Editor's Choice

Risk of early- and late-onset Alzheimer disease and related dementia in adults with cerebral palsy

ELHAM MAHMOUDI[1,2] | PAUL LIN[2] | NEIL KAMDAR[2,3,4,5,6,7] | GABRIELLA GONZALES[1] | ALEXANDRA NORCOTT[8,9] | MARK D PETERSON[2,3]

1 Department of Family Medicine, Michigan Medicine, University of Michigan, Ann Arbor, MI; **2** Institute for Healthcare Policy and Innovation, Michigan Medicine, University of Michigan, Ann Arbor, MI; **3** Department of Physical Medicine and Rehabilitation, Michigan Medicine, University of Michigan, Ann Arbor, MI; **4** Department of Obstetrics and Gynecology, Michigan Medicine, University of Michigan, Ann Arbor, MI; **5** Department of Emergency Medicine, Michigan Medicine, University of Michigan, Ann Arbor, MI; **6** Department of Surgery, Michigan Medicine, University of Michigan, Ann Arbor, MI; **7** Department of Neurosurgery, Michigan Medicine, University of Michigan, Ann Arbor, MI; **8** Department of Internal Medicine, Division of Geriatrics and Palliative Medicine, Michigan Medicine, University of Michigan, Ann Arbor, MI; **9** Department of Internal Medicine, Geriatric Research Education and Clinical Center (GRECC), Ann Arbor Healthcare System, Ann Arbor, MI, USA.

Correspondence to Elham Mahmoudi at University of Michigan, North Campus Research Complex, 2800 Plymouth Road, Building 14, Room G234, Ann Arbor, MI 48109, USA.
E-mail: Mahmoudi@med.umich.edu

This original article is commented by Engelborghs on page 284 of this issue.

PUBLICATION DATA
Accepted for publication 29th July 2021.
Published online 8th September 2021.

ABBREVIATION

ADRD	Alzheimer disease and related dementia

AIM To examine the risk of Alzheimer disease and related dementia (ADRD) among adults with cerebral palsy (CP).

METHOD Using administrative insurance claims data for 2007 to 2017 in the USA, we identified adults (45y or older) with a diagnosis of CP (*n*=5176). Adults without a diagnosis of CP were included as a typically developing comparison group (*n*=1 119 131). Using age, sex, ethnicity, other demographic variables, and a set of chronic morbidities, we propensity-matched individuals with and without CP (*n*=5038). Cox survival models were used to estimate ADRD risk within a 3-year follow up.

RESULTS The unadjusted incidence of ADRD was 9 and 2.4 times higher among cohorts of adults 45 to 64 years (1.8%) and 65 years and older (4.8%) with CP than the respective unmatched individuals without CP (0.2% and 2.0% among 45–64y and 65y or older respectively). Fully adjusted survival models indicated that adults with CP had a greater hazard for ADRD (among 45–64y: unmatched hazard ratio 7.48 [95% confidence interval {CI} 6.05–9.25], matched hazard ratio 4.73 [95% CI 2.72–8.29]; among 65y or older: unmatched hazard ratio 2.21 [95% CI 1.95–2.51], matched hazard ratio 1.73 [1.39–2.15]).

INTERPRETATION Clinical guidelines for early screening of cognitive function among individuals with CP need updating, and preventative and/or therapeutic services should be used to reduce the risk of ADRD.

Despite improvements in obstetric and neonatal care, the prevalence of cerebral palsy (CP) has been consistent over the past 50 years, remaining at an incidence of 2 to 2.5 per 1000 births.[1–4] Advancements in medicine have allowed most individuals with CP to live into late adulthood. However, there is limited evidence on potential long-term complications associated with CP.[1,5] Although CP is known to negatively affect coordination and contributes to muscle stiffness and tremors,[6] emerging evidence suggests that people with CP may undergo accelerated brain aging.[1,7–9] CP pathology involves injury to or defects of the central nervous system including the frontal and prefrontal cortex, cerebellum, and other sections of the brain that control executive function, working memory, and movement.[10–12] The association of infection and inflammation with CP may put adults with CP at a heightened risk of Alzheimer disease and related dementia (ADRD) later in life.[2,3,13,14]

ADRD is an umbrella term for a progressive cognitive spectrum disorder and is the sixth leading cause of death in the USA.[15] Approximately 5 million adults aged 65 years and older were diagnosed with ADRD in 2014. This number is expected to grow to 14 million by 2060.[15] Clinical descriptions of ADRD include cognitive degeneration, particularly severe memory deterioration; struggles with time, place, and personhood; changes in behavioral patterns; decline in language; and regression in daily living.[16] Although age is considered the main risk factor for ADRD, research has shown that certain medical conditions may also increase risk.[17]

Through inflammatory responses following infection at birth or shortly after, CP may lead to large increases in cytokine production, which could put an infant's immature brain at risk of damage.[2,3] Furthermore, injury to cerebral white matter is a common issue in children with CP.

