conditions =	
9					9/ 205 (4·4%) deaths	
0						
21					All-contributing factors in death:	
2					death:	
3					Down syndrome:	
4					Respiratory infection = $22/57$	
5					(38.6%) deaths	
6					Aspiration/ reflux/ choking =	
7					11/ 57 (19·3%) deaths	
8					Other respiratory conditions =	
9					<5/ 57 deaths	
0						
0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 2 3 4 5 6 7 8 9 0 1 2 2 3 4 5 6 7 8 9 0 1 2 2 3 4 5 6 7 8 9 0 1 2 2 3 4 5 6 7 8 9 0 1 2 2 3 4 5 6 7 8 9 0 1 2 2 3 4 5 6 7 8 9 0 1 2 2 3 4 5 6 6 7 8 9 0 0 1 2 2 3 4 5 6 6 7 8 9 0 0 1 2 2 3 4 5 5 6 6 7 7 8 9 0 0 1 5 6 7 7 8 9 0 0 1 5 7 8 9 0 0 1 5 7 8 8 9 0 0 1 5 7 8 8 9 5 6 7 7 8 8 9 5 6 6 7 7 8 8 9 5 6 7 7 8 8 9 5 6 7 7 8 8 9 8 7 8 8 8 7 8 8 8 8 8 8 8 8 8 8 8 8 8					Without Down syndrome:	
2						
3					Respiratory infection = $49/205$	
4					(23.9%) deaths Aspiration/ reflux/ choking =	
5					Aspiration/reflux/choking = $41/205 (20.2\%)$ deaths	
6					Other respiratory conditions =	
/					$31/205 (15 \cdot 1\%)$ deaths	

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2 3 Dupont et al	N=446	Respiratory	Not available	Not available	Not available	Not available
<b>4</b> (1987) <sup>40</sup>	deaths / 7134 (5·9%)	deaths common cause of death				
	people with	in people with				
	mild ID	ID (all ages)				
	N=277	Tests of				
D	males	significance				
	N=169	only; respiratory				
1	females	deaths were more common				
2		for males with				
5 1		ID (all ages),	U L			
+ 5		and females	6			
6		aged 35-64,				
2 3 4 5 6 7		versus		2		
0		population of Denmark 1977				
2 Durvasula 1(2002) <sup>29</sup> 2 3 4 5 5 7 8 9 0 1 2 3 4 4 5 5 5 7 8 9 0 1 2 3 4 4 5 5 5 7 8 9 0 1 2 3 4 4 5 5 5 5 5 5 5 5 7 8 9 0 1 2 3 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5	40/693 (6%)	14/40 (35%)	For people under 40,	Not available	Not available	Age, gender, Down syndrome,
$(2002)^{29}$	deaths	deaths	respiratory and external		Not available	myelodysplastic syndrome
ן ````````````````````````````````````			deaths were most common,			
2 3			for people over 40, cancer			
4			and respiratory deaths were most common	· · · · · · · · · · · · · · · · · · ·	$\mathbf{>}$	
5			Age: 7/14 deaths in under		· M.	
6			25-year-olds and 6/14			
7			deaths in 40+ year olds			
8			Sex: 11/14 deaths in males			
9			Conditions: 2/14 had			
)			Down syndrome &			
ן כ			dementia, 1/14 had myelodysplastic syndrome,			
2 3			1x Battens disease			
	N=124 /	N=13 /124	Respiratory disease was	Pneumonia was most	Not available	Epilepsy (active seizures)
5al (1996) <sup>15</sup>	1478 (8.4%)	(10%) deaths	common cause of death for	common cause of death, but		
5	people with	were respiratory	people with ID and	rarely reported as underlying		
6 7	ID (all ages),	disease for	epilepsy but SMR was not	cause		
8 9	over 9,992	people with ID vs n=3.9	possible due to small sample size	Pneumonia was most		
	person-years	expected,	sample size	common cause of death in		
0 1	1		1		1	
2				14		
3			Fermentin	h. http://heatenanicharia.com/		
			For peer review or	nly - http://bmjopen.bmj.com/s	site/about/guidelines.xhtml	

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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	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	SMR 3·3 (95% CI 2·0, 5·5) (adjusted for age and sex)		people with both epilepsy and ID		
	severity of ID, epilepsy and cerebral palsy are available in appendix N=664 deaths for people with ID (all ages) over 59,279.7 person-years Crude rate	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)	Not available	Not available
19 Glover et al 20(2017) <sup>8</sup> 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38	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)	(adjusted for age and sex)		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).	en onj	

