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Mental Health, Suicidality, and Underrecognized Psychological Burden in Premanifest Huntington's Disease: Insights From the Pre-HDBOI Study

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BACKGROUND

- Huntington's disease (HD) is a slow, progressive, irreversible, inherited neurodegenerative disorder characterized by motor, cognitive, and behavioral (including psychiatric) manifestations[1,2]
- Early intervention, prior to the onset of disabling symptoms, is regarded as one of the key therapeutic goals in HD because there are no current disease-modifying treatments for this fatal disease[3-5]
  - As such, improved understanding of the onset and burden of HD-related symptoms may help inform optimal treatment timing[6,7]
- Evidence suggests additional, underexplored challenges can affect this group, including high rates of anxiety, depression, and suicidal ideation; however, existing studies on this population have emphasized clinical features, particularly early cognitive impairment[6,8,9]
  - Despite this, evidence describing the multidimensional burden experienced by individuals with premanifest HD (PwPHD), including mental-health effects, remains limited[6]

OBJECTIVES

- To characterize the prevalence and severity of mental-health symptoms, the occurrence of suicidal ideation, and healthcare professionals' (HCPs') perspectives on symptom recognition and unmet psychological needs in PwPHD

METHODS

- The Pre-HDBOI study is a multinational, cross-sectional, retrospective study conducted across the US and EU-5 in collaboration with the European Huntington's Association, as well as other local HD Patient Advocacy Groups
- The enrolled PwPHD sample was composed of individuals aged ≥18 years with a family history of HD, who were either:
  - Premotor manifest HD: HD-prodromal (including perimanifest; Stage 2 – HD-Integrated Staging System [ISS]) OR HD-gene carriers (Stage 0/1 – HD-ISS)[10]
  - At-risk of HD
- Data for this study were collected between Q4 2024–Q3 2025 via 2 surveys: the PwPHD Survey (PS) and the Health Care Professional Survey (HCP-S)
  - The PS collected individual-level data on sociodemographic characteristics, HD-related resource utilization, symptom burden (including cognitive and behavioral symptoms experienced in the preceding 12 months, self-harm, and suicidal ideation), and health-related quality of life
    - In addition, the PS included validated questionnaires to assess anxiety and depression: the Overall Anxiety Severity and Impairment Scale (OASIS), a 5-item self-report measure for severity and impairment associated with anxiety disorders,[11] and the Overall Depression Severity and Impairment Scale (ODSIS), a 5-item self-reported measure of depressive symptoms and their effect on daily functioning[12]
  - The HCP-S, completed by HD specialist clinicians, assessed clinical profiles, healthcare utilization, early symptom recognition, and remaining unmet patient needs
- All analyses were descriptive, and no data imputation or hypothesis testing were performed
- The study was conducted under European Pharmaceutical Market Research Association/European Society for Opinion and Marketing Research standards, with electronic informed consent and study confirmed as exempt from ethics via Health Research Authority website

RESULTS

Results From the PwPHD

- The study sample included 153 individuals (Spain, n=36; Italy, n=33; USA, n=32; UK, n=26; France, n=24; Germany, n=2)
  - The sociodemographic characteristics of this group are outlined in **Table 1**

