# Physical, Cognitive, and Psychosocial Characteristics Associated with Mortality in Chronic TBI Survivors: A National Institute on Disability, Independent Living, and Rehabilitation

# **Research Traumatic Brain Injury Model Systems Study**

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### ABSTRACT

**OBJECTIVE:** To compare a group of individuals who died more than one year post-traumatic brain injury (TBI) with a matched group of survivors and to identify physical function, cognitive function, and/or psychosocial function variables associated with mortality.

**DESIGN:** Secondary analysis of data from a multicenter longitudinal cohort study.

**SETTING:** Acute inpatient rehabilitation facilities and community follow-up.

**PARTCIPANTS:** Individuals 16 years and older with a primary diagnosis of TBI.

MAIN OUTCOME MEASURES: Functional Independence Measure (FIM<sup>TM</sup>), Disability Rating Scale, Participation Assessment with Recombined Tools Objective, Extended Glasgow Outcome Scale, Satisfaction With Life Scale.

**RESULTS:** Individuals who died were distinguishable from their surviving counterparts. They demonstrated significantly poorer global functioning on all physical, cognitive, and psychosocial functioning variables at their most recent study follow-up visit prior to death. FIM Motor demonstrated the largest difference between survival groups, suggesting that independence in mobility may be particularly indicative of likelihood of longer-term survival.

**CONCLUSIONS:** These findings may inform continued research to elucidate functional characteristics of individuals post-chronic TBI prior to their death and to identify opportunities for prevention of accelerated death and interventions to improve health, longevity, and quality of life.

**KEY WORDS:** chronic health, death, longitudinal outcomes, traumatic brain injury

### **INTRODUCTION**

Traumatic brain injury (TBI) is an important and growing health concern due to its high prevalence and deleterious effects on overall health. The rate of TBI in older adults is increasing, and increased age at time of injury is associated with worse outcomes post-TBI.<sup>1,2,3,4</sup> Furthermore, regardless of age, TBI is increasingly recognized as a chronic disease process in some individuals, as many survivors have longstanding medical problems that may worsen over time.<sup>5,6</sup> It is therefore not entirely surprising that the mortality rate is significantly higher in people with TBI who survive at least one year post-injury.<sup>7-15</sup> Compared to the general population, those with TBI experience a reduction in life expectancy of 6-7 years.<sup>9,10,16</sup> Among those who survive at least one year post-injury, greater injury severity is associated with greater mortality risk.<sup>3,7,17</sup> A study performed in the United States based on the Traumatic Brain Injury Model Systems (TBIMS) National Database (NDB) found that individuals with moderate-severe TBI who survive at least one year post-injury are 37 times more likely to die of seizures, 12 times more likely to die of septicemia, and four times more likely to die from pneumonia as compared to individuals in the general population of similar age, gender, and race.<sup>17</sup> In a study investigating mortality risks based on age at time of TBI, Harrison-Felix and colleagues<sup>16</sup> determined that teenagers, young adults, and middle-aged adults, in particular, were at risk for early mortality. In the same study,<sup>16</sup> the authors reported a greater risk of death by external causes (including unintentional injuries, accidental poisoning, and homicide) among individuals who were injured before age 35 compared to age, gender, and race/ethnicity-matched peers in the general population. Conversely, individuals injured after age 35 had a greater risk of death from a variety of chronic medical conditions such as respiratory and digestive diseases, sepsis, and pneumonia.<sup>16</sup> While the oldest age group (85+) had similar mortality rates to the matched

population, they were more likely to die of respiratory diseases and aspiration pneumonia compared to their uninjured peers.<sup>16</sup> These results suggest that reduced life expectancy among adults who survive a moderate-severe TBI have different causes of death than the general population, and some of the medical conditions leading to death may be treatable or preventable. An important limitation of this body of work is that current knowledge about causes of death among survivors of TBI comes from death certificates, which are often inaccurate or incomplete;<sup>18-22</sup> thus, these results may not accurately estimate the true causes of death. Very little is known about the causal chain of events preceding premature death in TBI survivors. As a consequence, there may be missed opportunities for prevention or intervention that may prolong health and/or positively impact quality of life.