 DOI: 10.1111/dmcn.15044

Cerebral white matter regulates neuron transmission and cognition among the regions and hemispheres of the brain.[18] The cingulum is a bundle of cerebral white matter fibers that are interconnected with multiple parts of the brain, controlling motor and cognitive functions.[6,18] Injury to cerebral white matter has been linked with cognitive decline and may increase the risk of ADRD among adults with CP.[1] To date, no large-scale study in the USA has examined the hazard of early- and late-onset ADRD in adults with CP.

In this study, we examine a private national claims database to examine time to diagnosis and adjusted hazard ratio of incident ADRD, comparing adults with and without CP. Our study highlights a gap in understanding ADRD risk among adults with CP. Such information is needed to develop more comprehensive and patient-centered clinical guidelines for this population.[19] Our main hypothesis is that adults with CP are at greater risk of ADRD and have shorter ADRD-free survival than adults without CP.

What this paper adds

- Early-onset Alzheimer disease and related dementia (ADRD) was significantly higher among adults with cerebral palsy (CP) than controls.
- CP increases the risk of early-onset ADRD more than it increases the ADRD risk at an older age.
- There was a higher prevalence of preventable chronic conditions and sedentary lifestyle among this patient cohort.

METHOD

Data source

We used national, private administrative claims from the Clinformatics Data Mart (OptumInsight, Eden Prairie, MN, USA). OptumInsight is a deidentified claims database capturing all healthcare encounters and reimbursement for over 80 million privately insured people throughout their enrollment. Although clinical evaluation is a criterion standard for assessing ADRD risk, claims data are used extensively in epidemiological analyses.[15,20] A medical provider allocates a diagnosis code after a clinical encounter, which is consequently recorded in insurance claims for billing purposes. Although challenges exist in underdiagnosis and misdiagnosis of certain types of dementia,[21] sensitivity and specificity of Medicare claims data for diagnosis of ADRD have been reasonable, ranging between 0.85 to 0.89 and 0.64 to 0.95 respectively.[20]

Sample selection

This study aimed to examine early- and late-onset ADRD.[22] All adults aged 45 years or older at the time of enrollment starting from 2007 to 2017 were deemed potentially eligible for analysis. We excluded individuals with less than 12 months of continuous enrollment so that there was a sufficient history of service utilization for comorbidity history. All medical claims, excluding laboratory and outpatient pharmacy, were considered to identify required diagnosis codes for conditions of interest. A schematic flow diagram is presented in Figure S1 (online supporting information).

Identification of patients with CP

Since CP is a congenital disorder, all enrolled members with CP were considered to have the condition at the time of enrollment. To allow sufficient follow-up for individuals with CP, we retained those with 4 or more continuous years of enrollment after their starting date of enrollment on the plan (starting from 2007), with 1 year of enrollment as the lookback period and 3 years as the follow-up. All enrolled members with a diagnosis of CP were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) (Table S1, online supporting information). The USA switched to ICD-10 codes in October 2015.[23] To ensure enough follow-up years for analysis of ADRD risk, we only used ICD-9 codes for diagnosis of CP.

We identified a comparison group without CP using the same inclusion criteria. The additional exclusion criteria for identifying this group included removal of individuals with disabling neurological disorders such as multiple sclerosis and spinal cord injury during their enrollment. We removed these conditions because research indicates they may also increase ADRD risk.[24] Furthermore, our aim was to compare the risk of ADRD between adults with CP and the non-neurologically complex group (typically developing comparison group). Among the remaining individuals without CP, a 20% simple random sample (representative of enrolled members)[25] was selected to represent the comparison group. Post hoc analyses of demographic and baseline characteristics were compared between the 20% random sample and all comparison individuals to ensure no unintentional sampling bias was introduced by random selection.

Outcome

The primary outcome was days to incident ADRD after 12 months of enrollment on the patient's plan. ADRD was identified in the follow-up period using ICD-9-CM or ICD-10-CM diagnosis codes on any single claim (Table S2, online supporting information). If multiple claims on different service dates were identified, the first claim service date after CP was considered the incident date of ADRD.

Covariates and comorbidities

Basic demographic and socioeconomic variables included age, sex, ethnicity, Elixhauser comorbidity index,[26] US Census Division, educational attainment, and net worth. We divided age into two categories (45–64y and 65y+) to assess the risk of both early- and late-onset ADRD. Additionally, we identified psychological, cardiometabolic, and musculoskeletal conditions that were prevalent in the 1-year lookback period before index CP to adjust risk for relevant health conditions. Psychological, cardiometabolic, and musculoskeletal conditions were identified using a single claim with appropriate ICD-9 codes (Table S3, online supporting information).

