

## Original Research Article

# Cognitive, Behavioral, and Functional Outcomes of Suspected Mild Traumatic Brain Injury in Community-Dwelling Older Persons Without Mild Cognitive Impairment or Dementia



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**Background:** Traumatic brain injury is associated with greater risk and earlier onset of dementia. **Objective:** This study investigated whether later-life changes in subjective cognition and behavior – potential markers of Alzheimer disease – could be observed in cognitively unimpaired older persons with a history of suspected mild traumatic brain injury (smTBI) earlier in life and whether changes in cognition and behavior mediated the link between smTBI and daily function. **Methods:** Data for 1392 participants from the Canadian Platform for Research Online to Investigate Health, Quality of Life, Cognition, Behaviour, Function, and Caregiving in Aging were analyzed. A validated self-reported brain injury screening questionnaire was used to determine the history of smTBI. Outcomes were measured using the Everyday Cognition scale (for subjective cognitive decline [SCD]), Mild Behavioral Impairment (MBI) Checklist, and Standard Assessment of Global Everyday Activities (for function). Inverse probability of treatment weighted logistic and negative binomial regressions were used to model smTBI (exposure) associations with SCD and MBI statuses, and Everyday Cognition-II and MBI Checklist total scores, respectively. Mediation analyses were conducted using bootstrapping. **Results:** History of smTBI was linked to higher odds of SCD (odds ratio = 1.45, 95% confidence interval: [1.14–1.84]) or MBI (odds ratio = 1.75, 95% confidence interval: [1.54–1.98]), as well as 24% (95% confidence interval: [18%–31%]) higher

Everyday Cognition-II and 52% (95% confidence interval: [41%–63%]) higher MBI Checklist total scores. Finally, SCD and MBI mediated approximately 45% and 56%, respectively, of the association between smTBI history and poorer function, as indicated by higher Standard Assessment of Global Everyday Activities total scores. **Conclusions:** smTBI at any point in the life course is linked to poorer cognition and behavior even in community-dwelling

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*older persons without MCI or dementia. Older persons with smTBI may benefit from early dementia risk assessment using tools that measure changes in cognition and behavior. Interventions for declining*

*cognition and behavior may also be beneficial in this population to address functional impairment.*

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**Key words:** traumatic brain injury, dementia, mild behavioral impairment, subjective cognitive decline, aging.

Traumatic brain injury (TBI) is a major contributor to mortality worldwide, with nearly 70 million people expected to suffer from TBI annually.<sup>1</sup> Although TBI can occur at all ages, adolescents and older persons are more vulnerable.<sup>2</sup> Moreover, older persons are subject to the highest and fastest rising incidence of TBI, most often due to falls.<sup>3</sup> TBI occurs when a mechanical insult (i.e., head strike) results in acute clinical symptoms including confusion, amnesia, and loss of consciousness.<sup>4</sup> TBI may have long-term cognitive and functional consequences, including a greater risk of dementia, particularly due to Alzheimer disease (AD).<sup>5,6</sup> The substantial prevalence of TBI and its link to dementia warrant efforts to better understand and mitigate its long-term neurological consequences.

The pathological processes that cause dementia, most commonly AD, begin years before dementia onset.<sup>7</sup> Thus, detecting AD at preclinical stages and initiating early interventions may effectively and feasibly reduce the global burden of AD dementia. This strategy may be even more important among persons who have suffered from TBI, due to the link between TBI and AD pathology, which can lead to a younger age of onset of cognitive decline.<sup>8–10</sup> Delaying the onset of dementia by even a year has been estimated to reduce the number of cases by approximately one million.<sup>11</sup> Furthermore, emerging AD disease-modifying therapies and secondary prevention programs likely yield greater benefit when administered at earlier disease stages.<sup>12</sup>

Subjective cognitive decline (SCD) is a neurocognitive construct developed to facilitate earlier detection of initial-stage AD.<sup>13</sup> Characterized by self- or informant-reported cognitive decline without impaired performance on objective cognitive tests,<sup>13</sup> SCD may emerge up to 10 years before AD-related dementia onset.<sup>14</sup> Approximately 27% of persons with SCD will develop mild cognitive impairment (MCI), involving objectively impaired cognition, and 14% will decline to dementia: a relative risk of 2.07 compared to non-SCD.<sup>15</sup> Like changes in cognition, behavioral changes can

emerge as sequelae of underlying AD. These later-life emergent and persistent changes in behavior, known as mild behavioral impairment (MBI),<sup>16</sup> precede AD dementia and sometimes emerge in advance of even MCI.<sup>17–19</sup> In addition to facilitating early AD detection, MBI has been linked to several adverse health outcomes, including impairments in gait, hearing, and sleep, lower quality of life, and greater frailty and loneliness.<sup>20–25</sup> These findings suggest that MBI may, itself, serve as a target outcome for therapeutic interventions or prevention strategies.<sup>26</sup>

As persons with a history of TBI are at higher risk of AD dementia,<sup>6</sup> with a younger age of onset compared to those with no history of TBI,<sup>8,9</sup> they may benefit from earlier risk assessment (i.e., SCD and MBI), even in the absence of clinically significant cognitive impairment. To date, most of the literature on TBI and dementia has focused on symptoms that occur later in the course of AD.<sup>10</sup> Whether sequelae of initial AD are measurable in community-dwelling cognitively unimpaired older persons with a history of TBI is not fully understood. Furthermore, better understanding the link between TBI and later life psychiatric consequences has additional implications for improving function and quality of life in older persons. Hence, the purpose of this study was to compare both SCD and MBI symptoms in cognitively unimpaired older persons with or without a history of suspected mild TBI (smTBI). We further explored whether any observed SCD or MBI symptoms could account for potential links between smTBI and changes in daily function. We hypothesized that persons with smTBI would be more likely to show symptoms of SCD and MBI, even in the absence of objective cognitive impairment.

