

Fatigue experience in individuals with sickle cell disease, thalassemia, and pyruvate kinase deficiency

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BACKGROUND

- Hereditary hemolytic anemias (HHAs), including sickle cell disease (SCD), thalassemia, and pyruvate kinase (PK) deficiency, are rare inherited hematologic disorders¹
- HHAs are characterized by the impairment of red blood cell health and function, leading to a wide range of symptoms, clinical complications, and reduced health-related quality of life (HRQoL)^{2–4}
- Fatigue is among the most frequently reported symptoms across SCD, thalassemia, and PK deficiency^{5–9}
- The Red Cell Revolution™ (RCR™) is an advisory council supported by Agios Pharmaceuticals, Inc., comprising members from the SCD, thalassemia, and PK deficiency communities¹⁰
 - Members include patients, caregivers, patient advocates, specialist clinicians, and Agios representatives
- An RCR™ initiative on unmet research needs in these HHAs identified physical fatigue and emotional fatigue as key factors with a substantial effect on HRQoL¹⁰; however, the full spectrum of patients' experiences of fatigue and its impacts on their lives are poorly understood
- The objective of this study was to explore the patient experience of physical, mental, and emotional fatigue across SCD, thalassemia, and PK deficiency

METHODS

Eligibility criteria

- Adults (≥18 years) with a clinician-confirmed diagnosis of SCD, α- or β-thalassemia, or PK deficiency, living in the United States
- Participants were excluded if they self-reported a clinical diagnosis of depression or hypothyroidism or were participating in an interventional clinical trial for their HHA
- All participants provided informed consent prior to taking part in the study, and they had the right to end their participation at any time

Recruitment

- Participants were recruited via the RCR™ and specialist recruitment agencies
- Recruitment was targeted to provide a diverse participant sample across a range of age groups and HHA indications
 - Targeted overall sample size was a maximum of N=60, n=20 for each HHA

Interview structure

- Interviews were conducted using an institutional review board-approved, semi-structured interview guide
- One-to-one interviews were conducted remotely by experienced qualitative researchers and lasted ~45 minutes
- Interviews explored participants' experiences of physical, mental, and emotional fatigue and their impacts

Data analysis

- Interviews were conducted between November 2024 and July 2025
- Transcripts were analyzed in ATLAS.ti using content analysis for concept elicitation^{11,12}
- Quantitative demographic, health, and fatigue impact data were summarized descriptively
- Ranking and saliency analyses identified the most bothersome types and impacts of fatigue
- Not all participants were asked every question; therefore, reported sample proportions include missing data and should not be interpreted as relative or representative frequencies

RESULTS*

Participants

- This analysis included data from 58 participants across the HHAs (**Table 1** and **Table 2**)
 - In the later stages of recruitment, planned targets for the HHA subgroups (age group and transfusion status) were relaxed due to the rarity of the conditions, in particular PK deficiency (**Table 1**)

Table 1. Participant sample summary

Indication (n recruited)	Age group, years			Total n (%)
	18–39	40–49	≥50	
SCD (20/20)	7	8	5	20 (100)
Thalassemia (20/20)				
Alpha	3	2	2	7 (35)
Beta, transfusion-dependent	3	2	3	8 (40)
Beta, non–transfusion-dependent	3	2	0	5 (25)
PK deficiency (18/20)				
Regularly transfused	4	0	3	7 (39)
Not regularly transfused	2	2	7	11 (61)
Total	22	16	20	58 (100)

