

Dimension analysis of ENVISION study EQ-5D data to assess relationship between annualized attack rate and chronic symptoms in patients with acute hepatic porphyria

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Conclusions

- These results suggest that patients with AHP experience chronic symptoms, such as pain/discomfort or anxiety/depression, that are not associated with acute AHP attacks or predicted by historical AAR
- Expanding the definition of AAR to include less severe attacks did not meaningfully affect the results
- This analysis builds on earlier findings,^{1,4} and suggests that the chronic impact of AHP on HRQoL should be assessed regularly to guide treatment management decisions
- Additional research is needed to characterize disease burden in patients with lower historical AAR who, to date, have not been included in clinical trials

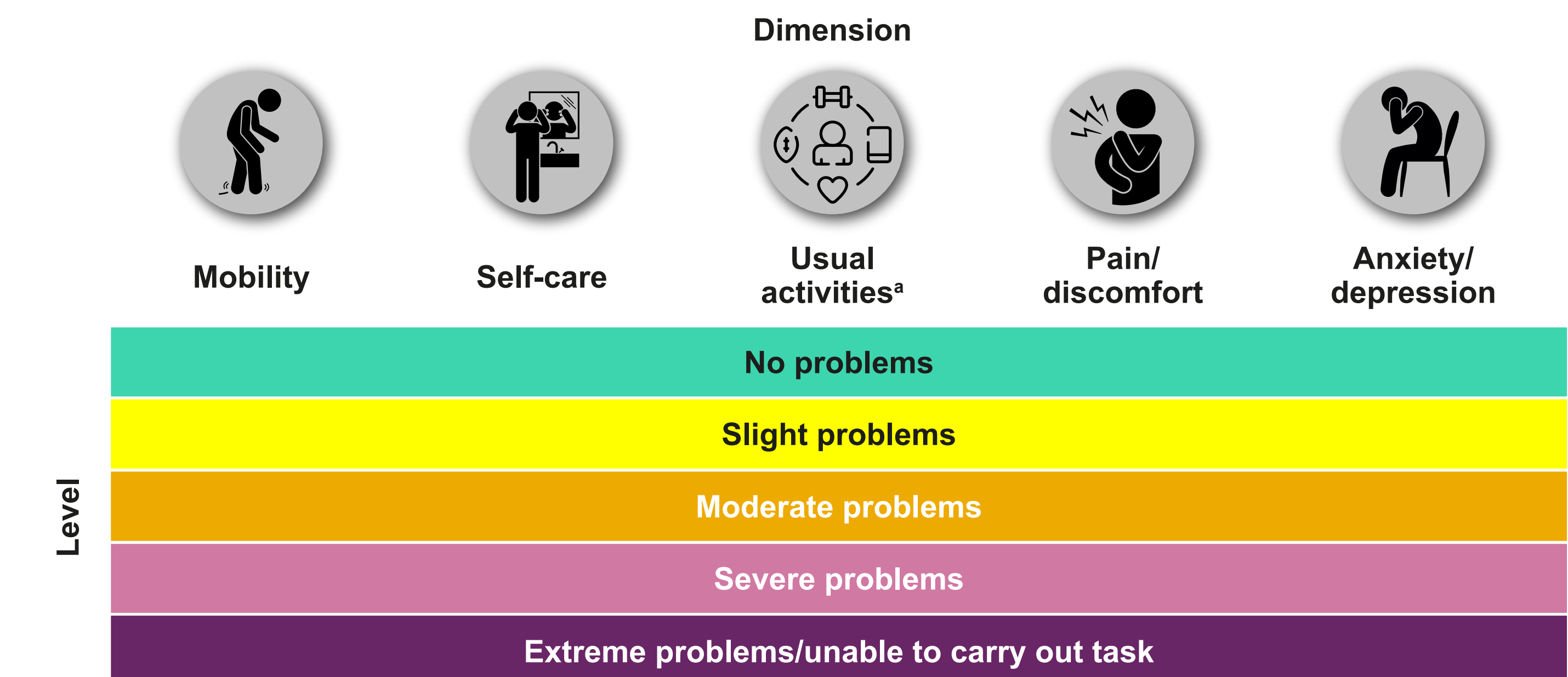
Introduction

- Acute hepatic porphyria (AHP) comprises a group of 4 rare, genetic, multisystemic disorders caused by defects in the heme biosynthesis pathway:⁵
 - acute intermittent porphyria (AIP)
 - hereditary coproporphyria (HCP)
 - variegate porphyria (VP)
 - δ-aminolevulinic acid dehydratase deficiency porphyria (ADP)
- Patients with AHP experience acute attacks, characterized by pain, neurological symptoms, and altered mental status⁵
 - In clinical studies,^{1,4,6} acute attacks were defined as attacks requiring hospitalization, urgent care, or intravenous hemin administration
 - AHP severity is typically defined by attack frequency via annualized attack rate (AAR)
- Data suggest that patients with AHP also have chronic symptoms that occur between acute attacks,^{7,8} which may contribute to overall symptom burden and health-related quality of life (HRQoL)
