Osteoporosis International (2021) 32:7–22
https://doi.org/10.1007/s00198-020-05548-0

REVIEW

Burden of disease associated with X-linked hypophosphataemia in adults: a systematic literature review

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Received: 3 March 2020 / Accepted: 8 July 2020 / Published online: 24 July 2020

Abstract

Summary This systematic review collated evidence on the burden of XLH in adults. Data captured highlight the substantial ongoing burden of XLH in adulthood and identified unmet needs. Greater awareness and understanding of the impact of XLH in adulthood are needed to improve care and outcomes in adults with XLH.

Introduction X-linked hypophosphataemia (XLH) is a rare metabolic bone disease characterized by renal phosphate wasting and musculoskeletal manifestations. Whilst the disease's impact in children is well documented, information on the effects of this progressive, debilitating condition on adults is lacking. This systematic review aimed to collate existing evidence on the burden of XLH in adulthood to identify unmet needs.

Methods MEDLINE, Embase and Cochrane Library databases and recent congress reports were searched on 19 February 2019 for English-language publications describing the medical, humanistic and socio-economic impact of XLH in adults (≥ 18 years old). In addition, a structured Internet search was conducted.

Results Of the 2351 articles identified, 91 met the selection criteria along with 44 congress abstracts. Data show that adults with XLH experience a range of clinical manifestations, particularly skeletal deformities and (pseudo)fractures, along with pain, dental abnormalities and impaired physical function and mobility. XLH in adulthood impacts on quality of life and places limitations on daily activities. The level of healthcare resource utilization among adults with XLH is indicative of substantial socio-economic burden; further research is needed to quantitate the economic impact on the healthcare system, society and patients. Adults with XLH may not receive appropriate care and treatment; a possible explanation for this is a lack of awareness among healthcare professionals.

Conclusion XLH in adults is associated with considerable disease burden and unmet needs. Forthcoming studies and increased awareness of the impact of XLH in adulthood should help to improve management of XLH in adulthood and patient outcomes.

Keywords Familial hypophosphataemic rickets · Illness burden · Quality of life · Systematic review · Unmet needs · X-linked hypophosphataemia

Introduction

X-linked hypophosphataemia (XLH; OMIM: #307800) is a rare, genetically determined metabolic bone disease [1]. It is characterized by renal phosphate wasting and altered mineral metabolism, which cause a diverse range of clinical manifestations including skeletal and dental abnormalities that first become apparent during early childhood [2, 3]. XLH is caused by mutations in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*), which lead to elevated circulating concentrations of the phosphatonin fibroblast growth factor 23 (FGF23) [1, 2]. Elevated FGF23 levels affect bone mineralization and skeletal development via several mechanisms [4]. These include chronic hypophosphataemia

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-020-05548-0) contains supplementary material, which is available to authorized users.

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and inappropriate (low to low normal) levels of active vitamin D (1,25-dihydroxyvitamin D), as well as local, autocrine/paracrine mechanisms that are not yet fully elucidated [4].

In children, XLH presents as a broad range of clinical manifestations including rickets and associated limb deformities, impaired growth, pain and dental abnormalities, which together result in reduced health-related quality of life (HRQoL) [3, 5, 6]. Focus in clinical practice is on the management of the disease during childhood, while the skeleton is still developing, with treatment aiming to improve growth and reduce skeletal deformities [2, 3]. Until recently, standard treatment for children with XLH consisted of active vitamin D analogues (calcitriol or alfacalcidol) and multiple daily doses of phosphate until growth was complete [2, 3]. Burosumab, a fully human monoclonal antibody against FGF23, is now approved conditionally in Europe for the treatment of XLH with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons [7]. XLH in adulthood has received less clinical attention; there is currently no consensus regarding the use of conventional supplementation therapy in adults, although treatment of symptomatic adults is recommended [8], and no disease-specific treatments are approved for adults with XLH in Europe. However, burosumab is approved for both adult and paediatric use in several countries outside of Europe, including the USA, where it is indicated for the treatment of XLH in adults and children 6 months of age and older [9]. There is increasing recognition that XLH imposes a substantial clinical burden in adults [6, 10, 11]. In addition, several large studies have confirmed reduced HRQoL in adults with XLH [12–14], but this evidence has not been compiled. There is a need to collate data on the burden of XLH during adulthood, including the social, psychological and financial challenges that adults with XLH experience, to support wider adoption of appropriate treatment beyond adolescence and to improve patient outcomes.

The aim of this systematic review was therefore to collate existing evidence on the humanistic and economic burden of XLH in adults to gain an understanding of the unmet needs associated with the disease in adulthood.

Methods

There were two parts to this analysis: a systematic review of the published medical literature and a structured Internet search to capture additional sources of evidence. Initial literature searches were broad in scope, owing to the expected low frequency of publications on XLH in adulthood. Search terms used were designed to capture all available information on XLH.

Systematic literature review

A systematic review of the literature was performed in accordance with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. All publications including data pertaining to the unmet needs of adults with XLH published in English before 19 February 2019 were included. Publications containing information on children and adults were included only if results were presented separately for adults. Case studies, cohort studies, cross-sectional studies, randomized controlled trials and narrative review articles were included.

Literature searches

Searches of the following databases were performed using Ovid on 19 February 2019: Embase (covering publications from 1974 to the present), Ovid MEDLINE (covering publications from 1946 to the present) and the Cochrane Library, comprising the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials, the Cochrane Methodology Register, the National Health Service Economic Evaluation Database, the Health Technology Assessment database and the American College of Physicians Journal Club Archives. Abstracts from all conferences held in the previous 5 years (February 2014 to February 2019) available in the Northern Light Life Sciences Conference Abstracts database were searched manually. Search terms for the systematic review are presented in Supplementary Table S1.

Selection of eligible publications

Titles and abstracts of publications captured in the searches were screened by a reviewer for potential relevance to the topic of interest based on predefined eligibility criteria. Eligible publications were those containing information on the epidemiology and/or humanistic burden of XLH in adults (≥ 18 years old), as well as those including evidence on the economic burden associated with XLH in adulthood. Uncertainties regarding relevance were resolved by a second reviewer after initial screening. Relevant publications for inclusion were then confirmed by reviewing the full text of all publications meeting the eligibility criteria at title/abstract screening.

