Full title: Higher prevalence of non-skeletal comorbidity related to X-linked hypophosphataemia: a UK CPRD parallel cohort study

Short title: Comorbidities in XLH

Authors:

Samuel Hawley1, Nick J Shaw2, 3, Antonella Delmestri1, Daniel Prieto-Alhambra1,4, Cyrus Cooper5, Rafael Pinedo-Villanueva1\*, M Kassim Javaid1,5\*

Corresponding author:

M. Kassim Javaid,

Botnar Research Centre,

Windmill Road, Oxford,

OX3 7LD, UK

kassim.javaid@ndorms.ox.ac.uk

ORCiD: 0000-0001-7985-0048

Affiliations:

1Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

2Birmingham Women’s and Children’s Hospital NHS Foundation Trust, Birmingham, UK

3Institute of Metabolism & Systems Research, University of Birmingham

4GREMPAL Research Group, Idiap Jordi Gol and CIBERFes, Universitat Autònoma de Barcelona and Instituto de Salud Carlos III, Barcelona, Spain

5MRC Lifecourse Epidemiology Unit, University of Southampton

Keywords:

X-linked Hypophosphataemia, Epidemiology, Comorbidity, Psychosocial Deprivation, Mental Health, Natural History

Key messages:

(1) XLH was here associated with a significant burden of comorbidity broadly defined as endocrinological and neurological conditions with three times the risk of depression

(2) Deprivation as measured by index of multiple deprivation (IMD) was significantly higher among individuals with XLH and associated with more higher rates of comorbidities.

(3) Care pathways for for individuals for XLH should highlight the need to actively screen and manage common comorbidities

**Abstract**

Objectives: X-Linked hypophosphataemic rickets (XLH) is a rare multisystemic disease of mineral homeostasis that has a prominent skeletal phenotype. The aim of this study was to describe additional comorbidities in XLH patients compared to general population controls.

Methods: The Clinical Practice Research Datalink (CPRD) GOLD was used to identify a cohort of XLH patients (1995-2016), along with a non-XLH cohort matched (1:4) on age, sex and GP practice. Using the CALIBER portal, phenotyping algorithms were used to identify the first diagnosis (and associated age) of 273 comorbid conditions during patient follow-up. Fifteen major disease categories were used and the proportion of patients having ≥1 diagnosis was compared between cohorts for each category using logistic regression and repeated according to Index of Multiple Deprivation (IMD).

Results: There were 64 and 256 patients in the XLH and non-XLH cohorts, respectively. There was increased prevalence of endocrine (OR 3.46 [95% CI: 1.44 to 8.31]) and neurological (OR 3.01 [95% CI: 1.41 to 6.44] disorders among XLH patients. Across all specific comorbidities, four were at least twice as likely to be present in XLH cases, but only depression met the Bonferroni threshold: OR 2.95 [95%CI: 1.47 to 5.92]. Distribution of IMD among XLH cases indicated greater deprivation than the general population.

Conclusion: We describe a higher risk of mental illness in XLH patients compared to matched controls, and greater than expected deprivation. These findings may have implications for clinical practice guidelines and decisions around health and social care provision for these patients.

**Introduction**

X-Linked hypophosphataemic rickets (XLH) is a rare multisystemic disease of mineral homeostasis that has a prominent skeletal phenotype characterized by renal phosphate wasting due to mutations in the PHEX gene (1). It is the most common form of heritable rickets(2). The key molecular mechanism involves excess fibroblast growth factor 23 (FGF23) production, a phosphatonin first identified in autosomal dominant hypophophosphataemic rickets(3) and tumour induced osteomalacia (4, 5). XLH usually manifests early in life with shortened height and bowing of the legs, and while these can be improved with phosphate and activated vitamin D pharmacotherapy, they likely persist into adulthood along with increased risk of arthritis, dental abscesses and enthesopathy (calcification of tendons and ligaments) (2, 6). While previous studies have demonstrated the prevalence and incidence of comorbidities in cohort studies based on attendees to specialist centres, the proportion of comorbidities that is attributable to XLH in the community setting is not known. We have previously demonstrated an unexpected increase in mortality in patients with XLH (7). Our primary aim was to describe the comorbidities associated with XLH throughout the life lifespan using routine medical data.

