Factors associated with remission of post-Traumatic Brain Injury fatigue in the years following traumatic brain injury (TBI): A TBI Model Systems Module Study.

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Abstract

BACKGROUND: Post-traumatic brain injury fatigue (PTBIF) is a major problem in the years after traumatic brain injury (TBI), yet little is known about its persistence and resolution. **OBJECTIVE:** To identify factors related to PTBIF remission and resolution. **METHODS:** TBI Model System registrants at 5 centers who participated in interviews at either 1 and 2 years post-injury (Y1-2 Cohort), or 2 and 5 years post injury (Y2-5 Cohort). Characteristics of participants with PTBIF remission were compared to those with PTBIF persistence. Variables studied included the presence of and changes in disability, sleep dysfunction, mood, and community participation. **RESULTS:** Functional independence Measure did not differ significantly between groups or over time. In the Y1-2 Cohort the Fatigue Resolved group scored significantly better on the Disability Rating Scale and Pittsburgh Sleep Quality Index. In the Y2-5 Cohort the Fatigue Resolved group scored significantly higher on a measure of community participation. **CONCLUSIONS:** Less than half of the sample in each cohort experienced a remission of PTBIF between time points. Persistence of PTBIF from one to two years post-injury is associated with disability, sleep disturbance, and depression while persistence of fatigue beyond two years post-injury appears to be related to participation level, underscoring the potential impact of effective surveillance, assessment, and treatment of this condition in optimizing life after TBI. Differences in fatigue progression may point to the presence of different types of PTBIF.

1. Introduction

Fatigue is one of the most common symptoms reported after a traumatic brain injury (TBI), affecting between 21% and 73% of individuals with TBI [1, 2]. Symptoms of post-TBI fatigue (PTBIF) can present soon after injury and become chronic. Van der Naalt and colleagues (1999) noted that at 1 month post injury, 57% of the sample reported fatigue, dropping to 45% at 6 months and one year [1]. Another study reported that 73% of individuals continue to experience fatigue as a chronic problem 5 years post-injury [3].

Cantor and colleagues (2013, p. 876) noted that PTBIF is "often associated with a felt sense of disproportionate exertion and associated mental or physical exhaustion and inability to perform". PTBIF is a central fatigue condition, resulting from a neurologic insult to the brain and different from peripheral fatigue, which describes muscle and physical limitations [4]. Other neurologic conditions such as stroke, multiple sclerosis, Parkinson's disease, and fibromyalgia have central fatigue as a common symptom.

Fatigue is often rated as the worst symptom experienced after a TBI [5, 6]. Individuals with PTBIF tend to report higher levels of disability and lower satisfaction with life than individuals with TBI without fatigue complaints [7, 8]. In fact, studies have shown that the presence of PTBIF may prevent return to work [9]. PTBIF has not been found to be associated with age or injury severity [3, 10].

Although fatigue after TBI has been associated with other conditions or symptoms, such as depression, anxiety, pain, and sleep disturbance [11], studies suggest that PTBIF can present as a distinct condition [7, 12]. While multiple studies have evaluated PTBIF characteristics and correlates, longitudinal studies specifically looking at the resolution of PTBIF are scarce. The current study compared patients with resolution of PTBIF to those who continued to have

symptoms over time in order to add to the literature using longitudinal data to better understand factors that may be associated with PTBIF remission. Although mere associations may not indicate causality, they are important to identify in order to direct future research to determine which factors are causal or have mediating or moderating properties. In this way, a more solid foundation is formed upon which treatment interventions can be developed and tested for efficacy.

2. Methods

2.1. Participants

Participants were recruited from individuals already enrolled in the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) TBI Model Systems program (TBIMS) National Database (NDB). The TBIMS NDB is a prospective longitudinal multicenter study that collects data about the demographics, injury characteristics, and outcomes of individuals with TBI who have received inpatient rehabilitation at TBIMS sites. Criteria for inclusion in the TBIMS NDB study include:

(1) Presence of TBI of at least moderate severity (as defined by posttraumatic amnesia at least 24 hours, trauma-related intracranial neuroimaging abnormalities, or loss of consciousness with a duration of more than 30 minutes);

(2) Glasgow Coma Scale score of less than 13 upon admission to the emergency department;

(3) Age 16 or older at the time of injury;

(4) Admission to a TBIMS trauma hospital no later than 72 hours after injury;

(5) Participation in comprehensive rehabilitation at a TBIMS brain injury inpatient

rehabilitation program (inpatient rehabilitation facility or rehabilitation hospital unit, skilled nursing facility, or long-term acute care hospital);

(6) Informed consent provided by the patient, or family/legal guardian if patient did not have capacity.

