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Abstract

Introduction: Gitelman syndrome (GS) is a rare inherited salt-losing tubulopathy with limited clinical data.

Methods: Therefore, surveys were conducted with GS physicians in Europe and GS patients in the Netherlands to compare findings with the general population.

Results: Data from 587 patients (25% pediatric) across 13 countries showed 93% were genotyped, with 94% having variants in *SLC12A3*. Children with GS were shorter and lighter than the general population, with lower body weight persisting into adulthood. The sex distribution was uneven, with more males in childhood and more females in adulthood. GS patients had the expected electrolyte disorders, but also significantly lower blood phosphate levels. Positive correlations were found between blood magnesium and potassium, and potassium and aldosterone. Physicians reported muscle cramps, salt craving, and muscle weakness as most common GS symptoms. GS patients scored worse than the general population in fatigue, physical and cognitive function, and ranked salt craving and polydipsia-polyuria as the most severe symptoms. Symptom burden was higher in adult females and patients with lower blood magnesium. Treatment mainly consisted of potassium (94%) and magnesium (50%) supplementation. Potassium-sparing medication (used in 33%) slightly increased blood potassium levels (3.2 vs. 3.1 mmol/l). Adult GS patients had a high prevalence of chondrocalcinosis (15%) and elevated blood cell counts (26%). Compared to the general population, adult GS patients had lower rates of chronic kidney disease and hypertension, a similar rate of diabetes, but a higher rate of albuminuria or proteinuria (28%).

Conclusions: These findings provide new insights into GS, highlight disease burden, and suggest areas for future research.

Keywords: Genetics; Hypokalemia; Hypomagnesemia; Patient-reported outcomes; Tubulopathy.

Introduction

Gitelman syndrome (GS) is an autosomal recessive salt-losing tubulopathy that is caused by genetic variants in *SLC12A3* leading to loss-of-function of the sodium-chloride cotransporter (NCC).¹ Because GS impairs the overall function of the distal convoluted tubule, it leads to disturbances in sodium, chloride, potassium, magnesium, calcium and acid-base balance.² Clinically, this is characterized by high urinary excretions of sodium, chloride, potassium and magnesium leading to activation of the renin-angiotensin system, hypokalemia, metabolic alkalosis and hypomagnesemia. Furthermore, GS is characterized by low urine calcium excretion, possibly due to increased calcium reabsorption in the proximal tubule.^{3, 4} The symptoms of GS are related to the fluid and electrolyte disturbances and include salt craving, polydipsia-polyuria, and muscle cramps.⁵ Calcium retention and hypomagnesemia can cause calcifications leading to chondrocalcinosis or choroidal calcifications.^{6, 7}

GS is a rare disease with an estimated prevalence of 1 in 40,000 people⁸, although this may vary per by ethnicity, with higher prevalence reported in Asian populations.⁹ Nevertheless, there is limited information on clinical characteristics, symptoms and long-term outcomes. A Kidney Disease: Improving Global Outcomes (KDIGO) controversy conference on GS identified several knowledge gaps, including effects on normal development, genotype-phenotype correlations, sex differences, patient-related outcomes and long-term clinical outcomes, including the prevalence of chronic kidney disease (CKD), proteinuria, hypertension and diabetes.¹⁰ Recently, two European surveys were conducted on two other tubulopathies – distal renal tubular acidosis and nephrogenic diabetes insipidus – revealing several new insights into physical and intellectual development, patient symptoms and long-term outcomes.^{11, 12} These studies illustrate the ability to obtain clinically relevant insights on rare diseases when combining data from multiple centers and countries.

The aim of this study was therefore to study the clinical characteristics, symptoms, and long-term outcomes of GS using a European survey. Similar to the two previous surveys, we compared the data of patients with GS to the National Health and Nutrition Examination Survey (NHANES) data, which is a publicly available general population cohort.¹³ Because this cohort is from the United States, we also added a European reference population using the Rotterdam Study from The Netherlands.¹⁴ Furthermore, we conducted a patient survey focusing on patient-reported outcomes. Our study identified several novel aspects of GS with clinically relevant implications.

Methods

Physician and patient survey

Members of the European Reference Network for Rare Kidney Diseases (ERKNet) were contacted via email to participate in an electronic survey to provide data on patients with a clinical or genetic diagnosis of GS. This survey was open from January 8th to August 1st 2024. A total of 66 questions were asked about demographics, genetics, laboratory values, extra-renal features, symptoms, and long-term outcomes (**Supplement**). Regarding symptoms, we asked physicians to report whether patients experienced one or more GS-specific symptoms⁵, as well as fatigue. In case of missing information or if provided data points were noted to be outliers, corresponding clinicians were contacted via e-mail for completion and/or verification of data. In addition to the physician survey, a patient survey was circulated among GS patients in The Netherlands from October 1st 2024 to January 1st 2025 (**Supplement**). For this survey we used the Patient-Reported Outcomes Measurement Information System (PROMIS) with questions on six domains.¹⁵ Furthermore, we asked patients to score GS-specific symptoms on a 5-point Likert scale.⁵ The physician and patient surveys were approved by the medical ethics committee of the Erasmus Medical Center (MEC-2023-0511). Physicians confirmed that patients signed informed consent through ERKNet, or that consent was obtained according to local regulations. GS patients participating in the patient survey signed informed consent. Electronic data capture was done with Castor EDC (The Netherlands).

Definitions

We used the age of 18 years to separate the cohort into a pediatric and adult group. For children, height and weight were expressed as standard deviation scores (SDS). These values were compared to reference data from the World Health Organization (WHO) for height and the Center for Disease Control (CDC) for weight. For laboratory values we asked physicians to specify the range in which the patient's values were usually in to avoid bias due to intermittent outliers. Plasma renin and aldosterone were transformed to

concentrations using established conversion factors.^{16, 17} Based on physician-reported symptoms, we calculated a total symptom score. Kidney function was assessed using estimated glomerular filtration rate (eGFR) with the 2009 CKD-EPI equation, as recommended for European populations.¹⁸ For children, we used the Schwartz formula.¹⁹ The prevalence of CKD and degree of albuminuria were assessed using the KDIGO classification.²⁰ Hypertension was defined as blood pressure > 140/90 mmHg for adults or >95th percentile for children.²¹ Diabetes mellitus was defined as random glucose $\geq$ 11.1 mmol/l (200 mg/dL), fasting glucose $\geq$ 7.0 mmol/l (125 mg/dL) or the use of medication for diabetes mellitus.²²

Reference populations

As control groups for the adult GS patients we used two cohorts from the general population, including NHANES from the United States (participants' age $\geq$ 18 years)¹³ and the Rotterdam Study from the Netherlands (participants' age $\geq$ 40 years).¹⁴ Both reference populations were used to compare height, weight and body mass index (BMI) with matching for age and sex. Both reference populations were also used for comparison of the laboratory data on electrolytes and acid-base balance except when data were available in only one cohort. The data on long-term outcomes were compared with the NHANES data because it allowed for better age-matching, except for albumin-to-creatinine ratio, which was only available in the Rotterdam Study.

