PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The risk of dementia in adults with cerebral palsy: A matched cohort study using general practice data
AUTHORS	Smith, Kimberley; Peterson, Mark; Victor, Christina; Ryan, Jennifer

VERSION 1 – REVIEW

REVIEWER	Sandra Julsen Hollung Cerebral Palsy Registry of Norway, Vestfold Hospital Trust, Norway
REVIEW RETURNED	14-Aug-2020

GENERAL COMMENTS	Thank you for the opportunity to review this paper. It is very well written, interesting, and a pleasure to read, well done. The paper shows that although persons with CP had a higher risk of developing dementia, the risk was attenuated when controlling for comorbidities. I have some comments/suggestions for you to consider, and hope they will help you to further improve the paper: 1. Matched controls could be better defined in the abstract and methods/participants section; “three age, sex and GP-practice matched controls without CP.” I interpret that both people with CP and matched controls were identified through GP data, or more precisely the CPRD database. I suggest to simplify the description. Also, it is written differently throughout the paper, for example in the abstract/objectives: “primary care practice matched controls” and methods/participants paragraph 2 “practice matched controls” 2. Article Summary: you write a “large cohort study,” I think this is a bit relative considering only 72 were diagnosed with dementia. It is also not written/described as such anywhere else in the paper. I suggest rewording to exclude the term “large.” 3. Introduction, first paragraph: • Definition of CP: the term “infarct” is not commonly added here; an infarct may be a cause of the injury. • I am surprised to see that “verbal communication” is listed as a most common presenting feature of CP along with gross and fine motor function. While it is certainly among the most common associated impairments, I suggest deleting, as there are many more common associated impairments. 4. Methods/participants: • While there is a statement referring to 3 references about participant selection, I think it is very important (since this paper is about people with CP) to clearly define/describe this population in the paper. For those of us who are not familiar with Read codes (maybe only used in UK?), please define what codes were used (add to an appendix, as you did for dementia Read codes (appendix II)). Not all research groups/countries define CP in the

	same way, and I would not only like to see the Read codes, but also understand what “for each patient identified as having CP” means? In addition, does CP refer to congenital or postneonatal CP? You may not have this information, but this should be mentioned as this may affect your results. • You mention “data was of sufficient quality to be used for assessment,” what does this mean, please clarify. What did you deem as sufficient? There is no mention of missing data anywhere in the paper (it is marked as N/A in the STROBE checklist)? In my experience, it is unlikely that all people in this study would have complete data for each variable. If the code was not present in the database, was it assumed that the comorbidity wasn’t present? 5. Methods/confounders, last sentence: there may be a typo in the categorization of GP visits as 2-11.9? 6. Methods/statistical analysis: again, missing data and how it was handled? If N/A, please also describe. 7. Results/descriptive data: participant characteristics: please clarify mean age of sample. Does this mean only those with CP or not CP, or both? 8. Tables: I suggest looking at examples of papers on the BMJ Open website. Your tables could be improved. Remember that tables should be self explanatory. Pay special attention to table 2, this table has terms (cerebral palsy in title but CP below) and abbreviations (HR, ID) that are not defined. If you have % in the column header, you do not need a % behind every result number below. What are the numbers in () under Incidence per 1000 person years, possibly confidence intervals? This is not explained in the paper under statistical analysis? What are the 1’s under No CP? Please be consistent with decimals throughout paper, tables and appendixes. Also, in table 3, the n numbers are not correct? CP=19 and No CP=53? 9. I appreciate the honesty in the discussion section about the limitations of this study, and suggestions for further studies with larger cohorts. One point that I am missing is about the correctness/completeness of the CPRD and HES datasets. Are there any references to the reliability/validity of these datasets and how it may affect your results. In my experience, it is likely that some people with CP maybe missing from the dataset, or have an erroneous CP diagnosis, or any of the other reported comorbidities/conditions/confounders.

REVIEWER	Paola Gilsanz Kaiser Permanente Division of Research
REVIEW RETURNED	19-Aug-2020

GENERAL COMMENTS	The possible association between cerebral palsy and dementia risk is an interesting topic and I’m happy these authors are investigating it. Below are some comments that may further strengthen the paper. Main comments: • The causes of early onset dementia may differ from later onset dementia and I suggest the authors conduct sensitivity analyses separating early vs later onset dementia. • The cohort starts to follow individuals as young as 18, when they are likely not at risk for dementia. I recommend the authors start dementia follow-up at an older age or justify why they are starting dementia follow up at such an early age. Other comments:

	• It would be helpful to readers if the authors were explicit that this is a dynamic cohort in which people with CP can join between 1987 to 2015. • It would be helpful for readers if the authors spell out intellectual disability (as opposed to saying ID) in abstract. • The abstract states that the mean age of participants was 33.3 years. I assume this is at baseline but please make it explicit. • Please provide more information regarding how age was operationalized for the purposes of matching. • I am not very familiar with the datasets used in this paper and have a few questions related what they include. Is it possible for some one to have transfer out of the CPRD database and then return? If so, how are these individuals handled in these analyses? Does the HES include information related to dementia diagnoses prior to the implementation of ICD-10 codes since the start of dementia follow-up time is 1987? • I recommend the authors use age as the timescale for their Cox proportional hazards models and calculate age adjusted incidence rates with confidence intervals.