## MATERIALS AND METHODS

### Study Design

The Canadian Platform for Research Online to Investigate Health, Quality of Life, Cognition, Behaviour,

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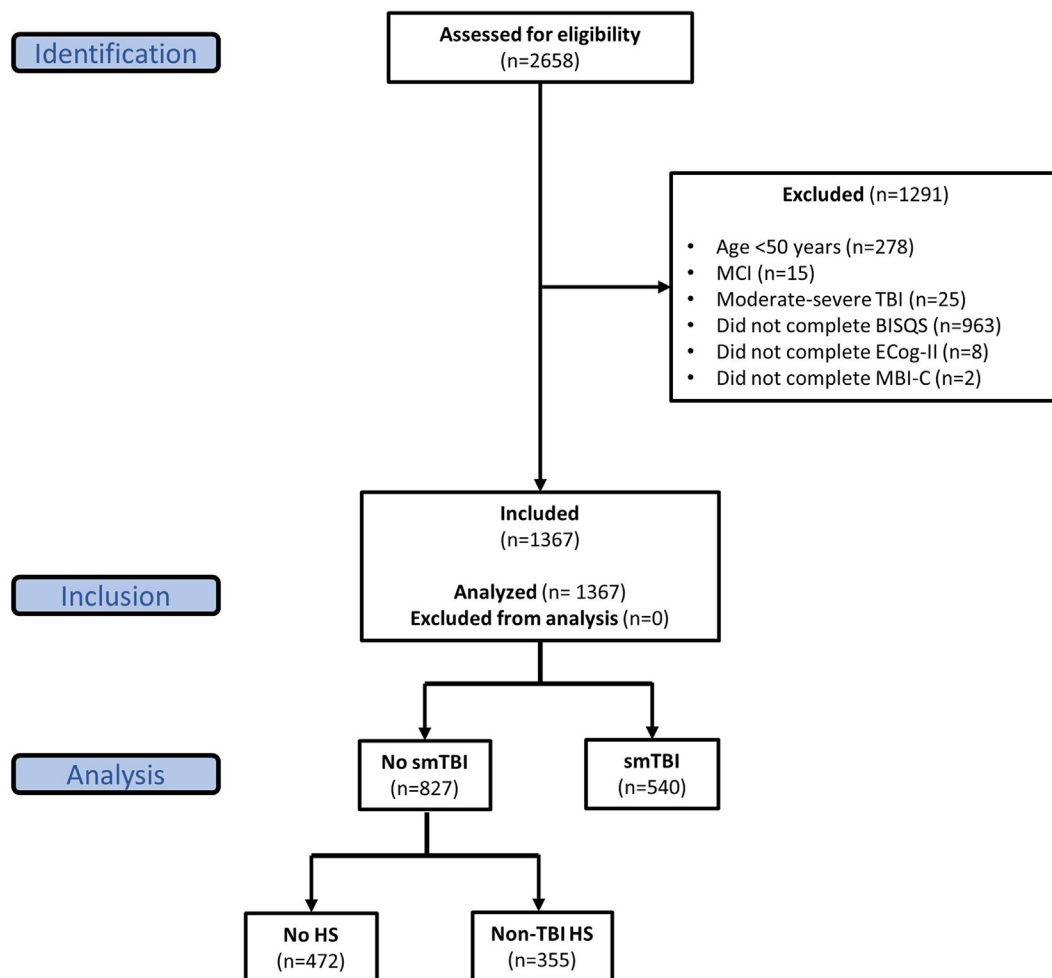
Function, and Caregiving in Aging is a nation-wide online longitudinal observational cohort study of brain aging.<sup>27</sup> Participants must have confirmed that they did not have a dementia diagnosis before enrolling in the study; MCI was not an exclusion criterion at enrolment, though self-reported clinical diagnosis of MCI was used as an exclusion criterion during participant selection. After registration, participants completed annual assessments on demographics, health, cognition, behavior, function, lifestyle, and other factors related to brain health and aging. Participants were given 6 months from registration to complete all assessments, of which 8 were mandatory and the remaining 9 were optional. Ethics approval for the

study was obtained from the Conjoint Health Research Ethics Board at the University of Calgary (REB21-1065). A detailed description of the study procedure and existing cohort has been published elsewhere.<sup>27</sup>

### Participants

The present cross-sectional analysis was a complete-case analysis of 1367 participants (Figure 1). Of the 2658 participants assessed for eligibility, 278 were excluded for age <50 years, 15 for having reported receiving a clinical diagnosis of MCI, 25 for having reported moderate-severe TBI, 963 for having not completed the optional Brain Injury Screening

**FIGURE 1. Participant Flow Diagram.** BISQS = Brain Injury Screening Questionnaire – Short form; ECog-II = Everyday Cognition Scale II; HS = head strike; MBI-C = Mild Behavioral Impairment Checklist; MCI = mild cognitive impairment; smTBI = suspected mild traumatic brain injury



Questionnaire – Short form, 8 for having not completed the Everyday Cognition II (ECog-II) scale, and 2 for having not completed the Mild Behavioral Impairment Checklist (MBI-C). Of the remaining 1367 participants, all had completed the Standard Assessment of Global Everyday Activities (SAGEA).

