HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2019 February 22.

Published in final edited form as:

J Alzheimers Dis. 2018 ; 66(2): 717–723. doi:10.3233/JAD-180586.

Traumatic brain injury and age of onset of dementia with Lewy bodies

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Abstract

Background—Traumatic brain injury (TBI) with loss of consciousness (LOC) has been associated with earlier onset of mild cognitive impairment, frontotemporal dementia, Parkinson's disease, and Alzheimer's disease (AD), but has not been examined as a risk factor for earlier onset of dementia with Lewy bodies (DLB).

Objective—The purpose of this study was to assess the association between a history of TBI and the age of onset of DLB.

Method—Data from 576 subjects with a clinical diagnosis of DLB were obtained from the National Alzheimer's Coordinating Center (NACC). Analyses of Covariance examined whether self-reported history of remote TBI with LOC (i.e., > 1 year prior to the first Alzheimer's Disease Center visit) was associated with earlier DLB symptom onset.

Results—Controlling for sex, those with a history of remote TBI had an approximately 1.5-year earlier clinician-estimated age of onset ($F = 0.87$, $p = 0.35$) and 0.75-years earlier age of diagnosis ($F = 0.14$, $p = 0.71$) of DLB compared to those without a history of TBI, though the differences did not reach statistical significance. Analysis of subjects with autopsy-confirmed diagnoses was underpowered due to the low number of TBI+ subjects.

Conclusions—Remote TBI with LOC was not significantly associated with DLB onset, despite being a significant risk factor for cognitive decline and earlier age of onset in other neurodegenerative conditions. Replication of these results using a larger cohort of DLB subjects with and without a TBI history who have undergone autopsy is indicated, as our TBI+ subjects did

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CONFLICT OF INTEREST/DISCLOSURE STATEMENT

The authors have no conflict of interest to report.

show a slightly earlier onset of about 1.5 years. Further investigations into other potential DLB risk factors are also warranted.

Keywords

traumatic brain injury; Lewy body disease; dementia; age of onset

INTRODUCTION

A history of traumatic brain injury (TBI) with loss of consciousness (LOC) is increasingly recognized as a risk factor for all-cause dementia [1, 2], Alzheimer's disease (AD) [3–9], mild cognitive impairment (MCI) [10], and frontotemporal dementia (FTD) [11–13]. However, there is limited research investigating the relationship between TBI and dementia with Lewy bodies (DLB). As a syndrome, DLB is characterized by the presence of at least two of the following core clinical features: fluctuating cognition, recurrent visual hallucinations, REM sleep behavior disorder and spontaneous features of parkinsonism. Pathologically, this neurodegenerative disorder is defined by the presence of cortical Lewy bodies consisting of α-synuclein [14]. Most studies examining TBI as a risk factor for synucleinopathies have focused on the related disorder of Parkinson's disease (PD), with mixed results [15–19]. A 2013 meta-analysis of 22 studies investigating head trauma and PD found that TBI may increase the risk of PD by a pooled factor of 1.57 [16]. Additionally, a study of sibling pairs with PD found that sustaining a TBI of any severity was associated with an average 3.3-year earlier onset of PD [20]. A meta-analysis published in 2014 focused on mild TBI and PD analyzed five of the studies included in the 2013 meta-analysis [16] and reported a lack of association between mild TBI and PD [18]. The two largest population studies in these meta-analyses, from Denmark [19] and Sweden [21], both reported the risk for PD to be greatest soon after the head injury and dissipates over time, raising concerns for reverse causation, where head injuries preceding the PD diagnosis may be a consequence of prodromal PD rather than causing PD. To address this issue, a more recent investigation [15] assessed the risk of PD associated with TBI and non-TBI physical traumas, as well as different TBI factors, including age of injury, severity, frequency and the interval between injury and PD diagnosis, and reported a 44% increase in risk of being diagnosed with PD after TBI compared to non-TBI trauma, with significantly higher risk proportional to severity and frequency that supports a dose-response relationship. A subsequent study has also reported that an earlier age at first head injury is associated with PD, though the overall association between head injury and PD was not significant [17]. Several studies have reported on the accumulation of α-synuclein following TBI, both in cases of fatal head injury [22] as well as non-human TBI models [23, 24]. Along these lines, a recent study by Crane and colleagues reported that a history of TBI with LOC may be a risk factor for increased Lewy bodies at autopsy as well as the onset and progression of PD [25]. This evidence would suggest that TBI might also increase the risk for developing DLB or hasten its onset due to the accumulation of Lewy body pathology. However, despite this potential link, investigations into the relationship between TBI and DLB are limited.