**Methods**

*Study design and participants*

The study design and participants have been previously described (7) and are summarized here. This parallel cohort study used the UK Clinical Practice Research Datalink (CPRD) GOLD – a primary care database containing routinely collected electronic medical records for approximately 7% of the UK population that contains data on comorbidities using Read codes (8). A cohort of all potential XLH patients (1995 to 2016) was first generated using an initial list of Read codes and potential XLH cases were graded by two clinicians with expertise in XLH as either ‘highly likely’, ‘likely’, ‘possible’, ‘unlikely’ or ‘unable to determine’ as previously described(7). Four non-XLH general population control patients were matched to each XLH patient on age, sex and GP practice, all measured at time of first Read code pertaining to XLH diagnosis after a patient was one year of age. For the present investigation, only the potential XLH cases that were graded very likely or likely by either clinical grader (kappa for inter-grader agreement previously reported as 0.98 (7)), along with their matched non-XLH controls were retained in analyses. Linkage to hospital data was available for 58% of the cohort and this was used to record their Index of Multiple Deprivation (IMD).

We interrogated the CPRD dataset using previously defined and published Read code lists (9) to identify diagnoses of non-communicable comorbid conditions for all included XLH cases and controls, with only the first occurrence of a given condition being considered per patient. Only phenotyping code lists that pertained to primary care diagnoses were used, i.e. aspects relating to secondary care hospital data or test data were not considered. All code lists are available from the open-access CALIBER portal (10). Specifically, a list of 273 conditions (supplementary table S1) identifiable in primary care were investigated, all of which have been described previously as being involved in intensive health-care resource utilization (9). We made an adaptation to one of these code lists, changing ‘wrist fracture’ to ‘non-hip fracture’ by adding codes for other sites including pelvis, spine, shoulder and tibia amongst other fracture sites. For primary analyses the 273 individual conditions were merged into 15 major disease categories, as defined previously (9), analogous to ICD10 chapters. For secondary analyses each of the conditions was considered individually.

*Statistical analyses*

Patient-level data flags were created to identify the presence of at least one recorded comorbidity code for each of the 15 major condition categories and for each of the 273 specific conditions. Patient age at the first recording of each comorbid category/condition was also derived. The time window for each patient in which this search was made was from the latest of enrolment into the CPRD, and date of GP practice being recognized as ‘up to standard’ (i.e. as contributing data of sufficient quality), up to the earliest of the date of data download, and patient transference out of practice owing to death or loss to follow-up.

The derived variables were then aggregated separately for XLH and non-XLH cohorts. The proportion of patients affected (i.e. having ≥1 diagnosis) by each of these conditions was formally compared between the cohorts using univariable logistic regression models yielding odds ratios (OR). P-values from these models were interpreted relative to a Bonferroni corrected threshold to account for multiple testing, allowing the significance level of 0.05 to be tailor transformed according to the number of comparisons being performed. In primary analyses the proportion of patients receiving ≥1 diagnosis of any condition within the broader disease categories was the outcome of interest, while secondary analyses investigated each of the 273 conditions individually. These comparisons were only conducted for categories and conditions that affected ≥10% of either cases or controls. This 10% cutoff was used given our interest in conditions that affect a considerable and clinically relevant proportion of the population, which was necessary given the large number of phenotyping code lists available for investigation relative to a limited sample size.

In analyses of individual comorbidities, the relative frequency of affected patients (≥1 diagnosis of a condition) according to XLH/non-XLH cohort was depicted graphically against the mean age at earliest recorded diagnosis for each condition. The OR for disease occurrence alongside corresponding p-values were presented using smile plots (11).

*Sensitivity analysis*

Two sensitivity analyses were performed. The first was to examine the distribution of IMD quintiles within the XLH cohort and repeat the descriptive component of the main analysis (reporting the occurrence of conditions by main disease categories for the XLH and non-XLH cohorts) stratified by below versus above national average IMD. We did this to explore potential differences in natural history, given that there may plausibly be differences in service provision as well as many relevant patient and life-style risk factors according to socio-economic status. Secondly, logistic regression models were used to compare the occurrence of individual categories/conditions that were recorded in ≥5% in either XLH or non-XLH cohorts rather than the 10% cutoff used in the main analysis.

