BMJ Open

Risk of dementia in adults with cerebral palsy: a matched cohort study using general practice data

Kimberley J Smith ,[1] Mark D Peterson,[2] Christina Victor,[3] Jennifer M Ryan[4]

To cite: Smith KJ, Peterson MD, Victor C, *et al*. Risk of dementia in adults with cerebral palsy: a matched cohort study using general practice data. *BMJ Open* 2021;**11**:e042652. doi:10.1136/bmjopen-2020-042652

► Prepublication history and additional materials for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-042652).

Received 10 July 2020
Revised 08 November 2020
Accepted 25 November 2020

[1]FHMS, University of Surrey, Guildford, UK
[2]Physical Medicine & Rehabilitation, University of Michigan, Ann Arbor, Michigan, USA
[3]College of Medical Health and Life sciences, Brunel University College of Health and Life Sciences, Uxbridge, UK
[4]Public Health and Epidemiology, Royal College of Surgeons in Ireland, Dublin, Ireland

Correspondence to
Dr Kimberley J Smith;
Kimberley.j.smith@surrey.ac.uk

ABSTRACT

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

Design Retrospective cohort study.

Setting UK GPs 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 three controls who were matched for age, sex and GP. In total, 1703 adults with CP and 5109 matched controls were included in the analysis. The mean baseline age of participants was 33.30 years (SD: 15.48 years) and 46.8% of the sample were female.

Primary outcome New diagnosis of dementia during the follow-up period (earliest date of 1987 to latest date of 2015).

Results During the follow-up, 72 people were identified with a new diagnosis of dementia. The overall proportion of people with and without CP who developed dementia was similar (CP: n=19, 1.1%; matched controls n=54, 10.0%). The unadjusted HR suggested that people with CP had an increased hazard of being diagnosed with dementia when compared with matched controls (HR 2.69, 95% CI 1.44 to 5.00). This association was attenuated when CP comorbidities (sensory impairment, intellectual disability and epilepsy) were accounted for (HR 1.92, 95% CI 0.92 to 4.02).

Conclusions There was no difference in the proportion of people with CP and matched controls who were diagnosed with dementia during the follow-up. Furthermore, while there was evidence for an increased hazard of dementia among people with CP, the fact that this association was attenuated after controlling for comorbidities indicates that this association may be explained by comorbidities rather than being a direct result of CP. Findings should be interpreted with caution due to the low number of incident cases of dementia.

Strengths and limitations of this study

- This is the first study that has ever looked at the incidence of dementia in adults with cerebral palsy (CP).
- This is a large cohort study with 1703 adults with cerebral palsy (and 5109 age, sex and general practice-matched controls) followed up for a mean of 6.5 years (minimum 0.04 to maximum 28.0 years).
- Only 72 people were diagnosed with dementia during the follow-up, limiting the ability to conduct additional stratified analyses for proposed effect modifiers.
- We were not able to account for subtype of CP or dementia within our analyses.

INTRODUCTION

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.[1 2] The most commonly presenting feature of CP is impaired gross and fine motor functioning, which can lead to difficulties with gait, balance and posture.[3] However, additional comorbidities commonly observed in this population can include issues such as intellectual disability (ID), epilepsy, cognitive difficulties, behavioural difficulties and sensory impairments.[3 4]

Life expectancy for people with CP is similar to the general population, especially in the absence of severe impairments.[5 6] While the brain injury that causes CP is non-progressive,[7] there is evidence that ageing with CP is associated with a higher risk of developing secondary conditions and complications such as frailty, sarcopenia, osteoporosis, osteoarthritis, heart disease and chronic obstructive pulmonary disease.[8–11] However, there is a lack of research examining whether adults with CP may have an increased risk of developing age-related cognitive disorders, such as dementia.

Dementia is the diagnostic term used to capture a progressive acquired syndrome that impacts brain pathology and presents symptomatically as a substantial decline in cognitive functioning across multiple domains.[12] It is estimated that 47 million people worldwide live with dementia, and that by 2050, this will increase to 131 million.[13] There have been a number of different risk factors proposed to increase a person's risk of developing

dementia. The most commonly observed in the general population are advanced age, vascular risk factors, poorer baseline cognition, genetics and family history.[14] However, there is a recognition that there is also an increased risk of dementia in people living with long-term conditions. Common comorbidities in CP such as sensory impairments, ID and epilepsy[3 4] are also known risk factors for the development of dementia.[15–17] Furthermore, some of the complications that adults with CP have a higher risk of developing, such as metabolic abnormalities, cardiovascular disease and depression,[9 10 18 19] are all linked with a greater risk of dementia in the general population.[20 21]

Alongside the possible role of comorbidities and complications in increasing the risk of dementia among people with CP, it has been suggested that CP could lead directly to dementia due to the underlying brain injury.[22] However, the evidence linking brain injury with dementia is conflicting.[23]

To the best of our knowledge, no peer-reviewed published study has examined whether CP is associated with dementia. The aim of this study is to examine whether people with CP have a higher risk of developing dementia than age, sex and general practice (GP)-matched controls using longitudinal data from the Clinical Practice Research Datalink (CPRD) database and linked Hospital Episode Statistics (HES).

METHODS

Datasets

We used the CPRD database, which collects consultation data from 4.4 million people in 674 consenting GPs across the UK.[24] CPRD obtained approval from a national research ethics committee for researchers to use deidentified data for observational research subject to the approval of a study protocol from the Independent Scientific Advisory Committee (online supplemental appendix 1). On approval of a protocol, researchers are able to access deidentified clinical data routinely recorded by GPs such as clinical events, prescriptions, diagnostic testing, lifestyle information, preventative care or anthropometric measures. 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. Participants were followed up for a mean of 6.5 years (minimum 0.04 to maximum 28.0 years).

Diagnosis of dementia in the UK can take place in either a hospital or GP settings. Therefore, we also used patient-level linked HES data to identify cases of dementia. HES data contains information on hospital utilisation including admissions, outpatient appointments and accident and emergency attendance. CPRD has linked HES data for approximately 60% of patients in England and Wales.