Statistical analysis

Bivariate analyses of baseline characteristics between patients with CP and the typically developing comparison group were examined for meaningful differences. For categorical variables, column percentages were compared between both groups using Cohen's *h* effect size calculations.[27] For large sample studies, such as those using administrative claims, the Cohen's *h* effect size calculation is used since these studies are typically statistically overpowered. For continuous variables, means and standard deviations (SDs) were calculated, and Cohen's *d* standardized mean differences were used to ascertain clinically meaningful differences between groups.

For individuals with CP, we captured a history of all documented comorbid conditions in the year of enrollment on their insurance plan before the index inclusion date. For randomly sampled comparison individuals, all patients with sufficient continuous enrollment within the study period of 4 years were randomly assigned a time zero to begin follow-up. The selection of the randomly assigned date required 1 year of enrollment to collect information about comorbid conditions, and 3 years of post-index date follow-up to measure incident ADRD. The random assignment of the dates was determined assuming a uniform distribution across a specified interval of candidate dates that met pre- and post-index dates. This approach was used to address potential bias of selecting patients who were systematically younger during their enrollment on the plan for the sampled comparison group.

To compare disease-free ADRD survival of patients with CP and the comparison group, patients with no evidence of ADRD during the 1-year lookback period were graphed with Kaplan–Meier product-limit survival curves for a 3-year period post-index diagnosis of CP. To establish incidence in claims, we used a 1-year lookback period from the index date to obtain evidence of any service utilization with a diagnosis of ADRD. Patients with ADRD in the 1-year lookback period were excluded from the product-limit survival curves and other subsequent analyses.

To estimate the risk of incident ADRD, we constructed parametric Weibull survival models to estimate hazard ratios for ADRD, comparing patients with CP and the typically developing group. The rationale for using these models is explained in Table S4 and Figure S3 (online supporting information). First, we used a bivariate regression to estimate the unadjusted hazard ratio for ADRD comparing the two groups. Second, to estimate the adjusted hazard ratio, we performed multivariable regression to adjust for demographics, socioeconomics, and Elixhauser comorbidity index. To assess the association of CP and age on incident ADRD, we also interacted CP (binary variable) with our categorical age variables (45–64y and 65y+) (Table S5 and Fig. S4, online supporting information; area under curve 0.81; *C*-statistic [standard error, SE] 0.80 [0.00]).

Finally, to account for selection bias attributable to patients with CP, we performed propensity-score matching. Specifically, we estimated the propensity to be in the CP group using multivariable logistic regression adjusting for demographics, individual comorbidities, and socioeconomic variables. We used a one-to-one caliper matching algorithm with a caliper size of 0.0001 without replacement. To assess covariate balance, post-matched analyses of effect sizes were compared between those with CP and the typically developing group. All patients were right censored if they did not experience ADRD in the follow-up period or disenrolled from the plan (Table S6 and Fig. S5, online supporting information; area under curve 0.81; C-statistic [SE] 0.80 [0.01]).

This study was deemed exempt by the Institutional Review Board at the University of Michigan. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). All hazard ratios included a calculation of the 95% confidence interval (CI). Statistical testing was two-tailed with a significance level of 0.05. Effect sizes used a 0.2 meaningful difference cutoff.

RESULTS

Table 1 presents unadjusted characteristics of individuals with and without CP within our unmatched and matched cohorts during the 1-year lookback period. The average amount of enrollment time for those with and without CP was 8 years (SD 3y 6mo) and 7 years 8 months (SD 3y 5mo) respectively. Most individuals were in the 45- to 64-year-old age group (with CP 62.9% [*n*=3256]; without CP 55.0% [*n*=615 964]). Females represented 50.4% (*n*=2608) and 53.6% (*n*=599 699) of adults with and without CP respectively. There were no substantial differences in ethnicity between adults with and without CP, the majority were white in both groups (individuals with CP 60.9% [*n*=3151]; comparison group 63.4% [*n*=709 899]). There were no large differences between the CP and comparison groups in their education. For example, about 53.4% (*n*=2763) of people with CP versus 52.7% (*n*=589 285) of people without had less than a college degree. People without CP had a higher net worth. For example, 16.9% (*n*=851) of people with CP versus 26.5% (*n*=296 541) of those without had a net worth of more than US$500 000. There were no effect size differences between the post-matched CP and comparison groups.

In Table S7 (online supporting information), adults with and without CP were compared on prevalence of certain psychological, cardiometabolic, and musculoskeletal conditions. In the unmatched cohorts, the prevalences of all conditions, including any that were psychological (27.0% vs 15.9%), cardiometabolic (58.9% vs 51.8%), and musculoskeletal (46.7% vs 32.5%), were higher among people with CP than those without. No significant difference in chronic conditions remained between post-matched CP and comparison groups.

