

Cognitive Performance and Self-Reported Functioning in Huntington's Disease: Results from a Real-World Study

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Background

- Cognitive impairment in Huntington's Disease (HD) leads to difficulties in higher-order functioning tasks such as multi-tasking, organizing thoughts, planning, and decision making, and is a key driver of functional impairment starting in the early stages of HD.^{1,2}
- Reduced cognitive functioning in HD impacts individuals across multiple aspects of daily living, including driving, the ability to work, social, and family life, and the ability to manage personal finances.^{1,2} These functioning changes lead to loss of employment, and ultimately loss of independence over time.^{3,4} However, cognitive changes in the early stages of HD are often overlooked and not well characterized in natural history studies.

Objective

- To report characteristics of individuals with HD in this real-world data study to understand their patient journey, including the burden of HD on activities of daily living, health-related quality of life (HRQoL), functional independence, and work productivity from an early cross-sectional data cut.

Methods

- To measure the holistic impact of HD on the lives of individuals with HD, Sage Therapeutics, Inc. is conducting a real-world study in collaboration with PicnicHealth which integrates prospectively collected patient reported outcome (PRO) and cognitive measures data with medical records and claims data for individuals with HD in the United States (US). This analysis focuses on the initial cross-sectional PRO data for enrolled participants to date, including demographics and clinical characteristics.
- Adults (≥18 years at the time of study enrollment) with a physician-confirmed diagnosis of HD or a clinically confirmed positive genetic test for a mutant huntingtin (mHTT) gene variant were enrolled into the PicnicHealth research platform between June and September 2022.
- PROs and cognitive measures assessed at enrollment included self-reported Unified HD Rating Scale - Total Functional Capacity (self-reported TFC), Digit Symbol Substitution Test (DSST), EQ-5D-5L index score and visual analogue scale (VAS), Work Productivity and Activity Impairment-HD (WPAI-HD), and HD Everyday Functioning Scale-Short Form (Hi-DEF-SF).

PRO and cognitive performance measures included in the study:

- Self-reported TFC** assesses the clinical features and function in HD from a patient's perspective across five domains – occupation, finances, domestic chores, activities of daily living, and care-level; scores range from 13 (HD stage I) to 0 (HD stage V).⁵
- DSST** assesses cognitive function; scores range from 0 to 133, with a lower score indicating worse performance.⁶
- Hi-DEF-SF** measures functional deficits across stages; mean transformed scores range from 0 and 100, with a higher score representing a greater functional deficit due to HD.⁷
- EQ-5D-5L index score and VAS** assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; index scores range from 0 to 1 and VAS scores range from 0 to 100, with a lower score representing worse HRQoL.⁸
- WPAI-HD** assesses the impact of HD on ability to work and perform regular activities; scores for the four main outcomes are expressed in percentages, with a higher percentage representing greater impairment.⁹ Outcomes are: absenteeism (% work time missed due to HD), presenteeism (% impairment while working due to HD), work productivity loss (% overall work impairment due to HD), and activity impairment (% activity impairment due to HD).

