

Introduction

- Narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH) are chronic sleep disorders primarily characterized by excessive daytime sleepiness (EDS)^{1,2}
- Independent of EDS, people living with narcolepsy and IH may also experience cognitive impairment³⁻⁶
 - Cognitive impairment includes issues with attention, memory, problem-solving, and processing information, which can affect education, employment, social relationships, and overall health-related quality of life (HRQoL)^{5,7}
 - Patients may experience symptoms of cognitive impairment even while taking medications for narcolepsy or IH^{7,8}
 - It is unclear how symptoms of cognitive impairment are associated with common measures of HRQoL assessed among those with narcolepsy, including the Functional Outcomes of Sleep Questionnaire - Short Form (FOSQ-10) and EuroQol-5D-5L index (EQ-5D-5L)
 - Cognitive impairment is thus an important aspect of the overall clinical evaluation of those living with narcolepsy and IH^{6,6}

Objective

- The ASPIRE study characterized symptoms of NT1, NT2, and IH including cognitive impairment
 - This study also explored the association between cognitive impairment and functional and HRQoL outcomes

Methods

Study design

- The ASPIRE study was an online survey of participants with NT1, NT2, and IH conducted in alignment with the US Food and Drug Administration Patient-Focused Drug Development Guidance on the collection and use of patient experience data (Table 1)^{9,10}
- Participants were recruited through Rare Patient Voice (RPV, a qualified third-party research panel), the Hypersomnia Foundation, and the Sleep Consortium. Participants who completed and submitted the survey received a nominal honorarium

Table 1: Study population

NT1 (n = 116)	NT2 (n = 127)	IH (n = 123)
Participants were ≥ 18 years of age, resided in the US, and reported a clinician's diagnosis of NT1, NT2, or IH		

IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; US, United States.

Statistical analysis

- No imputation methods were used for missing data. Data from participants who did not complete the survey were not included in analyses
- Descriptive analyses included means and standard deviations (SDs), for continuous variables, and frequencies and percentages for categorical variables
- Differences in patient outcomes were examined using one-sample *t* tests, two-sample *t* tests, and analysis of variance. Statistical significance was defined as *P* < 0.05 (two-sided) without adjustment for multiplicity

Study measures and outcomes

Symptom severity

- Cognitive impairment was evaluated with the British Columbia Cognitive Complaints Inventory-Expanded version (BC-CCI-E)
 - The original British Columbia Cognitive Complaints Inventory (BC-CCI) contains 6 items to assess concentration, memory, word finding, expressing thoughts, slow thinking, and problem solving
 - Scores (range 0–18) were categorized as none/minimal (0–4), mild (5–8), moderate (9–14), or severe (15–18)
 - The expanded version contains 3 additional items to evaluate the impact of cognitive impairment on daily life

Burden on functional and HRQoL outcomes

- Daily functioning was assessed using the FOSQ-10
- Work and activity impairment were evaluated using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)
- Self-reported health status was assessed using the EQ-5D-5L, including the visual analogue scale (EQ VAS)