Participants

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, eg, the Read Code F23y400 is linked to the clinical term 'ataxic diplegic CP') (see online supplemental appendix 2). For each patient identified as having CP, we obtained data for three age, sex and GP practice-matched controls without CP. Each included patient was required to be 18 or older and have data that was judged to be research standard (ie, data were 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).

The index date for the study was the latest of the following: (a1) The date the patient registered with their GP; (2) The date that their data became research standard and (3) The year within which they turned 18. Following exclusions based on these criteria we identified 1705 people with CP who were matched to 5115 age, sex and GP practice-matched controls without CP. Participants were matched for age based on their year of birth. Two patients with CP and their respective matched controls (n=8) were removed from the analysis as the patients with CP had a diagnosis of dementia identified in HES records that preceded the index date. This left a total of 1703 adults with CP and 5109 matched controls. The index date for each control was set as the same date as their matched patient with CP. For more information about participant selection please see.[8 9 18]

Identification of dementia

To identify dementia in CPRD, we used Read codes developed by the Cambridge Primary Care Unit[25] as well as previous research that has used CPRD data to diagnose dementia.[26] For a list of read codes used see online supplemental appendix 2. Read codes relating to a history of dementia, family history of dementia or dementia check-up were not included as we were interested in the first recording of a dementia diagnosis. To identify dementia using HES data, we used the following ICD-10 codes: E512, F00, F01, F02, F03, F10.6, F10.7, G30 or G31.0 as documented in previous work.[26]

We identified the date of the first recording of a dementia diagnosis following the index date. For those people who were identified as having a diagnosis of dementia in both the CPRD and HES datasets, we used the earlier date of diagnosis as the event date. 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).

Confounders

We examined chronic conditions associated with both CP and dementia as potential confounders. Using Read Codes in Smith *et al*[18] Ryan *et al*[9] or the Cambridge Primary Care Unit codelists[25] we identified diabetes, heart disease, stroke, depression, ID, epilepsy and sensory impairment (visual and/or hearing impairment). For each condition, we only included those that occurred before the dementia

event date (eg, a depression diagnosis needed to be made prior to the dementia diagnosis to be included as a confounder). We also included average annual GP visits as a potential confounder, as people with CP may attend their GP more frequently than those without CP, and those who attend the GP more often may be more likely to be diagnosed with dementia. We categorised average GP visits as 0–2 visits per year, 2–11.9 visits per year or ≥12 visits per year following Smith *et al*.[18]

Statistical analysis

Descriptive statistics were calculated to present the characteristics of the sample, and cross-tabulations calculated to determine potential differences in baseline characteristics between people with CP and matched controls. A descriptive analysis was performed to determine the ages at which dementia diagnoses were made in people with CP and matched controls. We also calculated the incidence rate of dementia per 1000 person-years for both groups.

We used stratified Cox proportional hazards regression with dementia diagnosis as the outcome to compare the hazard of dementia between patients with and without CP. The hazards regression was first run unadjusted (model 1). In model 2, we adjusted for CP comorbidities that have been proposed to be risk factors for dementia (ID, sensory impairment and epilepsy). In model 3, we adjusted for CP complications also associated with dementia risk (diabetes, stroke, heart disease) and average GP visits.

Prior to running the Cox proportional hazards regression, we plotted scaled Schoenfeld residuals against time to assess the assumption of proportional hazards, and the assumption of proportionality was met. All analyses were conducted using STATA V.16.0.

Sensitivity analyses

We reran the model excluding any cases of dementia that were identified within 12 months of the index date, as these could indicate prevalent rather than incident cases of dementia (as on registering at a new practice a person may have any prevalent conditions recorded by their new GP as a diagnosis). We also ran a second sensitivity analysis only including people aged 40 or older at baseline to account for the fact that dementia is typically seen in people who are older.

Patient and public involvement

There was no patient and public involvement in the design of this study.

RESULTS

Descriptive data: participant characteristics

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=3118) of the sample were female. Sample characteristics stratified by CP status are described in table 1. Cross-tabulation analyses revealed that the sample with CP were more likely to have a higher annual number of GP visits, and more likely to have a baseline diagnosis of stroke, epilepsy and/or sensory impairment (table 1). In addition, we found that the sample with CP were less likely to have a baseline diagnosis of diabetes or heart disease than the matched control group (table 1).

Risk of dementia

In total, 72 people were diagnosed with dementia during the follow-up period (table 2). A total of 53 (1.04%) people from the matched control group developed dementia over a median of 10.95 years of follow-up (minimum of 0.14 years to maximum of 28.01 years). Whereas a total of 19 (1.12%) people with CP developed dementia over a median of 7.15 years of follow-up (minimum of 0.04 years to maximum of 27.94 years). The dementia incidence rate for people with CP was 0.0013 per 1000 person-years, and 0.0009 per 1000 person-years (table 2).

Unadjusted stratified Cox modelling indicated that people with CP had an increased hazard of dementia compared with age-matched, sex-matched and GP-matched controls without CP (HR 2.69, 95% CI 1.44 to 5.00, p=0.002). However, after adjusting for CP comorbidities the association became non-significant (HR 1.92, 95% CI 0.92 to 4.02, p=0.08) and remained non-significant in the fully-adjusted model (see table 2). Of the 72 people who were diagnosed with dementia we found that 47% (n=9) of people with CP who were diagnosed with dementia were aged 65 years or younger, compared with 5.7% (n=3) of people who did not have CP (table 3).

Results from our first sensitivity analysis excluding any dementia diagnoses made within 12 months of the index date revealed that a total of 51 people without CP (1.00%) and 16 people with CP (0.94%) were diagnosed with dementia (online supplemental appendix 3). As with the primary analysis, there was evidence for an unadjusted increased hazard of dementia in adults with CP when compared with matched controls (HR 2.50, 95% CI 1.28 to 4.86, p=0.007), whereas after adjusting for CP comorbidities, the association was attenuated (HR 1.95, 95% CI 0.90 to 4.22, p=0.09) and remained non-significant in the fully adjusted model (HR 1.90, 95% CI 0.75 to 4.79, p=0.18). For our second sensitivity analysis, we examined whether only including people aged 40 or older at baseline had an impact on our results (see online supplemental appendix 3). For this analysis, the sample size was reduced to 490 people with CP and 1470 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 with matched controls in unadjusted analyses (HR 2.46, 95% CI 1.20 to 4.33, p=0.014), which was also attenuated after accounting for CP comorbidities (HR 1.07, 95% CI 0.70 to 3.36, p=0.29) (see online supplemental appendix 3).