**Results**

Out of 522 patients initially identified with a possible Read code for XLH, 64 were retained as being graded either very likely or likely, along with their 256 matched controls. Characteristics of these patients are included in table 1. Median age at first recorded code pertaining to XLH was 12.5 years with an overall median follow-up of 10.2 (IQR: 6.8 to 16.4) years. 45% were aged 16 years or older and 70.5% were female. There were a total of 41,976 eligible recorded event/diagnosis codes during study follow-up among the 320 individuals included in analyses, with the median number per patient being 119 (IQR: 53 – 233) and 80 (IQR: 33 – 177) for XLH and non-XLH patients, respectively.

In analyses of the 15 condition categories, nine were present in ≥10% of the XLH cohort while six were present in ≥10% of the non-XLH cohort (table 2). In terms of a differential burden of categorized conditions between cohorts, there was a significantly higher occurrence of neurological (OR=3.01 [95% CI: 1.41 to 6.44]; p=0.0046) and endocrine (OR=3.46 [95% CI: 1.44 to 8.31]; p=0.0054) comorbidities in XLH patients (table 2). Categorized mental health conditions were also elevated (OR=1.90 [95%CI: 0.99 to 3.62]), although did not meet statistical significance (p=0.053) considering the multiple testing (table 2). Specific conditions that particularly contributed to the greater burden of categorized neurological conditions in the XLH cohort were epilepsy (4.7% versus 0.4%) and migraine (10.9% versus 4.7%) (supplementary table S1). Those that contributed to the raised categorized endocrine system conditions were hyperparathyroidism (6.3% versus 0%) and obesity (7.8% versus 1.6%) (supplementary table S1).

In secondary analyses, out of the 273 individual conditions investigated, nine were recorded in at least 10% of XLH and/or non-XLH patients which in age ascending order (for XLH patients) were: acne, dermatitis, asthma, rhinitis, migraine, depression, enthesopathy, anxiety and hypertension (figure 1, supplementary table S1). Rates of four of these were at least twice as high in the XLH versus non-XLH cohort: depression (OR=2.95 [95% CI: 1.47 to 5.92]), migraine (OR=2.50 [95% CI: 0.94 – 6.62]), rhinitis (OR=2.40 [95% CI: 1.20 to 4.80]) and hypertension (OR=2.12 [95% CI: 0.82 to 5.50]) (figure 1A, supplementary table S2), although the strength of evidence for this elevation was only considered significant for depression given the Bonferroni corrected p-threshold of 0.00556 (figure 2B, supplementary table S2).

*Sensitivity analyses*

Of the 37 (58%) XLH patients with linked IMD data, a significantly higher than expected proportion were below the national IMD average (24/37 [63%], p=0.011) (Figure 2). When the prevalence of comorbidities was examined only among XLH patients with a worse than average IMD along with their non-XLH counterparts, XLH patients still had more conditions affecting the endocrine system (13% versus 4%), mental health (33% versus 17%), musculoskeletal (17% versus 9%) and neurological conditions (21% versus 5%), although the statistical significance was not assessed given the small numbers (supplementary figure S1). Skin conditions appeared less prevalent in low IMD XLH patients relative to their non-XLH controls: 25% versus 40% (supplementary figure S1). Among XLH patients with higher than average IMD, only the endocrine conditions comorbidity category was elevated compared to matched non-XLH patients (15% versus 2%), while other categories appeared similarly prevalent or less so (supplementary figure S1).

When main analyses were repeated including all conditions in logistic regression models if they affected ≥5% of XLH cases or controls, rather than the 10% cut-off, results were very similar as to main analyses, except the statistical significance of the higher rate of endocrine system conditions (at the category level) was no longer below the Bonferroni corrected threshold of p=0.005 (supplementary table S3). Depression was still significantly elevated among XLH cases, and while rhinitis, obesity, migraine, osteoarthritis and chronic kidney disease were also higher in XLH patients relative to the non-XLH patients (OR>2.00), the evidence for these was weak (0.01≤p≤0.1) given the multiple testing involved (supplementary figure S2).