Figure 1 presents the incident ADRD among the 45- to 64-year-old and 65 year and older unmatched and matched cohorts of adults with and without CP. Among the

Table 1: Descriptive characteristics of adults with (case) and without (comparison) cerebral palsy

	Unmatched			Matched		
Cerebral palsy	Shows	Comparison	Effectsize[a]	Case	Comparison	Effect size[a]
Overall	5176	1 119 131		5038	5038	
Full enrollment length (y:mo)						
Mean (SD)	8:0 (3:6)	7:8 (3:5)		8:1 (3:6)	7:7 (3:5)	
Median (Q1–Q3)	7:0 (5:2–10:0)	6:11 (5:0–9:8)		7:0 (5:2–10:0)	6:8 (5:0–9:2)	
Time after eligibility start date (y:mo)						
Mean (SD)	6:0 (2:4)	5:7 (2:4)		6:0 (2:4)	5:6 (2:2)	
Median (Q1–Q3)	5:8 (4:0–7:10)	5:0 (3:10–7:0)		5:8 (4:0–7:10)	5:0 (3:10–6:11)	
Age group						
45–64y	3256 (62.9)	615 964 (55.0)	0.16	3154 (62.6)	3116 (61.8)	0.02
65y+	1920 (37.1)	503 167 (45.0)	–0.16	1884 (37.4)	1922 (38.2)	–0.02
Sex						
Female	2608 (50.4)	599 699 (53.6)	–0.06	2529 (50.2)	2579 (51.2)	–0.02
Male	2568 (49.6)	519 432 (46.4)	0.06	2509 (49.8)	2459 (48.8)	0.02
Ethnicity						
Asian	97 (1.9)	33 800 (3.0)	–0.07	96 (1.9)	94 (1.9)	0.00
Black	539 (10.4)	91 274 (8.2)	0.08	517 (10.3)	497 (9.9)	0.01
Hispanic	390 (7.5)	91 832 (8.2)	–0.03	383 (7.6)	371 (7.4)	0.01
Unknown	999 (19.3)	192 326 (17.2)	0.05	953 (18.9)	949 (18.8)	0.00
White	3151 (60.9)	709 899 (63.4)	–0.05	3089 (61.3)	3127 (62.1)	–0.02
Education						
<12th grade	37 (0.7)	6380 (0.6)	0.01	37 (0.7)	39 (0.8)	–0.01
High school diploma	1616 (31.2)	286 990 (25.6)	0.12	1568 (31.1)	1557 (30.9)	0.00
<Bachelor's degree	2763 (53.4)	589 285 (52.7)	0.01	2681 (53.2)	2703 (53.7)	–0.01
Bachelor's degree+	603 (11.6)	184 220 (16.5)	–0.14	595 (11.8)	576 (11.4)	0.01
Unknown	157 (3.0)	52 256 (4.7)	–0.09	157 (3.1)	163 (3.2)	–0.01
Net worth						
Unknown	1254 (24.2)	173784 (15.5)	0.22	1162 (23.1)	1144 (22.7)	0.01
<US$25 000	1057 (20.4)	149626 (13.4)	0.19	1033 (20.5)	1055 (20.9)	–0.01
US$25 000–149 000	841 (16.2)	179914 (16.1)	0.00	831 (16.5)	817 (16.2)	0.01
US$150 000–249 000	476 (9.2)	116851 (10.4)	–0.04	471 (9.3)	487 (9.7)	–0.01
US$250 000–499 000	697 (13.5)	202415 (18.1)	–0.13	694 (13.8)	690 (13.7)	0.00
US$500 000+	851 (16.4)	296541 (26.5)	–0.25	847 (16.8)	845 (16.8)	0.00

Source: the 2007–2017 OptumInsight. Data are *n* (%) unless otherwise stated. [a]Effect size equal to or >0.20 considered significant. Q1–Q3, quartile 1 and quartile 3; SD, standard deviation.