In an attempt to identify precursors of premature death, a recent study used the TBIMS NDB to compare global functional trajectories of individuals with moderate-severe TBI who died after surviving at least five years post- injury with those who survived for the entire follow-up period (up to 20 years post-injury) using individual growth curve analysis.<sup>23</sup> Although similarly impaired at time of rehabilitation admission, the group that died (n=159) presented with worse functional abilities one year post-injury and demonstrated a steeper, more constant decline over time on the Glasgow Outcome Scale--Extended than did the group of survivors (n=3711).<sup>23</sup> These findings suggest that it may be possible to identify those at risk for shortened longevity based on precipitous functional decline.

To investigate early indicators of mortality risk in elderly individuals post-moderatesevere TBI, a small-scale retrospective chart review was conducted at one TBIMS site on individuals aged 55 and older who received inpatient rehabilitation at some point during a 5-year period and compared those who died between 1-5 years post-injury (n=30) and those who survived (n=30; matched on age, sex, ethnicity, pre-injury level of education, and discharge FIM scores).<sup>24</sup> Those who died were significantly more likely to have a diagnosis of abnormality of gait (53% vs. 27%), were more likely to take respiratory medication (32% vs. 7%), diabetes medication (35% vs. 10%), and, overall, were prescribed more medications at rehabilitation discharge compared to survivors.<sup>24</sup>

Injury severity is also an important predictor of mortality, particularly in acute care and population-based TBI samples. Greater injury severity (moderate-severe TBI as compared to mild TBI) is associated with reduced short-term survival,<sup>25-27</sup> but the differences between mild TBI and moderate-severe TBI in terms of long-term survival rates are less pronounced.<sup>25,27</sup> Other commonly recognized risk factors for premature death following TBI include older age,<sup>10,12,13</sup> being unemployed at the time of injury,<sup>10,13</sup> being male, being single at the time of injury, having a premorbid history of stroke, and having injuries to the back or chest.<sup>13</sup> A history of premorbid substance abuse and mental health problems were also more common among those with mortality.<sup>11,13</sup>

The purpose of the current study was to compare data of TBIMS NDB participants who died at any time to a matched sample of NDB survivors and identify physical function, cognitive function, and/or psychosocial function variables associated with mortality. By controlling for previously identified characteristics associated with chronic TBI mortality and examining physical, cognitive, and psychosocial measures of function simultaneously across a large number of individuals, this study builds upon what is already known about elevated risk for health decline and mortality after chronic moderate-severe TBI.

### **METHODS**

# **Participants**

Participants were individuals with TBI who were enrolled in the TBIMS NDB, which is funded by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR). The TBIMS defines TBI as damage to brain tissue caused by an external mechanical force as evidenced by medically documented loss of consciousness (LOC) or posttraumatic amnesia (PTA) or by objective neurologic findings on examination of physical or mental status that is attributed to the brain injury. TBIMS NDB inclusion criteria include LOC greater than 30 minutes, PTA duration greater than 24 hours, Emergency Department Glasgow Coma Scale score of less than 13, or intracranial neuroimaging abnormalities. To be eligible for the TBIMS NDB, the individual with TBI must be at least 16 years of age at the time of injury, have received medical care in a TBIMS-affiliated trauma center within 72 hours of injury; have been transferred directly from acute care to an affiliated inpatient brain injury rehabilitation program; and informed consent must be provided by participant or legal proxy. After enrollment, pre-injury, injury, and post-injury data are collected. Participation in the NDB study started in 1988 and involves prospective follow-up interviews with study enrollees or proxies at 1, 2, and 5 years post-injury, and every 5-year interval thereafter. Each TBIMS NDB site has received local institutional review board (IRB) human studies approval for study participation and, consistent with that site's IRB specifications, is responsible for obtaining informed written consent for all study-eligible patients enrolled.

As of June 30, 2016, a total of 14257 participants at least one year post-injury were available in the TBIMS NDB. From this sample, there were 2019 participants (14.2%) identified who had died ("cases"), with 1572 of these having known expiration dates after their 1-year

follow-up interview. In addition to excluding nonsurvivor cases with unknown date of death (n = 48) or death prior to 1-year follow-up interview (n = 399), cases missing key matching variables (age, gender, PTA duration; n = 85) or whose last follow-up was not valid (i.e., lost, refused, incarcerated, withdrew, or no funding; n = 275) or not at a regularly scheduled follow-up interval (n = 49) were excluded, resulting in a final sample of 1163 nonsurvivors available for matching. The remaining 12238 participants (43417 follow-up records) who were not identified as having died were considered as surviving controls. Surviving controls missing key matching variables (age, gender, PTA duration; n = 578) were excluded. All follow-up interviews from controls that were not valid or not at a regularly scheduled follow-up interval were also excluded, resulting in a final sample of 29473 follow-up interviews from 10839 surviving controls available for matching. The sample flowchart is shown in Figure 1.

