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The Real-World Experience of Niemann-Pick Disease Type C: Patient and Caregiver Perspectives to Inform Future Therapeutic and Policy Directions

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Abstract

Background

Niemann–Pick disease Type C (NPC) is a rare, autosomal recessive lysosomal disorder caused by pathogenic variants in NPC1 or NPC2, resulting in defective intracellular cholesterol and lipid trafficking, progressive neurodegeneration, and marked clinical heterogeneity across age of onset and disease course. Although recent therapeutic approvals have expanded the treatment landscape in some regions, global inequities in diagnosis, clinical management, and therapy access remain substantial. Patient and caregiver burden represents a substantial and frequently underrecognized component of the disease's overall impact, encompassing progressive functional decline, complex multidisciplinary care needs, significant psychosocial stress, and long-term socioeconomic consequences for affected families.

Methods

This first phase of a two-part, international cross-sectional survey was conducted in collaboration with the International Niemann-Pick Disease Registry (INPDR), Niemann-Pick UK, Aston University, and global patient advocacy partners. Adults with a confirmed NPC diagnosis and caregivers of affected individuals were recruited from 16 countries between January and July 2025. The survey collected patient- and caregiver-reported data on demographics, symptom manifestations, and treatment utilization, with additional contextual information on diagnostic pathways and care experiences. Quantitative responses were summarized using descriptive statistics, and open-text responses were thematically coded to contextualize reported clinical and care patterns.

Results

A total of 102 respondents completed the survey (12 adults with NPC, 41 caregivers of adults, 49 caregivers of minors). Neurological involvement was nearly universal across all subgroups (92–100%), and neuropsychiatric symptoms were frequently reported. Participants described substantial multidimensional burden encompassing loss of independence, impaired social participation, and high caregiving intensity. Treatment patterns revealed substantial variability in single- and combination therapy regimens. Prominent unmet needs included persistent diagnostic delays, fragmented care pathways, inadequate access to newly approved or regionally restricted therapies, and inconsistent implementation of clinical management guidelines.

Conclusions

This study provides a multi-country assessment of patient and caregiver experiences in NPC, highlighting substantial variation in diagnostic pathways, symptom burden, and treatment access across regions. The findings underscore the need for improved diagnostic awareness, more consistent access to available therapies, and the development of standardized patient-reported outcome measures to better inform patient-centered care and future therapeutic development.

Keywords: Niemann-Pick disease Type C; lysosomal storage disorder; patient-reported outcomes; neurodegeneration; caregiver burden; global health equity; rare disease

Background

Niemann-Pick disease Type C (NPC) is a rare, autosomal recessive, heterogeneous neurovisceral lysosomal disorder caused by pathogenic genetic variants in either *NPC1* or *NPC2*, which encode proteins essential for intracellular lipid trafficking. Loss of NPC1 or NPC2 protein function disrupts the egress of cholesterol and other lipids from late endosomes and lysosomes, leading to the intracellular accumulation of unesterified cholesterol and glycosphingolipids¹. This lysosomal lipid storage progressively impairs cellular homeostasis, particularly in neurons, and drives multisystem pathology characterized by progressive neurodegeneration and visceral involvement^{2,3}. NPC has an estimated birth prevalence of approximately 1 in 120,000 live births, though recent molecular and newborn screening studies indicate that the true prevalence is likely higher due to diagnostic challenges, phenotypic variability, and under-recognition in adult-onset cases⁴. NPC manifests along a broad clinical continuum, ranging from acute neonatal liver disease and early infantile developmental delay to adolescent- and adult-onset neuropsychiatric decline⁵. Common neurological hallmarks include vertical supranuclear gaze palsy, cerebellar ataxia, dystonia, dysarthria, dysphagia, and progressive cognitive impairment, often accompanied by visceral involvement such as hepatosplenomegaly and pulmonary dysfunction.

