PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Respiratory-associated deaths in people with intellectual disabilities: a systematic review and meta-analysis
AUTHORS	Truesdale, Maria; Melville, Craig; Barlow, Fiona; Dunn, Kirsty; Henderson, Angela; Hughes-McCormack, Laura; McGarty, Arlene; Rydzewska, Ewelina; Smith, Gillian; Symonds, Joseph; Jani, Bhautesh; Kinnear, Deborah

VERSION 1 – REVIEW

REVIEWER	Maarten Cuypers, PhD Radboud university medical center, Netherlands
REVIEW RETURNED	02-Oct-2020

GENERAL COMMENTS	Authors reviewed literature on respiratory-associated deaths in the ID population, based on publications from 1985 onwards. 17 studies were deemed eligible for narrative synthesis, and 10 studies provided data for meta-analysis. Results indicated a higher rate of respiratory-related deaths, in particular from pneumonia. Authors conclude that respiratory deaths are potentially avoidable and that future research should focus on reducing these risks for avoidable, premature deaths. The review was preregistered at Prospro. Overall, authors delivered a well-written manuscript which builds a case for focussing on preventing respiratory diseases among people with ID. Introduction is concise and correct, the reason to conduct this review and its relevance are well described. Methodology is sound and clear. Results are comprehensible and seem complete. Few minor comments could further improve this work: Abstract: Study population and control group comparators become not entirely clear from the abstract. If results speak of lesser rates, what is the reference group? The Article summary gives a different number of deaths (n=1,844 ID respiratory deaths only) than the Results section of the abstract (n=27,394 deaths, both ID and non-ID deaths) which is confusing. Discussion is rather short and could be more in-depth on some aspects: - Not sure if this work needs to be linked to Covid-19, as it already has relevance for clinical practice and research. There are, however, already some references available on the vulnerability of people with ID for Covid-19 and respiratory deaths to support the paragraph on page 24/25, which is now without references. For example https://doi.org/10.1016/j.dhjo.2020.100969 and https://doi.org/10.1111/jir.12739

	- Authors refer at some points in the m/s to avoidable mortality. Formal definition for avoidable mortality, of which pneumonia is a listed cause, include age bounds up to which certain deaths are considered avoidable. For most avoidable causes, this cutoff is at 75 years of age. Even in optimal circumstances, people with ID are likely to die because of a competing cause before the age of 75. Thus, by definition, improving (statistical) avoidable mortality in the ID population is difficult. In the context of this work, I assume use authors used a more practical definition of avoidable mortality, it would be good to clarify. - Authors claim that covering 1,844 respiratory deaths among people with ID globally since 1985 is a strength of the study. Most results, however, come from relatively small sampled studies, in particular when comparing to mortality studies conducted in the general population. Sensitivity analyses focussed on quality, but did these also give insight on sensitivity for sample size alone, and would more high quality and large-sampled population-based studies not be preferred future research as well? - As most of the studies included for review relied on death certificate data, the risk for underestimation of the true respiratory death rate should be discussed as well. One the most reported causes on the death certificate of people with ID is the ID itself. As this problem only occurs in ID population, true causes of death remain underestimated. 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. See, for example: https://doi.org/10.1111/j.1365-2788.2012.01614.x and https://doi.org/10.1111/jar.12448

REVIEWER	Simone Reppermund University of New South Wales, Australia
REVIEW RETURNED	09-Oct-2020

GENERAL COMMENTS	This systematic review and meta-analysis on rates of respiratory-associated deaths and associated risk factors in people with intellectual disability has been well conducted and is well written. The results have clinical and health policy implications with regards to the development of guidelines to reduce premature mortality due to respiratory disorders in people with intellectual disability. I have the following comments: 1) I wonder if the authors could justify their decision to include studies with samples comprising at least 70% people with intellectual disability? Why 70% and did the results differ between studies with samples including only people with intellectual disability? If 30% of a total sample have quite different health and mortality profiles without being reported separately, the results for the total sample could be misleading. I suggest adding a sensitivity analysis to check for change in results when excluding studies with heterogeneous samples. 2) The interrater reliability for abstract and full-text screening was only moderate (kappa= .57 and .58). This should be explained further. What has been done when there was a disagreement between raters? 3) Please add more details about the quality rating. How were studies categorized as weak, moderate, or strong?