REVIEWER	Deborah E. Thorpe, PT, PhD The University of North Carolina at Chapel Hill United States
REVIEW RETURNED	27-Aug-2020

GENERAL COMMENTS	This is a well-written original paper presenting the risk of incident dementia in adults with cerebral palsy (CP) compared to age, sex and primary care matched controls. The methodology of secondary data analysis on large data sets to answer these questions is very appropriate.This paper is the first to address incident dementia in a large cohort of adults with CP and begins to discern whether incidence of dementia is a result of the diagnosis of CP itself or perhaps a result of the associated co-morbidities that develop secondary to the disorder. This paper emphasizes that adults with CP have an increased hazard of developing dementia and that continuing research into dementia by severity of CP and presence of secondary co-morbidities is warranted. We have speculated for some time (secondary to clinical observations) that adults with CP experience mental health disorders at an equal or elevated rate as compared with peers without CP. These results and those in the future will help to develop appropriate screening and intervention for dementia for individuals with cerebral palsy.

REVIEWER	Dr. Arlene Mannion National University of Ireland, Galway
REVIEW RETURNED	03-Sep-2020

GENERAL COMMENTS	Summary of paper: The manuscript entitled 'The risk of dementia in adults with cerebral palsy: A matched cohort study using general practice data' is an interesting study on the risk of dementia in adults with cerebral palsy and the role that comorbidities play in this risk. The study included 1,703 adults with cerebral palsy and 5,109 matched controls. Strengths of the manuscript include a large sample size collected from a longitudinal database. Abstract:

	1. Adjust wording so that each section reads as a whole sentence on its own, rather than a short number of words. More detail needed on Objectives, Design, Setting. Article Summary: 2. This should focus on the strengths of the study and the novel findings, rather than only focusing on the limitations of the study. Introduction: 3. When discussing the comorbidities associated with Cerebral Palsy, include other comorbidities such as sleep problems, gastrointestinal symptoms and autism spectrum disorder, and include literature to support the occurrence of these comorbidities. 4. The authors make the point that no study has examined whether CP is associated with dementia. However, before making this point, it would be the important to include the following in the Introduction, as well as including how the current study expands upon this previous research: Smith K, Peterson M, Victor C, Ryan J. INCIDENCE OF DEMENTIA IN ADULTS WITH CEREBRAL PALSY: A UK COHORT STUDY. Innov Aging. 2018;2(Suppl 1):980. doi:10.1093/geroni/igy031.3628 Holtzman DM: Role of apoE/Aβ interactions in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy. J. Mol. Neurosci.17(2),147–155 (2001) Results: 5. p.9. Need to give the n of participants as well as percentage. Discussion: 6. While comorbidities such as intellectual disability, epilepsy, and sensory impairments were considered as comorbidities, other comorbidities such as other medical conditions, including gastrointestinal symptoms and sleep problems were not included. The lack of these comorbidities should be discussed as a limitation of the study. 7. Greater emphasis needs to be placed on the novelty and significance of the findings in the conclusion paragraph. Style and Formatting: 8. All n, SD, p etc. should be in italics. 9. p.5 Correct typo '131 million'

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Sandra Julsen Hollung
Institution and Country: Cerebral Palsy Registry of Norway, Vestfold Hospital Trust, Norway
Please state any competing interests or state 'None declared': None declared

Thank you for the opportunity to review this paper. It is very well written, interesting, and a

pleasure to read, well done.
The paper shows that although persons with CP had a higher risk of developing dementia, the risk was attenuated when controlling for comorbidities.
I have some comments/suggestions for you to consider, and hope they will help you to further improve the paper:

1. Matched controls could be better defined in the abstract and methods/participants section; "three age, sex and GP-practice matched controls without CP." I interpret that both people with CP and matched controls were identified through GP data, or more precisely the CPRD database. I suggest to simplify the description. Also, it is written differently throughout the paper, for example in the abstract/objectives: "primary care practice matched controls" and methods/participants paragraph 2 "practice matched controls"

Response: We have re-worked the phrasing in the abstract so that hopefully this is clearer and have also tried to make phrasing more consistent:

Abstract

Objectives: *Determine the risk of incident dementia in adults with cerebral palsy (CP) compared to age, sex and general-practice (GP) matched controls.*

Design*: Retrospective cohort study.*

Setting*: UK general practices linked into the Clinical Practice Research Datalink (CPRD).*

Participants*: CPRD data were used to identify adults aged 18 or older with a diagnosis of CP. Each adult with CP was matched to 3 controls who were matched for age, sex and GP-practice.*

2. Article Summary: you write a "large cohort study," I think this is a bit relative considering only 72 were diagnosed with dementia. It is also not written/described as such anywhere else in the paper. I suggest rewording to exclude the term "large."