PK, pyruvate kinase; SCD, sickle cell disease

Table 2. Self-reported participant demographics and health history

Demographics and health data	SCD n=20	Thalassemia n=20	PK deficiency n=18	Total N=58
Age at interview, years				
Mean (SD)	43.0 (12.3)	40.3 (9.5)	47.8 (15.5)	43.5 (12.7)
Median (range)	42.5 (19–72)	41.0 (20–55)	51.5 (20–74)	42.5 (19–74)
Sex at birth, n (%)				
Female	19 (95)	15 (75)	12 (67)	46 (79)
Race, n (%)^a				
Black or African American	19 (95)	0	0	19 (33)
White	0	7 (35)	18 (100)	25 (43)
Asian	0	9 (45)	0	9 (16)
Prefer not to say	1 (5)	0	0	1 (2)
Other	0	4 (20) ^b	0	4 (7)
Hispanic/Latino, n (%)				
No	18 (90)	19 (95)	15 (83)	52 (90)
Highest level of education completed, n (%)				
Graduate/postgraduate degree	4 (20)	6 (30)	4 (22)	14 (24)
Bachelor's degree	4 (20)	9 (45)	2 (11)	15 (26)
Associate's degree	1 (5)	1 (5)	5 (28)	7 (12)
Some college	8 (40)	2 (10)	1 (6)	11 (19)
High school diploma (or equivalent)	2 (10)	2 (10)	6 (33)	10 (17)
Some high school, but no diploma	1 (5)	0	0	1 (2)
Time since diagnosis, years				
Mean (SD)	40.6 (9.4)	31.2 (16.4)	43.4 (13.8)	38.2 (14.3)
Median (range)	42.0 (19–55)	32.0 (0–51)	48.5 (20–60)	41.5 (0–60)
Number of blood transfusions in the past 12 months				
Mean (SD)	3.0 (5.3)	8.5 (11.4)	6.0 (4.6)	5.8 (7.9)
Median (range)	0 (0–20)	4.0 (0–44)	4.0 (0–17)	3.5 (0–44)

^aRace was self-reported by participants. An open text field was included under the "Other race" option for participants to complete if they wished

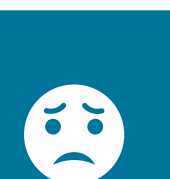
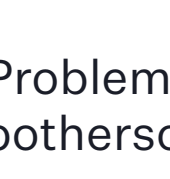
^bn=1 for each of: Asian and Black; Asian and White; Mediterranean; Multicultural. PK, pyruvate kinase; SCD, sickle cell disease; SD, standard deviation

Experience with fatigue

- All 58 participants reported experiencing fatigue
- Participants described fatigue as tiredness, which persisted despite sleep or rest, and was also commonly described as having low energy levels (eg, "weak," "drained") or feeling "exhausted" or "heavy"
- Across the three HHAs, participants ranked physical fatigue (n=31/54) as the most bothersome type, followed by mental fatigue (n=18/53) and emotional fatigue (n=9/49)^a
- The most frequently reported impacts of fatigue were on physical functioning (n=56/58), daily living (n=55/58), and work/education (n=54/58) (**Figure 1**)

^aDenominators represent the number of participants who ranked each fatigue type

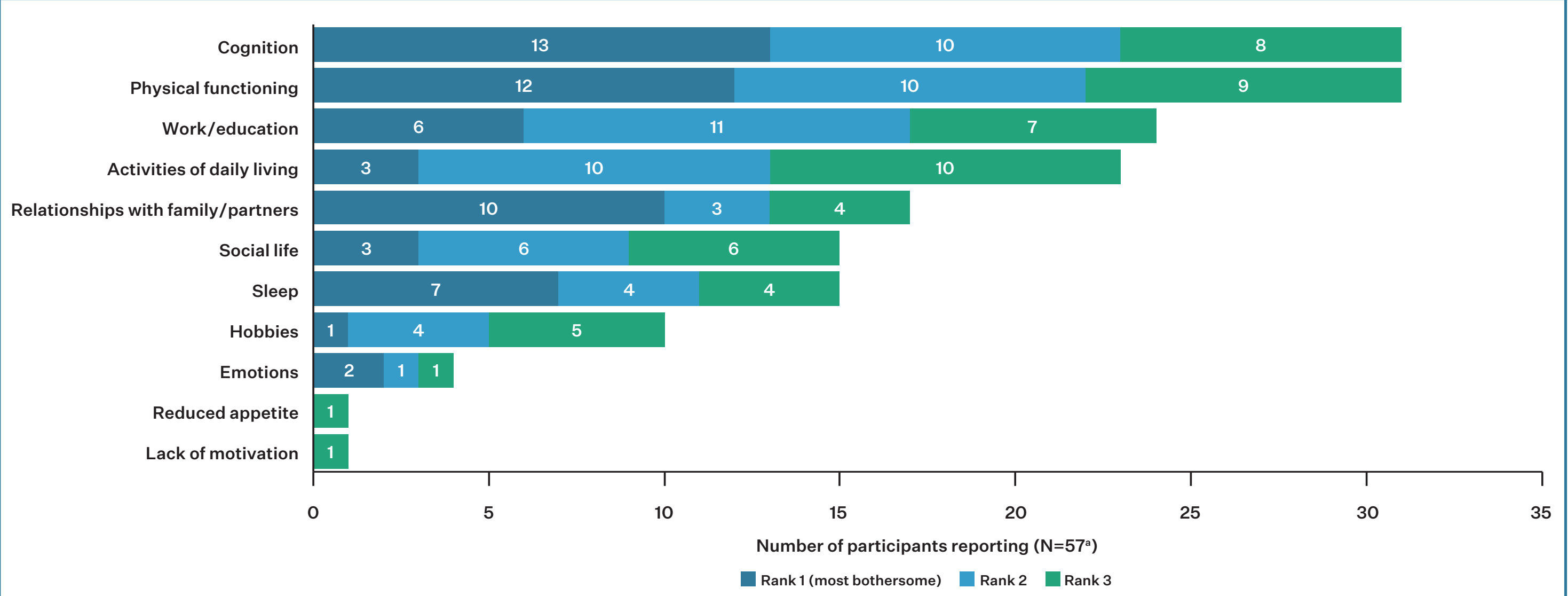
Figure 1. Reported frequency of the impacts of fatigue (N=58)