	Minor comments Page 3, line 39-40: please check the sentence. You used 'were excluded' twice.

REVIEWER	KAI JIN University of Edinburgh
REVIEW RETURNED	07-Dec-2020

GENERAL COMMENTS	This meta-analysis of standardized mortality ratios (SMRs) of respiratory cause of mortality in people with ID showed pooled respiratory SMRs was 10.86 (95% CI 5.32, 22.19 p<0.001) for all age group, and SMR was 6.53 (4.29-9.96) in adult people with ID. SMRs from pneumonia cause of death was 26 (5.63-126.24). However, the study aims, methods and results require clarification and explanation. Important issues: 1. Meta-analysis of SMRs of resp cause of death in ID compared with general population: The forest plot from all the figures showed the general population have higher risk of resp cause of death than the ID population, which were against with the conclusion of this study. Please clarify. 2. In methods, authors stated the primary goal of the analysis was to investigate if the SMRs of respiratory death differ for individual with and without intellectual disabilities. However, in the results (page 23/45 line 50-53) authors reported "comparative results (ID vs general population) for death … reported in 10/17". What was the reason to include another 7 studies without comparation groups in the review? 3. Authors also aimed to review the evidence the risk factors in ID population: however, there were no sufficient data and results provided in the study to answer this aim. Introduction: 1. page 4: line 6 "The range of standardised mortality ratios (SMRs) due to respiratory disorders for people with intellectual disabilities are very high in some studies, and much lower in others" The sentence requires more evidence to support. E.g. does this conflicting evidence have any aspects due to study methodology, study population? 2. What was already know about the resp specific mortality rates in the literature, any differences for age, gender, level of ID, which would help to set up the scene for this review. 3. What is the knowledge gap and significant for this study? Methods 1. Eligibility: Page 5/45,line 36- 39 "To be included in the meta-analysis, studies had to report SMRs with …or provide sufficient data to calculate SMRs": This would reword as "…. based on external comparison group or to have presented data allowing such outcomes to be derived" 2. Data extraction (page 6/45) requires more details: e.g. data sources, country of study, bassline study years, duration of follow-up, sample size, number of observed and expected events, level of adjustment (age, gender) et al. 3. Please provide definition of ID (s ascertainment of ID). 4. Assessment of study and outcome quality (Page 6/45): wondering what is the reason to use Standard Quality Assessment Criteria for Evaluating Primary research Paper from a variety of Fields? Please provide the quality assessment results in the appendix (for assessing the risk of bias).

	5. Summary of outcomes and statistical analysis (page 11/45), a. line 11: were age-gender SMRs extracted from each study? If yes, please specify and also for the SMRs in table 2 b. how many studies that provide equitant data instead of SMR or HR? c. How many studies reported HRs and what the associations were examined? d. Indicate the resp cause of death would not limit to ICD 9 and 10 e. Line 21: “Random effects meta-analysis (inverse of the variance method) was used to calculate the weighted mean all cause SMR across studies” Was the all cause or resp specific cause? This sentence is not clear and need to rewrite as “random effects meta-analysis weighted by the inverse of the variance was used to calculate the log SMR and then back-transformed the data to obtain the pooled SMRs. f. Line 30: “with the Q value and associated p value being used to assess the statistical significance of any difference in means”. This is not clear and misleading. The Q-statistic is the weighted sum of squared differences between the observed effects and the weighted average effect. Q values and associated p values is used to assess the heterogeneity between studies and is from a chi-squired statistical values. I would recommend just to report I2 statistic for heterogeneity across the studies as shown in the lines 42. g. Line 32: specify what effect size of “the magnitude of the differences and associated confidence interval (ci) were reported” h. line 36: “potential factors for consideration include … ethnicity”: how were these related to the analysis? i. need to provide the information for the subgroup analysis which has been performed and shown in the results (e.g. adult, pneumonia) j. need to report how to access publication bias and provide the results 6. Need to indicate Random effects model was used to calculate the pooled effect estimates since a high level of heterogeneity was expected Results 1. Page 12/45 line 15 : There were two cohorts in one study, this should provide in the summary results as 11 cohorts in 10 studies for meta-analysis. 2. 23/45 line 24: what does “an operational system” refer to? 3. 23/45 Line 27: individual respiratory disorders: what is the purpose of this paragraph? Was this paragraph to summarize the most common cause of death within the respiratory disorder? 4. 24/45 line 25: factors contributing to respiratory associated death: This paragraph lack of enough data to compare the results, e.g., for sex, what were results to support “a significant factor’ and what were results for “not consistent”; which effect size used to compare, e.g. HR, OR , SMR? 5. 24/45 line 44: this paragraph should have a separate heading for age group. Were all studies compared with general population? if not , what was the reason to include those without comparison group. 6. Meta-analytical outcomes a. 25/45: line 2 “ necessary data” require clear description, eg. reporting SMR, HR or equivalent;