#### smTBI Classification

Information about lifetime history of head strikes (HSs) was assessed using the Brain Injury Screening Questionnaire – Short form, a validated self-reported TBI screening tool.<sup>28</sup> Participants report the presence and severity of HS across 7 settings: vehicle accidents, moving objects, falling, sports/leisure, physical abuse/assault, military service, and other. Where applicable, participants are prompted on the number of HS sustained and whether they resulted in acute symptoms of feeling dazed/confused or experiencing a loss of consciousness, lasting a specified duration. Consistent with the 2023 American Congress of Rehabilitation Medicine diagnostic criteria,<sup>4</sup> we identified participants as having smTBI if they reported feeling dazed/confused or experiencing loss of consciousness after their most severe HS. The term “suspected” was used given that self-reported symptoms were the only evidence suggestive of brain injury. Although some participants ( $n = 25$ , 1.9%) reported loss of consciousness >30 minutes post-HS, thereby exceeding the upper threshold for mild TBI, there was insufficient statistical power to analyze this group separately. Hence, these participants were excluded (Figure 1). Participants who reported experiencing their most severe HS without acute clinical symptoms (dazed/confused or loss of consciousness) were categorized as Non-TBI HS. The reference group therefore consisted of both participants with Non-TBI HS and those who did not report experiencing any HS (No HS). A sensitivity analysis, which involved varying the reference group (only Non-TBI HS vs only No HS), was conducted.

#### Measures

Outcome measures were the ECog-II, MBI-C, and SAGEA; all self-reported. Briefly, the ECog-II evaluates changes in everyday cognition and function related to memory, language, visuospatial function, and executive function across 41 items. Each item is scored 0–3 (0 = no change, 1 = occasionally worse, 2 = consistently

a little worse; 3 = much worse) relative to a participant’s own baseline. We operationalized subjective cognitive decline (SCD+) based on a score of  $\geq 2$  (i.e., consistently a little or much worse) on any ECog-II item.<sup>29</sup> Although objective cognitive testing are available in Canadian Platform for Research Online to Investigate Health, Quality of Life, Cognition, Behaviour, Function, and Caregiving in Aging, smTBI associations with these cognitive tests have already been published elsewhere, and therefore were not analyzed.<sup>30</sup>

MBI symptom severity was evaluated using the MBI-C, a tool to measure MBI symptoms in older persons (age  $\geq 50$  years) without dementia, following the International Society to Advance Alzheimer’s Research and Treatment – Alzheimer’s Association (ISTAART-AA) MBI research diagnostic criteria.<sup>16,31</sup> The self-reported MBI-C has been validated in online cohorts of cognitively normal older persons.<sup>19,32,33</sup> The MBI-C comprises 34 items across 5 domains: decreased motivation (6 items), affective dysregulation (6 items), impulse dyscontrol (12 items), social inappropriateness (5 items) and abnormal perception or thought content (5 items). Participants indicated if symptoms persisted for at least 6 months and marked a deviation from longstanding patterns of behavior, in alignment with MBI criteria. Symptom severity was rated on a scale from 0 – 3 (0 = absent), with higher scores indicating greater severity. Domain scores were the sum of their items and global MBI symptom severity (range = 0 – 104) was sum of domain scores. A validated MBI-C score  $\geq 8$  was used to classify MBI+ participants.<sup>34-36</sup> Although ISTAART-AA MBI criteria require that symptoms cannot be attributable to another psychiatric condition, participants with psychiatric history were not excluded from this study as the MBI-C inherently distinguishes new symptoms from chronic and/or recurrent ones.<sup>31</sup>

The SAGEA comprises 15 items related to functional status over the past month for cognitive activities of daily living (e.g., remembering conversations), applied cognitive activities of daily living (e.g., organizing activities), instrumental activities of daily living (e.g., managing finances), mobility (e.g., using stairs), and basic activities of daily living (e.g., dressing).<sup>37</sup> Each item is scored 0–3 (0 = no difficulty, 3 = severe difficulty), and an extra 1 point is added, up to a maximum of 3, for tasks where participants required assistance. The total SAGEA score was calculated as

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the sum of all 15 item scores, resulting in a maximum possible score of 45, with higher scores indicating greater functional impairment.

### Statistical Analysis

Demographic, cognitive, behavioral, and functional measures were summarized for the entire cohort and stratified by smTBI status using means, standard deviations, ranges, and percentages.

As the Brain Injury Screening Questionnaire – Short form was an optional questionnaire, we attempted to identify potential self-selection bias by comparing demographics of complete- and incomplete-case participants. Furthermore, we used inverse probability of treatment weighting to correct for bias that may have been introduced by a complete-case analysis approach.<sup>38</sup> Specifically, measured demographic variables (age, sex, education, marital status, language, handedness, ethnocultural origins) were used in a logistic regression to predict the probability of participants being a complete-case. Participants were assigned a higher weight if they were less likely to be a complete-case (i.e., more similar to incomplete-cases). The inverse of these weights was used for subsequent statistical modelling in order to balance out these known covariates between case groups.

To model smTBI associations with SCD+ and MBI+ statuses, we conducted 2 separate logistic regression models with smTBI status as the exposure variable. Coefficients from the models were exponentiated to derive odds ratios (ORs). As the severity of SCD and MBI symptoms (i.e., total ECog-II and MBI-C scores, respectively) were also of interest, we employed negative binomial regression, given that ECog-II and MBI-C statistical distributions resembled overdispersed (variance > mean) Poisson distributions (i.e., right-skewed whole numbers). Exponentiated coefficients ( $\exp[b]$ ) estimated from negative binomial regression models represent the factor change in the outcome variable (ECog-II or MBI-C total score) in participants with smTBI relative to those without. As part of a secondary analysis, we analyzed smTBI associations with individual ECog-II and MBI-C domain scores.