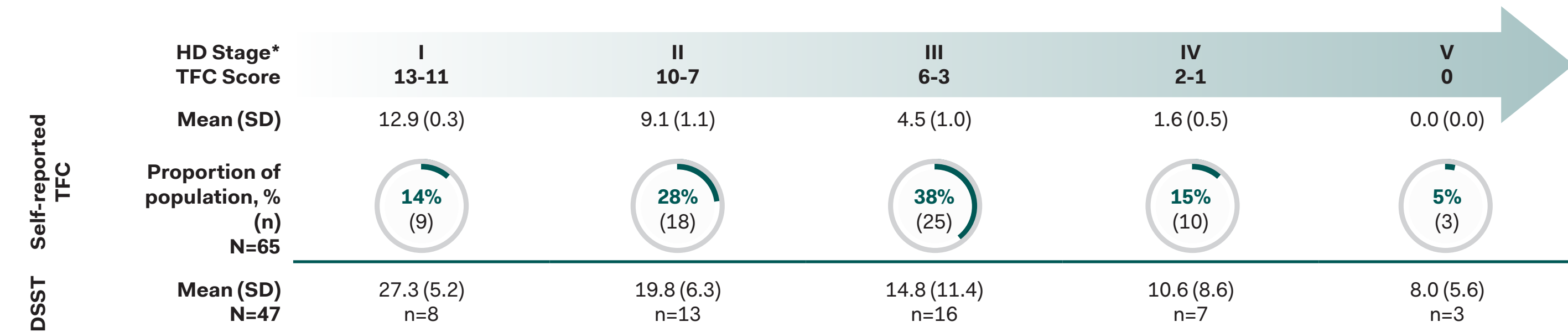
Results

- Ninety-seven participants were enrolled at this interim data cut; of these, 65 participants had self-reported TFC scores at baseline.
- Of the 97 participants, demographics and clinical characteristics were: 59% female; 90% White, 3% Black/African American, 7% other race; mean age 47 years (SD: 13; range: 24-74); US location, 31% Midwest, 12% Northeast, 38% South, 19% West; >70% cognitive/psychological symptoms, 74% motor symptoms.
- Mean CAG repeats were 43.80 (SD: 3.45; range: 38.00-60.00) in the 76 participants with this information.

SELF-REPORTED TFC AND DSST SCORES

- Mean self-reported TFC was 6.3 (SD: 3.9; FIGURE 1) and 22-82% of participants (n=65) reported substantial impact (score 0-1) across all five domains.
- Scores for cognitive performance, as measured by DSST, were worse among individuals with lower self-reported TFC scores as compared with those with higher self-reported TFC scores, indicating a negative impact of HD on cognition with increasing disease severity.
- 55% of participants reported substantial difficulty (score of 0-1; i.e. either unable without help or able to do some but not all) in accomplishing daily living tasks without help (TABLE 1).

FIGURE 1: DISEASE SEVERITY BY TFC AND DSST IN PATIENTS WITH SELF-REPORTED TFC (n=65)



*Shoulson-Fahn I-V staging system.¹⁰ DSST, Digit Symbol Substitution Test; HD, Huntington's disease; SD, standard deviation; TFC, total functional capacity.

TABLE 1: SELF-REPORTED TFC DOMAIN LEVEL RESULTS BY STAGE (n=65)

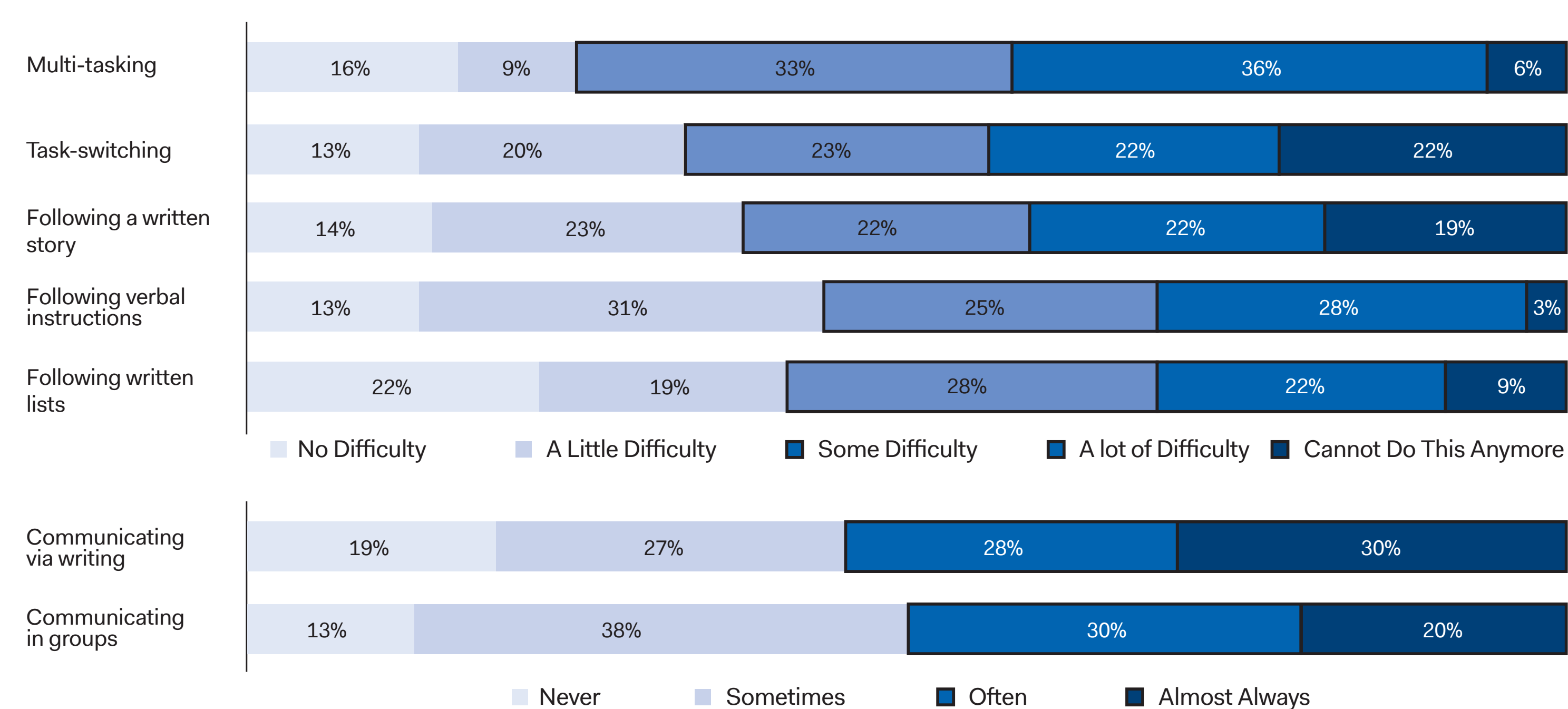
TFC category	Increasing disease severity				
	Stage I: TFC 13-11 Premanifest, manifest I (n=9)	Stage II: TFC 10-7 Manifest II (n=18)	Stage III: TFC 6-3 Manifest III (n=25)	Stage IV: TFC 2-1 Manifest IV (n=10)	Stage V: TFC 0 Manifest V (n=3)
Occupation	0.0	88.9	96.0	100.0	100.0
Finances	0.0	5.6	88.0	100.0	100.0
Domestic chores	0.0	50.0	96.0	100.0	100.0
Activities of daily living	0.0	5.6	88.0	100.0	100.0
Care level	0.0	0.0	16.0	70.0	100.0