	b. Page 25/45: line 11-14: the results indicate that resp mortality … after adjustment (at the study level) for age and sex differences: please clarify these were age and sex adjusted SMR extracted from each study for analysis? Figure 1. need to add the heading/title and figure number in each of the figure. 2. Effect size was not log[odds ratio], please correct 3. the forest plot figures do not support the results reported in the text. From the figures the results would interpret as the general population have 10.86 higher risk of mortality compared to ID. 4. Is the 2nd forest plot for adults? Please specify in the heading of the figure. There were 5 studies that include adults only in this figure. The results session should also specify the number of studies reporting adults only, children only and combined both and children.

VERSION 1 – AUTHOR RESPONSE

Reviewer	Comments and author responses
1	Abstract: Study population and control group comparators become not entirely clear from the abstract. If results speak of lesser rates, what is the reference group? RESPONSE: The reference group is people without intellectual disabilities. This has been added to the abstract to make it clear to the reader. The Article summary gives a different number of deaths (n=1,844 ID respiratory deaths only) than the Results section of the abstract (n=27,394 deaths, both ID and non-ID deaths) which is confusing. RESPONSE: In order to make it clearer to the reader the article summary and results section of the abstract has been amended to: “Data from 90,302 people with ID and 13,808 deaths from all causes in people with ID were extracted’.
	Discussion is rather short and could be more in-depth on some aspects: - Not sure if this work needs to be linked to Covid-19, as it already has relevance for clinical practice and research. There are, however, already some references available on the vulnerability of people with ID for Covid-19 and respiratory deaths to support the paragraph on page 24/25, which is now without references. For example https://doi.org/10.1016/j.dhjo.2020.100969 and https://doi.org/10.1111/jir.12739 RESPONSE: Thank you for highlighting this. We had added the recommended citations on page 26 in the discussion and in the reference section.
	Authors refer at some points in the m/s to avoidable mortality. Formal definition for avoidable mortality, of which pneumonia is a listed cause, include age bounds up to which certain deaths are considered avoidable. For most avoidable causes, this cut-off is at 75 years of age. Even in optimal circumstances, people with ID are likely to die because of a competing cause before the