To our knowledge, only one exploratory analysis, by Boot and colleagues, has evaluated TBI as a risk factor for developing DLB [26]. Those authors compared subjects with a clinical

diagnosis of probable DLB (n = 147) to sex- and age-matched healthy controls (n = 294) in three longitudinal studies of aging and dementia at Mayo Clinic. In that investigation, TBI of any severity was not found increase the likelihood of DLB [26]. Recently, we have published a series of papers investigating the onset of neurodegenerative disorders in those with and without a history of TBI and LOC, showing an earlier onset of MCI, AD, and FTD in those with a history of TBI [10, 27–29]. To add to the sparse literature examining TBI history in DLB, the current study evaluated the relationship between a self-reported remote history of TBI with LOC and symptom onset in DLB.

MATERIALS AND METHODS

Subjects

Data were obtained from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and Neuropathology Data Set (NDS). NACC has collected demographic, genetic, clinical, and autopsy data on healthy controls and subjects diagnosed with various dementias via approximately annual visits from National Institute on Aging-funded U.S. Alzheimer's Disease Centers (ADC) since September 2005 [30]. Subjects with data from UDS versions 1 and 2 who were aged 45 years or older and had a primary clinical diagnosis of DLB were selected for inclusion. A team of multi-disciplinary ADC clinicians or a single clinician at each ADC formulated the diagnosis of DLB using established diagnostic criteria [31]. In total, data were drawn from 31 ADCs in this sample, using data from September 2005 to March 2015. Available autopsy diagnoses using the 2005 3rd consortium criteria [31] were reviewed to determine if the accuracy of clinical diagnoses was similar to recently published frequencies [32].

Measures

The NACC dataset consisted of three questions related to TBI history that were answered by the subject and/or informant during ADC visits. ADC clinicians asked subjects if they had ever sustained a TBI resulting in LOC < 5 minutes or ≥ 5 minutes, or if their TBI resulted in a chronic deficit. Responses were coded as *absent*, *recent/active* (TBI < 1 year ago or required ongoing treatment), *remote/inactive* (TBI ≥ 1 year ago with recovery or no current treatment), or *unknown*. Data comparing a history of single versus multiple TBIs were not available in this version of the NACC dataset. In addition, injury severity cut-offs in the available data were arbitrary, and TBIs resulting in LOC < 5 minutes or ≥ 5 minutes were combined into a single category of TBI with any LOC. To reduce the effect of recent injuries and to examine the effect of remote TBI, only those who reported a TBI occurring ≥ 1 year prior to the time of diagnosis were included. Subjects who sustained a TBI occurring < 1 year prior to the initial visit or anytime thereafter were excluded to reduce the likelihood of more acute effects. Finally, to reduce the possibility that residual cognitive deficits influenced the diagnosis of DLB, those who reported chronic deficits from their TBI were excluded.

The age of DLB onset was assessed using the NACC variable of the estimated age of symptom onset, defined as the ADC clinician's estimated age of cognitive decline based on subject/informant report, medical records, and observation. Factors including demographics

(e.g. sex, race, education), cardiovascular factors (e.g., smoking and history of stroke), first-degree family member with dementia, apolipoprotein E ε4 status (Apoe4; number of alleles), and depression (i.e., recent and lifetime history) were examined as potential covariates.

Statistical Analyses

Chi-square and independent *t* tests were used to assess whether subjects with a history of TBI with LOC (TBI+) and those without (TBI−) differed by demographics, number of years smoking, history of remote stroke, number of Apoe4 alleles, family history of dementia, and history of depression. Any significant differences that were identified in these variables were used as covariates in primary analyses. Analyses of Covariance (ANCOVA) were used to assess whether age of DLB onset significantly differed between TBI+ and TBI− groups. Missing data were assessed for each individual analysis and subjects missing relevant data were excluded. All analyses were conducted using IBM SPSS Statistics V24 (IBM Corp, SPSS Statistics V24, Armonk, New York, USA, 2015) with $p < 0.05$ as the level of significance.