Disease onset and progression in NPC are highly heterogeneous, contributing to substantial diagnostic complexity and frequent delays in recognition. Reported diagnostic delays commonly exceed five years, reflecting the nonspecific nature of early clinical manifestations, overlap with other neurological and psychiatric disorders, and limited awareness among clinicians, particularly in adolescent and adult-onset presentations^{6,7}. Historically, therapeutic options for NPC were extremely limited, with supportive and symptomatic management forming the

cornerstone of care. For nearly two decades, miglustat, a substrate reduction therapy that inhibits glycosphingolipid synthesis, was the only disease-modifying therapy available, receiving regulatory approval in Europe and several other regions while remaining accessible in the United States primarily through off-label use^{8–10}. Recent regulatory approvals have expanded the therapeutic landscape. In 2024, the U.S. Food and Drug Administration approved N-acetyl-L-leucine (Aqneursa) and arimoclomol (Miplyffa)¹¹ for the treatment of NPC, representing important advances in disease-targeted therapy. Aqneursa subsequently received European Medicines Agency approval in January 2026⁷ whereas arimoclomol remains approved only in the US, underscoring persistent disparities in therapeutic availability across global health systems¹². Differences in regulatory pathways, payer coverage, specialist infrastructure, and national treatment guidelines continue to contribute to variability in access to care and therapeutic implementation across regions⁶. Moreover, despite these recent advances, no curative therapy currently exists, and the long-term clinical effectiveness and real-world impact of emerging treatments on disease progression, functional outcomes, and quality of life remain incompletely characterized^{11,13}.

Given these persistent diagnostic and therapeutic challenges, a more comprehensive understanding of the real-world burden of NPC across the disease spectrum is needed, including its impact on both affected individuals and their caregivers. This study aimed to characterize demographic characteristics, symptom profiles, and treatment utilization patterns among individuals with NPC using patient- and caregiver-reported data. By capturing experiences across multiple countries, the study also seeks to contextualize variability in clinical management and access to therapy, generating evidence that may inform clinical practice, health-system planning, and efforts to improve equitable access to available and emerging treatments.

Conceptual Framework

To support interpretation of the survey findings and their translational relevance, we developed an author-derived conceptual framework that situates NPC burden within an integrated biopsychosocial and health-systems model informed by current literature^{6,7}. In this framework, the primary biological substrate of disease consists of NPC1- or NPC2-related lysosomal lipid trafficking dysfunction, which drives progressive neurodegeneration and multisystem clinical involvement. This biological burden manifests clinically as accumulating functional impairment, including deterioration in mobility, swallowing, speech, cognition, and independence, while also contributing to heterogeneous neuropsychiatric and behavioral manifestations that may further worsen disability and complicate care¹⁴. At the patient and family level, these impairments generate substantial caregiver burden, including high-intensity daily care demands, emotional distress, social restriction, and work or financial disruption¹⁵. Surrounding these individual-level effects is the health-system context, encompassing diagnostic delay, access to specialist expertise, multidisciplinary care coordination, treatment availability, and reimbursement conditions [7]. At the broadest level, therapeutic inequity across countries and health systems shapes differential access to disease-modifying therapies, clinical trials, and supportive services, thereby influencing the timeliness and quality of longitudinal management. Accordingly, NPC burden is conceptualized not as a purely biological consequence of lysosomal dysfunction, but as the product of interacting molecular, clinical, psychosocial, and systemic determinants. This framework provides a pragmatic structure for identifying intervention targets across the care continuum, including earlier diagnosis, standardized monitoring, multidisciplinary care delivery, improved outcome measurement, and more equitable access to available and emerging therapies⁶.

Methods

Study Design and Participants

This investigation represents the first phase of a two-phase mixed-methods international study jointly conducted by Niemann-Pick UK and the International Niemann-Pick Disease Registry (INPDR), in partnership with the National Niemann-Pick Disease Foundation (USA), Niemann-Pick Canada (Canada), Australian NPC Disease Foundation (Australia), International Niemann-Pick Disease Alliance (UK), and Aston University (UK). The overarching goal of the program is to generate a comprehensive, patient-centered understanding of the clinical, psychosocial, and systemic burdens associated with NPC, while also informing future care frameworks and policy recommendations. Phase I was designed as a cross-sectional, web-based survey aimed at establishing a foundational quantitative dataset on disease burden, unmet needs, and treatment experiences, which will subsequently inform the qualitative exploration in Phase II.