### Insert Figure 1 about here

#### **MEASURES**

To expand upon the known effects of age, gender, and time post-injury on mortality with a broad examination of functional characteristics that may be positively impacted by strategies or intervention, the following physical, cognitive, and psychosocial function variables were examined. All published measurement tools used are psychometrically sound (i.e. reliable and valid) and are widely used by clinicians and researchers specializing in TBI.

#### **Physical function variables**

• Functional Independence Measure (FIM<sup>TM</sup>)<sup>28,29</sup>

The current study specifically considered the FIM Motor subscale, comprised of 13 of the 18 items and with total FIM Motor scores ranging from 13 (total assistance) to 91

(complete independence), and item scores for Bladder Management and Bowel Management.<sup>30-33</sup>

# **Cognitive function variables**

• Disability Rating Scale (DRS)<sup>34-36</sup>

We considered total DRS scores which range from '0' (no disability) to '29' (extreme vegetative state), and we also considered scores on the DRS Communication/Verbal item (e.g., oriented, confused) which range from "0" (oriented) to '4' (no sounds or communication).

• *FIM cognitive score*<sup>28,29</sup>

Collectively, 5 of the 18 items comprise a FIM Cognitive Score which ranges from '5' to '35.'

• Participation Assessment with Recombined Tools Objective (PART-O)<sup>37,38</sup>

We considered each domain (Out and About, Productivity, Social) and Total scores, with each item per domain being scored on a 5-point sale ( $^{\circ}0' =$ low functioning to  $^{\circ}5' =$ high functioning).

# **Psychosocial function variables**

• FIM Social Score<sup>28,29</sup>

We considered the social interaction item or domain score, which has been investigated in previous TBI studies.<sup>31</sup>

• Extended Glasgow Outcome Scale (GOS-E)<sup>39,40</sup>

Outcome in each of eight broad areas of function is rated on an 8-point scale ('1' representing death and '8' representing upper good recovery).

• Satisfaction With Life Scale (SWLS)<sup>41,42</sup>

Each item is rated on a 7-point scale ('1' = strongly disagree to '7' = strongly agree).

Higher scores represent greater life satisfaction.

## Matching Algorithm

A 1:1 matching algorithm was conducted to match the last record of a nonsurvivor with a record from a corresponding surviving control on the following characteristics: years post-injury (1, 2, 5, 10, 15, and 20), age at injury ( $\pm$  1 year), sex (male/female), and PTA duration as a measure of injury severity and categorized into the following groups: 0-14 days, 15-28 days, 29-70 days, > 70 days.<sup>43,44</sup> For the nonsurvivors, only the last follow-up record was used for matching. However, for the surviving controls, multiple follow-up records over time (e.g., 1-, 2-, 5-, 10- years) were available. As such, the algorithm matched cases with 20-year follow-up records first, followed by cases with 15-, 10-, 5-, 2-, and then 1-year follow-up records. This strategy was implemented so that any surviving control with a follow-up record at the corresponding year was considered as a match for a case as long as the control had not been matched in a prior step. This allowed nonsurvivors to be matched from a sample of all possible surviving controls. As summarized in Table 1, this algorithm produced 1107 matched pairs of subjects, with 95.2% of nonsurvivors being matched.

### Insert Table 1 about here

#### **DATA ANALYSIS**

Paired comparisons using the matched sample were made between nonsurvivors and surviving controls on a number of physical function, cognitive function, and psychosocial function outcome variables. Sample sizes for these paired analyses decreased due to missing outcome data from either the case or the control. Missing data rates ranged from 1.1% to 42.7%. These rates were higher for variables that were more recently added to the TBIMS NDB (e.g., PART) or variables collected only via self- (as opposed to proxy) report (e.g., SWLS).