Statistics

Data were complete for physician and patient-reported symptoms and $\geq$ 90% available for all other data, except for data on genetic variants (84%), height and BMI in adults (85% and 84%), blood bicarbonate (84%), albuminuria/proteinuria (76%), plasma aldosterone (57%) and plasma renin (53%). Data were not imputed for analysis. Kolmogorov–Smirnov tests were performed to assess normality of the data. Data following a normal distribution were expressed as mean $\pm$ standard deviation. Non-normally distributed

data were expressed as median with interquartile range (IQR). Differences between or within groups were analyzed using χ^2 or Fisher's exact test, Student's t-test, Mann–Whitney U-test or one-way analysis of variance (ANOVA) with Tukey's post-hoc test, whichever was appropriate. Associations between dependent and independent variables were analyzed using linear regression. Matching between GS patients and the reference populations was performed using the MatchIt package in R with a 1:3 case-control ratio via the optimal matching method. The patient survey data were analyzed using PROMIS which enables comparison with the general population using Cliff's delta.^{15, 23} All statistical analyses were performed using R (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographics and genetics

A total of 587 GS patients from 13 European countries were available for analysis, including 148 pediatric patients and 439 adult patients (**Table 1, Table S1**). Sex was unevenly distributed with males being more prevalent in childhood (61%) and females in adulthood (60%, $p < 0.05$ for both). The average age at last follow-up was 12 for the pediatric patients and 39 for the adult patients; the age at diagnosis was 7 and 25 years of age, respectively. Females were older at diagnosis (23 ± 15 vs. 18 ± 15 years, $p < 0.01$). Reported ethnicities were predominantly White (>80%), followed by Arab and Asian ethnicities (each ~5%). Educational attainment in adult GS patients was comparable to the average level across the European Union (**Table S2**). Genetic testing was performed in >90% of patients most often using a gene panel (42%), Sanger sequencing (26%) or whole exome/genome sequencing (16%) (**Figure 1A**). In the majority of patients known pathogenic variants in *SLC12A3* were identified, usually in a compound heterozygous fashion. Most of the pathogenic variants constituted missense variants (61%) followed by nonsense variants and insertions-deletions (**Figure 1B**).

Growth and body weight

In children with GS, the median SDS for height and weight was below zero, but in only 10 (7%) and 16 children (11%) this was < -2 SDS (**Figure 2A-B**). In adults with GS, the median height, weight and BMI was significantly lower compared to one or both of the reference populations (**Figure 2C-E**). We next analyzed if the differences were caused by the Rotterdam Study reference group, because people from the Netherlands are relatively tall.²⁴ When we restricted our comparison to Dutch patients with GS, height was no longer significantly different, but body weight and BMI were still lower (**Figure 2F**).

Laboratory values

Adult GS patients had significantly lower blood values for potassium, magnesium, sodium, chloride, and phosphate compared to one or both reference populations (**Figure 3A-E**). Conversely, blood values for calcium and bicarbonate were significantly higher compared to one or both reference populations (**Figure 3F-G**). Blood magnesium and potassium levels were weakly correlated (**Figure 3H**). Blood magnesium levels were slightly lower in homozygous patients compared to compound heterozygous patients (0.63 vs. 0.66 mmol/L, **Figure S1**). Compared to male patients, female patients had higher blood chloride levels (98 ± 4 vs. 97 ± 3 mmol/l), but lower blood calcium (2.4 ± 0.1 vs. 2.5 ± 0.1 mmol/l) and bicarbonate levels (28 ± 3 vs. 29 ± 3 mmol/l, all $p < 0.01$). In children with GS, the values for the electrolytes and bicarbonate were similar to adults, except for the expected higher phosphate levels (**Table S3**). Plasma renin and aldosterone level were in the high range for plasma renin and in the normal range for plasma aldosterone (**Figure 4A-B**). Patients using non-steroidal anti-inflammatory drugs had lower plasma renin, but not aldosterone levels (**Table S4**). We identified a significant but weak association between blood potassium and plasma aldosterone (**Figure 4C**). Urine calcium excretions were low (median 1.1 mmol/day in 24h urine and 0.06 mmol/mmol in spot urine, **Figure S2**).

Extra-renal features

Chondrocalcinosis was reported in none out of 147 pediatric patients and in 66 out of 435 adult patients (15%) (**Table 2**). Hyperparathyroidism was reported in 2 out of 142 (1%) pediatric patients and in 11 out of 434 (3%) adult patients. One of these patients was hypercalcemic. Any elevated blood cell count was present in 18 out of 146 (12%) pediatric patients and in 115 out of 437 adult patients (26%). Erythrocytosis was reported with a similar frequency in pediatric and adult patients (7% for both), whereas thrombocytosis and leukocytosis were more common in adult patients (11 vs. 6% and 13 vs. 1%, respectively). The average hematocrit values for patients with erythrocytosis were 0.45 ± 0.03 L/L

(children) and 0.50 ± 0.04 L/L (adults). The average thrombocyte and leukocyte counts were 460 ± 163 and $12.6 \pm 2.1 \times 10^9/L$ (similar values for adults and children). The prevalence of elevated blood cell counts in patients using potassium-sparing medication was higher, although this did not reach statistical significance (**Table S5**). Any bacterial infection and any allergy were reported in 10 and 12% of the patients, respectively; individual infections or allergies were reported in 1–10% of patients (**Table S6**).

Physician and patient reported symptoms

Physicians reported fatigue, muscle cramps, and salt craving as the most common symptoms for children with GS with prevalences of 20-24% (**Figure 5A**). The same symptoms were also most commonly reported in adults with GS, but with higher prevalences (fatigue 60%, muscle cramps 41%, salt craving 25%, **Figure 5B**). The patient survey was distributed to 58 GS patients in the Netherlands, with 38 patients (26 females, 12 males; age 47 ± 15 years) completing it. In this analysis, salt craving, nycturia, polyuria and polydipsia were identified as the most severe GS symptoms (average scores ≥ 3 on 5-point scale, **Figure 5C**). The total symptom score was significantly higher in adult female GS patients (**Figure 6A**). Furthermore, a significant trend was identified between lower blood potassium and magnesium levels and higher total symptom score (**Figure 6B-C**). PROMIS also enabled a standardized comparison of six domains between GS patients and the general population (**Figure 7**). This analysis showed that GS patients performed significantly worse than the general population with regard to fatigue, physical function and cognitive function with a small to moderate effect-size (Cliff's delta's ~ 0.25).