Heslop et al	N= 247	n=37 (15%)	Not available	Not available	Not available	Reduced smoking in ID group
$(2014)^6$	deaths in	deaths had				p=0.02
	people with ID aged 4+	underlying cause due to				
	Rate of	respiratory				
	death 16.2	diseases,				
	per 1000	vs 14.0%				
0	person years					
1	Median age	Wales deaths				
	of death: 64	(p=0.66)				
2	(52, 75).	<b>u</b> ,				
2 3 4 5 6 7	Additional;					
5	all-cause					
5	mortality for					
7	sex, ID					
	severity,			$\sim 0$		
9	amenable					
0	mortality,					
1	patient care,					
2	& accommodat					
8 9 0 1 2 3 4	ion available					
4	in appendix					
<b>F</b>	270/2,026	Not available	Not available	Bronchopneumonia: N=56	Not available	Not available
6(1998) <sup>11</sup>	(13.3%)			(48%) (Wandsworth)		
7	deaths			N=69 (45%) (Kensingston)		
8	116/1,081			COPD Emphysema:		
9	(10.7%)			N=1 (Wandsworth)		
0	deaths on			N=1 (Kensingston)	07/	
1	Wandsworth			Asphyxia:		
2	register			N=4 (Wandsworth)		
3	154/945			N=1 (Kensingston)		
1	(16.3%)			Respiratory other:		
5	deaths on			N=4 (Wandsworth)		
б	Kensington			N=4 (Kensingston)		
<sup>5</sup> Hollins et al 6(1998) <sup>11</sup> 7 8 9 0 1 2 3 4 5 5 6 7 8 9 9	register					
8				52% of all deaths had a diagnosis of pneumonia		

1 2						
<ul> <li><sup>3</sup> Hosking et</li> <li><sup>4</sup> al (2016)<sup>24</sup></li> <li><sup>5</sup></li> <li><sup>6</sup></li> <li><sup>7</sup></li> <li><sup>8</sup></li> <li><sup>9</sup></li> <li><sup>10</sup></li> <li><sup>11</sup></li> <li><sup>12</sup></li> <li><sup>13</sup></li> </ul>	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
14Janicki et al 15(1999) <sup>22</sup> 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40	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
41				17		

3 4 5			of death for females across ages.			
<ul> <li>Ng et al.</li> <li>(2017)<sup>12</sup></li> <li>(2017)<sup>12</sup></li> <li>9</li> <li>10</li> <li>11</li> <li>12</li> <li>13</li> <li>14</li> <li>15</li> <li>16</li> <li>17</li> <li>18</li> <li>19</li> <li>20</li> <li>21</li> <li>22</li> <li>23</li> <li>24</li> </ul>	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
25Oppewal et 26 <sub>al</sub> (2018) <sup>27</sup> 27 28 29 30 31 32 33 34 35 36 37 38 39 40	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

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$ \begin{array}{c} 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ 10 \\ 11 \\ 12 \\ 13 \\ 14 \\ 15 \\ 16 \\ 17 \\ 18 \\ Patja et al \\ 19 \\ Patja et al \\ 1111/23 \\ 10 = 46 \cdot 9 \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 31 \\ 32 \\ 33 \\ 34 \\ 35 \\ 36 \\ Patrix (1 - 1) \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 31 \\ 32 \\ 33 \\ 34 \\ 35 \\ 36 \\ Patrix (1 - 1) \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 31 \\ 32 \\ 33 \\ 34 \\ 35 \\ 36 \\ Patrix (1 - 1) \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 31 \\ 32 \\ 33 \\ 34 \\ 35 \\ 36 \\ Patrix (1 - 1) \\ 21 \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 31 \\ 32 \\ 33 \\ 34 \\ 35 \\ 36 \\ Patrix (1 - 1) \\ 21 \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 31 \\ 32 \\ 33 \\ 34 \\ 35 \\ 36 \\ Patrix (1 - 1) \\ 21 \\ 21 \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 31 \\ 32 \\ 33 \\ 34 \\ 35 \\ 36 \\ Patrix (1 - 1) \\ 21 \\ 21 \\ 21 \\ 21 \\ 21 \\ 21 \\ 21 \\ 21$	<ul> <li>% cause 322/1093 ID=29%;</li> <li>Primary cause 241/1095 ID=22%</li> <li>Respiratory diseases second largest cause of ID death</li> <li>SMR=3.76 (CI 3.31 to 4.27)*</li> <li>(adjusted for age and sex)</li> </ul>	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)
37Raitauso et 38al (1997) <sup>13</sup> 39 40	s 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)