Data extraction

Data from the full text of publications meeting the inclusion criteria were extracted into an Excel workbook. Information on publication type, study design, sample size, participant demographics (including, if available, country, sex, average

age, age at occurrence of first XLH manifestation and at diagnosis of XLH and treatment information), history of clinical manifestations and procedures and use of pain medication was extracted. Data on the following were also captured: the impact of XLH on HRQoL, home life, work and education, history of use of assistive devices for disability, home modifications, economic burden of the disease, epidemiology, disease awareness and any other data considered by the reviewer to pertain to the unmet needs of adults with XLH. Publications that reported on the same study were grouped at this stage to avoid repetition in the reporting of results. Where both a journal article and congress abstract(s) were published on a specific study, only data from the article are presented. Where two congress abstracts reported data from different patient cohorts from the same study that had not been published as a journal article, both sets of data are presented, with the common source study noted. Aspects of XLH in adulthood reported in the research and case study publications were assessed to identify common themes.

Assessment of evidence quality

Non-clinical trial research studies (cohort and cross-sectional studies) were evaluated for quality of evidence using the Newcastle–Ottawa Scale (Supplementary Table S2) [16].

Structured review of sources of evidence on the Internet

The systematic review was augmented by a structured Internet search, which was conducted using Google on 8 March 2019. The search terms used in the structured Internet search are presented in Supplementary Table S3. Sources of information on the unmet needs of adults with XLH that were not included in the systematic review were identified from websites captured in the search by a single reviewer, with any uncertainties regarding relevance resolved by a second reviewer. Any data considered by the reviewer to be relevant to the topic of interest were extracted from these sources into an Excel workbook.

Results

The PRISMA diagram for the selection of eligible publications is shown in Fig. 1. Overall, 135 publications met the criteria for inclusion (91 journal articles and 44 conference abstracts). Among the 91 journal articles, there were 40 case study publications (which described a total of 56 adults with XLH), 32 research articles (including 17 cohort studies, 13 cross-sectional studies and two clinical trials; reported sample sizes ranged from 2 to 134 adults with XLH) and 19 review articles. Quality of evidence from the non-clinical trial research studies was rated as good, satisfactory and poor for 6 [17–22], 14 [10, 11, 23–34] and 10 [35–44] studies, respectively. Of the 44 conference abstracts, 13 described case studies (which included 12 adults with XLH not described in the journal articles), 27 described research studies (reported sample sizes ranged from 5 to 195 adults with XLH) and four were reviews.

The research and case study publications identified in this systematic review predominantly reported on three aspects of XLH in adulthood: (1) XLH-related manifestations and procedures, (2) clinical management and awareness of XLH in adults and (3) impact of XLH on quality of life. The numbers of publications reporting on these aspects are shown in Fig. 2. Limited data on the epidemiology of XLH were reported [40, 45]. None of the publications specifically assessed the economic impact of XLH in adults on the healthcare system or society.

XLH-related manifestations and procedures

Most ($n = 48/59$) research publications described the clinical manifestations of XLH. Of these, 24 publications covering 20 distinct studies reported the percentage of participants who had experienced specific manifestations (Table 1). The clinical features of XLH in adults reported in these studies comprised musculoskeletal manifestations (such as limb abnormalities, short stature, osteoarthritis, osteomalacia, fractures, muscle weakness, enthesopathy, joint stiffness and spinal stenosis), dental problems, pain, ambulation difficulties (including impaired mobility and gait disturbance), renal complications, fatigue, hyperparathyroidism, loss of balance, hearing loss and tinnitus. Structured assessments of physical performance were not reported. Concerning the musculoskeletal burden of XLH in adults, one cohort study reported a high prevalence of pseudofractures (45%; $n = 10/22$), as well as a high prevalence of early-onset osteoarthritis and enthesopathy in 55% and 33% of patients younger than 30 years, respectively [36]. In patients 30–66 years of age, the prevalence of osteoarthritis and enthesopathy were as high as 80% and 100%, respectively [36]. Pain was often documented in the studies; the proportion of participants experiencing pain (of any type) varied widely between the studies, ranging from 45 ($n = 9/20$) in a phase 1/2 clinical trial [50] to 100% ($n = 17/17$; [38] $n = 18/18$) [41] in a cohort study and an interview-based study. Hypertension was reported in one research publication; 27% ($n = 6/22$) of adult patients in that retrospective chart review had a history of hypertension [27]. Few publications discussed differences in disease severity between men and women; however, a retrospective cross-sectional study in 52 adults with XLH rated as good quality found that women had fewer sites of enthesopathy and were less likely to have severe dental disease than men [20]. Available data consistently demonstrated stunted growth in both men and women (Table 1). Limited data were available on body constitution (weight, body mass index [BMI] and body fat percentage); however,