Treatment

Patients were treated with supplementation of potassium (94%), magnesium (50%) and sodium chloride (15%), potassium-sparing medications (33%), or combinations of these. Patients who used potassium-sparing medication had slightly but significantly higher blood potassium levels (3.2 vs. 3.1 mmol/l, **Figure**

8A). When the patients were divided further according to the main treatment combinations, we identified no significant differences in blood potassium levels (**Figure 8B**). We identified a positive association between the daily amount of potassium supplementation and 24-hour urinary potassium excretion (**Figure 8C**), but not blood potassium level (**Figure 8D**). When blood magnesium levels were analyzed based on the type of magnesium supplementation or no supplementation, a significant difference was observed at the group level, but not between the subgroups (**Figure 8E**). Patients who used magnesium supplements did not have a higher blood potassium (**Figure 8F**), but a higher daily magnesium supplementation was associated with a higher blood potassium level (**Figure 8G**).

Long-term outcomes

Adult GS patients were found to have a significantly lower prevalence of hypertension and a similar prevalence of diabetes mellitus when compared to the age- and sex-matched NHANES group (**Figure 9A-B**). Adult GS patients more often had normal kidney function and less often stage G2 and G3 CKD (**Figure 9C**). When analyzing eGFR at age of last follow-up, the relationship between eGFR and age ran at a higher level in GS patients, but followed a course that was parallel to the NHANES population (**Figure 9D**). Among the children with GS in this cohort, there was one child with hypertension, one child with CKD stage G3a and no children with diabetes mellitus. Data on the assessment of albuminuria or proteinuria were available in 93% of children and 76% of adults with GS (**Table S7**). Twenty percent of children and 28% of adults with GS had albuminuria or proteinuria in at least one measurement (**Figure 9E**). Adults with a higher CKD stage more often had albuminuria or proteinuria, but the prevalence of albuminuria or proteinuria was not higher in those with a more rapid eGFR decline (**Figure 9E, Table S7**). When compared to the Rotterdam Study, stage A2 and A3 albuminuria were significantly more common in adult GS patients than in the general population (**Figure 9F**).

Subgroup analysis

Because GS was not genetically confirmed in all patients, we performed a subgroup analysis restricted to the genotyped patients (398 out of the 439 adults, 91%; 147 out of the 148 children, 99%). This analysis showed that the conclusions regarding height and body weight, laboratory values, extra-renal features, symptoms, treatment, and long-term outcomes remained unchanged, except for one association that became non-significant (the association between blood potassium and plasma aldosterone, r^2 0.015, p-value 0.06, **Table S8**).

Discussion

Gitelman syndrome (GS) is a rare disease, which complicates a full understanding of its disease burden, natural progression, and potential management strategies. The aim of this study was to analyze the clinical characteristics, symptoms, and long-term outcomes of GS through a European survey conducted among physicians treating these patients. This allowed us to establish the largest cohort of children and adults with GS reported to date. Additionally, we conducted a patient survey to explore patient-reported outcomes related to both general and GS-specific symptoms. The findings offer several new insights into GS, which will be discussed below.

Growth in children with GS was below average, but the mean height for most children fell within two standard deviations. This finding aligns with a previously reported small cohort of children with GS.²⁵ Additionally, no significant differences in height were observed in adults with GS compared to reference populations, suggesting catch-up growth. However, body weight was notably lower in adults with GS. Interestingly, in rats, potassium deficiency reduced food intake and inhibited muscle and body weight gain, potentially through its effect on insulin-like growth factor 1.²⁶ This suggests that the lower body weight in patients with GS may be due to electrolyte imbalances or the disease's impact on appetite. Previous studies have also demonstrated that other tubulopathies, such as distal renal tubular acidosis and nephrogenic diabetes insipidus, can affect normal development in height and weight.^{11, 12}

The genetic analysis showed a distribution between compound heterozygous and homozygous variants of ~60-40% in children and ~75-25% in adults with overall ~60% missense variants, which is in line with previous reports.²⁷⁻²⁹ We identified no clear genotype-phenotype correlations, except for slightly lower blood magnesium levels in homozygous patients. Previous studies in Asia did identify genotype-phenotype correlations, including lower blood chloride and potassium levels in patients with truncating

variants²⁸, earlier age of onset and lower urine calcium excretion in homozygous patients³⁰, and lower blood magnesium levels in Japanese patients with a mutational hotspot.²⁹ Analysis of these factors was not possible in this study due to the lack of variant-specific data.

The laboratory data in our study confirm the biochemical profile of GS, but also reveal some less well-known aspects. For example, blood phosphate levels were significantly lower in adult GS patients than in the general population. This tendency towards hypophosphatemia has also been observed in two previous smaller cohorts and was ascribed to renal phosphate wasting.^{31, 32} It would be relevant to study if low blood phosphate levels contribute to symptoms in GS patients. Another finding was that blood potassium was positively associated with plasma aldosterone. In the context of GS, this well-established physiological relationship implies that hypokalemia suppresses plasma aldosterone. This may explain the relatively normal plasma aldosterone levels in our cohort. Hypokalemia-induced suppression of aldosterone may also contribute to hypomagnesemia, as aldosterone has been identified as a factor contributing to magnesium reabsorption in patients with GS.³³ If so, this effect would be in addition to the established downregulation of the magnesium transporter TRPM6 observed in GS.³

Our study also examined the extra-renal manifestations of GS. Chondrocalcinosis was reported in 15% of adult GS patients, which is 2-3 times higher than the prevalence in the general population.³⁴ The true prevalence of chondrocalcinosis is probably even higher as a previous prospective study with systematic screening for chondrocalcinosis detected it in 79% of the GS patients.⁷ Another striking finding was the high prevalence of elevated blood counts. Isolated erythrocytosis has a prevalence of 0.3% in the general population³⁵, whereas it was reported in 7% of the GS patients. High angiotensin II levels may be responsible for increasing erythropoietin levels in GS patients.^{36, 37} It is unclear if activation of the renin-angiotensin system also explains the effect on platelets and leukocytes. A recently reported extra-renal

manifestation of GS is a higher susceptibility to infectious and allergic disease, possibly mediated by impaired interleukin-17 responses.³⁸ The rates of infectious and allergic diseases in our survey were not clearly higher than those in the general population, although underreporting may play a role as these aspects of the disease may not yet be systematically evaluated by physicians.