To address our second study objective, we conducted mediation analyses to determine whether SCD or MBI status mediated the association between smTBI

and changes in daily function, as measured by the SAGEA (Figure 2). These mediation analyses involved modelling the presence of SCD + or MBI+, separately, as a function of smTBI status using logistic regression, as previously described, and then SAGEA total score as a function of smTBI covaried for either SCD+ (Path A) or MBI+ (Path B), using negative binomial regression. Based on these models, bootstrapping with 5000 simulations was used to estimate direct (i.e., effect of smTBI on SAGEA scores) and indirect (i.e., effect of smTBI on SAGEA scores via SCD + or MBI+) effects. We report coefficients for the direct and indirect effects, and the proportion of the total effect that was mediated.

To address potential confounders, a separate inverse probability of treatment weighting procedure was conducted to balance observed covariates including age, sex, years of education, marital status, and ethnocultural origins across exposure groups (i.e., no TBI, non-TBI HS, smTBI). We assumed that probabilities previously generated by inverse probability of treatment weighting to address self-selection bias were independent of probabilities generated to balance confounders, and as such, used the product of self-selection and confounder balancing weights to adjust each regression model accordingly. The overall performance of inverse probability of treatment weighting was confirmed by inspecting the coefficient of variance, effective sample sizes, and standardized mean differences of covariates.

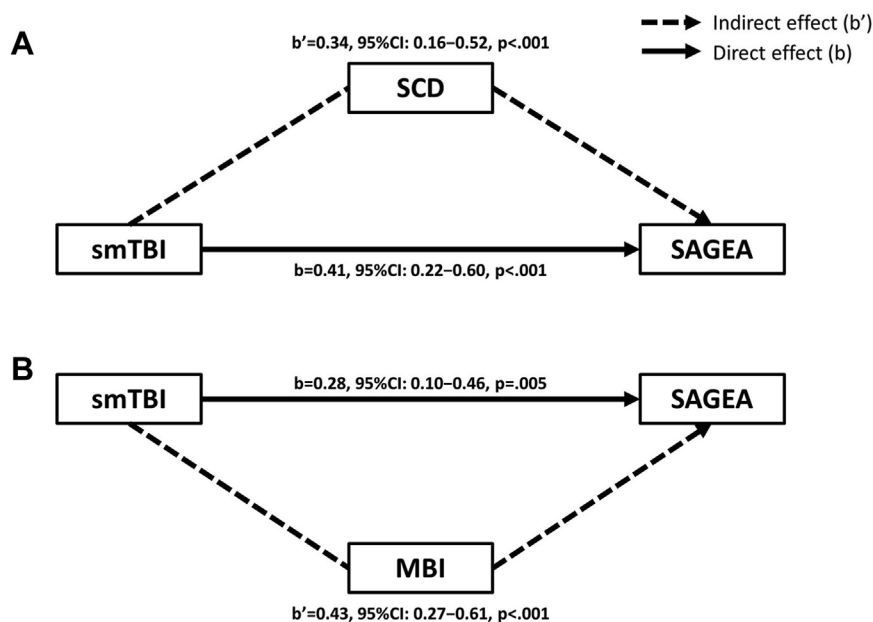
To reduce the risk of type I error due to multiple comparisons, we adjusted all *P*-values of interest (6 comparisons excluding the sensitivity analysis; 2 for smTBI associations with SCD + status and ECog-II total score; 2 for smTBI associations with MBI + status and MBI-C total score; and 2 for mediation analyses) using the Benjamini-Hochberg procedure based on false discovery rate to obtain false discovery rate-corrected *q*-values. These *q*-values are reported alongside unadjusted *P* values, where appropriate. Statistical significance was defined by  $q < 0.05$ .

## RESULTS

### Sample Characteristics

Across the entire cohort (81.2% assigned female sex at birth), the mean  $\pm$  standard deviation age and years of

**FIGURE 2.** smTBI and Function Mediation Analyses. Mediation analysis was performed using bootstrapping with 5000 simulations. Total effects can be derived by summing direct and indirect effect coefficients. The exposure and outcome variables for all mediation analyses were smTBI status and SAGEA total score (higher scores indicate poorer daily function), respectively. Path model A tested the effect of SCD as the mediator. Path model B tested the effect of MBI as the mediator. MBI = mild behavioral impairment; SCD = subjective cognitive decline; smTBI = suspected mild traumatic brain injury



education completed were  $64.8 \pm 7.5$  and  $15.8 \pm 4.5$  years, respectively [Table 1]. Most participants were married or cohabitating (77.3%) and generally reported having European (84.8%) and North American (47.3%) ethnocultural origins (multiselect origins allowed). SCD+ and MBI+ were present in 27.0% and 24.3% of all participants, respectively. Compared to those excluded for not completing the assessments required for analysis (i.e., incomplete cases), complete-case participants were more likely to have been assigned female sex at birth (81.7% vs 75.3%,  $P < 0.001$ ). There were no significant differences between complete-case and incomplete-case participants in other demographic variables.

Nearly two-thirds of all participants (65.5%) reported having sustained  $\geq 1$  HS throughout their lifetime, with an average of  $2.6 \pm 5.3$  total HS across  $1.2 \pm 1.1$  settings. However, only 39.5% of the entire cohort sustained a HS that met smTBI criteria. Among those with smTBI, the most common sources were sports/leisure activities (38.3%), followed by falls (36.5%), moving objects (25.6%), vehicle accidents (21.3%), abuse (4.6%), other (3.0%), and military activities (0.4%).