Impact	Examples of the negative impacts of fatigue	Illustrative quote
 Physical functioning (n=56)	Difficulty with exercising, walking, climbing stairs, lifting/carrying objects, and standing	"There's only so much I can do before I'm just... even on the treadmill, I can't do the running or the jogging. I have to do, like, a slow walk and even when I do that, my heart rate is, like, 150, 160, from a slow walk, which is crazy. And I'm watching the people around me, like, jog or run or – and it's just, like, it's, kind of, sad." (Participant with SCD)
 Activities of daily living (n=55)	Difficulty with household chores, cooking, hygiene routines, driving, and other general errands/tasks	"You know, I want to be able to take a shower and finish getting dressed without having to sit down and rest. It-it's very draining, you know. It's, like, um, if you have a cold or a flu, there's an end in sight. With this, there is no end in sight." (Participant with regularly transfused PK deficiency)
 Work and/or education (n=54)	Missed work, poorer performance or fewer hours at work, having to miss school, or being prevented from enrolling in college	"Um, definitely less productive, um, the more tired I am, um, and less motivated, honestly." (Participant with NTD β-thalassemia)
 Sleep (n=52)	Difficulty falling asleep, staying awake throughout the day, or staying asleep; partaking in frequent naps	"I'll wake up in the middle of the night and I can't get back to sleep. [...] I would say a couple of times a week I'm making – waking up in the middle of the night, and then having a hard time going back to sleep, and I don't know why." (Participant with not regularly transfused PK deficiency)
 Cognition (n=51)	Impacts on cognitive abilities/functions, such as memory, concentration, decision-making, verbal/written communication, and causing participants to experience brain fog	"Oh, my god. Err, just, it's been affecting – I've noticed in the past probably year, I've noticed my 'memory' really 'declining.' Um, and it-it's, kind of, scary 'cause I'm thinking I may need, um, probably a physician, to go see, like, some sort of whoever takes care of memory issues, but I'm, I'm wondering if it is due to the fatigue, like, a, kind of – I, I'm feeling right now, I'm feeling that it is, because I feel so fatigued that, you know, my mental clarity isn't quite there." (Participant with NTD β-thalassemia)
 Relationships and social life (n=50)	Disruption to relationships with friends, family, and romantic partners/spouses. Activities/events with family and friends were frequently disrupted; judgment or a lack of understanding from others was often experienced	"You know, maybe your family member has an event that they're doing, being a part of, and you have tickets to it and you just can't go because you're overtired. Or maybe you have a family member having a birthday party,, and you say you're going to go, but you get to that day and you're just too tired, or... you're having pain, and you can't go." (Participant with SCD)
 Emotions (n=46)	Negative/distressing emotions and emotional experiences, such as sadness/depression, anxiety, irritation/anger, frustration, lack of motivation, and embarrassment	"It can work on your mind, and it could either put you in a depression, it can make you want to give on – give up on life, you could be suicidal, too. It can make you want to just say, um, I don't want to say the words, like, well, I just want to die. So, that-that's what I mean 'mentally.'" (Participant with SCD)
 Hobbies (n=41)	Disruption of engagement in hobbies, including impacts on traveling, reading, learning languages, going on holidays/vacations, and arts and crafts	"I like to go outside. I'm really an outdoors guy. I like to go hiking, I like to, I like to go, I like to go bike riding, whether it be, like, on a trail or outside or, like, in the city. Um, all these things, 100%, can be affected, right, by, by the fatigue 'cause even if you have them planned, you're, you're so much more likely to bail on those plans because of the fatigue you feel." (Participant with TD β-thalassemia)