TFC, total functional capacity.

HI-DEF-SF

- For each Hi-DEF-SF item, ≥ 50% of participants reported at least some difficulty (FIGURE 2).
- Mean Hi-DEF score across all respondents (n=64) was 47.6 (range: 11-86). The proportion of respondents with at least some difficulty in all items increased with decreasing self-reported TFC levels (TABLE 2).
- Of participants with self-reported TFC scores 13-11 (Stage I), 11% reported at least some difficulty in multi-step tasks, following written story/spoken instructions, and conveying thoughts in a group.
- Most participants with self-reported TFC scores 10-7 (Stage II) reported at least some difficulty in multi-step tasks (72%) and switching between two activities (56%).

FIGURE 2: HI-DEF-SF RESULTS FOR TOTAL POPULATION (N=64)



Hi-DEF-SF, Huntington's Disease Everyday Functioning short form.

TABLE 2: PROPORTION OF INDIVIDUALS WITH AT LEAST SOME DIFFICULTY* ON HI-DEF-SF ITEMS BY SELF-REPORTED TFC (n=63)[†]

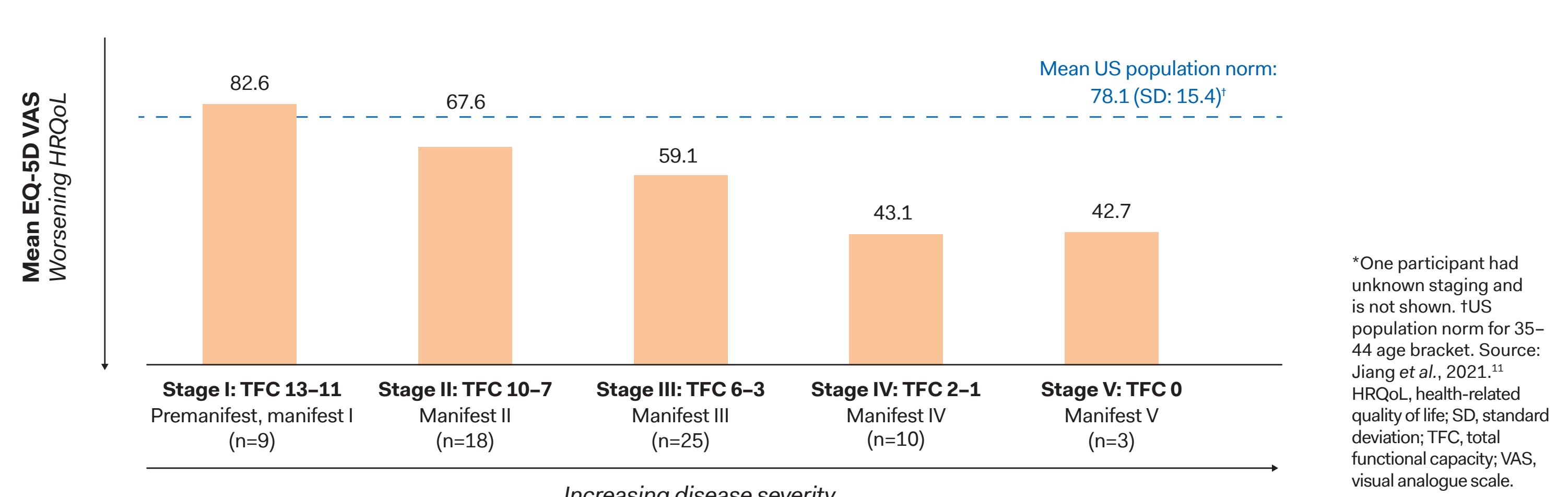
Task	Increasing disease severity				
	Stage I: TFC 13-11 Premanifest, manifest I (n=9)	Stage II: TFC 10-7 Manifest II (n=18)	Stage III: TFC 6-3 Manifest III (n=24)	Stage IV: TFC 2-1 Manifest IV (n=9)	Stage V: TFC 0 Manifest V (n=3)
Multi-tasking	11.1	72.2	87.5	100.0	100.0
Task-switching	0.0	55.6	83.3	100.0	100.0
Following a written story	11.1	38.9	83.3	88.9	100.0
Following verbal instructions	11.1	27.8	75.0	88.9	100.0
Following written lists	0.0	38.9	75.0	100.0	100.0
Communicating via writing	11.1	33.3	58.3	77.8	100.0
Communicating in groups	0.0	38.9	70.8	77.8	100.0