Response: The fact that only 72 people were diagnosed with dementia is mentioned to be a limitation, however the description pertains to the total cohort size, which is relatively large (especially for this population). Therefore, we have left the description as a large cohort study, as this is a strength of this study. Please note that this section was meant to have the header 'strengths and limitations of this study', and so we have noted what we felt were the most notable strengths and limitations of the work.

3. Introduction, first paragraph:

- **Definition of CP: the term "infarct" is not commonly added here; an infarct may be a cause of the injury.**

Response: Thank you for pointing this out, we have removed the term 'infarct' so this sentence now reads as such:

"Cerebral palsy (CP) is the clinical term used for a spectrum of heterogeneous aetiologies and symptoms that result from an injury to the developing human brain"

- **I am surprised to see that "verbal communication" is listed as a most common presenting**

feature of CP along with gross and fine motor function. While it is certainly among the most common associated impairments, I suggest deleting, as there are many more common associated impairments.

Response: Thank you for pointing this out, we have removed verbal communication, and the sentence now reads as the following:

"The most commonly presenting feature of CP is impaired gross and fine motor functioning, which can lead to difficulties with gait, balance and posture."

4. Methods/participants:

- **While there is a statement referring to 3 references about participant selection, I think it is very important (since this paper is about people with CP) to clearly define/describe this population in the paper. For those of us who are not familiar with Read codes (maybe only used in UK?), please define what codes were used (add to an appendix, as you did for dementia Read codes (appendix II)). Not all research groups/countries define CP in the same way, and I would not only like to see the Read codes, but also understand what "for each patient identified as having CP" means? In addition, does CP refer to congenital or postneonatal CP? You may not have this information, but this should be mentioned as this may affect your results.**

Response: We have included an example of a Read Code and linked term in text to help people who may not be as familiar with what Read Codes are:

"To identify people with CP, we used Read codes (unique alphanumeric codes that link to specific clinical terms relating to CP recorded in GP data: e.g., the Read Code F23y400 is linked to the clinical term 'ataxic diplegic cerebral palsy')"

And also included the list of terms within the appendix as suggested. For ease of you checking I have also included that list for you below:

Read Code	***Description***
F23y400	*Ataxic diplegic cerebral palsy*
F23y000	*Ataxic diplegic cerebral palsy*
F137.11	*Athetoid cerebral palsy*
F137000	*Athetoid cerebral palsy*
F2B..00	*Cerebral palsy*
F2Bz.00	*Cerebral palsy NOS*
F230100	*Cerebral palsy with spastic diplegia*
F23..00	*Congenital cerebral palsy*
F23y300	*Dyskinetic cerebral palsy*
F23..12	*Infantile cerebral palsy*
F23y200	*Spastic cerebral palsy*
F230111	*Spastic diplegic cerebral palsy*
F2B1.00	*Spastic hemiplegic cerebral palsy*
F2B0.00	*Spastic quadriplegic cerebral palsy*
F23yz00	*Other infantile cerebral palsy NOS*
Fyu9000	*[X]Other infantile cerebral palsy*
F23y.00	*Other congenital cerebral palsy*
F23y100	*Flaccid infantile cerebral palsy*
F2By.00	*Other cerebral palsy*
Fyu9.00	*[X]Cerebral palsy and other paralytic syndromes*
F23z.00	*Congenital cerebral palsy NOS*

F23..11 Congenital spastic cerebral palsy
F23y600 Choreoathetoid cerebral palsy

- **You mention "data was of sufficient quality to be used for assessment," what does this mean, please clarify. What did you deem as sufficient? There is no mention of missing data anywhere in the paper (it is marked as N/A in the STROBE checklist)? In my experience, it is unlikely that all people in this study would have complete data for each variable. If the code was not present in the database, was it assumed that the comorbidity wasn't present?**

Response: There were no missing data as we requested data for all people with a diagnosis of CP (as determined by a diagnosis of CP) and research standard data (plus 3 matched controls). We then examined their data. We have changed the description of the study from a longitudinal cohort study to retrospective cohort study so that this may make more sense (as we are only including people who have data in the analysis in the first place). There are also difficulties with inferring information about 'missing data' using this kind of dataset. Whereas with a traditional epidemiological study that collects routine data we can know what data is missing, this is clinical GP data and so data will only be collected if people attend their GP (therefore, we can't realistically know what is missing as everyone goes to the GP for different reasons, and they aren't asked yes/no whether they have a list of pre-specified conditions in the same way that we would see in an epidemiological study).

We have included the following to clarify what is meant by data having sufficient quality:

i.e., data was of sufficient quality to be used for assessment including criteria such as the patient having a complete and valid first registration date that follows their date-of-birth and the GP practice not having any significant gaps in recording data

5. Methods/confounders, last sentence: there may be a typo in the categorization of GP visits as 2-11.9?

Response: I understand why you would think this is, it would be very difficult to visit the GP 11.9 times! As this was a mean number of visits that we calculated based on how many visits on average a person had with their GP prior to being censored/event date it was possible that some people could have a value of 11.9 and we opted to use 12 as the cutpoint for frequent GP visits. Therefore, 11.9 was where we set the upper boundary.