RESULTS

Clinical, demographic, and sample characteristics

After excluding six subjects as outliers for time of dementia onset to diagnosis (i.e., ≥ 3 SDs above the mean), a total of 576 subjects with available TBI history and DLB diagnosis were included. Autopsy data concerning Lewy body disease were available in 191 of these subjects. Of these, 73% (n = 140) had an *intermediate* or *high likelihood* that the pathologic findings were associated with DLB clinical syndrome according to the 2005 Consortium Criteria [31]. The frequencies obtained in this sample are similar to recently published information [32].

Among the study sample, 526 reported no history of TBI (TBI−) and 50 reported a history of remote TBI with no chronic deficit (TBI+). Demographic information is provided in Table 1. The sample was largely Caucasian and generally well educated, with an average of 14.61 years of education (Table 1). Missing data were as follows: one subject was missing information regarding race, 13% (n = 76) were missing family history of dementia information, 31% (n = 181) were missing Apoe4 status, 7% (n = 38) were missing number of years smoking cigarettes, 4% (n = 25) were missing history of stroke, and 3% (n = 16) were missing recent and lifetime depression history. No subjects were missing education, sex, age of diagnosis, or age of estimated onset. There were significantly more males in the TBI+ group (86%) than the TBI− group (70%, p = 0.014), so sex was used as a covariate in subsequent analyses. The TBI+ and TBI− groups did not differ in race, years of education, number of years smoking cigarettes, family history of dementia, number of Apoe4 alleles, lifetime depression, depression within 2 years of diagnosis, or remote history of stroke (Table 1).

Of subjects with autopsy data with an intermediate or high likelihood that the pathologic findings were associated with DLB clinical syndrome, 131 reported no history of TBI (TBI

−) and 9 reported a history of remote TBI with no chronic deficit (TBI+). Due to the limited sample size of TBI+ subjects, statistical analyses comparing groups were not carried out in this neuropathological sample.

TBI history and age of DLB symptom onset and diagnosis

The average estimated age of DLB onset was 1.49 years earlier for the TBI+ group (M = 68.08, SD = 8.96) compared to the TBI− group (M = 69.57, SD = 8.09). Similarly, the TBI+ group (M = 73.75, SD = 9.34) had a 0.75-year earlier diagnosis than the TBI− group (M = 74.5, SD = 7.71). Controlling for sex, no significant differences between TBI+ and TBI− groups (mean age of estimated DLB symptom onset, $F(1, 573) = 0.87$, $p = 0.35$; mean age of DLB diagnosis, $F(1, 573) = 0.14$, $p = 0.71$) were observed.

DISCUSSION

A history of TBI has been found to be related to an increased risk and earlier onset of several neurodegenerative conditions. In this study, we compared the average age of DLB onset in those with and without a history of TBI in 576 subjects with the clinical syndrome DLB in the NACC database. While the 50 subjects with DLB and a history of TBI had an approximately 1.5-year earlier onset of symptoms and 0.75-years earlier diagnosis of DLB compared to those without a history of TBI, the differences did not reach statistical significance.

This study marks only the second time in the literature that TBI has been investigated as a potential risk factor for DLB. The previous study was an exploratory investigation into 19 risk factors that may contribute to DLB conducted by Boot and colleagues [26], which showed that, in a cohort of 147 subjects with DLB, 18 of whom reported a history of head injury, a self-reported history of head injury was not associated with a significantly increased risk of developing DLB compared to control subjects (odds ratio of 1.4, 95% confidence interval 0.7 – 2.6, p value 0.33). Despite methodological differences, our findings are in keeping with the prior negative findings for a relationship between TBI and increased risk of DLB and support the conclusion that a history of TBI is not associated with significantly earlier onset or risk of developing DLB.

