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ORIGINAL ARTICLE

# Long-term health-related quality of life outcomes of adults with pediatric onset of frequently relapsing or steroid-dependent nephrotic syndrome

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## Abstract

**Background** Long-term psychosocial outcomes and health-related quality of life (HRQOL) in adults with pediatric onset of frequently relapsing or steroid-dependent idiopathic nephrotic syndrome (FRNS or SDNS) remain to be determined.

**Methods** In this prospective cohort study, 59 adults with pediatric onset of FRNS/SDNS and persistent active glomerular disease in adulthood completed the GEDEPAC-2 questionnaire exploring 11 well-being domains. Data were compared to the French general population (FGP) with standardized incidence ratio ([SIR]; adjusted for period, age, gender). Regression models were performed to identify predictive factors of psychosocial well-being.

**Results** In 82% of cases, the questionnaire was completed while the participants (n = 59; 47 men; median age = 32 years; median number of relapses = 13) were in complete remission (under specific therapy in 76% of cases). Participants had higher educational degree than in the FGP (SIR = 6.3; $p < 0.01$) and more frequently a managerial occupation (SIR = 3.1; $p < 0.01$). Social integration was acceptable with regard to marital status and experience of sexual intercourse, but experiences of discrimination were far more frequent (SIR = 12.5; $p < 0.01$). The SF-12 mental component summary (MCS) score was altered (Z-score = − 0.6; $p < 0.01$) and mean multidimensional fatigue inventory (MFI-20) global fatigue score appeared high (12). Transfer from pediatric to adult healthcare was followed by a period of discontinued care for 33% of participants. Multivariate analysis revealed a close relationship between MFI-20, physical health, and MCS.

**Conclusions** This study shows that pediatric onset FRNS and SDNS may have a long-term negative impact on mental HRQOL and highlights the impact of fatigue, which is often not adequately considered in routine care.

Vincent Audard and Hélène Mellerio have contributed equally to this work and are joint senior authors.

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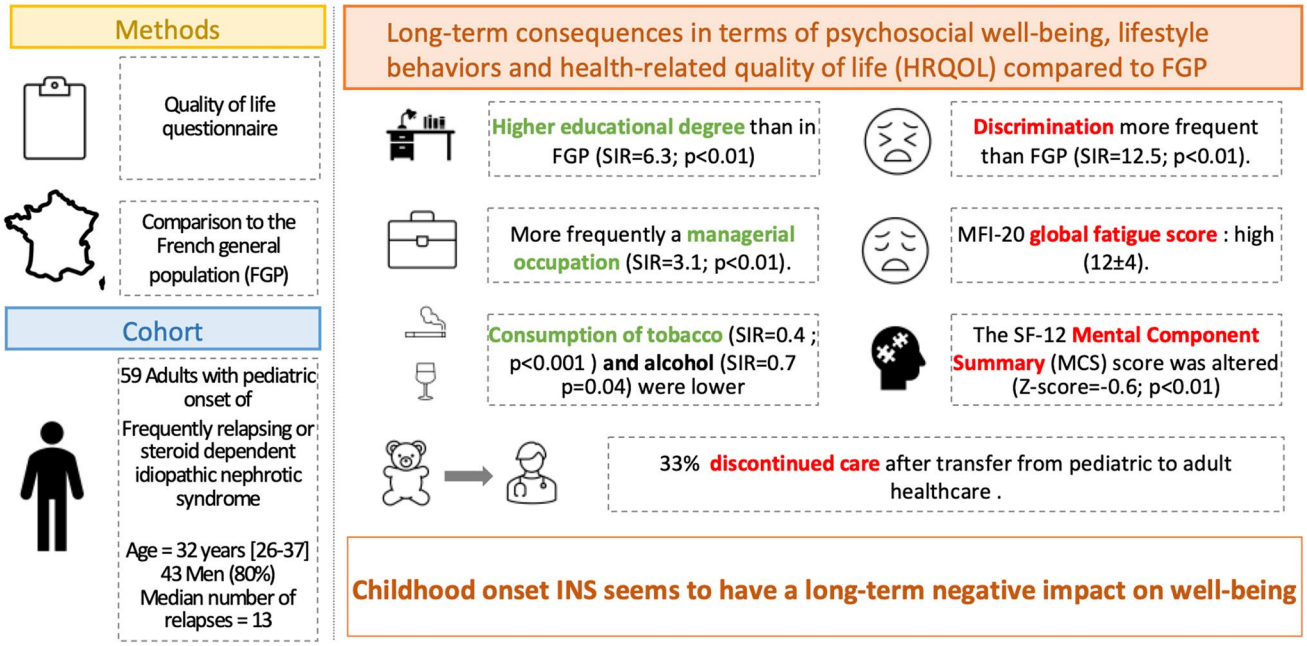
**Graphic abstract**




**Keywords** Idiopathic nephrotic syndrome · Quality of life · Education · Family life · Socioprofessional status · Long-term outcomes