**Discussion**

In this study, we describe the life course burden of comorbidity among XLH patients, relative to matched non-XLH controls, in terms of broad disease categories and specific comorbid conditions. We demonstrate greater burden of conditions broadly defined as neurological, or endocrinological in XLH patients, alongside a significant elevation in depression which affected 25% of XLH cases relative to 10% of matched general-population controls. Our findings suggest a higher than expected prevalence of deprivation among XLH patients and that a higher prevalence of mental health, neurological and musculoskeletal conditions was particularly apparent in XLH patients with greater deprivation versus their matched controls.

The finding of more mental illness in people with XLH was unexpected. Most research into the burden of XLH and management guidelines for XLH has focused on skeletal and dental aspects of XLH (12, 13) (14-19). Further, using generic quality of life tools, no clinically meaningful deficit in mental wellbeing was seen in adults using EQ-5D-5L(20) or SF10 (21). In contrast, qualitative approaches have detected significant issues around mental wellbeing. A thematic analysis of free text responses to the UK regulatory consultation for Burosumab demonstrated that people with XLH frequently reported a negative psychological impact, particularly during adolescence (22). Qualitative semi-structured interviews in adults with XLH have also elicited impacts around depression and frustration (23). This suggests that generic tools may be insensitive to capture mental health issues in people with XLH. Further detail is needed to describe how to assess and manage the mental as well as physical aspects of health in this patient group.

Why patients with XLH have lower mental health is not well understood, but likely reflects the consequences of bone pain, deformity and reduced mobility and function (24, 25). The need to regularly attend multiple clinics that can require considerable time and energy for patients to co-ordinate has been noted as a source of stress, along with a perceived need of some patients to “fight for funding” for off-label drugs or for personal care and mobility (26). While recent clinical practice recommendations include the psychologist as part of the multidisciplinary team for managing people with XLH (27, 28), further work is needed to explore the potential impact of pharmacotherapy on these non-skeletal features of XLH across the life course. It has been suggested some symptoms could be due to continuing effects of elevated FGF23 (25), the target of burosumab (29). Issues around delayed diagnosis, misdiagnosis, cycles of symptom improvement-relapse and lack of definitive prognosis may also contribute to poor mental health (26).

Given that mutations responsible for XLH are not thought to be predicted by social deprivation or associated lifestyle factors, the finding that people with XLH have worse indices of deprivation suggests that a diagnosis of XLH is associated with downward social mobility, a process of health selection, where an individual’s health affect socioeconomic status more than social causation, where an individual’s socioeconomic status affects health (30). This is a novel finding with little reported in the literature regarding associations between rare bone diseases and social deprivation and social mobility. In cardiovascular studies, health selection has been demonstrated to operate more during childhood with social causation influencing health outcomes in later adulthood (31). The inter-generational transmission of XLH is likely to worsen deprivation, but this information was not available in CPRD. Worsening deprivation scores are known to predict health outcomes in later life relevant to XLH such as fragility fractures (32), oral health (33) as well as mental wellbeing (34) and reduced survival (35). Understanding that people with XLH are at higher risk of deprivation may influence the design of care pathways by requiring the inclusion of expertise in benefits and other aspects of social care across the life course (36), as well as education (37, 38) and employment (39).

One of the key strengths of this analysis is the availability of routinely and prospectively collected health data over a median follow-up of approximately 10 years per patient. The CPRD GOLD is a large sample of the UK population, previously shown to be representative in terms of age, sex and ethnicity (8, 40). The included breadth of data allowed for a detailed and conservative approach to XLH case ascertainment. This, in conjunction with a large number of readily available phenotyped conditions (9) within this data resource allowed a comprehensive investigation of comorbid conditions throughout the lifespan of XLH patients in relation to matched non-XLH patients of near identical age, sex and geographic profile.

However, no validated algorithm exists for confirming the diagnosis of XLH in the primary care setting and the limitations from this are discussed in our previous paper. (41). While we attempted to address the occurrence of mimicking conditions in case ascertainment, we cannot rule out the possibility of misclassification, especially given that the potential for miscoding rare disease is likely higher in the primary care setting where coding is probably completed by a clinician, nurse or administrative staff with little training in rare diseases. Likewise, while the availability of pre-existing phenotyping code lists, developed by a panel of 10 clinicians with expertise spanning the range of recorded conditions enabled the investigation of an extensive number of comorbid conditions (9), little data exists on the internal validity of these codes. Several other limitations to using this approach have also previously been acknowledged, such as the existence of a possible time-lag between disease onset and the first coded event for a given condition, and the ‘clinical iceberg’ phenomenon where only a proportion of individuals with a given condition will actually demonstrate the health care seeking behavior to attend a GP and have the condition recorded (9). This is likely to be especially so for those with only mild or moderate symptoms.

