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Development of the Cold Agglutinin Disease Symptoms and Impact Questionnaire (CAD-SIQ)

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Abstract

Objectives: Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia. This study aimed to identify disease-related symptoms and impacts important to patients with CAD, and to develop a novel CAD-specific patient-reported outcome measure.

Methods: Adults with CAD were randomly selected from a United States patient panel to participate in concept elicitation (CE) interviews to identify important symptoms and impacts or cognitive debriefing (CD) interviews to assess the comprehension and relevance of the draft item set.

Results: Overall, 37 adults were included (mean [range] age 67.2 [35–87] years). In CE interviews ($n = 16$), the most frequently reported CAD-related symptoms were reactions to cold environments and fatigue (both 93.8%). CAD had negative impacts on enjoyable activities (81.3%) and daily activities (75.0%). Following CE, standard survey methodological principles were used to develop a draft item pool of 14 concepts. Items were refined through three iterative rounds of CD interviews ($n = 21$), yielding 11 final items: fatigue; cold sensitivity; dyspnea; wearing extra clothing; limited physical, social, and enjoyable activities; difficulty with usual activities; mood; frustration; and anxiety/stress.

Conclusions: The novel 11-item CAD-Symptoms and Impact Questionnaire provides a measure of the symptoms and impacts of CAD that are important to patients.

KEYWORDS

cold agglutinin disease, conceptual model, instrument development, patient interviews, patient-reported outcome

Novelty statements

What is the new aspect of your work?

This work describes the development of a novel patient-reported outcome (PRO) measure, the CAD-Symptoms and Impact Questionnaire (CAD-SIQ), which, to our knowledge, is the first PRO measure designed to assess the patient experience with CAD.

Presented in part at the Virtual 62nd American Society of Hematology (ASH) Annual Meeting and Exposition, December 5–8, 2020, and at the virtual 63rd ASH Annual Meeting and Exposition, December 11–14, 2021.

What is the central finding of your work?

CAD was found to negatively impact numerous aspects of participants' daily lives, with fatigue and reactions to cold environments reported as the most bothersome and important symptoms to treat. The 11-item CAD-SIQ provides a brief measure of the symptoms and impacts that are most important and relevant to patients with CAD.

What is (or could be) the specific clinical relevance of your work?

The CAD-SIQ has the potential for use in clinical practice and in observational studies to assess the status of patients. Furthermore, with additional work including psychometric evaluation, the CAD-SIQ may be suitable for use in clinical trials as an endpoint to better understand patients' experiences and to support the meaningfulness of changes in other efficacy endpoints.

1 | INTRODUCTION

Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia in which cold agglutinin immunoglobulin M autoantibodies bind to red blood cells, resulting in agglutination and complement-mediated hemolysis.[1] This process occurs during exposure to cold environments, but can also take place during the normal cooling of blood in the peripheral circulation.[1,2] CAD accounts for approximately 15%–25% of all autoimmune hemolytic anemia.[3] There is a lack of data from large population studies of CAD; however, recent studies indicate a prevalence of 10–20.5 per million and an incidence of 1.8–1.9 per million in Northern European countries.[4–6]

In addition to cold-induced circulatory symptoms, patients with CAD experience a variety of symptoms due to chronic anemia and hemolysis (including fatigue, weakness, and shortness of breath), and are at an increased risk of thrombotic events, hospitalization, and early mortality.[2,5,7–9] Management of CAD includes lifestyle modifications, red blood cell transfusions, and supportive care, such as erythropoietin and folic acid supplementation.[3,10] Sutimlimab (Enjaymo; Sanofi) is a classical complement inhibitor indicated for the treatment of hemolysis in adults with CAD, and is the first treatment approved by the United States Food and Drug Administration for adult patients with CAD.[11,12]

There is limited knowledge of the patient experience with CAD and its impact on their lives. In addition, there is a lack of existing disease-specific patient-reported outcome (PRO) measures to assess the symptoms and disease impact of CAD and that are appropriate for clinical practice and use in clinical trials or observational studies of patients with CAD.[13] Therefore, the objectives of this study were first to identify disease-related symptoms and impacts that are most important to patients with CAD and to better understand the patient experience with CAD; and second, to develop a novel CAD-specific PRO measure that can be further evaluated in future studies.