**Abbreviations**

| | |
|---|---|
| CC | Chronic condition |
| FGP | French general population |
| FRNS | Frequently relapsing nephrotic syndrome |
| HRQOL | Health-related quality of life |
| INS | Idiopathic nephrotic syndrome |
| MCS | Mental component summary |
| NS | Nephrotic syndrome |
| OR | Odds ratio |
| PCS | Physical component summary |
| SDNS | Steroid-dependent nephrotic syndrome |
| SF-12 | Short Form questionnaire 12 |
| SIR | Standardized incidence ratio |

## Introduction

Idiopathic nephrotic syndrome (INS), is the most frequent glomerular disease in children and a major cause of primary nephrotic syndrome (NS) in adults [1]. While steroid therapy remains the cornerstone of the initial treatment [2], a major concern in the management strategy is the risk of relapse after withdrawal of steroids or steroid dependency to maintain complete remission. Overall, more than 50% of adults experience at least one relapse [3] and more than 50% of children have a frequently relapsing NS (FRNS) or a steroid-dependent NS (SDNS) [1, 4]. To reduce the risk of adverse effects related to prolonged steroid therapy [5], immunosuppressive agents may be added to maintain remission [1]. Finally, the natural history of INS, with periods of relapse and remission, makes it a chronic condition (CC), interfering in childhood as in adulthood with well-being, a multidimensional concept composed of both objective and subjective elements, including health-related quality of life (HRQOL) [6]. Nevertheless, HRQOL of children with FRNS or SDNS has been poorly studied. In 45 children with steroid-sensitive INS compared with healthy children, Ruth et al. found impaired HRQOL and decreased psychosocial adjustment, associated with cytotoxic medication use and with a poor family climate [7]. Other studies have highlighted that the duration and activity of INS negatively impact psychological well-being in children [8, 9]. Roussel el al. showed that HRQOL was significantly altered in children with SDNS with no difference between those receiving rituximab or oral immunosuppressive agents [10]. In adulthood, only one study, without a control group, has investigated the social status of adults with pediatric-onset INS [11], but HRQOL was not evaluated. Such data are however desperately needed to identify risk factors to prevent a potentially negative impact and to provide accurate information on

possible long-term issues in children affected by INS. In this study we sought to investigate psychosocial well-being, lifestyle behaviors and HRQOL of adults with pediatric onset of FRNS or SDNS and with persistent active glomerular disease in adulthood.

## Methods

### Study design

We conducted a cross-sectional study, comparing a set of clinical, psychosocial and HRQOL outcomes of adult patients with pediatric onset of FRNS or SDNS to the data of the French general population (FGP) matched for age, gender, and period.

### Population

Participants were recruited by the network of French rare disease centers dedicated to the management of INS between May 2016 and May 2017. In each center within the network, patients were identified from electronic medical registers. Inclusion and exclusion criteria are detailed in Online resource 1. Eligible patients were invited to participate by an information letter sent by e-mail. After receipt of their written informed consent, patients were included and sent secure online access codes to complete the questionnaire. This study was performed in accordance with the ethical standards of the Helsinki Declaration and the protocol was approved by the Ethics Committee of "Assistance Publique - Hôpitaux de Paris" (no. 15.582).

### Variables

Demographic, histological, biological, and therapeutic data were assessed in medical records. Definition of INS in children, chronic kidney failure, weight excess and complete remission are given in Online resource 2. Social and HRQOL outcomes were assessed using the GEDEPAC-2 questionnaire [12], exploring long-term outcome in adults suffering from a CC with pediatric onset through 11 fields of well-being (education, employment, housing, material security, social life, civic engagement, leisure, health including transition from pediatric to adult care, risk behavior, QOL, sexuality). It includes 109 items, 31 indicators comparable to FGP data gathered by INSEE (French National Institute of Statistics and Economic Studies) and 3 QOL scales validated in French. The Short Form-12 questionnaire (SF-12) [13], is made up of 8 physical and mental health subscales which can be summarized with a physical and a mental component summary (PCS and MCS, respectively), scored from 0 to 100 (higher scores indicating higher QOL). The Treatment Burden Questionnaire (TBQ) [14] explores the daily psychosocial impact of the treatment though 15 items scored from 0 to 10 (higher scores indicating higher impact; global score below 59 indicating an acceptable burden of treatment [15]). The 'general fatigue' dimension (4 items) of the Multidimensional Fatigue Inventory questionnaire (MFI-20) [16] assessed global fatigue through a score from 4 to 20 (a higher score indicating a higher degree of fatigue).