Results

Participant demographics and disposition

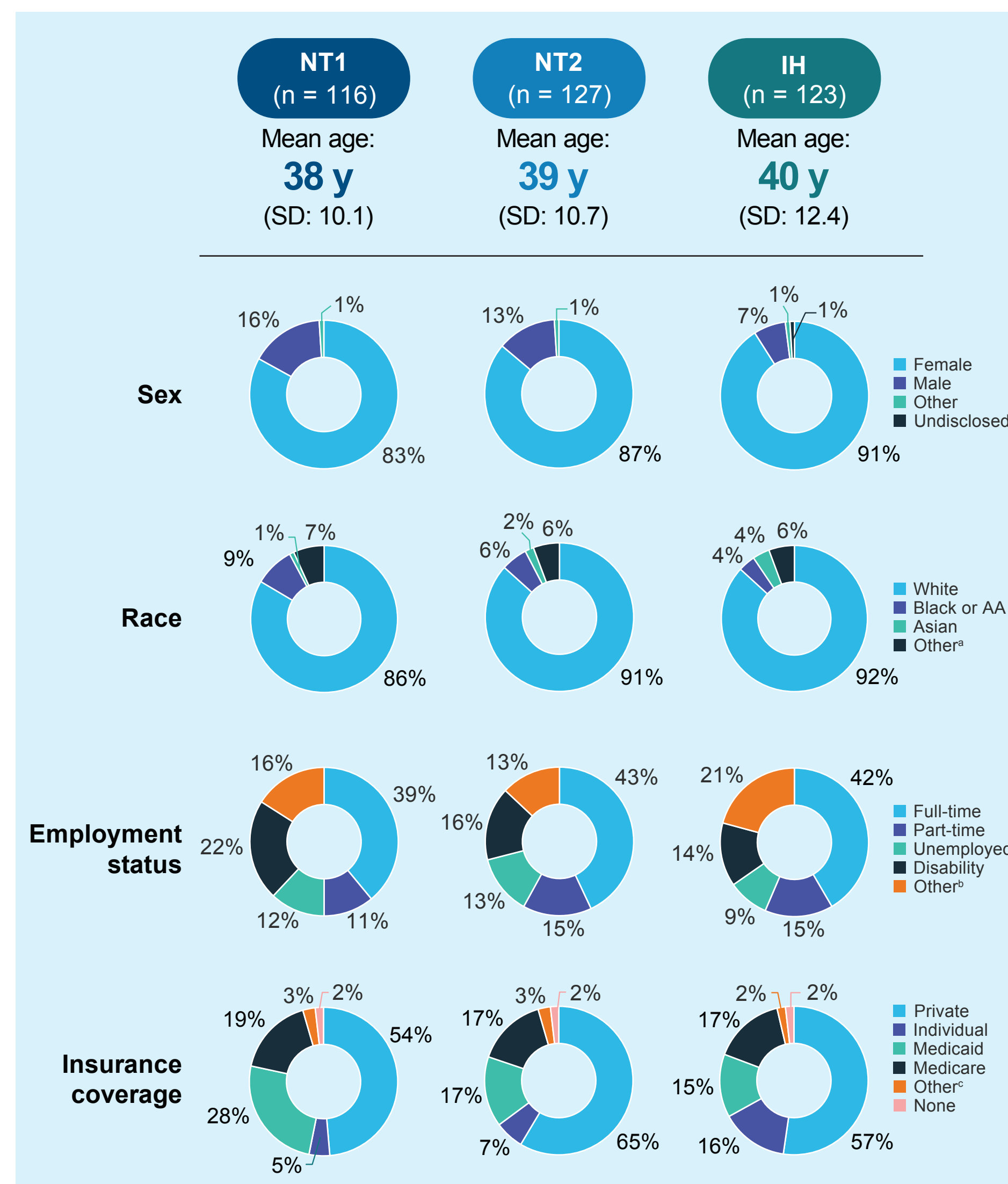
- A total of 366 participants (NT1= 116; NT2 = 127; IH = 123) were included. Baseline characteristics are shown in Figure 1
- Many participants were taking nonstimulant wake-promoting agents (modafinil, armodafinil, solriamfetol, and pitolisant; 30.1%–48.3%), or stimulants (methylphenidates or amphetamines; 43.1%–48.8%)
 - Almost half (48.3%) of participants with NT1 were taking antidepressants for cataplexy

Cognitive impairment

- The mean (SD) BC-CCI score for all participants was 9.2 (4.22), which is in the moderate range
 - Mean (SD) scores were similar across groups (NT1: 9.75 [4.07]; NT2: 8.69 [4.29]; IH: 9.22 [4.26])
- Eighty-nine percent of all participants reported mild-to-severe cognitive impairment, defined as a BC-CCI score > 4 (NT1: 92%; NT2: 86%; IH: 88%) (Figure 2A)
- Responses to individual items on the BC-CCI were similar across groups (Figure 2B)
- Participants endorsed high rates of symptom burden in occupational functioning as well as leisure and social engagement on additional items of the BC-CCI-E (Figure 2C)