6. Methods/statistical analysis: again, missing data and how it was handled? If N/A, please also describe.

Response: Please see response above.

7. Results/descriptive data: participant characteristics: please clarify mean age of sample. Does this mean only those with CP or not CP, or both?

Response: As controls were matched for age this refers to both, we have clarified this in the paper:

"The mean age of the sample (both adults with CP and their matched controls) was 33.3 years (SD: 15.5 years"

8. Tables: I suggest looking at examples of papers on the BMJ Open website. Your tables could be improved. Remember that tables should be self explanatory. Pay special attention to table 2, this table has terms (cerebral palsy in title but CP below) and abbreviations (HR, ID)

that are not defined. If you have % in the column header, you do not need a % behind every result number below. What are the numbers in () under Incidence per 1000 person years, possibly confidence intervals? This is not explained in the paper under statistical analysis? What are the 1's under No CP? Please be consistent with decimals throughout paper, tables and appendixes. Also, in table 3, the n numbers are not correct? CP=19 and No CP=53?

Response: Thank you for pointing out these inconsistencies. These have now been amended in the tables and I have included a copy of the amended table below (nb 1 refers to the reference group which has been clarified):

Table 2: Risk of dementia in people with CP (n=1703) compared with age, sex and GP practice-matched controls (n=5109).

	Events n (%)	*Person years in 1,000s*	*Incidence per 1,000 person years (95% CI)*	*Model 1* *HR (95% CI) and p-value*	*Model 2* *HR (95% CI) and p-value*	*Model 3* *HR (95% CI) and p-value*
No CP	53 (1.04)	56.66	0.00094 (0.0007-0.0012)	1 (Reference)	1 (Reference)	1 (Reference)
CP	19 (1.12)	14.57	0.00130 (0.0008-0.0020)	2.69 (1.44-5.00), p=.002	1.92 (0.92-4.02), p=.08	1.76 (0.73-4.25), p=.21

Abbreviations: CI (confidence interval); HR (hazard ratio)

Model 1: Unadjusted

Model 2: Adjusted for baseline (i.e., pre-dementia) ID, sensory impairments and epilepsy.

Model 3: Adjusted for model 2 plus baseline (i.e., pre-dementia) diagnosis of diabetes, heart disease, stroke, depression, and average annual GP visits.

9. I appreciate the honesty in the discussion section about the limitations of this study, and suggestions for further studies with larger cohorts. One point that I am missing is about the correctness/completeness of the CPRD and HES datasets. Are there any references to the reliability/validity of these datasets and how it may affect your results. In my experience, it is likely that some people with CP maybe missing from the dataset, or have an erroneous CP diagnosis, or any of the other reported comorbidities/conditions/confounders.

Response: There is no sensitivity study that has ever looked at case completeness for CP in a dataset of this kind. However, we have acknowledged this limitation within our discussion:

"An additional limitation pertains to the dataset used; there is no study that has formally examined the sensitivity of CPRD data for identifying people with CP which could lead to possible issues with missing data for adults with CP. It is also worth noting that HES data only captured 60% of practices in England and Wales, and so there is also a possibility of missing dementia diagnoses."

Reviewer: 2
Reviewer Name: Paola Gilsanz
Institution: Kaiser Permanente Division of Research
Please state any competing interests or state 'None declared': None declared.

The possible association between cerebral palsy and dementia risk is an interesting topic and I'm happy these authors are investigating it. Below are some comments that may further strengthen the paper.

Main comments:

- **The causes of early onset dementia may differ from later onset dementia and I suggest the authors conduct sensitivity analyses separating early vs later onset dementia.**

Response: I do wholeheartedly agree! However, we have acknowledged this within the discussion, and due to the low numbers of people diagnosed this would not be a feasible analysis which I would have concerns about the validity of:

"Furthermore, while there were some interesting observations within this study (such as the higher proportion of people with CP who were diagnosed with an early-onset dementia which is defined as onset at 65 or younger), the low numbers of participants who were diagnosed with dementia meant that we were not able to explore this finding with formal inferential statistics."

- **The cohort starts to follow individuals as young as 18, when they are likely not at risk for dementia. I recommend the authors start dementia follow-up at an older age or justify why they are starting dementia follow up at such an early age.**

Response: This was something that was initially considered (only including people at the age of 40 or older), however as you point out below this is a dynamic cohort and so only including people who were 40 or older at baseline could mean that we miss out on some interesting cases who could be in the study for longer. To determine whether this had a notable impact on our results we have included a second sensitivity analysis where we have only included people who were aged 40 or older at baseline, and the results look fairly consistent (please see below for the included text and table to be included in Appendix III:

"For our second sensitivity analysis we examined whether only including people aged 40 or older at baseline had an impact on our results (see Appendix III). For this analysis the sample size was reduced to 490 people with CP and 1,470 matched controls. A total of 16 (3.27%) of people with CP developed dementia, whereas 52 (3.54%) of the matched controls developed dementia. The results from the Cox Proportional Hazards Regression also indicated an increased hazards of developing dementia in adults with CP when compared to matched controls in unadjusted analyses (HR 2.46, 95% CI: 1.20-4.33, p=.014), which was also attenuated after accounting for CP co-morbidities (HR 1.07, 95% CI: 0.70-3.36, p=.29) (see Appendix III)."