The current findings with respect to DLB, however, are in contrast with our previous findings between TBI history and onset of several other neurodegenerative conditions. In our study of subjects with a well-characterized clinical history of AD, a history of TBI was associated with a significantly earlier average age of onset by approximately 2.5 years [27, 29]. Those findings are consistent with some [3–9], but not all studies investigating TBI in AD [33–35]. Similarly, TBI has been associated with an approximately 3-year earlier age of FTD symptom onset and diagnosis [10], supporting other studies that have found a significant relationship between TBI and increased risk of FTD [11–13]. In PD, TBI was concluded to be a risk factor (pooled OR = 1.57) for the development of PD in a meta-analysis of 22 studies [16]. The negative findings in this study are curious when compared to one study that found a 3-year earlier age of PD onset [20], which is neuropathologically similar to DLB. Taken together, these findings suggest that TBI may increase the risk of

several neurodegenerative diseases to varying degrees, perhaps due to disease-specific neuropathological mechanisms.

Although TBI may be a risk factor for earlier onset of AD, FTD, and PD, why TBI did not appear to be significantly associated with the earlier onset of DLB remains unclear. PD has a similar neuropathological profile to DLB, with the accumulation of α-synuclein-containing Lewy bodies and Lewy neurites, and several studies have shown an increased risk of developing PD after TBI [15–17]. Interestingly, in their recent analysis of data from three prospective cohort studies with a total of 7,130 subjects, Crane and colleagues showed that a history of TBI with LOC was associated with incident PD, progression of parkinsonism, and findings of cortical Lewy bodies at autopsy. TBI history was not, however, related to cognitive impairment or dementia in PD that is typically associated with cortical Lewy bodies [25]. Gardner and colleagues have hypothesized that TBI may decrease motor reserve or accelerate a pre-existing neurodegenerative cascade, or even trigger a de novo cascade [15]. Jafari and colleagues posited neuroinflammation, mitochondrial dysfunction, or glutamate toxicity as mechanistic possibilities for the association between TBI and PD [16]. If these factors are indeed playing a role, then perhaps the pathological changes instigated by TBI promote either an earlier or more prevalent movement disorder manifestation of synucleinopathy to result in a PD phenotype as opposed to the cognitive manifestations of DLB. Alternatively, the impact of TBI on synucleinopathy may be restricted to brainstem-predominant α-synuclein pathology typical of PD, but not sufficient for more diffuse cortical spread of α-synuclein to the degree necessary to induce cognitive impairment and dementia seen in DLB. Clearly, further investigation is warranted to investigate the differential impact of TBI on neurodegenerative diseases.

There are several limitations and caveats to the present study. First, while the difference in age at onset and diagnosis of DLB in those with a history of TBI was not statistically significant, the TBI+ sample did have an onset 1.49 years earlier than the TBI- group, and showed a symptom onset that was 0.75 years earlier. When compared to our previous studies investigating earlier onset in other neurodegenerative diseases in relation to a history of TBI, substantially smaller group sizes due to the lower frequency of DLB in the NACC dataset could make it difficult to detect a statistically significant difference in the present sample. Although this is the largest study to date investigating TBI and risk of DLB, future studies could aim to investigate this relationship in larger samples, perhaps using combined datasets. In addition, due to the confines of the available data, age of injury was not obtained in the previous versions (i.e., UDS versions 1 and 2) of NACC's data collection forms, making it impossible to explore the interactions between more recent versus remote TBIs. Similarly, other injury-related information, such as the mechanism of injury, subsequent injury-related medical complications, TBI severity, or history of multiple TBIs were not available in the previous versions of NACCs data collection forms and thus were not incorporated into our analysis. These are important factors for characterizing TBI, and should be assessed in future studies to better understand the role of TBI and risk of neurodegenerative diseases including DLB. Also, given the limited autopsy data available at this time, the diagnosis of DLB was based on clinical criteria. Lastly, as with many other NACC-based investigations, subjects in the current study were largely well-educated, male Caucasians who were

recruited via clinician referral or self-referred into a voluntary longitudinal observational study, which may not accurately represent the general population.