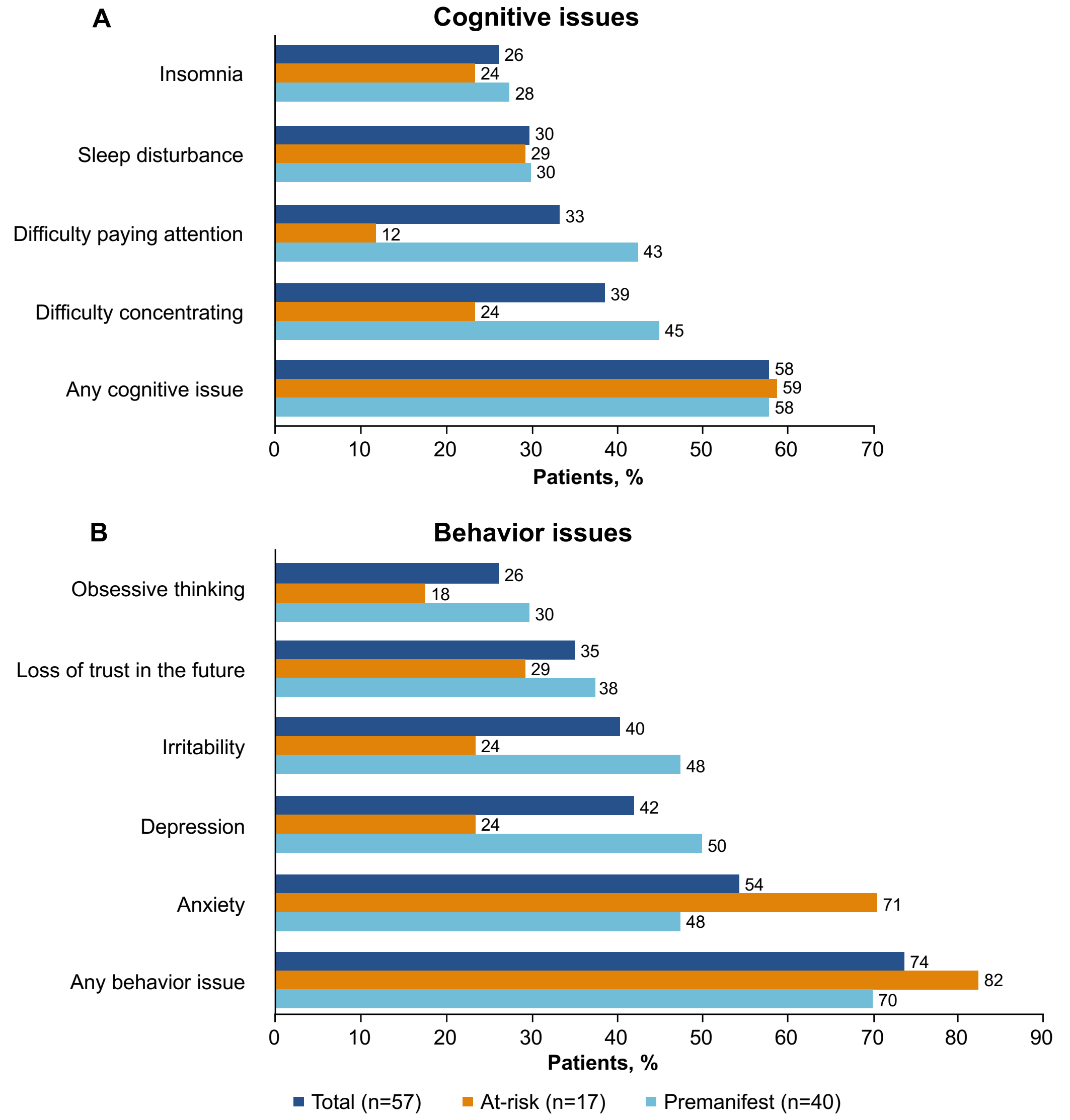
Table 1. PwPHD Sociodemographic Characteristics

Characteristic	Premanifest (n=90)	At-risk (n=63)	Total (N=153)
Age, mean (SD), y	39.5 (9.1)	33.3 (9.8)	37.0 (9.9)
Sex, female, n (%)	59 (65.6)	50 (79.4)	109 (71.2)
Ethnicity, n (%)			
White	83 (92.2)	55 (87.3)	138 (90.2)
Black	2 (2.2)	0 (0.0)	2 (1.3)
Asian	0 (0.0)	2 (3.2)	2 (1.3)
Other/prefer not to say	5 (5.5)	6 (9.5)	11 (7.2)
Employment status, n (%)			
Employed full time	62 (68.8)	38 (60.3)	100 (65.3)
Employed part time	10 (11.1)	3 (4.8)	13 (8.5)
Student	3 (3.3)	18 (28.5)	21 (13.7)
Retired/on sick leave	3 (3.3)	1 (1.6)	4 (2.6)
Homemaker/caregiver	5 (5.6)	0 (0.0)	5 (3.3)
Other[a]	7 (7.8)	3 (4.8)	10 (6.5)

PwPHD, patients with premotor manifest Huntington's disease.
[a]The employment query allowed for selection of "other" as an open text reply, and answers could not be summarized under the already existing categories.