Risk of dementia in people with Cerebral Palsy (n=490) compared with age, sex and practice-matched controls (n=1,470) when aged 40 or older at baseline.

	Events n	*Person years in 1,000s*	*Incidence per 1,000 person years*	*Model 1* *HR (95% CI) and p-value*	*Model 2* *HR (95% CI) and p-value*	*Model 3* *HR (95% CI) and p-value*
No CP	52 (3.54%)	17.38	0.0030 (0.0023-0.0039)	1 (Reference)	1 (Reference)	1 (Reference)
CP	16 (3.27%)	4.30	0.0037 (0.0023-0.0061)	2.46 (1.20-4.33), p=.014	1.07 (0.70-3.36), p=.29	0.69 (0.54-3.58), p=.49

Other comments:

- **It would be helpful to readers if the authors were explicit that this is a dynamic cohort in which people with CP can join between 1987 to 2015.**

Response: We have made this clearer within our methods:

"The data requested for this study covers the period 1987 to 2015 and participants could be enrolled in the study at any time between these years."

- **It would be helpful for readers if the authors spell out intellectual disability (as opposed to saying ID) in abstract.**

Response: We have made the suggested change:

"This association was attenuated when CP co-morbidities (sensory impairment, intellectual disability and epilepsy) were accounted for (HR: 1.92, 95% CI: 0.92, 4.02)."

- **The abstract states that the mean age of participants was 33.3 years. I assume this is at baseline but please make it explicit.**

Response: We have made the suggested change:

"The mean baseline age of participants was 33.30 years (SD: 15.48 years) and 46.8% of the sample were female."

- **Please provide more information regarding how age was operationalized for the purposes of matching.**

Response: Age was based on date of birth and participants were matched based on their year of birth. We have clarified this in the methods:

"…we identified 1,705 people with CP who were matched to 5,115 age, sex and GP-practice matched controls without CP. Participants were matched for age based on their year of birth."

- **I am not very familiar with the datasets used in this paper and have a few questions related what they include. Is it possible for some one to have transfer out of the CPRD database and then return? If so, how are these individuals handled in these analyses? Does the HES include information related to dementia diagnoses prior to the implementation of ICD-10 codes since the start of dementia follow-up time is 1987?**

Response: Transfer out of CPRD was one of the reasons for being treated as censored for the sake of this analysis (therefore they could not be re-admitted to the study again):

"Where no event of dementia was identified participants were followed-up to the earliest of the following: transfer out of CPRD, death or the end of the follow-up period (November 2015)."

Having checked the data only codes pertaining to ICD-10 were included and unfortunately our data agreement means that we have had to destroy our original copies of the data and would not be able to identify any people with ICD-9 codes. However, as most people were identified through their GP surgery (or the earlier date was through their GP surgery) we don't anticipate this would have much impact on our results.

- **I recommend the authors use age as the timescale for their Cox proportional hazards models and calculate age adjusted incidence rates with confidence intervals.**

Response: We appreciate this point, but when we use age as the timescale for the Cox Proportional Hazards model it does not make any difference to the results (as the analysis is a stratified analysis that compares people with CP to age-matched controls and so changing the timescale from time since start of the study to birth year does not change anything, as the underlying model is comparative). Furthermore, this kind of analysis is something we have done in previous studies and we wish to remain consistent with that. Calculating age-adjusted incidence rates would likely require stratifying our analysis by age band, which we unfortunately would not have the power to do due to the low number of people who developed dementia (this would likely result in unstable estimates with wide confidence-intervals). However, we agree if the data were suitable it would be very useful to have age-adjusted incidence rates.

Reviewer: 3

Reviewer Name: Deborah E. Thorpe, PT, PhD

Institution and Country: The University of North Carolina at Chapel Hill, United States

Please state any competing interests or state 'None declared': None declared

This is a well-written original paper presenting the risk of incident dementia in adults with cerebral palsy (CP) compared to age, sex and primary care matched controls. The methodology of secondary data analysis on large data sets to answer these questions is very appropriate.This paper is the first to address incident dementia in a large cohort of adults with CP and begins to discern whether incidence of dementia is a result of the diagnosis of CP itself or perhaps a result of the associated co-morbidities that develop secondary to the disorder. This paper emphasizes that adults with CP have an increased hazard of developing dementia and that continuing research into dementia by severity of CP and presence of secondary co-morbidities is warranted. We have speculated for some time (secondary to clinical observations) that adults with CP experience mental health disorders at an equal or elevated rate as compared with peers without CP. These results and those in the future will help to develop appropriate screening and intervention for dementia for individuals with cerebral palsy.

Response: Thank you for taking the time to read through this paper and provide us with this comment.