*See right of figure. †One participant had unknown staging and is not shown. Hi-DEF-SF, Huntington's Disease Everyday Functioning short form; TFC, total functional capacity.

EQ-5D-5L

- Mean EQ-5D VAS score across respondents (n=66) was 61 (range: 4-100)
- The proportion of respondents with moderate, severe or extreme problems generally increased with lower self-reported TFC scores, particularly for the domains of mobility, self-care, and usual activities (FIGURE 3).
- There was no noticeable impact of HD on EQ-5D scores at Stage I, with values similar to US population norms.¹¹

FIGURE 3: MEAN EQ-5D VAS BY SELF-REPORTED TFC (n=65)*

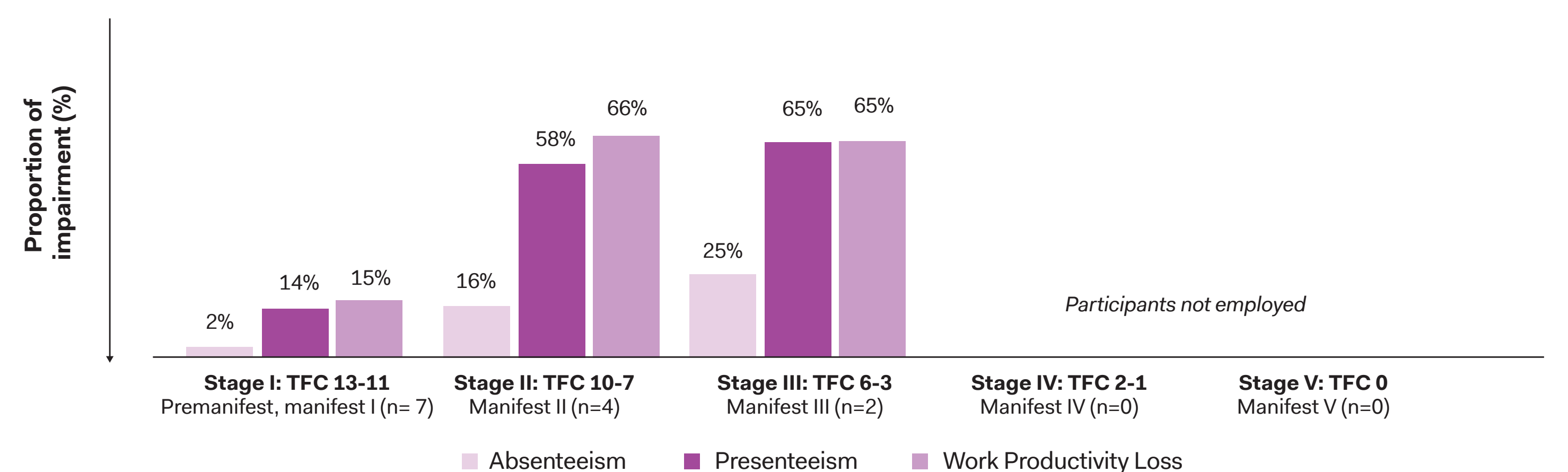


WPAI-HD

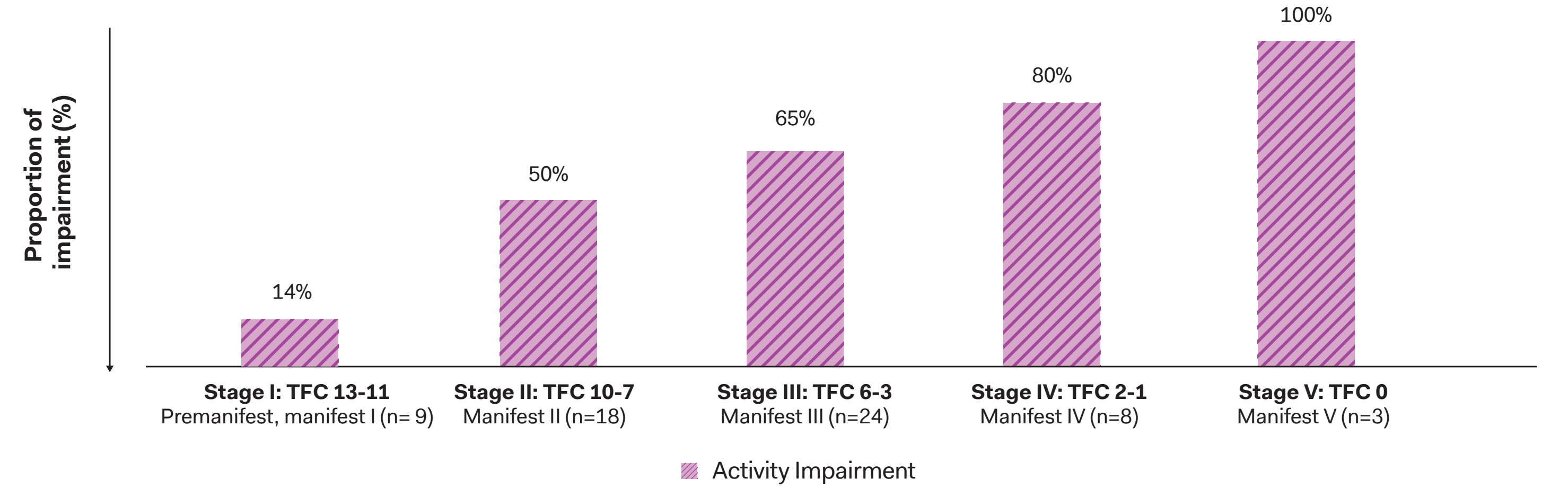
- Work and activity impairment, assessed by WPAI-HD, increased as self-reported TFC scores decreased.
- Participants with Stage I HD also reported work impairment: 2% absenteeism, 14% presenteeism, 15% work productivity loss, respectively, and 14% activity impairment, indicating an impact of HD on ability to work even in the pre-manifest stage.
- Participants with Stage IV or Stage V HD reported unemployment and therefore did not report on work-related impairment items. However, their overall activity impairment was reported as 80% and 100%, respectively, indicating severe impact of HD in these later stages (FIGURE 4).

FIGURE 4: WPAI-HD RESULTS BY SELF-REPORTED TFC

(A) Percentage of absenteeism, presenteeism, and work productivity loss by self-reported TFC stages (n=13)*



(B) Percentage of activity impairment by self-reported TFC stage (n=62)