A unique aspect of our study is the availability of both physician and patient-reported symptoms. This comparison revealed that physicians reported salt craving, polydipsia, polyuria, and nycturia in only ~20% and ~5-10% of patients, respectively, whereas patients scored this as the most severe symptoms. Fatigue was reported as the most prevalent symptom by physicians. In patients, this symptom was assessed more objectively by using the PROMIS approach.¹⁵ GS patients had worse outcomes for fatigue as well as physical and cognitive function compared to the general population. These findings are largely in agreement with a previous survey among 50 GS patients, which also showed a high prevalence of salt craving, nycturia and fatigue and significantly lower scores for physical and emotional health than healthy subjects using the RAND-36 health-related quality of life questionnaire.⁵ In our study, the total symptom score based on the physician-reported symptoms was higher for adult females than for males. Possible explanations are that women with GS have a higher disease burden or express these symptoms more clearly to their physicians. Women with GS are therefore more likely to be diagnosed than men, which may account for the higher prevalence of adult female GS patients in our cohort. In childhood, boys, however, seem to be more severely affected. Male patients presented at a younger age, which was previously also observed in a single-center cohort of 101 GS patients, where 47% of males and 26% of females presented before the age of 18 years.³⁹ In this previous study, females with GS also had less severe electrolyte disorders, which is similar to what we observed. Male sex in combination with the nature of the *SLC12A3* variant may determine GS severity.⁴⁰ Female rats have higher abundances of total and

phosphorylated NCC⁴¹ and NCC is also enhanced by estrogen.⁴² Possibly these sex differences in NCC regulation allow female patients with GS to partially rescue the genetic NCC inhibition.

Our study captures the current management of GS in Europe, which involves supplementation of potassium, magnesium and/or sodium, sometimes in combination with potassium-sparing medications. Our data do not allow firm conclusions on treatment in GS because of confounding by indication. However, a number of findings merit further consideration. For example, our data indicated that a higher dose of potassium supplementation was associated with a higher urinary potassium excretion but not higher blood potassium levels. In contrast, both a higher blood magnesium level and a higher dose of magnesium supplementation were associated with a higher blood potassium level, although the strength of these associations was weak. These observations support previous studies showing improvement of blood potassium with magnesium supplementation.^{43, 44} This is also relevant as we found that lower blood magnesium levels were more strongly associated with a higher symptom burden than lower blood potassium levels. Patients receiving potassium-sparing drugs had a slightly but significantly higher blood potassium levels, which is consistent with the results from a previous randomized clinical trial.⁴⁵ Future studies should investigate whether magnesium supplementation deserves a more prominent role in the treatment of GS, although it is important to prevent its gastro-intestinal side-effects. Additionally, research should address whether potassium-sparing drugs improve patient-relevant outcomes beyond simply increasing blood potassium levels.

One of the specific aims of this cohort was to investigate the long-term outcomes of GS. When compared to a matched reference population, we observed a significantly lower prevalence of hypertension and CKD, a similar prevalence of diabetes and a significantly higher prevalence of albuminuria or proteinuria. A previous smaller study suggested that GS patients develop hypertension with age despite its salt-losing

phenotype⁴⁶, but we were unable to confirm this finding. Furthermore, abnormal glucose metabolism and insulin secretion have been reported in GS⁴⁷, but this did not translate into a higher prevalence of overt diabetes in our cohort. A recent study showed that the prevalence of kidney failure in GS patients is very low (0.9%) and contrasts with other inherited tubulopathies (prevalence 15-90%).⁴⁸ This is in line with our findings which demonstrate a lower prevalence of CKD and normal decline in eGFR with age. One caveat is that GS patients often have lower body weight, which may result in an underestimation of CKD prevalence when using creatinine-based eGFR. Other inherited tubulopathies are frequently accompanied by hypercalciuria, which may explain why GS does not increase the risk of progressive loss of kidney function.⁴⁸ Albuminuria and proteinuria, however, were very common in GS patients with a prevalence similar to that in patients with diabetes with preserved kidney function.⁴⁹ A previous smaller study identified a similar prevalence of proteinuria and linked this to higher angiotensin II levels.⁵⁰ Nine of the patients in this previous study were biopsied showing hypertrophy of the juxtaglomerular apparatus, tubulointerstitial and intrarenal vascular changes and glomerulopathy. Another report of a kidney biopsy with electron microscopy showed variability in glomerular basement membrane thickness and podocyte foot effacement.⁵¹ GS therefore represents a unique form of kidney injury characterized by glomerular and tubulo-interstitial damage that does not lead to progressive CKD. The contribution of hypokalemia and the activated renin-angiotensin system to kidney injury in GS remains to be determined.⁵² Considering the possible role of angiotensin II, it would be interesting to study the effects of angiotensin receptor blockers on proteinuria in GS, potentially improving hypokalemia and erythrocytosis as well.⁵³

The strengths of our study are the large sample size, the use of two reference populations and the combination of a physician and patient survey. The most important limitation of this study is that the physician survey was a retrospective cross-sectional cohort review with data captured via an online form. This emphasizes the need for a comprehensive international registry to collect longitudinal granular data

on this rare disorder, as is currently being done in an ERKNet subregistry. Another limitation is that we did not collect data on the diagnostic triggers for GS, which can range from clear symptoms to incidental findings such as hypokalemia.

In conclusion, this European study on GS has revealed several new aspects of the disease, including lower body weight, sex differences, reduced blood phosphate levels, and a higher prevalence of albuminuria compared to the general population. Our study also underscores the importance of the interaction between magnesium and potassium balance. Additionally, the patient survey highlights the significant burden of disease, encompassing both general and GS-specific symptoms. Many of these findings have clinical implications and clearly establish a research agenda for future studies.

Disclosure statement

The authors have nothing to disclose.

Data statement

All data are available in the main text or in the Supplementary Material. Raw data sets are available by request to the corresponding author.

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Supplementary Material

- **Table S1** : European countries contributing to the survey (PDF)
- **Table S2** : Level of education (PDF)
- **Table S3** : Laboratory values for electrolytes and bicarbonate in children with Gitelman syndrome (PDF)
- **Table S4** : Plasma renin and aldosterone in patients with or without the use of non-steroidal anti-inflammatory drugs (PDF)
- **Table S5** : Prevalence of elevated blood cell counts in patients with or without potassium-sparing medication (PDF)
- **Table S6** : Infections and allergies (PDF)
- **Table S7** : eGFR, eGFR decline, and albuminuria/proteinuria (PDF)
- **Table S8** : Subanalysis including genotyped patients (PDF)
- **Figure S1** : Blood magnesium in patients with compound heterozygous or homozygous variants (PDF)
- **Figure S2** : Urine calcium excretion (PDF)
- **Physician survey (PDF)**
- **Patient survey (PDF)**

Supplementary information is available at KI Report's website.