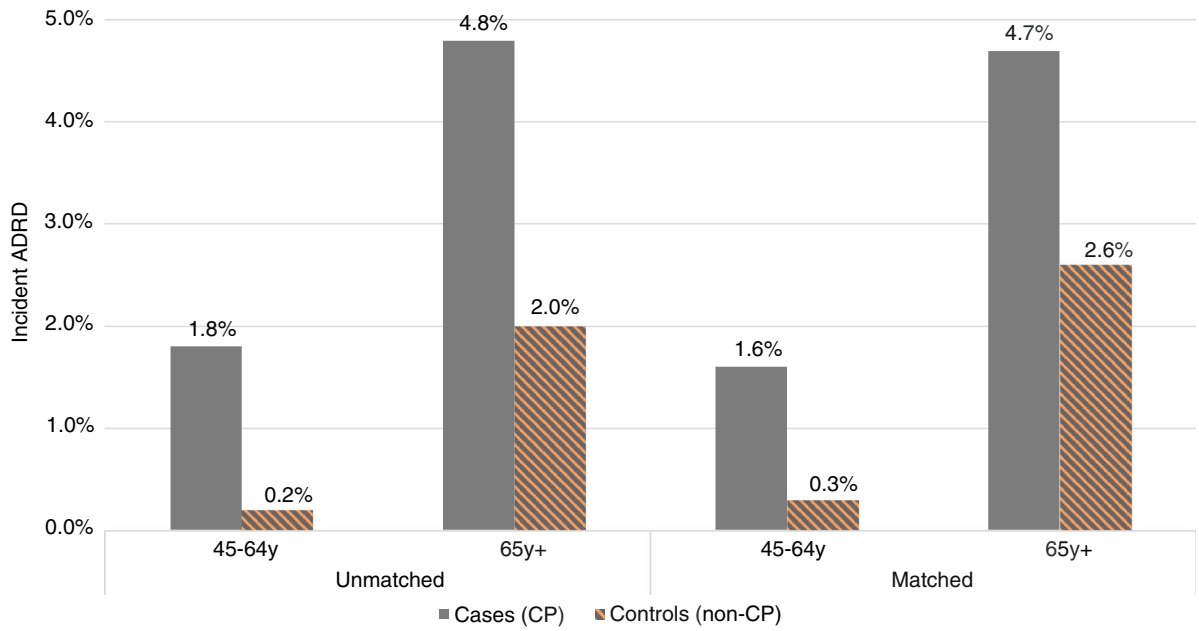

Figure 1: Unmatched and matched average incidences of Alzheimer disease and related dementia (ADRD) among individuals with and without cerebral palsy (CP).

unmatched cohort, the incidence rate of ADRD was nine times higher among those 45 to 64 years old with CP (1.8%) than those without (0.2%). Among the 65 year and older group, 4.8% of people with CP versus 2.0% of those without had incident ADRD. The results among the matched cohorts were similar.

Kaplan–Meier curves in Figure 2 display the ratios of differences in ADRD-free survival probabilities between adults with and without CP. On average, within a 3-year follow-up, ADRD-free survival probability was about nine times higher among the 45- to 64-year-old comparison cohort than the corresponding group with CP (Fig. 2a); and it was about two times higher among the 65 year and older comparison cohort than in the same age-range of those with CP (Fig. 2b). The results for matched cohorts were similar (Fig. S2, online supporting information).

Table 2 presents hazard ratios for incident ADRD among our two age groups. Within the younger cohorts (45–64y), adjusted unmatched and matched hazard ratios for cases were 7.48 (95% CI 6.05–9.25) and 4.73 (95% CI 2.72–8.29) respectively. Among the older cohorts (65y+), adjusted unmatched and matched hazard ratios were 2.21 (95% CI 1.95–2.51) and 1.73 (95% CI 1.39–2.15) respectively. Regression results are presented in Tables S5 and S6.

DISCUSSION

In this study, we compared the relative risk of incident ADRD in adults with CP and adults without CP. Three major findings developed. First, the risk of incident ADRD is substantially higher among adults with CP than their counterparts without. Second, CP increases the risk of early-onset ADRD more than it increases the ADRD risk at an older age (65y+). Finally, the difference in risk of incident ADRD between our unmatched and matched cohorts revealed that it is plausible that ADRD risk might be due to a higher prevalence of secondary chronic conditions among the population with CP. Our findings revealed a critical need for updating clinical guidelines for adults with CP to preserve cognitive function.

Despite advances that have improved longevity among people with CP, most research and clinical care has focused on the pediatric period and/or challenges related to limits in range of motion and pain.[28] Research shows that adults with CP have poor muscle development, may experience gradual functional decline, and are at increased risk of secondary chronic conditions.[29] Our results were indicative that, without intervention, adults living with CP may also be at a heightened risk of cognitive decline and incident ADRD. Consequently, the scope of care for people with CP needs to expand beyond the pediatric period and include monitoring for additional complications such as secondary chronic conditions and cognitive decline.

Furthermore, CP poses a substantially higher ADRD risk among middle-aged adults (early onset) than it does among older people (65y+). The risk of incident ADRD increases with age for everyone. Thus, although people with CP are still at a greater risk of ADRD as they age, compared with other older adults, the late-onset ADRD risk is plausibly lower than early-onset ADRD because the probability increases with age for everyone.