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 <sup>Smith</sup> et al 19 <sup>(2020)<sup>10</sup></sup> 20 21	N = 106 (0.6%) deaths SMR = 11.6 (95% CI;	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) Underlying cause of death: N = 8/106 (8%) deaths All-contributing	Underlying cause of death: General population: 17/ 458 (4%) deaths All-contributing factors in 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. Underlying cause of death: Pneumonia including influenza; <5/ 106 All-contributing factors in death:	General populations: All-contributing factors in death: Pneumonia = 21/ 458 (4.6%) deaths	Not available
20 21 22 23 24 25 26 27 28 29 30 31 32Trollor et al 33(2017) <sup>25</sup> 34 35 36 37 38 39	732 / 19362 ID=4% SMR=1·3 (1·2 to 1·5)	factors in death: <b>n</b> = 55. CMR = <b>81</b> .7 (95% CI; <b>62</b> .7, 106.4) <b>deaths</b> SMR = 55.3 (95% CI; 42.5, 72.1) ( <b>adjusted for</b> <b>age and sex</b> ) <b>632/732</b> ID=86.3% had cause of death information	General population: n = 51. CMR = 1·4 (95% CI; 1·1, 1·8) deaths	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 Not available	Not available	Not available
37 38 39 40 41		78 ID=12% 4 <sup>th</sup> top cause using the ID ABI conversion		20		



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		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	1 6			
yrer &	503/2995	SMR=5·46	Not available	Bronchopneumonia;	Male; SMR=2·28 (95% CI;	Gender
AcGrother	(17%)	(95% CI 4·58,	Not available	SMR=6·47 (95% CI 5·00	2.02-2.56) O=278, E=121.8.	Gender
$(2009)^{23}$	deaths	6.46)		8·23), O=66, E=10·2.	Female; SMR=3.24 (95% CI;	
)	SMR=2.77	(adjusted for		Other respiratory; SMR=	2·83-3·69). O=225, E=69·4.	
	(95% CI	age and sex)		4.64 (CI 3.58 to 5.91).		
	2.53, 3.03).	- '		O=65, E=14·0.		

 \*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 parative .

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<sup>31</sup> 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.

## 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<sup>2</sup>= 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<sup>2</sup>=99% to I<sup>2</sup>= 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 pneumoniarelated deaths occurring among individuals with severe and profound intellectual

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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 are hot widened during this crisis.

Interventions should focus on the pediatric age group. Among the studies included in this metaanalysis 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,

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errors and omissions by having two or more reviewers conduct comprehensive searches, assess study quality and extract descriptive data. Due to the low prevalence ( $\sim 1\%$ ) 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 metaanalysis 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.

**Funding** This work was supported by The Scottish Government grant number (HSCD 169698)

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<sup>2</sup>= 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<sup>2</sup>=99% to I<sup>2</sup>= 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<sup>2</sup>= 99.0%.

