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The humanistic burden of immunoglobulin A nephropathy on patients and care-partners in the United States

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Abstract

Purpose This cross-sectional survey study quantified the humanistic burden of immunoglobulin A nephropathy (IgAN), in terms of physical and mental health-related quality of life (HRQoL) and work productivity, among adults with primary IgAN and their care-partners.

Methods HRQoL was assessed (01/31/22 – 05/31/23) with validated tools including the KDQoL-36 (with SF-12), GAD-7 (anxiety), PHQ-9 (depression), and WPAI: SHP (work productivity). Participant characteristics and total/domain scores were summarized; selected outcomes were compared to an external, kidney disease-free cohort.

Results 117 adults with IgAN and their care-partner pairs, and one adult without a care-partner, were included. The mean ages of patients and care-partners were 38.0 (SD: 8.6) and 40.2 (11.8) years, respectively; 55.9% and 43.6% were female. Mean physical and mental SF-12 scores for patients were 46.7 (SD: 8.0) and 41.9 (9.2), respectively, and 50.7 (7.3) and 43.7 (10.24) for care-partners. Both SF-12 components for patients, and the mental component for care-givers, were significantly worse compared to the US general population. Among patients, 27.1% had moderate/severe anxiety and 49.2% reported at least moderate depression. Compared to external controls, patients experienced significantly higher severity of anxiety (6.6 vs. 5.4) and depression (8.1 vs. 6.6; both $p < 0.0001$). Among care-partners, 13.7% experienced moderate anxiety and 37.8% experienced moderate/moderately-severe depression. Among employed individuals, both groups reported IgAN-related absenteeism (8.8–9.4%), presenteeism (25.1–25.9%), and overall work impairment (30.4–30.5%).

Conclusion US adults with IgAN and their care partners experience impairments to mental and physical HRQoL and heightened levels of depression and anxiety, underscoring the need for effective IgAN therapies and care-partner support.

Keywords Care-partners · Health-related quality of life · Humanistic burden · Immunoglobulin A nephropathy · Kidney disease

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Introduction

Immunoglobulin A nephropathy (IgAN) is a rare kidney disease characterized by the buildup of IgA in the kidneys which reduces kidney function and can ultimately lead to kidney failure [1]. IgAN is a prevalent cause of chronic glomerular disease worldwide and has an annual incidence of 1.29 cases per 100,000 persons in the United States (US) [2, 3]. The disease typically progresses over many years and often remains undiagnosed until individuals present with symptoms such as proteinuria, renal insufficiency, gross hematuria, and hypertension [2, 4]. Although the rate of progression varies among populations [5], approximately 40% of patients progress to kidney failure within 10 years of diagnosis [6–8]. The average age at IgAN diagnosis is just 41 years [9], during a young adult's prime working years.

In addition to the clinical impact, IgAN also poses a substantial economic burden to healthcare systems worldwide, largely due to high costs associated with kidney failure, dialysis, and transplantation [2, 10, 11]. However, far less is known about the humanistic burden associated with the disease among affected patients or their care-partners, including the impact of the disease on mental and physical health-related quality of life (HRQoL) and work productivity. With progression, IgAN is associated with maintenance dialysis [1], necessitating ongoing outpatient visits which may interfere with work or other facets of life. Further, patients with kidney disease frequently suffer from anemia and fatigue [12, 13], which may contribute to work absenteeism or presenteeism. Chronic kidney disease (CKD) is associated with higher risk of depression, even in earlier stages [14], and a similar finding has been reported for IgAN [15]. Despite the existing literature, there remains a paucity of data quantifying the real-world humanistic burden, including HRQoL, among adults with IgAN in the US and, in particular, the burden on their care-partners [16, 17].

HONUS (**H**umanistic Burden **o**f Rare Kid**N**ey Diseases: **U**nderstanding the impact of FSGS and IgAN on Patients and Caregivers **S**tudy) is a multi-national, cross-sectional survey designed in consultation with people with IgAN or focal segmental glomerulosclerosis (FSGS), as well as clinical community members (ClinicalTrials.gov Identifier: NCT05200871). The goal of the HONUS study is to quantify the humanistic burden of rare kidney diseases from both the patient and caregiver (care-partner) perspectives [18]. A detailed understanding of the humanistic burden of IgAN is crucial to meeting the unmet medical needs of this patient population and for identifying areas to improve the support of care-partners. Thus, the objective of this study was to quantify the humanistic burden and impact of IgAN among affected adults in the US, as well as to understand the burden from the perspective of care-partners.

Methods

Study overview

The current analysis focuses on adults with IgAN and their care-partners in the US who participated in HONUS. The HONUS study enrolled adults with IgAN or FSGS, their care-partners, and adult caregivers of children/adolescents with IgAN or FSGS from five nations (US, Spain, United Kingdom, Germany, and France). Survey data collection in the US occurred between January 31, 2022, and May 31, 2023. Adults with IgAN and their care-partners, as well as adult caregivers of children/adolescents with IgAN, in the US were recruited to the HONUS study from two patient advocacy groups (NephCure Kidney International and the IGA Nephropathy Foundation of America) and two US-based medical centers (University of North Carolina Kidney Center and Kaiser Permanente (Kaiser Foundation Research Institute). Eligible patients were recruited to the survey via email, phone, or oral invitations. Invitees voluntarily participated in the survey, administered as a secure online questionnaire, and provided informed consent. Participants were compensated at fair market value upon survey completion.