- Among the 153 recruited PwPHD, 37% (n=57) reported ≥1 HD-related symptom within the prior year with 44.4% (n=40) premanifest and 27.0% (n=17) at-risk
- Cognitive issues affected 33/57 individuals (57.9% of those who reported ≥1 symptom; **Figure 1A**)
- Behavioral issues were common, affecting 42/57 individuals (73.7% of those who reported ≥1 symptom); among these, 28/42 (66.7%) were premanifest HD and 14/42 (33.3%) were at-risk individuals. Anxiety and depression were the most frequently reported behavioral symptoms in the last 12 months (**Figure 1B**)

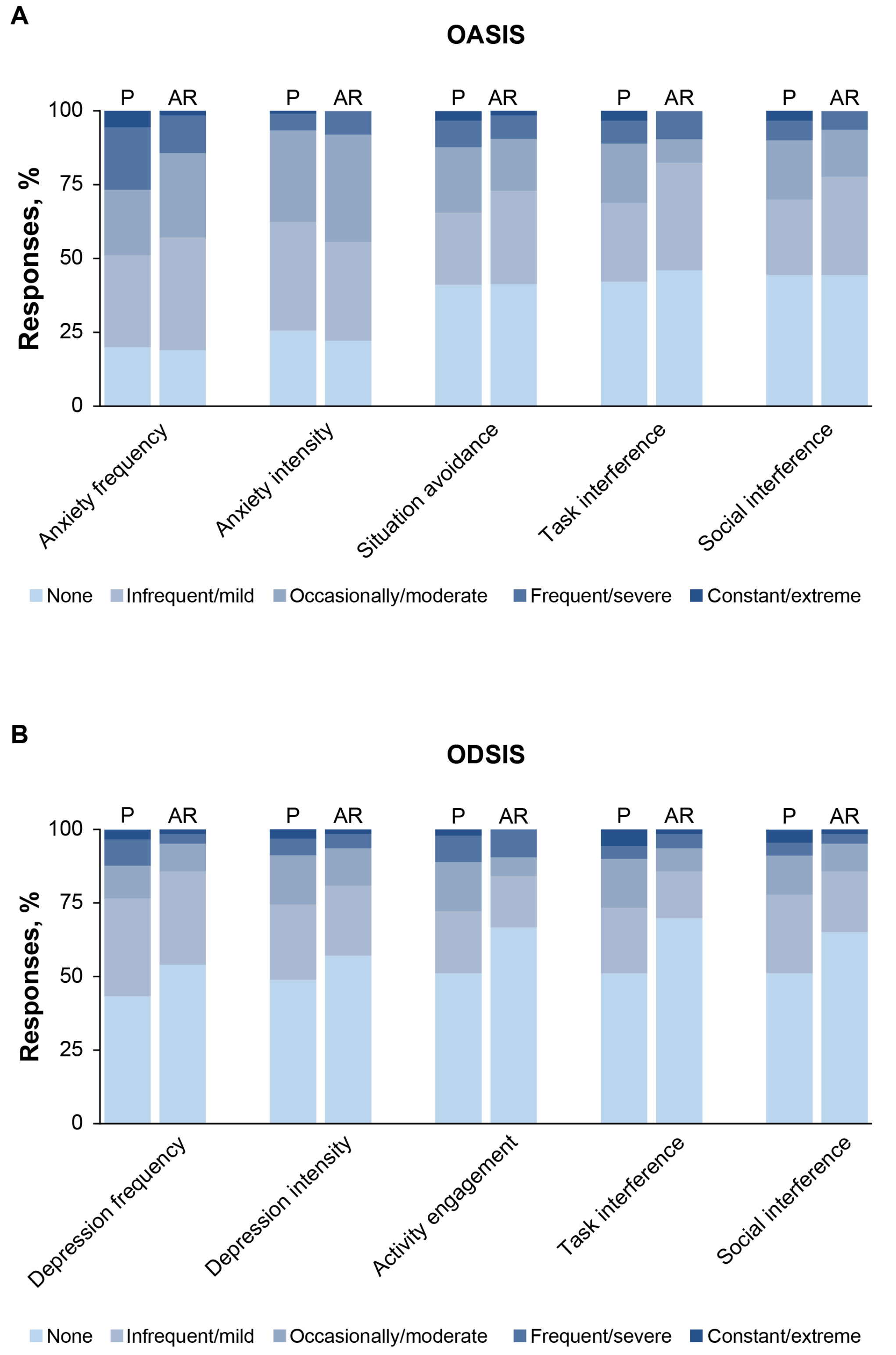
Figure 1. Overall Health Reported by PwPHD[a]