Table 1 Characteristics of participants

		Cerebral palsy (n=1703)		Matched controls (n=5109)		
		N	%	N	%	X^2
Baseline age	<40	1213	71.22	3639	71.23	–
	40–49	223	13.68	669	13.09	
	50–59	134	7.87	402	7.87	
	60–69	77	4.52	231	4.52	
	≥70	56	3.29	168	3.29	
Sex	Male	906	53.20	2718	53.20	–
	Female	797	46.80	2391	46.80	
Average GP visits per year	0–2 per year	133	7.80	716	14.01	X^2=329.14, p<0.001
	2.1–11.9 per year	1177	69.11	4029	78.86	
	≥12 per year	393	23.08	364	7.12	
Depression	Yes	310	18.20	864	16.91	X^2=1.494, p=0.22
	No	1393	81.80	4245	83.09	
Diabetes	Yes	60	3.52	253	4.95	X^2=5.95, p=0.02
	No	1643	96.48	4856	95.05	
Heart disease	Yes	182	10.69	640	12.53	X^2=4.08, p=0.04
	No	1521	89.31	4469	87.47	
Stroke	Yes	69	4.05	99	1.94	X^2=23.73, p<0.001
	No	1634	95.95	5010	98.06	
Sensory impairment	Yes	298	17.50	535	10.47	X^2=58.76, p<0.001
	No	1405	82.50	4574	89.53	
Epilepsy	Yes	427	25.07	70	1.37	X^2=928.36, p<0.001
	No	1276	74.93	5039	98.63	
Intellectual disability	Yes	361	21.20	24	0.47	X^2=1000, p<0.001
	No	1342	78.80	5085	99.53	

This table presents the distribution of the sociodemographic and health-related characteristics of patients within the sample.

DISCUSSION

Results from this analysis provide the first evidence that CP is associated with an increased hazard of developing dementia, but that this increased hazard is explained by the presence of CP comorbidities. It is also worth noting that the proportion of those who developed dementia did not differ between people with and without CP and the overall incidence rate of dementia was low for both groups. However, a higher proportion of those people with CP who were diagnosed with dementia were diagnosed with dementia at 65 or younger when compared with those who did not have CP though the low number of dementia cases and descriptive analyses limit inferences.

Our results indicated that the observed association between CP and dementia was attenuated after adjusting for CP comorbidities. However, there is heterogeneity in

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

	Events n	Events %	Person-years in 1000s	Incidence per 1000 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 to 0.0012)	1 (reference)	1 (reference)	1 (reference)
CP	19	1.12	14.57	0.00130 (0.0008 to 0.0020)	2.69 (1.44 to 5.00), p=0.002	1.92 (0.92 to 4.02), p=0.08	1.76 (0.73 to 4.25), p=0.21

Model 1: unadjusted.
Model 2: adjusted for baseline (ie, predementia) ID, sensory impairments and epilepsy.
Model 3: adjusted for model 2 plus baseline (ie, predementia) diagnosis of diabetes, heart disease, stroke, depression and average annual GP visits.
CP, cerebral palsy; GP, general practice; ID, intellectual disability.

Table 3 Age at dementia diagnosis

Age at diagnosis	CP diagnosed with dementia (n=19)		No CP diagnosed with dementia (n=53)	
	N	%	N	%
<50	3	15.79	2	3.77
50–65	6	31.58	2	3.77
66–80	3	15.79	17	32.08
≥80	7	36.84	32	60.38

CP, cerebral palsy.

the kinds of comorbidities that people with CP can present with in adulthood. Brown and Eunson[27] suggested that comorbidities in CP can be split into cocausal comorbidities (comorbidities caused by the same underlying brain pathology which includes ID), complications (secondary comorbidities that arise due to complications of living with CP, such as osteoarthritis) and co-occurring comorbidities (comorbidities that are not linked with CP directly). There is evidence that cocausal, co-occurring comorbidities and complications linked with CP are all linked with an increased risk of dementia in general population samples. Cocausal and co-occurring comorbidities such as ID, epilepsy and sensory impairments are all independently associated with an increased risk of dementia.[15–17] Furthermore, complications such as cardiovascular disease and depression are also linked with an increased risk of dementia.[20 21]

The results from our analyses indicated that the increased hazard was attenuated when we controlled for cocausal CP comorbidities: sensory impairment, epilepsy and ID. However, it is worth noting that while all these CP comorbidities have been linked to dementia,[15–17] it is ID that is most consistently implicated as being a risk factor for dementia.[28] It is estimated that 20%–45% of people with CP have comorbid ID,[29 30] and evidence from the general population indicates that ID is linked with a greater risk of dementia.[15] 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] It is possible that comorbid ID could be an important modifier of dementia risk in this population. However, due to the low number of participants who developed dementia we were unable to conduct stratified analyses to examine this with our data.

Due to the low number of people with CP who developed dementia, we were not able to look at which risk factors were linked with an increased risk of dementia in adults with CP. There are a broad range of risk factors implicated in dementia risk beyond CP comorbidities such as vascular risk factors, older age, baseline cognition, lifestyle and genetic risk.[14] Future work could examine the risk factors that predict dementia in people living with CP and whether these are the same or different to the risk factors observed in the general population. If risk factors in adults with CP are different to the general population, this would indicate that targeted interventions and screening for adults with CP would be important.

In thinking about CP and risk of dementia, we also need to be aware of the contemporary landscape of dementia research. There is an increasing awareness that rather than focusing on individual risk factors that we need to examine clusters of risk factors. A systematic review published in 2019 indicated that as the number of risk factors associated with dementia increased that the risk of developing dementia also increased.[32] Interestingly people with ID have a higher likelihood of having additional CP comorbidities that also increase the risk of dementia such as epilepsy[30 33] and sensory impairment.[34] Therefore, future work should consider how CP comorbidities could cluster together in predicting the risk of dementia in adults with CP.