The survey and all associated patient-facing materials were granted an exemption from full review by the Pearl Institutional Review Board on June 21, 2021, and the study is compliant with the Health Insurance Portability and Accountability Act and Declaration of Helsinki. Data collected via the online surveys were de-identified.

Study population

The eligibility criteria for the study population in HONUS have been previously published [19]. Briefly, people were eligible for study inclusion if (1) they were aged ≥18 years (adults) and had a self-reported, physician-provided diagnosis of IgAN, with renal biopsy confirmation of the diagnosis; or (2) were a care-partner for someone with a self-reported, physician-provided diagnosis of IgAN as above. Care-partners were defined as an adult (e.g., spouse, parent, sibling, relative, or friend) providing direct disease-related support to an adult (aged ≥18 years) or child/adolescent (aged 8–17 years) with IgAN. Additionally, all participants were required to be able to provide informed consent and be located in the US. People with IgAN (and their care-partners/caregivers) were excluded from the study if they had IgAN secondary to another condition, a history of malignancy other than adequately treated basal cell or squamous cell skin cancer, a co-existing glomerular disease (e.g., membranous nephropathy or lupus nephritis), or were participating in a kidney disease clinical trial and

potentially receiving active treatment as part of the trial at the time of recruitment.

Study outcomes

Demographic information collected during the survey included self-reported age, sex, race/ethnicity, and marital, employment, and insurance status. Race/ethnicity information was collected to permit matching on this variable with the external control group.

HRQoL survey instruments

HRQoL was assessed among adults with IgAN and care-partners using disease-specific and general survey instruments. Adults with IgAN were assessed with the Kidney Disease Quality of Life Instrument (KDQoL-36) and asked about their most burdensome symptoms. Care-partners were assessed with SF-12, a general health questionnaire that assesses the impact of health on everyday life [20]. The KDQoL-36 is a short form of the KDQOL-SF™ (v1.3) that includes the 12-Item Short Form Survey (SF-12) as a generic core along with questions about the burden, symptoms/problems, and effects of kidney disease [21]. The most burdensome symptoms were assessed based on how much individuals with IgAN were bothered by the following: facial swelling, abdominal swelling, embarrassment, dry mouth, constipation, bone or joint pain, headache, restless legs syndrome, and lower back pain. Responses were scored on a scale of 1 to 5 (i.e., "not at all bothered" = 1, "somewhat bothered" = 2, "moderately bothered" = 3, "very much bothered" = 4, and "extremely bothered" = 5). The recall period was the 4 weeks prior to the survey.

Both adults with IgAN and their care-partners were assessed with the Generalized Anxiety Disorder Assessment (GAD-7), Patient Health Questionnaire-9 (PHQ-9), and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI: SHP) survey [22]. The GAD-7 is a 7-item instrument used to measure or assess the severity of generalized anxiety disorder [23], while the PHQ-9 is the 9-item depression module from the full PHQ and measures the severity of depression [24].

Separately, IgAN-related fear and uncertainty for the future was measured among both groups using a 5-point Likert scale; both the frequency and the effect of fear and uncertainty were assessed. Frequency was assessed based on how often respondents experienced fear and uncertainty for the future due to the disease, with higher scores indicating more frequent fear and uncertainty (i.e., "never" = 1, "rarely" = 2, "sometimes" = 3, "often" = 4, and "always" = 5). Effect was assessed based on how much fear and uncertainty affected the respondents, also using a 5-point scale with higher scores indicated a greater effect (i.e., "not at all" = 1, "a little" = 2, "somewhat" = 3, "quite a bit" = 4, and "very much" = 5).

Comparison with external control cohort

Description of external cohort

Mental health and work productivity outcomes of adults with IgAN were compared to those of an external, kidney disease-free control cohort from the 2023 US National Health and Wellness Survey (NHWS) [25]. The NHWS is an online, patient-reported health survey conducted annually among ~75,000 US adults. The NHWS survey is divided into a base questionnaire completed by all respondents, which assesses demographics, diseases experienced and diagnosed, and health outcomes such as quality of life, work productivity, and healthcare resource utilization. Additional disease modules, completed by eligible respondents reporting diagnosis of that specific disease, provide deeper insights on a given healthcare condition. Many respondents in the NHWS are not diagnosed with a condition or illness, providing a natural balance of both "healthy" respondents and respondents diagnosed with a given condition or illness. Multiple studies have found the NHWS survey data to be valid and reliable when compared to other existing data sources, including government health statistics (e.g., US Census, National Health Interview Survey, National Health and Nutrition Examination Survey) [26–32].

NHWS cohort sampling

For the purposes of this comparative analysis, the "healthy" general population respondents were compared to HONUS respondents on questionnaire items, including the GAD-7, PHQ-9, and WPAI. Respondents to the NHWS were recruited through an existing, general-purpose (i.e., not health care-specific) web-based consumer panel. All panelists explicitly agreed to be a panel member, register with the panel through a unique e-mail address, and complete an in-depth demographic registration profile. Quota sampling by age, sex, and race/ethnicity was used to ensure that the NHWS sample was representative of the adult population in the US; quota targets were obtained each year using the latest estimates from the International Database of the US Census Bureau.