Mean/percentages of outcome variables were summarized for all participants with non-missing data in each group. Due to the large sample size, we anticipated that a number of comparisons would be statistically significant, but not necessarily be clinically meaningful. Therefore, we determined *a priori* that standardized effect sizes would be used to determine the relative importance of findings in addition to performing statistical tests. Cohen's d, calculated using a weighted pooled standard deviation of both groups<sup>45</sup> was used to calculate the effect size for mean differences, whereas Cohen's h (based on the arcsine transformation of proportions)<sup>46</sup> was used for differences between proportions. Effect sizes between 0.2 and 0.5 were considered small, those between 0.5 and 0.8 were considered medium; and those larger than 0.8 were considered large. Mixed-effects models were used to test for differences between the groups. Mixed-effects models were selected due to their capacity to handle the paired nature of the data, ability to model both continuous and dichotomous outcome variables, and robustness to missing data from one member of the pair. Mean differences between groups along with 95% confidence intervals are reported for continuous outcomes, and odds ratios are reported for dichotomous outcomes.

### RESULTS

The distribution of age, sex, and PTA group for the unmatched sample of nonsurviving cases and surviving controls is summarized in Table 2. Groups were similar with respect to sex (p = 0.14) and PTA duration (p = 0.33) however, cases were significantly older than controls (mean age 59.2 vs. 38.2 year p < 0.0001). As expected, the last available follow-up tended to be sooner after injury for nonsurviving cases as compared to surviving controls (p < 0.0001).

## Insert Table 2 about here

Table 3 summarizes the distribution of age, sex, PTA group, and post-injury year for the matched sample of nonsurvivors and surviving controls. The average age at injury in both groups after matching was approximately 58 years old, and 72% were male. Eighty-six percent of deaths occurred within 10 years of injury and 96% within 15 years of injury.

# Insert Table 3 about here

The means and standard deviations of various medical, cognitive, and psychosocial function variables are summarized for nonsurvivors and matched surviving controls in Table 4. Mixed-effects models indicated that nonsurvivors had significantly worse outcomes at the last follow-up prior to their death as compared to matched surviving controls for all examined variables (all *p*-values < 0.0001). Estimated differences and associated confidence intervals based on these models are summarized in Table 3. Within the set of physical function variables, effect sizes ranged from 0.415 (small) to 0.627 (medium). In particular, nonsurvivors had 11.2 units lower FIM Motor scores on average compared to surviving controls. Within the set of cognitive function variables, effect sizes ranged from 0.112 (negligible) to 0.600 (medium). In particular, nonsurvivors had 3.3 units lower FIM Cognitive scores and 2.5 units lower DRS Total Scores. Within the set of psychosocial functional variables, effect sizes ranged from 0.347 (small) to 0.488 (small). In particular, SWLS scores were 2.6 units lower on average for nonsurvivors as compared to surviving controls.

### Insert Table 4 about here

### DISCUSSION

The current study evaluated differences in physical, cognitive, and psychosocial function measured at the last study visit among individuals with TBI who died and matched survivors. The goal of this work was to identify potentially modifiable risk factors and opportunities for prevention and/or intervention that may help extend longevity, healthy function and life quality after TBI. We observed significant differences on all physical, cognitive, and psychosocial function variables chosen *a priori*, such that individuals who died performed worse during their most recent study visit on all assessments of these domains of function relative to their surviving counterparts, despite being comparable on other characteristics that might put them at risk for death.

Individuals who died had significantly worse functioning on several indicators of physical function, including subscales from the FIM (i.e., Motor, Bladder Management, and Bowel Management). Among the indicators of physical function investigated in this study, FIM Motor demonstrated the largest difference between survival groups, suggesting that independence in mobility may be particularly indicative of likelihood of longer-term survival. Indices of cognitive function showed a range of effect sizes for differences between those who died and lived. Aggregate measures of clinician-rated cognitive function (i.e., DRS total and FIM Cognitive) better differentiated the two groups and exhibited medium effect sizes, while individual subscales of cognitive function (i.e., DRS Communication/Verbal), though statistically significant, had smaller effect sizes. Those who died also participated less actively in their communities (as measured by PART subscales and total score). Finally, differences were found between groups on each of our psychosocial function variables; the most robust among these was the GOS-E, and mean scores across groups suggest that the distinction between "upper moderate disability" and "upper severe disability" may reflect differences in ability to carry out daily self-care tasks that are particularly important to health maintenance.