Participants who were able to take part in the TBIMS follow-up interviews typically conducted at 1, 2, and 5 years post-injury were recruited for the current study from five collaborating TBIMS centers: Mount Sinai Medical Center in New York, NY; Santa Clara Valley Medical Center in San Jose, CA; Kessler Foundation in West Orange, NJ; Carolinas Rehabilitation in Charlotte, NC; and JFK Johnson Rehabilitation Institute in Edison, NJ. Data collection took place between 2007 and 2012. In addition to the above inclusion criteria, only individuals with TBI who were able to complete the follow-up interviews independently were enrolled into the current study. For feasibility reasons, certain centers collected data at years 1 and 2 post injury and others at years 2 and 5 (See Cantor et al., 2012)[7]. There were a total of 237 participants with complete data at two time points. For the purposes of the current investigation examining factors associated with the remission of PTBIF, only individuals with complete data at two time points who had PTBIF at T1 were included (N=79).

2.2. Measures

2.2.1. Outcome Measures

The ***Functional Independence Measure™ (FIM)*** is an index of motor and cognitive ability [13] and consists of 18 items with a Likert-type rating scale ranging from need for total assistance (1) to complete independence (7). Items can be divided into motor and cognitive domains. The FIM has been shown to have good internal consistency (Cronbach's α between .86

and .97) with TBI populations and to be sensitive to changes in functional ability from admission to discharge and follow-up [14-17].

The ***Disability Rating Scale (DRS)*** is used to examine functional recovery of individuals with TBI during and after rehabilitation [18, 19]. The DRS consists of eight items addressing three categories identified by the World Health Organization (WHO) as components of disablement: impairment, disability, and handicap. It has been shown to be a valid measure of disablement with good inter-rater reliability and test-retest reliability [20, 21]. Scores range from 0 (no disablement) to 29 (maximum disablement).

The ***Patient Health Questionnaire (PHQ-9)*** [22] is a screening tool for depression consisting of 9 items derived from the PRIME-MD, a broader, multi-disorder health questionnaire [23]. The PHQ-9 has good test-retest reliability (r = .84) and excellent internal consistency (α = .86-.89) [22]. The PHQ-9 has good criterion and construct validity, and good test-retest reliability in individuals with TBI [24].

The ***Satisfaction with Life Scale (SWLS)*** is a five-item self-report measure of global life satisfaction [25, 26]. The SWLS has shown to be valid and reliable and has been used in a wide range of age groups and applications [26]. It has convergent validity with other scales and assessments of subjective well-being as well as discriminant validity from measures of emotional well-being [25, 27]. The SWLS also has high internal consistency and high temporal stability [25]. Additionally, the SWLS has been shown to be sensitive to changes in life satisfaction following clinical interventions [27].

The ***Participation Assessment with Recombined Tools (PART-O***; [28] is a 24-item self-report measure of community integration following a TBI that was developed using items from other existing instruments measuring participation. Subjects are asked to reflect on a specific

timeframe and respond to questions on their typical level of societal participation and the close relationships they have (social supports, household activities and their social and community integration). The scale has been in use as part of the TBIMS follow up interview since 2007. PART–O subscales (Productivity, Social Relations, and Out and About in the Community) allow for the characterization of how one participates [28]. The measure has been shown to have good construct and concurrent validity and item reliability, allowing one to reliably measure meaningful differences among people with varying levels of participation [29].

The ***Pittsburgh Sleep Quality Index (PSQI)*** is a validated measure that uses 9 items to examine sleep quality and disturbances of sleep and to assesses insomnia symptoms, including difficulty initiating sleep or maintaining sleep, as well as their frequency and duration, and factors that may affect sleep (e.g., pain, medications) [30]. Scores exceeding 5 are indicative of a sleep disorder [31]. The PSQI has been shown to be sensitive to sleep disturbances after TBI [32].

2.2.2. Measurement of Fatigue

Multidimensional Assessment of Fatigue (MAF) [33] is a self-report measure operationalizing four domains of fatigue: severity, distress, impact on activity, and timing. The first 15 questions on this measure are used to calculate a Global Fatigue Index (GFI), with scores that range from 0 to 50. The higher the score, the greater the individual's fatigue, with individuals reporting no fatigue were assigned a score of 0. Englander and colleagues [34] used scores of 27 and above as an abnormal amount of fatigue after brain injury, although *average* fatigue scores for TBI samples have been reported as high as 24.4, SD=11.7, and 28.4, SD=11.3 [8, 35]. The current study used GFI scores over 21 to indicate PTBIF based on Cantor et al.

(2008), and used a 5-point difference to indicate a minimal clinically important difference based on data derived from previous studies [36, 37].

2.3. Data Analysis

2.3.1. Descriptive Statistics

Data were collected on two separate cohorts. The Y1-2 Cohort was surveyed at one and two years post-injury (N=47) and the Y2-5 Cohort was surveyed at two and five years post-injury (N=32). A chi-square analysis showed no significant differences between cohorts on demographics and injury characteristics shown in Table 1. One-way Analysis of Variance (ANOVA) showed no significant differences between the cohorts on age, education, and hospitalization variables shown in Table 2.