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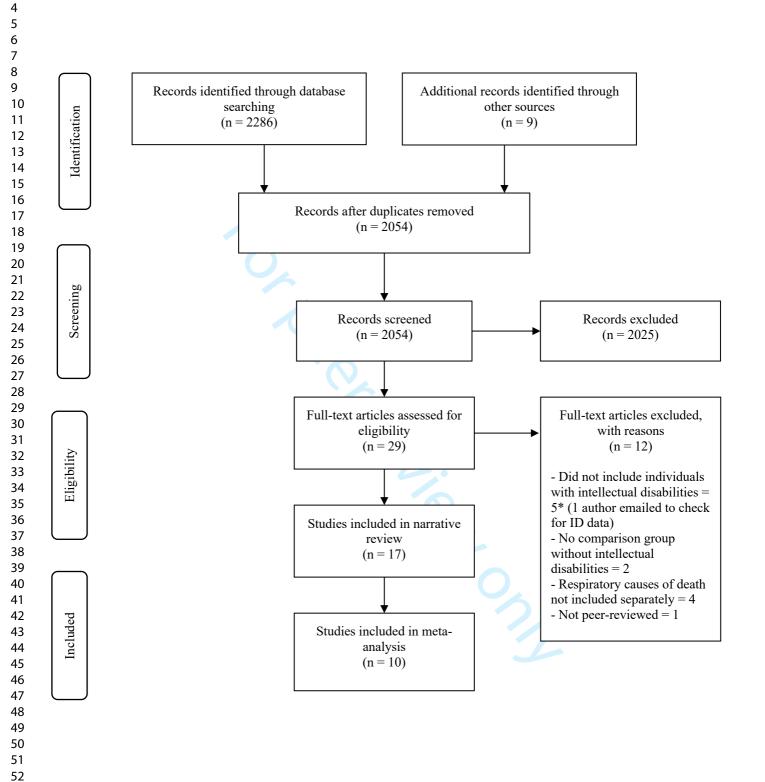
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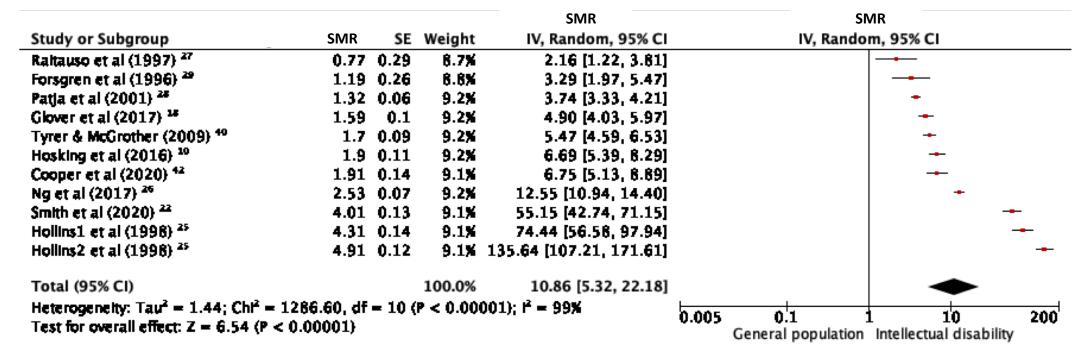
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# Figure 2: Forest plot of respiratory associated mortality



1 2					
- 3 4 5	Figure 3: Forest plot for adu	ults only			
6	Study or Subgroup	SMR SE Weight	IV, Random, 95% CI		/R om, 95% Cl
7	Forsgren et al (1996) 29	1.19 0.26 16.6%	3.29 [1.97, 5.47]	Iv, Kallut	_ <b></b>
8	Tyrer & McGrother (2009) 49	1.7 0.09 21.1%			•
9	Hosking et al (2016) <sup>10</sup> Cooper et al (2020) <sup>42</sup>	1.9 0.11 20.7% 1.91 0.14 20.1%	6.69 [5.39, 8.29] 6.75 [5.13, 8.89]		
10	Ng et al (2017) 25		12.55 [10.94, 14.40]		•
11	Total (95% CI)	100.0%	6.53 [4.29, 9.96]		•
12	Heterogeneity: Tau <sup>2</sup> = 0.21; Chl <sup>2</sup> =	74.88, df = 4 (P < 0.00001		0.005 0.1	1 10 200
13	Test for overall effect: Z = 8.73 (P <	: 0.00001}		General population	Intellectual disability
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3	Figure 4: Forest plot pneu	monia related mortality	
4		SMR SMR	
5	Study or Subgroup	SMR SE Weight IV, Random	
6	Tyrer & McGrother (2009) <sup>40</sup> Glover et al (2017) <sup>18</sup>	1.87 0.13 25.0% 6.49 [5.0 2.04 0.14 25.0% 7.69 [5.85	03, 8.37]
7 8	Hollins1 et al (1998) <sup>25</sup> Hollins2 et al (1998) <sup>25</sup>	4.31 0.14 25.0% 74.44 [56.58 4.91 0.12 25.0% 135.64 [107.21,	8, 97.94]
9			
10	Total (95% Cl) Heterocenetics Taud = 2.50: Chil = 4	100.0% 26.65 [5.63, 33.15, df = 3 (P < 0.00001); l <sup>2</sup> = 99%	
11	Test for overall effect: Z = 4.14 (P <		0.002 0.1 1 10 500 General population Intellectual disability
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# **Appendix 1: Search strategy**

# Embase- Ovid, 2016-

Sear	rch 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\$
6	or intel\$)).tw.
6.	((development\$) 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
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Sear	ch 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 difficilt*))					
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\$) 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					
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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