NHWS cohort weighting

NHWS controls were weighted via iterative proportional fitting [33] to align their distributions with those observed in adults with IgAN in HONUS based on key sociodemographic

attributes and presence of thyroid disease (Table S1). A priori variables of interest were selected to be matched on. Sampling weights were calculated on the NHWS population (based on the characteristics of the HONUS sample) through iterative proportional fitting, commonly known as "raking". This weighting method is used when dealing with data sources where the joint distribution of the covariates' cell counts is either unknown or expected to be small [34]. T-tests (for continuous variables) and Rao-Scott corrected chi-square tests (for categorical variables) comparing the weighted NHWS sample to the respective HONUS sample were used to evaluate the success of the weighting procedure in controlling for baseline differences in the selected covariates. Non-significant differences ($p > 0.05$ from the corresponding statistical tests) between the groups were taken as evidence of a successful balance. Standardized difference was also calculated, with a threshold of less than 0.2 considered indicative of acceptable balance between HONUS and NHWS after weighting [35].

Analysis

The characteristics (i.e., age, sex, working status) and HRQoL outcomes of adults with IgAN and care-partners collected from the online surveys were summarized descriptively. Total scores, composite scores, and/or domain/scale scores of the standardized survey instruments were calculated based on their published scoring manuals. Continuous variables were summarized as mean, median, and standard deviation (SD); categorical variables were summarized as frequency and percentage.

Indirect comparisons of outcomes were performed between the HONUS IgAN cohort and weighted NHWS controls to inform on the relative burdens of IgAN after "controlling" for differences in selected covariates using independent samples t- tests for continuous variables and Rao-Scott corrected chi-square tests for categorical variables. PHQ-9, GAD-7, and WPAI: SHP scores were compared between adults with IgAN in HONUS and weighted NHWS external controls using independent t-test with robust variance estimation [36] for mean scores in NHWS or Rao-Scott corrected chi-square tests. To accurately compute population estimates from the weighted NHWS sample, first order Taylor Series Linearization (also known as the "robust variance" estimation approach) was used to estimate the mean and standard error, which considers the variability of the sampling weights [36]. Cohen's d, a type of effect size index, was reported, with Cohen's d of 0.2, 0.5, and ≥ 0.8 indicating small, medium, and large effect sizes, respectively [37].

A two-sided $p < 0.05$ was considered statistically significant. Analyses were conducted in SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC) or R version 4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population and demographics

A total of 117 adults with IgAN and care-partner pairs, and one adult without a care-partner, were included in the analysis (Table 1). Four adult caregivers of children/adolescents with IgAN provided survey responses but were not included in the analyses due to the small sample size.

The average age of adults with IgAN ($N = 118$) was 38.0 (SD: 8.6) years; 55.9% were female, 80.5% were White, and 67.0% were employed full time. Among care-partners ($N = 117$), the average age was 40.2 (SD: 11.8) years, and 43.6% were female, 82.9% were White, and 82.9% were employed full time. Most care-partners of adults with IgAN were spouses/life-partners (87.9%), with the rest being a parent, friend, sibling, child, or other relative.

Disease characteristics of adults with IgAN

On average, adults with IgAN had been living with the disease for 6.2 (SD: 5.0) years, with 2.8 (SD: 6.9) months from first symptoms to diagnosis (Table 2). At the time of the study, 30.5% of adults with IgAN had Stage 1 or 2 CKD, 39.0% had Stage 3, 17.8% had Stage 4, and 3.4% had Stage 5 with or without dialysis; 5.9% had experienced kidney failure and received a kidney transplant. Most (85.6%) patients had comorbidities, and the four most commonly reported disorders were hypertension (37.3%), anemia (27.1%), depression (17.8%), and thyroid disease (16.1%).

HRQoL

Among adults with IgAN, mean SF-12 scores, reflecting the prior four weeks, were 46.7 (SD: 8.0) for the physical component and 41.9 (SD: 9.2) for the mental component, lower (worse) than the scores reported for the US general population (both 50 [10]) [38]. Among care-partners, mean SF-12 scores were 50.7 (SD: 7.3) for the physical component but 43.7 (SD: 10.2) for the mental component; the mental component score was also lower than that of the US general population [38]. The KDQoL-36 scores among adults with IgAN were 47.5 (SD: 25.7) for the burden of kidney disease, 62.7 (SD: 17.1) for symptoms/problems, and 66.0 (SD: 18.1) for the effects of kidney disease, with lower scores reflecting worse HRQoL.

In the two weeks prior to the survey, over one-quarter of adults with IgAN (27.1%) reported experiencing moderate

Table 1 Sociodemographic characteristics (HONUS cohort)