PLACE TABLE 1 ABOUT HERE

PLACE TABLE 2 ABOUT HERE

2.3.2. Determination of Post TBI Fatigue and its remission.

Two Fatigue Change groups were created. Individuals who had PTBIF at both time points were designated as the Fatigue Unresolved group (FU), and those who had PTBIF at T1 but not at T2 and had achieved the minimal clinically important difference on the GFI as described earlier were designated as the Fatigue Resolved group (FR). FR for 30% of the Y1-2 Cohort and for 44% of the Y2-5 Cohort. There were no significant differences between cohorts in terms of percentage of individuals who experienced resolution of PTBIF ($\chi^2 = 1.6$, $df = 1$, $p =$

0.203). The analyses examining outcome variables were run separately for each of the two cohorts.

2.3.3. Analysis to examine outcome variables associated with remission of PTBIF

Group differences were examined over time using a mixed 2 (Fatigue Change group) x 2 (follow-up time point) Analysis of Variance (ANOVA). Where a significant main effect was observed, planned comparisons were conducted to further examine the effect. Bonferroni correction for multiple comparisons was used where appropriate.

3. Results

3.1. Descriptives of GFI in the FR and FU groups.

Y1-2 Cohort: The FU group had GFI scores ranging from 21 to 44 at T1 and 22 to 48 at T2. The FR group had GFI scores ranging from 21 to 46 at T1 and 0 to 21 at T2. At T1 the mean GFI values for the FU ($M = 31.9$, $SD = 7.2$) and FR groups ($M = 30.7$, $SD = 7.7$) showed no significant difference, $F(1,45) = 0.3$, $p = 0.601$.

Y2-5 Cohort: The FU group had GFI scores ranging from 21 to 46 at T1 and 23 to 50 at T2. The FR group had GFI scores ranging from 22 to 39 at T1 and 0 to 22 at T2. At T1 the mean GFI values for the FU ($M = 31.3$, $SD = 8.1$) and FR groups ($M = 33.4$, $SD = 8.7$) showed no significant difference, $F(1,30) = 2.5$, $p = 0.124$.

3.2. Functional Independence and Level of Disability

Neither of the two cohorts showed any significant differences on FIM scores between FR and FU groups. However, the Y1-2 Cohort showed a significant main group effect on the DRS, with significantly higher scores (indicating increased disability) for the FU group $F(1,45) = 4.3$, $p = 0.043$. Group comparisons with Bonferroni correction at each time point showed no significant difference in DRS scores between groups at T1, $F(1,45) = 1.8$, $p = 0.181$. At T2,

however, a significant difference was observed after a noticeable divergence from one to two years post injury, $F(1,45) = 6.2$, $p = 0.016$. No significant differences in DRS were found for the Y2-5 Cohort. See Figure 1.

PLACE FIGURE 1 ABOUT HERE

3.3. Sleep Quality

For the Y1-2 Cohort, there was a significant main effect for Time, $F(1,45) = 6.7$, $p = 0.013$, and a significant Time x Group interaction, $F(1,45) = 7.2$, $p = 0.010$. The FR group showed improved sleep quality compared with the FU group, $F(1,45) = 8.9$, $p = 0.005$. Group comparisons with Bonferroni correction at each time point showed no significant difference in sleep quality between groups at T1, $F(1,45) = 1.9$, $p = 0.179$, followed by a significant difference at T2, $F(1,45) = 19.6$, $p < 0.001$, after a noticeable decrease in PSQI (i.e., improved sleep quality). See Figure 2.

For the Y2-5 Cohort, there were no significant differences between fatigue resolution groups. However, a main effect was found for change over time with both groups showing significant improvement in sleep quality from 2 to 5 years post-injury, $F(1,26) = 8.0$, $p = 0.009$.

PLACE FIGURE 2 ABOUT HERE

3.4. Depression and Satisfaction with Life

In the Y1-2 Cohort, there was a significant between-subjects effect with the FU group showing significantly greater levels of depression on the PHQ-9, $F(1,46) = 7.1$, $p = 0.011$. There was no significant effect between groups at T1 but there was at T2, $F(1,45) = 7.6$, $p = 0.008$. See Figure 3.

PLACE FIGURE 3 ABOUT HERE

With regard to the SWLS, there were no significant differences between groups and no significant changes in either group over time. For the Y2-5 Cohort, there were no significant differences in PHQ-9 or SWLS between FR and FU groups.

3.5. Community Participation

There were no significant effects found between fatigue resolution groups in the Y1-2 Cohort. In the Y2-5 Cohort, there was a significant between subjects effect showing that the FR group tended to have higher PART-O scores than the FU group, $F(1,26) = 5.0$, $p = 0.035$.