While this is the first study that examined the risk of dementia in people with CP, there are a number of limitations that should be borne in mind when interpreting results. Due to the small number of people who developed dementia over the follow-up generalisability of the results may be limited. 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. 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 practice in England and Wales, so there is also a possibility of missing dementia diagnoses. There is a need for more work (with larger cohorts) to determine whether CP is linked with an increased risk of early-onset dementia, and whether this is explained by CP comorbidities.

It is also worth noting that CP is the umbrella diagnosis given to a heterogeneous spectrum of aetiologies and physical symptoms. We were unable to account for this heterogeneity within this study (eg, CP subtype, presence and severity of brain pathology, baseline cognitive functioning or gross motor function). More careful consideration of CP heterogeneity could reveal interesting insights into the mechanisms explaining the observed findings. Finally, there are different subtypes of dementia (eg, Vascular dementia, Alzheimer's disease, etc), and we did not explore associations with each type within our study.

Our results indicate a clear need for future research studies to examine the risk of dementia associated with CP in order to better understand whether CP is linked with dementia, and whether this risk might be explained by CP comorbidities as suggested in this study. There is also a broader need for more work to examine cognitive decline and dementia in this population, and work to help us understand what factors could predict cognitive decline and dementia in order to target interventions. This could have important clinical applications, as there is currently little guidance around clinical monitoring for cognitive decline or dementia in adults with CP.

To conclude, this research provides the first evidence that adults with CP may have an increased hazard of being

diagnosed with dementia compared with the general adult population but that this is likely driven by CP comorbidities rather than being a direct impact of having a diagnosis of CP. More research is needed to confirm this finding and determine which specific comorbidities may drive the association between CP and dementia.

Acknowledgements Additional contributors to the overall project and protocol who were not involved in this particular substudy were Nana Anokye (Brunel University London), Neil O'Connell (Brunel University London), Nicola Ryan (Hospital Clínico San Carlos) and Silvia Liverani (Queen Mary's University London).

Contributors JR was the lead for the project and protocol submitted to CPRD (see online supplemental appendix 2), and all authors (KS, JR, CV and MDP) were involved in the design of the study. JR and KS conducted the analyses for this study. KS drafted the manuscript and all study authors had input into revising the manuscript (KS, JR, CV and MDP).

Funding This study was supported by a Research Catalyst Award from Brunel University London.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Access to CPRD data is only given to named researchers on approval of a protocol, and researchers agree to a data sharing agreement that only allows data to be accessed by named researchers. The data are not openly accessible and it is not possible to share data. We have shared the readcodes used for this analysis in online supplemental appendix 2.

ORCID iD

Kimberley J Smith http://orcid.org/0000-0002-1323-627X

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PROTOCOL INFORMATION

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced guidance on the content of protocols for research using CPRD data. This guidance is available on the CPRD website (www.cprd.com/ISAC). All protocols using CPRD data which are submitted for review by ISAC must contain information on all the areas detailed below. If a specific area required by ISAC is not applicable to your protocol, please provide the justification underneath the relevant heading.

The protocol section (next page) has pre-defined headings and the protocol must be written using these headings. Additional headings are not acceptable; however, supplementary information may be placed in one or more of the appendices providing this information is essential and an appropriate reference to it is made within the protocol. Unless very short, codes lists should be placed in an Appendix. Applications will be regarded as invalid and returned to the applicant if any of the headings below are missing or if additional sections are included.

Please note that ISAC will not consider any application where the protocol exceeds 12 pages (excluding sections A-F of the application form and annexes). Annexes should be kept to a minimum and contain only vital information that could not be provided in the main protocol section. A font-size of at least 12 should be used. Protocols not exceeding 15 pages would be acceptable if ISAC has required a resubmission where additional information is requested.

Please note, your protocol will not be reviewed by ISAC if it falls short of the above requirements. You are advised to speak to the Secretariat if you have any queries.

Voluntary registration of ISAC approved studies:

Epidemiological studies are increasingly being included in registries of research around the world, including those primarily set up for clinical trials. To increase awareness amongst researchers of ongoing research, ISAC encourages voluntary registration of epidemiological research conducted using MHRA databases. This will not replace information on ISAC approved protocols that may be published on the CPRD website. It is for the applicant to determine the most appropriate registry for their study. Please inform the ISAC secretariat that you have registered a protocol and provide the location.

Smith KJ, *et al. BMJ Open* 2021; 11:e042652. doi: 10.1136/bmjopen-2020-042652

Protocol Section

The following headings **must** be used to form the basis of the protocol. Pages should be numbered. All abbreviations must be defined on first use.

A. Lay Summary (Max. 200 words)

Please provide a succinct overview of your proposed research in plain English i.e. non-technical language. This should cover the background, purpose of the study and the potential importance of the findings. References and abbreviations should be avoided. If you have ticked the "other" box in response to question 4 on the application form, up to an additional 100 words should be used to describe the benefit to public health expected from the study.

Approximately 1 in every 400 adults in the UK has cerebral palsy. Cerebral palsy is a condition that results from an injury to the developing brain that primarily affects a person's ability to move. Adults with cerebral palsy experience a number of secondary conditions with age such as chronic fatigue and pain. These symptoms feed into a negative cycle of declines in mobility, physical inactivity, and physical deconditioning, which may lead adults with CP to develop chronic diseases such as heart disease. A recent study reported that adults with cerebral palsy in the US have significantly higher estimates of stroke, hypertension, other heart conditions and arthritis, compared with adults without cerebral palsy. To date, the prevalence of chronic diseases hasn't been investigated in adults with cerebral palsy in the UK. We propose to examine the prevalence of chronic diseases, medical resource utilisation and associated costs, and causes of mortality among adults with cerebral palsy in the UK. This will provide important information for planning future healthcare provision for adults with cerebral palsy in the UK.

B. Technical Summary (Max. 200 words)

Please provide a succinct overview of the objectives, methods and data analysis for the proposed research. Avoid the use of references in this section.