	age of 75. Thus, by definition, improving (statistical) avoidable mortality in the ID population is difficult. In the context of this work, I assume use authors used a more practical definition of avoidable mortality, it would be good to clarify. RESPONSE: This is a very interesting point, which we will definitely consider further in future studies. For this study we used the ONS definition of avoidable mortality, which does not include any age bounds.
	Authors claim that covering 1,844 respiratory deaths among people with ID globally since 1985 is a strength of the study. Most results, however, come from relatively small sampled studies, in particular when comparing to mortality studies conducted in the general population. Sensitivity analyses focussed on quality, but did these also give insight on sensitivity for sample size alone, and would more high quality and large-sampled population-based studies not be preferred future research as well? RESPONSE: We did not do a separate sensitivity analysis using sample size alone because it is included in the overall quality rating. Nonetheless, this is an important and valid point and we have added sentences to the strengths and limitations section of the discussion. "Although the meta-analysis enables synthesis of data from a large sample, many of the individual studies reported on small samples and are at increased risk of bias. It is encouraging that there have been several larger studies in recent years and future research should focus on reporting respiratory mortality in representative, population-based samples."
	As most of the studies included for review relied on death certificate data, the risk for underestimation of the true respiratory death rate should be discussed as well. One the most reported causes on the death certificate of people with ID is the ID itself. As this problem only occurs in ID population, true causes of death remain underestimated. 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. See, for example: https://doi.org/10.1111/j.1365-2788.2012.01614.x and https://doi.org/10.1111/jar.12448 RESPONSE: We agree and have included this in the limitations section and added the references accordingly in page 28
2	I wonder if the authors could justify their decision to include studies with samples comprising at least 70% people with intellectual disability? Why 70% and did the results differ between studies with samples including only people with intellectual disability? If 30% of a total sample have quite different health and mortality profiles without being reported separately, the results for the total sample could be misleading. I suggest adding a sensitivity analysis to check for change in results when excluding studies with heterogeneous samples. RESPONSE: It is common for studies investigating and health and health inequalities in intellectual disabilities to include samples encompassing broader spectrum of (neuro-) developmental disabilities (e.g. studies with autism cohorts where some participants also have co-occurring intellectual disabilities). We wanted our systematic review to be as comprehensive as possible. For this reason, for studies where not all the sample had intellectual disabilities and where results for the group with intellectual disabilities were not presented separately, we specified a threshold of at least 70% with ID. At the full text review stage, we identified three studies which focused on disabilities other than ID: Reid et al. – sample with cerebral palsy where N=1,782/3,507 participants had ID and results are presented separately for this group

	Shavelle et al. – autism where 48.19% of the sample also had ID and results are presented separately. Stankiewicz et al. 2018 included a sample with intellectual and developmental disabilities, but did not present data separately for participants with ID only. Therefore, we emailed this author to check if >70% of sample had ID. They replied, but didn't have the necessary data to check, so the paper was excluded. Given the above, we did not need to conduct any additional sensitivity analyses on the basis of the sample composition, as all reviewed papers included samples with ID only except for Reid et al. and Shavelle et al. where results for the ID subgroup were presented separately.
	The interrater reliability for abstract and full-text screening was only moderate (kappa= .57 and .58). This should be explained further. What has been done when there was a disagreement between raters? RESPONSE: Page 5: we have specified that any disagreements between the 2 raters were resolved via discussion with a third researcher. We have also clarified that the Cohen's kappa is a robust yet conservative measure of agreement as it accounts for change agreements, as this could explain the moderate agreement scores.
	Please add more details about the quality rating. How were studies categorized as weak, moderate, or strong? RESPONSE: Page 5: Provides additional details on completing the quality assessment and clarifies this was based on an item checklist with scores calculated as percentages and categorised using the cut offs listed.
	Page 3, line 39-40: please check the sentence. You used 'were excluded'twice. RESPONSE: Thank you for highlighting this mistake. This has been amended accordingly.
3	This meta-analysis of standardized mortality ratios (SMRs) of respiratory cause of mortality in people with ID showed pooled respiratory SMRs was 10.86 (95% CI 5.32, 22.19 p<0.001) for all age group, and SMR was 6.53 (4.29-9.96) in adult people with ID. SMRs from pneumonia cause of death was 26 (5.63-126.24). However, the study aims, methods and results require clarification and explanation. RESPONSE: These main findings were a result of conducting sub-group meta-analyses. The adults only SMRs were found to be lower than the pooled respiratory SMRs in people with ID because we know that child deaths are extremely rare in the control population, so the ratio comes down on excluding child deaths. The SMR for pneumonia cause of death is higher than 10.86 because once you remove other control-heavy respiratory conditions like asthma attacks, COPD, and lung cancer. So essentially weve excluded other respiratory killers likely to be high in controls.
	Meta-analysis of SMRs of resp cause of death in ID compared with general population: The forest plot from all the figures showed the general population have higher risk of resp cause of death than the ID population, which were against with the conclusion of this study. Please clarify. RESPONSE: We thank the reviewer for noting this error. The labels on the forest plots have been adjusted to accurately reflect the conclusion of the study, that the ID population is at higher risk of