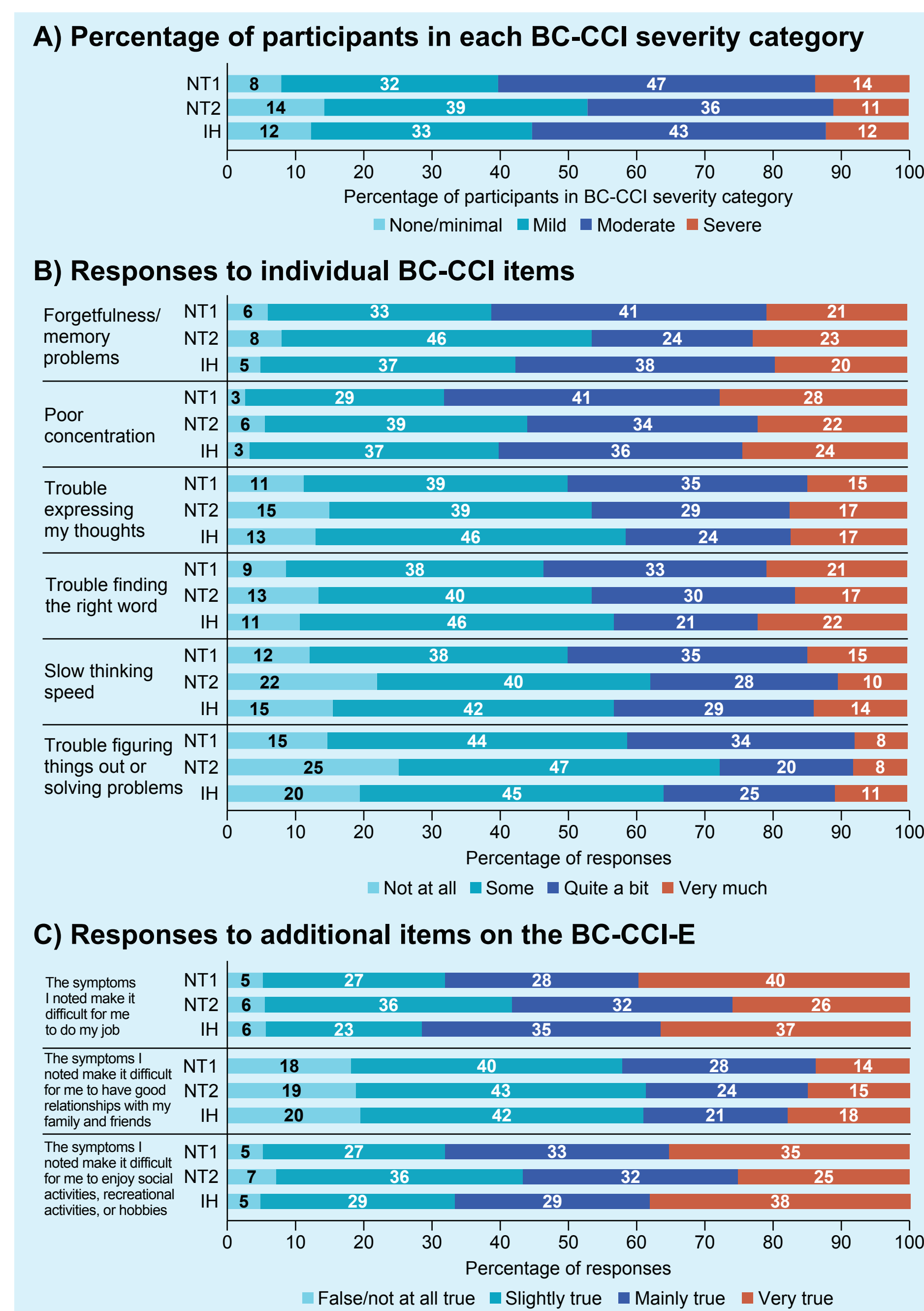
Results continued

Figure 1: Study participant baseline characteristics by diagnosis group



“Other” category includes response options of “American Indian or Alaska Native,” “Native Hawaiian or Other Pacific Islander,” “Other,” and “Prefer not to answer.” Percentages may exceed 100% because some participants reported multiple races.
“Other” category includes response options of “Student,” “Stay-at-home parent/homemaker,” “Retired,” “Voluntary job,” and “Prefer not to answer.”
“Other” category includes response options of “Veterans administration/TRICARE” and “I don’t know.” Percentages may exceed 100% because participants could report enrollment in multiple types of insurance.
AA, African American; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation; y, years.