NTD, non-transfusion-dependent; PK, pyruvate kinase; SCD, sickle cell disease; TD, transfusion-dependent

- Problems with cognition and physical functioning were the impacts of fatigue most frequently ranked among the top three most bothersome by participants (both n=31/57) (**Figure 2**)
 - For cognition, these were primarily "brain fog," difficulties with concentration, and/or memory problems
 - For physical functioning, these were primarily unresolvable tiredness and/or feeling drained, weak, or exhausted

Figure 2. Most bothersome impacts of fatigue across HHAs¹³



*One participant with thalassemia did not complete the ranking exercise. HHA, hereditary hemolytic anemia

Triggers of fatigue

- The most frequently reported triggers of fatigue were exertion (n=14/58), inadequate rest (n=12/58), and exercise and work/education (both n=10/58)
 - Pain (eg, from vaso-occlusive crisis), temperature, and medication were almost exclusively reported as triggers of fatigue by participants with SCD

Fatigue management

- The most frequently reported strategies for the management of fatigue were resting (n=30/58), to keep going/push through (n=13/58), and taking naps (n=11/58)

Discussing fatigue with physicians

- Most participants had discussed their experience of fatigue with their physician (n=47/56)
 - Reasons for not discussing fatigue included feeling it was just part of their condition and that nothing could be done so it was not worth discussing
- Participants' experiences discussing fatigue with physicians were mixed (24 positive experiences, 16 negative)
 - Negative experiences included not feeling listened to or feeling like the physician did not take action to address the fatigue

Fatigue experiences across individual HHAs

- Participant-reported experiences of fatigue were generally aligned across all three HHAs; however, some slight differences were identified
- Many participants with SCD reported experiencing fatigue daily (n=10/17), whereas participants with PK deficiency reported unpredictability of "good and bad days" (n=7/8)
 - An equal proportion of participants with thalassemia reported fatigue as a daily experience (n=3/8) or as unpredictable (n=3/8)
- Notably, cognition impacts were most frequently ranked among the top three most bothersome impacts to participants with SCD (n=11/20) and PK deficiency (n=13/18), but physical functioning impacts were top three most bothersome to those in the thalassemia group (n=12/19)

Conceptual model

- A conceptual model representing the many impacts of fatigue across the HHAs was developed based on participant responses
- The model demonstrated reciprocal relationships, where fatigue impacted activities of daily living, which in turn exacerbated fatigue (**Supplemental Figure 1** via QR code)

CONCLUSIONS

- Fatigue is a complex, debilitating symptom experienced by those with SCD, thalassemia, and PK deficiency**
- In this study, participants with these conditions recognized and reported differing physical, mental, and emotional manifestations of fatigue**
- Although physical fatigue was identified as the most bothersome type, mental and emotional fatigue also contributed substantially to participants' overall fatigue burden**
 - These findings further characterize these often less well-described manifestations of mental and emotional fatigue in HHAs**
- The cognitive impacts of fatigue were considered among the most bothersome impacts, highlighting a previously under-recognized aspect of fatigue burden**

This study highlights the critical importance of raising awareness of the various manifestations and broad impacts of fatigue to better inform patient care across HHAs

*Some data included in this poster have been previously published (abstract only) by the European Hematology Association (EHA) 2026 Congress¹³

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References and author disclosure information are available via the QR code