*49 participants reported they were not employed and therefore did not respond to work-related questions. Absenteeism: % work time missed due to a problem; Presenteeism: % impairment while working due to a problem; Activity Impairment: % activity impairment due to a problem; Work productivity loss: % overall work impairment due to a problem. TFC, total functional capacity; WPAI-HD, Work Productivity and Activity Impairment: Huntington's Disease V2.0.

Conclusions

- Many individuals with HD experience cognitive impairment across all stages of HD, impacting their independence and ability to function. These findings show increasing disease severity according to self-reported TFC corresponds to lower scores on cognitive performance test, higher proportions of participants with cognitive functioning difficulties, and impaired activities of daily living, work, HRQoL, and functioning.
- The Hi-DEF-SF, which measures the impact of cognitive impairment on functioning, has the potential to track the burden in early stages of HD, and provide a granular understanding of the day-to-day difficulties experienced by individuals with HD.
- EQ-5D demonstrated limited ability to detect HRQoL impairment for participants with early HD, despite work and domestic chores-related difficulties reported on self-reported TFC, and functional impairments observed via the Hi-DEF-SF scale at Stage I.
- This study intends to enroll up to 400 participants with HD in the US, and will remain open for ≥ 2 years to better understand the impact cognitive changes have on medical outcomes, health care utilization, work ability, self-reported functioning, and overall independence.

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