Figure 2: Cognitive impairment as assessed by BC-CCI and BC-CCI-E in participants diagnosed with NT1, NT2, or IH

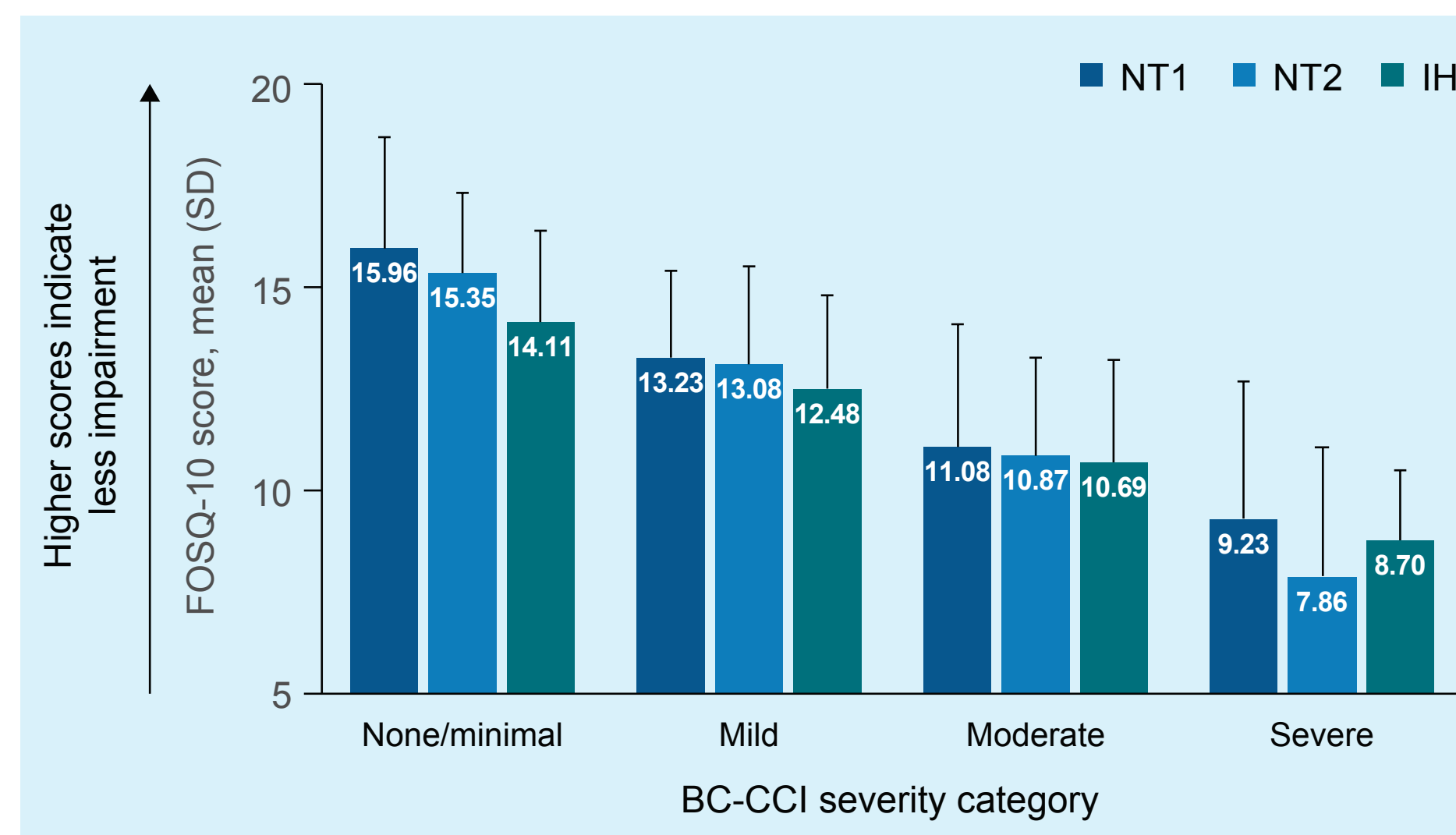


BC-CCI, British Columbia Cognitive Complaints Inventory; BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2.