The aim of this study is to examine the prevalence of chronic diseases, medical resource utilisation and associated costs, and causes of mortality among adults with cerebral palsy (CP) in the UK. We will identify adults with CP and matched controls without CP. Chronic diseases of interest are type 2 diabetes mellitus, asthma, chronic obstructive pulmonary diseases, hypertensive diseases, ischaemic heart diseases, other heart diseases, cerebrovascular diseases, chronic pain, arthritis, depression and anxiety, dementia, osteoporosis, incontinence, cancers (i.e. oesophageal, colon, lung, breast, prostate), falls, diseases of the digestive system, hearing impairment, visual impairment. Medical resource utilisation will be identified as the number of primary care and outpatient consultations, the rate and length of hospitalisation, and number of prescriptions issued and investigations ordered. For each outcome, a regression model will be fitted, adjusting for covariates (body mass index, ethnicity, smoking status, alcohol consumption, marital status, education, income, level of disability, and level of physical activity). Overall mortality rates and mortality rates stratified by the most frequent ICD-10 chapter headings will be calculated. Standardised mortality rates will

be calculated as a ratio of the observed number of deaths among adults with CP to the expected number of deaths in the general population.

C. Objectives, Specific Aims and Rationale

Please include:
(i) The broad research objectives
(ii) The specific aims; any hypotheses to be tested should be stated here.
(iii) An explanation of how achievement of the specific aims will further the research objectives

The objective of this project is to examine the prevalence of chronic diseases, medical resource utilisation and associated costs, and causes of mortality among adults with cerebral palsy in the UK.

The specific research aims are to:

1. Identify the prevalence of chronic diseases in adults with CP in the UK in comparison to the general population.
2. Identify medical resource utilisation and costs among adults with CP in the UK in comparison to the general population.
3. Identify the major causes of death among adults with CP in the UK.

Hypothesis 1: There will be a higher prevalence of chronic diseases among adults with CP in comparison to adults without CP

Hypothesis 2: There will be higher medical resource utilisation among adults with CP in comparison to adults without CP

Hypothesis 3: There will be higher medical costs among adults with CP in comparison to adults without CP

Hypothesis 4: There will be higher mortality rates due to chronic conditions among adults with CP in comparison to adults without CP

D. Background

Please provide a succinct review of the relevant background literature with references so as to explain the purpose of the study. Please ensure that you refer to any previous research in CPRD that is related, providing published references and, when known, the ISAC Protocol Number

Approximately 1 in every 400 adults in the United Kingdom (UK) has cerebral palsy (CP).[1] Cerebral palsy is a neurodevelopmental condition resulting from an insult to the developing brain that primarily affects movement and posture.[2] Although CP is traditionally thought of as a non-progressive paediatric condition the rate of childhood mortality is declining[3] resulting in a growing population of adults with CP; a population whose healthcare needs are poorly understood. Life expectancy for adults with CP varies considerably according to severity of motor disability.[4] However, a 15-year old with CP who is able to walk unaided (as are approximately 50% of adolescents with CP[5,6]) is now expected to live to 70 years of age.[4]

Although the underlying injury to the brain that leads to CP does not progress with time,[2] adults with CP experience a number of secondary conditions with age. Primary complaints include chronic fatigue, pain and musculoskeletal problems.[7,8,9] These symptoms feed into a negative cycle of accelerated declines in mobility, physical inactivity, and losses of lean body mass.[10,11,12] The morphologic and functional decline observed in young and middle aged adults with CP is similar to that seen in older adults without CP,[13] and may predispose them to developing chronic diseases at a much younger age.

While research into the wellbeing of children with CP is rapidly expanding, there continues to be much to be learned and disseminated about the wellbeing of adults with CP. Although adults with CP frequently express concern about their future health status,[14] no study has reported the prevalence and type of age-related conditions experienced by adults with CP in the UK. To compound this, the provision of integrated services for people with CP is commonly withdrawn before a person reaches 18 years.[14] Knowledge of the health status and medical resource utilisation of adults with CP is urgently required in order to adequately plan service provision for this ageing population.

A recent study reported that adults with CP in the US have significantly higher estimates of chronic diseases including stroke, hypertension, other heart conditions and arthritis, compared with adults without CP.[15] This study raises important questions about potentially preventable health complications in this population.

Although these findings represent a significant addition to the literature, the study had three limitations, including: 1) it was limited to a US population; 2) it relied on self-report data to identify people with CP and to estimate prevalence rates of chronic diseases; 3) it included a relatively small sample of 1,015 adults with CP. In order to address these limitations we propose to examine the prevalence of age- and lifestyle-related chronic diseases, medical resource utilisation and associated costs, and causes of mortality among adults with CP in the UK, using a representative sample of adults with CP from the Clinical Practice Research Datalink (CPRD).

E. Study Type

Specify whether the study will be primarily descriptive, exploratory, hypothesis testing or a methodological piece of research.

The study type is "hypothesis testing". We will report descriptive statistics to describe the prevalence of chronic diseases, medical resource utilisation and associated costs, and causes of mortality, among adults with and without cerebral palsy. We will also conduct statistical tests to test the hypotheses stated in Section C.

F. Study Design

Describe the overall research design (for example, case-control, cohort) and reasons for choosing the proposed study design.

A cross-sectional design will be used to address the objective of this study. The prevalence of chronic diseases, medical resource utilisation and costs, and causes of mortality will be determined among adults with cerebral palsy from the index date to the first of (a) end of data collection, (b) date of transfer out of the practice area, or (c) death.

G. Sample Size

Please provide an estimate of sample size, and, where possible, a formal power calculation. An estimate of the expected number of patients available in the CPRD database should normally be included.

Review of the CPRD GOLD database has identified 2, 979 acceptable patients (≥18 years) with a record for cerebral palsy during the period 01/01/1987 – 30/11/2015 whilst registered at an up-to-standard practice. Approximately 55% of these patients are eligible for linkage to HES and ONS.

We will include all adults with CP in this study as this sample size is substantially larger than previous studies that have investigated the prevalence of chronic diseases in adults with CP. The sample size will be smaller for estimates of utilisation, costs and mortality as only approximately 55% of 2,979 acceptable patients identified will have linked data (i.e. approximately 1,638 acceptable patients).