2 | METHODS

2.1 | Study design

This qualitative study was conducted in the United States between February 2020 and March 2021, comprising several phases (Figure S1). A targeted literature and instrument review revealed a lack of existing fit-for-purpose measures[13]; thus, concept elicitation (CE) interviews were conducted to identify the key symptoms and impacts of CAD and to better understand CAD and its treatment from the patient perspective. A new item set for a CAD-specific PRO measure was developed based on concepts identified in the CE interviews and the literature. Cognitive debriefing (CD) interviews were then conducted during which the content validity of the item set was evaluated, and the items were refined and modified to finalize a new PRO measure.

2.2 | Interview participants

All interview participants were recruited from Sanofi's proprietary patient panel (CAD Patient Panel) of approximately 1250 patients and caregivers of patients with CAD in the United States. Panel participants were recruited from a variety of sources, including clinician referrals, advocacy groups, and web-based surveys. One half of the panel was invited to participate in an initial round of CE interviews, while the other half was invited to participate in a second round of interviews, including an abbreviated CE section and CD.

For each sample, a number (*n*) was chosen to select every nth person from each of the four United States census regions (Northeast, Midwest, West, South) to receive an email invitation to participate in the study. This process was replicated every 3–4 business days until all sample members had been sent an e-mail and invited to participate or until the sample was met.

Individuals interested in participating in the study completed a screening questionnaire to determine their eligibility. Eligible interview participants were ≥18 years of age with a self-reported diagnosis of CAD (primary CAD) or cold agglutinin syndrome (formerly known as secondary CAD; diagnosis based on an underlying condition, such as an infection, another autoimmune disease, or current/active lymphoma[10,14]). All interview participants were required to be able to read, speak, and understand English and be willing and able to participate in a 60-min telephone interview/web conference. Caregivers of people with CAD were not eligible to participate in the interviews.

2.3 | Informed consent and ethical approval

The study was conducted in accordance with the International Conference on Harmonisation (2016) Guideline for Good Clinical Practice and local regulatory requirements and laws. All interview participants provided verbal informed consent before interviews were conducted.

2.4 | CE interviews

CE interviews are used to identify or generate concepts of importance to a population of interest or content for a new measure. In the current study, the initial CE interviews were designed to collect concepts (i.e., symptoms and impacts) that were relevant and important to people with CAD. All interviews were conducted by two experienced researchers, using a semi-structured interview guide to ensure consistency while maintaining a conversational tone and encouraging spontaneity of answers.

At the beginning of each interview, participants were asked open-ended questions about their experiences with CAD and its treatment. These were followed by targeted questions designed to ensure that potential concepts of interest were captured if not raised spontaneously. Participants were also asked to provide feedback on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) subscale; data from this part of the study have been published in part elsewhere.[15]

Interviews were recorded and transcribed, with all personally identifiable information removed from the transcripts. Participants were compensated for their time and effort in taking part in the interviews.

2.5 | Development of the CAD-Symptoms and Impact Questionnaire (CAD-SIQ)

A novel item set for CAD was developed in accordance with best practice,[16–19] based on the concepts identified in the first round of CE interviews and a previously conducted targeted literature and instrument review (published elsewhere).[13] Standard survey methodological principles were used to develop the draft item pool to address concepts of interest based on the symptoms and impacts identified as important to interview participants. Development of these items was guided by the following principles: items worded succinctly to facilitate response; number of items limited to minimize patient burden; items have potential to change over time with effective treatment; items naturally related to the response options; item concepts are generalizable across the target population and to people with varying clinical presentations of the disease; and items use a short recall period to facilitate accurate recall (when appropriate). The wording of items reflected the terminology used by participants.

Multiple items were developed for each concept to allow testing and refinement of variable question wording by CD. The draft item pool was reviewed by external experts prior to testing.

2.6 | CD interviews

CD is the process of determining if items in a measure are relevant to the population of interest, as well as clear and easy to understand. The same researchers conducted three iterative rounds of CD interviews that began with a brief CE phase, followed by CD of the draft item pool. The goals of each round of interviews were to evaluate the content validity of the draft items, identify any problems with item wording or response options, and refine the draft items as needed. Subsequent rounds of interviews tested the adequacy of any modifications based on the previous round of interviews and informed any further revisions required to optimize the items. Poorer-performing items were removed, and respondent feedback guided the selection of items for revision and development of new items.

In each round, participants received a copy of the draft items, and the items were also displayed via web during the interview. During the interview, participants were asked to respond verbally to each item, give their thoughts on the items overall, and describe their thought processes when responding to the items. Interviewers also probed to better understand how participants interpreted and selected an answer for each item. Responses for each item were assessed on a verbal response scale (five response options: not at all, a little bit, somewhat, quite a bit, very much) covering a 7-day recall period.