Cognitive impairment and daily functioning

- The mean (SD) FOSQ-10 score for the overall study cohort was 11.79 (3.07)
- Participant scores for the FOSQ-10 were similar across groups, with a mean (SD) of 11.89 (3.28) for NT1, 12.03 (3.09) for NT2, and 11.45 (2.84) for IH
 - Scores demonstrated meaningful impairment on the FOSQ-10, with all groups scoring significantly below the normative value of 17.8 (all *P* < 0.001)¹¹
- Participants with mild-to-severe cognitive impairment had lower mean FOSQ-10 scores versus those with no or minimal cognitive impairment (11.37 vs 15.04, *P* < 0.001). Results were consistent across groups (NT1: 11.55 vs 15.96 [*P* < 0.001]; NT2: 11.48 vs 15.35 [*P* < 0.001]; IH: 11.08 vs 14.11 [*P* < 0.001])
 - Across all groups, FOSQ-10 scores decreased as cognitive impairment increased (all *P* < 0.001) (Figure 3)

Figure 3: FOSQ-10 scores by BC-CCI severity category and diagnosis group

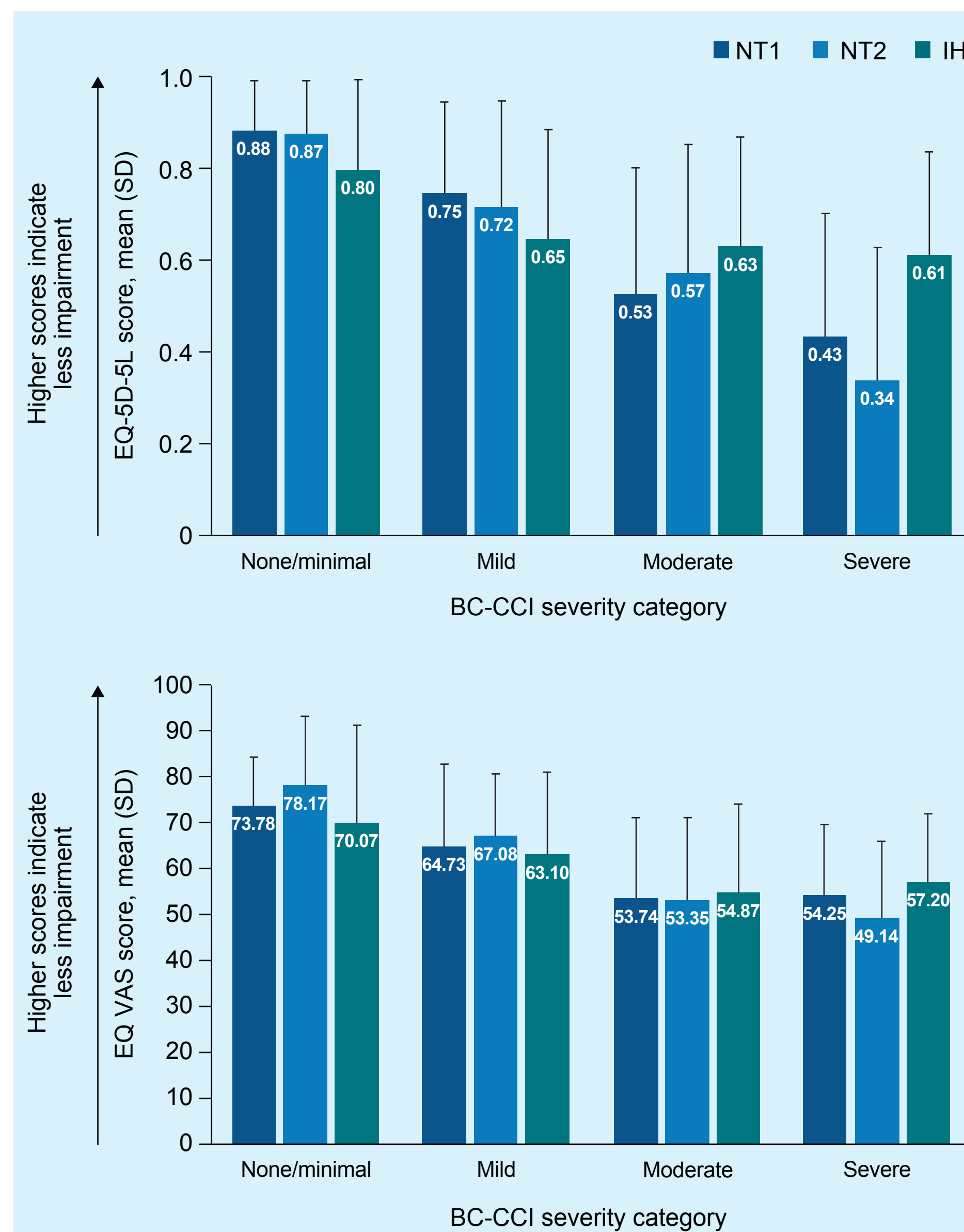


BC-CCI, British Columbia Cognitive Complaints Inventory; FOSQ-10, Functional Outcomes of Sleep Questionnaire - Short Form; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation.