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Table 1. Demographics and genetic data.

Characteristics	All patients (n = 587)	Pediatric patients (n = 148)	Adult patients (n = 439)
Female sex, n (%)	323 (55)	57 (39)	266 (60)
Age at last follow-up (years)	32.4 ± 17.3	12.1 ± 3.9	39.3 ± 14.4
Age at diagnosis (years)	20.5 ± 14.8	7.2 ± 4.0	25.2 ± 14.3
Ethnicity			
Arab, n (%)	33 (6)	13 (9)	20 (5)
Asian	27 (5)	8 (5)	19 (4)
Black	1 (0.2)	1 (1)	0 (0)
Mixed	13 (2)	10 (7)	3 (1)
White	494 (84)	108 (73)	386 (88)
Not reported	19 (3)	8 (5)	11 (3)
Genotyped, yes (%)	545 (93)	147 (99)	398 (91)
<i>SLC12A3</i> variant(s) identified	514 (94)	144 (98)	370 (93)
Compound heterozygous	374 (73)	88 (61)	286 (77)
Homozygous	140 (27)	56 (39)	84 (23)
Consanguinity, n (%)	63 (11)	39 (26)	24 (5)

Table 2. Extra-renal features in Gitelman syndrome.

Extra-renal feature	All patients*	Children*	Adults*
Chondrocalcinosis, n/total n (%)	66/582 (11)	0/147 (0)	66/435 (15)
Hyperparathyroidism, n/total n (%)	13/576 (2)	2/142 (1)	11/434 (3)
Any elevated blood cell count, n/total n (%)	133/583 (23)	18/146 (12)	115/437 (26)
• Erythrocytosis, n (%)	40 (7)	10 (7)	30 (7)
• Thrombocytosis, n (%)	55 (9)	9 (6)	46 (11)
• Leukocytosis, n (%)	59 (10)	1 (1)	58 (13)

Footnote: *The total number of patients for whom these data were available was variable and therefore specified for each extra-renal feature (data availability 96-100%).

Figure legends

Figure 1: Distribution of genetic testing and identified genetic variants.

(A) Out of the 545 patients who were genotyped, the type of genetic testing was specified in 506 patients (data availability 93%).

(B) Out of the 514 patients in whom *SLC12A3* variant(s) were identified, the type of variant was specified in 424 patients (data availability 83%).

Abbreviations: MLPA, multiplex ligation-dependent probe amplification; WES, whole exome sequencing; WGS, whole genome sequencing.

Figure 2: Height, weight and body mass index in children and adults with Gitelman syndrome (GS).

(A-B) In girls and boys with GS height **(A)** and weight **(B)** were analyzed using a Standard Deviation Score (SDS) based on data from the World Health Organization (height) or the Center for Disease Control (weight).

(C-E) In adult GS patients, height **(C)**, weight **(D)** and body mass index (BMI) **(E)** were compared with one or two age- and sex-matched reference populations, including the Rotterdam Study and National Health and Nutrition Examination Survey (NHANES).

(F) To account for differences in height and weight between countries, height, weight and BMI were also compared between GS patients from the Netherlands and healthy participants from the Rotterdam Study. Available data are reported below the graphs.

Figure 3: Laboratory values in adult patients with Gitelman syndrome.

(A-G) Blood values for potassium **(A)**, magnesium **(B)**, sodium **(C)**, chloride **(D)**, phosphate **(E)**, calcium **(F)**, and bicarbonate **(G)**. Blood magnesium was only available in the Rotterdam Study, while blood

bicarbonate was only available in the National Health and Nutrition Examination Survey (NHANES). Electrolytes and bicarbonate were measured in plasma (62%) or serum (38%) in the 549 patients for whom this was reported. Available data are reported below the graphs. Statistical analysis was performed using one-way analysis of variance with Tukey's post-hoc test.

(H) The association between blood magnesium and blood potassium was analyzed using linear regression; for this analysis data from 422 patients were available.

Figure 4: Plasma renin and aldosterone in children and adults with Gitelman syndrome.

(A) The dashed lines indicate the upper levels of normal for plasma renin in males (blue, 103 mU/L) and females (purple, 63 mU/L).

(B) The dashed line indicates the upper level of normal for plasma aldosterone (694 pmol/L).

(C) The association between blood potassium and plasma aldosterone was analyzed using linear regression; for this analysis data from 247 patients were available.

The available data are shown below the box plots. The renin and aldosterone data were converted to concentrations using established conversion factors.^{16, 17}

Figure 5: General and Gitelman syndrome-specific symptoms reported by physicians and patients.

(A) The prevalence of symptoms is shown in percentages as reported by physicians for 148 children with Gitelman syndrome (GS).

(B) The prevalence of symptoms is shown in percentages as reported by physicians for 439 adults with GS.

(C) The burden of GS-specific symptoms (scale 0 – 5) as reported by 38 adult GS patients from the Netherlands is shown as average $\pm$ standard deviation.

Figure 6:

- (A)** Total symptom score in adult female and male patients with Gitelman syndrome.
- (B)** Trend analysis between blood potassium levels and total symptom score.
- (C)** Trend analysis between blood magnesium levels and total symptom score.

Figure 7: Results from the patient reported outcome measurement information system (PROMIS) on six domains in 38 adult patients with Gitelman syndrome (yellow) and the general population (grey). The domains include fatigue, anxiety and sleep disturbance (for which higher T-score means that performance is worse than the general population) and physical function, cognitive function, and social roles (for which lower T-score means that performance is worse than the general population). Cliff's delta is reported with 95% confidence intervals. Cliff's delta was calculated using the effsize package in R (version 0.8.1, 2022).

Figure 8: Laboratory values in relation to treatment in children and adults with Gitelman syndrome.

- (A)** Blood potassium levels were compared in patients who did or did not use potassium-sparing diuretics.
- (B)** Blood potassium levels were further analyzed by specific treatment regimens, including potassium-sparing (K-sp) diuretics, mineralocorticoid receptor antagonists (MRA), non-steroidal anti-inflammatory drugs (NSAIDs) and/or potassium supplementation (K suppl).
- (C)** The association between the amount of potassium supplementation and urinary potassium excretion (n = 188)
- (D)** The association between the amount of potassium supplementation and blood potassium (n = 537).
- (E)** Blood magnesium levels were analyzed in patients who did or did not use magnesium (Mg) supplementation divided by the type of magnesium supplement, including Mg-citrate, Mg-gluconate, Mg-glycerophosphate (Mg-GP), Mg-lactate, and Mg-oxide.