	respiratory causes of death than the general population. This has been corrected in Appendix 3, p35; figure 2, p38; figure 3, p39; figure 4, p40.
	In methods, authors stated the primary goal of the analysis was to investigate if the SMRs of respiratory death differ for individual with and without intellectual disabilities. However, in the results (page 23/45 line 50-53) authors reported “comparative results (ID vs general population) for death … reported in 10/17”. What was the reason to include another 7 studies without comparation groups in the review? RESPONSE: Some of the included studies did not have a matched general population comparison group in the typical way but instead have calculated SMRs from general population data. For example, Raitasio et al...”calculated the ratio of observed (O) and expected (E) cases. Expected rates for the different causes of death were calculated using the mortality rates of the general Finnish population.” We hope this clarifies the reasons for inclusion of the 7 studies with general population comparisons.
	page 4: line 6 “The range of standardised mortality ratios (SMRs) due to respiratory disorders for people with intellectual disabilities are very high in some studies, and much lower in others” The sentence requires more evidence to support. E.g. does this conflicting evidence have any aspects due to study methodology, study population? RESPONSE: We thank the reviewer for highlighting this important point. We have elaborated on the differences across studies, as follows: "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"
	Authors also aimed to review the evidence the risk factors in ID population: however, there were no sufficient data and results provided in the study to answer this aim. RESPONSE: We agree that this is a problem with the existing evidence base because it prevents the development of targeted interventions to reduce the inequalities in respiratory mortality. We have expanded the section in the limitations section to encompass this point. Page 27: “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.”
	Introduction: What was already know about the resp specific mortality rates in the literature, any differences for age, gender, level of ID, which would help to set up the scene for this review. What is the knowledge gap and significant for this study? RESPONSE: We thanks the reviewer for their comment. We have elaborated on the specific mortality rates and differences across studies as follows (see page 3): "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"
	Methods Eligibility: Page 5/45,line 36- 39 "To be included in the meta-analysis, studies had to report SMRs with …or provide sufficient data to calculate SMRs": This would reword as "…. based on external comparison group or to have presented data allowing such outcomes to be derived" RESPONSE: We have changed to wording to the reviewers suggested wording "based on external comparison group or to have presented data allowing such outcomes to be derived".
	Data extraction (page 6/45) requires more details: e.g. data sources, country of study, bassline study years, duration of follow-up, sample size, number of observed and expected events, level of adjustment (age, gender) et al. RESPONSE: We have provided additional details within the data extraction section specifying the specific data we extracted.
	Please provide definition of ID (s ascertainment of ID). RESPONSE: The WHO definition of intellectual disabilities is provided in the opening paragraph of the manuscript. However, to clarify that this is the definition adopted in this paper we have added the following sentence on page 3: "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" Most of the studies included in the systematic review and meta-analysis (n=16/17) ascertained intellectual disabilities via electronic health and care administrative records. Therefore, ascertainment of ID was based on inclusion criteria outlined in each study. In common with all intellectual disabilities record linkage studies slight variation in cohort ascertainment is observed. For example, Raitasuo et al (1997) reported on medical case notes for residents living in a residential unit for people with intellectual disabilities. For the purposes of this systematic review and metanalysis, ID was ascertained if the included studies provided a clear outline of their ascertainment process. To make this clear in the manuscript we have amended the following sentence on page 3 line 28: "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"
	Assessment of study and outcome quality (Page 6/45): wondering what is the reason to use Standard Quality Assessment Criteria for Evaluating Primary research Paper from a variety of Fields? Please provide the quality assessment results in the appendix (for assessing the risk of bias).