Interviews again were recorded and transcribed, with all personally identifiable information removed from transcripts. Participants were compensated for their time and effort in taking part in the interviews.

2.7 | Conceptual model development

A conceptual model of the symptoms and impacts of CAD was developed using pooled data from both rounds of CE interviews.

2.8 | Data analysis

Interviewer field notes, transcripts, and qualitative analysis software (ATLAS-ti 7.5 or higher) were used to identify trends across all interviews to generate themes or patterns in the way participants described their experiences with CAD and to summarize the CD results.

3 | RESULTS

3.1 | Participants

A total of 37 participants took part in the interviews (CE interviews, $n = 16$; CD interviews, $n = 21$). Baseline characteristics of the overall interview sample are presented in Table 1. Mean (range) age was 67.2

TABLE 1 Characteristics of study participants.

	Total participants ($N = 37$)
Age, years, mean (range)	67.2 (35–87)
Sex, *n* (%)	
Male	10 (27.0)
Female	27 (73.0)
Race/ethnicity, *n* (%)	
White	36 (97.3)
Mixed	1 (2.7)
Education, *n* (%)	
High school or GED	1 (2.7)
Technical or associate degree	4 (10.8)
Some college	4 (10.8)
College degree	13 (35.1)
Professional degree	15 (40.5)
Employment status, *n* (%)	
Full-time	11 (29.7)
Part-time	3 (8.1)
Not employed/retired	22 (59.5)
Disability	1 (2.7)
Residence, *n* (%)	
Northeast	8 (21.6)
Midwest	9 (24.3)
South	9 (24.3)
West	11 (29.7)
Disease type, *n* (%)	
CAD	30 (81.1)
CAS	7 (18.9)

Abbreviations: CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; GED, general education department.

(35–87) years, most participants were female (73.0%) and White (97.3%), and the sample was geographically diverse. Most participants (81.1%) had a diagnosis of primary CAD and, on average, had been diagnosed with CAD approximately 6.5 years before the interview (range: 4 months to 42 years). Approximately 40.0% of the sample were employed at the time of the interview.

3.2 | Symptoms of CAD reported in CE interviews

The most frequently reported symptoms of CAD from the initial CE interviews ($n = 16$) were reactions to cold environments ($n = 15$; 93.8%; e.g., cold or numb feet/hands, skin discoloration, muscle aches, and headaches) and fatigue ($n = 15$; 93.8%), described as fatigue, tiredness, or lack of energy (Figure 1). Participant quotes describing frequently reported symptoms are shown in Table 2.

Most participants ($n = 12/15$; 80%) with fatigue reported that they experienced it daily, 46.7% ($n = 7/15$) reported that their fatigue was worse during colder months, and 33.3% participants ($n = 5/15$) reported that it was worse after physical exertion. At the time of the interview, six participants reported that they were quite bothered by their CAD-related fatigue (on a 5-point scale ranging from "not at all bothered" to "extremely bothered"); six were a little bothered; and three were somewhat bothered. No participant stated that they were extremely bothered by their fatigue.

Other frequently reported symptoms (Figure 1) included breathlessness ($n = 11$; 68.8%), difficulties thinking/concentrating ($n = 11$; 68.8%), and sleep disturbance ($n = 7$; 43.8%). Less common symptoms of CAD included weakness, dark urine, sweating, dizziness, headaches, leg pain/cramps, ringing in the ears, and bruising (Figure 1).

3.3 | Impacts of CAD reported in CE interviews

Most participants ($n = 13$; 81.3%) reported that they had given up or limited activities they enjoy due to their symptoms, including outdoor activities (e.g., gardening, participating in leisure activities like swimming or skiing) and socializing with family and friends (Figure 2). Other frequently reported unfavorable impacts of CAD were on day-to-day activities ($n = 12$; 75.0%) such as housework and chores; physical health/activities ($n = 11$; 68.8%) such as ability to exercise; and social/leisure life and relationships ($n = 11$; 68.8%) such as interacting with family and/or friends and hobbies. More than half of participants reported a negative impact of CAD on their ability to start or finish tasks ($n = 10$; 62.5%), concentration/memory ($n = 10$; 62.5%), and moods/emotions ($n = 9$; 56.3%) (Figure 2). Participant quotes describing frequently reported impacts are shown in Table 2.