- ENVISION was a multicenter, randomized, double-blind, placebo-controlled, phase 3 study (NCT03338816) investigating the effects of givosiran in patients with AHP aged ≥12 years with a historical AAR ≥4^{1,2}
- Objective of this *post hoc* analysis is to examine the relationship between AAR and the burden of symptoms between attacks, using an expanded definition of AAR to better capture the full spectrum of disease severity

Methods

- Baseline was defined as the assessment period before randomization and givosiran dosing (day -60 to -1)
- At baseline, study participants completed the EQ-5D survey to describe their health on that day
 - EQ-5D:
 - Standardized questionnaire to evaluate HRQoL across 5 dimensions and severity levels (**Figure 1**)^{1,4,9,10}
 - Dimension scores are assumed to reflect chronic symptoms of AHP because it is unlikely that patients would be experiencing acute attacks during clinic visits when the questionnaire was administered
- Historical AAR was calculated based on number of attacks requiring hospitalization, urgent care, or hemin administration at home in the 6 months before randomization
 - This analysis used an expanded definition of AAR (eAAR) that also included:
 - attacks requiring a healthcare facility visit
 - attacks without hemin use at home
- Relationship between EQ-5D dimension level at baseline and historical eAAR was determined by Spearman correlation coefficients and logistic regression among a pooled population of patients from givosiran and placebo groups
- Data are reported descriptively; nominal *p* values are included for context

Figure 1. EQ-5D assessment system



^aThe usual activities dimension asks respondents to evaluate the severity of problems in carrying out their usual activities, such as work, study, housework, family, or leisure activities.