Reviewer: 4

Reviewer Name: Dr. Arlene Mannion

Institution: National University of Ireland, Galway

Please state any competing interests or state 'None declared': None declared

Summary of paper:

The manuscript entitled 'The risk of dementia in adults with cerebral palsy: A matched cohort study using general practice data' is an interesting study on the risk of dementia in adults with cerebral palsy and the role that comorbidities play in this risk. The study included 1,703 adults with cerebral palsy and 5,109 matched controls. Strengths of the manuscript include a large sample size collected from a longitudinal database.

Abstract:

1. Adjust wording so that each section reads as a whole sentence on its own, rather than a short number of words. More detail needed on Objectives, Design, Setting.

Response: The phrasing of the abstract is consistent with many papers that are published in this journal and we also have a word-limit to consider. For the sake of brevity and clarity the abstract will be left as statements rather than sentences.

Article Summary:

2. This should focus on the strengths of the study and the novel findings, rather than only focusing on the limitations of the study.

*Response: Your comment made me realise that I had not used the correct heading for this section (so thank you for pointing this out). The journal stipulates the following about that section…**An Article Summary, placed after the abstract, consisting of the heading 'Strengths and limitations of this study'**, and containing up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. They should not include the results of the study.*

Therefore, hopefully the amended section header should make it clearer that this is strengths and limitations rather than study summary.

Introduction:

3. When discussing the comorbidities associated with Cerebral Palsy, include other comorbidities such as sleep problems, gastrointestinal symptoms and autism spectrum disorder, and include literature to support the occurrence of these comorbidities.

Response: I agree that there are a number of co-morbidities that have not been mentioned specifically. Beyond the three you have drawn our attention to there are a range of other issues that are linked with CP. However, I feel drawing attention to specific co-morbidities is beyond the scope of this paper, and instead we opted to use broad descriptors (i.e.., behavioural difficulties) to capture this range of possible co-morbidities.

4. The authors make the point that no study has examined whether CP is associated with dementia. However, before making this point, it would be the important to include the following in the Introduction, as well as including how the current study expands upon this previous research:

Smith K, Peterson M, Victor C, Ryan J. INCIDENCE OF DEMENTIA IN ADULTS WITH CEREBRAL PALSY: A UK COHORT STUDY. Innov Aging. 2018;2(Suppl 1):980. doi:10.1093/geroni/igy031.3628

Holtzman DM: Role of apoE/Aβ interactions in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy. J. Mol. Neurosci.17(2),147–155 (2001)

Response: The first is an abstract of this work that was published at a conference, and adding this into the paper wouldn't make much sense (as it a previous, and lower quality, iteration of this work). I have also examined the second suggested paper and I cannot see anything that may be relevant for this paper as I cannot see anything that pertains to cerebral palsy (please do point out if you think I have missed something!). As such, I disagree that reference to either of these abstracts is

necessitated.

Results:

5. p.9. Need to give the n of participants as well as percentage.

Response: We have added in the n as requested:

"The mean age of the sample (both adults with CP and their matched controls) was 33.3 years (SD: 15.5 years) and 46.8% (n=3,118) of the sample were female."

Discussion:

6. While comorbidities such as intellectual disability, epilepsy, and sensory impairments were considered as comorbidities, other comorbidities such as other medical conditions, including gastrointestinal symptoms and sleep problems were not included. The lack of these comorbidities should be discussed as a limitation of the study.

Response: I am afraid that I must respectfully disagree with the reviewer on this point. We included conditions that would act as confounders (variables that share an association with both the predictor and the outcome that could explain the relationship between the predictor and outcome). Gastrointestinal symptoms are not linked with dementia and there is a lack of evidence on sleep disorders in adults with CP, so including that as a confounder would not be theoretically justifiable. Given that the association was attenuated after accounting for the CP co-morbidities that we did include there would not be any real rationale for including more co-morbidities (as we have already shown that the association is attenuated).

7. Greater emphasis needs to be placed on the novelty and significance of the findings in the conclusion paragraph.

Response: I feel that the existing conclusion has already stated the novelty of the findings, and given all the limitations with the study I do not think that it is responsible of me as a researcher to state that these results have more significance than they do. When writing this paper I tried to think of adults with cerebral palsy who would be reading this work, and not over-stating the importance of findings (I think sometimes researchers can do more harm than good when they try and overstate the importance of what they have done). As such, I feel that the conclusion adequately sums up what we did without over-stating the importance of results.

Style and Formatting:

8. All n, SD, p etc. should be in italics.

Response: Having checked the formatting requirements for this journal it is not stipulated that all these have to be in italics (and indeed having checked some of the published papers this is not done for any of the papers that I looked at). Given that this is not a requirement for this journal I have opted not to do this.

Reponse: This would be something that would be applicable for APA formatting, however

9. p.5 Correct typo '131 million'

Response: Thanks for pointing this out! This has now been changed:

"It is estimated that 47 million people worldwide live with dementia, and that by 2050 this will increase to 131 million."