The majority of participants ($n = 11$; 68.8%) reported that they had made lifestyle/behavioral changes to help limit their CAD symptoms, such as wearing extra clothing in places where they might be cold, stop working, restricting travel, or changing retirement plans. All participants ($n = 16$) reported that their CAD-related fatigue and reactions to cold environments were among their most bothersome and/or most important symptoms to treat. Participant quotes describing desired outcomes from treatment are shown in Table 2.

3.4 | Development and testing of the CAD-SIQ

Fourteen concepts identified from the initial CE interviews were used to develop a draft item pool (Table S1). Draft items were evaluated and tested as part of the CD interviews in three iterative rounds of interviews (Round 1: $n = 8$; Round 2: $n = 7$; and Round 3: $n = 6$).

3.5 | CD interviews

Results from the brief CE phase of the CD interviews were largely consistent with those from the initial round of CE interviews. The most frequently reported symptoms included reactions to cold environments ($n = 21$; 100.0%), fatigue/tiredness/lack of stamina or energy ($n = 20$; 95.2%), and breathlessness ($n = 17$; 81.0%). Most

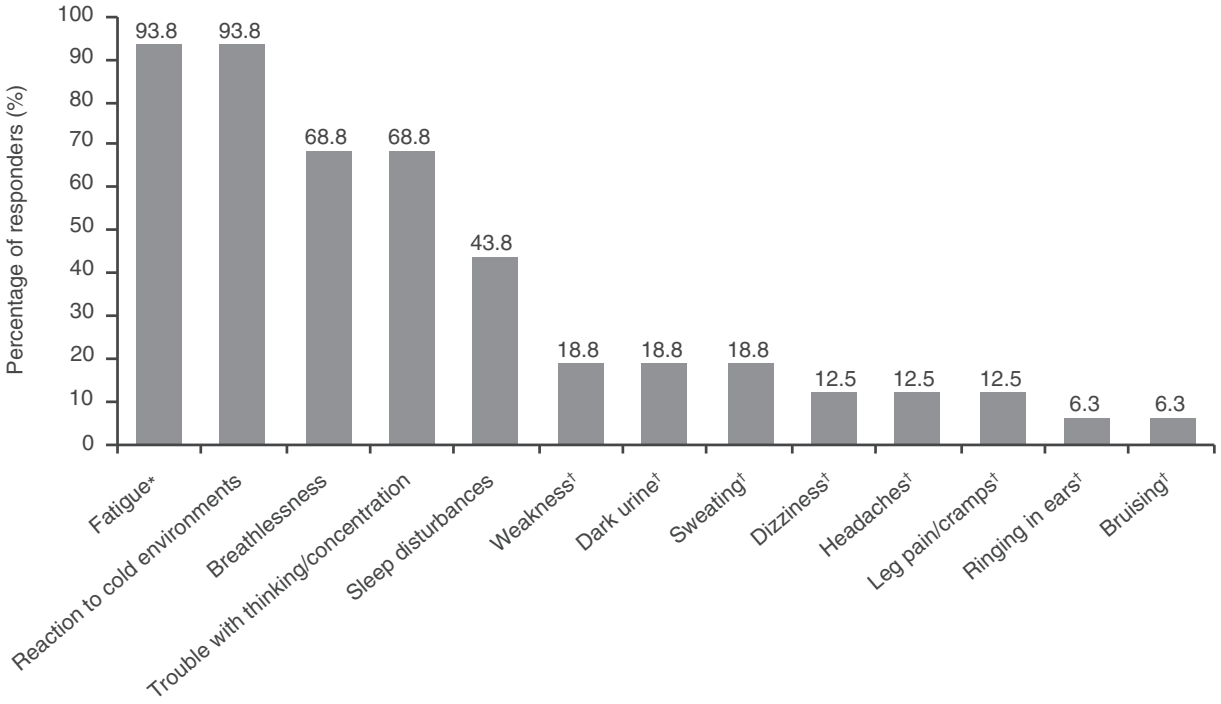

FIGURE 1 Participant-reported symptoms of CAD ($N = 16$). *Described by participants as fatigue, tiredness, and lack of energy. †These symptoms were spontaneously reported by participants and not uniformly probed. CAD, cold agglutinin disease.

participants reported that they wear extra clothing because of CAD ($n = 19$; 90.5%) and that having CAD had an impact on their physical activities ($n = 17$; 81.0%). Many participants reported they have given up or limited activities they enjoy because of CAD ($n = 16$; 76.2%). Fatigue ($n = 10$; 47.6%) and reactions to cold environments ($n = 7$; 33.3%) were reported as the most bothersome aspects of CAD; three participants (14.3%) reported that a lack of cure bothers them the most.