Results

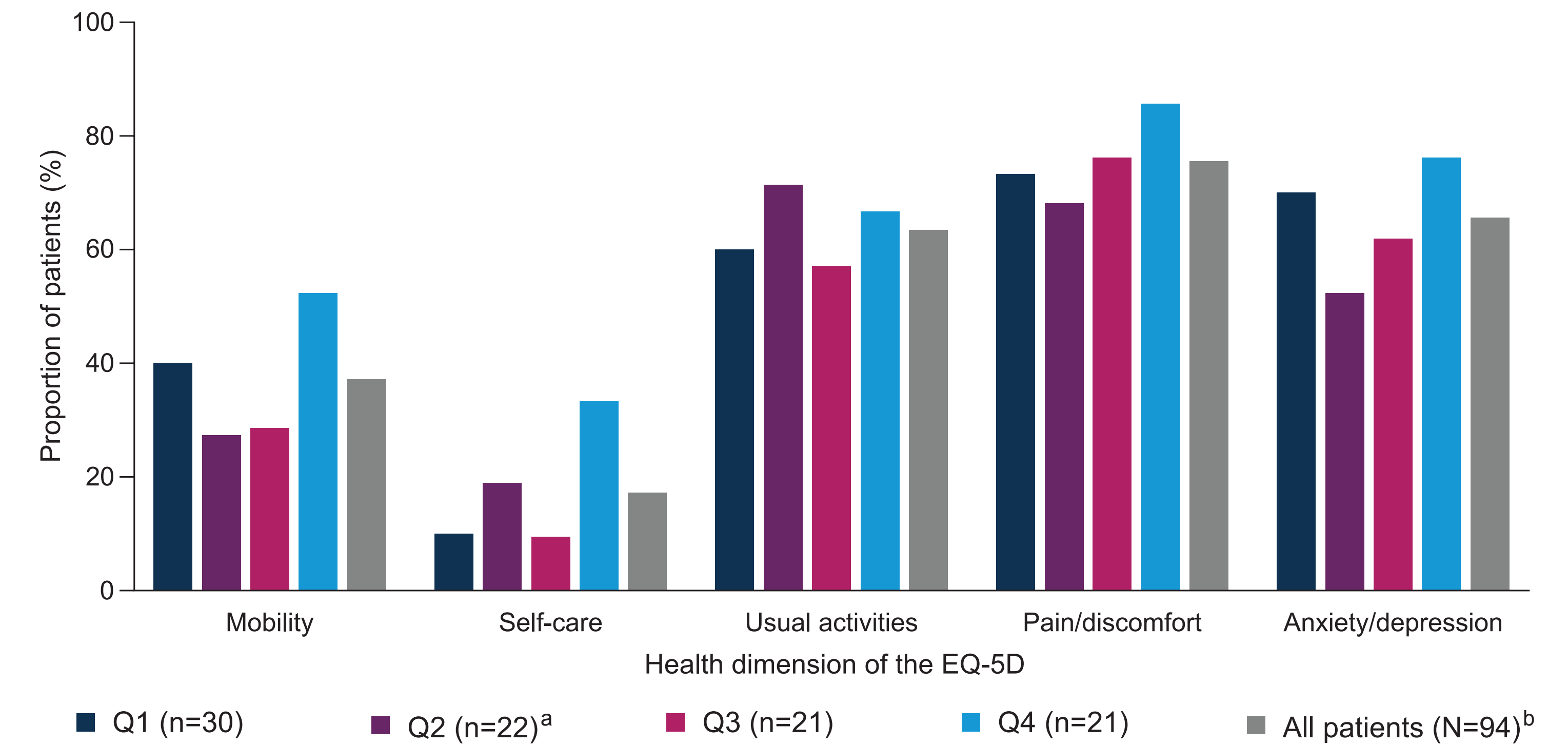
- 94 patients (89.4% [84/94] women) were enrolled and included in this analysis (**Table 1**)
 - Mean (standard deviation) age: 39 (11.4) years
 - Median (range) historical eAAR: 8 (4-50)
 - 52.1% of patients (49/94) reported prior chronic symptoms between attacks, defined as symptoms of porphyria when not having an attack daily or on most days before the study

Table 1. Demographics and clinical characteristics of patients stratified by historical eAAR quartiles