	Adults with IgAN (*N* = 118)	Care-partners of adults with IgAN (*N* = 117)
Age		
Mean ± SD, years	38.0 ± 8.6	40.2 ± 11.8
Median [range], years	36.0 [24.0, 72.0]	38.0 [20.0, 85.0]
Sex, N (%)		
Male	51 (43.2%)	65 (55.6%)
Female	66 (55.9%)	51 (43.6%)
Other/Unknown	1 (0.9%)	1 (0.9%)
Race, N (%)		
Asian and Pacific Islander	9 (7.6%)	8 (6.8%)
Black	8 (6.8%)	9 (7.7%)
Hispanic	5 (4.2%)	5 (4.3%)
Native American	1 (0.9%)	0 (0.0%)
Other[a]	1 (0.9%)	2 (1.7%)
Prefer not to answer	1 (0.9%)	0 (0.0%)
White	95 (80.5%)	97 (82.9%)
Marital status, N (%)		
Single	10 (8.5%)	6 (5.1%)
Married	102 (86.4%)	104 (88.9%)
Divorced	3 (2.5%)	4 (3.4%)
Widowed	1 (0.9%)	2 (1.7%)
Prefer not to answer	2 (1.7%)	1 (0.9%)
Employment status, N (%)		
Employed, full time	79 (67.0%)	97 (82.9%)
Employed, part time	7 (5.9%)	9 (7.7%)
Self employed	1 (0.9%)	4 (3.4%)
Unemployed, Looking for work	13 (11.0%)	1 (0.9%)
Unemployed, Not looking for work	7 (5.9%)	0 (0.0%)
Retired	0 (0.0%)	1 (0.9%)
Disability	5 (4.2%)	1 (0.9%)
Student	2 (1.7%)	1 (0.9%)
Homemaker	4 (3.4%)	3 (2.6%)
Insurance status,[b] N (%)		
Private insurance	60 (50.9%)	--
Medicare	52 (44.1%)	--
Medicaid	42 (35.6%)	--
Other[c]	3 (2.5%)	--
Care-partner relationship with patient		
Spouse/life partner	--	102 (87.9%)
Parent	--	4 (3.5%)
Friend	--	4 (3.5%)
Other relative	--	3 (2.6%)
Sibling	--	2 (1.7%)
Child	--	1 (0.9%)

Abbreviations: IgAN: immunoglobulin A nephropathy; SD: standard deviation.

Notes: [a] "Other" was reported as "Turkish race" for $n = 1$ patient and $n = 1$ caregiver, and "multiracial- White and Ashkenazi" for $n = 1$ caregiver. [b] Categories are not mutually exclusive. [c] Includes other public insurance (e.g., Veterans Affairs, Tricare, Affordable Care Act Exchanges)

Table 2 Disease characteristics (HONUS cohort)

	Adults with IgAN (*N* = 118)
Time from first symptoms to IgAN diagnosis[a]	
Mean ± SD, months	2.8 ± 6.9
Median [IQR], months	0.3 [0.2, 1.4]
Missing, N (%)	21 (17.8%)
Time since IgAN diagnosis[b]	
Mean ± SD, years	6.2 ± 5.0
Median [IQR], years	5.5 [2.9, 8.4]
Missing, N (%)	10 (8.5%)
CKD stage, N (%)	
Stage 1–2	36 (30.5%)
Stage 3	46 (39.0%)
Stage 4	21 (17.8%)
Stage 5	4 (3.4%)
With dialysis	3 (2.5%)
Without dialysis	1 (0.9%)
Kidney failure, received transplant	7 (5.9%)
Do not know	4 (3.4%)
Comorbidities, N (%)	101 (85.6%)
Top four comorbidities	
Hypertension	44 (37.3%)
Anemia	32 (27.1%)
Depression	21 (17.8%)
Thyroid disease	19 (16.1%)

Abbreviations: IgAN: immunoglobulin A nephropathy; IQR: interquartile range; SD: standard deviation.

Notes:[a] Calculated among $n = 97$ patients with this information. [b] Calculated among $n = 108$ patients with this information

or severe anxiety as assessed by the GAD-7 (Fig. 1A) and approximately half (49.2%) reported experiencing at least moderate depression as assessed by the PHQ-9 (Fig. 1B). Additionally, 13.7% of care-partners experienced moderate anxiety and 37.8% experienced moderate to moderately severe depression in the 2 weeks prior to the survey (Fig. 1C and D). Adults with IgAN had significantly higher severity of anxiety (6.6 vs. 5.4, Cohen's d: 0.22, $p < 0.0001$) and depression (8.1 vs. 6.6, Cohen's d: 0.23, $p < 0.0001$) compared to external controls, although the effect sizes were small (Table S2).

Most burdensome symptoms and fear/uncertainty about the future

The top three most burdensome symptoms reported by adults with IgAN (i.e., rated as somewhat [score of 2] to extremely [score of 5] bothered by) were lower back pain (76.3%), constipation (75.4%), and bone or joint pain (67.8%) (Fig. 2A).

Almost all (96.6%) adults with IgAN and their care-partners (99.2%) reported feeling fear and uncertainty about the future due to the disease (i.e., rated as "rarely" [17.8%