PLACE FIGURE 4 ABOUT HERE

4. Discussion

The current study examined changes among individuals with TBI in various outcomes, including disability, sleep dysfunction, mood, and community participation, as a function of post-TBI fatigue. Less than half of the sample indicated a remission of PTBIF between time points.

The lack of significant findings with regard to functional independence (FIM) may be due to a ceiling effect in the FIM with both groups being close to the maximum FIM rating at T1 and having very little room to improve. Disablement ratings (DRS), on the other hand, increased slightly over time in the FU group while in the FR group the mean remained stable, resulting in significant group differences at T2.

Previous cross sectional research failed to find any significant relationship between PTBIF and participation [8]. In the current analysis, the Y2-5 Cohort showed significantly higher participation in the FR group. Yet, neither group showed any change in participation over time. In other words, in the FR group, participation was just as high at the initial time point as it was at follow up at 5 years post-injury. While this lack of change over time may be consistent with the previous findings by Cantor et al. [8], the difference between groups suggest that there may be another unmeasured variable to explain why this group difference was found.

In the Y1-2 Cohort, Sleep quality (PSQI) tended to remain quite stable for the FU group while those experiencing a remission of fatigue showed a notable decline in sleep difficulties by the second year post-injury. It should be noted that the FR group falls below 5, which on the PSQI would be classified as not having significant sleep disturbance. The Y2-5 Cohort began with PSQI values comparable to the FU group of the Y1-2 Cohort and showed no significant group differences. All those with PTBIF at 2 years post-injury in this group represented a more chronic phase after TBI where PSQI scores remained above the cutoff through the 5 year mark regardless of whether or not there was a resolution of fatigue.

For both cohorts, depression was comparable at T1 with notable divergence at T2. This difference was only significant for the Y1-2 Cohort but the general trend of reduced depression was seen in the FR Groups. This is not surprising given the relationship between fatigue and depression and the item content on the PHQ-9 inquiring about tiredness and lack of energy.

Like previous cross sectional research, these results show a relationship between the lingering of fatigue with increased disability, ongoing of sleep disturbance, and depression [7]. However, these findings look at these relationships from a longitudinal perspective to show that differences in fatigue from 1 to 2 years post injury appear to be associated with more change

over time than is seen in the other cohort at 2 to 5 years post-injury. This mirrors what is often observed in TBI recovery where accelerated recovery may be noted in the acute phase of rehabilitation with additional change being more asymptotic or at a slower rate [40, 41]. In addition, the relationship between fatigue and life satisfaction or functional independence found in cross-sectional studies were not found when looking at fatigue resolution over time. This may be due to the dichotomization into FR and FU groups as opposed to viewing MAF scores as a continuum in a correlational analysis. It may also be due to a restricted range in the current sample which only included individuals with PTBIF at their initial follow-up interview. Satisfaction with life remained stable over time in each group suggesting there may be factors other than the resolution of fatigue that may be influencing life satisfaction over time.

At least two therapeutic alternatives can be proposed when an individual presents with PTBIF in order to resolve the fatigue as quickly as possible. The first would be to assess and address sleep dysfunction issues; in the group of individuals whose PTBIF resolved more acutely, the sleep quality also improved. Improving sleep quality may decrease PTBIF in a select group of individuals. For those persons whose PTBIF does not resolve after treating sleep dysfunction, assessment and treatment of concomitant depression may prove an effective management technique.

Limitations

Limitations of the current study should be noted to understand the findings in proper context. A ceiling effect on the FIM could be seen as a limitation inherent in the measure such that it lacks sensitivity in differentiating among individuals who are functioning at a higher level. In this respect, perhaps the FIM is more suitable for its most common use – the evaluation of functional status throughout the course of inpatient rehabilitation, as opposed to measurements

taken at one or more years after discharge. Another limitation was identified in the GFI generated using the MAF. Among those who showed remission of PTBIF at T2 based on the cut-off score on the GFI, approximately half obtained scores of 0. It is important to point out that the first question on the MAF asks, "[Over the past week] To what degree have you experienced fatigue?" Possible responses range from 1 (not at all) to 10 (a great deal). For participants who responded "not at all," the measure was discontinued and they received a GFI score of 0. This created a kurtotic distribution where the mode was 0 and the next highest value was 7.5 However, by discontinuing the questionnaire at this point for those providing the lowest possible rating, a dichotomy is created whereby these individuals have less opportunity for variation because all receive a GFI of 0. Those scoring 2-10 on this initial item at T2 showed greater variability with GFI scores ranging from 7.5 to 20.9.