Furthermore, given our approach of matching each XLH patient to four non-XLH controls on age, sex and GP practice at the time of earliest READ code pertaining to XLH, the resultant follow-up time overall is disproportionately sampled from a younger population that is predominantly female. While this facilitates valid comparison of XLH patients versus controls, caution is required in interpreting the burden of comorbidity across the life course, particularly in older age where we had less follow-up time to include in analyses. Likewise, while we compared burden of comorbidity in XLH vs the general population at various levels (condition categories and individual conditions), given the nature of studying a rare disease we were underpowered to statistically demonstrate what may be meaningful changes in the less prevalent comorbidities. This was especially the case in exploratory analyses stratified by IMD, where further work is needed on larger samples to confirm and further elucidate the relatively higher increase in comorbidity (particularly neurological and mental health conditions) among XLH patients from more deprived areas. The importance of more research on this topic is further underlined by the observation that XLH patients here tended to reside in areas of higher deprivation (figure 2) than would be expected given the generalizability of CPRD GOLD in terms of IMD (42).

Another limitation is that we did not include aspects of phenotyping code lists dependent on secondary care hospital data, mainly because only approximately 60% of our sample had available linkage to such data. This did restrict our investigation to non-communicable conditions, with exclusion of approximately 25 available machine readable algorithms for infections/infectious conditions (9). Test data has also been shown to be subject to large practice (43), temporal and age-related variation (44), and given the added challenges of interpreting test results in the context of missing reference ranges etc., we opted to use only diagnosis Read codes. Despite this fact, our inclusion of 273 conditions, considered individually and as 15 grouped categories provides a comprehensive investigation at varying degrees of granularity. Finally, we recognize that dental complications are common in XLH (45), however, due to the nature of provision of dental care in the UK healthcare system, information on dental comorbidity was not collected.

**Conclusion**

We have confirmed the excess of comorbidities associated with neurological and endocrine conditions in XLH patients compared with matched controls, and have identified higher prevalence of psychological health issues and worse social deprivation. These findings have implications for clinical practice guidelines and decisions around health and social care provision for this patient group.

Funding

Kyowa Kirin International provided funding for this project to the University of Oxford. The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interest

Outside the submitted work, SH , NS and AD report no conflicts of interest. DPA reports grants from AMGEN, UCB Biopharma and Les Laboratoires Servier. CC reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB. RPV has received research funding from Kiowa Kirin, and lecture fees and/or consulting honoraria from Amgen, UCB, Kyowa Kirin Hakin, and Mereo Biopharma. MKJ reports grants from AMGEN, Kyowa Kiran Hakin and consultanties from AMGEN, Internis, consilient Health, Mereo Biopharma, Kyowa Kirin Hakin and UK

Figure Legends

Figure 1: presence of comorbidities\* in XLH cases and non-XLH controls

Figure 2: distribution of IMD (national quintiles) within cases with linked data (n=38)

REFERENCES

1. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. The HYP Consortium. Nature genetics. 1995;11(2):130-6.

2. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2011;26(7):1381-8.

3. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nature genetics. 2000;26(3):345-8.

4. Cai Q, Hodgson SF, Kao PC, Lennon VA, Klee GG, Zinsmiester AR, et al. Brief report: inhibition of renal phosphate transport by a tumor product in a patient with oncogenic osteomalacia. The New England journal of medicine. 1994;330(23):1645-9.

5. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(11):6500-5.

6. Pettifor JM. What's new in hypophosphataemic rickets? Eur J Pediatr. 2008;167(5):493-9.

7. Hawley S, Shaw NJ, Delmestri A, Prieto-Alhambra D, Cooper C, Pinedo-Villanueva R, et al. Prevalence and mortality of individuals with X-linked hypophosphataemia: a United Kingdom real world data analysis. The Journal of clinical endocrinology and metabolism. 2020;105(3):1-8.

8. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology. 2015.