Taken together, results of the current study suggest that individuals in the TBIMS who expire are distinguishable from their surviving counterparts years prior to death. Specifically, nonsurvivors demonstrated poorer global functioning at their most recent study visit. It should be noted that our groups showed highly significant statistical differences across all measures examined. While this may be in part attributable to our large sample sizes, the effect sizes across the majority of *a priori* determined measures were categorized as approximately "medium." As such, these results suggest there is a global decline in functioning prior to death, rather than specific harbingers that may be identified as treatable risk factors and targets for intervention. As such, future studies may seek to examine differences between survivors and non-survivors earlier on in their TBI recovery or to collect more detailed information about medical health and lifestyle factors that may contribute to health and longevity in this cohort. Indeed, discovery of modifiable mortality risk factors may allow for more proactive health promotion among family and caregivers, including targeted prevention and early intervention efforts (e.g., greater motor activity; increased community participation).<sup>47,48</sup>

This study has limitations that warrant consideration. The measures included in the TBIMS NDB are designed to characterize global outcomes after TBI, and more granular information about health behaviors, access to medical care, and medical risk factors which may contribute most strongly to mortality risk are not available in this national database. Most TBIMS NDB measures are subjective and based on self-report, and awareness and recall bias may impact reporting. Depending on the interval between last study visit and death, the data available to characterize decedents in this study could have been collected as many as 5 years prior to death and may not represent the most relevant or pressing factors associated with mortality. Additionally, results of this study are based on individuals with moderate-severe TBI who receive inpatient rehabilitation and chose to participate in longitudinal research, and findings may not represent individuals who do not receive specialized inpatient rehabilitation, or who declined or discontinued research participation. To address gaps in previous literature, participants in this study were matched on key attributes related to injury status and risk of death, allowing us to more clearly observe what may differentiate those who expire from those who survive following TBI. While participants were matched on defined ranges of PTA duration and time since injury, it was not practical to match participants on the exact number of days which may have allowed for some variability in actual number of days.

The current study contributes incrementally to knowledge regarding mechanisms associated with mortality after TBI. Despite well-documented reductions in life expectancy among survivors of TBI, much remains to be learned. Better understanding of the specific clinical conditions, health behaviors, and external supports that lead to death among individuals who survive the injury itself will require prospective data collection conducted proximal to death through in-depth interview with informants. Further work in this area may elucidate opportunities for secondary and tertiary prevention and timely intervention of consequences of TBI in this at-risk group.

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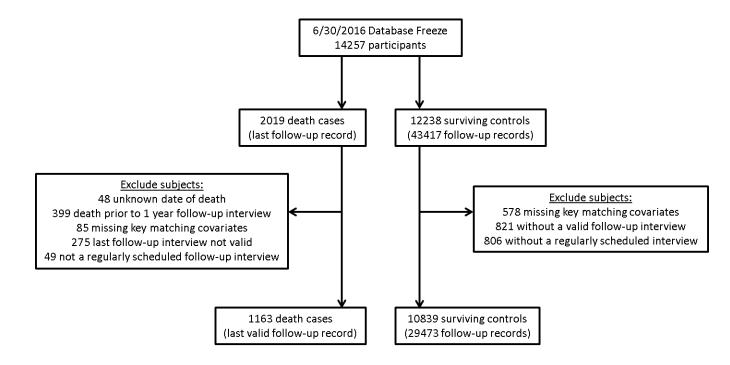
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			Matched	Unmatched
	Cases	Controls	Cases	Cases
20 Year	16	378	13	3
15 Year	36	1225	31	5
10 Year	117	3201	107	10
5 Year	335	6075	316	19
2 Year	407	8105	399	8
1 Year	252	9116	241	11
Total	1163		1107	56
			(95.2%)	(4.8%)

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Note: First, 13 of the 16 cases were matched with records from all 378 controls who also had
20 year records. Next, 31 of 36 cases were matched with records from all 1225 controls who had
15 year records (as long as the control had not been matched with their 20 year record). This
process was repeated to match 10, 5, 2, and 1 year records.

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	Nonsurvivor Cases	Survivor Controls	
	( <i>N</i> = 1163)	(N = 10839)	
Age, mean (SD)	59.2 (19.3)	38.2 (17.7)	
Sex, <i>n</i> (%)			
Male	829 (71.3%)	7946 (73.3%)	
Female	334 (28.7%)	2893 (26.7%)	
PTA Group, <i>n</i> (%)			
0 – 14 days	395 (34.0%)	3563 (32.9%)	
14 – 28 days	260 (22.4%)	2686 (24.8%)	
29 – 70 days	388 (33.4%)	3538 (32.6%)	
> 70 days	120 (10.3%)	1052 (9.7%)	
Most Recent Follow-Up Interview, n (%)			
1 year	252 (21.7%)	1287 (11.9%)	
2 years	407 (35.0%)	2585 (23.8%)	
5 years	335 (28.8%)	3438 (31.7%)	
10 years	117 (10.1%)	2196 (20.3%)	
15 years	36 (3.1%)	955 (8.8%)	
20 years	16 (1.4%)	387 (3.5%)	