It is also important to note that this study was limited to a select group of individuals who survived TBI and required inpatient rehabilitation. Thus, the findings may not represent all individuals with PTBIF. In addition, the Y1-2 Cohort and Y2-5 Cohort studied here were relatively small (N=47 and N=32, respectively). They represent a smaller portion of participants in the original larger study where the sample size was closer to 100 in each cohort. This was due to purposeful extraction of only those individuals with PTBIF at T1 in order to examine factors associated with remission of PTBIF. Further study on larger samples are needed to provide a better understanding of causal, mediating, and/or moderating factors with greater generalizability in order to develop effective interventions for PTBIF.

In addition, self-report measures and retrospective assessment were used to characterize insomnia, fatigue and function which may be impacted by recall and self-awareness which may be particularly limited among individuals with TBI.

5. Conclusion

Less than half of the sample experienced a remission of PTBIF between time points. Persistence of fatigue appears to be related to level of disability and depression, underscoring the potential impact of effective surveillance, assessment, and treatment of this condition in optimizing quality of life after TBI. Differences in fatigue progression may point to the presence of different types of PTBIF.

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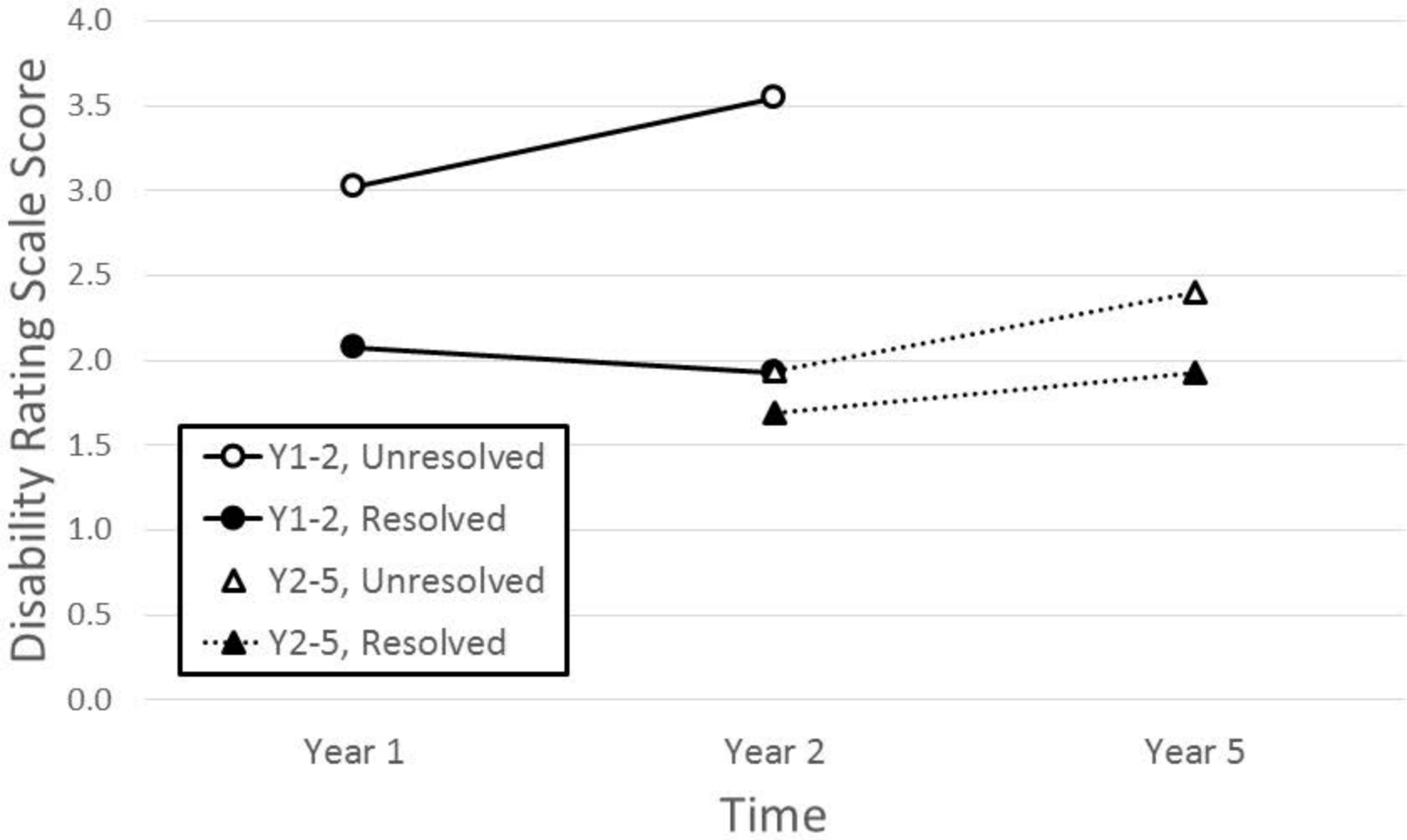
Table 1: Sample Demographics and Injury Characteristics by Cohort