The Phase I survey was developed collaboratively with input from clinicians, patient advocates, caregivers, and registry representatives to ensure relevance, inclusivity, and content validity. The English-language version of the questionnaire was deployed online between January and July 2025 using a secure digital survey platform compliant with international data protection standards, including GDPR. The instrument included structured questions covering demographic characteristics, diagnostic journey, clinical symptoms, treatment access and experiences, caregiver impact, and awareness of available guidelines or support resources. Pilot testing with a small sample of community members ensured clarity and usability prior to global dissemination.

Eligible respondents were adults aged 18 years or older who either had a confirmed diagnosis of NPC (based on genetic or biochemical testing) or served as primary caregivers for an affected individual (adults >18 years or minor <18 years) with a confirmed NPC diagnosis. Diagnosis status was self-reported by the participant. Participants were required to be fluent in English and to provide informed consent prior to enrollment. Informed consent was obtained online, with participants able to discuss the study and ask any study-related questions with the study team. Participants were stratified into three groups: adults with NPC (self-report), caregivers of adults with NPC, and caregivers of minors (<18 years of age) with NPC. Minor variations in question structure were implemented between participant groups to reflect the responder's relationship with NPC.

Prior to analysis, all responses obtained were reviewed and filtered for data quality elements, including identifying fraudulent and duplicate responses while also assessing response completeness. Responses which were identified as fraudulent, duplicate, or insufficiently complete were removed from the analysis dataset.

Recruitment was facilitated through patient registries, advocacy group mailing lists, social media channels, and clinician signposting to maximize diversity and representativeness within the NPC community. Ethical approval and study governance were obtained and maintained through the study lifecycle, which ensured adherence to principles of patient autonomy, confidentiality, and transparency (HRA IRAS ID: 350386; UK Research Ethics Committee: 24/WA/0359).

Survey Instrument

The survey instrument was a structured, web-based questionnaire designed to capture a comprehensive, multidimensional picture of the lived experience of NPC among affected individuals and their caregivers. Developed collaboratively by Niemann-Pick UK, the INPDR, and an international advisory panel of clinicians, researchers, and patient advocates, the instrument was informed by existing registry datasets, validated rare disease survey frameworks, and qualitative insights from community stakeholders. The content was iteratively refined through expert review and pilot testing to ensure clarity, relevance, and cross-cultural applicability. The survey was created and administered online via Qualtrics (Provo, UT) and was designed to be completed in approximately 50 minutes. Question types included multiple-choice, matrix, and scaled-response formats, supplemented by optional open-ended questions to elicit narrative insights. To ensure content validity and respondent comprehension, the survey underwent cognitive testing with a subset of patients and caregivers prior to launch. The instrument was designed in English for Phase I, with translation and cultural adaptation procedures planned for Phase II to support multilingual implementation and cross-country comparisons.

The survey was composed of several core modules encompassing key domains of disease impact and management. This analysis includes:

- **Demographics and Diagnosis:** Captured participant characteristics such as age, sex, geographic location, relationship to the affected individual, and diagnostic history, including age at symptom onset, time to diagnosis, and diagnostic method.
- **Symptom Burden and Disease Trajectory:** Assessed neurological, cognitive, visceral, and psychiatric manifestations of NPC, their progression over time, and their impact on daily functioning and quality of life. Participants were asked to rate symptom severity and

progression using Likert-scale measures and open-text responses to capture contextual detail.

- Utilization of Approved, Investigational, or Expanded Access Therapies.