Moreover, the greater risk of ADRD in our unmatched versus matched cohorts might be explained by a higher prevalence of secondary comorbid conditions among adults

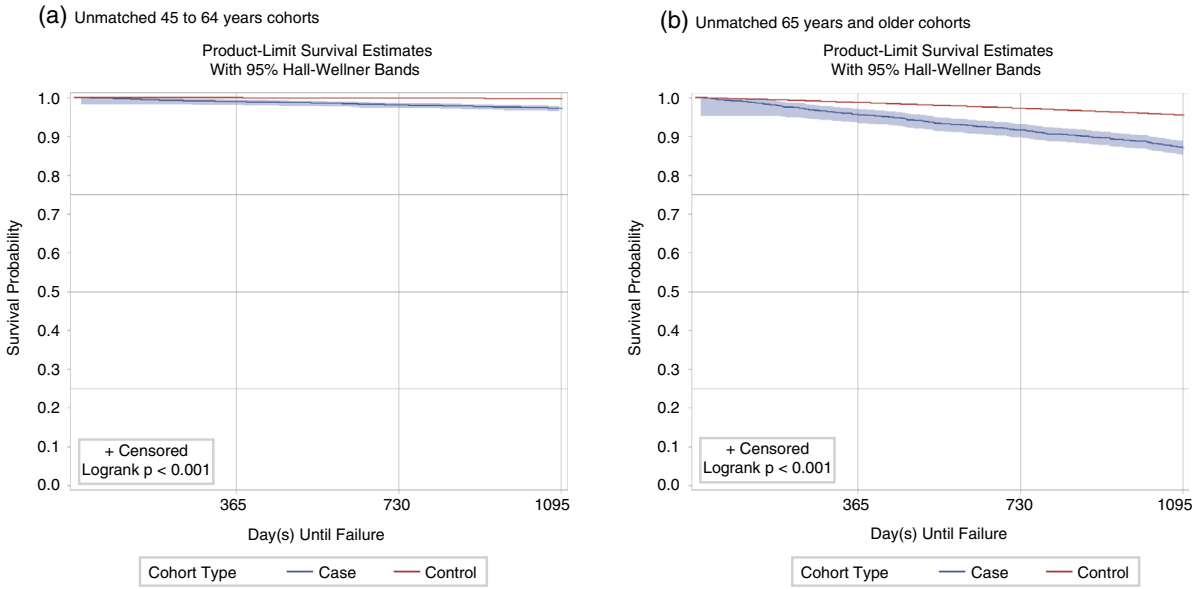

Figure 2: Unmatched Kaplan–Meier product-limit survival curves (3y) for adults with and without cerebral palsy (CP).

Table 2: Hazard ratios of early- and late-onset ADRD among adults with CP

	Unmatched cohort		Matched cohort	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Among those 45–64y of age (early onset)	10.22 (8.26–12.64)	7.48 (6.05–9.25)	5.18 (2.97–9.02)	4.73 (2.72–8.29)
Among those 65y or older (late onset)	2.99 (2.64–3.40)	2.21 (1.95–2.51)	1.88 (1.51–2.34)	1.73 (1.39–2.15)

As with incidence estimates, all survival models used cerebral palsy (CP) and comparison cohorts, which required a 1-year clean period with no evidence of Alzheimer disease and related dementia (ADRD). To estimate the hazard ratio of CP among each age group, we examined the categorical age group (45–64y and 65y+) with CP. Regression models for fully adjusted unmatched and matched cohorts are reported in Tables S5 and S6 (online supporting information). $p<0.001$ for all values.

with CP. Chronic psychological, cardiometabolic, or musculoskeletal conditions are associated with a diagnosis of ADRD.[30,31] Compared with the general adult population, people with CP have a more sedentary lifestyle with inadequate levels of physical and/or social activities.[29] Our own results and the work of others have shown a substantially higher prevalence of a broad range of preventable chronic conditions among adults with CP than typically developing comparison individuals.[32,33] Enabling a more active living environment (through physical or occupational therapy) and using preventative strategies in healthcare (such as early screening for preventable chronic illnesses) may not only reduce the risk of secondary chronic conditions but may also preserve cognitive function. More research on the association between high prevalence of certain chronic conditions and ADRD risk among adults with CP is warranted.

ADRD is a neurodegenerative condition, mainly defined by gradual cognitive decline and frailty causing extensive burden to patients, caregivers, and the healthcare system.[34] Our findings call for a careful examination of the types of care that may reduce the risk of cognitive decline among people with CP. Physical and therapeutic rehabilitative services may provide some neurological preservation.[28] More research on how to lessen the risk of cognitive decline among people with CP is merited. For example, future research may focus on examining the efficacy of early cognitive screening, development of evidence-based preventative care, or greater use of physical or occupational therapy.

This study had several limitations. First, owing to errors in administrative claims' diagnostic codes, confirmatory identification of CP may not always have been accurate. Although our estimates of CP and reported chronic conditions may not be 100% accurate, previous research indicates that claims-based estimates have high sensitivity and specificity. However, it is well known that certain conditions such as ADRD are underdiagnosed.[35,36] It is therefore conceivable that our measures for incident ADRD diagnosis were underestimated. Second, without availability of the Gross Motor Function Classification System in claims data, it is hard to define CP severity. Development of a longitudinal national registry for this patient population will enable researchers and clinicians to conduct more granular examination of this topic. Finally, although we matched and risk-adjusted our models for a limited set of socioeconomic variables, we had no data on levels of physical activity, lifestyle choices, or degree and type of social and cognitive engagements, all of which have been shown to be associated with ADRD risk.[15] Finally, OptumInsight is not a nationally representative sample of the US adult population, and thus the results of this study may not be generalizable.