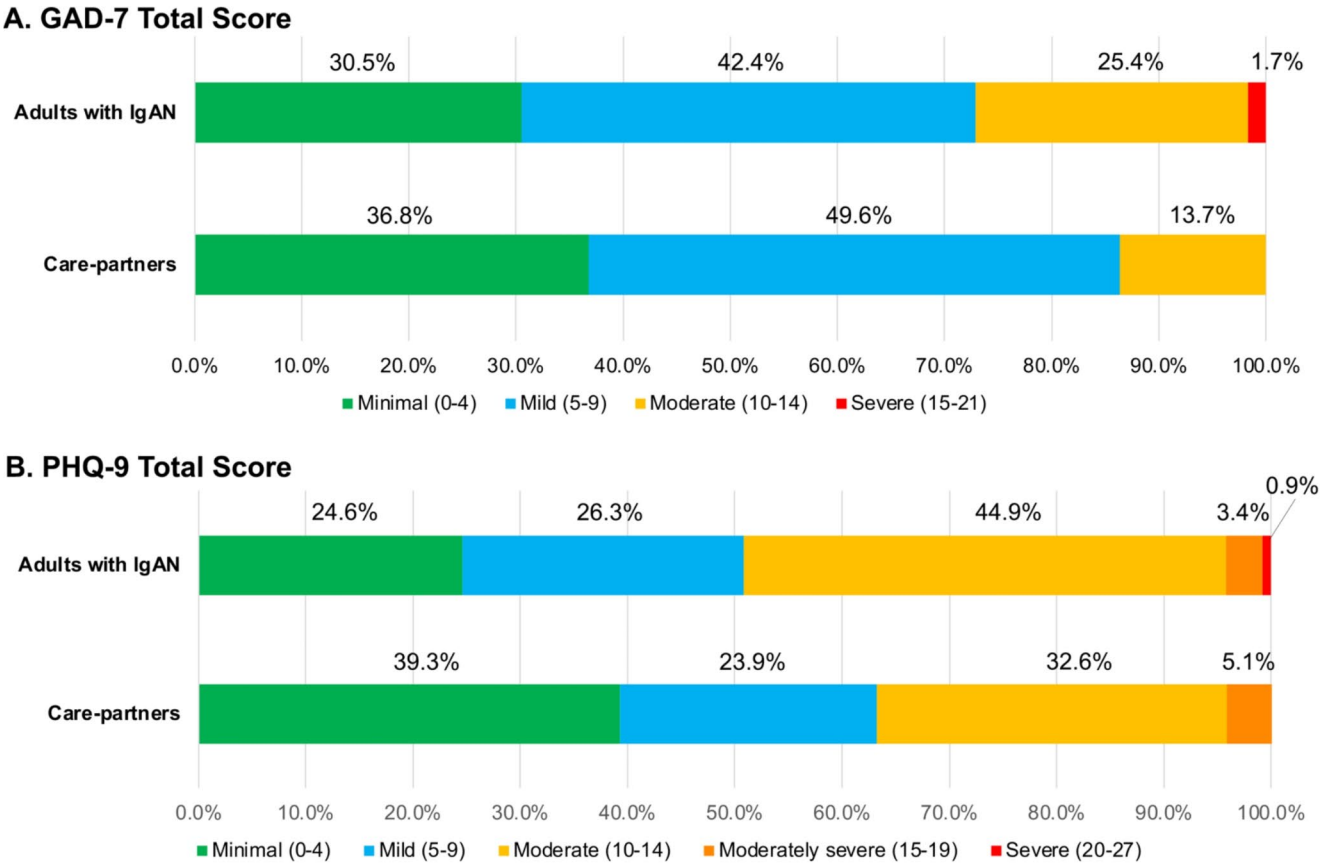


Fig. 1 GAD-7[a] (anxiety)(**A**) and PHQ-9[b] (depression)(**B**) total scores among adults with IgAN and their care-partners
Abbreviations: IgAN: immunoglobulin A nephropathy; GAD-7: General Anxiety Disorder-7; PHQ-9: Patient Health Questionnaire-9.
Notes:[a]GAD-7 is calculated by assigning scores of 0, 1, 2, and 3 to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. GAD-7 total score for the seven items ranges from 0 to 21, with 0–4 indicating minimal anxiety, 5–9 indicating mild anxiety, 10–14 indicating moderate anxiety, and 15–21 indicating severe anxiety. The recall period is the past 2 weeks. [b] PHQ-9 scores are calculated based on how frequently a person experiences feelings of depression. Each "not at all" response is scored as 0; "several days" is 1, "more than half the days" is 2, and "nearly every day" is 3. The sum value of these responses gives the total score, with 0–4 indicating minimal depression, 5–9 indicating mild depression, 10–14 indicating moderate depression, 15–19 indicating moderately severe depression, and 20–27 indicating severe depression. The recall period is the past 2 weeks

and 26.5%, respectively], "sometimes" [27.1% and 30.8%], "often" [46.6% and 39.3%], or "always" [5.1% and 2.6%]) (Fig. 2B, **top**). Similarly, almost all adults with IgAN (94.7%) and their care-partners (93.2%) were impacted by their fear and uncertainty about the future to some degree, and 11.4% and 19.0%, respectively, reported that it impacted them "very much" (Fig. 2B, **bottom)**.

Work productivity

The majority (72.0%, $n=85$) of adults with IgAN and nearly all (93.2%, $n=109$) care-partners had worked in the past 7 days. Employed adults with IgAN and care-partners reported 8.8% and 9.4%, respectively, of working time missed (absenteeism), 25.9% and 25.1% of impairment while working (presenteeism), and 30.5% and 30.4% overall work impairment due to IgAN-related reasons (Fig. 3).

Activity impairment due to IgAN-related reasons was substantial among adults with IgAN (34.0% [SD: 24.4]) and their care-partners (29.2% [25.1]). Compared to weighted external controls, adults with IgAN experienced significantly greater overall work impairment (30.5% vs. 23.7%, Cohen's d: 0.24, $p<0.0001$) and significantly greater activity impairment (34.0% vs. 26.6%, Cohen's d: 0.26, $p<0.0001$). The absolute differences between HONUS and NHWS for absenteeism (8.8% vs. 10.1%; Cohen's d: -0.06, $p<0.0001$) and presenteeism (25.9% vs. 28.1%; Cohen's d: -0.07, $p<0.0001$) were small but statistically significant (Table S2).