	RESPONSE: Since we decided not to exclude any studies on the basis of their methodological design this tool allowed us to assess the quality of a variety of quantitative designs in studies potentially eligible for inclusion in our review. The quality assessment results can be found in table 1.
	Summary of outcomes and statistical analysis (page 11/45), a. line 11: were age-gender SMRs extracted from each study? If yes, please specify and also for the SMRs in table 2 RESPONSE: We have added on page 11:"If SMRs were reported by specific causes, sex, age group, level of intellectual disability, socio-economic status or ethnicity, these were collected and presented for potential analysis (see table 2)" We have updated Table 2 to include information on adjustment variables for each SMR or HR reported. (adjustment for age, sex, etc). In addition, in the meta-analytical outcomes section, page 25, more information on adjustment within studies, for age and sex: “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.” b. how many studies that provide equitant data instead of SMR or HR? RESPONSE: One study, Patja et al. 2001, provided Observed and Expected calculations for their SMRs for men and women, for respiratory mortality. This was then used by the authors to calculate the SMR for all sexes. This has now been made clearer in Table 2 using a Table footnote. c. How many studies reported HRs and what the associations were examined? RESPONSE: On page 11 (line 18) the following has been added in brackets "(studies with relevant SMRs n=8 and HR n=2)." Additionally, more detail on hazard ratios and what these analyses were adjusted for has been included in Table 2. No associations were examined in the meta-analysis due to a lack of relevant data. Instead we presented an evidence synthesis of all studies (page 21). d. Indicate the resp cause of death would not limit to ICD 9 and 10 RESPONSE: We have added after Respiratory disorder definition in Table 1: "(e.g. ICD codes or other definitions)" e. Line 21: “Random effects meta-analysis (inverse of the variance method) was used to calculate the weighted mean all cause SMR across studies” Was the all cause or resp specific cause? This sentence is not clear and need to rewrite as “random effects meta-analysis weighted by the inverse of the variance was used to calculate the log SMR and then back-transformed the data to obtain the pooled SMRs. RESPONSE: This has been revised as suggested (page 11 line 21). This has been made clearer in methods page 11, that this applied to all meta-analyses, and reference to all-cause SMR has been removed. “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” f. Line 30: “with the Q value and associated p value being used to assess the statistical significance of any difference in means”. This is not clear and misleading. The Q-statistic is the weighted sum of squared differences between the observed effects and the weighted average effect. Q values and associated p values is used to assess the heterogeneity between studies and is from a chi-squired statistical values. I would recommend just to report I2 statistic for heterogeneity across the studies as shown in the lines 42. RESPONSE: This has been revised as suggested (page 11 line 30). We have removed the following from page 11, line 30: "with the Q value and associated p value being used to assess the statistical significance of any difference in means." g. Line 32: specify what effect size of “the magnitude of the differences and associated confidence interval (ci) were reported” RESPONSE: We have included the following clarification on page 11 “The magnitude of the back-transformed ratio and associated confidence interval (CI) were also reported using the Chi-squared statistic I2.” h. line 36: “potential factors for consideration include … ethnicity”: how were these related to the analysis? RESPONSE: We have removed the sentence "Potential factors for consideration included sex, age group, level of intellectual disabilities, socio-economic status and ethnicity." We have replaced this, earlier on in this section (page 11 line 8), with the following: "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)" i. need to provide the information for the subgroup analysis which has been performed and shown in the results (e.g. adult, pneumonia) RESPONSE: We have added the following clarification on page 11: “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.” j. need to report how to access publication bias and provide the results RESPONSE: We have chosen not to report a funnel plot or Egger’s test for assessment of publication bias. According to the Cochrane Handbook for conducting reviews*, the minimum number of studies for a funnel plot should be at least 10 studies in the meta-analysis, because plots based on fewer studies are considered inappropriate. The tests should also not be used if studies are of similar size (similar standard errors of estimates). We have found that the majority of our studies were of similar size; and had similar log-standard errors; five of the included studies in our meta-analysis were of similar size (between 1,000-3,000 people) with all log-errors residing between 0.06 and 0.3. However, without evidence of funnel plot asymmetry from conducting an appropriate test, we have included non-reporting bias as a potential limitation in our review. On page 25 of the discussion, we have stated: “We have not included assessment of non-reporting or publication bias.” *****: Cochrane Handbook, Chapter 13, Assessing risk of bias due to missing results in a synthesis. Accessed Jan 2021: https://training.cochrane.org/handbook/current/chapter-13

