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REVIEW

Prevalence of hypophosphatasia in general and selected patient populations: a systematic review

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Abstract

Summary Hypophosphatasia (HPP) has diverse manifestations overlapping other skeletal and rheumatic disorders. This systematic review assessed frequency of HPP in select and general clinical populations with persistently low alkaline phosphatase (ALP) activity. Undiagnosed HPP was frequently identified. Clinicians should consider HPP for patients with persistently low ALP and hallmark manifestations.

Background Diagnosis of hypophosphatasia (HPP) can be missed owing to its rare disease status and heterogeneous manifestations that can overlap with other skeletal or rheumatic disorders. The objective of this systematic review was to assess the frequency of HPP among patients with persistently low alkaline phosphatase (ALP) activity and determine overall HPP prevalence in the general population.

Methods English language articles published from January 1, 2015, to September 29, 2025, were identified in PubMed and Embase and through manual searching. Observational studies conducted in patients of any age from general and select clinical populations (e.g., rheumatology, endocrinology) were included if the frequency of HPP or potential HPP was reported or could be enumerated from results. Risk of bias was assessed based on 4 predefined criteria. HPP prevalence was determined from general clinical population studies with the lowest risk of bias.

Results A total of 710 articles were retrieved; 27 met the inclusion criteria. The frequency of genetically confirmed HPP among patients with persistently low ALP activity in studies with low risk of bias (≥3 predefined criteria) was 10.4–26.2% in general clinical populations, 46.4–56.5% in rheumatology populations, and 57.1–87.5% in osteoporosis populations. The total prevalence of HPP in the general population may be 17.6–36.0 per 100,000 population based on 3 studies meeting all 4 criteria.

Conclusion Undiagnosed patients with HPP were frequently identified in studies of ALP screening, highlighting the importance of screening. Clinicians should consider a diagnosis of HPP for patients with persistently low ALP and hallmark manifestations.

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Introduction

Hypophosphatasia (HPP) is an inherited, systemic, metabolic rare disease that affects people of all ages with a broad spectrum of clinical manifestations [1]. HPP is caused by deficient activity of tissue-nonspecific alkaline phosphatase (ALP) and accumulation of its substrates: inorganic pyrophosphate (PPi; an inhibitor of mineralization), pyridoxal 5′-phosphate (PLP; the active metabolite of vitamin B_6), and phosphoethanolamine (PEA) [2]. Manifestations of HPP can be skeletal, such as reduced bone mineralization, fractures/pseudofractures, rickets (in children), and early loss of teeth, and nonskeletal, such as muscle weakness, musculoskeletal pain, fatigue, neurologic symptoms, and impaired mobility. The manifestations can occur at any age and may result in cumulative morbidity and reduced quality of life [3, 4].

Because of its heterogeneous clinical presentation, HPP can be overlooked or misdiagnosed in adults with osteoporosis, fibromyalgia, chronic fatigue syndrome, seronegative rheumatoid arthritis, calcium pyrophosphate deposition disease, or osteoarthritis, among other rheumatologic disorders [5–10]. When detected in the perinatal period or in infancy, HPP may be misdiagnosed as osteogenesis imperfecta or other skeletal dysplasias [11]. Awareness of HPP among healthcare professionals is generally low, and increased awareness is needed to reduce diagnostic delays and decrease the risk of misdiagnosis or inappropriate treatment [12–14]. In adults, misdiagnosis as osteoporosis is particularly harmful, as bisphosphonates and other antiresorptive therapies used in the treatment of osteoporosis may worsen the hypomineralization experienced by patients with HPP. Bisphosphonates, in particular, inhibit bone resorption by osteoclasts and prevent bone remodeling, a process that renews bone tissue to repair microdamage [15]. When bone remodeling is prevented, ALP activity, already deficient in patients with HPP, is further reduced, which can increase the risk of atypical femoral fractures in patients with unrecognized HPP [16].

This review had two objectives. The first objective was to assess the frequency of potential HPP cases that were identified via ALP screening across general and selected clinical populations and to evaluate diagnostic practices and implications for clinical misdiagnosis. The second objective was to estimate the total prevalence of HPP in the general population using studies with the lowest risk of bias based on the exclusion of secondary causes of low ALP activity, the inclusion of ALP substrate assessment, and the *ALPL* variant analysis.