Results

Participant Characteristics

Responses were obtained from 102 participants who represented 16 countries (Fig. 1). The five most represented countries of residence were the United States (n = 42, 41.2%), the United Kingdom (n = 23, 22.5%), Australia (n = 13, 12.7%), Canada (n = 6, 5.9%), and Switzerland (n = 3, 2.9%), with India also represented at the same frequency (n = 3, 2.9%). Table 1 summarizes the demographic characteristics of respondents and individuals with NPC across three groups: adults with NPC (self-report, n = 12), caregivers of adults (n = 41), and caregivers of minors (n = 49). Individuals with NPC were older in the adult cohorts (mean age 38.2 and 35.2 years) compared with minors (9.8 years), with a corresponding gradient in age at diagnosis (29.0 years in self-reporting adults, 24.3 years in caregiver-reported adults, and 4.2 years in minors). The sex distribution of affected individuals was balanced across groups, with females comprising 41–50%. Caregivers were predominantly female (73% among adult caregivers and 82% among caregivers of minors), with a mean age of 61.4 years for caregivers of adults and 41.1 years for caregivers of minors. Most caregivers were married, particularly among caregivers of minors (90%), and the majority were parents, with mothers representing the largest proportion (63% for adult caregivers and 78% for minors). Household size was larger among families of minors (mean 3.5) compared with adult groups (2.3–2.55), reflecting the presence of dependent children. Collectively, these data illustrate differences in age at diagnosis, caregiver demographics, and household composition across the disease spectrum.

Table 1. Demographics and characteristics of individuals with NPC and participants by responder type.

	Adult (>18y) (Self-report) (n = 12)	Caregiver of Adult (n = 41)	Caregiver of Minor (<18y) (n = 49)
Age of individual with NPC, years	38.2	35.2	9.8
Age at diagnosis, years (mean, IQR)	29.0, IQR = 30.3	24.3, IQR = 10.8	4.2, IQR = 6.2
Sex of individual with NPC	50% F	46% F	41% F
Sex of respondent	—	73% F	82% F
Age of respondent, years	—	61.4	41.1
Marital status of respondent	S 42%, M 50%, D 8%	S 7%, M 78%, D 10%	S 14%, M 90%, D 2%
Relationship to individual with NPC	—	Mom 63%, Dad 22%, Spouse 5%, Sibling 5%, Other 5%	Mom 78%, Dad 22%
Average household size	2.3 (25% have children)	2.55	3.5

S = single; M = married; D = divorced/separated; F = female; IQR = interquartile range.

Table 2 summarizes timing of symptom onset and diagnosis across participant groups. No prenatal diagnoses were reported among adults, while 2% (n = 1) of minors were diagnosed before birth. Among adults with NPC, symptom onset most commonly occurred after age 15, reported in 83% of self-respondents and 48% of caregiver-reported adults, with an additional 45% of caregiver respondents indicating onset around mid-childhood (approximately 8.3 years) and 7% reporting uncertainty. In contrast, symptom onset in minors was predominantly early, with reported age at approximately 3.7 years. Age at diagnosis followed a similar pattern,

occurring later in adults (mean 29.0 years, IQR 30.3 for self-report; 24.3 years, IQR 10.8 for caregiver-reported adults) compared with minors (mean 4.2 years, IQR 6.2). These findings illustrate a marked difference in disease recognition between early-onset and later-onset presentations, with substantially earlier diagnosis in pediatric cases relative to adult cohorts.

Table 2. Symptom onset and diagnosis of individuals with NPC by responder type.

Group	Dx before birth (%)	Age at symptom onset	Age at diagnosis, years
Adult (self-report)	0	83% >15 years; 17% not sure	29.0, IQR = 30.3
Adult (caregiver)	0	48% >15 years; 45% ~8.3 years; 7% not sure	24.3, IQR = 10.8
Minor (caregiver)	2	96% ~3.7 years; 4% not sure	4.2, IQR = 6.2

Dx = Diagnosis

Clinical Characteristics

Neurological involvement was nearly universal across the cohort (96% overall), affecting 92% of adults with NPC, 100% of caregiver-reported adults, and 93% of children. There was a comparable mean number of neurological manifestations across subgroups (range 2.8–3.4 symptoms), consistent with the progressive, multisystem neurodegenerative trajectory of NPC. Reported deficits spanned cerebellar, cortical, and basal ganglia domains, including ataxia, dysarthria, dystonia, dysphagia, and cognitive decline. Seizures were present in 43% overall (38% adults self-report, 42% caregivers of adults, 46% caregivers of children) and were frequently described as difficult to control. On average, 2.1 approved or prescribed medications were administered daily to individuals experiencing seizures. Cataplexy was reported in 19%

overall (23%, 19%, and 17% across the respective groups), reinforcing the widespread neuroanatomical involvement characteristic of lysosomal lipid trafficking disorders.