### Statistical analysis

Qualitative variables are described as frequencies (percentages), quantitative variables as means (± standard deviation, [SD]) or median [interquartile range] (min–max), respectively, for Gaussian and non-Gaussian distribution. For comparisons of quantitative data we used: Z-scores (adjusted for period, age and gender; a Z-score of 0 corresponds to the mean value of the FGP) for SF-12 (PCS and MCS) and Chi-square test for sexuality concerns. For comparisons of qualitative data we used standardized incidence ratio ([SIR], adjusted for period, age, gender ± educational level or maternal educational level, depending on the studied factors; a SIR of 1 corresponds to the mean percentage of the FGP). FGP data were obtained from various national institutes or national studies, detailed in a previous article [12]. Regression models were performed to identify predictors of well-being (linear models for MFI-20 and SF12; logistic models for education, professional status, and discontinued care). Selection of variables was carried out by a stepwise procedure adjusted for age and gender (significance level for entering an effect into the model = 0.2; for staying in the model = 0.05). Results are expressed as odds ratio (OR) with 95% confidence interval (CI). Analyses were conducted using SAS®-v9.6 software (SAS Institute Inc., Cary, NC). All tests were bilateral (significance level = 0.05).

## Results

### Demographic, clinical, biological, and pathological characteristics and therapeutic data

A total of 71 adults with pediatric onset INS fulfilled the inclusion criteria. Among them, 59 (median age = 32 years [26–37]; men = 47 (80%)) completed the questionnaire (Online resource 3). Clinical, biological, and pathological characteristics and therapeutic data, available for 54 participants (median age = 32 years [27–38]; men = 43 (80%)) are summarized in Table 1. At the time of the study, the median number of relapses was 13 [9–21] and 66% (33/50)

had presented more than 10 relapses since the onset of the disease. After excluding from the analysis two participants on renal replacement therapy, median estimated glomerular filtration rate at inclusion was 112 ml/min/1.73 $m^2$ [99–123] and participants were considered to be in complete remission of NS in 82% of cases (under specific therapy in 76% of cases). Reported comorbidities consisted mainly in side effects of steroid therapy (Table 1).

## Educational level, professional life

When adjusted for age, gender, and maternal educational level, participants were more likely to have obtained a higher-level educational degree compared to the FGP (≥ 3-year university degree: SIR = 6.3 [4; 8.6]) and less likely to have a vocational training certificate (SIR = 0.2 [0; 0.4]) (Table 2). Consistent with educational level, professional occupation was significantly different from the FGP, with more participants holding managerial occupations than expected (statistically different between INS participants and the FGP regarding management and academic professions: SIR = 3.1 [1.9; 4.4], and for factory workers: SIR = 0.2 [0.0; 0.5]). According to gender, we did not find that employment and unemployment were different from the FGP (Online resource 4). Professional inactivity was less frequent in participants than in the FGP (SIR = 0.4 [0.0; 0.8]) (Table 2). Thirty-three percent of participants (19/57) experienced difficulties in finding work, in most cases due to the disease burden (27%, 4/15). In 27% of respondents (15/56), the choice of occupation was strongly influenced by their previous medical history. Mean monthly income from work, including social allowances, was 2948 euros compared to 2988 euros in the FGP. A comparison of monthly income between different categories of the FGP is shown in Online resource 5.

## Family and social life

The proportion of persons living with a partner was not different between participants and the FGP (Table 2) and, among participants, 38% (20/53) had biological children (median = 2 [1; 3]; men: 33% (14/42); women: 55% (6/11)). Three quarters of the participants declared having suffered from discrimination, far higher than in the FGP (SIR = 12.5 [8.8; 16.2]), at school (66%), by friends (42%), work colleagues (39%), family members (11%), or employers (9%). Due to the direct consequences of INS, 41% of participants (24/58) had renounced sports activities during adulthood and 50% (25/50) during childhood. A total of 59% (34/58) had given up school trips, most often because of the treatment burden (85%, 29/34). As shown in Table 2, the proportions of current tobacco smokers and current alcohol users were significantly lower in participants than in the FGP (current tobacco smokers: SIR = 0.4 [0.2; 0.7]; alcohol users: SIR = 0.7 [0.5; 1]). Median age at first sexual intercourse, was 19 years [18–23] in women, significantly higher than in the FGP (p = 0.03; median difference from the FGP of 1.6 years [0.4–5.8]). Conversely, no difference was found for men (18 years [17–19]; p = 1.0; median difference from the FGP of 0.0 years [− 0.9–1.5]). High satisfaction with sexual life was less frequent than in the FGP (SIR = 0.3 [0.1; 0.6]) (Table 2). Only 9% (5/53) of participants declared having already talked about sexuality with a doctor.

## Health-related quality of life

The PCS of participants was not different from the FGP (PCS Z-score = 0.0 [− 0.3; 0.3]; p = 0.9) but the MCS was significantly more altered (MCS Z-score = − 0.6 [− 0.9; − 0.3]; p < 0.001). The mean global fatigue score (MFI-20) was 12 (± 4) (Online resource 6). The Treatment Burden Questionnaire revealed an acceptable level of burden for 44 participants (75%) but emphasized four domains impacting daily life: "Frequent healthcare as a reminder of the chronic condition" (O), "Diet constraints" (L), "Having to remind oneself not to forget medication" (C) and "Arranging appointments and scheduling doctors' visits and lab tests" (I) (Fig. 1).