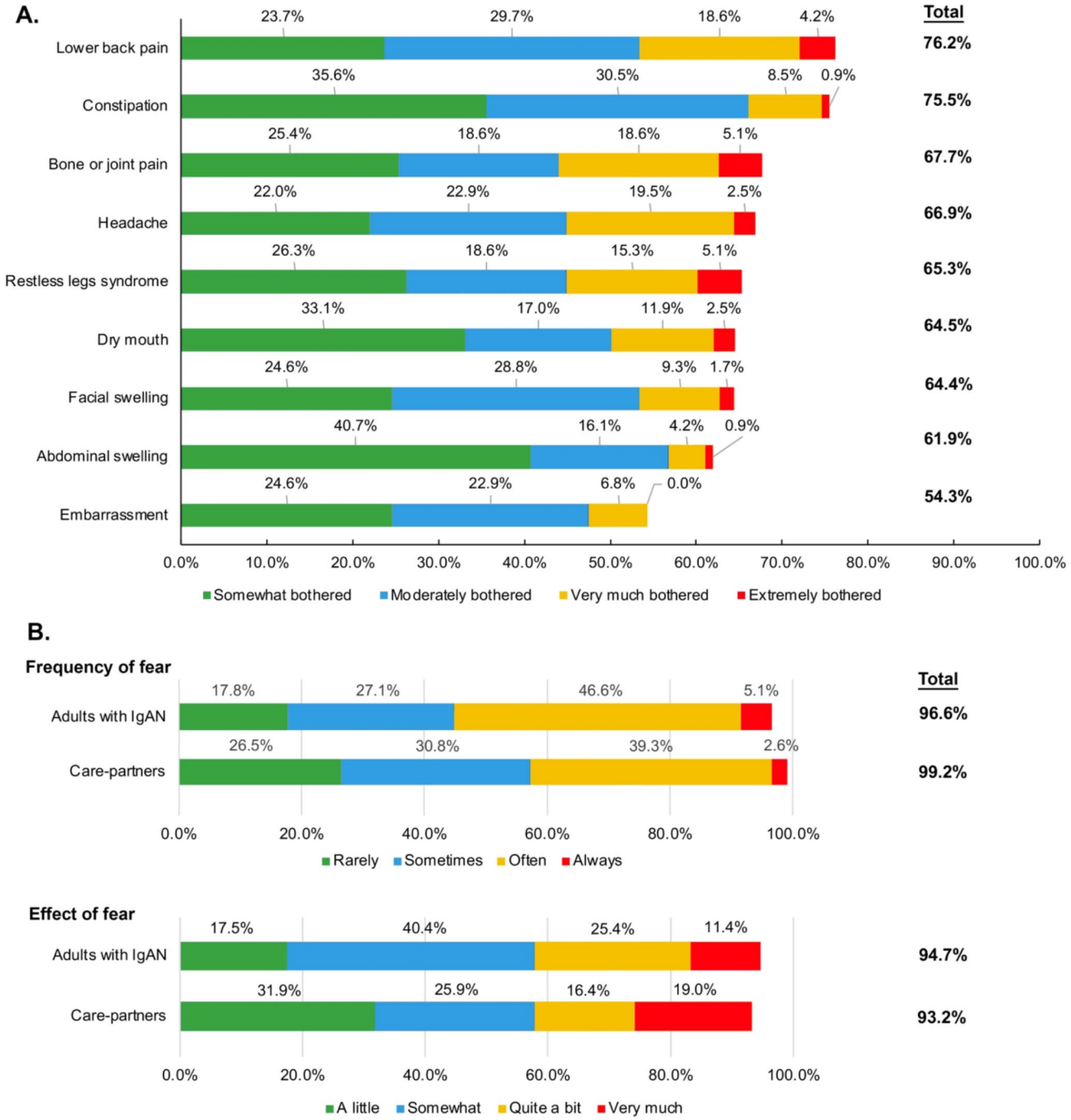


Fig. 2 Most burdensome symptoms among adults with IgAN (**A**) and fear/uncertainty about the future[a], due to the disease, among adults with IgAN and care-partners (**B**)

The totals in bold text refer to the total proportion of the cohort that affirmatively reported some degree of the outcome. Abbreviation: IgAN, immunoglobulin A nephropathy.

Notes: [a] Frequency of IgAN-related fear was calculated among all ($n = 118$) adults with IgAN and all ($n = 117$) care-partners. Effect of IgAN-related fear was calculated among $n = 114$ adults with IgAN ($n = 4$ missing [3.4%]) and $n = 116$ care-partners ($n = 1$ missing [0.9%])