9. Kuan V, Denaxas S, Gonzalez-Izquierdo A, Direk K, Bhatti O, Husain S, et al. A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service. Lancet Digit Health. 2019;1(2):e63-e77.

10. CALIBER open-access portal <https://www.caliberresearch.org/portal/phenotypes/chronological-map> [08/10/2019].

11. Newson R. Multiple-test procedures and smile plots. The Stata Journal. 2003;3(2):109-32.

12. Hardy DC, Murphy WA, Siegel BA, Reid IR, Whyte MP. X-linked hypophosphatemia in adults: prevalence of skeletal radiographic and scintigraphic features. Radiology. 1989;171(2):403-14.

13. Stickler GB, Morgenstern BZ. Hypophosphataemic rickets: final height and clinical symptoms in adults. Lancet (London, England). 1989;2(8668):902-5.

14. Beck-Nielsen SS, Brusgaard K, Rasmussen LM, Brixen K, Brock-Jacobsen B, Poulsen MR, et al. Phenotype presentation of hypophosphatemic rickets in adults. Calcified tissue international. 2010;87(2):108-19.

15. Emma F, Cappa M, Antoniazzi F, Bianchi ML, Chiodini I, Eller Vainicher C, et al. X-linked hypophosphatemic rickets: an Italian experts' opinion survey. Ital J Pediatr. 2019;45(1):67-.

16. Raimann A, Mindler GT, Kocijan R, Bekes K, Zwerina J, Haeusler G, et al. Multidisciplinary patient care in X-linked hypophosphatemic rickets: one challenge, many perspectives. Wiener medizinische Wochenschrift (1946). 2020:10.1007/s10354-019-00732-2.

17. Lambert A-S, Zhukouskaya V, Rothenbuhler A, Linglart A. X-linked hypophosphatemia: Management and treatment prospects. Joint, bone, spine : revue du rhumatisme. 2019;86(6):731-8.

18. Şıklar Z, Turan S, Bereket A, Baş F, Güran T, Akberzade A, et al. Nationwide Hypophosphatemic Rickets Cohort Study. Journal of clinical research in pediatric endocrinology. 2019:10.4274/jcrpe.galenos.2019..0098.

19. Chesher D, Oddy M, Darbar U, Sayal P, Casey A, Ryan A, et al. Outcome of adult patients with X-linked hypophosphatemia caused by PHEX gene mutations. J Inherit Metab Dis. 2018;41(5):865-76.

20. Forestier-Zhang L, Watts L, Turner A, Teare H, Kaye J, Barrett J, et al. Health-related quality of life and a cost-utility simulation of adults in the UK with osteogenesis imperfecta, X-linked hypophosphatemia and fibrous dysplasia. Orphanet journal of rare diseases. 2016;11(1):160.

21. Skrinar A, Dvorak-Ewell M, Evins A, Macica C, Linglart A, Imel EA, et al. The Lifelong Impact of X-Linked Hypophosphatemia: Results From a Burden of Disease Survey. J Endocr Soc. 2019;3(7):1321-34.

22. Ferizović N, Marshall J, Williams AE, Mughal MZ, Shaw N, Mak C, et al. Exploring the Burden of X-Linked Hypophosphataemia: An Opportunistic Qualitative Study of Patient Statements Generated During a Technology Appraisal. Advances in therapy. 2020;37(2):770-84.

23. Theodore-Oklota C, Bonner N, Spencer H, Arbuckle R, Chen C-Y, Skrinar A. Qualitative Research to Explore the Patient Experience of X-Linked Hypophosphatemia and Evaluate the Suitability of the BPI-SF and WOMAC® as Clinical Trial End Points. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(8):973-83.

24. Khazem LR. Physical disability and suicide: recent advancements in understanding and future directions for consideration. Curr Opin Psychol. 2018;22:18-22.

25. Lo SH, Lachmann R, Williams A, Piglowska N, Lloyd AJ. Exploring the burden of X-linked hypophosphatemia: a European multi-country qualitative study. Qual Life Res. 2020.

26. Nunn R. "It's not all in my head!" - The complex relationship between rare diseases and mental health problems. Orphanet J Rare Dis. 2017;12(1):29.