Cognitive impairment and self-reported health status

- Overall, participants showed impairment on the EQ-5D-5L and EQ VAS scores, with mean (SD) scores of 0.64 (0.27) and 60.13 (18.52), respectively
- Mean EQ-5D-5L (NT1: 0.61; NT2: 0.65; IH: 0.65; all *P* < 0.001) and EQ VAS (NT1: 58.87; NT2: 61.7; IH: 59.68; all *P* < 0.001) scores were similar across all three groups
 - Mean scores for all groups were below the normative benchmark of 0.85, indicating meaningful impairment on both measures (all *P* < 0.001)¹²
- Participants with mild-to-severe cognitive impairment had lower mean EQ-5D-5L and EQ VAS scores versus those with no or minimal cognitive impairment (EQ-5D-5L: 0.61 vs 0.85 [*P* < 0.001]; EQ VAS: 58.28 vs 74.33 [*P* < 0.001]).
- Across all groups, EQ-5D-5L and EQ VAS scores were inversely associated with cognitive impairment, with lower scores observed at higher BC-CCI severity categories (between group significance for both scales in NT1 and NT2 was *P* < 0.001; in the IH group, significance was *P* = 0.086 and *P* = 0.023 for the EQ-5D-5L and EQ VAS, respectively) (Figure 4)
- On average, the most severe EQ-5D-5L dimensions in all diagnosis groups were “Activity,” “Pain or Discomfort,” and “Anxiety or Depression”

Figure 4: EQ-5D-5L and EQ VAS scores by BC-CCI severity category and diagnosis group



BC-CCI, British Columbia Cognitive Complaints Inventory; EQ-5D-5L, EuroQol-5D-5L; EQ VAS, EuroQol Visual Analogue Scale; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation.

Cognitive impairment and work

- Participants had high levels of activity impairment, describing 60% or more of their daily activities as being affected by narcolepsy or IH (Figure 5)
- Of those employed (NT1: 50%; NT2: 58%; IH: 56%), participants reported over 45% of their work as being impaired (Figure 5)
 - Total work impairment was also high across subtypes and was largely driven by presenteeism while at work