During the CD phase of the interviews, participants provided feedback on their interpretation and understanding of the instructions, questions, and response options, as well as on the relevance and importance of the concept captured by each item. All participants ($n = 21$) reported that the instructions text was clear and easy to understand and interpreted the text consistently and as intended. All participants reported that the verbal response scale was clear and easy to use, that they found the five response options to be distinct from each other, and that the 7-day recall period was easy to apply. No modifications to these elements were made during the interviews.

The draft items tested in each round of interview and the rationale behind any modifications are presented in Supplementary data Table S1. Items relating to difficulty concentrating, difficulty with memory, and sleep disturbance were deleted after Round 1 due to low endorsement or lack of association with CAD. Six of 15 participants who took part in the first two rounds of interviews considered things other than CAD in their responses. Thus, for uniformity across the impact items, the phrase, "because of CAD," was added to all impact items after Round 2 and tested in Round 3. No additional concepts for inclusion in the draft item set were endorsed by the majority of participants. Two participants suggested adding dark urine and one participant each suggested adding pain and nausea, all of which are associated with reactions to cold environments. However, these items were not added to the draft item set given their low frequency of reporting by participants. Furthermore, these additional symptoms are captured in the sensitivity to cold temperatures item.

The CD resulted in a final set of 11 items for the CAD-SIQ, relating to: fatigue; cold sensitivity; dyspnea; wearing extra clothing; limited physical, social, and enjoyable activities; difficulty with usual activities; mood; frustration; and anxiety/stress.

Participants generally found the final 11-item questionnaire to be comprehensive of their experiences with CAD, easy to understand, and simple to answer. They also reported that it was easy to recall symptoms and impacts they had experienced over the last 7 days. Participants indicated that the concepts in the questionnaire of most importance to them were reactions to cold environments ($n = 12$), fatigue ($n = 8$), physical activity ($n = 8$), enjoyed activities ($n = 6$), wearing extra clothing ($n = 5$), and usual and social activities (both $n = 5$). While some participants noted that certain concepts were not as relevant to them as others (e.g., shortness of breath), nearly all participants reported that the concepts included in the final item set would be relevant to gain a better understanding of individuals' experiences with CAD.

3.6 | Conceptual model

Based on data from both rounds of CE interviews ($n = 37$), a conceptual model of the symptoms and impacts of CAD was developed

TABLE 2 Participant quotes from CE interviews describing frequently reported symptoms and impacts of CAD and desired outcomes from treatment.

	Example participant quotes
Symptoms of CAD	
Fatigue	"I really feel like I could take a nap…if I close my eyes, I'm going to fall asleep…that's the fatigue. I just want to sleep" "I have no energy. I try to get things done, and I just end up having to take a nap before I get done with what I wanted to do. I can't finish chores and things like that" "I [have] a low energy level from the moment I get up…if I'm doing something around the house. or if I'm working so to speak, I have to try to limit myself to half a day because then I'm just physically and mentally wore out"
Reaction to cold environments	"If the water's colder than 70 [degrees], my hands will get really red and look bluish almost" "…during the fall and winter and early spring, I cannot be outside for prolonged periods of time…my hands turn purple, and now my face turns purple also. The longer I am out, the more it spreads, and then it becomes painful. It's pretty much a daily occurrence for me" "I have the extreme feeling [of] cold, [and I'm] tired, very tired and weak"
Breathlessness	"It's like I can't catch my breath when it's really cold. It's like your breath is taken away, it's so weird" "If it's 45 degrees outside, I feel like it's hard for me to breath"
Trouble with thinking/ concentration	"[I have trouble with] not being able to remember a name of something…" "Lately, I've had a little trouble with concentration"
Impacts of CAD	
Gave up/limited enjoyable activities	"It [CAD] has kept me from doing a lot of the things that I planned to do, or [I] change my plans, and some days, I'm so fatigued that it'll be 4 o'clock before I realize the day's gone by because I'm just so tired. [For example], where I would go do some more gardening, or I would go shopping or something, I don't do that anymore, and I will want to go for something, and I'll just change my mind, and I just don't go" "I don't walk the dog anymore because it's just not warm enough…We have 5 acres, and I was an avid gardener, and I can't do that anymore because I can't be outside besides going to the car with a scarf over my face"
Day-to-day activities	"I used to be able to vacuum the entire bottom floor. Now I stop. I finish it another day" "I just can't get my thoughts together when I'm trying to figure out Is it time to pay bills? Should I pay the bills? I just can't get the energy up to do it"
Physical health/ activities	"I'm a motorcycle rider and having CAD has affected my riding so actually I sold my motorcycle after 40 years" "I live on a farm, and I train horses, and I downhill ski, and bunch of other stuff, but…my hemoglobin, or my blood, breaks down at 54 degrees, so in the winter, I have a heated jacket that's electric…and I stay really warm. I just try to stay in the house as much as I can"
Social/leisure life and relationships	"Well, I am not as social. [It is] just sort of too much trouble to get dressed up and go anywhere" "I don't see the grandkids as often…you miss out on going to events with your kids, like Christmas plays or something that the kids are in because of the exposure [to cold]"
Desired outcomes from treatment	
Elimination or minimization of fatigue	"Increase my stamina. Give me energy…just let me get back to the things I used to do [and] go above and beyond the daily activities of daily living" "It would prevent the fatigue [so] I can go back to being who I used to be, get my social life back, get myself back in shape again, go for my walks, go to the gym, just get my life back".
Elimination or minimization of reactions to cold environments	"Gosh, if it was a miracle [drug], it'd make me feel warm, and if it gave me a little energy, that would be great. I think [those] to me are the most debilitating…you just don't have the strength to do them, and the cold, [I'm] shivering all the time." "[An ideal medication] would stop me from having a reaction, and I wouldn't be affected by cold temperatures, and I'd go back to pre-diagnosis, initial diagnosis."