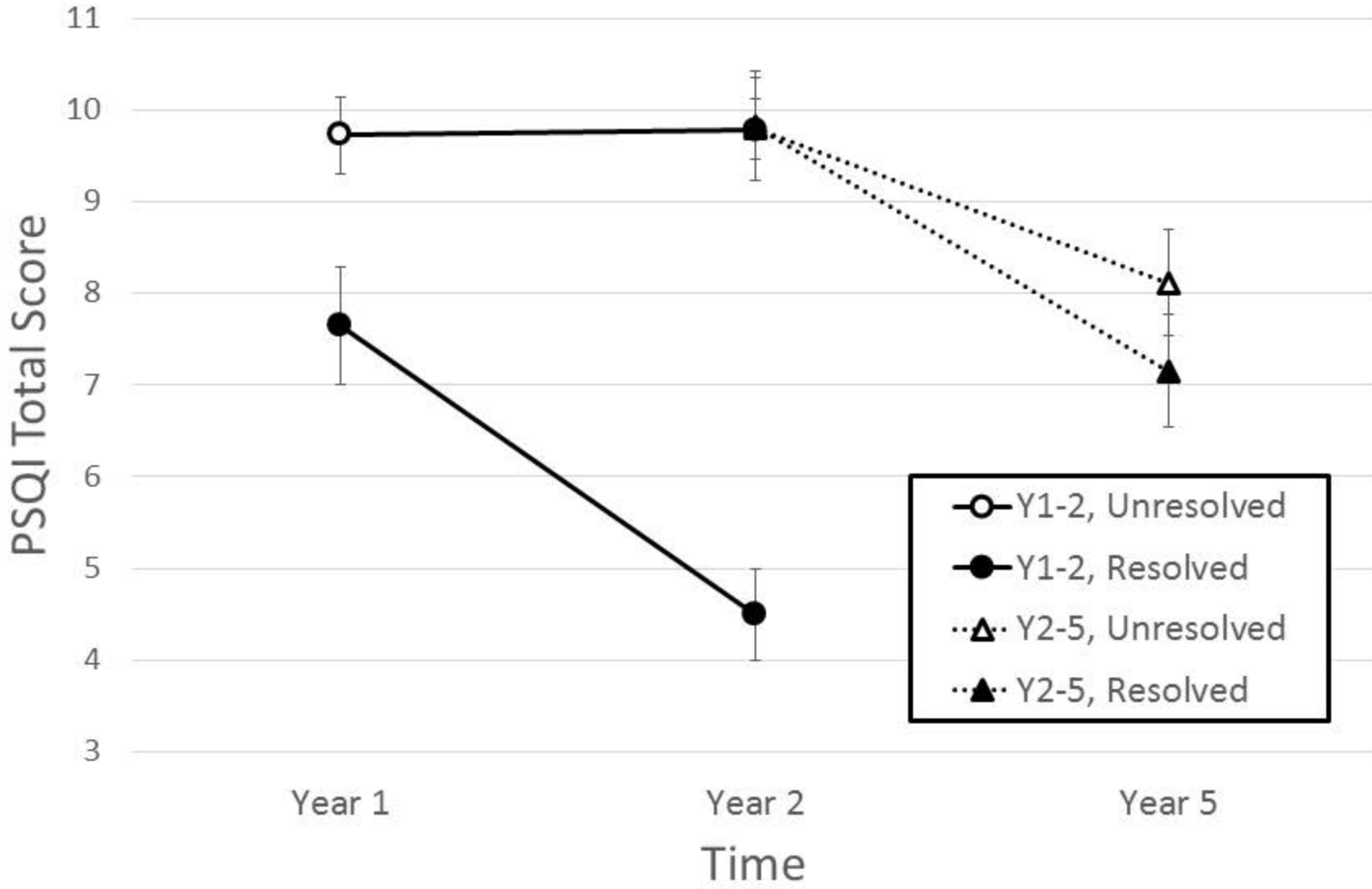
	Cohort Y1-2 (N=47)		Cohort Y2-5 (N=32)	
	count	%	count	%
Gender				
Female	15	32%	8	25%
Male	32	68%	24	75%
Race/ethnicity				
Non-Hispanic White	28	60%	25	78%
Non-Hispanic Black	4	9%	1	3%
Hispanic	11	23%	5	16%
Other	4	9%	1	3%
Marital Status				
Single	20	43%	13	41%
Married	17	36%	12	37%
Divorced, Separated, Widowed	10	21%	7	22%
Injury Severity				
Moderate	31	66%	21	66%
Severe	16	34%	11	34%
Cause of Injury				
Vehicular	27	57%	22	69%
Fall	15	32%	4	13%
Assault	3	6%	3	9%
Sports or Other	2	4%	3	9%