(F) Blood potassium levels were compared in patients who did or did not use magnesium supplementation.

(G) The association between the amount of magnesium supplementation and blood magnesium was analyzed (n = 302).

The data were analyzed using Student's t-test (A, F), one-way analysis of variance with Tukey's post-hoc test (B, E) and linear regression (C, D, G).

Figure 9: Long-term outcomes in adult patients with Gitelman syndrome.

(A) Comparison of the prevalence of hypertension in GS patients who were age- and sex-matched to participants of the National Health and Nutrition Examination Survey (NHANES).

(B) Comparison of the prevalence of type 2 diabetes mellitus in GS patients who were age- and sex-matched to participants of the NHANES.

(C) Distribution of chronic kidney disease (CKD) stages G1, G2 and G3 in GS patients (orange) and age- and sex matched participants of NHANES (green).

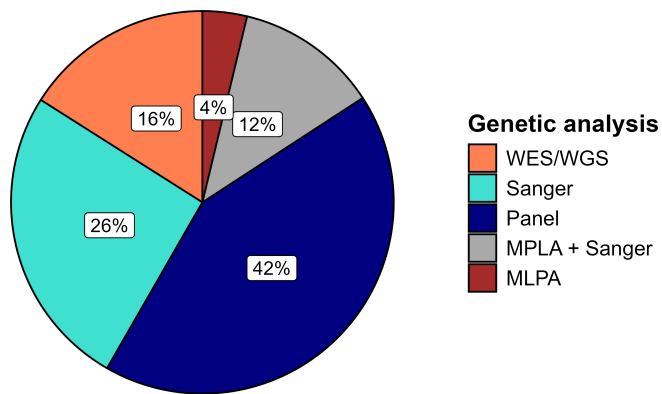
(D) Association between age and estimated glomerular filtration rate (eGFR) at last follow-up in GS patients (n = 430) and age- and sex-matched participants from the NHANES cohort (n = 1314).

(E) Presence of albuminuria or proteinuria in children and adults with GS with further distribution in adults by CKD stage and eGFR decline (see also **Table S5**).

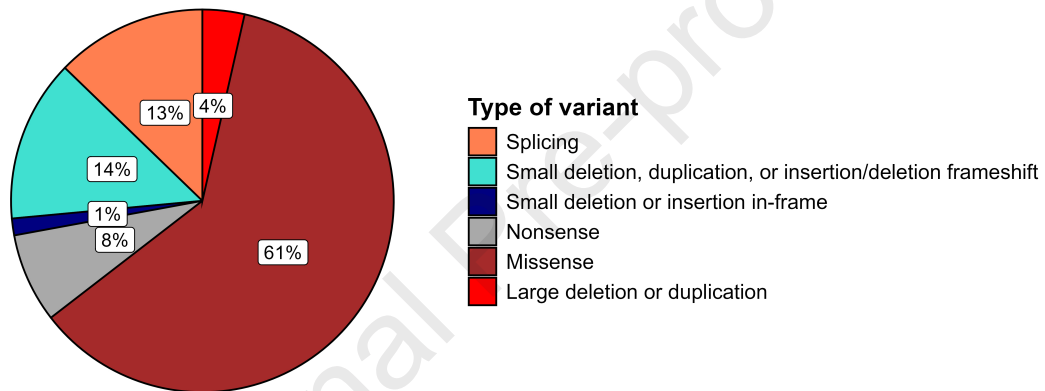
(F) Comparison of urine albumin to creatinine ratios in adult GS patients (orange) and age- and sex-matched participants from the Rotterdam Study (blue). A1 < 3 mg/mmol, A2 3-30 mg/mmol, A3 > 30 mg/mmol.

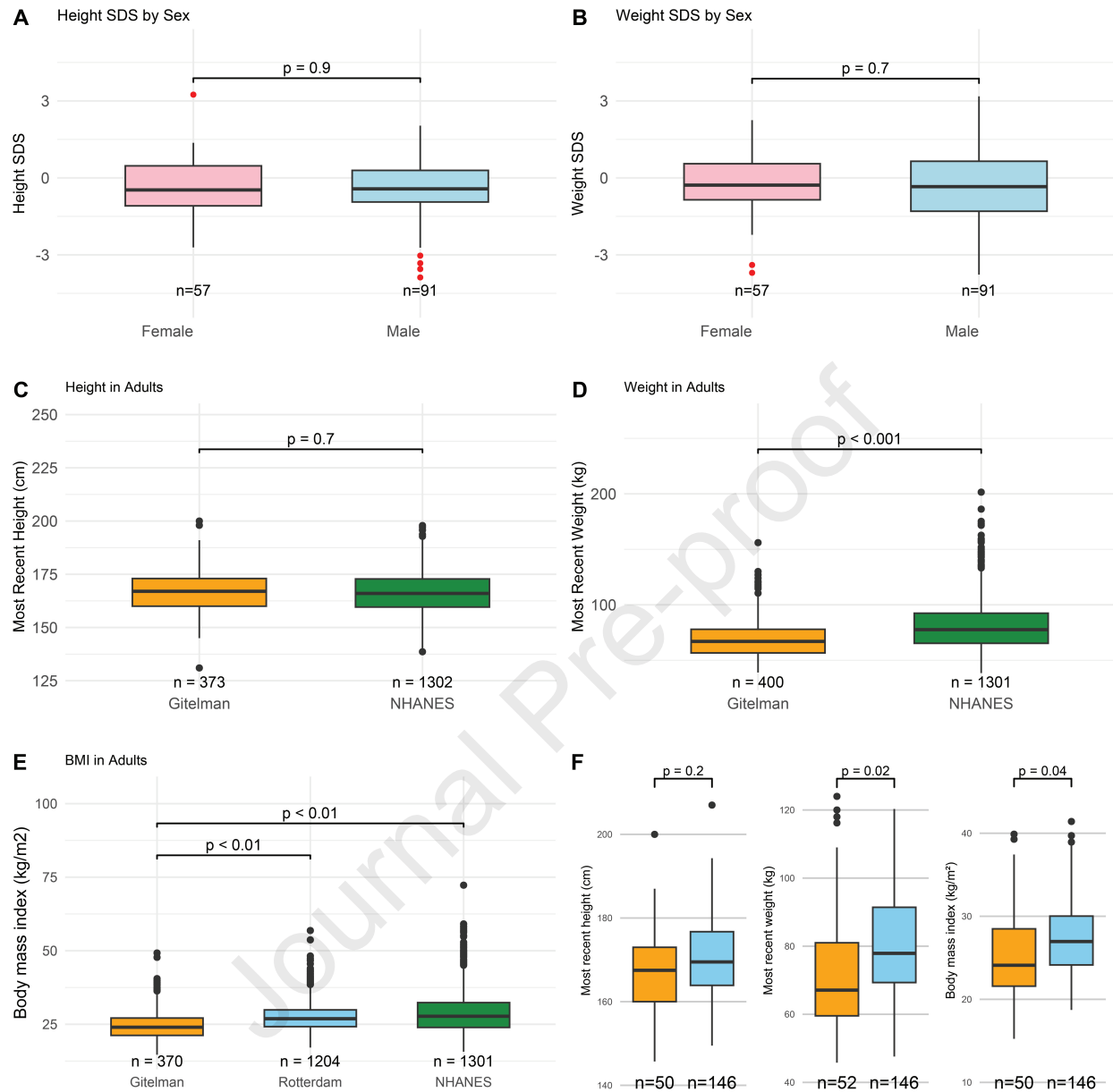
The data were analyzed using Student's t-test (A, B, C, F) or linear regression (D).