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

3 4	11	Stankiewicz E, Ouellette-Kuntz H, McIsaac M, Shooshtari S, Balogh R. Patterns of mortality among adults with intellectual and developmental	<70%* of participants had intellectual disabilities.
5 6		disabilities in Ontario. <i>Can J Public Health</i> 2018; <b>109(5-6):</b> 866-872	*We emailed this author to
7 8		disabilities in Ontario. Can 5 Fublic Treatin 2018, 109(3-0): 800-872	check if >70% of sample had ID
9			- they replied but didn't have
10 11			the data to check, so it was
12 13			excluded.
14 15	12	Tyrer F, Smith LK, McGrother CW. Mortality in adults with moderate to	Respiratory causes of death not
16		profound intellectual disability: a population-based study. J Intellect	included separately.
17 18		Disabil Res, 2007; 51(7): 520-527.	
19         20         21         22         23         24         25         26         27         28         29         30         31         32         33         34         35         36         37         38         39         40         41         42         43         44         45         46         47         48		Disabil Res, 2007; 51(7): 520-527.	

#### Sensitivity A- minus Raitasuo

	614D 65		SMR	SMR	
Study or Subgroup	SMR SE	Weight	IV, Random, 95% CI	IV, Random,	95% CI
Forsgren et al (1996) 29	1.19 0.26	9.7%	3.29 [1.97, 5.47]		
Patja et al (2001) 28	1.32 0.06	10.1%	3.74 [3.33, 4.21]		•
Glover et al (2017) 18	1.59 0.1	10.1%	4.90 [4.03, 5.97]		+
Tyrer & McGrother (2009) 49	1.7 0.09	10.1%	5.47 [4.59, 6.53]		+
Hosking et al (2016) 10	1.9 0.11	10.0%	6.69 [5.39, 8.29]		+
Cooper et al (2020) 42	1.91 0.14	10.0%	6.75 [5.13, 8.89]		+
Ng et al (2017) 26	2.53 0.07	10.1%	12.55 [10.94, 14.40]		
Smith et al (2020) 22	4.01 0.13	10.0%	55.15 [42.74, 71.15]		+
Hollins1 et al (1998) 25	4.31 0.14	10.0%	74.44 [56.58, 97.94]		-
Hollins2 et al (1998) 25	4.91 0.12	10.0%	135.64 [107.21, 171.61]		+
Total (95% CI)		100.0%	12.67 [6.01, 26.73]		•
Heterogeneity: Tau <sup>2</sup> = 1.43; Chl <sup>2</sup> = 12	60.95, df = 9 (f	< 0.000	01); $l^2 = 99\%$	0.005 0.1 1	da al
Test for overall effect: Z = 6.67 (P < 0					1'0 20 tellectual disability

#### Sensitivity B- minus Raitasuo and Tyrer

				SMR	SMR
Study or Subgroup	SMR	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Forsgren et al (1996) 29	1.19		10.8%	3.29 [1.97, 5.47]	
Patja et al (2001) 28	1.32	0.06	11.2%	3.74 [3.33, 4.21]	•
Glover et al (2017) 18	1.59	0.1	11.2%	4.90 [4.03, 5.97]	-
Hosking et al (2016) <sup>10</sup>	1.9	0.11	11.2%		
Cooper et al (2020) 42	1.91	0.14	11.1%	6.75 [5.13, 8.89]	-
Ng et al (2017) 26	2.53	0.07	11.2%	12.55 [10.94, 14.40]	•
Smith et al (2020) 22	4.01	0.13	11.1%	55.15 [42.74, 71.15]	-
Hollins1 et al (1998) 25	4.31	0.14	11.1%	74.44 [56.58, 97.94]	-
Hollins2 et al (1998) 25	4.91	0.12	11.1%	135.64 [107.21, 171.61]	-
Total (95% CI)			100.0%	13.92 [6.02, 32.15]	•
Heterogeneity: Tau <sup>2</sup> = 1.62; C	hl² = 1219.00	, df =	8 (P < 0	.00001); i² = 99%	0.005 0.1 1 10 20
Test for overall effect: Z = 6.10				<b>· ·</b>	0.005 0.1 1 10 20 General population Intellectual disability
					ceneral population intercetaal abability

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# 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). For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	11

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# 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 <sup>2</sup> ) for each meta-analysis.	11
	1	Page 1 of 2	
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
7 8 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	<u> </u>		
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
5 6 7		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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.e information, visit: Bage 2 or 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