## Transition from pediatric to adult health care

Transfer to adult health care occurred at a median age of 19 years [18–20], with a feeling of appropriate timing for 78% of the participants (40/51) and of a continuity in the medical care for 74% (37/50). Only 35% (18/52) had been prepared for transition. In adult health care, most parents (46/51) attended the first medical appointments (parents not wanting to attend = 4/51; adolescents not wanting their parents to attend = 1/51). During the 5 years following the transfer, 29% (14/49) changed hospitals and 33% (17/51) had a period of discontinued care (median duration = 12 months [6–21]).

## Correlation of clinical and socio-demographic parameters with the social and HRQOL outcomes

In multivariate analysis, none of the studied factors was associated with the highest level of education (Online resource 7). PCS was the only factor significantly correlated with professional status (OR = 1.1 [1.0; 1.2], p = 0.04). MCS was associated with the global fatigue score (OR = 1.5 [0.9; 2.2], p < 0.001), and the global fatigue score (MFI-20) was

**Table 1** Clinical, biological, and pathological characteristics and therapeutic management of the participants

| | Available data[a] | Results |
|---|---|---|
| Demographic data | | |
| Age (years) | n = 59/59 | 32 [26–37] (21–59) |
| Gender—male | n = 59/59 | 47 (80) |
| Data about past history of INS | | |
| Age at 1st episode of INS (years) | n = 52/54 | 3 [2–6] (1–16) |
| Number of relapses | n = 50/54 | 13 [9–21] (2–40) |
| 1–5 relapses | | 4 (8) |
| 6–10 relapses | | 13 (26) |
| 11–15 relapses | | 12 (24) |
| 16–20 relapses | | 8 (16) |
| > 20 relapses | | 13 (26) |
| Number of treatment lines[b] | n = 54/54 | 3 [2–4] (0–6) |
| Renal biopsy findings | | |
| Participants who underwent kidney biopsy | n = 47/54 | 36 (77) |
| Delay between first episode of INS and renal biopsy (years) | n = 33/36 | 4 [1–12] (0–23) |
| Type of glomerular disease | n = 36/36 | |
| Minimal change disease | | 29 (81) |
| Focal segmental glomerulosclerosis | | 5 (14) |
| Diffuse mesangial proliferation | | 2 (5) |
| Clinical data and laboratory parameters at the time of the study | | |
| Body mass index (kg/m$^2$) | n = 52/59 | 24 [22–26] (18–39) |
| < 25 | | 34 (66) |
| [25–30] | | 13 (25) |
| ≥ 30 | | 5 (10) |
| Systolic blood pressure (mmHg) | n = 46/54 | 125 [120–133] (109–160) |
| Diastolic blood pressure (mmHg) | n = 46/54 | 76 [70–80] (50–100) |
| Renal function—eGFR[c] (ml/min/1.73 m$^2$) | n = 50/52 | 112 [99–123] (15–165) |
| Normal renal function (eGFR > 60 ml/min/1.73 m$^2$) | | 46 (92) |
| Chronic renal failure (eGFR ≤ 60 ml/min/1.73 m$^2$) requiring RRT | | 2 (4) |
| Chronic renal failure under RRT | | 2 (4) |
| Chronic dialysis | | 1 (2) |
| Kidney transplantation | | 1 (2) |
| Urine protein to creatinine ratio (mg/mmol creatinine) | n = 50/54 | 0 [0–11] (0–1239) |
| < 100 mg/mmol | | 45 (90) |
| 100–300 mg/mmol | | 3 (6) |
| > 300 mg/mmol | | 2 (4) |
| Complete remission status[d] | n = 50/54 | |
| Remission | | 41 (82) |
| Including remission under specific therapy | n = 33/41 | 25 (76) |
| Non remission | | 9 (18) |
| Treatment | n = 45/54 | |
| Specific therapy for idiopathic INS[e] | | 34 (76) |
| Corticosteroids only | | 11 (24) |
| Corticosteroids associated with 1 immunosuppressive therapy | | 8 (18) |
| Corticosteroids associated with 2 immunosuppressive therapies | | 1 (2) |
| Immunosuppressive therapy alone | | 3 (7) |
| Rituximab alone | | 7 (16) |
| Corticosteroids in association with rituximab | | 3 (7) |
| Rituximab in association with tacrolimus | | 1 (2) |
| No treatment | | 11 (24) |

**Table 1** (continued)

| | Available data[a] | Results |
|---|---|---|
| Comorbidities | | |
| Stretch marks | n = 52/59 | 20 (38) |
| Acne | n = 53/59 | 19 (36) |
| Hirsutism | n = 53/59 | 13 (25) |
| Hypertension | n = 54/54 | 13 (24) |
| Osteoporosis | n = 53/59 | 8 (15) |
| Growth delay with growth hormone therapy | n = 53/59 | 9 (17) |
| Depressed state | n = 54/59 | 6 (11) |
| Thrombophlebitis | n = 53/59 | 5 (9) |
| Asthma | n = 53/59 | 5 (9) |
| Arrhythmia | n = 53/59 | 4 (8) |
| Cataract | n = 53/59 | 3 (6) |
| Sleep disorder | n = 54/59 | 3 (6) |
| Diabetes | n = 52/54 | 2 (4) |