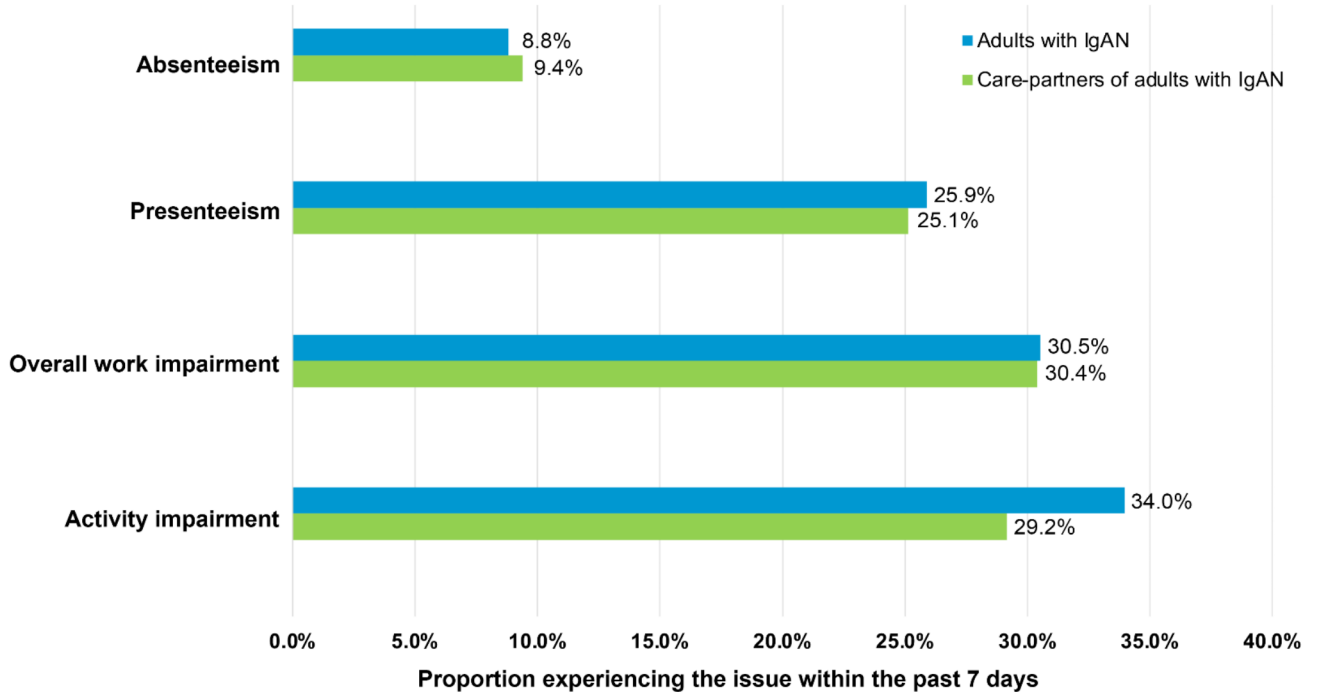


Fig. 3 Work productivity among adults with IgAN and their care-partners, measured with WPAI: SHP
Abbreviations: IgAN: immunoglobulin A nephropathy; WPAI: SHP: Work Productivity and Activity Impairment Questionnaire: Specific Health Problem
Notes: The proportions reporting absenteeism (work time missed) and overall work impairment were only assessed among respondents who were employed at the time of survey (adults with IgAN: $n = 88$; care-partners: $n = 110$). Presenteeism (impairment while working) was assessed among respondents who were employed and worked in the past 7 days (adults with IgAN: $n = 85$; care-partners: $n = 109$). Activity impairment was assessed among all respondents. The recall period was the past 7 days.

Discussion

To our knowledge, this is the first study to evaluate the humanistic burden associated with IgAN from the both the patient and caregiver perspectives using a cross-sectional survey in the US. The present findings indicate that US adults with IgAN experienced heightened mental and physical HRQoL impairments, as well as significantly greater overall work impairment and activity impairment, compared to the general US population. Although only 17.8% of adults with IgAN reported having depression as a comorbidity, approximately half (49.2%) had PHQ-9 scores indicating at least moderate depression, suggesting underdiagnosis or low awareness of the disorder in this population. Strikingly, the care-partners of adults with IgAN also had considerably worse mental HRQoL compared to the general US population, as well as impaired work productivity. The vast majority of adults with IgAN, as well as their care partners, reported feeling fear and uncertainty about the future due to the disease and to be impacted to some degree by that fear and uncertainty.

There are few published studies with which to compare the current findings, underscoring the understudied nature of the humanistic burden of IgAN in the US. For example, a 2023 systematic review by Jhaveri et al. summarizing the existing evidence on the global burden of IgAN identified only three studies reporting on the humanistic impact (i.e., HRQoL or health state utility outcomes), none of which were based solely in the US [39]. Specifically, the identified studies of the humanistic impact of IgAN reported patient preferences in China and the US [40], HRQoL for people with IgAN in Poland [41], and the impact of an exercise intervention on the HRQoL of people with IgAN in China [15]. The patient preferences study conducted in the US and China (Marsh et al. [40]) included 40 adults with IgAN, 25 of whom were in the US. It reported that patients placed the greatest value on avoiding end-stage kidney disease and infections, and on improvements in short-term quality-of-life [40]. The study conducted in Poland (Mizerska-Wasiak et al. [41]) assessed HRQoL among 51 pediatric patients (mean age of 14.5 years) with IgAN with the Kidscreen-52 questionnaire. The findings indicated worse physical and psychological wellbeing in Polish children with IgAN compared to their healthy peers [41], similar to the present findings among US adults. The third identified study was a prospective observational study among adults with IgAN

in China (Zhao et al. [15]), which reported that the SF-36 mental (44.7 [SD: 7.9]) and physical (41.6 [7.2]) component scores were worse than the general US population, also similar to the present study. However, we note that eligible participants in Zhao et al. had at least mild depression and an older mean age (58.1 years) than the present study (38.0 years).

An international, retrospective study using data from a cross-sectional survey of IgAN nephrologists (reporting on 306 IgAN cases) and people with IgAN ($n = 68$) assessed the impact of IgAN on daily functioning and work productivity using the WPAI-General Health tool [42]. At the time of the survey, participants reported 7.9% missed work time (i.e., absenteeism), 24.3% impairment while working (i.e., presenteeism), and 32.9% overall work impairment. These findings are similar to the present results of 8.8% absenteeism, 25.9% presenteeism, and 30.5% overall work impairment among adults with IgAN, noting use of a slightly different version of the WPAI in the current study. However, it should be mentioned that both absenteeism and presenteeism were lower among adults with IgAN in this study compared to the external controls, although the absolute differences were small.