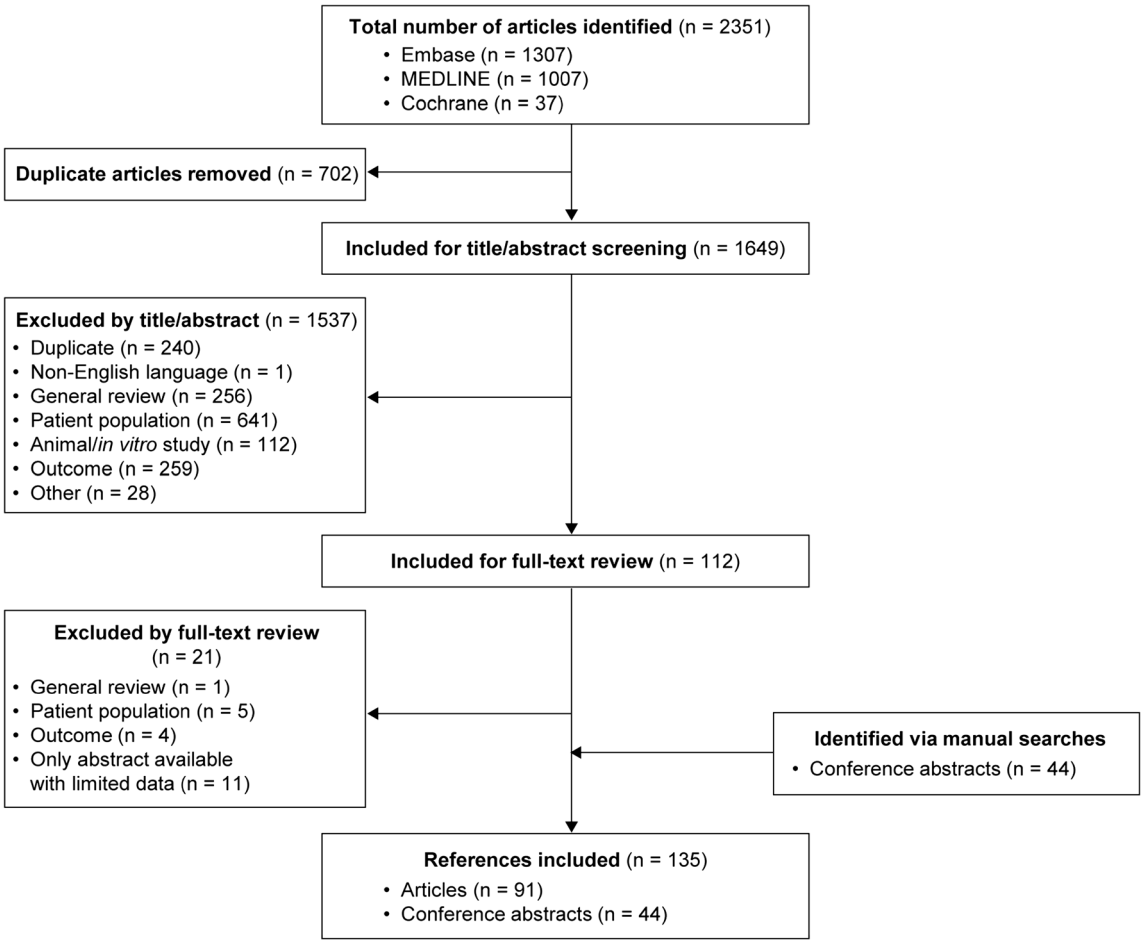

Fig. 1 PRISMA diagram of included and excluded references. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

when reported, mean or median BMI was over 25 kg/m^2, suggesting a possible predisposition to adiposity and being overweight (Table 1) [18, 20, 34, 48].

Data on clinical manifestations in 68 adults with XLH were also reported in case study publications, which generally focused on specific manifestations or complications and did not provide comprehensive medical histories. The most frequently reported manifestations were limb deformity ($n = 37$), pain ($n = 30$), short stature ($n = 30$) and impaired mobility ($n = 22$; Supplementary Fig. S1).

In the research studies with available data on surgical procedures, a high proportion of adults with XLH (≥ 57%) reported a history of orthopaedic surgeries (Table 1). In a phase 3 clinical trial, a history of orthopaedic surgery was reported in 69% ($n = 92$) of 134 patients (65% female), even though most of them (81%) had received conventional supplementation therapy with phosphate and/or active vitamin D metabolites or analogues during childhood [12]. Data relating to the appropriateness of this therapy in individual patients were not available. In addition, 68% of these patients were receiving analgesics at baseline, and 22% were taking opioids [12]. In a web-based survey of 150 adults with XLH (information on sex was not reported), 65% ($n = 97$) reported at least one orthopaedic surgery, including osteotomy (63%), knee replacement (12%) and hip replacement (8%) in their medical history [14]. Current phosphate/vitamin D therapy was reported by 62% of the individuals in the study [14].

Clinical management and awareness of XLH in adults

Several publications that included information relating to clinical management indicated that many adults with XLH stop receiving treatment and may not be followed up after childhood [2, 3, 14, 53]. For example, in a survey of 150 adults with XLH published in 2015, 38% of the respondents were not receiving phosphate/vitamin D at the time of participation in the study, despite 97% of all respondents reporting bone or joint pain [14]. Limited information on the level of awareness of XLH in adults among clinicians was reported in the literature; however, this emerged as a key theme highlighted by numerous authors of publications included in the systematic review [33, 54–61].

Complications associated with conventional supplementation therapy were reported inconsistently, although hyperpara-

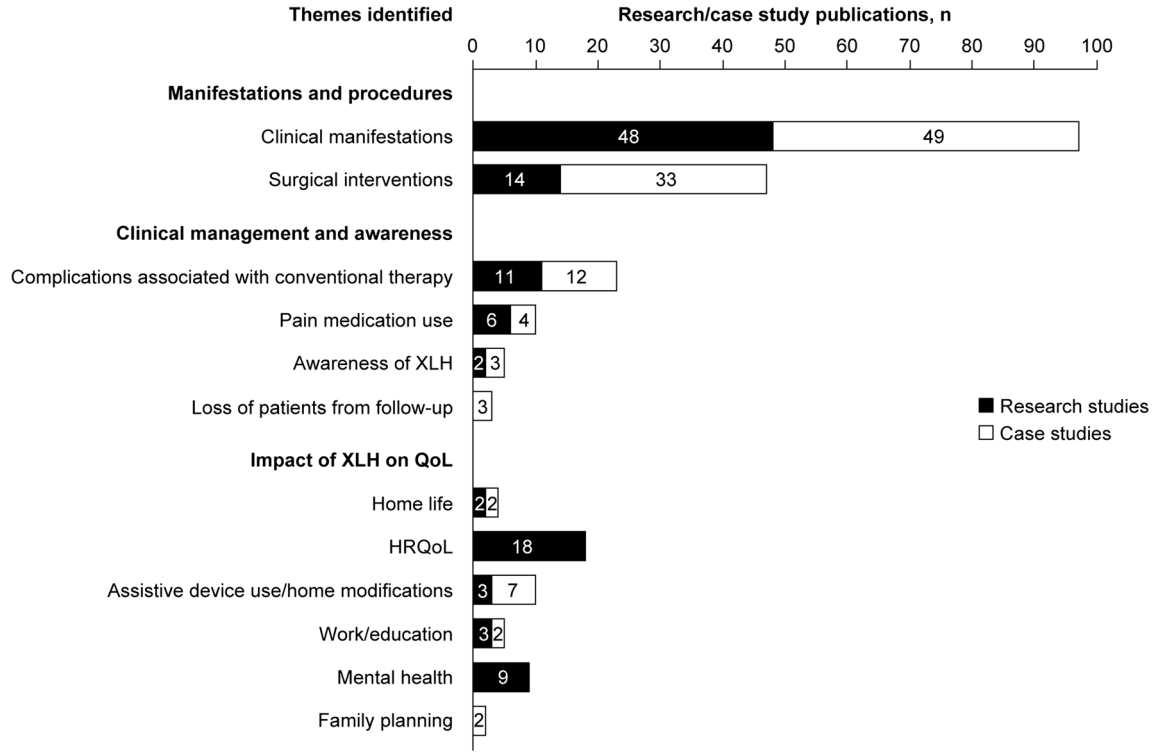

Fig. 2 Number of research and case study publications ($n = 112$) that include specific aspects of XLH in adulthood. Research study articles/conference abstracts ($n = 59$) and case study articles/conference abstracts ($n = 53$) were included in this analysis. HRQoL, health-related quality of life; QoL, quality of life; XLH, X-linked hypophosphataemia