Note: Qualitative variables are described as frequencies (percentages), quantitative variables as means (standard deviation, SD) or median [interquartile range] (min–max) respectively for Gaussian and non-Gaussian distribution

*INS* idiopathic nephrotic syndrome, *eGFR* estimated glomerular filtration rate, *RRT* renal replacement therapy

[a]Self-reported data from 59 participants were analyzed but relevant clinical data were available for only for 54 participants

[b]Except steroid therapy

[c]Glomerular filtration rate (GFR) was estimated (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation

[d]Complete remission: participants with a urine protein to creatinine ratio below 30 mg/mmol (participants under dialysis or grafted cannot be considered in complete remission)

[e]Participants treated with rituximab were considered as being under specific therapy if they had received rituximab during the previous 6 months

strongly related to mental and physical QoL (OR = 0.2 [0.1; 0.3] and 0.2 [0.1; 0.2], respectively, both $p < 0.001$).

### Identification of factors associated with discontinued care after transition from pediatric to adult health care

In univariate analysis, both MCS and MFI-20 appeared to be correlated to discrimination (OR = − 10.9 [− 17.2; − 4.6] and − 4.0 [− 6.1; − 1.8], respectively; both p = 0.001) and MCS also appeared to be correlated to hirsutism (OR = − 8.3 [− 15.3; − 1.3], p = 0.02) (Online resource 7). In multivariate analysis, discontinued care after transition from pediatric to adult health care was significantly associated with the feeling of needing to contact their pediatrician again (OR = 0.2 [0.0; 0.7], p = 0.02) (Table 3). The adult nephrologist clinician's lack of awareness of the young patient's medical history appeared to be correlated with discontinued health care in univariate but not in multivariate analysis (OR = 5.8 [1.1; 31.7], p = 0.04).

## Discussion

This study provides the first comprehensive overview of the quality of life and well-being of adult patients with pediatric-onset FRNS or SDNS and persistent disease in adulthood.

Consistent with previous studies [5], our cohort, which included 59 adults with a prolonged history of INS, exhibited preserved renal function (only two patients with end-stage kidney disease). We can therefore consider that the responses to the questionnaire reflect the specific consequences of INS rather than those due to severe chronic renal failure. Among side effects of specific therapies, hypertension, excess weight, thrombophlebitis and dermatological disorders seemed to be more frequent in our population than in other studies [11, 17, 18]. This difference could likely be explained in part by our method of collecting information. Indeed, participants may be more confident about sharing details of the impact of their CC when completing an anonymous online questionnaire than during a medical appointment [19]. Conversely, osteoporosis and cataract were reported in only 15% and 6% of our participants, respectively, versus 36% and 20% when systematically assessed by prospective clinical examination [20].

**Table 2** Educational level and professional, social, and sex life of the participants compared to the french general population by indirect standardization, matched for age, gender, and period