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Acknowledgments

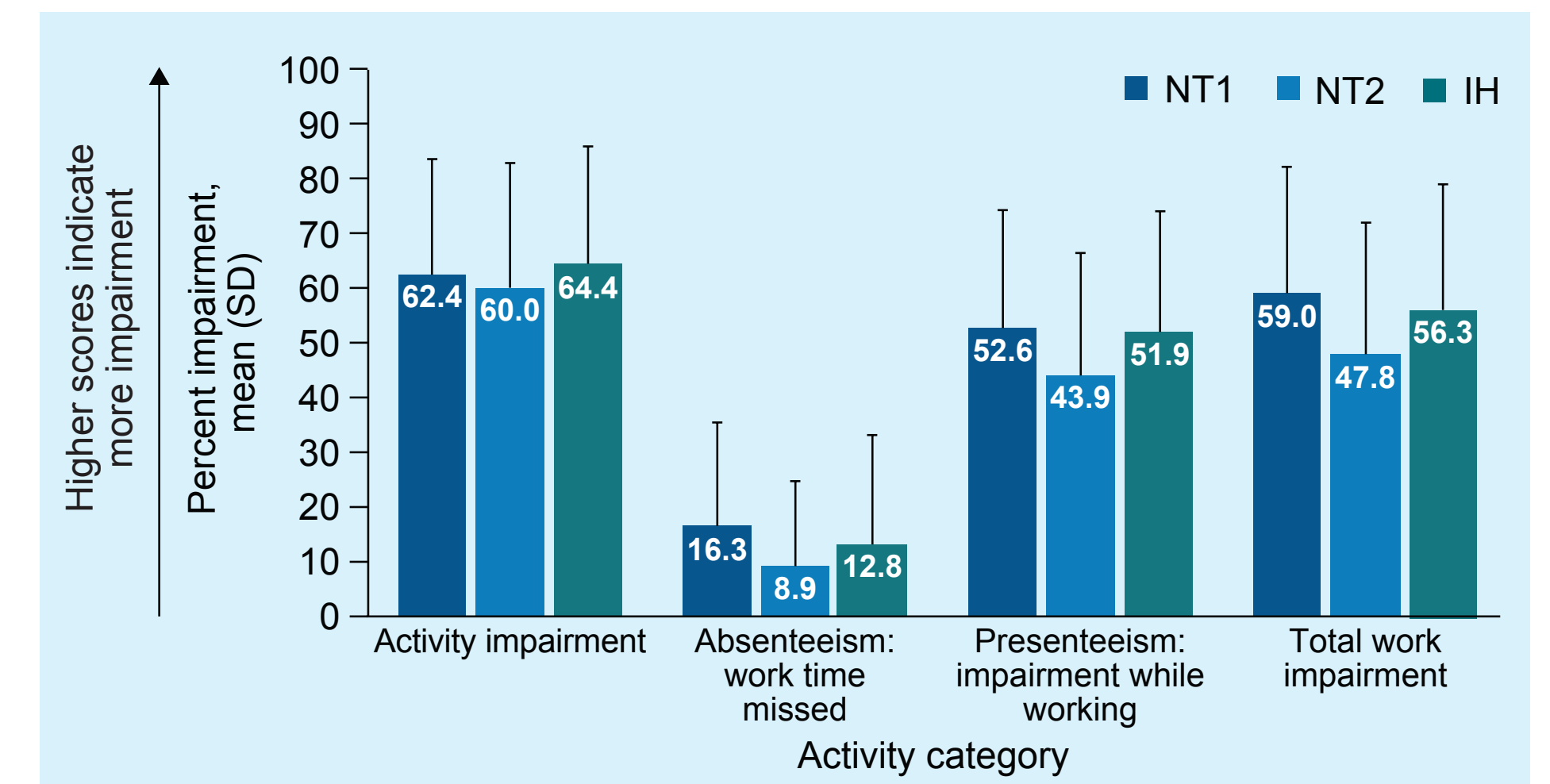
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Disclosures

MJD and GM are employees and shareholders of Alkermes. JLT and KM are employees of IQVIA Inc. CW-W received payment for expert testimony, support for attending meetings and/or travel, and holds leadership or fiduciary roles with Hypersomnia Foundation and Sleep Consortium. LJ has received grants or contracts (disbursed to Hypersomnia Foundation and Sleep Consortium) from Jazz, Centessa, Harmony Biosciences, Avadel, Alkermes, Takeda Pharmaceuticals, and Zevra; received consulting fees from Takeda Pharmaceuticals and Harmony Biosciences; and holds a leadership or fiduciary role with Hypersomnia Foundation.