In conclusion, our findings presented here do not suggest a statistically significant relationship between a self-reported history of remote TBI with LOC and an earlier onset of DLB symptoms or diagnosis. This is consistent with previous findings suggesting that TBI history is not associated with developing DLB [26]. Our present findings, however, contrast with our previous studies indicating that a history of remote TBI with LOC was associated with a significantly earlier onset of MCI, AD and FTD by approximately 2.5 to 3 years [10, 27–29]. The mechanisms by which TBI may increase the risk of developing different neurodegenerative diseases, or even the phenotypic expression within a neuropathological process, remains poorly understood and warrants further investigation. Such studies should focus on comparing the effects of TBI on AD and FTD as well as the motor and cognitive presentations of synucleinopathies.

ACKNOWLEDGEMENTS

This work was supported in part by the University of Texas Southwestern Alzheimer's disease Center (NIH/NIA grant number P3012300-19) and the Texas Alzheimer's Research and Care Consortium (TARCC). The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

REFERENCES

[1]. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K (2014) Traumatic brain injury and risk of dementia in older veterans. Neurology 83, 312–319. [PubMed: 24966406]

[2]. Wang HK, Lin SH, Sung PS, Wu MH, Hung KW, Wang LC, Huang CY, Lu K, Chen HJ, Tsai KJ (2012) Population based study on patients with traumatic brain injury suggests increased risk of dementia. J Neurol Neurosurg Psychiatry 83, 1080–1085. [PubMed: 22842203]

[3]. Schofield PW, Tang M, Marder K, Bell K, Dooneief G, Chun M, Sano M, Stern Y, Mayeux R (1997) Alzheimer's disease after remote head injury: an incidence study. J Neurol Neurosurg Psychiatry 62, 119–124. [PubMed: 9048710]

[4]. Guo Z, Cupples LA, Kurz A, Auerbach SH, Volicer L, Chui H, Green RC, Sadovnick AD, Duara R, DeCarli C, Johnson K, Go RC, Growdon JH, Haines JL, Kukull WA, Farrer LA (2000) Head injury and the risk of AD in the MIRAGE study. Neurology 54, 1316–1323. [PubMed: 10746604]

[5]. Mayeux R, Ottman R, Maestre G, Ngai C, Tang MX, Ginsberg H, Chun M, Tycko B, Shelanski M (1995) Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology 45, 555–557. [PubMed: 7898715]

[6]. Nemetz PN, Leibson C, Naessens JM, Beard M, Kokmen E, Annegers JF, Kurland LT (1999) Traumatic brain injury and time to onset of Alzheimer's disease: a population-based study. Am J Epidemiol 149, 32–40. [PubMed: 9883791]

[7]. Mortimer JA, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Rocca WA, et al. (1991) Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. Int J Epidemiol 20 Suppl 2, S28–35. [PubMed: 1833351]

[8]. Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, Phillips C, Gau BA, Welsh-Bohmer KA, Burke JR, Guralnik JM, Breitner JC (2000) Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 55, 1158–1166. [PubMed: 11071494]

[9]. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A (2003) Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry 74, 857–862. [PubMed: 12810767]

[10]. LoBue C, Wilmoth K, Cullum CM, Rossetti HC, Lacritz LH, Hynan LS, Hart J, Jr., Womack KB (2016) Traumatic brain injury history is associated with earlier age of onset of frontotemporal dementia. J Neurol Neurosurg Psychiatry 87, 817–820. [PubMed: 26359171]

[11]. Rosso SM, Landweer EJ, Houterman M, Donker Kaat L, van Duijn CM, van Swieten JC (2003) Medical and environmental risk factors for sporadic frontotemporal dementia: a retrospective case-control study. J Neurol Neurosurg Psychiatry 74, 1574–1576. [PubMed: 14617722]

[12]. Kalkonde YV, Jawaid A, Qureshi SU, Shirani P, Wheaton M, Pinto-Patarroyo GP, Schulz PE (2012) Medical and environmental risk factors associated with frontotemporal dementia: a case-control study in a veteran population. Alzheimers Dement 8, 204–210. [PubMed: 22465176]

[13]. Deutsch MB, Mendez MF, Teng E (2015) Interactions between traumatic brain injury and frontotemporal degeneration. Dement Geriatr Cogn Disord 39, 143–153. [PubMed: 25531628]