PwPHD, patients with premotor manifest Huntington's disease.
[a]Of those who reported medical issues in the last year only (n=57/153).

- Furthermore, the OASIS validated questionnaire indicated that most participants experienced occasional symptoms of anxiety (58.8%; n=90/153) of mild to moderate intensity (68.6%; n=104/153). PwPHD reported that these symptoms occasionally disrupted daily tasks for 74.5% of the sample (114/153 reporting mild interference), or social activities for 73.2% (112/153 reporting mild disruption; **Figure 2A**)
- With regard to depression, most participants indicated (via the validated ODSIS questionnaire) infrequent symptoms of depression (80.4%; n=123/153) of little to mild intensity (77.1%; n=118/153). PwPHD reported these symptoms as rarely interfering with daily tasks (78.4%; n=120/153 noted mild interference); however, some level of depression was present in a substantial proportion of the PwPHD sample (**Figure 2B**)

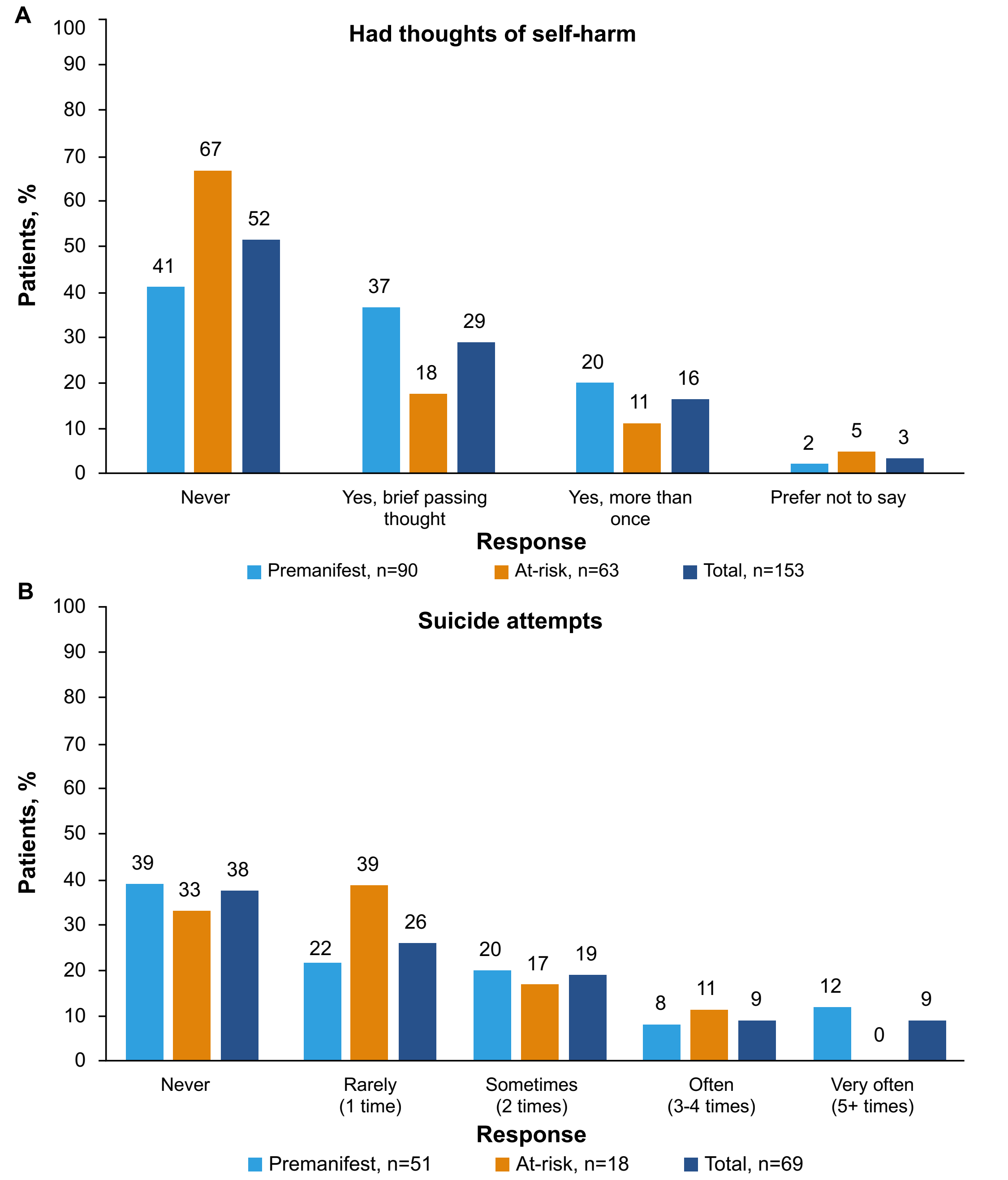
Figure 2. (A) OASIS Anxiety and (B) ODSIS Depression Questionnaire Results



PwPHD, patients with premotor manifest Huntington's disease.
AR, at-risk; OASIS, Overall Anxiety Severity and Impairment Scale; ODSIS, Overall Depression Severity and Impairment Scale; P, premanifest.

- Thoughts of self-harm were reported by 45% (n=69) of participants, ranging from occasional thoughts of self-harm to recurrent episodes, with higher prevalence in the premanifest subgroup compared with those at-risk (**Figure 3A**)
  - Of those reporting suicidal ideation, 62.3% (n=43/69) reported ≥1 prior suicide attempt, and 17.4% (n=12/69) reported frequent attempts of ≥3 times (**Figure 3B**)