Abbreviations: CAD, cold agglutinin disease; CE, concept elicitation.

(Figure 3). The model demonstrates that the most common CAD-related symptoms identified by participants (i.e., reactions to cold environments and fatigue) may be accompanied by other less frequent symptoms. Additionally, CAD-related impacts are very common and range from wearing extra clothing for warmth to giving up various activities and developing depression or anxiety.

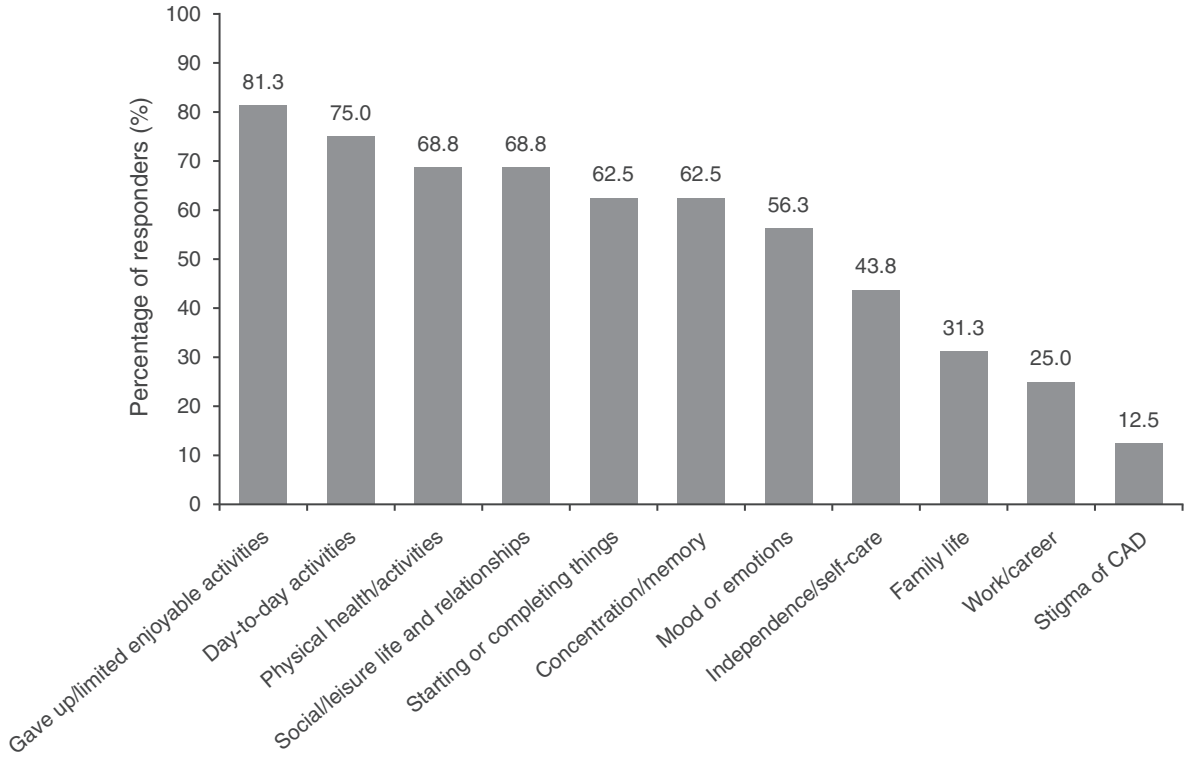

FIGURE 2 Participant-reported negative impacts of CAD ($N = 16$). All impacts were probed if they were not spontaneously reported by participants. CAD, cold agglutinin disease.

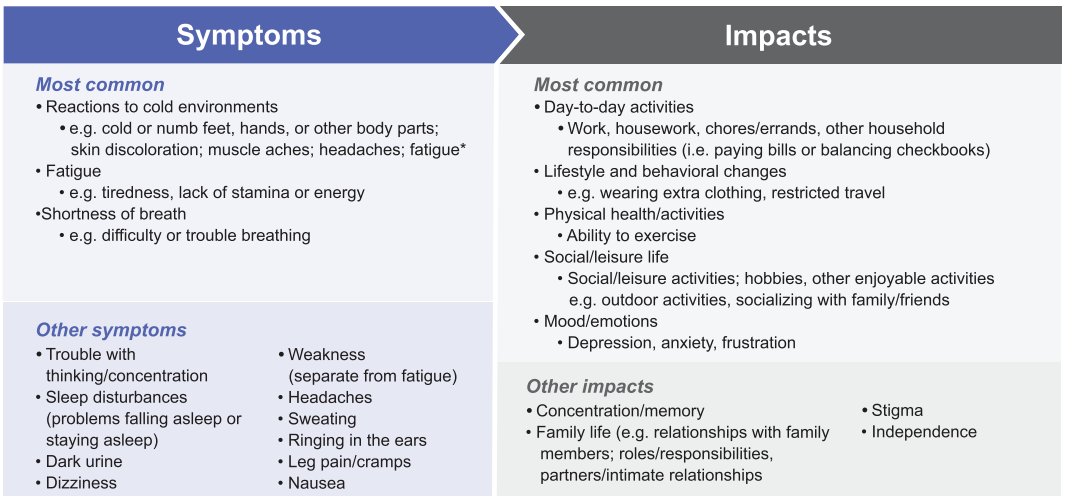

FIGURE 3 Conceptual model of the symptoms and impacts of CAD. The conceptual model was devised based on results from both rounds of CE interviews ($n = 37$). *Fatigue can occur on its own anytime and can occur (or worsen) as a reaction to cold stimuli. CAD, cold agglutinin disease; CE, concept elicitation.

4 | DISCUSSION

This qualitative study of adults with CAD in the United States demonstrated that CAD impacts numerous aspects of participants' physical health, daily lives, and relationships. Based on these findings, a novel, 11-item questionnaire was developed to measure symptoms and impacts important to people with CAD.

Consistent with previous studies, fatigue and reactions to cold environments were reported by participants as the major symptoms related to CAD.[2] In the present study, 93.8% of patients reported reactions to cold environments and fatigue, this is partly in line with results from a large retrospective multicenter study in Norway that reported that 91% of patients with CAD had cold-induced circulatory symptoms.[20] Comparatively, a retrospective

study in the United States reported that 39% of patients experienced cold-induced symptoms and 21%–40% experienced fatigue (at diagnosis or during disease course).[2] The high proportion of patients who identified fatigue as a major symptom of CAD in this study is a new observation, and may suggest that this symptom is underreported in medical records and thus underrepresented in retrospective chart-review analyses. Most participants also reported shortness of breath and problems with concentration, while more than one-third experienced sleep disturbance. In the phase 3 CARDINAL trial (NCT03347396) of sutimlimab in CAD, baseline FACIT-Fatigue scores were comparable to other serious chronic conditions such as advanced cancer or rheumatoid arthritis.[21] The negative impact of CAD-associated symptoms on participants' lives ranged from minimal (e.g., wearing extra clothing) to substantial (e.g., stop working, change in retirement plans). There is limited awareness of CAD in the medical community, and a lot is still unknown in terms of clinical features and outcomes.[3,4,22] Recent data indicate that, while some cold-induced symptoms may be transient, patients with CAD can experience persistent chronic hemolysis regardless of season.[23] The insights from our interviews with adults with CAD highlight a need to better understand and quantify the impact of CAD and its treatment on patient quality of life.