Table 2: Distribution of sample characteristics in the unmatched sample

SD = standard deviation

12

13

	Nonsurvivor	Survivor
	Cases	Controls
Age, mean (SD)	58.1 (19.0)	58.0 (19.0)
Sex, <i>n</i> (%)		
Male	800 (72.3%)	800 (72.3%)
Female	307 (27.7%)	307 (27.3%)
PTA Group, <i>n</i> (%)		
0 – 14 days	383 (34.6%)	383 (34.6%)
14 – 28 days	242 (21.9%)	242 (21.9%)
29 – 70 days	370 (33.4%)	370 (33.4%)
> 70 days	112 (10.1%)	112 (10.1%)
Post Injury Follow-Up, <i>n</i> (%)		
1 year	241 (21.8%)	241 (21.8%)
2 years	399 (36.0%)	399 (36.0%)
5 years	316 (28.6%)	316 (28.6%)
10 years	107 (9.7%)	107 (9.7%)
15 years	31 (2.8%)	31 (2.8%)
20 years	13 (1.2%)	13 (1.2%)

14 Table 3: Distribution of sample characteristics in the matched sample (N = 1107 pairs)

SD = standard deviation

Table 4: Results from matched comparison (N Pairs = 1107)       107)	
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	Nonsurvivor Cases		Survivor Controls			Mixed Model		
		Mean (SD)		Mean (SD)		Difference (SE)		
Physical Function Variables	N	/ Count (%)	N	/ Count (%)	Effect Size	/ Odds Ratio	95% CI	<i>p</i> -value
FIM Motor	1015	70.75 (25.21)	1026	82.07 (15.27)	0.627 †	-11.22 (0.85)	(-12.89, -9.55)	< 0.0001
FIM Bladder Management	1030	5.54 (2.27)	1034	6.44 (1.43)	0.434 *	-0.90 (0.08)	(-1.05, -0.74)	< 0.0001
FIM Bowel Management	1028	5.70 (2.17)	1034	6.53 (1.30)	0.415 *	-0.83 (0.07)	(-0.97, -0.68)	< 0.0001
Cognitive Function Variables								
FIM Cognitive	1036	26.95 (8.46)	1038	30.28 (5.74)	0.529 †	-3.30 (0.29)	(-3.88, -2.73)	< 0.0001
DRS Communication/Verbal	1042	0.37 (0.80)	1032	0.23 (0.47)	0.112	0.13 (0.03)	(0.08, 0.19)	< 0.0001
DRS Total	1024	5.63 (5.49)	1000	3.09 (3.56)	0.601 †	2.53 (0.19)	(2.16, 2.90)	< 0.0001
PART Out and About	702	0.97 (0.81)	883	1.40 (0.79)	0.328 *	-0.43 (0.04)	(-0.51, 0.36)	< 0.0001
PART Productivity	706	0.47 (0.64)	888	0.81 (0.80)	0.268 *	-0.34 (0.03)	(-0.40, -0.27)	< 0.0001
PART Social	685	1.61 (0.99)	872	2.08 (1.03)	0.332 *	-0.47 (0.05)	(-0.57, -0.36)	< 0.0001
PART Total	684	1.02 (0.66)	871	1.43 (0.69)	0.328 *	-0.41 (0.03)	(-0.48, 0.34)	< 0.0001

SWLS	634 20.16 (8.56) 8	22.81 (7.89)	0.411 *	-2.64 (0.41)	(-3.45, -1.83)	< 0.0001
FIM Social	1041 5.66 (1.74) 10	6.27 (1.16)	0.347 *	-0.60 (0.06)	(-0.73, -0.48)	< 0.0001
GOSE Total	1022 4.77 (1.89) 10	5.71 (1.86)	0.488 *	-0.94 (0.08)	(-1.09, -0.79)	< 0.0001
17	SD = standard deviation	n; SE = standard error	; CI = confidence in	nterval		
18	Effect Size ( $\Delta$ ): * Small 0.2	$\leq \Delta \leq 0.5, \dagger$ Medium	$0.5 < \Delta \le 0.8, $ La	rge $0.8 < \Delta$		
19						
20						
21						