In terms of the burden among care-partners of adults with IgAN, Gilbertson et al. [43] conducted a global systematic review of studies reporting on the burden of care and HRQoL among 5,367 caregivers of adults receiving maintenance dialysis. The HRQoL of caregivers, and particularly mental health, was poorer compared to the general population, in line with prior reports of HRQoL among caregivers for people with other chronic diseases [43]. Similar to the present results, the majority of caregivers in the identified studies were patients' spouses or life-partners and their HRQoL was usually better than that of the patients they cared for, although their mental health was particularly affected. Additionally, a social media study among caregivers of people with IgAN noted that the low availability of detailed information and lack of counseling caused emotional stress [44], pointing to a potential area of needed support for care-partners.

A recent (2022) study by Zhou et al. [45] elicited utility values for IgAN health states from the United Kingdom general public via computer-assisted telephone interviews. The respondents were presented with nephrologist-validated written vignettes describing different health states for IgAN associated with different CKD stages, proteinuria levels, and dialysis status; time trade-off methods were used to estimate utility values. The results indicated that IgAN health states had reduced utility values compared to full health, with CKD stage progression, proteinuria level, and dialysis associated with further utility decrements. Thus, that study's results reflect the present real-world findings that the symptoms and experience of IgAN are associated with negative impacts to HRQoL. Further, as only 3.4% of the study population of adults with IgAN had stage 5 CKD, the presence of severe CKD and its complications cannot fully account for the present results.

The current results from the HONUS study contribute to the sparse existing literature by quantifying the humanistic burden of US adults with IgAN as well as their care-partners. Nevertheless, this study is also subject to several limitations, some of which are inherent to survey studies. First, selection bias may exist as adults with IgAN and their care-partners who voluntarily participated in the survey may differ from those who did not. For example, 56% of the survey patient participants were female, although IgAN is reported to be more prevalent in males vs. females in North America and Europe [46]. This could be related to the greater representation of females in patient advocacy groups [47]. In addition, missing responses may differ from non-missing responses (e.g., disease characteristics). Second, the study relied on self-reported survey responses and therefore could be subject to recall bias or other biases. Additionally, participants' self-reported disease history and diagnosis of comorbidities may differ from a clinician's assessment. Third, patients' most burdensome symptoms may change over time depending on duration of disease, treatment, and other factors; the current results represent a snapshot in time during the survey's conduct. Finally, participant responses may be influenced by the COVID-19 pandemic given that data collection was conducted between 2022 and 2023. This broader circumstance may also impact health outcomes and reported HRQoL.

Conclusions

This cross-sectional survey study conducted among US adults with IgAN and their care-partners identified impairments to mental and physical HRQoL, as well as heightened levels of depression and anxiety, compared with the US general population. Further, both groups exhibited high rates of fear and uncertainty for the future and negative impacts to their work productivity due to IgAN. This study contributes valuable data on the humanistic burden of IgAN in the US and underscores the need for effective therapies for patients as well as the importance of support for their care partners.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11136-024-03813-x.

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Author contributions Conceptualization: MB, JS, UF, DG, KB, KK-Z, KH, DR, BS, PS, KT, AP-M, BH, Z-YZ, NCH, AW, IN, CX, JL. Data curation: Z-YZ, NCH, AW, IN, CX, JL, BLB, AKJ. Resources: Z-YZ, NCH, AW, IN, CX, JL. Formal analysis: Z-YZ, NCH, AW, IN, CX, JL, BLB, AKJ. Supervision: MB. Software: Z-YZ, NCH, AW, IN, CX, JL, BLB, AKJ. Funding acquisition: MB, BH. Investigation: DG, KG, KH, BS, AP-M, Z-YZ, NCH, AW, IN, CX, JL, BLB, AKJ. Methodology: MB, Z-YZ, NCH, AW, IN, CX, JL, BLB, AKJ. Validation: Z-YZ, NCH, AW, IN, CX, JL. Visualization: Z-YZ, NCH, AW, IN, CX, JL. Project administration: MB. Writing- original draft: MB, Z-YZ, NCH, AW. Writing- review and editing: All authors.

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Declarations

Ethics approval The survey and all associated patient-facing materials were granted an exemption from full review by the Pearl Institutional Review Board on June 21, 2021, and the study is compliant with the Health Insurance Portability and Accountability Act and Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Competing interests Bruce Hendry is an employee of Travere Therapeutics, Inc. and holds stock/options. Mark Bensink is Managing Director of Benofit Consulting, which received consulting fees from Travere Therapeutics, Inc. for this work. Justyna Szklarzewicz, Ute Floege, Daniel Gallego, Keisha Gibson, Kamyar Kalantar-Zadeh, Kelly Helm, Dale Robinson, Bonnie Schneider, Philip Smith, Kjell Tullus, and Ali Poyan-Mehr received consultancy fees from Travere Therapeutics, Inc. for this work. Bridget L Balkaran and Adam K Jauregui are employees of Oracle Life Sciences, which received consultancy fees from Travere Therapeutics, Inc. for this work. Jingyi Liu, Chunyi Xu, Ian Nason, Aolin Wang, Nisha C. Hazra and Zheng-Yi Zhou are employees of Analysis Group, which received consultancy fees from Travere Therapeutics, Inc. for this work.

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