	Need to indicate Random effects model was used to calculate the pooled effect estimates since a high level of heterogeneity was expected RESPONSE: We have made our methods section clearer as to the planned use of random effects: Page 11 now states: "Random effects meta-analysis was undertaken using RevMan. Included studies reported either: …" "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." "For the random effects meta-analysis, heterogeneity was expected in the pooled result. Therefore, the Chi-squared I^2 statistic was chosen…"
	Results 1. Page 12/45 line 15 : There were two cohorts in one study, this should provide in the summary results as 11 cohorts in 10 studies for meta-analysis. RESPONSE: We have amended this sentence, page 12 to: "We identified 2,063 studies, 17 were included in the narrative synthesis and 10 studies (11 cohorts) in the meta-analysis."
	2. 23/45 line 24: what does "an operational system" refer to? RESPONSE: We have amended this section on page 23 to: "The remaining four studies included in the systematic review did not report their definitions define of respiratory disorders". 3. 23/45 Line 27: individual respiratory disorders: what is the purpose of this paragraph? Was this paragraph to summarize the most common cause of death within the respiratory disorder? RESPONSE: Thank you for your comment- we have made clarifications to the paragraph to ensure it is clear that this paragraph covers the causes of death from respiratory disorders, disaggregated. The paragraph on page 23 now reads: **"Causes of death from respiratory disorders** Thirteen papers reported on cause of deaths from individual respiratory disorders.[8,10-15,22-24,26-28] Pneumonia was reported as a cause of death in 12 studies.[8,10-15,22,23,26,27], five studies reported deaths from pneumonitis related to aspiration[8,10,12,14,24], five studies reported on chronic obstructive pulmonary disease (COPD)[11,12,14,26,27], one study reported on asthma[31] and one reported respiratory cancer deaths.[8]"
	24/45 line 25: factors contributing to respiratory associated death: This paragraph lack of enough data to compare the results, e.g., for sex, what were results to support "a significant factor' and what were results for "not consistent"; which effect size used to compare, e.g. HR, OR , SMR? RESPONSE: We thank the reviewer for this feedback. The heading and paragraph have been re-written to include more specific details on the evidence we synthesised regarding factors associated with respiratory deaths, on page 24: **"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 [14,22,23,30] (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 SMR 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."
	24/45 line 44: this paragraph should have a separate heading for age group. Were all studies compared with general population? if not, what was the reason to include those without comparison group. RESPONSE: We have amended the paragraph to include an appropriate heading, and more detail on the studies: "Four studies included comparison with the general population for respiratory causes of death, while one included children and young people without intellectual disabilities as the control [10]. All analyses were limited by the small numbers of death."
	Meta-analytical outcomes a. 25/45: line 2 " necessary data" require clear description, eg. reporting SMR, HR or equivalent; RESPONSE: We appreciate that the meaning of this sentence was not very clear and have provided further clarification by including the following text on page 24 line 2 'Ten studies reported the necessary data to calculate (SMR, hazard ratio, or data necessary to calculate these) and were included in the meta-analysis…'
	Page 25/45: line 11-14: the results indicate that resp mortality …after adjustment (at the study level) for age and sex differences: please clarify these were age and sex adjusted SMR extracted from each study for analysis? RESPONSE: Thank you for bringing this important point to our attention. We have now clarified this in the text; this was the case with an exception for one study (Raitasuo et al 1997) where the SMR was adjusted for age but not sex, and another study which did explicitly stipulate whether sex-specific age bands had been used in calculating the age-adjusted SMRs (Hollins et al. 1998). We have amended the text on page 25: "At the individual study level, this was adjusted for age (all studies) and for sex in all studies except two, where this was not clear[11,13])."
	Figure 1. need to add the heading/title and figure number in each of the figure. RESPONSE: This has been added accordingly as suggested on pages 41-43.
	the forest plot figures do not support the results reported in the text. From the figures the results would interpret as the general population have 10.86 higher risk of mortality compared to ID. RESPONSE: We thank the reviewer for noting this error. The label on the forest plot has been adjusted to accurately reflect the conclusion of the study, that the ID population is at higher risk of respiratory causes of death than the general population. This has been corrected on figure 2, p39.