thyroidism and nephrocalcinosis were described in several publications (Fig. 2) [14, 23, 29, 38, 62–71]. In one example, out of 150 adults with XLH who responded to a web-based survey, hyperparathyroidism and nephrocalcinosis were reported by 33% and 25%, respectively [14]. All of the individuals who reported these conditions were receiving phosphate/vitamin D at the time of the survey [14]. Data on how complications were managed were also sparse. However, six cases of parathyroidectomy being recommended following the development of tertiary hyperparathyroidism were documented in the case studies [53, 62, 63, 65, 69, 70].

Prescription pain medication use by adults with XLH was documented in two research studies, in which approximately 70% of participants were receiving pain medication of some type and 18 to 22% of all participants were taking opioids (Table 1) [12–14]. The use and effectiveness of supportive treatment measures such as physiotherapy, occupational therapy and exercise interventions were not consistently reported.

Impact of XLH on quality of life

Impact on HRQoL and pain

HRQoL and/or pain in adults with XLH, as assessed using validated instruments, were reported in 14 publications describing eight distinct studies (Table 2). These data demonstrated that XLH had a substantial and wide-ranging negative impact on HRQoL in adulthood, particularly relating to physical function and pain. For example, baseline scores relating to physical aspects of the 36-item Short-Form Health Survey (SF-36) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) indicated poor HRQoL in 28 adults with XLH participating in a clinical trial [76]. In a larger, phase 3 clinical trial, 72% of 134 participants reported Brief Pain Inventory (BPI) worst pain scores of higher than 6.0, indicating severe pain [12]. Furthermore, a study of 24 adults with XLH reported more severe impairment in every domain of the 5-level EuroQol 5-dimension (EQ-5D-5L) questionnaire relative to normative data [11]. In that publication, mobility problems were recorded by 88% of participants compared with 26% of the general population; pain and discomfort were recorded by 92% of participants compared with 42% of the general population sample. When these individuals with XLH were compared with adults with osteogenesis imperfecta ($n = 43$) or fibrous dysplasia ($n = 42$), overall HRQoL was found to be similar across all three groups, with adults with XLH more likely to have experienced problems with mobility, self-care and usual activity than those with the other conditions [11].

HRQoL among adults with XLH ($n = 52$) participating in a paired cohort study was significantly worse than that of age-matched adults with axial spondyloarthritis ($n = 52$), a chronic

Table 1 XLH-related manifestations and surgeries reported in the included research studies

Publication information		Patient population					Data on manifestations, surgeries and pain		
Reference	Publication type(s)	Sample size	Female, *n* (%)	Average age, years	Average height, cm; weight, kg; BMI, kg/m^2; and body fat, %	XLH-specific treatment, *n* (%)	Manifestations reported (% of total sample experiencing manifestation)	Surgeries reported (% of total sample with history of surgery)	Pain medication (% of total sample who had received pain medication)
Berndt et al. (1996) [23]	Journal article	23	19 (83%)	Median, 29	Mean height (range), women 152.4 (140–171), men 157 (144–168)	Vitamin D and phosphate at last investigation, 8 (35%); vitamin D and phosphate ever, 19 (83%); never been treated, 4 (17%)	Impaired joint mobility (100%), mild scoliosis (78%), dental problems (61%), enthesopathy (48%), fractures (39%), nephrocalcinosis (35%), hyperparathyroidism (13%)	Orthopaedic surgery (57%)	NR
Chaussain-Miller et al. (2003) [17]	Journal article	16[a]	12 (75%)	Mean (range), 37 (28–52)	NR	No therapy or phosphate and vitamin D until adulthood, 7 (44%); Phosphate and vitamin D (replaced when available with 1α-hydroxy vitamin D3) from infancy, 9 (56%)	Dental abnormalities (100%)[b]	NR	NR
Che et al. (2015/2016) [10, 46]; Briot et al. (2014) [47]	Journal article [10] and conference abstracts [46, 47]	52	37 (71%)	Mean (SD), 42 (13)	NR	Phosphate supplements, 31 (65%); vitamin D 29 (59%); vitamin D analogues 32 (67%) at the time of the study	Pain (90%), osteoarthritis (85%), enthesopathy (64%), fracture (36%)	Lower limb surgery (64%)	Analgesics (31%), NSAIDs (24%)
Chesher et al. (2018) [34]	Journal article	59[c]	40 (68%)	Median (range), 37 (17–79	Median height (IQ range), women 153 (146–156), men 162 (158–168); median BMI (IQ range), women 27.6 (24.8–33.7), men 25.3 (23.5–30.2)	Phosphate supplements and vitamin D analogues, 40 (68%)	Hip/knee joint disease (32%), degenerative ankle/foot joint disease 12%), Achilles enthesopathy (10%), dental abnormalities (63%), hearing loss (14%), renal disease (42%)	At least one osteotomy (42%), knee replacement (5%), hip replacement (3%)	NR
Connor et al. (2015) [20]	Journal article	52	34 (65%)	Mean (SD), 39 (14)	Participants with height Z-score < − 2, 36 (70%); mean BMI (SD), 33.9 (9.2); mean body fat (SD), 35.1 (11.5)	0% of adult life with treatment (phosphate and vitamin D analogues or high-dose vitamin D), 8 (15%); > 0% to < 100% of adult life with treatment, 27 (52%); 100% of adult life with treatment, 17 (33%)	Impaired mobility (18%), severe dental disease (62%)	At least one osteotomy (65%)	Any pain medication (73%)
Davies et al. (1984) [39]	Journal article	22[a]	10 (45%)	Mean (range), 38 (18–75)	NR	NR	Hearing loss (55%), vertigo (32%), tinnitus (36%)	NR	NR
Harrison et al. (1976) [44]	Journal article	7[c]	5 (71%)	Mean (range), 24 (17–30)	Mean height (range), 150 (125–160)	Vitamin D therapy at time of study, 2 (29%); vitamin D therapy ever, 5 (71%); phosphate supplements, 0 (0%)	Osteomalacia (100%), skeletal deformities (71%)	NR	NR
		134	87 (65%)	Mean (SD), 40 (12)					