Our study had several strengths. To our knowledge, this study was the first large-scale, longitudinal analysis of national claims data examining the risk of developing early- and late-onset ADRD among privately insured individuals with CP in the USA. Conducting large observational studies has proved to be a feasible and efficient research approach, providing access to a large patient population data over time.[15,37]

In short, we found that adults with CP are at greater risk of incident ADRD, particularly its early onset. Some of this increased risk might be explained by a sedentary lifestyle and a higher prevalence of preventable chronic conditions among this patient cohort. Future biomarker-based research may shed some light on potential etiological connections between CP and ADRD. To conclude, more research is necessary to develop clinical guidelines and recommendations for healthy brain aging in adults with CP.

ACKNOWLEDGEMENTS

This research was developed under grants from the Alzheimer's Association (AARG-NTF-20-685960) and the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR 90RTHF0001-01-00). The authors have stated that they had no interests that might be perceived as posing conflict or bias.

DATA AVAILABILITY STATEMENT

We used private insurance claims data for this study. Data sharing not applicable.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Schematic flow diagram.

Figure S2: Kaplan–Meier ADRD-free survival curves among matched cohorts of adults with and without CP (cases and controls).

Figure S3: Log-negative-log of the estimated survival function.

Figure S4: Time-dependent area under the curve for the fully adjusted unmatched regression model.

Figure S5: Time-dependent area under the curve for the fully adjusted matched regression model.

Table S1: Diagnostic codes for cerebral palsy.

Table S2: Diagnostic codes for Alzheimer's disease and related dementia.

Table S3: Diagnostic codes for comorbid conditions.

Table S4: Rationale for using the parametric Weibull regression.

Table S5: Regression results for unmatched cohorts of adults with and without cerebral palsy.

Table S6: Regression results for matched cohorts of adults with and without cerebral palsy.

Table S7: Incident of chronic conditions among adults with (case) and without (control) cerebral palsy.