Neuropsychiatric manifestations were reported by 75% overall and demonstrated marked heterogeneity by age and reporter type (Fig. 2). Depression was most common among adults (32% self-report; 27% caregiver-reported adults) but rare in children (2%). Behavioral disorders (e.g., ADHD) were most frequently endorsed by caregivers of adults (22%) compared with adults self-reporting (5%) and pediatric caregivers (14%). Personality disorders were reported exclusively by caregivers of adults (22%). Additional conditions including bipolar disorder (9%, 7%, 0%), psychosis (5%, 5%, 6%), obsessive-compulsive disorder (5%, 2%, 0%), eating disorders (9%, 2%, 0%), post-traumatic stress disorder (14%, 7%, 2%), and autism spectrum traits (5%, 2%, 10%) were present at lower but clinically meaningful frequencies, underscoring the phenotypic breadth of NPC-related neuropsychiatric involvement.

Table 3. Treatment utilization and age at initiation across cohorts.

Group	Miglustat			Arimoclomol			L-Acetyl-Leucine	
	Age init. (y)	Current (%)	Prior* (%)	Age init. (y)	Current (%)	Prior (%)	Age init. (y)	Current (%)
Adult (self)	25.1	75	0	27.8	50	0	43.5	50
Adult (caregiver)	22.1	56	27	32.0	20	5	31.1	34
Minor (caregiver)	5.9	78	10	9.7	31	2	12.2	29

*Previously taken refers to previously utilized treatment subsequently discontinued.

Table 3 summarizes treatment exposure, timing of initiation, and current versus prior use across the three participant groups. Miglustat was the most commonly utilized therapy across all cohorts, with high rates of current use in both adults and minors (75% in self-reporting adults,

56% in caregiver-reported adults, and 78% in minors). Age at initiation was substantially earlier in minors (5.9 years) compared with adults (22.1–25.1 years), possibly reflecting differences in age at diagnosis or symptom onset. A notable proportion of caregiver-reported adults (27%) and minors (10%) reported prior, but not current, miglustat use. Use of newer therapies was more variable. Arimoclomol was reported in 50% of self-reporting adults, compared with lower current use in caregiver-reported adults (20%) and minors (31%), with minimal prior discontinuation across groups. L-acetyl-leucine showed similar uptake, with 50% current use among self-reporting adults, 34% among caregiver-reported adults, and 29% among minors. Overall, these data demonstrate high reliance on miglustat, earlier treatment initiation in pediatric populations, and more limited but emerging uptake of recently approved therapies across cohorts.

Discussion

This international, English-speaking patient- and caregiver-reported survey provides a cross-sectional characterization of demographic patterns, symptom burden, and treatment utilization in NPC across 16 countries. Consistent with established clinical understanding, neurological manifestations were widely reported, including motor dysfunction, seizures, and cataplexy, alongside substantial neuropsychiatric involvement. The observed distribution of symptoms across respondents reinforces the multisystem and heterogeneous nature of NPC. Differences between reported age at symptom onset and age at diagnosis indicate persistent diagnostic delay within the cohort, although the study design does not permit precise quantification of delay duration. These findings are consistent with known challenges in early recognition, particularly in later-onset phenotypes, but should be interpreted descriptively rather than as population-level estimates.

The cohort reflects substantial heterogeneity in disease presentation, duration, and functional status, spanning early-onset, rapidly progressive forms to later-onset phenotypes with more gradual neurological decline. Caregiver-reported data indicate a wide range of caregiving intensity, with a substantial proportion describing high daily care needs. While these findings are consistent with the progressive and disabling nature of NPC, the study was not designed to quantify caregiver burden using validated instruments, and results should therefore be interpreted as indicative rather than definitive measures of burden.

Geographic representation across multiple regions enabled descriptive assessment of variability in treatment access and care delivery. Differences in access and availability of disease-modifying therapies suggest heterogeneity in health-system structures and implementation of NPC standards of care. However, the study was not designed to formally compare health systems or quantify access disparities, and these observations should be interpreted as contextual rather than causal.