H. Data Linkage Required (if applicable)

Please provide a synopsis of the purpose(s) for which the each of the linkages requested in section 18 of the application form is required.

We require linkage to ONS mortality data in order to determine cause of death among adults with cerebral palsy.

We require linkage to basic Hospital Episode Statistics (HES) data in order to identify medical resource utilisation in secondary care i.e. outpatient appointments and hospitalisations.

Considering linked data is only available for a sub-population of adults with cerebral palsy we will report medical resource utilisation and costs, and causes of death in this sub-population only.

I. Study Population

Define the source and study population, in terms of persons, place, time period, and listing the criteria which will be used to select the study population from the CPRD, i.e any inclusion or exclusion criteria. Please make clear any restrictions imposed by the use of linked datasets.

The cohort of adults with cerebral palsy will consist of any acceptable patient within CPRD GOLD with a Read code for cerebral palsy (preliminary codelist in appendix 1), with at least one day of up-to-standard follow-up as an adult (aged 18 or over) in the study window.

The index date for each patient will be defined as the latest of the cerebral palsy diagnosis date, the 1st of January of the year the patient became aged 18, or the date the patient registered with the GP. Patients included in the study will be followed from the index date to the first of (a) end of data collection, (b) date of transfer out of the practice area, or (c) death.

It is acknowledged that patients are only eligible for data linkage if they are (i) registered at a participating English practice prior to the transfer of identifiers to the trusted third party for matching (ii) had a valid identifier for linkage (either NHS number or postcode), (iii) had not opted out or dissented from CPRD or the linkage scheme.

We will therefore only report medical utilisation and costs, and causes of mortality, in a sub-population of adults with linked HES and ONS data, respectively.

J. Selection of comparison group(s) or controls

Describe the criteria for eligibility and the procedure for control selection.

Adults with cerebral palsy will be matched by year of birth, sex, and practice with up to six patients without a diagnosis of cerebral palsy.

The index date of an adult with cerebral palsy will defined the index date of his or her matched control(s).The controls must have a complete case history for the duration that the adult with CP is registered at an up-to-standard practice.

K. Exposures, Outcomes and Covariates

For exposures and outcomes operational definitions (or procedures for developing them) must be provided, supported by preliminary code lists placed in an Annex. A comprehensive list of covariates should also be provided for any study which is not purely descriptive.

A first event of the following chronic diseases will be identified using a record of a Read code from the clinical file identifying that the disease has occurred (Appendix 2): type 2 diabetes mellitus, asthma, bronchitis, emphysema and other chronic obstructive pulmonary diseases, hypertensive diseases, ischaemic heart diseases, other heart diseases (including pulmonary embolism, heart failure, atrial fibrillation and flutter), falls, diseases of the digestive system, hearing impairment, cerebrovascular diseases, chronic pain, osteoarthritis, rheumatoid arthritis, depression and anxiety, dementia, osteoporosis, incontinence, cancers (i.e. oesophageal, colon, lung, breast, prostate), hearing impairment, and visual impairment.

Medical resource utilisation will be identified using the following variables:

- The overall primary care consultation rate will be calculated as the sum of all recorded consultations in primary care. Each consultation will be classified by consultation type and staff type using information from the Consultation file.
- The overall rate of outpatient consultations will be calculated as the sum of all recorded outpatient appointments in the outpatient HES data.
- The overall hospitalisation rate will be calculated as the sum of all recorded hospital admissions in the subpopulation of people with linked HES data.
- The length of hospitalisation will be calculated by subtracting the admission date from the discharge date in the inpatient HES data.
- The number of prescriptions issued will be identified from the Therapy file.

- The number of investigations ordered including pathology and diagnostic services will be identified from the Test file. These will be grouped by investigation type.

The cost associated with medical resource utilisation will be identified as follows:

- Each primary care consultation will be assigned an average cost as listed in the Unit Cost of Health and Social Care 2010 from the Personal Social Services Research Unit.
- Each outpatient visit will be allocated an outpatient tariff.
- The cost of inpatient admissions will be calculated using NHS Reference Costs.
- Each prescription will attributed a net ingredient cost from the corresponding year of the Prescription Cost Analysis.
- Each investigation will be allocated a cost using NHS Reference Costs.

Causes of death will be identified and grouped using ICD-10 chapter headings recorded in the ONS death register.

We propose to identify the following covariates from the Clinical file using the most recent record prior to index date: obesity, ethnicity, smoking status, alcohol consumption, marital status, education, income, level of mobility, and level of physical activity. However, the final covariates included in analysis will depend on the level of missing data, the mechanism of missing data, and the type of data recorded.

L. Data/ Statistical analysis

This section should cover both the analytic methods and also the analyses which are to be performed to meet all the specific aims listed earlier. It is important to ensure that this section is clear and specific about any comparisons which will be made.

Age-adjusted prevalence rates for each chronic disease will be calculated for adults with and without cerebral palsy. For each chronic disease, medical resource utilisation variable, and cost associated with each medical resource utilisation variable, a regression model will be fitted, adjusting for significant covariates. All analyses will be completed using Stata, version 13 (StataCorp LP), with 2-sided 95% confidence intervals and $p<0.01$ to determine significance. Overall mortality rates and rates stratified by the most frequent ICD-10 chapter headings for adults with cerebral palsy will be calculated per 10,000 person years. For each cause of death we will calculate the age- and sex- specific mortality rates in the general population using data from the ONS. Standardised mortality ratios (SMRs) with 95% confidence intervals will be calculated as $SMR = \Sigma O_i/E_i$ where E_i is the sum of the expected deaths and O_i is the sum of the observed deaths. Results will be stratified according to age group and level of mobility.

M. Plan for addressing confounding

Purely descriptive studies are exempt from this requirement. All other studies should here provide some discussion of what they are doing in the design and/or analysis to control for confounding.

Controls will be matched to adults with cerebral palsy for age, gender and practice. All regression models will include potential confounding factors (obesity, ethnicity, smoking status, alcohol consumption, marital status, education, income, level of mobility, level of physical activity). However, the final covariates included in analysis will depend on the level of missing data, the mechanism of missing data, and the type of data recorded.

N. Plan for addressing missing data

The potential for missing data should be identified and how it will be addressed discussed here.