Supplemental material and digital poster available via the QR code

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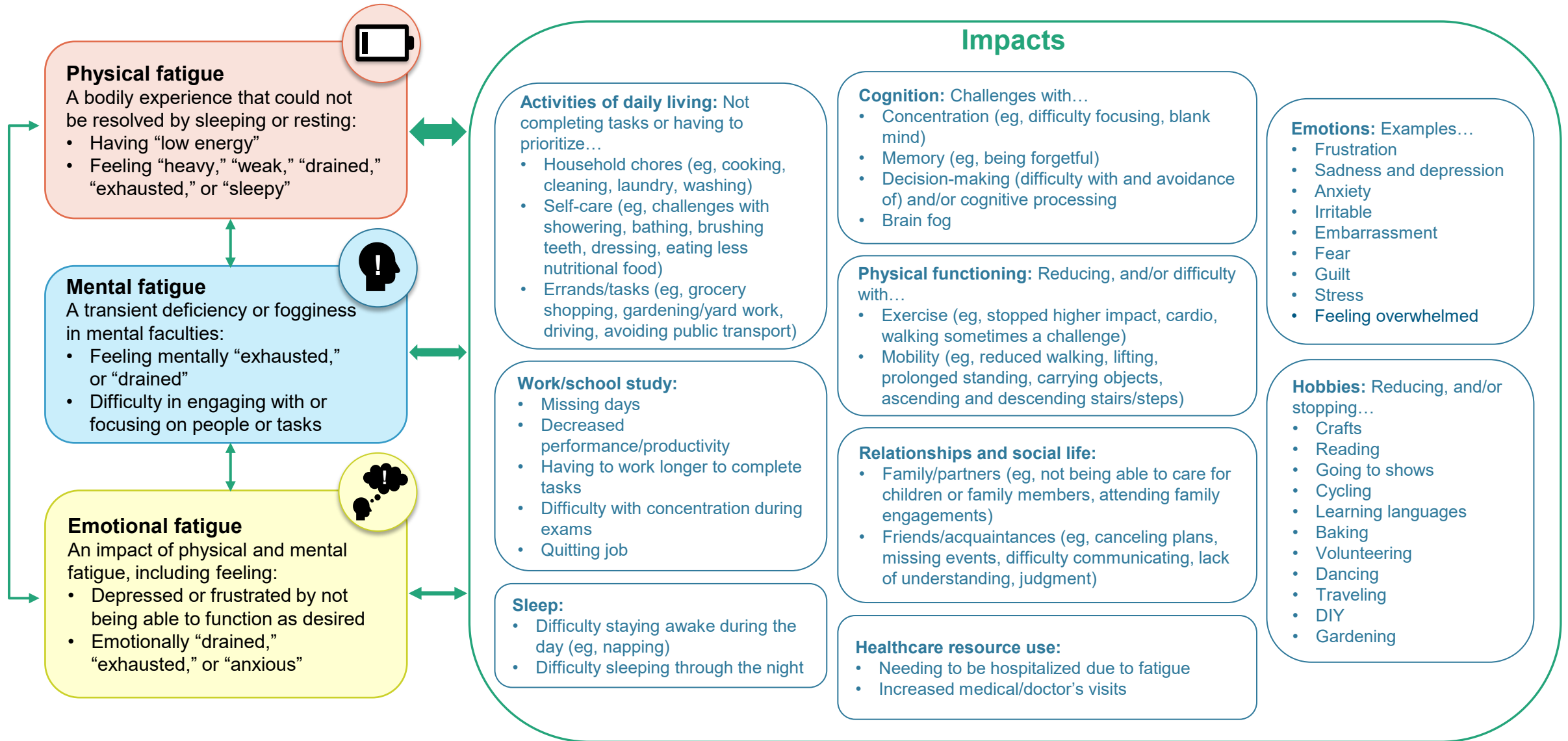
^aEmployee of Agios Pharmaceuticals, Inc. at time of research

Results

Conceptual model

- A conceptual model representing the many impacts of fatigue across the HHAs was developed based on participant responses
- The model demonstrated reciprocal relationships, where fatigue impacted activities of daily living, which in turn exacerbated fatigue (**Supplemental Figure 1**)

Supplemental Figure 1. Conceptual model of fatigue in HHAs



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