Table 1 (continued)

Publication information		Patient population					Data on manifestations, surgeries and pain		
Reference	Publication type(s)	Sample size	Female, *n* (%)	Average age, years	Average height, cm; weight, kg; BMI, kg/m^2; and body fat, %	XLH-specific treatment, *n* (%)	Manifestations reported (% of total sample experiencing manifestation)	Surgeries reported (% of total sample with history of surgery)	Pain medication (% of total sample who had received pain medication)
Insogna et al. (2018) [12]; Portale et al. (2018) [48]	Journal article [12] and conference abstract [48]				Mean height (SD), 152 (10.7); mean height Z-score (SD), −2.3 (1.3); mean height percentile (SD), 6.8 (12.5); mean BMI (SD), 30.3 (7.6)	Phosphate and vitamin D metabolites or analogues ever, 121 (90%); phosphate alone, 4 (3%); vitamin D metabolites or analogues alone, 6 (5%)	Enthesopathy (99%), severe pain[d] (72%), osteoarthritis (63%), nephrocalcinosis (55%), fracture/pseudofracture (52%)	Orthopaedic surgery (69%)	Any pain medication (68%), any opioid (22%)
Javier et al. (2013) [49]	Conference abstract	43	32 (74%)	Average (range), 42 (21–80)	NR	Most patients did not receive XLH-specific therapy (some younger patients were treated during childhood)	Pain (60%), fatigue (58%)	NR	Analgesics (~ 50%)
Nakamura et al. (2017) [27]	Journal article	22[e]	12 (55%)	Mean (range), 32 (19–65)	Mean height (range), women 149 (138–162), men 156 (141–162)	Phosphate and vitamin D analogues, 16 (73%); vitamin D analogues alone, 5 (23%)	Nephrocalcinosis (68%), hypertension (27%), hyperparathyroidism (23%), chronic renal dysfunction (9%)	NR	NR
Reid et al. (1989) [36]	Journal article	22	16 (73%)	Mean (range), 40 (20–66)	Mean height (range), women 147 (128–162), men 158 (140–168); mean weight (range), women 70.5 (47.2–104.6), men 70.2 (57.8–97.2)	Phosphate and vitamin D or vitamin D analogues at time of study or 1 month before, 6 (27%); phosphate and vitamin D or vitamin D analogues ever, 14 (64%); vitamin D alone ever, 4 (18%)	Osteomalacia (100%), dental problems (91%), joint pain (82%), genu varum (77%), osteoarthritis (55% of patients aged < 30 years; 80% of patients aged ≥ 30 years), limitation in joint movements (46%), pseudofracture (45%), gait disturbance (32%), bone pain (36%), enthesopathy (33% of patients aged < 30 years; 100% of patients aged ≥ 30 years), muscle weakness (27%), difference in leg length of ≥ 2 cm (23%), scoliosis (14%), fracture (9%), spinal stenosis (5%)	Osteotomy (64%)	NR
Ruppe et al. (2016) [50]	Conference abstract	20	14 (70%)	Mean (range), 50 (23–69)	NR	KRN23 (last dose ≥ 12 months at enrolment)	Enthesopathy (100%), joint stiffness (100%), impaired mobility (100%), short stature (95%), bowing of tibia/fibula (95%), dental abnormalities (85%), gait disturbance (85%), fracture/pseudofracture (~ 50%), pain (45%), hyperparathyroidism (30%)	Osteotomy (65%)	NR

Table 1 (continued)

Publication information		Patient population					Data on manifestations, surgeries and pain		
Reference	Publication type(s)	Sample size	Female, *n* (%)	Average age, years	Average height, cm; weight, kg; BMI, kg/m^2; and body fat, %	XLH-specific treatment, *n* (%)	Manifestations reported (% of total sample experiencing manifestation)	Surgeries reported (% of total sample with history of surgery)	Pain medication (% of total sample who had received pain medication)
Salcion-Picaud et al. (2018) [51]	Conference abstract	81	55 (68%)	Mean (SD), 42 (14)		Phosphate and/or vitamin D during childhood, 63 (78%); phosphate and/or vitamin D analogues at time of study, 41 (51%)	Skeletal abnormalities (88%), pain (80%), joint pain (71%), hip osteoarthritis (65%), spinal stenosis (63%), bone pain (22%)	NR	Analgesics (40%)
Salcion-Picaud et al. (2018) [52]	Conference abstract	31	22 (71%)	Mean, 27.3	NR	NR	Limb abnormalities (55%)	NR	NR
Shanbhogue et al. (2018) [18]	Journal article	27	19 (70%)	NR; range 18–73	Median height (IQ range), non-treated [*n* = 16] 163 (157–167), treated [*n* = 11] 158 (156–166); median weight (IQ range), non-treated 72 (66–89), treated 70 (67–79); median BMI (IQ range), non-treated 27 (25–34), treated 28 (26–31)	Phosphate and vitamin D analogues, 11 (41%)	Fracture (18%)	NR	NR
Skrinar et al. (2015) [13]	Conference abstract[f]	195	NR	Mean (range), 46 (18–74)	NR	NR	Joint pain (89%), gait disturbance (86%), bone pain (73%), fracture/pseudofracture (44%)	NR	Regular pain medication use (69%), opiates (20%)
Skrinar et al. (2015) [14]	Conference abstract[f]	150	NR	Median (range), 46 (18–73)	NR	Phosphate/vitamin D therapy, 93 (62%)	Joint and bone pain (97%), restricted range of motion (93%), short stature (87%), gait disturbance (83%), bowing of the tibia/fibula (78%), osteoarthritis (60%), bowing of the femur (67%), fracture/pseudofracture (47%), hyperparathyroidism (33%), nephrocalcinosis (25%)	Any orthopaedic surgery (65%), osteotomy (63%), knee replacement (12%), hip replacement (8%)	Any pain medication (70%), opioids (18%)
Song et al. (2007) [37]	Journal article	11[a]	10 (91%)	Mean (range), 33 (18–60)	NR	Phosphate and vitamin D, 6 (55%); phosphate only, 1 (9%); vitamin D only, 1 (9%)	Bowing of the legs (100%), dental abnormalities (82%)	Osteotomy (82%)	NR
Stickler and Morgenstern (1989) [29]	Journal article	52[g]	31 (63%)[h]	NR	NR	Vitamin D only, 17 (33%); vitamin D and phosphate, 32 (62%); vitamin D analogues and phosphate, 11 (21%)	Leg pain (50%), knee pain (35%), renal failure (6%), hip and back pain (2%), shoulder pain (2%)	Kidney transplant (4%)	NR
Sullivan et al. (1992) [38]	Journal article	17[a]	8 (47%)	Mean (range), 38 (20–65)	NR	Phosphate and active vitamin D, 14 (82%);	Bone or joint pain (100%)	Osteotomy (53%)	NR