Characteristic/demographic	Q1 (n=30)	Q2 (n=22)	Q3 (n=21)	Q4 (n=21)	All patients (N=94)
Age at screening, years, mean (SD)	39.5 (11.8)	37.5 (11.6)	39.8 (12.1)	38.2 (10.4)	38.8 (11.4)
Female, n (%)	29 (96.7)	19 (86.4)	20 (95.2)	16 (76.2)	84 (89.4)
Years since diagnosis, median (range)	5.3 (0.2-35.5)	5.1 (0.1-38.5)	3.7 (1.1-43.3)	9.9 (0.7-31.3)	6.6 (0.1-43.3)
Historical eAAR, median (range)	4 (4-4)	6 (6-8)	12 (10-18)	24 (20-50)	8 (4-50)
History of hemin prophylaxis, n (%)	17 (56.7)	7 (31.8)	6 (28.6)	10 (47.6)	40 (42.6)
History of chronic symptoms between attacks, n (%)	12 (40.0)	14 (63.6)	13 (61.9)	10 (47.6)	49 (52.1)
Urinary ALA, ^{a,b} mmol/mol					
Mean (SD)	14.5 (9.5)	18.9 (18.8)	19.8 (10.5)	22.4 (16.3)	18.5 (14.1)
Range	0.7-36.8	2.2-88.9	3.3-42.7	6.0-82.0	0.7-88.9
Urinary PBG, ^{a,c} mmol/mol					
Mean (SD)	38.4 (25.3)	48.1 (34.4)	46.9 (23.0)	59.5 (34.3)	47.3 (29.9)
Range	0.4-96.1	11.0-150.0	0.4-106.5	8.9-147.2	0.4-150.0

^aNormalized to creatinine. ^bMedian ALA in healthy individuals: 0.46 mmol/mol. ^cMedian PBG in healthy individuals: 0.02 mmol/mol. ALA, δ-aminolevulinic acid; eAAR, expanded definition of annualized attack rate; N, total number of patients included; n, patients included per subgroup; PBG, porphobilinogen; Q, quartile; SD, standard deviation.

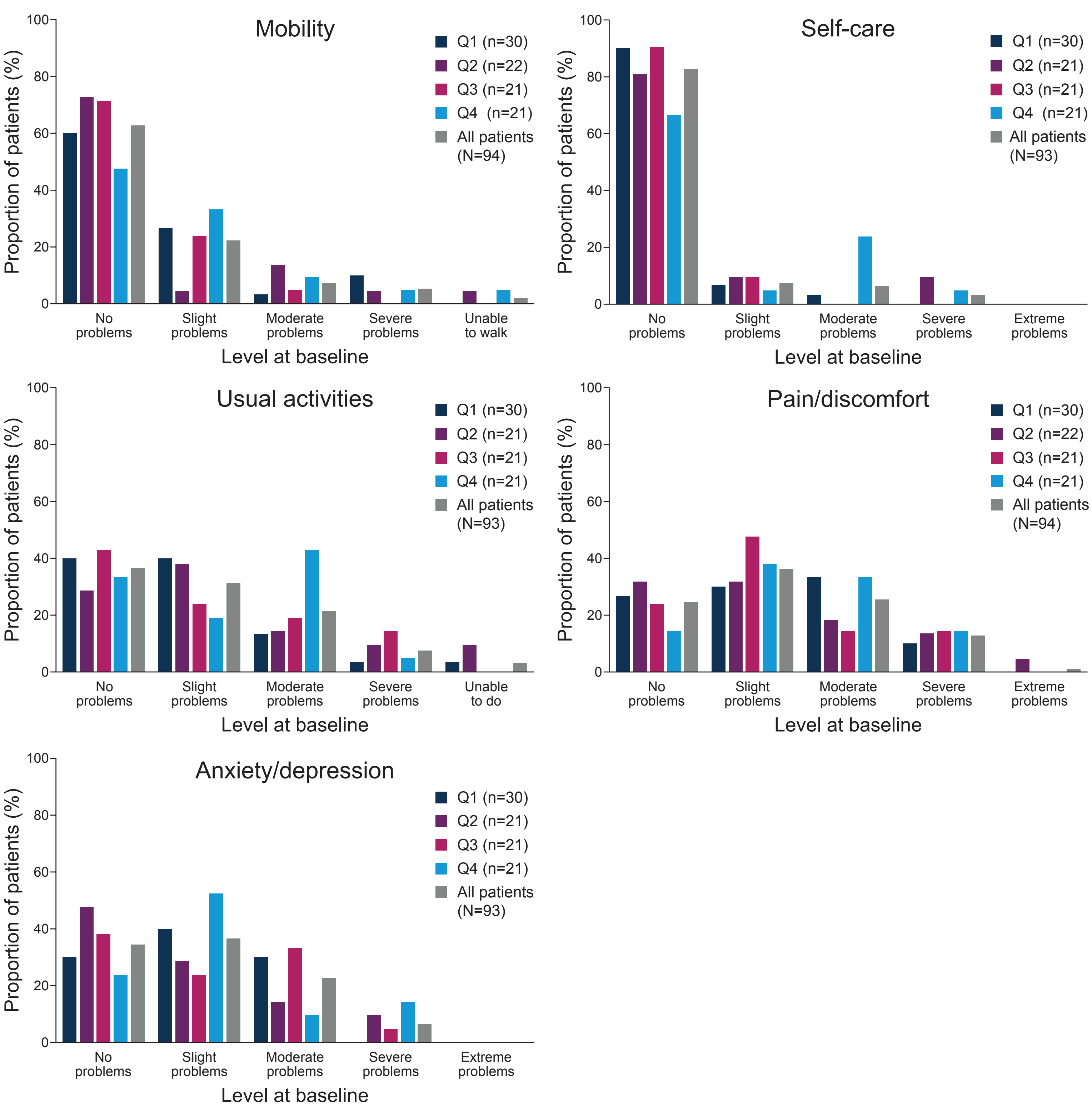
Figure 2. Proportion of patients reporting any problems in each EQ-5D dimension at baseline, stratified by historical eAAR quartiles