| Variable | Observed n (%) | Expected n (%) | SIR (95% CI) | p value |
|---|---|---|---|---|
| Education | | | | |
| Highest level attained[a] (n = 47) | | | | |
| None | 0 (0) | 9 (20) | | |
| Primary school certificate[b] | 0 (0) | 8 (18) | | |
| Secondary education general certificate[c] | 0 (0) | 4 (9) | | |
| Vocational training certificate | 2 (4) | 12 (26) | 0.2 [0; 0.4] | < **0.001** |
| Baccalaureate[d] | 8 (17) | 5 (11) | 1.5 [0.5; 2.5] | 0.35 |
| 2-year university degree | 9 (19) | 3 (6) | 3.2 [1.1; 5.4] | **0.04** |
| 3-year university degree or higher | 28 (60) | 5 (10) | 6.3 [4; 8.6] | < **0.001** |
| No grade failure during primary school (n = 58) | 57 (98) | 55 (95) | 1.1 [0.7; 1.5] | 0.74 |
| Professional life | | | | |
| Occupation (n = 48) | | | | |
| Farmers | 1 (2) | 1 (2) | 1.0 [0.0; 5.8] | 0.63 |
| Independent tradespeople, shopkeepers, business owners | 1 (2) | 2 (4) | 0.4 [0.0; 1.2] | 0.16 |
| Management and academic professions | 23 (48) | 7 (15) | 3.1 [1.9; 4.4] | **0.001** |
| Intermediate professions | 9 (19) | 11 (23) | 0.8 [0.3; 1.4] | 0.53 |
| Low-level employees | 7 (15) | 9 (19) | 0.8 [0.2; 1.4] | 0.54 |
| Factory workers | 3 (6) | 13 (27) | 0.2 [0.0; 0.5] | < **0.001** |
| Inactive | 4 (8) | 6 (13) | 0.7 [0.0; 1.4] | 0.40 |
| Current work status (n = 55) | | | | |
| Employed | 43 (78) | 41 (74) | 1.1 [0.9; 1.2] | 0.38 |
| Unemployed and seeking work | 8 (15) | 5 (8) | 1.8 [0.5; 3] | 0.22 |
| Inactive | 4 (7) | 10 (18) | 0.4 [0.0; 0.8] | **0.003** |
| Working hours (n = 41) | | | | |
| Full-time | 37 (90) | 37 (89) | 1.0 [0.7; 1.3] | 0.9 |
| Part-time | 4 (10) | 5 (11) | 0.9 [0.0; 1.8] | 0.80 |
| Employment contract (n = 35) | | | | |
| Permanent contract | 31 (89) | 30 (86) | 1.0 [0.7; 1.4] | 0.84 |
| Fixed-term contract | 4 (11) | 3 (9) | 1.2 [0.0; 2.4] | 0.71 |
| Interim and apprenticeship contract | 0 (0) | 1 (6) | | |
| Family and social life | | | | |
| Marital status (n = 58) | | | | |
| Married or living with a partner | 24 (41) | 16 (28) | 1.5 [0.9; 2.1] | 0.11 |
| Single | 34 (59) | 40 (69) | 0.9 [0.6; 1.1] | 0.32 |
| Divorced | 0 (0) | 2 (3) | | |
| Experience of discrimination (n = 58) | 44 (76) | 3.5 (6) | 12.5 [8.8; 16.2] | < **0.001** |
| Voted in 1st round of presidential elections (n = 54) | 44 (82) | 42.9 (79) | 1.0 [0.7; 1.3] | 0.87 |
| Licensed drivers (n = 58) | 54 (93) | 52 (90) | 1.0 [0.8; 1.3] | 0.78 |
| Current tobacco users (n = 54) | 9 (17) | 20.6 (38) | 0.4 [0.2; 0.7] | < **0.001** |
| Current alcohol users (n = 54) | 34 (63) | 46 (85) | 0.7 [0.5; 1.0] | **0.04** |
| Renunciation of health care (n = 58) | 16 (28) | 14 (24) | 1.1 [0.6; 1.7] | 0.63 |
| Sex life characteristics | | | | |
| Experience of sexual intercourse (n = 53) | 51 (96) | 44 (83) | 1.2 [0.9; 1.5] | 0.33 |
| Sex life satisfaction (n = 52) | | | | |
| Very satisfied | 7 (14) | 21 (40) | 0.3 [0.1; 0.6] | < **0.001** |
| Quite satisfied | 35 (67) | 25 (48) | 1.4 [1; 1.9] | 0.09 |
| Little satisfied | 9 (17) | 4 (8) | 2.1 [0.7; 3.4] | 0.12 |
| Not satisfied | 1 (2) | 2 (4) | 0.5 [0.0; 1.4] | 0.27 |