REFERENCES

1. Coq JO, Delcour M, Massicotte VS, Baud O, Barbe MF. Prenatal ischemia deteriorates white matter, brain organization, and function: implications for prematurity and cerebral palsy. *Dev Med Child Neurol* 2016; **58** (Suppl 4): 7–11.
2. MacLennan AH, Thompson SC, Gecz J. Cerebral palsy: causes, pathways, and the role of genetic variants. *Am J Obstet Gynecol* 2015; **213**: 779–88.
3. Wainwright MS. Pharmacogenomics of Alzheimer's disease and cerebral palsy: implications of the apolipoprotein E genotype. *Future Med* 2007; **2**: 353–6.
4. Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. *JAMA Pediatr* 2017; **171**: 897–907.
5. Hutton J, Pharoah P. Effects of cognitive, motor, and sensory disabilities on survival in cerebral palsy. *Arch Dis Child* 2001; **86**: 84–90.
6. Haak P, Lenski M, Hidecker MJ, Li M, Paneth N. Cerebral palsy and aging. *Dev Med Child Neurol* 2009; **51**(Suppl 4): 16–23.
7. Ryan JM, Allen E, Gormley J, Hurvitz EA, Peterson MD. The risk, burden, and management of non-communicable diseases in cerebral palsy: a scoping review. *Dev Med Child Neurol* 2018; **60**: 753–64.
8. Whitney DG, Hurvitz EA, Ryan JM, Devlin MJ, Caird MS, French ZP, et al. Noncommunicable disease and multimorbidity in young adults with cerebral palsy. *Clin Epidemiol* 2018; **10**: 511.
9. Peterson MD, Kamdar N, Hurvitz EA. Age-related trends in cardiometabolic disease among adults with cerebral palsy. *Dev Med Child Neurol* 2019; **61**: 484–9.
10. Binks JA, Barden WS, Burke TA, Young NL. What do we really know about the transition to adult-centered health care? A focus on cerebral palsy and spina bifida. *Arch Phys Med Rehabil* 2007; **88**: 1064–73.
11. Jenks KM, De Moor J, Van Lieshout EC. Arithmetic difficulties in children with cerebral palsy are related to executive function and working memory. *J Child Psychol Psychiatry* 2009; **50**: 824–33.
12. Bodimeade HL, Whittingham K, Lloyd O, Boyd RN. Executive function in children and adolescents with unilateral cerebral palsy. *Dev Med Child Neurol* 2013; **55**: 926–33.
13. Muo R, Schindler A, Vernero I, Schindler O, Ferrario E, Frisoni GB. Alzheimer's disease-associated disability: an ICF approach. *Disabil Rehabil* 2005; **27**: 1405–13.
14. Dunn N, Mullee M, Perry H, Holmes C. Association between dementia and infectious disease. *Alzheimer Dis Assoc Disord* 2005; **19**: 91–4.
15. Matthews KA, Xu W, Gaglioti AH, Holt JB, Croft JB, Mack D, et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥ 65 years. *Alzheimers Dement* 2019; **15**: 17–24.
16. Muò R, Schindler A, Vernero I, Schindler O, Ferrario E, Frisoni GB. Alzheimer's disease-associated disability: an ICF approach. *Disabil Rehabil* 2005; **27**: 1405–13.
17. Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, et al. Cardiac disease associated with increased risk of nonamnestic cognitive impairment: stronger effect on women. *JAMA Neurol* 2013; **70**: 374–82.
18. Marks BL, Katz LM, Styner M, Smith JK. Aerobic fitness and obesity: relationship to cerebral white matter integrity in the brain of active and sedentary older adults. *Br J Sports Med* 2011; **45**: 1208–15.
19. American Academy for Cerebral Palsy and Developmental Medicine (AACPDM). Fact Sheet. Care of Adults with Cerbral Palsy [Internet]. https://www.aacpdm.org/UserFiles/file/fact-sheet-pcp-doc-101415.pdf. Accessed 1 Jul 2021.
20. Taylor DH Jr, Østbye T, Langa KM, Weir D, Plassman BL. The accuracy of Medicare claims as an epidemiological tool: the case of dementia revisited. *J Alzheimers Dis* 2009; **17**: 807–15.
21. Gianattasio KZ, Prather C, Glymour MM, Ciarleglio A, Power MC. Racial disparities and temporal trends in dementia misdiagnosis risk in the United States. *Alzheimers Dement* 2019; **5**: 891–8.
22. Johns Hopkins Medicine. Early-onset Alzheimer's disease [Internet]. https://www.hopkinsmedicine.org/health/conditions-and-diseases/alzheimers-disease/earlyonset-alzheimer-disease. Accessed 1 Jul 2021.
23. Khera R, Dorsey KB, Krumholz HM. Transition to the ICD-10 in the United States: an emerging data chasm. *JAMA* 2018; **320**: 133–4.
24. Mahmoudi E, Lin P, Peterson MD, Meade MA, Tate DG, Kamdar N. Traumatic spinal cord injury and risk of early and late onset Alzheimer's disease and related dementia: large longitudinal study. *Arch Phys Med Rehabil* 2021; **102**: 1147–54.
25. Waksberg J. Sampling methods for random digit dialing. *J Am Stat Assoc* 1978; **73**: 40–6.
26. Li B, Evans D, Faris P, Dean S, Quan H. Risk adjustment performance of Charlson and Elixhauser comorbidities in ICD-9 and ICD-10 administrative databases. *BMC Health Serv Res* 2008; **8**: 1–7.
27. Bezeau S, Graves R. Statistical power and effect sizes of clinical neuropsychology research. *J Clin Exp Neuropsychol* 2001; **23**: 399–406.
28. Aisen ML, Kerkovich D, Mast J, Mulroy S, Wren TAL, Kay RM, Rethlefsen SA. Cerebral palsy: clinical care and neurological rehabilitation. *Lancet Neurol* 2011; **10**: 844–52.
29. Peterson M, Gordon P, Hurvitz E. Chronic disease risk among adults with cerebral palsy: the role of premature sarcopoenia, obesity and sedentary behaviour. *Obesity Rev* 2013; **14**: 171–82.
30. Bhat NR. Linking cardiometabolic disorders to sporadic Alzheimer's disease: a perspective on potential mechanisms and mediators. *J Neurochem* 2010; **115**: 551–62.
31. Wilson RS, Arnold SE, Schneider JA, Kelly JF, Tang Y, Bennett DA. Chronic psychological distress and risk of Alzheimer's disease in old age. *Neuroepidemiology* 2006; **27**: 143–53.
32. Peterson MD, Ryan JM, Hurvitz EA, Mahmoudi E. Chronic conditions in adults with cerebral palsy. *JAMA* 2015; **314**: 2303–5.
33. Smith KJ, Peterson MD, O'Connell NE, Victor C, Liverani S, Anokye N, Ryan JM. Risk of depression and anxiety in adults with cerebral palsy. *JAMA Neurol* 2019; **76**: 294–300.
34. Barnes DE, Yaffe KJTLN. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 2011; **10**: 819–28.
35. Lin P-J, Kaufer DI, Maciejewski ML, Ganguly R, Paul JE, Biddle AK. An examination of Alzheimer's disease case definitions using Medicare claims and survey data. *Alzheimers Dement* 2010; **6**: 334–41.
36. Amjad H, Roth DL, Sheehan OC, Lyketsos CG, Wolff JL, Samus QM. Underdiagnosis of dementia: an observational study of patterns in diagnosis and awareness in US older adults. *J Gen Intern Med* 2018; **33**: 1131–8.
37. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000; **342**: 1878–86.