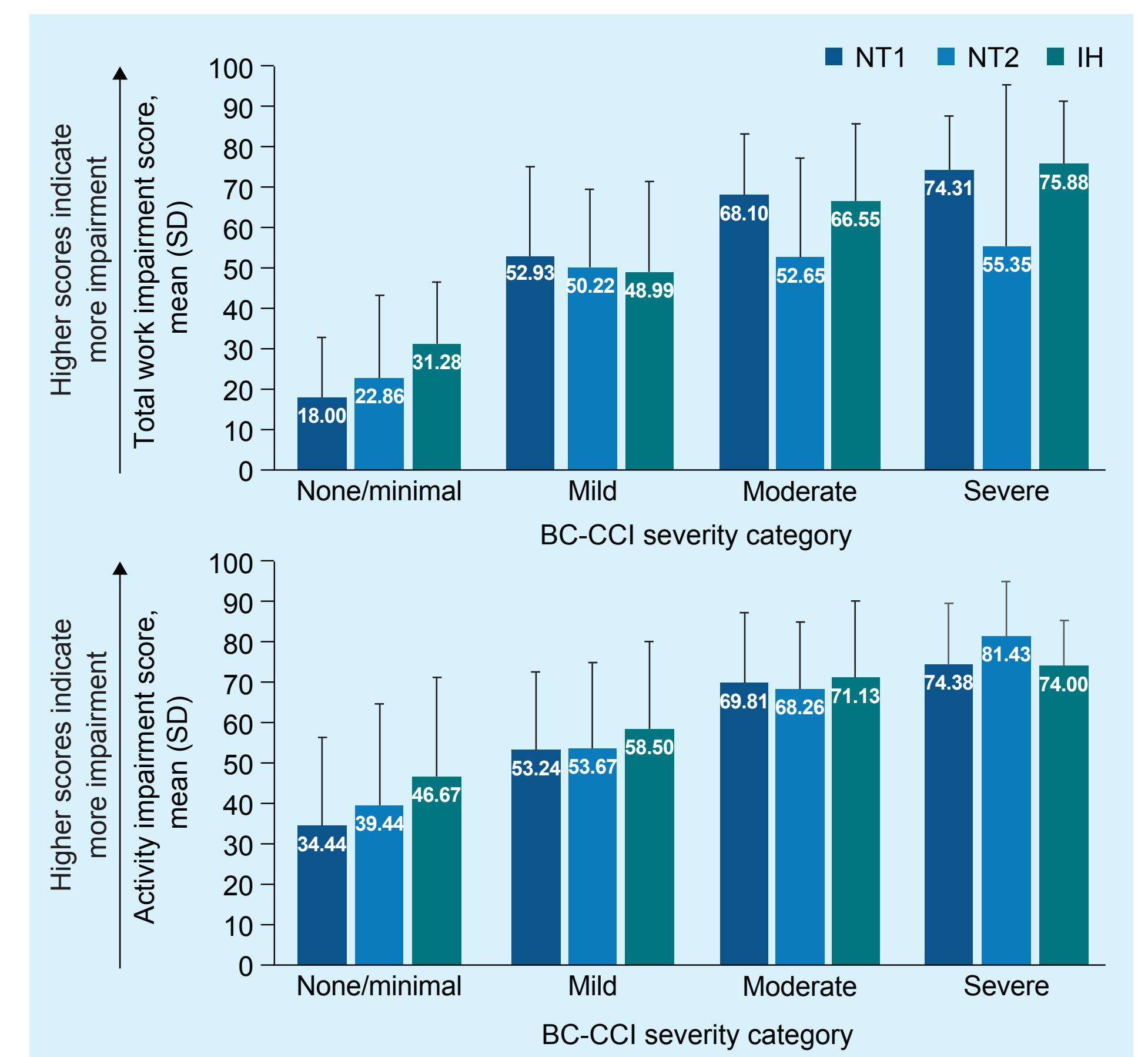
- Participants in all groups who reported mild-to-severe cognitive impairment had greater impairments in work (58% vs 25%; *P* < 0.001) and activity (65% vs 41%; *P* < 0.001) versus those with no or minimal cognitive impairment
- Total work impairment and activity impairment were greater in participants with more severe cognitive impairment (*P* < 0.001 for all comparisons) (Figure 6)

Figure 5: WPAI:SHP scores by diagnosis group



IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

Figure 6: WPAI:SHP total work impairment and activity impairment scores by BC-CCI severity category and diagnosis group



BC-CCI, British Columbia Cognitive Complaints Inventory; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

Study limitations

- Though physician diagnosis of narcolepsy or IH was self-reported, confidence in diagnosis was supported by recruitment from RPV and advocacy groups
- Online survey administration limited participation to those with internet access and those who were interested in participating
- This study used a convenience sample, which may not reflect overall patient populations
- Participants from advocacy groups may have distinct experiences and a more active role in understanding and managing their conditions compared with the wider populations living with NT1, NT2, and IH

Conclusions

- Cognitive impairment was common across participants with NT1, NT2, and IH
 - Nearly 90% of all participants reported mild-to-severe cognitive impairment
- Cognitive impairment was associated with significant burden across outcomes
 - The most significant burden was observed for participants with more severe cognitive impairment
- This study highlighted the need to address the common and burdensome symptom of cognitive impairment for those living with NT1, NT2, and IH
 - It also highlighted the importance of using established and relevant patient-reported outcome measures in research to support standardized interpretation and characterization of disease burden and treatment benefit



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