Table 1 (continued)

Publication information		Patient population					Data on manifestations, surgeries and pain		
Reference	Publication type(s)	Sample size	Female, *n* (%)	Average age, years	Average height, cm; weight, kg; BMI, kg/m^2; and body fat, %	XLH-specific treatment, *n* (%)	Manifestations reported (% of total sample experiencing manifestation)	Surgeries reported (% of total sample with history of surgery)	Pain medication (% of total sample who had received pain medication)
						active vitamin D only, 1 (6%)			
Theodore-Oklota et al. (2018) [41]	Journal article	18	15 (83%)	Mean (range), 42 (20–60)	NR	Phosphate, 11 (61%); vitamin D, 10 (55%)	Joint pain (100%), stiffness/difficulty bending limbs/joints (100%), fatigue (83%), dental abscesses (78%), weakness (50%), short stature (56%), bone pain (67%), bone bowing (67%), bone weakness (44%), muscle pain (44%), loss of balance/vertigo (39%), loss of hearing (28%), tinnitus (28%)	NR	NR

Data are presented as available in the publications. Research studies with relevant information were included in this analysis. Research studies were identified from both journal articles and congress abstracts that were included in this systematic review. Publications reporting the same study have been grouped; where both a congress abstract and a journal article were published on a specific study, data from the article are presented

[a] These studies also included children; only data for adults (aged ≥ 18 years) are presented here

[b] Necrosed or endodontically treated teeth (100% of patients); ≥ 2 missing permanent teeth (56% of patients)

[c] These studies included individuals aged 17 years

[d] Severe pain was defined as a worst pain score of > 6.0 on the Brief Pain Inventory

[e] Data on XLH-specific treatment were not available for one patient; data on height were not available for one male and one female patient

[f] These abstracts present different data from the same study; this study has been published as a journal article since the systematic review was performed [6]

[g] Data on manifestations were not available for two patients

[h] Data on sex were not available for three patients

BMI, body mass index; IQ, interquartile; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; XLH, X-linked hypophosphataemia

Table 2 Studies investigating HRQoL and pain in adults with XLH

Publication/study information				Patient population					Pain/HRQoL data	
Reference	Publication type(s)	Study design	Country	Sample size	Female, n (%)	Available data for average age, years	XLH-specific treatment, n (%)	Pain medication (% of sample)	Study instruments	Results
Che et al. (2016) [10, 46]; Briot et al., 2014 [47]	Conference abstract [46] and journal articles [10, 47]	Paired- cohort study	France	52	37 (71%)	Mean (SD), 42 (13)	Phosphate supplements, 31 (65%); vitamin D 29 (59%); vitamin D analogues 32 (67%) at the time of the study	Analgesics (31%), NSAIDs (24%)	HAQ, RAPID3, SF-36, VAS	Mean (SD) scores: HAQ, 0.69 (0.56); RAPID3, 12.1 (6.4); SF-36 PCS, 49.5 (20.5); SF-36 MCS, 57.9 (21.3); VAS, 50.0 (26.0)
Forestier-Zhang et al. (2016) [11, 72]	Conference abstract [72] and journal article [11]	Survey	UK	24[a]	19 (79%)	Mean (SD), 46 (16)	NR	NR	EQ-5D-5L, VAS	EQ-5D-5L: anxiety/depression (58% of patients), pain/discomfort (92%), mobility problems (88%), problems with usual activity (75%), problems with self-care (50%); VAS, 60.8 (26.9)
Insogna et al. (2018) [12]	Journal article	Randomized, double-blind, placebo-controlled, phase 3 trial	USA, France, UK, Ireland, Italy, Japan, South Korea	134	87 (65%)	Mean (SD), 40 (12)	Phosphate and vitamin D metabolites or analogues ever, 121 (90%); phosphate alone, 4 (3%); vitamin D metabolites or analogues alone, 6 (5%)	Any pain medication (68%), any opioid (22%)	BPI	BPI worst pain > 6.0 at baseline: $n = 96$ (72%)
Parisi et al. (2016) [73]	Conference abstract	Case-control study	NR	9 (and 9 individuals without XLH)	NR	Mean (SD), 54 (5)	NR	NR	Functional measures (ABC, LEFS)	Mean (SD) scores: ABC percentage of self-confidence in perceived balance and fall risk, 62.3 (17.6) vs 95.9 (3.1) [$p = 0.001$]; LEFS, 0.45 (0.19) vs 0.98 (0.02) [$p = 0.0001$]
Pinedo-Villanueva et al. (2017) [74]	Conference abstract	Survey	UK	31 (aged			≥16 years)	20 (65%)	Median (range), 48 (16–79)	NR
NR	SF-36v1	Mean scores: emotional well-being, 73.7; role limitations due to emotional problems, 71.0; role limitations due to social functioning, 65.3; pain, 49.6; physical functioning, 45.6; general health perceptions, 45.8;								

Table 2 (continued)