27. Haffner D, Emma F, Eastwood DM, Duplan MB, Bacchetta J, Schnabel D, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2019;15(7):435-55.

28. Rothenbuhler A, Schnabel D, Högler W, Linglart A. Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH). Metabolism: clinical and experimental. 2020;103S:153892-.

29. Zhang X, Peyret T, Gosselin NH, Marier JF, Imel EA, Carpenter TO. Population pharmacokinetic and pharmacodynamic analyses from a 4-month intra-dose escalation and its subsequent 12-month dose titration studies for a human monoclonal anti-FGF23 antibody (KRN23) in adults with X-linked hypophosphatemia. J Clin Pharmacol. 2015.

30. Dahl E. Social mobility and health: cause or effect? Bmj. 1996;313(7055):435-6.

31. Elovainio M, Ferrie JE, Singh-Manoux A, Shipley M, Batty GD, Head J, et al. Socioeconomic differences in cardiometabolic factors: social causation or health-related selection? Evidence from the Whitehall II Cohort Study, 1991-2004. Am J Epidemiol. 2011;174(7):779-89.

32. Bhimjiyani A, Neuburger J, Jones T, Ben-Shlomo Y, Gregson CL. The effect of social deprivation on hip fracture incidence in England has not changed over 14 years: an analysis of the English Hospital Episodes Statistics (2001-2015). Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2018;29(1):115-24.

33. Brennan DS, Spencer AJ. Health-related quality of life and income-related social mobility in young adults. Health Qual Life Outcomes. 2014;12:52.

34. Kivimäki M, Batty GD, Pentti J, Shipley MJ, Sipilä PN, Nyberg ST, et al. Association between socioeconomic status and the development of mental and physical health conditions in adulthood: a multi-cohort study. Lancet Public Health. 2020;5(3):e140-e9.

35. Demakakos P, Biddulph JP, de Oliveira C, Tsakos G, Marmot MG. Subjective social status and mortality: the English Longitudinal Study of Ageing. Eur J Epidemiol. 2018;33(8):729-39.

36. Marmot M. Social justice, human rights and health equity. J Public Health (Oxf). 2020.

37. Krzyżanowska M, Mascie-Taylor CG. Biosocial correlates of inter-generational social mobility in a British cohort. J Biosoc Sci. 2013;45(4):481-96.

38. Laine JE, Baltar VT, Stringini S, Gandini M, Chadeau-Hyam M, Kivimaki M, et al. Reducing socio-economic inequalities in all-cause mortality: a counterfactual mediation approach. Int J Epidemiol. 2019.

39. Laaksonen E, Lallukka T, Lahelma E, Ferrie JE, Rahkonen O, Head J, et al. Economic difficulties and physical functioning in Finnish and British employees: contribution of social and behavioural factors. Eur J Public Health. 2011;21(4):456-62.

40. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, vanStaa T, Grundy E, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. Journal of public health. 2014;36(4):684-92.

41. Hawley S, Shaw NJ, Delmestri A, Prieto-Alhambra D, Cooper C, Pinedo-Villanueva R, et al. Prevalence and Mortality of Individuals With X-Linked Hypophosphatemia: A United Kingdom Real-World Data Analysis. The Journal of clinical endocrinology and metabolism. 2020;105(3):dgz203.

42. Jain A, van Hoek AJ, Walker JL, Mathur R, Smeeth L, Thomas SL. Identifying social factors amongst older individuals in linked electronic health records: An assessment in a population based study. PLoS One. 2017;12(11):e0189038.

43. O'Sullivan JW, Stevens S, Oke J, Hobbs FDR, Salisbury C, Little P, et al. Practice variation in the use of tests in UK primary care: a retrospective analysis of 16 million tests performed over 3.3 million patient years in 2015/16. Bmc Medicine. 2018;16.

44. O'Sullivan JW, Stevens S, Hobbs FDR, Salisbury C, Little P, Goldacre B, et al. Temporal trends in use of tests in UK primary care, 2000-15: retrospective analysis of 250 million tests. Bmj-Brit Med J. 2018;363.

45. Hanisch M, Bohner L, Sabandal MMI, Kleinheinz J, Jung S. Oral symptoms and oral health-related quality of life of individuals with x-linked hypophosphatemia. Head & face medicine. 2019;15(1):8-.