#### smTBI Associations with Cognition, Behavior, Function

Sustaining smTBI throughout the life course was linked to 1.47 times higher odds of SCD+ (95% confidence interval [CI]: 1.16–1.87,  $P = 0.002$ ,  $q = 0.002$ ) and 1.77 times higher odds of MBI+ (95% CI: 1.56–2.01,  $P < 0.001$ ,  $q < 0.001$ ) [Table 2 and Figure 3]. The associations remained consistent regardless of whether the reference group consisted of only no HS (SCD + OR = 1.56, 95% CI: 1.18–2.07,  $P = 0.002$ ; MBI + OR = 1.83, 95% CI: 1.58–2.12,  $P < 0.001$ ) or non-TBI HS (SCD + OR = 1.36, 95% CI: 1.01–1.84,  $P = 0.04$ ; MBI + OR = 1.61, 95% CI: 1.38–1.87,  $P < 0.001$ ) participants.

smTBI was also associated with 1.25 times higher ECog-II total score (95% CI: 1.19–1.32,  $P < 0.001$ ,  $q < 0.001$ ) and 1.54 times higher MBI-C total score (95% CI: 1.43–1.66,  $P < 0.001$ ,  $q < 0.001$ ) (Table 2 and Figure 3). These coefficients corresponded to an approximately 2-point higher score in the smTBI group relative to the pooled reference group for both the ECog-II (13.2 vs 10.7) and MBI-C (6.6 vs 4.3). Like smTBI associations with SCD+ and MBI+, smTBI

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**TABLE 1. Participant Characteristics Stratified by smTBI Status**

Variable	Total	No HS	Non-TBI HS	smTBI	<i>P</i>
N	1367	472	355	540	
Age (years)	64.8 (7.5), 50–94	65.4 (7.8), 50–94	65.1 (7.4), 50–89	64.1 (7.2), 50–89	0.02
Female sex	1117 (81.7)	417 (88.3)	292 (82.3)	408 (75.6)	<0.001
Education (years)	15.8 (4.5), 0–29.4	15.3 (4.6), 0–29.4	16.3 (4.3), 2–29.4	15.8 (4.4), 1–29.4	0.002
Ethnocultural origins					
North American	646 (47.3)	235 (49.8)	173 (48.7)	238 (44.1)	0.16
European	1159 (84.8)	381 (80.7)	309 (87)	469 (86.9)	0.01
Caribbean	8 (0.6)	1 (0.2)	3 (0.8)	4 (0.7)	0.41
South American	10 (0.7)	3 (0.6)	3 (0.8)	4 (0.7)	0.94
African	10 (0.7)	1 (0.2)	4 (1.1)	5 (0.9)	0.25
Asian	39 (2.9)	11 (2.3)	12 (3.4)	16 (3.0)	0.66
Oceanic	7 (0.5)	2 (0.4)	2 (0.6)	3 (0.6)	0.95
Marital status	1057 (77.3)	372 (78.8)	275 (77.5)	410 (75.9)	0.66
SCD status	369 (27.0)	108 (22.9)	90 (25.4)	171 (31.7)	0.005
ECog-II score					
Total	11.7 (11.2), 0–99	10.8 (11.0), 0–88	10.7 (9.2), 0–53	13.2 (12.4), 0–99	<0.001
Memory	4.6 (3.7), 0–25	4.4 (3.7), 0–24	4.4 (3.3), 0–17	5.0 (4.0), 0–25	0.008
Language	3.2 (3.4), 0–24	3.0 (3.3), 0–24	3.0 (3.0), 0–19	3.5 (3.6), 0–23	0.03
Visuospatial	0.8 (1.5), 0–18	0.7 (1.4), 0–14	0.7 (1.3), 0–8	0.9 (1.7), 0–18	0.07
Executive	3.1 (4.4), 0–39	2.7 (4.1), 0–35	2.6 (3.2), 0–17	3.8 (5.1), 0–39	<0.001
MBI status	332 (24.3)	92 (19.5)	73 (20.6)	167 (30.9)	<0.001
MBI-C score					
Total	5.2 (7.3), 0–65	4.3 (6.8), 0–65	4.3 (5.1), 0–28	6.6 (8.6), 0–49	<0.001
Decreased motivation	1.6 (2.5), 0–18	1.3 (2.4), 0–18	1.3 (1.9), 0–9	2.1 (2.9), 0–15	<0.001
Affective dysregulation	1.7 (2.6), 0–17	1.5 (2.5), 0–16	1.4 (2.1), 0–12	2.1 (2.9), 0–17	<0.001
Impulse dyscontrol	1.5 (2.4), 0–20	1.2 (2.2), 0–20	1.2 (1.6), 0–8	1.9 (2.9), 0–20	<0.001
Social inappropriateness	0.2 (0.7), 0–9	0.2 (0.7), 0–8	0.2 (0.6), 0–7	0.3 (0.8), 0–9	0.01
Psychosis	0.2 (0.6), 0–7	0.1 (0.5), 0–4	0.2 (0.5), 0–5	0.3 (0.8), 0–7	<0.001
SAGEA score					
Total	3 (3.7), 0–27	2.7 (3.5), 0–24	2.5 (2.8), 0–14	3.4 (4.2), 0–27	<0.001
Cognitive ADLs	1.0 (1.2), 0–7	0.9 (1.1), 0–7	0.9 (1), 0–5	1.2 (1.3), 0–7	<0.001
Applied cognitive ADLs	0.9 (1.4), 0–9	0.9 (1.5), 0–9	0.8 (1.3), 0–9	1.0 (1.4), 0–9	0.06
Instrumental ADLs	0.6 (1.3), 0–8	0.6 (1.3), 0–8	0.5 (1.1), 0–6	0.6 (1.3), 0–8	0.34
Mobility	0.3 (0.8), 0–6	0.3 (0.7), 0–6	0.2 (0.7), 0–6	0.4 (0.9), 0–6	0.04
Basic ADLs	0.2 (0.6), 0–5	0.1 (0.5), 0–5	0.1 (0.4), 0–3	0.2 (0.7), 0–5	0.001