Identification of missing data: We will distinguish the nature of missing data by checking the applicability of the data collection to unit of observations individuals - item not applicable or true missing (i.e. non response).

Assessing patterns of missing data: Where data is genuinely missing, patterns of missing data will be examined using descriptive statistics. To examine the mechanisms under which missing data occurs, statistical tests of association between dummy variables representing item non-response and other factors in the dataset.

Replacing missing data: Standard methods of replacing missing data (e.g. multiple imputation method) will be used, allowing for type of variables [e.g. as described by Marston et al. (2010)[16]], to replace item non-response. Imputation models will be fitted using variables that predict missingness and the outcome variable.

O. Limitations of the study design, data sources and analytical methods

The general limitations of the databases and observational research are well-known. Specific consideration of the potential impact of such limitations should be provided in the context of the proposed study.

A diagnosis of cerebral palsy may not be recorded for adults with cerebral palsy who present with a mild disability. Severity of disability may not be accurately recorded. The prevalence of chronic diseases may also be underestimated if diagnoses are not accurately recorded in CPRD. Similarly, confounding factors such as level of physical activity are self-reported and therefore may be under- or over-estimated. The cause of death among people with cerebral palsy is often recorded as “cerebral palsy”[17] and therefore death due to chronic diseases may be underestimated. Although the linked data HES data is limited to England, patients in linked practices were shown to be representative of the whole GPRD population.[18]

There is likely to be a high proportion of missing data for variables such as ethnicity, marital status, body mass index. As a result we may not be able to include potential confounding variables in our analysis.

When reporting data we will exclude data where a cell contains < 5 events.

P. Patient or user group involvement (if applicable)

Please indicate whether you have or intend to involve patient groups in your study. Such involvement is encouraged by ISAC and required for studies which directly involve patients.

We have an advisory group of adults with cerebral palsy who have helped us to identify the outcomes of interest. Adults with cerebral palsy have read the lay summary and provided us with feedback. They will also assist us with the dissemination of the results to the public through lay publications.

Q. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

ISAC expects most studies that it approves to be published in the scientific literature and considers it an ethical obligation for any study with potential public health implications. In cases where multiple publications are likely to arise, a publication plan should be provided in this section.

We plan to publish two articles in the following target journals:

1. "The prevalence of chronic diseases and causes of death among adults with cerebral palsy in the UK" in the *BMJ.*
2. "Medical resource utilisation and associated expenditure among adults with cerebral palsy in the UK" in *PLoS Medicine.*

R. References

Please provide a numbered list of references at the end of the protocol.

1. Prevalence and characteristics of children with cerebral palsy in Europe. *Dev Med Child Neurol*. 2002;44:633-640
2. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, Dan B, Jacobsson B. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol*. 2007;109:8-14
3. Brooks JC, Strauss DJ, Shavelle RM, Tran LM, Rosenbloom L, Wu YW. Recent trends in cerebral palsy survival. Part I: Period and cohort effects. *Dev Med Child Neurol*. 2014;56:1059-1064
4. Brooks JC, Strauss DJ, Shavelle RM, Tran LM, Rosenbloom L, Wu YW. Recent trends in cerebral palsy survival. Part II: individual survival prognosis. *Dev Med Child Neurol*. 2014;56 (11) 1065-71
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6. Beckung E, Hagberg G, Uldall P, Cans C. Probability of walking in children with cerebral palsy in Europe. *Pediatrics*. 2008;121:e187-192
7. Hilberink SR, Roebroeck ME, Nieuwstraten W, Jalink L, Verheijden JM, Stam HJ. Health issues in young adults with cerebral palsy: towards a life-span perspective. *J Rehabil Med.* 2007;39:605-611

8. Jahnsen R, Villien L, Aamodt G, Stanghelle JK, Holm I. Musculoskeletal pain in adults with cerebral palsy compared with the general population. *J Rehabil Med.* 2004;36:78-84
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11. Ryan JM, Crowley VE, Hensey O, Broderick JM, McGahey A, Gormley J. Habitual physical activity and cardiometabolic risk factors in adults with cerebral palsy. *Res Dev Disabil*. 2014;35:1995-2002
12. Noble JJ, Fry NR, Lewis AP, Keevil SF, Gough M, Shortland AP. Lower limb muscle volumes in bilateral spastic cerebral palsy. *Brain Dev.* 2014;36:294-300
13. Peterson MD, Zhang P, Haapala HJ, Wang SC, Hurvitz EA. Greater adipose tissue distribution and diminished spinal musculoskeletal density in adults with cerebral palsy. *Arch Phys Med Rehabil*. 2015;doi: 10.1016/j.ampr.2015.06.007
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15. Peterson, MD., Ryan, JM., Hurvitz, EA. and Mahmoudi, E. Chronic conditions in a population-representative sample of adults with cerebral palsy. *JAMA*. 2015;314:2303-2305.
16. Marston, L., Carpenter, JR., Walters, KR., Morris, RW., Nazareth, I., and Petersen, I. Issues in multiple imputation of missing data for large general practice clinical databases. *Pharmacoepidemiol Drug Saf*. 2010;19:618-26. doi:10.1002/pds.1934. PubMed PMID: 20306452.
17. Strauss D, Cable W, Shavelle R. Causes of excess mortality in cerebral palsy. *Dev Med Child Neurol*. 1999;41:580-585.
18. Gallagher A, Puri S, van Staa TP. Linkage of the General Practice Research Database (GPRD) with Other Data Sources. *Pharmacoepidemiol Drug Saf.* 2011;20(s230).

Appendices

Appendices should be used for essential supporting information only (e.g. code-lists) and they must be cited within the body of the protocol.

Appendix 1. Codes-lists

Amendments

Amendment 1: Patients with cerebral palsy were matched for age, sex and practice to three controls without cerebral palsy as it was not possible to identify more than three matched controls per patient with cerebral palsy.

Amendment 2: We conducted a cohort study instead of a cross-sectional study as the outcome was a first event of disease. Therefore the objective of the study was amended to identify the incidence rather than the prevalence of disease. As a result incidence rates for each disease were calculated and Cox proportional hazards models were used to compare the hazard of each disease between patients with and without cerebral palsy.