Treatment utilization patterns reflect both historical and emerging therapeutic landscapes. Miglustat exposure was reported by a majority of respondents, consistent with its long-standing role as the primary disease-modifying therapy in many regions. While miglustat remains widely utilized, tolerability-related concerns represent a clinically relevant real-world consideration; 44% of adults, 67% of caregivers of minors, and 35% of caregivers of adults reported side effects, largely related to gastrointestinal symptoms. Reports of treatment discontinuation were observed but cannot be attributed to specific causes within this dataset. Similarly, access to newly approved therapies (N-acetyl-L-leucine and arimoclomol) was limited within the cohort,

reflecting early adoption dynamics and variability in regulatory and reimbursement pathways. These findings describe patterns of access and use but do not provide evidence regarding comparative effectiveness or treatment outcomes.

Neuropsychiatric manifestations were commonly reported across all age groups, with notable variability in symptom profiles. Depression emerged as the most frequently reported symptom overall, particularly among adult respondents, while behavioral disturbances (e.g., ADHD, personality-related symptoms) were more prominently reported in pediatric groups. Conditions such as OCD, eating disorders, and PTSD were also observed but with lower and more variable frequency. These patterns highlight the age-dependent and heterogeneous nature of neuropsychiatric involvement in NPC and reinforce the importance of systematic, developmentally appropriate neuropsychiatric assessment as part of routine clinical management.

Several methodological limitations should be considered. The study employed a cross-sectional, convenience sampling approach using advocacy networks and digital dissemination, resulting in a sample that likely reflects an engaged, network-connected population. Individuals with limited healthcare access, lower socioeconomic resources, advanced disease, or residence in non-English speaking regions may be underrepresented. A response rate could not be calculated due to the absence of a defined sampling frame. All data were self- or caregiver-reported and were not independently clinically verified, introducing potential recall and reporting biases. Additionally, caregiver-reported outcomes may differ systematically from patient-reported experiences, particularly for neuropsychiatric symptoms. Finally, the cross-sectional design precludes causal inference and limits interpretation to descriptive associations.

To address some of these limitations, Phase II of the survey will be disseminated in six additional languages alongside English to expand accessibility and improve representation across non-English speaking populations. The survey instrument will remain fundamentally unchanged to preserve methodological consistency and enable comparability across cohorts, while linguistic adaptation will facilitate inclusion of more diverse geographic and socioeconomic contexts.

Conclusions

Taken together, these findings provide a descriptive, multi-country snapshot of NPC as experienced by patients and caregivers, characterized by heterogeneous symptom expression, ongoing neurological and neuropsychiatric burden, and variable patterns of treatment utilization and care access. The results reinforce the complexity of NPC across the lifespan and support the need for standardized data collection approaches, including validated patient-reported outcome measures and longitudinal study designs. Future research incorporating broader geographic representation and harmonized methodologies will be important to more fully characterize global disease burden and inform clinical and health-system strategies.

List of Abbreviations

ADHD: Attention-deficit/hyperactivity disorder

GI: Gastrointestinal

INPDR: International Niemann-Pick Disease Registry

IQR: Interquartile range

NPC: Niemann-Pick Disease Type C

OCD: Obsessive-compulsive disorder

PTSD: Post-traumatic stress disorder

Declarations

Ethics Approval and Consent to Participate

Ethics approval was obtained and maintained throughout the study and was issued by the Health Research Authority, UK (IRAS ID: 350386; UK Research Ethics Committee: 24/WA/0359).

Informed consent to participate was obtained from all study participants.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to participant privacy but are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

KC, JH, TM, SC, and SB made significant contributions to the study conceptualization, design, data collection, analysis, interpretation of data, and revising the manuscript. All authors read and approved the final manuscript.