Publication/study information				Patient population					Pain/HRQoL data	
Reference	Publication type(s)	Study design	Country	Sample size	Female, n (%)	Available data for average age, years	XLH-specific treatment, n (%)	Pain medication (% of sample)	Study instruments	Results
		energy/vitality, 41.3; role limitations due to physical health, 45.6 (general UK population norms were higher in all dimensions)								
Ruppe et al. (2014) [75] (2016) [76, 77]	Conference abstracts [75, 77] and journal article [76]	Phase 1/2, open-label, dose-escalation trial	NR	28	17 (65%; $n = 26$)	Mean (SD), 42 (14; $n = 26$)	NR	NR	SF-36v2, WOMAC	Mean (SD) scores at baseline: SF-36v2 PCS, 41.4 (10.3); SF-36v2 MCS, 52.3 (10.3); WOMAC physical functioning, 29.3 (21.3); WOMAC stiffness, 42.8 (20.9)
Ruppe et al. (2016) [50]	Conference abstract	Phase 1/2, open-label extension study	NR	20	14 (70%)	Mean (range), 50 (23–69)	KRN23 (last dose ≥12 months at enrolment)	NR	BPI	Mean (range) scores at baseline: BPI pain at its worst in the past 24 h, 6.6 (3–10), BPI pain interference, 4.2 (1–9)
Skrinar et al. (2015) [13]	Conference abstract[b]	Survey	16 countries (70% participants in USA)	195	NR	Mean (range), 46 (18–74)	NR	Regular pain medication use (69%), opiates (20%)	BPI, WOMAC, SF-36v2	Mean scores: BPI pain severity, 3.6; BPI pain interference, 4.1 (data for other scores not provided)
Skrinar et al. (2015) [14]	Conference abstract[b]	Survey	NR	150	NR	Median (range), 46 (18–73)	Phosphate/vitamin D therapy, 93 (62%)	Any pain medication (70%), narcotics (18%)	BPI, WOMAC, SF-36v2	Mean scores: SF-36 bodily pain, 39.2; SF-36 physical functioning, 35.7; BPI pain severity, 3.6; BPI pain interference, 4.2; WOMAC pain severity, 7.9; WOMAC physical function, 27.4

Data are presented as available in the publications. Publications reporting the same study have been grouped. Where both a congress abstract and a journal article were published on a specific study, data from the article are presented

The BPI is scored from 0 to 10 with higher scores indicating worse pain; the HAQ is scored from 0 to 3 with higher scores indicating worse health; RAPID3 is scored from 0 to 3 with higher scores indicating worse health; the SF-36 is scored from 0 to 100 with higher scores indicating better QoL

[a] This study also included adults with osteogenesis imperfecta and fibrous dysplasia; only data for adults with XLH are presented here

[b] These abstracts present different data from the same study; this study has been published as a journal article since the systematic review was performed [6]

ABC, Activities-Specific Balance Confidence; BPI, Brief Pain Inventory; EQ-5D-5L, 5-level EuroQol 5-dimension questionnaire; HAQ, Health Assessment Questionnaire; HRQoL, health-related quality of life; LEFS, Lower Extremity Functional Scale; MCS, Mental Component Summary; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; PCS, Physical Component Summary; QoL, quality of life; RAPID3, Routine Assessment of Patient Index Data 3; SD, standard deviation; SF-36, 36-item Short-Form Health Survey; v1, version 1; v2, version 2; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; XLH, X-linked hypophosphataemia

rheumatological condition known to substantially reduce HRQoL [10]. Specifically, average scores on the visual analogue scale (VAS) for pain, the Physical Component Summary (PCS) of the SF-36 and the Routine Assessment of Patient Index Data 3 (RAPID3) reflected significantly poorer HRQoL among participants with XLH than those with axial spondyloarthritis (VAS pain, 50.0 vs 36.0; SF-36 PCS, 49.5 vs 58.3; RAPID3, 12.1 vs 8.9 for patients with XLH and axial spondyloarthritis, respectively; all $p < 0.05$). Health Assessment Questionnaire (HAQ) scores, which relate to functional disability and pain in rheumatic diseases, were similar in both groups of patients. For the adults with XLH in the study, HRQoL was found to deteriorate with increasing age [10]. Treatment with phosphate and vitamin D was significantly associated with better mental health, as measured by the Mental Component Summary of the SF-36, although not with other aspects of HRQoL [10].

Impact on home life and work

A negative impact of XLH on the home and work lives of adults with the disease was noted in several publications [13, 23, 24, 41, 50, 60, 78–81]. In interviews with 18 adults with XLH about their symptoms and functional limitations, participants reported that the condition had an impact on their work ($n = 14$) and housework ($n = 12$), as well as their ability to get dressed ($n = 10$), go shopping ($n = 10$), do laundry ($n = 10$) and other activities of daily living [41]. Additionally, several studies recorded the use of assistive devices for mobility among adults with XLH and/or highlighted a need for home modifications [13, 29, 41, 56, 78–82]. There was limited information available on the psychological impact of living with XLH or how the disease and its associated limitations affect partnership and family life. In the interviews with adults with XLH, two-thirds of the 18 participants reported feelings of sadness or depression [41].

Inability to work was found to be associated with both dental and psychosocial problems in a retrospective study of 23 adults with XLH [23]. Another study noted that unemployment and early retirement were more frequent among adults with XLH than in the general population [24]. None of the studies investigated the frequency with which adults with XLH need to take time off work as a consequence of the disease. Limited direct evidence was available regarding the financial burden of XLH on individuals. However, a cross-sectional study on dental health that included 36 adults with XLH in Denmark (rated as good quality) suggested that the high level of dental care received by adults with XLH represents a substantial economic burden carried by patients [19].

Evidence from the structured Internet search

A total of 19 web-based sources were identified from the structured Internet search (Supplementary Fig. S2), covering a wide range of topics including clinical manifestations and procedures, lack of disease awareness, complications associated with conventional supplementation therapy, family planning and financial pressure (Supplementary Table S4). These sources were distinct from those in the scientific literature as they contained testimonials from adults who had XLH themselves, as well as additional details from studies identified in the systematic review. For example, a congress poster describing results from a web-based survey included additional analyses to those presented in the published abstract [14, 83]. The poster reported that in 165 adults with XLH (median age [range], 45 [18–46, 48, 50, 53–71, 76, 78–84] years), average scores on the WOMAC were higher for pain (39.4 vs 14.1), stiffness (50.2 vs 20.1) and physical functioning (40.9 vs 15.4) than those reported in the general population, indicating poorer HRQoL [83]. Use of a walking device was reported by 32% of these individuals.