Amendment 3: The start of follow-up was amended to the latest of the date the patient registered with the general practice, the practice up-to-standard date, and the 1st January of the year in which the patient turned 18 years. The date of the first record of cerebral palsy was not used to define the start of follow-up. As cerebral palsy is a non-progressive disorder that is diagnosed usually within the first two years of birth and cannot be cured it was assumed that any record of cerebral palsy indicated the presence of cerebral palsy from childhood.

Amendment 4: It was decided, *a priori,* to remove patients with a Read code for a "family history of infantile cerebral palsy", "congenital diplegia", "congenital diplegia NOS", congenital hemiplegia" and "congenital quadriplegia" as these terms may not specifically refer to a patient with congenital CP.

Amendment 5: It was decided, *a priori,* to narrow the focus of the first and third aims to specifically identify the main types of non-communicable diseases and death due to non-communicable diseases. The types of non-communicable diseases that were identified were type 2 diabetes mellitus, chronic obstructive pulmonary diseases (bronchitis, emphysema, and other chronic obstructive pulmonary diseases), hypertensive diseases, ischaemic heart diseases, other heart diseases, cerebrovascular diseases, heart failure, colorectal cancer, lung cancer, breast cancer, and prostate cancer. These groupings were decided on prior to conducting statistical analysis.

Causes of death were categorised according to ICD chapter headings, malignant neoplasms, diseases of the circulatory system and diseases of the respiratory system, and sub-categorised as breast cancer, lung cancer, prostate cancer, colorectal cancer, hypertensive diseases, ischaemic heart diseases, cerebrovascular diseases, heart failure, chronic obstructive pulmonary diseases and asthma. This decision was made *a priori*.

Read Codes for Cerebral Palsy

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

Read Codes for Dementia

Read code	Description
E00..12	Senile/presenile dementia
E00..11	Senile dementia
F110.00	Alzheimer's disease
Eu02z14	[X] Senile dementia NOS
Eu02z00	[X] Unspecified dementia
Eu01.00	[X]Vascular dementia
E000.00	Uncomplicated senile dementia
F116.00	Lewy body disease
Eu00.00	[X]Dementia in Alzheimer's disease
Eu00z11	[X]Alzheimer's dementia unspec
E004.11	Multi infarct dementia
Eu01200	[X]Subcortical vascular dementia
Eu02300	[X]Dementia in Parkinson's disease
Eu01.11	[X]Arteriosclerotic dementia
F111.00	Pick's disease
Eu01100	[X]Multi-infarct dementia

Eu00112	[X]Senile dementia, Alzheimer's type
Eu02.00	[X]Dementia in other diseases classified elsewhere
E001.00	Presenile dementia
F110000	Alzheimer's disease with early onset
E002000	Senile dementia with paranoia
Eu01z00	[X]Vascular dementia, unspecified
E004.00	Arteriosclerotic dementia
E002100	Senile dementia with depression
E041.00	Dementia in conditions EC
Eu00011	[X]Presenile dementia, Alzheimer's type
Eu02500	[X]Lewy body dementia
Eu10711	[X]Alcoholic dementia NOS
E012.11	Alcoholic dementia NOS
E001300	Presenile dementia with depression
Eu02z16	[X] Senile dementia, depressed or paranoid type
Eu02000	[X]Dementia in Pick's disease
Eu00z00	[X]Dementia in Alzheimer's disease, unspecified
E001200	Presenile dementia with paranoia
Eu00200	[X]Dementia in Alzheimer's dis, atypical or mixed type
Eu01300	[X]Mixed cortical and subcortical vascular dementia
F110100	Alzheimer's disease with late onset
E00..00	Senile and presenile organic psychotic conditions
Eu02z13	[X] Primary degenerative dementia NOS
Eu02200	[X]Dementia in Huntington's disease
E003.00	Senile dementia with delirium
E001z00	Presenile dementia NOS
Eu00100	[X]Dementia in Alzheimer's disease with late onset
E002z00	Senile dementia with depressive or paranoid features NOS
Eu02400	[X]Dementia in human immunodef virus [HIV] disease
E004z00	Arteriosclerotic dementia NOS
E001000	Uncomplicated presenile dementia
E004000	Uncomplicated arteriosclerotic dementia
E004300	Arteriosclerotic dementia with depression
Eu00113	[X]Primary degen dementia of Alzheimer's type, senile onset
E002.00	Senile dementia with depressive or paranoid features
Eu01000	[X]Vascular dementia of acute onset
Eu00111	[X]Alzheimer's disease type 1
Eu02z11	[X] Presenile dementia NOS
Eu00000	[X]Dementia in Alzheimer's disease with early onset
E001100	Presenile dementia with delirium
Eu04100	[X]Delirium superimposed on dementia
Eu02100	[X]Dementia in Creutzfeldt-Jakob disease
E012.00	Other alcoholic dementia
Eu01y00	[X]Other vascular dementia
E004200	Arteriosclerotic dementia with paranoia
Eu01111	[X]Predominantly cortical dementia

E004100	Arteriosclerotic dementia with delirium
Fyu3000	[X]Other Alzheimer's disease
Eu00012	[X]Primary degen dementia, Alzheimer's type, presenile onset
Eu00013	[X]Alzheimer's disease type 2
Eu02y00	[X]Dementia in other specified diseases classif elsewhere
3AE3.00	GDS level 4 – moderate cognitive decline
3AE4.00	GDS level 5 – moderately severe cognitive decline
3AE5.00	GDS level 6 –severe cognitive decline
3AE6.00	GDS level 7 – very severe cognitive decline

Appendix III

Risk of dementia in people with Cerebral Palsy (n=1700) compared with age, sex and practice-matched controls (n=5098) when diagnosis occurred greater than 12 months past 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	51 (1.00%)	56.66	0.00090 (0.0007-0.0012)	1 (Reference)	1 (Reference)	1 (Reference)
CP	16 (0.94%)	14.57	0.00110 (0.0007-0.0018)	2.50 (1.28-4.86), p=.007	1.95 (0.90-4.22), p=.09	1.90 (0.75-4.79), p=.18

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.

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

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.