Figure 3. Thoughts of (A) Self-Harm and (B) Suicidal Ideation Reported by PwPHD

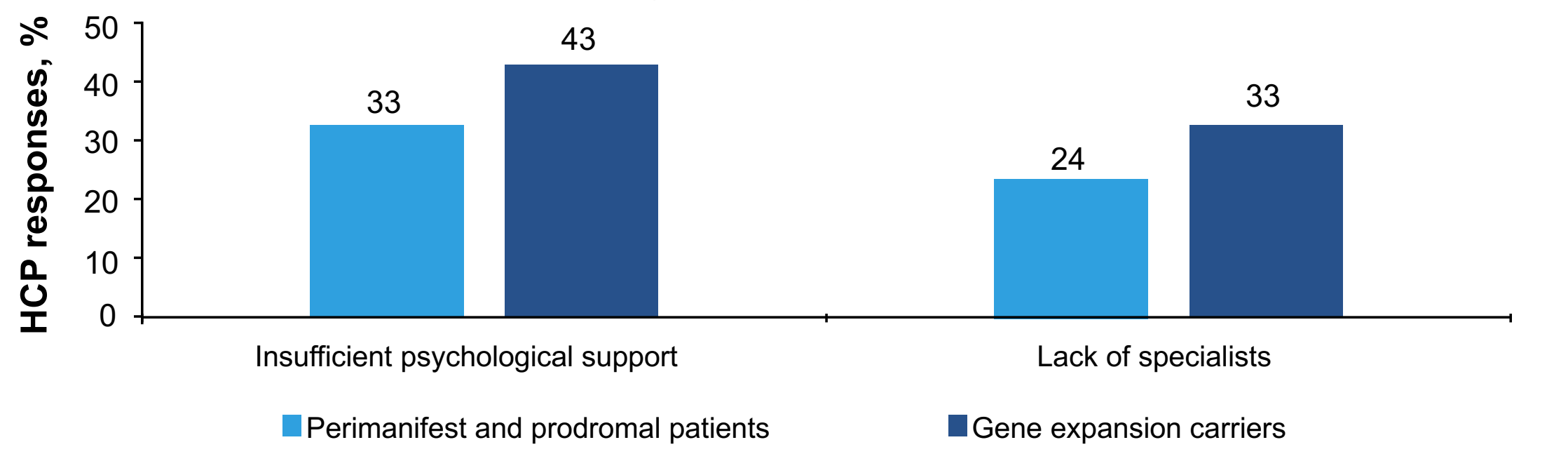


PwPHD, patients with premotor manifest Huntington's disease.

Results From the HCP group

- The HCP group included 21 individuals (Spain, n=5; UK, n=5; Italy, n=4; USA, n=3; France, n=2; Germany, n=2), of whom most were neurologists and psychiatrists, with 14 years' experience in managing HD, on average
- HCPs reported that, in their experience, ~60% of perimanifest patients, ~58% of prodromal patients, and ~73% of gene expansion carriers either did not recognize early symptoms or did not seek appropriate care for their symptoms
  - Among the 21 responding HCPs, suicidal ideation was reported as a behavioral issue by 1 (5%) for perimanifest patients, 3 (15%) for prodromal patients, and none for gene expansion carriers
- Key unmet needs identified by HCPs included insufficient access to psychological support (33% and 43%), and limited specialist resources (24% and 33%) for individuals in early disease stages (perimanifest/prodromal patients and gene expansion carriers, respectively; **Figure 4**)
- Patients were more likely to self-report psychological issues compared to the HCP sample, however clinicians did recognize a substantial need for further psychological support in this population, given the mental health burden noted in clinical practice

Figure 4. Key Unmet Needs for Premanifest Patients Identified by 21 HCPs



KEY TAKEAWAYS AND CONCLUSIONS

- Consistent with literature showing elevated suicide risk in HD populations, the high prevalence observed across at-risk and premanifest individuals in this cohort highlights substantial psychological burden prior to formal symptom manifestation or diagnosis, although direct comparisons with general population estimates are limited
- PwPHD experienced a substantial mental-health burden even before formal diagnosis; most notably, the at-risk group in this study reported higher levels of anxiety than the pre-manifest group[6,8,9]
- HCPs recognized several cognitive and behavioral symptoms among PwPHD/at-risk patients, including concentration difficulties, anxiety, and depression. However, their assessments may undercapture the full extent of patient-reported mental-health burden
  - Many patients in this study reported self-harm and/or suicidal ideation or attempts, yet very few HCPs reported observing suicidal ideation in their patients, suggesting the need for further research
- HCPs reported psychological support and specialist resources as key unmet needs
- These findings highlight critical unmet needs for PwPHD/at-risk patients. There is a demonstrated need to thoroughly screen for suicidality and related mental-health concerns to ensure appropriate identification and intervention are available for this vulnerable population

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DISCLOSURES

VB was an employee of uniQure at the time of this study and may own stock. **SL** and **BB** are employees of uniQure, and may hold stock and/or stock options. **HV** is a consultant for uniQure. **IRS** and **CM** are employees of Prime HCD, which received support from uniQure. **AA** has nothing to disclose.

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