Previously reported analyses conducted as part of this study found no existing PROs to adequately address the range of concepts deemed critical to CAD from the patient perspective.[13] The FACIT-Fatigue scale was also tested in this study to determine its relevance in the assessment of the impact of fatigue in CAD.[15] Respondents who participated in the CE interviews reported that the FACIT-Fatigue adequately captures concepts relevant and important to their personal experience with fatigue in CAD, and was considered to be clear and easy to understand.[15] However, although the FACIT-Fatigue has been used in clinical studies of CAD to demonstrate clinically meaningful improvements in fatigue in response to treatment with sutimlimab,[21] a need was identified for a PRO instrument that provides a broader assessment of the symptoms and impacts identified by participants as being relevant to their experience with CAD.

CAD-SIQ is a novel, 11-item questionnaire that addresses the symptoms and impacts identified as important to adults with CAD. All 21 participants who took part in the CD interviews found the new CAD-SIQ measure to be relevant to their experiences with CAD and easy to understand and answer. Further evaluation of the CAD-SIQ including its measurement properties, sensitivity of change and response to treatment, and correlation with disease characteristics is required for use in clinical studies and real-world registries. The identification of specific score thresholds to determine disease severity in a real-world setting is also needed to enable the screening and detection of clinical distress. However, we have shown that the CAD-SIQ adequately addresses the concepts critical to the measurement of CAD symptoms and impacts with utility for evaluating patient outcomes in real-world studies, for example, in the global Cold Agglutinin Disease Real-World EvidENCE (CADENCE) registry.[24] Upon evaluation of its psychometric properties, the CAD-SIQ may also be included in observational studies and clinical trials as an endpoint to better understand patients' experiences and to support the meaningfulness of changes in key efficacy endpoints (e.g., FACIT-Fatigue scores), as well as being used in clinical settings to evaluate the health status of patients. Combining CAD-specific PROs and general PRO instruments could also be considered in future studies for a more holistic approach.

The study findings are limited, however, by several factors. The overall sample was limited to participants who were interested in taking part in the interviews and may not be generalizable to all people with CAD. Similarly, while the sample was geographically diverse, representing all four census regions of the United States, the majority of participants were non-Hispanic White. Future studies should be designed to include a more representative sample of the global CAD population and to limit selection bias. Additionally, data on recent or previous treatments for CAD (e.g., rituximab use or blood transfusions) and hemoglobin levels were not systemically collected, which may have provided additional details in better understanding patients' experiences and how active their disease was at the time of the assessment. However, the CAD-SIQ was developed in accordance with industry best practice, and most symptoms and impacts included in the final item pool were identified early in the interview process, thus suggesting that concept saturation was attained, a conclusion supported by the fact that no additional concepts were identified by participants during the CD phase.

In conclusion, CAD was found to negatively impact upon numerous aspects of participants' daily lives, with fatigue and reactions to cold environments reported as the most bothersome and important symptoms to treat. The 11-item CAD-SIQ is a novel CAD-specific PRO instrument that measures the symptoms and impacts of CAD that are most important and relevant to patients. Future research is required to evaluate the responsiveness, validity, and reliability of the CAD-SIQ in both clinical trial and real-world settings.

AUTHOR CONTRIBUTIONS

Florence Joly: Interpretation of results. **Pronabesh DasMahapatra:** Interpretation of results. **Dana B. DiBenedetti:** Study design; conduct of research, analysis and reporting; interpretation of results. **Katherine Kosa:** Study design; conduct of research, analysis and reporting; interpretation of results. **Quentin A. Hill:** Study design; interpretation of results. All authors critically revised the manuscript for important intellectual content, approved the final version submitted, had full access to all the data, and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

Florence Joly and Pronabesh DasMahapatra: Employees and stockholders of Sanofi. Dana B. DiBenedetti and Katherine Kosa: Employees of RTI Health Solutions who received funding from Sanofi for the design and implementation upon which this manuscript is based. Quentin A. Hill: Has received consultancy fees from Amgen, Apellis, Argenx, Grifols, Incyte, Immunovant, Janssen, Novartis, Sanofi, Sobi, ReAlta, and honoraria from Alexion, Amgen, Apellis, Grifols, and Novartis.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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