	Is the 2nd forest plot for adults? Please specify in the heading of the figure. There were 5 studies that include adults only in this figure. The results session should also specify the number of studies reporting adults only, children only and combined both and children. RESPONSE: The second forest plot (figure 3) is for adults only. Figure titles have been added to all forest plots to make this clearer. The figure caption for the second forest plot is 'Figure 3: Forest plot for adults only. The pooled SMR for adults only was 5·85 (95% CI 4·73,7·22, p<0·001). Heterogeneity between studies was also reduced from I^2=99% to I^2= 56%by the exclusion of samples which included children.' We have adjusted the text on page 24 line 23 to specify exactly how many studies reported adults only, children only, and both adults and children '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.'
	Appendix 3 is cited after appendix 1 which makes your citations incorrect. Please have them cited in ascending order RESPONSE: Thank you for highlighting this error. This has been amended accordingly as suggested.

VERSION 2 – REVIEW

REVIEWER	Cuypers, Maarten Radboudumc
REVIEW RETURNED	01-Mar-2021

GENERAL COMMENTS	Authors have adequatelly adressed the reviewer comments. I have no further comments

REVIEWER	Reppermund, Simone UNSW Australia, Department of Developmental Disability Neuropsychiatry
REVIEW RETURNED	09-Feb-2021

GENERAL COMMENTS	The authors have addressed all comments and I have no further suggestions.

REVIEWER	Jin, Kai Centre for Medical Informatics, University of Edinburgh
REVIEW RETURNED	19-Feb-2021

GENERAL COMMENTS	Thanks very much for the authors' detail response. Some minor points: For all figures: 1. Forest plot: pls provide full name of ID under the forest plot 2. Odds ratio: please change to SMR Page 5/94: Line 32: "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" Were previous studies focused on particle age group only? Would need to have more concise summary. Could reword as "Respiratory cause of mortality in people with intellectual

	disabilities has not been systematically examined. Previous studies focused on xx or xx". 12/94 Line 37: ration : ? is ratio 25/94: Line 20 Factors associated: "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)." Please specify the factors associated with risk of respiratory cause of death at the beginning of the paragraph. 25/94 Line 30: SMS: is SMRs? 26/94: line 18 "where this was not clear": did this refer to those two studies that did not report sex ? need to reword

VERSION 2 – AUTHOR RESPONSE

For all figures:

1. Forest plot: pls provide full name of ID under the forest plot

2. Odds ratio: please change to SMR

Thank you for highlighting this. We have provided the full name 'intellectual disabilities' under each forest plot and changed odds ratio to SMR as requested.

Page 5/94: Line 32: "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"

Were previous studies focused on particle age group only?

One study was focused on children and young people [10], one study focused on older adults [12] and another study did not specify age [11].

Would need to have more concise summary.

We have reworded as your suggestion to: "Respiratory cause of mortality in people with intellectual disabilities has not been systematically examined. Previous studies focused on either children and young people [10] or older adults with intellectual disabilities [12].

12/94 Line 37: ration : ? is ratio

This spelling error has been corrected.

25/94: Line 20 Factors associated: "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)."

Please specify the factors associated with risk of respiratory cause of death at the beginning of the paragraph.

We have added to the beginning of the paragraph: “Age,, gender and severity of intellectual disability have been found to be associated with risk of respiratory cause of death.”

25/94 Line 30: SMS: is SMRs?

This has been corrected to read SMRs

26/94: line 18 “where this was not clear”: did this refer to those two studies that did not report sex? need to reword.

Yes, this refers to those two studies that did not report sex. This has been reworded to read:

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.