Ethnocultural origins are not mutually exclusive. All values have been rounded to one decimal place, except for *P* values which have been rounded to 2 or 3 decimal places, as appropriate. Continuous variables are shown in mean (standard deviation), range. Categorical variables are shown in n (%). Comparisons between groups were tested using independent samples t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables, as appropriate.

ADLs = activities of daily living; ECog-II = Everyday Cognition II scale; HS = head strike; MBI = mild behavioral impairment; MBI-C = Mild Behavioral Impairment Checklist; SAGEA = Standard Assessment of Global Everyday Activities; SCD = subjective cognitive decline; smTBI = suspected mild traumatic brain injury.

associations with ECog-II and MBI-C total scores remained consistent regardless of the reference group (Table 2).

The secondary analysis revealed that participants with smTBI reported more severe cognitive changes in all ECog-II domains, including memory (exp[b] = 1.15, 95% CI: 1.10–1.21, *P* < 0.001, language (exp [b] = 1.20, 95% CI: 1.13–1.27, *P* < 0.001), visuo-spatial function (exp[b] = 1.27, 95% CI: 1.15–1.39, *P* = 0.001), and executive function (exp[b] = 1.46,

95% CI: 1.36–1.57, *P* < 0.001). Participants with smTBI also reported more severe higher MBI-C scores in all domains: decreased motivation (exp [b] = 1.56, 95% CI: 1.43–1.71, *P* < 0.001), affective dysregulation (exp[b] = 1.52, 95% CI: 1.41–1.65, *P* < 0.001), impulse dyscontrol (exp[b] = 1.49, 95% CI: 1.37–1.62, *P* < 0.001), social inappropriateness (exp [b] = 1.58, 95% CI: 1.35–1.86, *P* < 0.001), and psychosis (exp[b] = 1.78, 95% CI: 1.52–2.08, *P* < 0.001).

**TABLE 2. smTBI Associations with Cognition and Behavior**

Exposure (ref)	Outcome		
	OR	95% CI	p/q
<b>SCD</b>			
smTBI status (no HS)	1.56	1.18–2.07	0.002
smTBI status (non-TBI HS)	1.36	1.01–1.84	0.04
smTBI status (pooled)	1.47	1.16–1.87	0.002/.002
<b>MBI+</b>			
smTBI status (no HS)	1.83	1.58–2.12	<0.001
smTBI status (non-TBI HS)	1.61	1.38–1.87	<0.001
smTBI status (pooled)	1.77	1.56–2.01	<0.001/<0.001
	<b>exp(b)</b>	<b>95% CI</b>	<b>p/q</b>
<b>ECog-II total score</b>			
smTBI status (no HS)	1.26	1.19–1.34	<0.001
smTBI status (non-TBI HS)	1.23	1.16–1.31	<0.001
smTBI status (pooled)	1.25	1.19–1.32	<0.001/<0.001
<b>MBI-C total score</b>			
smTBI status (no HS)	1.56	1.43–1.70	<0.001
smTBI status (non-TBI HS)	1.49	1.37–1.62	<0.001
smTBI status (pooled)	1.54	1.43–1.66	<0.001/<0.001

The pooled reference group consisted of participants with either no HS or non-TBI HS. Odds ratios (ORs) were estimated from logistic regression; they indicate the factor change in odds of having SCD or MBI+ between participants with smTBI relative to those without. Exponentiated coefficients (exp[b]) were estimated from negative binomial regression, and as such, represent the factor change in the outcome variable in participants with smTBI relative to those without. All *P*-values of interest were adjusted using the Benjamini-Hochberg procedure based on false discovery rate (FDR) to generate FDR-corrected *q*-values; *P*-values from sensitivity analyses that involved varying the reference group were not included in the adjustment.

ECog-II = Everyday Cognition II scale; HS = head strike; MBI-C = Mild Behavioral Impairment Checklist; smTBI = suspected mild traumatic brain injury.

Finally, participants with a history of smTBI had 1.33 times greater functional impairment as measured by higher SAGEA total score (95% CI: 1.24–1.42,  $P < 0.001$ ) relative to those without smTBI; equivalent to approximately a 0.7-point higher score (2.6 vs 3.4). The mediation analyses revealed that the association between smTBI and SAGEA was partially mediated by SCD + status (indirect  $b = 0.34$ , 95% CI: 0.16 – 0.52,  $P = 0.001$ ,  $q = 0.001$ ) and MBI + status (indirect  $b = 0.43$ , 95% CI: 0.27 – 0.61,  $P < 0.001$ ,  $q < 0.001$ ), accounting for 45.57% and 60.83% of the total effect,

respectively, when the mediation models were conducted separately (Figure 2).