VERSION 2 – REVIEW

REVIEWER	Sandra Julsen Hollung Cerebral Palsy Registry of Norway, Vestfold Hospital Trust, Norway
REVIEW RETURNED	17-Sep-2020

GENERAL COMMENTS	Thank you for this new version of the paper. I appreciate that the authors updated the paper according to the first round of reviewer's comments accordingly, well done. I only have a couple minor comments on this version: 1. Page 12, sentence: "In people with CP the presence of ID is linked to increased grey matter pathology, which is linked with an increasing risk of developing dementia." This sentence is written a bit "strongly," as though it is a definitive fact that among all people with CP who have ID, they also have grey matter pathology, which develops into dementia. I suggest a minor re-write, for example: In people with CP the presence of ID is often linked to increased grey matter, which may be linked with an increasing risk of developing dementia." 2. As I mentioned in the first review, your tables could be greatly improved. Tables present important information! I see that some improvements were made, but not consistently. Please make sure all 3 tables have the same formatting. Again, I suggest looking through how BMJ Open presents tables on the online versions. For example, when presenting descriptive statistics – 1 column for N and another for % (avoid n and % in the same column, as well as remove % after every number in all rows), and present only p-values and 95% CIs.

REVIEWER	Paola Gilsanz Kaiser Permanente Division of Research
REVIEW RETURNED	29-Sep-2020

GENERAL COMMENTS	I'd like to thank the authors efforts in replying to my prior comments. I only have one follow up comment: It would be helpful to see if/how effect estimates change if the follow up time were to start when ICD-10 codes were implemented since individuals can not obtain the outcome before then.

REVIEWER	Dr. Arlene Mannion National University of Ireland, Galway
REVIEW RETURNED	12-Oct-2020

GENERAL COMMENTS	While some of the feedback from the initial review has been addressed, there are still a number of remaining points that have not been addressed. Introduction: 1. When discussing the comorbidities associated with Cerebral Palsy, include other comorbidities such as sleep problems, gastrointestinal symptoms and autism spectrum disorder, and include literature to support the occurrence of these comorbidities.

	2. The authors make the point that no study has examined whether CP is associated with dementia. However, before making this point, it would be the important to include the following in the Introduction, as well as including how the current study expands upon this previous research: Smith K, Peterson M, Victor C, Ryan J. INCIDENCE OF DEMENTIA IN ADULTS WITH CEREBRAL PALSY: A UK COHORT STUDY. Innov Aging. 2018;2(Suppl 1):980. doi:10.1093/geroni/igy031.3628 Holtzman DM: Role of apoE/Aβ interactions in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy. J. Mol. Neurosci.17(2),147–155 (2001) Discussion: 3. While comorbidities such as intellectual disability, epilepsy, and sensory impairments were considered as comorbidities, other comorbidities such as other medical conditions, including gastrointestinal symptoms and sleep problems were not included. The lack of these comorbidities should be discussed as a limitation of the study. 4. Greater emphasis needs to be placed on the novelty and significance of the findings in the conclusion paragraph. Style and Formatting: 5. All n, SD, p etc. should be in italics.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Sandra Julsen Hollung
Institution and Country: Cerebral Palsy Registry of Norway, Vestfold Hospital Trust, Norway
Please state any competing interests or state 'None declared': None declared

Thank you for this new version of the paper. I appreciate that the authors updated the paper according to the first round of reviewer's comments accordingly, well done. I only have a couple minor comments on this version:
1. Page 12, sentence: "In people with CP the presence of ID is linked to increased grey matter pathology, which is linked with an increasing risk of developing dementia."
This sentence is written a bit "strongly," as though it is a definitive fact that among all people with CP who have ID, they also have grey matter pathology, which develops into dementia. I suggest a minor re-write, for example: In people with CP the presence of ID is often linked to increased grey matter, which may be linked with an increasing risk of developing dementia."
Response: We have made the suggested changes
In people with CP the presence of ID may be linked to increased grey matter pathology [30], which is linked with an increased risk of developing dementia [31].

2. As I mentioned in the first review, your tables could be greatly improved. Tables present important information! I see that some improvements were made, but not consistently. Please make sure all 3 tables have the same formatting. Again, I suggest looking through how BMJ Open presents tables on the online versions. For example, when presenting descriptive statistics – 1 column for N and another

for % (avoid n and % in the same column, as well as remove % after every number in all rows), and present only p-values and 95% CIs.
Response: We have made the suggested changes pertaining to n and %'s and tried to make sure formatting is consistent. However, the tables all present very different information and so we are not able to format each to look exactly the same. All the information presented in Table 2 is necessary for presenting the pertinent information for the survival analysis, and the presentation of this data is in keeping with previous work presented in other journals.

Reviewer: 2
Reviewer Name: Paola Gilsanz
Institution and Country: Kaiser Permanente Division of Research, USA
Please state any competing interests or state 'None declared': None declared.