Discussion

XLH in adults has received little attention, owing to the rarity of the disease and a clinical focus on management of the condition in children [2, 3]. This systematic review collated evidence relating to the burden of XLH in adulthood, demonstrating substantial unmet need. Data show that adults with XLH experience a spectrum of clinical manifestations that impair physical function, cause pain and reduce HRQoL [6, 10–12, 14, 36, 41, 76]. Consequently, these individuals frequently suffer a high burden of disease that has an impact on their home and work lives [23, 24, 41]. Despite this, many adults with XLH do not receive appropriate therapy, including symptomatic and supportive measures as well as conventional supplementation with phosphate and active vitamin D [2, 3, 8]. A plausible hypothesis is that this may indicate a lack of awareness among healthcare professionals and/or young adults with XLH of the need for ongoing specialist care and treatment in adulthood.

Data collated in the systematic review demonstrate the diversity of manifestations associated with XLH in adulthood, as well as the lifelong and progressive nature of the disease. Owing to abnormalities in childhood skeletal development, adults with XLH tend to be short and may have skeletal deformities and gait abnormalities [14, 36, 41, 50], with osteoarthritis developing as a consequence of both disease-specific metabolic alteration and long-term weight bearing on misaligned joints [6]. Pain, dental problems and hearing loss are reported with higher frequency in adults than in children [6, 36]. In addition, adults with XLH experience manifestations associated with

chronic hypophosphataemia and ongoing osteomalacia that are not typically reported in children [4, 6, 36]; these include fractures and pseudofractures, extraosseous calcifications, stiffness and impaired mobility [10, 12, 14, 36, 50]. Together, these manifestations contribute to a substantial burden of disease in adults with XLH.

The physical and psychological challenges of living with XLH extend beyond the direct effects of these clinical manifestations. Factors such as limited mobility, chronic pain and fatigue may have far-reaching consequences on mental wellbeing considering how they are likely to affect participation in sports and leisure activities [84]. This may also explain why people with XLH are often overweight, as suggested by the reports of mean or median BMI over 25 kg/m^2 [18, 20, 34, 48]. Furthermore, the psychological burden of living with a disorder that affects physical appearance should be considered. Thus, it is important to ensure continuous healthcare for adults with XLH from a coordinated multidisciplinary team, including physical therapy and mental health support where appropriate [8]. There are currently insufficient data in the medical literature on how to quantify and monitor functional deficits in adults with XLH, and the associated impacts on home and work lives. Considering the significant impact of physical ability on perceived quality of life, development of standards for assessing these aspects in adults with XLH is crucial. Such standards would enable clinicians to evaluate individual patient needs, inform treatment strategies and support longitudinal monitoring of disease progression and treatment outcomes.

The level of healthcare resource utilization among adults with XLH, including high frequencies of medical complications, surgical interventions and prescription medication usage [6, 12, 14], is indicative of significant economic burden. However, research is needed to establish the true economic impact on the healthcare system, society and the individual. In addition, robust long-term observational studies are needed to extend our understanding of the evolution of disease burden over an individual's lifetime and identify potential risk factors for declining physical function. To build on the growing HRQoL evidence base, future clinical trials in adults with XLH should include appropriate patient-reported outcome measures as endpoints. Further research characterizing the wide-ranging effects of the disease from the patient perspective, including the support received from families, friends, employers and wider society, will provide a comprehensive picture of the impact of XLH on the lives of adults with the condition. Research focusing on the clinical management and awareness of XLH in adults is also warranted. This should include studies to evaluate the impact and potential shortcomings of specific treatment strategies and studies to determine optimal assessments for measuring physical performance and disease burden in clinical practice.

The findings from this systematic review provide insights into the unmet needs associated with XLH in adulthood; however, several limitations should be considered, including the generally low quality of available evidence. Notably, although there have been very few clinical trials conducted in adults with this rare disease, the evidence from two-thirds of the non-randomized study publications included in this review was rated as satisfactory or good in the formal quality assessment performed. While case study publications are often narrow in scope, with few documenting comprehensive medical histories, these publications provided a rich source of qualitative information highlighting the broad nature of symptoms that adults with XLH experience. In addition, insights captured from narrative reviews, which are not typically included in systematic reviews, were considered important in this study given the rarity of XLH and the lack of data on aspects such as disease awareness. Other limitations include the heterogeneity of available data, in terms of study design and patient demographics, and the range of terminology used to describe symptoms, treatments and procedures, both of which preclude direct comparisons being made across different studies. Despite these limitations, this review provides a comprehensive summary of current evidence on the unmet needs of adults with XLH.

Data captured in this systematic review highlight that XLH in adulthood is associated with considerable disease burden and diminished quality of life, with individuals often experiencing severe pain, early onset osteoarthritis and progressive disability. There are key areas of unmet need and further research is needed to quantify the associated socioeconomic burden of XLH in adults and improve the multidisciplinary management of XLH in adults. It is plausible that the apparent lack of awareness among healthcare professionals and patients themselves of the need for ongoing disease management in adulthood contributes to the burden of disease. Increasing understanding of the impact of XLH in adulthood may facilitate continuity of multidisciplinary care for individuals as they transition from paediatric to adult services, and thereby improve outcomes.

Author contributions All authors contributed to the study design, interpretation of data and critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript for submission.

Funding information Medical writing support and assistance with the systematic review were provided by Dr. Emily Stock and Dr. Sarah Graham of PharmaGenesis London, UK, and funded by Kyowa Kirin International.

Data availability Data sharing requirements are not applicable to this article as the data were synthesized from previously published reports.

Compliance with ethical standards

As this was secondary research, no ethics approval or patient consent was required.

Guarantor Lothar Seefried.

Conflict of interest P. Harvengt is a member of RVRH-XLH (a member of the International XLH Alliance), which has received funding from Kyowa Kirin for the organization of educational events, and has provided unpaid consulting services to Kyowa Kirin. P. Harvengt is employed by GSK. This publication was prepared by P. Harvengt in his personal capacity. M. Smyth is a former employee of Kyowa Kirin. R. Keen has received honorarium and consultancy fees from Kyowa Kirin. L. Seefried has received honoraria for lectures and advice from Kyowa Kirin.

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