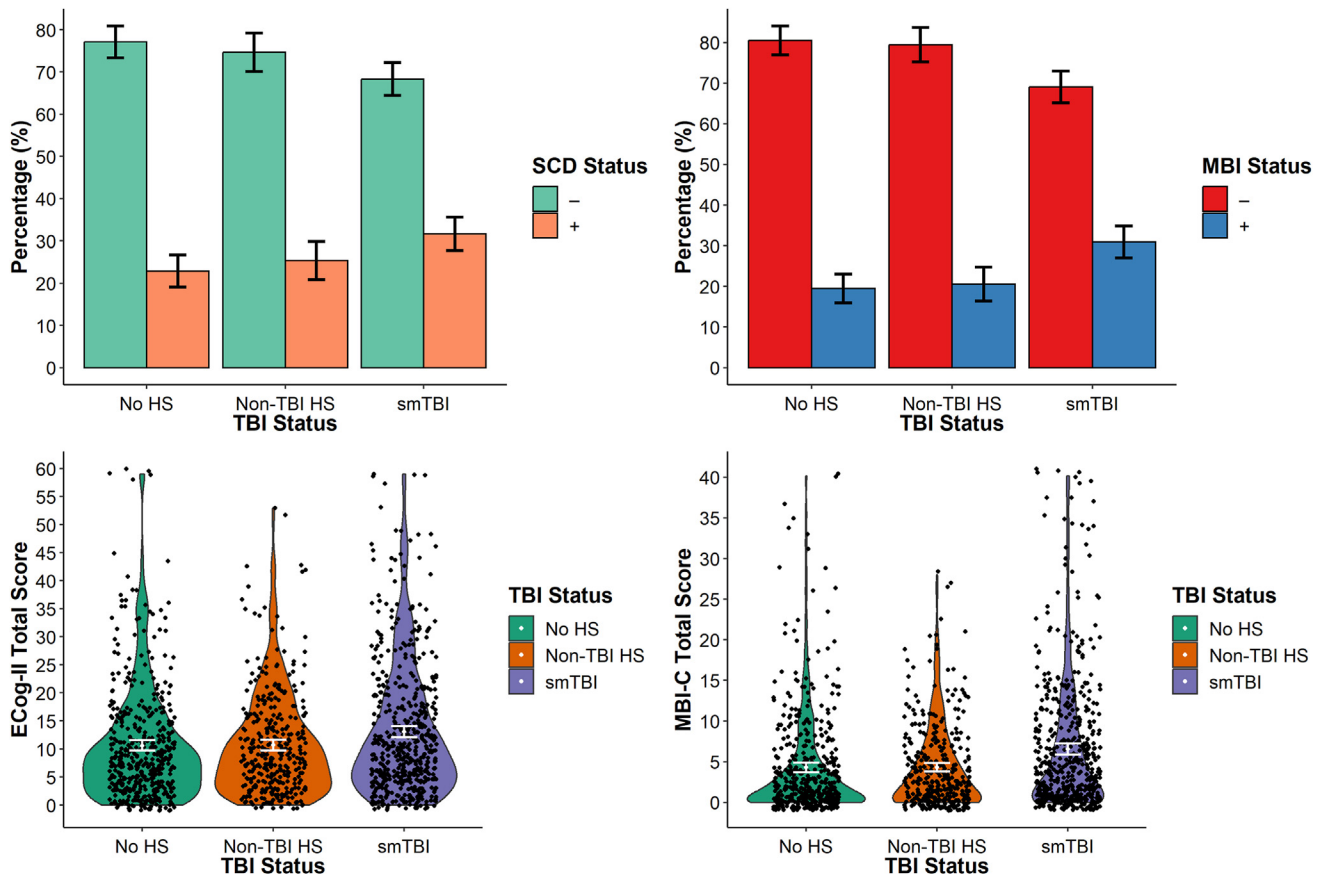
## DISCUSSION

Our study revealed measurable cognitive and behavioral changes, both indicative of elevated AD dementia risk, in community-dwelling older persons with a history of smTBI, even preceding objective cognitive impairment. Older persons with smTBI, when compared to non-TBI HS or no HS, report poorer memory, language, visuospatial function, and executive function. Furthermore, we observed a link between smTBI and greater symptoms of MBI in older age, which include decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and psychosis. These MBI findings suggest that TBI may have considerable consequences on psychiatric status later in life. Finally, smTBI may contribute to poorer daily function in older age through these changes in cognition and behavior.

A robust body of evidence supports the link between TBI and cognitive decline. A recent systematic review and meta-analysis of 32 studies representing over seven million individuals found that TBI was associated with a two-thirds greater risk of all-cause dementia, most commonly AD.<sup>6</sup> Further consistent with our findings are observations that TBI is associated with cognitive symptoms preceding AD dementia. Dementia-free older persons with mTBI performed worse on objective cognitive tests for attention, executive function, processing speed, and working memory, and reported poorer subjective memory, relative to participants with no head injuries.<sup>30,39</sup> We provide evidence that these subjective cognitive symptoms linked to TBI extend beyond memory to include language, visuospatial function, and executive function.