I'd like to thank the authors efforts in replying to my prior comments. I only have one follow up comment: It would be helpful to see if/how effect estimates change if the follow up time were to start when ICD-10 codes were implemented since individuals can not obtain the outcome before then.
Response: When we re-ran the analysis to only examine people enrolled from 1996 onwards (in the UK the ICD-10 started to be used in 1995) we had a total 5,516 people in the dataset, 41 of whom got a diagnosis of dementia during follow up (29 without CP which was 0.7% of the controls and 12 with CP which was 0.87% of people with CP).
The re-ran analysis found a significant unadjusted association between CP and the risk of being diagnosed with dementia during follow-up when compared with matched controls (HR 2.22, 95% CI: 1.11-5.05) which was again attenuated after controlling for confounders (HR 1.71, 95% CI: 0.47-6.23). As the overall estimate is not substantially effected (other than becoming less stable due to lowered power and wider confidence intervals) we don't feel that this additional analysis should be included in the paper, but we hope this helps to clarify for you that the change to ICD-10 didn't impact results.

Reviewer: 4
Reviewer Name: Dr. Arlene Mannion
Institution: National University of Ireland, Galway
Please state any competing interests or state 'None declared': None declared
While some of the feedback from the initial review has been addressed, there are still a number of remaining points that have not been addressed.

Response: I understand from the editor that our previous responses to the points below in our letter may not have been attached to the review, and I would like to reassure the reviewer that we did respond to each point that they made. We have included the responses below again.

Introduction:

When discussing the comorbidities associated with Cerebral Palsy, include other comorbidities such as sleep problems, gastrointestinal symptoms and autism spectrum disorder, and include literature to support the occurrence of these comorbidities.
Response: The reviewer is correct that there are a number of co-morbidities that have not been mentioned specifically. Beyond the three you have drawn our attention to there are a range of other issues that are linked with CP: it would be remiss to focus on these three specific co-morbidities, if we draw attention to those three then it raises the question why not all of the other specific co-morbidities? Drawing attention to every single co-morbidity linked with CP is beyond the scope of this paper, and instead we opted to use broad descriptors (i.e.., behavioural difficulties) to capture this range of possible co-morbidities.

The authors make the point that no study has examined whether CP is associated with dementia. However, before making this point, it would be the important to include the following in the Introduction, as well as including how the current study expands upon this previous research:

Smith K, Peterson M, Victor C, Ryan J. INCIDENCE OF DEMENTIA IN ADULTS WITH CEREBRAL PALSY: A UK COHORT STUDY. Innov Aging. 2018;2(Suppl 1):980. doi:10.1093/geroni/igy031.3628

Holtzman DM: Role of apoE/Aβ interactions in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy. J. Mol. Neurosci.17(2),147–155 (2001)
Response: The first is an abstract of this work that was published at a conference, there are many published papers that were previously abstracts at conferences that don't make reference to the abstract in the paper and we think it would read as odd to state that that the work was previously presented at a conference and published as an abstract (unless the reviewer and editors think otherwise?). We have changed the wording to make it clear that this refers to peer-reviewed published studies as we think that your point is that it isn't the first study per se:
"To the best of our knowledge, no peer-reviewed published study has examined whether CP is associated with dementia."
The second reference has no link to cerebral palsy (we have looked and cannot see anything that would be of relevance to this paper); please do correct us if we are wrong in this.

Discussion:
6. While comorbidities such as intellectual disability, epilepsy, and sensory impairments were considered as comorbidities, other comorbidities such as other medical conditions, including gastrointestinal symptoms and sleep problems were not included. The lack of these comorbidities should be discussed as a limitation of the study.
Response: We must respectfully disagree with the reviewer on this point. There is a very good theoretical reason to not include these as confounders and to not mention these as limitations. As I mentioned previously we included conditions that would act as confounders (variables that share an association with both the predictor and the outcome that could explain the relationship between the predictor and outcome). Gastrointestinal symptoms are not linked with dementia and there is a lack of evidence on sleep disorders in adults with CP, so including that as a confounder would not be theoretically justifiable. Given that the association was attenuated after accounting for the CP co-morbidities that we did include there would not be any real rationale for including more co-morbidities (as we have already shown that the association is attenuated).

7. Greater emphasis needs to be placed on the novelty and significance of the findings in the conclusion paragraph.
Response: I strongly feel this is not necessitated, and have left in the previous response. If other reviewers had raised the same issue I may have looked more carefully at this, but I think we need to think more about our role as socially responsible researchers when we are writing our research. The existing conclusion has already stated the novelty of the findings, and given all the limitations with the study I do not think that it is responsible of me as a researcher to state that these results have more significance than they do. When writing this paper I tried to think of adults with cerebral palsy who would be reading this work, and not over-stating the importance of findings (I think sometimes researchers can do more harm than good when they try and overstate the importance of what they have done). As such, I feel that the conclusion adequately sums up what we did without over-stating the importance of results.

Style and Formatting:

8. All n, SD, p etc. should be in italics.

Response: Having checked this is not a requirement for this journal, and all the papers that I examined online did not do this. As such, we have opted not to make this change.

VERSION 3 – REVIEW

REVIEWER	Paola Gilsanz Kaiser Permanente Northern California Division of Research, USA
REVIEW RETURNED	23-Nov-2020

GENERAL COMMENTS	I have no additional comments.

REVIEWER	Dr. Arlene Mannion National University of Ireland Galway
REVIEW RETURNED	20-Nov-2020

GENERAL COMMENTS	I would like to thank the authors for addressing all comments, and giving a thorough explanation of their rationale.