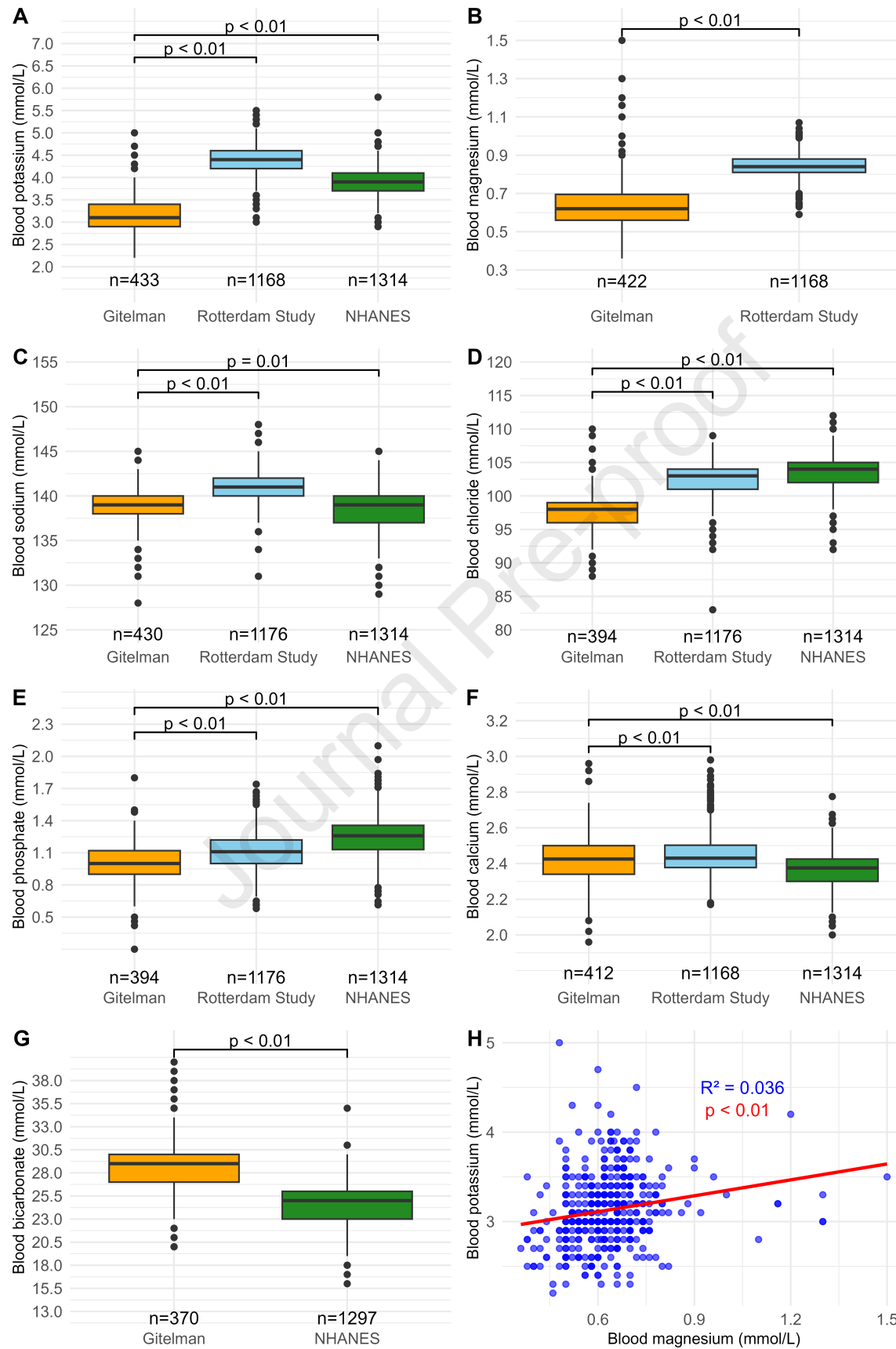
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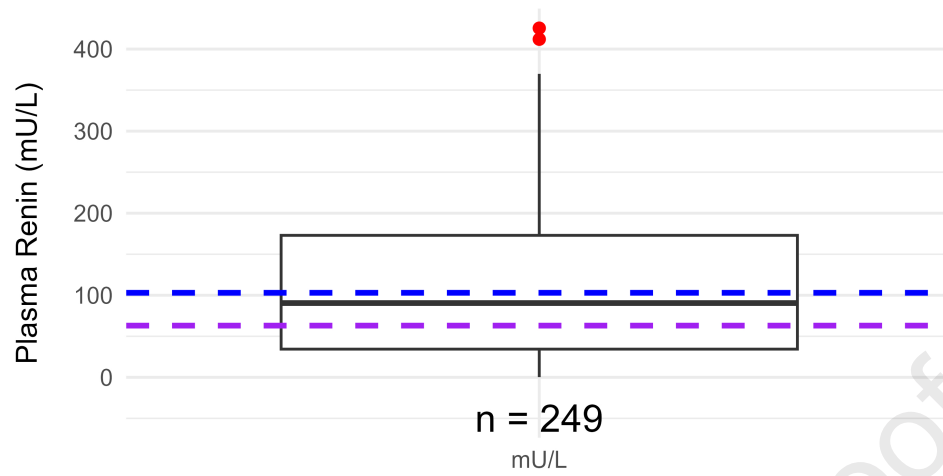
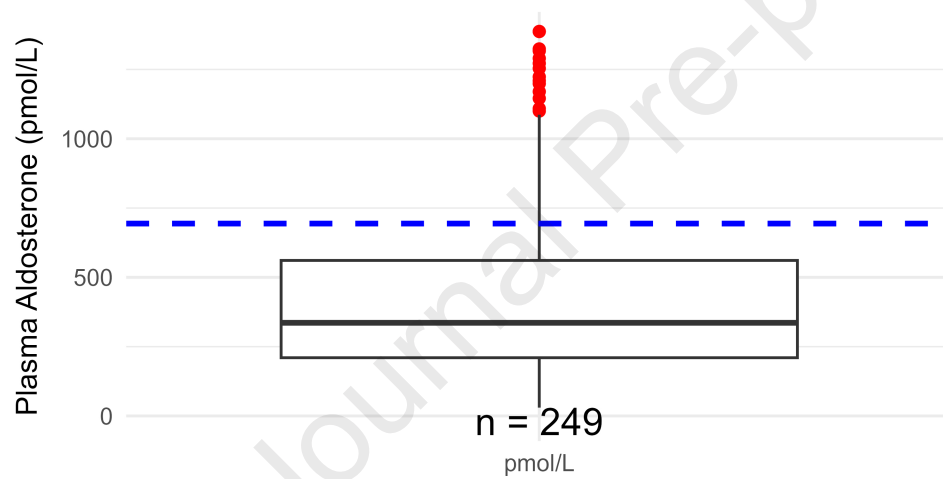
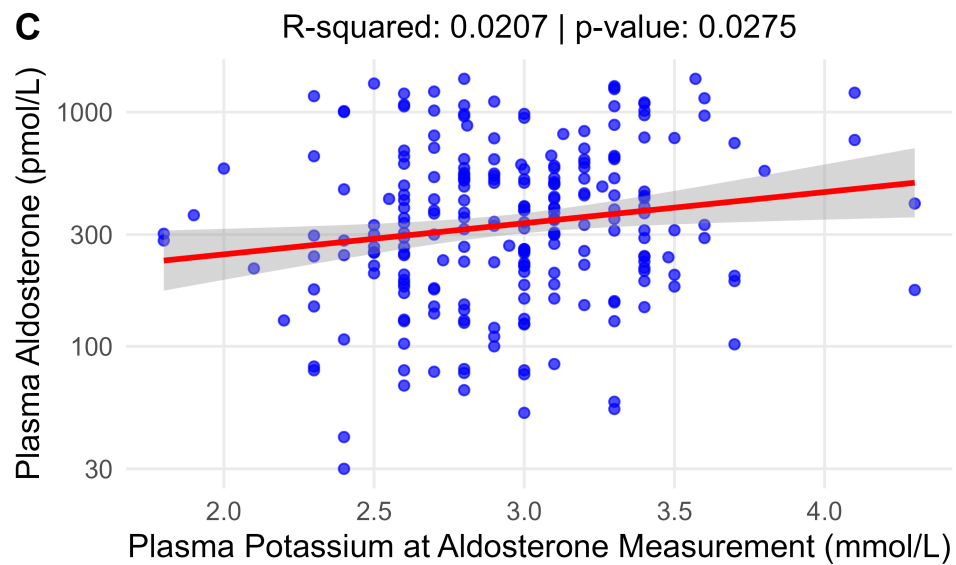
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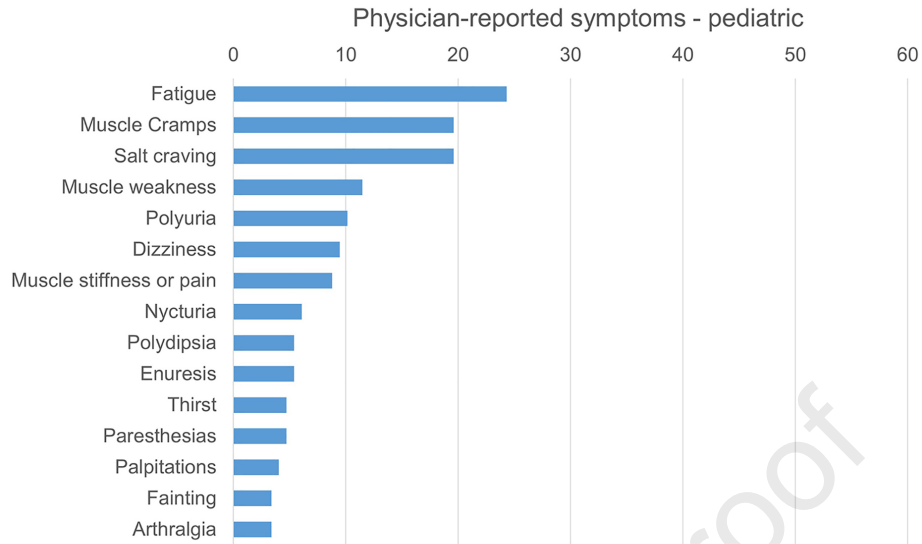