Later-life emergent and persistent changes in behavior (i.e., MBI) may also signal incipient cognitive decline and AD dementia.<sup>16</sup> Yet, relative to cognition, studies of TBI associations with MBI have only recently emerged. In the National Alzheimer's Coordinating Center Uniform Data Set, TBI of varying severities were associated with higher odds of MBI social inappropriateness and higher hazards for decreased motivation and psychosis among cognitively unimpaired older persons at baseline.<sup>40</sup> Likewise, in the Atherosclerosis Risk in Communities study, a history of

**FIGURE 3. Bar and Violin Plots for smTBI Associations with Cognition and Behavior.** Raw unadjusted data are presented. Error bars indicate 95% confidence intervals obtained through bootstrapping, independent of statistical modelling. 99% winsorization and jittering was applied to ECog-II and MBI-C total scores for visualization purposes. HS = head strike; MBI = mild behavioral impairment = SCD = subjective cognitive decline; smTBI = suspected mild traumatic brain injury; TBI = traumatic brain injury



≥2 HS was associated with higher odds of affective dysregulation and impulse dyscontrol.<sup>41</sup> Our findings expand upon these 2 studies through (1) the use of the MBI-C, a tool purposefully designed to measure MBI in dementia-free populations,<sup>31</sup> which allows for a more robust assessment of MBI by incorporating both symptom emergence and symptom persistence criteria and (2) sampling of community-dwelling functionally independent older persons in Canada. We demonstrate that smTBI is linked not only to higher odds of MBI, but also greater MBI symptom severity globally and in all 5 MBI domains. Older persons with a history of TBI may benefit from assessments of cognition and behavior, even in settings outside of specialized memory clinics.

Functional capacity to perform everyday tasks was poorer in older persons with a history of smTBI. These

differences were small in magnitude, likely due to the sample consisting of cognitively unimpaired, community-dwelling older persons. Yet, our data suggest that later-life changes in cognition and behavior linked to TBI may still contribute, at least partially, to functional decline. Furthermore, MBI has been associated with poorer gait,<sup>20</sup> hearing impairment,<sup>22</sup> frailty symptoms,<sup>21</sup> sleep disturbance,<sup>23</sup> loneliness,<sup>24</sup> and lower quality of life,<sup>25</sup> and has recently been recommended as a target for clinical trials.<sup>26</sup> Interventions targeting changes in cognition and behavior, informed by screening, may aid in mitigating later-life functional impairment associated with TBI, thereby reducing the long-term cumulative health burden of TBI.

Several potential mechanisms may underlie the link between TBI and later-life changes in cognition and behavior. Both SCD and MBI are recognized as

potential clinical manifestations of preclinical (i.e., cognitively unimpaired) and prodromal (i.e., MCI) AD.<sup>13,17</sup> Biomarker evidence of preclinical AD has been observed in a considerable proportion of persons with SCD,<sup>42</sup> and both imaging and neuropathological studies show quantitative associations between the severity of SCD symptoms and the extent of amyloid or tau pathology.<sup>43,44</sup> Similarly, greater levels of AD neuropathological burden, assessed through biofluid, imaging, and neuropathological measures, have consistently been observed in older persons with MBI.<sup>17,45–50</sup> Although not yet fully understood, TBI may contribute to AD via upregulation of amyloid precursor protein and hyperphosphorylation of tau at the acute stage, which may gradually evolve into amyloid- $\beta$  plaques and neurofibrillary tangles, respectively.<sup>10</sup> As such, TBI earlier in life may place older persons at greater risk for SCD and MBI by predisposing them to greater AD neuropathological burden. Future studies are needed to better understand the mechanisms through which TBI may contribute to SCD and MBI. It should also be noted that, while the focus of this study was on AD-related dementia, TBI may be associated with non-AD dementias, which may be investigated further in future research.

Multiple factors contribute to heterogeneity in the research surrounding TBI and risk for AD dementia.<sup>10</sup> Relevant to the present study are factors pertaining to the use of variable TBI diagnostic criteria and self-report versus clinician-determined diagnosis. To address these limitations, we applied the most recent 2023 American Congress of Rehabilitation Medicine diagnostic criteria for mTBI, and following their recommendations, explicitly used the term smTBI to acknowledge that self-reported symptoms were the only evidence suggestive of brain injury.<sup>4</sup> Moreover, because the Brain Injury Screening Questionnaire – Short form was an optional questionnaire in the Canadian Platform for Research Online to Investigate Health, Quality of Life, Cognition, Behaviour, Function, and Caregiving in Aging study, participants with specific characteristics could have been more likely to complete the questionnaire and therefore be included in the analysis (i.e., self-selection bias). We attempted to mitigate this bias by using inverse probability of treatment weighting to assign greater weights to complete-case participants if they more closely resembled incomplete-case participants. Yet, this approach only accounts for measured demographic variables, so

caution in generalizing results to a wider population remains warranted. Finally, we relied on self-report to exclude persons with MCI or dementia, which has the potential to have been misreported.

## CONCLUSIONS

Sustaining smTBI throughout the life course is linked to poorer subjective cognition and behavior, even in community-dwelling older persons without MCI or dementia. Not only are these changes in cognition and behavior linked to elevated dementia risk, but our findings suggest that they may contribute to poorer daily function. Hence, older persons with smTBI may benefit from early dementia risk assessment using tools that measure changes in cognition and behavior. Interventions targeting declining cognition and behavior may also be beneficial in this population to address functional impairment.

*Conflicts of Interest:* EES reported consulting (unpaid) for Alnylam Pharmaceuticals and Eli Lilly, and an advisory board (unpaid) for Eisai. ZI has served as an advisor/consultant to CADTH, EISAI, Lilly, Lundbeck/Otsuka, Novo Nordisk, and Roche. The remaining authors report no relevant conflicts of interest.

*Ethical Approval:* All participants provided electronic informed consent as part of the CAN-PROTECT online registration process. The research reported in this paper adhered to the ethical guidelines set forth by the Conjoint Health Research Ethics Board at the University of Calgary (REB21-1065).

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