^an=21 in Q2 for self-care, usual activities, and anxiety/depression dimensions. ^bN=93 in 'all patients' for self-care, usual activities, and anxiety/depression dimensions. eAAR, expanded definition of annualized attack rate; N, total number of patients included; n, patients included per subgroup; Q, quartile.

- For each dimension, the proportion of patients reporting any problems (defined as 'slight problems' or worse [**Figure 1**]) was generally similar across eAAR quartiles (**Figure 2**)
 - Most frequently reported EQ-5D dimensions for which all patients reported any problems:
 - pain/discomfort (75.5% [71/94])
 - anxiety/depression (65.5% [61/93])
 - usual activities (63.4% [59/93])
 - Mobility (37.2% [35/94]) and self-care (17.2% [16/93]) problems were reported less frequently
- The proportion of patients reporting each level for each dimension was similar across historical eAAR quartiles (**Figure 3**)
- Apart from self-care (which showed a weak-moderate correlation of 0.2195), no consistent correlations were observed between EQ-5D dimension levels and historical eAAR (Spearman correlation coefficients ~0; nominal *p* values >0.05; **Table 2**)
- Apart from self-care (odds ratio [95% confidence interval] 1.06 [1.01-1.12]), there were no apparent differences in the odds of reporting a problem in any EQ-5D dimension as a function of historical eAAR (nominal *p* values >0.05; **Figure 4**)

Figure 3. Proportion of patients reporting each level of each individual EQ-5D dimension at baseline, stratified by historical eAAR quartiles