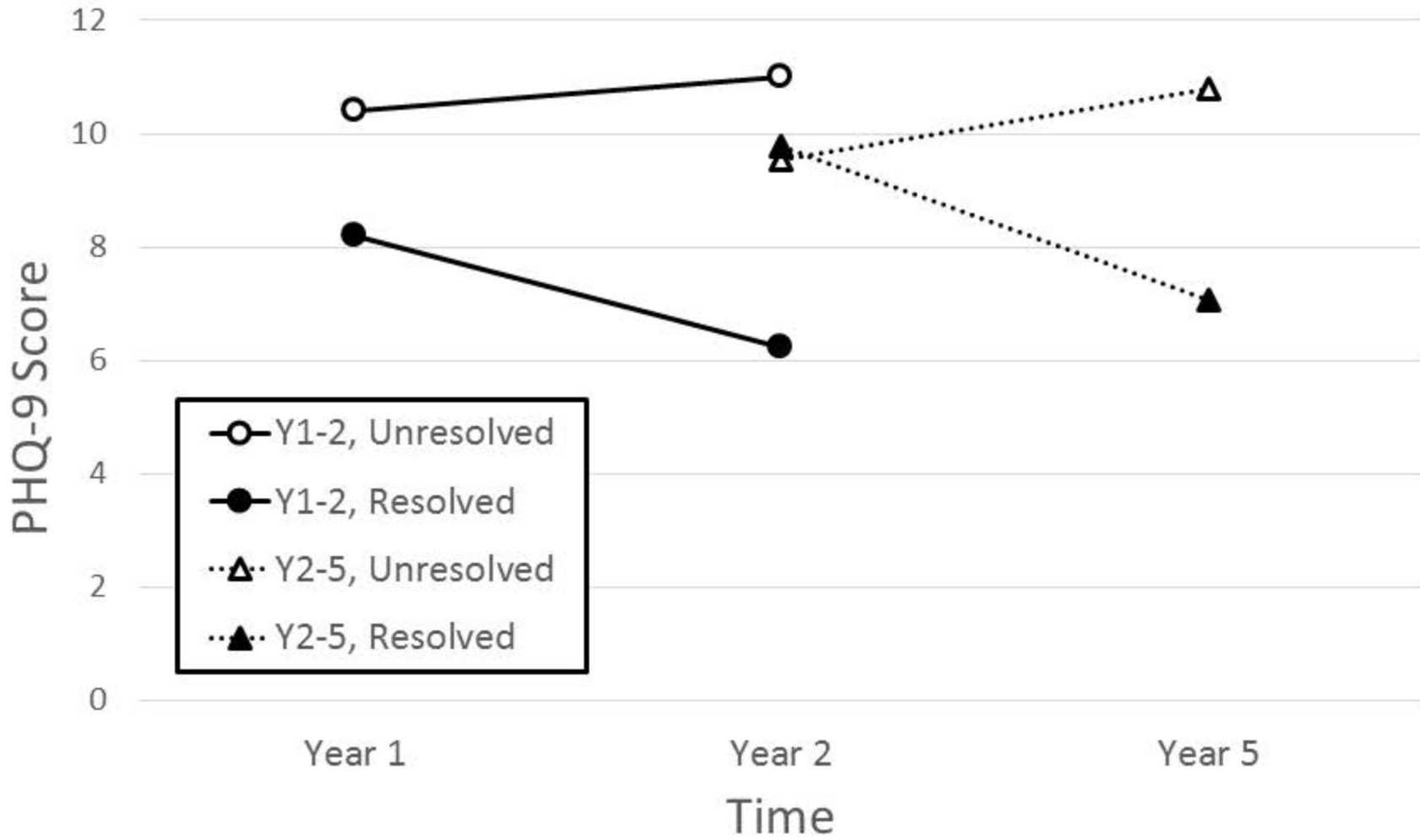
Table 2: Descriptive Statistics for Age, Education, and Hospitalization Variables by Cohort