Significant p values are in bold

[a]Adjusted for maternal educational level

[b]School-leaving qualification at end of primary education

[c]School certificate after 4 years of secondary education

**Table 2** (continued)

[d]High-school diploma

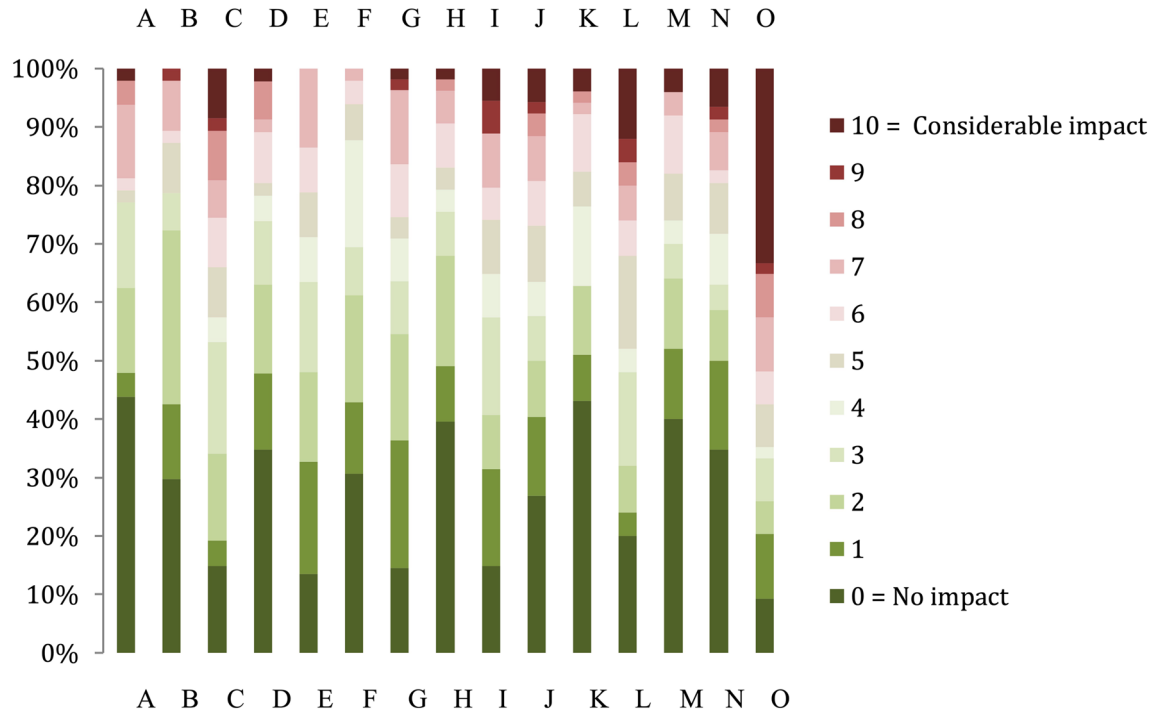



**Fig. 1** Scores of the 15 dimensions of the Treatment Burden Questionnaire. Dimensions: A: Taste, shape or size of the tablets and/or inconvenience caused by injections; B: Frequency of medication intake per day; C: Having to remind oneself not to forget medication; D: Specific constraints of medication intake; E: Lab tests and other exams (frequency, time spent, and inconvenience); F: Self-monitoring (for example: blood pressure, blood sugar: frequency, time spent, and inconvenience); G: Medical visits (frequency and time spent); H: Relationship with caregivers; I: Arranging appointments and scheduling doctors' visits and lab tests; J: Dealing with paperwork from health insurance agencies, welfare organizations, hospitals, and/or social care; K: Financial constraints, L: Diet constraints; M: Doctors' recommendations on regular physical activity, N: Social relationships (need for assistance, being ashamed to take medication in front of others), O: Frequent healthcare as a reminder of chronic condition

**Table 3** Factors correlated with discontinued care during the 5 years following transfer to adult care: uni- and multivariate analysis

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | P |
| Childhood disease management in only one pediatrics center | 0.7 [0.2; 3.4] | 0.68 | | |
| Being able to tell about disease with few words at transfer | 0.4 [0.0; 3.4] | 0.37 | | |
| Being aware of hospital emergency resources | 1.0 [0.2; 4.0] | 0.9 | | |
| Being aware of how to make medical appointment | 1.0 [0.2; 4.7] | 0.9 | | |
| Being able to go alone to medical appointment | 0.8 [0.2; 3.7] | 0.74 | | |
| Need to contact their pediatrician again after transfer | 0.2 [0.0; 0.7] | **0.02** | 0.2 [0.0; 0.7] | **0.02** |
| General practitioner support | 0.8 [0.2; 2.9] | 0.73 | | |
| Participant felt the adult nephrologist knew medical history | 5.8 [1.1; 31.7] | **0.04** | | |
| First adult medical appointment with parents | 0.9 [0.3; 3.1] | 0.85 | | |
| Age at disease onset | 0.9 [0.8; 1.1] | 0.29 | | |
| Number of relapses | 1.0 [0.9; 1.1] | 0.46 | | |
| Number of treatment lines[a] | 1.0 [0.6; 1.6] | 0.9 | | |

Significant p values are in bold

[a]Uni- and multivariate analyses were adjusted for age and gender

Overall social integration appeared to be acceptable, as illustrated by the rates of participants living with a partner, voting in the previous presidential elections, or having a driver's license. Thus, it is interesting to note the slightly better outcome concerning both educational level and occupational category. Considering the rate of non-responders, a recruitment bias, leading to the selection of patients who are more motivated and health literate, cannot be ruled out. Another possible hypothesis is that when a child is physically limited by a chronic condition, the parents tend to over-invest in their education rather than in leisure activities. This hypothesis is supported by the high frequency of sport renunciation at any age in our study and has previously been described in the setting of other CCs [21, 22]. Similar mechanisms were suggested by Skrzypczyk et al., who reported a high educational level in 40.9% of Polish adults with pediatric INS, compared to 19.2% in the general Polish population [11]. On the other hand, unemployment tended to be higher in our cohort than in the FPG, but without reaching statistical significance, and average monthly income seemed to be almost always lower than in the FGP in various categories, illustrating persistent professional insecurity in this population, as previously reported in adults who received a kidney transplant in childhood [23] and adults with pediatric-onset type 1 diabetes [22]. The heavy constraints of coping with a CC on a daily basis could explain the gap between having a satisfactory educational level and facing the reality of the labor market. In addition, it has been shown that young people with a CC had lower expectations for educational attainment and greater difficulty in achieving their desired degree, suggesting that they may acquire a socioeconomic disadvantage as they progress through educational settings [24]. It has also been reported that adults with pediatric chronic kidney disease lack confidence and social skills and thus encounter lifestyle limitations [25].

Contrary to other CCs [22], sex life, as well as affective life regarding rate of marital status, do not seem significantly impacted by the disease, suggesting that INS may not be a barrier to building a loving relationship. Thirty-eight percent of participants had biological children but, in the absence of a statistical analysis of the fertility rate due to the limited sample size of women in our study, this proportion should be interpreted cautiously, in view of the well-known fertility impairment directly related to the potential use of some cytotoxic therapies used in FRNS or SDNS [5]. In addition, a CC, and in particular its dissatisfying dermatological consequences, often impairs body image and frequently impacts emotional health and sexual life in adolescence.