[14]. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, Aarsland D, Galvin J, Attems J, Ballard CG, Bayston A, Beach TG, Blanc F, Bohnen N, Bonanni L, Bras J, Brundin P, Burn D, Chen-Plotkin A, Duda JE, El-Agnaf O, Feldman H, Ferman TJ, Ffytche D, Fujishiro H, Galasko D, Goldman JG, Gomperts SN, Graff-Radford NR, Honig LS, Iranzo A, Kantarci K, Kaufer D, Kukull W, Lee VMY, Leverenz JB, Lewis S, Lippa C, Lunde A, Masellis M, Masliah E, McLean P, Mollenhauer B, Montine TJ, Moreno E, Mori E, Murray M, O'Brien JT, Orimo S, Postuma RB, Ramaswamy S, Ross OA, Salmon DP, Singleton A, Taylor A, Thomas A, Tiraboschi P, Toledo JB, Trojanowski JQ, Tsuang D, Walker Z, Yamada M, Kosaka K (2017) Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 89, 88–100. [PubMed: 28592453]

[15]. Gardner RC, Burke JF, Nettiksimmons J, Goldman S, Tanner CM, Yaffe K (2015) Traumatic brain injury in later life increases risk for Parkinson disease. Ann Neurol 77, 987–995. [PubMed: 25726936]

[16]. Jafari S, Etminan M, Aminzadeh F, Samii A (2013) Head injury and risk of Parkinson disease: a systematic review and meta-analysis. Mov Disord 28, 1222–1229. [PubMed: 23609436]

[17]. Taylor KM, Saint-Hilaire MH, Sudarsky L, Simon DK, Hersh B, Sparrow D, Hu H, Weisskopf MG (2016) Head injury at early ages is associated with risk of Parkinson's disease. Parkinsonism Relat Disord 23, 57–61. [PubMed: 26725141]

[18]. Marras C, Hincapie CA, Kristman VL, Cancelliere C, Soklaridis S, Li A, Borg J, af Geijerstam JL, Cassidy JD (2014) Systematic review of the risk of Parkinson's disease after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 95, S238–244. [PubMed: 24581909]

[19]. Rugbjerg K, Ritz B, Korbo L, Martinussen N, Olsen JH (2008) Risk of Parkinson's disease after hospital contact for head injury: population based case-control study. BMJ 337, a2494. [PubMed: 19074944]

[20]. Maher NE, Golbe LI, Lazzarini AM, Mark MH, Currie LJ, Wooten GF, Saint-Hilaire M, Wilk JB, Volcjak J, Maher JE, Feldman RG, Guttman M, Lew M, Waters CH, Schuman S, Suchowersky O, Lafontaine AL, Labelle N, Vieregge P, Pramstaller PP, Klein C, Hubble J, Reider C, Growdon J, Watts R, Montgomery E, Baker K, Singer C, Stacy M, Myers RH (2002) Epidemiologic study of 203 sibling pairs with Parkinson's disease: the GenePD study. Neurology 58, 79–84. [PubMed: 11781409]

[21]. Fang F, Chen H, Feldman AL, Kamel F, Ye W, Wirdefeldt K (2012) Head injury and Parkinson's disease: a population-based study. Mov Disord 27, 1632–1635. [PubMed: 23143933]

[22]. Uryu K, Chen XH, Martinez D, Browne KD, Johnson VE, Graham DI, Lee VMY, J QT, Smith DH (2007) Multiple Proteins Implicated in Neurodegenerative Diseases Accumulate in Axons After Brain Trauma in Humans. Exp Neurol 208, 185–192. [PubMed: 17826768]

[23]. Acosta SA, Tajiri N, de la Pena I, Bastawrous M, Sanberg PR, Kaneko Y, Borlongan CV (2015) Alpha-synuclein as a pathological link between chronic traumatic brain injury and Parkinson's disease. J Cell Physiol 230, 1024–1032. [PubMed: 25251017]

[24]. Impellizzeri D, Campolo M, Bruschetta G, Crupi R, Cordaro M, Paterniti I, Cuzzocrea S, Esposito E (2016) Traumatic Brain Injury Leads to Development of Parkinson's Disease Related Pathology in Mice. Front Neurosci 10, 458. [PubMed: 27790086]