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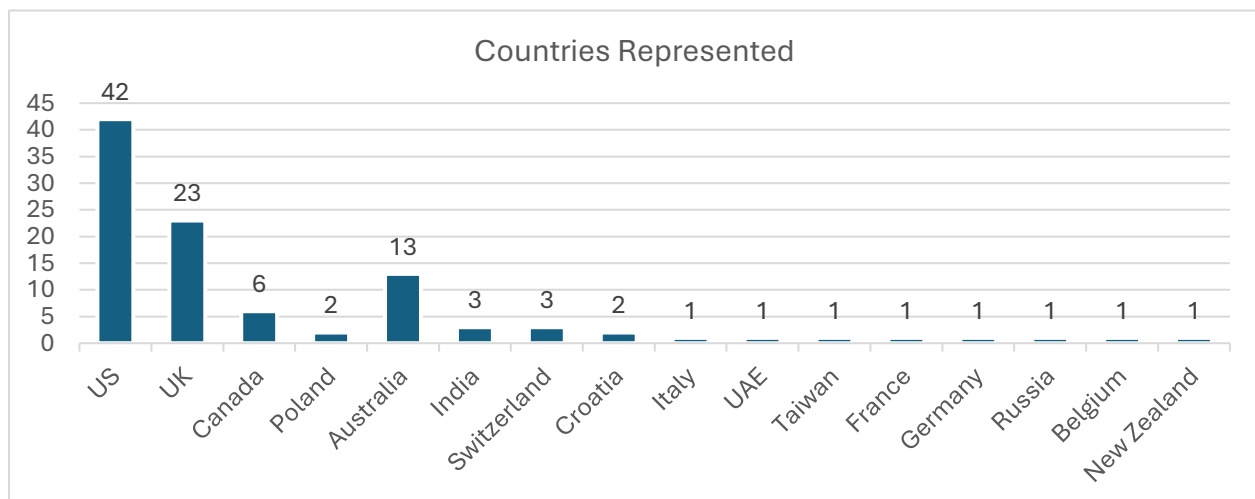
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Figures

Figure 1. Count of participants represented from 16 countries.



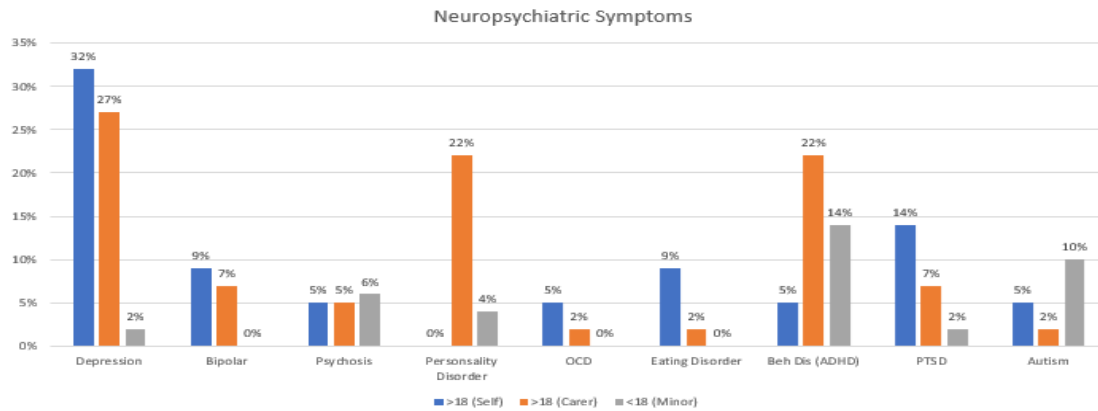


Figure 2. Percentage of respondents reporting neuropsychiatric symptoms across three groups: adults self-reporting symptoms (>18 Self), caregivers of adults with NPC (>18 Caregiver), and caregivers of children with NPC (<18 Minor). Reported symptoms include depression, bipolar disorder, psychosis, personality disorders, obsessive-compulsive disorder (OCD), eating disorders, attention-deficit/hyperactivity disorder (ADHD) or behavioral disorders, post-traumatic stress disorder (PTSD), and autism. The chart illustrates substantial variability in neuropsychiatric manifestations across age groups and reporter type, with depression, behavioral disorders/ADHD, and personality disorders emerging as the most frequently cited concerns. These patterns highlight the significant and heterogeneous psychiatric burden associated with NPC.