The apparent acceptable social integration must not obscure the psychological difficulties that adults with pediatric-onset FRNS or SDNS face, as suggested by the burden of mental load related to the chronic condition highlighted by the TBQ, the significantly decreased MCS score compared to the FGP and its close relationship to the global fatigue dimension. Thus, regarding multivariate analysis, factors related to daily life (physical and mental quality of life, hirsutism, fatigue, having a partner) seemed to be impacting, whereas factors related to history of disease severity were not significantly associated with any of the social and QOL outcomes. The MFI-20 global score could not be compared to the FGP owing to the absence of reference values. However, the observed level of fatigue was quite similar to that observed in cancer survivors (12.2 ($\pm$4.5)) [26], and it was higher than the mean observed in three Western general populations [26–28]. Thus, its association with both mental and physical health scores confirms that fatigue, although under-diagnosed, is a major determinant of chronic disease burden at any age [22]. Overall, these observations highlight that clinicians should not simply focus on disease activity but should also take into account aspects of the disease that patients have to cope with, such as mental health, fatigue or cutaneous stigmas associated with the treatment.

As described in other CCs [22, 23], discrimination experiences were 12 times more frequent than in the FPG. Using univariate analysis, we found a strong correlation between discrimination and both altered mental health and the global fatigue score. This finding underlines the crucial role of healthcare providers in checking on discrimination situations and providing support.

On investigating QOL in children with steroid-sensitive INS, Ruth et al. found that only the QOL subclass "social functioning" was impaired compared with controls [7], suggesting that childhood social events may have a long-term negative impact on adulthood mental health. In children with INS, QOL has been demonstrated to be associated with different severity markers, such as disease activity [8] and duration [9]. Of interest in our study, 82% of participants had "quiescent" INS due to specific treatment. We can hypothesize that the responses to the questionnaire would have been quite different had the patients presented nephrotic syndrome when they completed the questionnaire.

The transition from a pediatric unit to an adult health-care system is a crucial event in the management of adolescents with a CC and can be associated with non-adherence and with a negative impact on the optimal medical care [29]. In our cohort, more than 70% of participants had a positive impression of the transition and transfer process. Strikingly, 33% of participants experienced a long period of discontinued care, which is a well-known key factor associated with an increased risk of complications in people already exposed to adverse long-term health issues [29]. To promote a successful transition and to reduce the risk of loss to follow up, recommendations have been published [30]. In our cohort, interruption of medical care during the first 5 years in adult care concerned one third of participants and was significantly associated with patients having felt the need

to re-contact their pediatrician nephrologist, and not with their level of autonomy. Although a causal relationship could not be established, an adolescent's need to re-contact their pediatrician must alert practitioners to the adolescent's difficulties in integrating a care pathway in adult healthcare and should lead them to strengthen support for the patient and their family and explore all potential barriers to transition success. This highlights the difficulty in moving from the familiar pediatric world to the unknown world of adult care, especially when preparation for transition is insufficient or not based on a multidimensional approach to the CC [31].

The main strength of our study lies in its methodology, using the GEDEPAC-2 questionnaire [12], which adopts an exhaustive approach to well-being, ranging from clinical outcome to intimate concerns, and presents the advantage of allowing comparisons with the FGP. Our study has several limitations. The 71 patients we identified were likely not fully representative of the entire cohort of patients followed for pediatric onset FRNS or SDNS in France. As only 59 of the 71 identified patients completed the questionnaire, we cannot rule out a possible recruitment bias, inherent in this type of approach, and potentially leading to too optimistic conclusions.

Overall, despite the evidence of satisfactory social participation, our findings highlighting alterations in mental health scores of HRQOL and high rates of discrimination suggest a deleterious long-term impact of pediatric-onset FRNS or SDNS on well-being. Further studies are warranted to confirm our preliminary results regarding consequences for mental health, discrimination experiences, and frequent failure to transition successfully within the context of global disease management.

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**Author contributions** DS, CA, VA and HM designed the research study. M-SM, SG-C, AH, ED, JD, CR, FP, DC, SB, AH, KD, AD, CD, AK, DG, VE, PR, ZAM, IT, M-PM, PZ, OF, MLQ, AW, OB and DS collected the data provided clinical and biological information and critically reviewed the manuscript. M-SM, SG-C, AD, FL, VA and HM analyzed the data. M-SM, SG-C, FL, AB and HM performed statistical analysis. M-SM, AD, VA and HM wrote the manuscript. Each author contributed important intellectual content during manuscript drafting. All authors read and approved the final version of the manuscript.

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**Data availability** The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Code availability** Analyses were conducted using SAS®-v9.6 software (SAS Institute Inc., Cary, NC). Code generated during the current study is available from the corresponding author on reasonable request.

## Declarations

**Conflict of interest** Vincent Audard has received consulting fees from Addmedica, unrelated to the present study. The remaining authors have no relevant financial interests to disclose.

**Ethical approval** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of "Assistance Publique - Hôpitaux de Paris" (No. 15.582).

**Consent to participate** Written informed consent was obtained from all individual participants included in the study.

**Consent for publication** There is no identifying information from participants in this article.

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