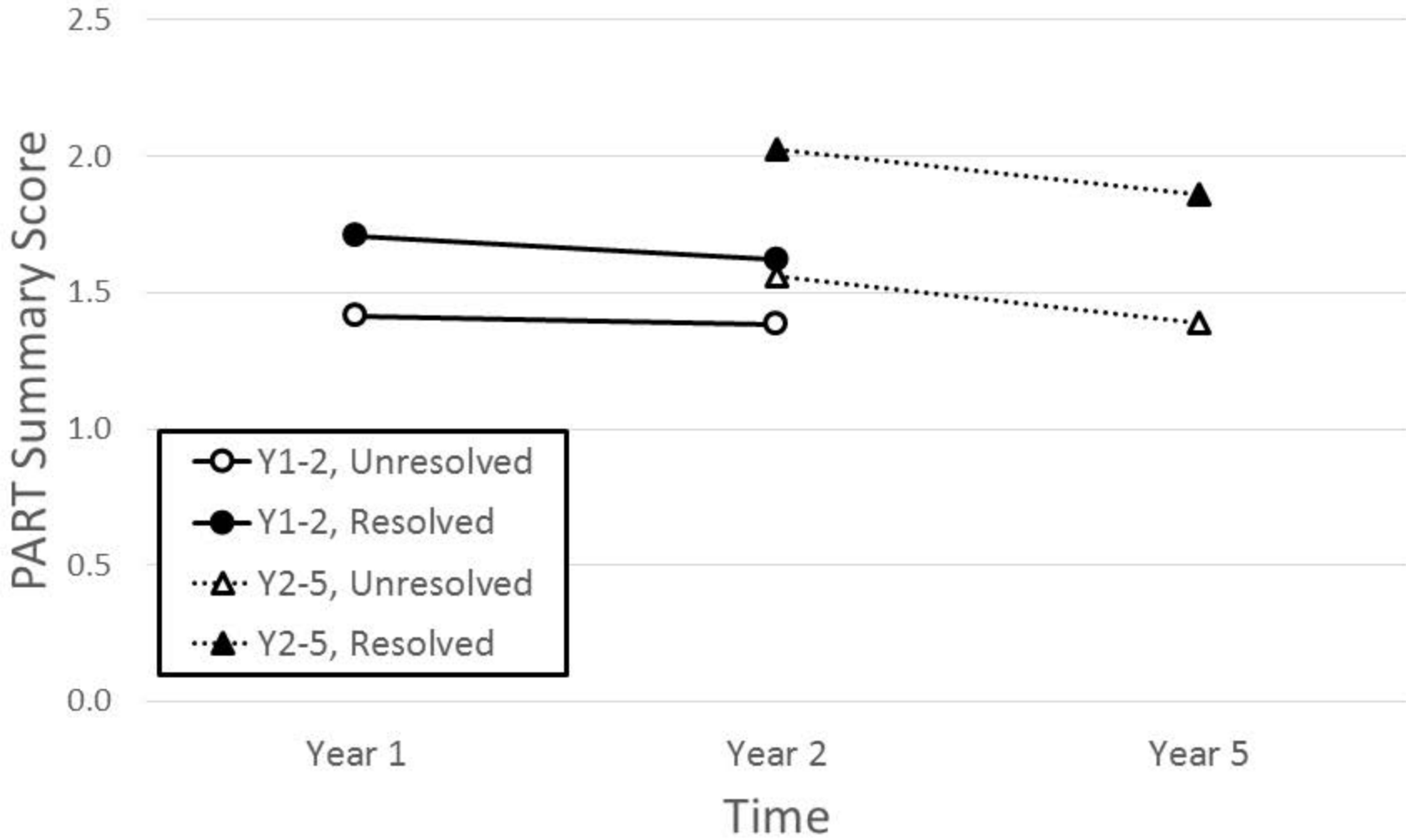
	Cohort Y1-2 (N=47)		Cohort Y2-5 (N=32)	
	M	SD	M	SD
Age at Injury	41.1	19.6	35.6	16.1
Years of Education	13.0	2.9	12.3	2.2
Days in Posttraumatic Amnesia	21.7	18.8	23.9	18.8
Length of Stay in Acute Care	19.4	14.6	22.3	16.5
Length of Stay in Rehabilitation	20.6	11	22.2	14.1
FIM at Rehabilitation Admission	50.1	23.9	47.8	22.2
FIM at Rehabilitation Discharge	94.5	15.8	99.3	14.6
DRS at Rehabilitation Admission	11.1	5	12.4	4.6
DRS at Rehabilitation Discharge	4.6	2	5.6	2.6

FIM: Functional Independence Measure; DRS: Disability Rating Scale


4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Disability Rating Scale Score
Y1-2, Unresolved
Y1-2, Resolved
Y2-5, Unresolved
Y2-5, Resolved
Year 1
Year 2
Year 5
Time


11
10
9
8
7
6
5
4
3
PSQI Total Score
Year 1
Year 2
Year 5
Time
Y1-2, Unresolved
Y1-2, Resolved
Y2-5, Unresolved
Y2-5, Resolved


12
10
8
6
4
2
0
PHQ-9 Score
Y1-2, Unresolved
Y1-2, Resolved
Y2-5, Unresolved
Y2-5, Resolved
Year 1
Year 2
Year 5
Time


2.5
2.0
1.5
1.0
0.5
0.0
PART Summary Score
Y1-2, Unresolved
Y1-2, Resolved
Y2-5, Unresolved
Y2-5, Resolved
Year 1
Year 2
Year 5
Time