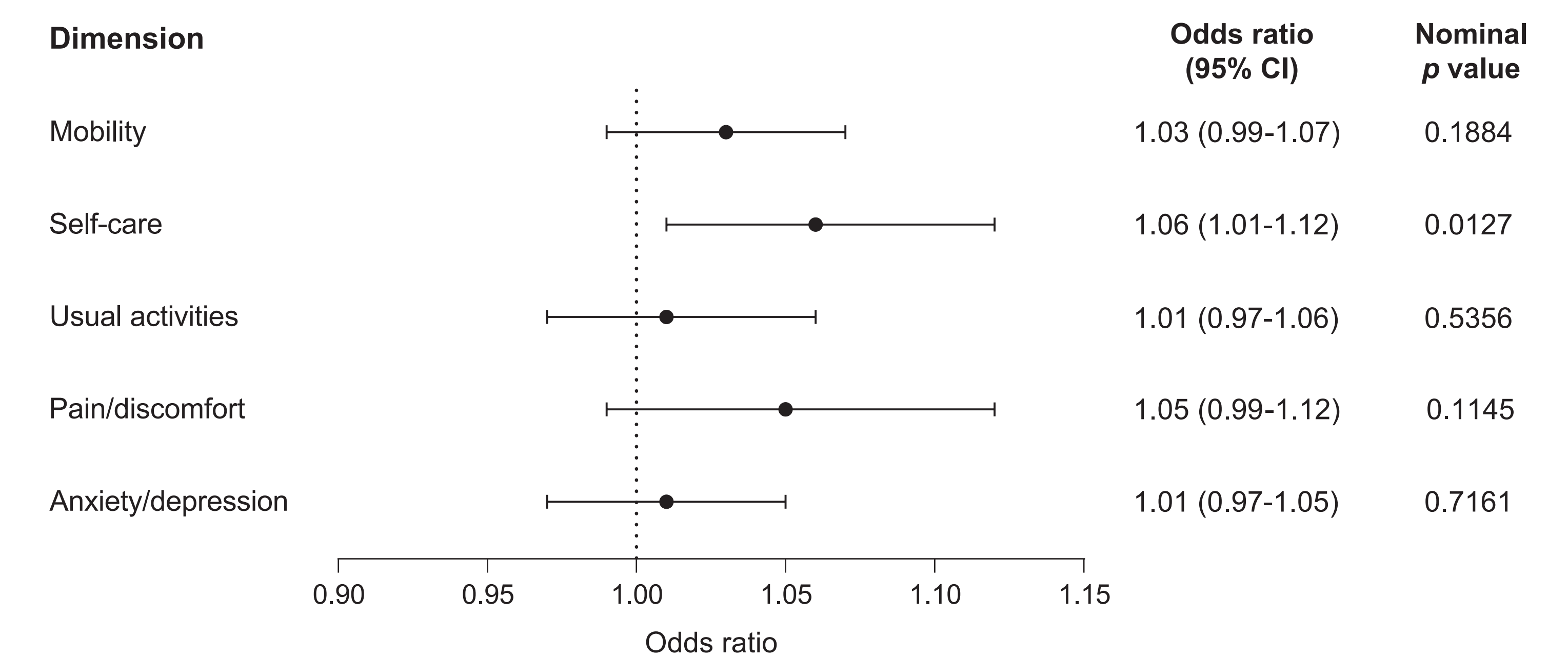
eAAR, expanded definition of annualized attack rate; N, total number of patients included; n, patients included per subgroup; Q, quartile.

Table 2. Analysis of the correlation between baseline EQ-5D dimension levels and historical eAAR

Dimension	Spearman correlation coefficient	Nominal <i>p</i> value
Mobility	0.0594	0.5696
Self-care	0.2195	0.0345
Usual activities	0.1067	0.3085
Pain/discomfort	0.0750	0.4725
Anxiety/depression	0.0412	0.6952

Individual dimension levels were coded as 1 (no problems), 2 (slight problems), 3 (moderate problems), 4 (severe problems), or 5 (extreme problems/unable to carry out task) for the Spearman correlation calculation. Spearman correlation coefficient can range from -1 to +1; values close to 0 indicate no relationship. eAAR, expanded definition of annualized attack rate.

Figure 4. Analysis of the relationship between historical eAAR^a and report of any problems across individual EQ-5D dimensions



^aEffect on odds ratios is per 1 unit increase in historical eAAR. Odds ratios, 95% CIs, and *p* values were calculated from a logistic regression model predicting individual EQ-5D levels of 2-5 (slight to extreme problems) vs level of 1 (no problems). CI, confidence interval; eAAR, expanded definition of annualized attack rate.

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