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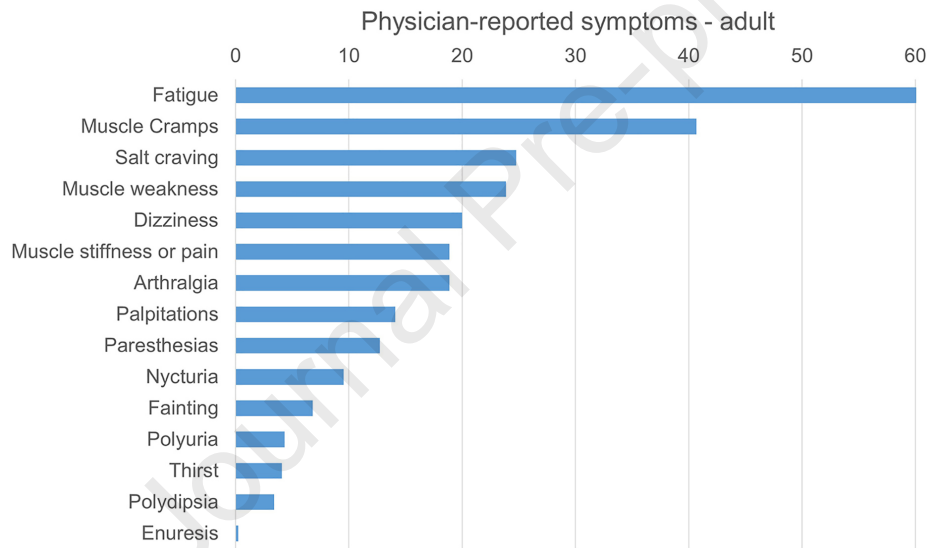
A**B****C**

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A



B



C