[25]. Crane PK, Gibbons LE, Dams-O'Connor K, Trittschuh E, Leverenz JB, Keene CD, Sonnen J, Montine TJ, Bennett DA, Leurgans S, Schneider JA, Larson EB (2016) Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings. JAMA Neurol 73, 1062–1069. [PubMed: 27400367]

[26]. Boot BP, Orr CF, Ahlskog JE, Ferman TJ, Roberts R, Pankratz VS, Dickson DW, Parisi J, Aakre JA, Geda YE, Knopman DS, Petersen RC, Boeve BF (2013) Risk factors for dementia with Lewy bodies: a case-control study. Neurology 81, 833–840. [PubMed: 23892702]

[27]. LoBue C, Wadsworth H, Wilmoth K, Clem M, Hart J, Jr., Womack KB, Didehbani N, Lacritz LH, Rossetti HC, Cullum CM (2017) Traumatic brain injury history is associated with earlier age of onset of Alzheimer disease. Clin Neuropsychol 31, 85–98. [PubMed: 27855547]

[28]. LoBue C, Denney D, Hynan LS, Rossetti HC, Lacritz LH, Hart J, Womack KB, Woon FL, Cullum CM (2016) Self-Reported Traumatic Brain Injury and Mild Cognitive Impairment: Increased Risk and Earlier Age of Diagnosis. J Alzheimers Dis 51, 727–736. [PubMed: 26890760]

[29]. Schaffert J, LoBue C, White CL, Chiang HS, Didehbani N, Lacritz L, Rossetti H, Dieppa M, Hart J, Cullum CM (2018) Traumatic Brain Injury History Is Associated With an Earlier Age of Dementia Onset in Autopsy-Confirmed Alzheimer's Disease. Neuropsychology

[30]. Morris JC, Weintraub S, Chui HC, Cummings J, Decarli C, Ferris S, Foster NL, Galasko D, Graff-Radford N, Peskind ER, Beekly D, Ramos EM, Kukull WA (2006) The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Dis Assoc Disord 20, 210–216. [PubMed: 17132964]

[31]. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M, Consortium on DLB (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65, 1863–1872. [PubMed: 16237129]

[32]. Skogseth R, Hortobagyi T, Soennesyn H, Chwiszczuk L, Ffytche D, Rongve A, Ballard C, Aarsland D (2017) Accuracy of Clinical Diagnosis of Dementia with Lewy Bodies versus Neuropathology. J Alzheimers Dis 59, 1139–1152. [PubMed: 28731443]

[33]. Dams-O'Connor K, Gibbons LE, Bowen JD, McCurry SM, Larson EB, Crane PK (2013) Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. J Neurol Neurosurg Psychiatry 84, 177–182. [PubMed: 23172868]

[34]. Helmes E, Ostbye T, Steenhuis RE (2011) Incremental contribution of reported previous head injury to the prediction of diagnosis and cognitive functioning in older adults. Brain Inj 25, 338–347. [PubMed: 21314278]

[35]. Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, Zhao QF, Li JQ, Wang J, Yu JT (2015) Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry 86, 1299–1306. [PubMed: 26294005]

Table 1.

Demographics of a clinically-diagnosed DLB sample with and without a history of remote TBI

	TBI+ (n = 50)	TBI− (n = 526)	*p*-value
Males, n (%)	43 (86)	366 (67)	0.014*
Caucasian, n (%)	49 (98)	455 (87)	0.06
Education in years, M (SD)	15.3 (3.7)	14.5 (3.6)	0.17
Years smoking, M (SD)	13.7 (14.1)	11.2 (15.7)	0.25
Family history of dementia, n (%)	24 (50)	256 (57)	0.38
Number of APOE ε4 alleles			0.63
Zero APOE ε4 alleles, n (%)	22 (56)	181 (51)	
One APOE ε4 allele, n (%)	13 (33)	146 (41)	
Two APOE ε4 alleles, n (%)	4 (10)	29 (8)	
Depression			
Lifetime, n (%)	27 (56)	305 (60)	0.65
Within 2 years of diagnosis, n (%)	22 (46)	286 (56)	0.18
Remote history of stroke, n (%)	3 (6)	39 (8)	0.74

* $p < 0.05$.

Note: APOE ε4 indicates apolipoprotein E *ε4*.