Methods

Search strategy

We conducted a systematic literature search for observational studies indexed in PubMed or Embase that were published between January 1, 2015, and September 29, 2025, with no geographic restrictions. Search terms included hypophosphatasia, ALP, and misdiagnoses or concomitant diagnoses (osteogenesis imperfecta, osteoporosis, osteoarthritis, rheumatoid arthritis, or fibromyalgia). The full search strings for each database are shown in Online Resource 1. Articles were included if the frequency of HPP or potential HPP was reported or could be enumerated from the results of an ALP-based screening approach within a defined population. Studies could report on patients of any age. Case reports or other studies precluding frequency estimates, studies without a clearly defined population (or denominator), animal studies, and articles in a language other than English were excluded. Articles were also identified through manual searching. Conference abstracts and non–peer-reviewed literature (such as preprints) were not included. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines; the protocol for the review was not registered.

Data extraction

The search and data extraction were conducted by JH, GW, and SF. Articles identified in the search were independently screened by two epidemiologists, and disagreements were reviewed by a third epidemiologist. Data were extracted in a prespecified data extraction table and included study details, setting, population, and denominator; ALP activity cutoff that the study classified as low; number of patients with persistently low ALP; HPP-related manifestations; *ALPL* genetic testing results; HPP case definition; and number of patients considered to have HPP according to the study authors. Where possible, the number of patients with elevated ALP substrates (PLP or PEA) and/or genetic confirmation was extracted. When the number of patients with HPP was not reported explicitly (regardless of genetic testing), the number of HPP cases was determined independently by the data extractors and further confirmed by clinical review based on data available on HPP-related manifestations, ALP substrate levels, and/or genetic testing results. For all included studies, results were separated into 2 major categories based on clinical setting: general clinical

populations and select patient populations. Select patient populations included those from rheumatology, endocrinology, or osteoporosis clinics, as well as patients with atypical femoral fractures or metatarsal fractures, both of which can be manifestations of HPP [17].

Bias assessment

The risk of bias in estimating the overall prevalence of HPP within general or select patient populations was assessed. Each study was assigned 1 point for each category of (1) generalizability (appropriate study population and a reported denominator), (2) appropriate ALP activity cutoff for age and sex and exclusion of alternative causes of low ALP, (3) assessment of HPP-related manifestations, and (4) ALP substrate and/or *ALPL* testing. Studies receiving all 4 points were deemed to have the lowest risk of bias. Because ALP reference intervals vary substantially by age and sex—particularly among children—studies that applied fixed cutoffs for children (eg, <40 U/L for all pediatric ages) were considered to have an elevated risk of bias [18].

Determination of HPP frequency and prevalence estimates in the general clinical population

For all included studies, we calculated the frequency of potential HPP as identified in the study as a proportion of the study population and as a proportion of patients with persistently low ALP activity. To explore the total prevalence of HPP in the general population, we selected studies that had a score of 4, indicating the lowest risk of bias as described above, as studies with lower scores lacked sufficient quality (e.g., missing denominator, inappropriate ALP cutoff). Furthermore, the studies had to have data available to enumerate the number of patients with HPP defined as having persistently low ALP not due to known secondary causes, HPP-related clinical manifestations, elevated substrates, and/or *ALPL* variant(s). As described above, cases were confirmed by clinical review. The *ALPL* variant(s) included ≥1 pathogenic variant, likely pathogenic variant, or variant of uncertain significance (VUS). Thus, patients included in our estimation of HPP prevalence had both biochemical and clinical features of HPP, and this may have differed from the definitions in the original studies. Given that not all patients in the identified studies were screened at each step, prevalence was estimated assuming that (1) all HPP cases in the study population were identified in the study (low estimate) and (2) those who were not tested for substrates and/or *ALPL* variants had the same positivity rate as those who were tested (high estimate). A midpoint between the low and high estimates was then considered as the total prevalence extrapolated from the study.

Classification of HPP manifestations

Data on HPP-related manifestations were classified according to body systems/categories previously reported in the Global HPP Registry [19]: (1) skeletal (bone deformity, rickets, fractures, and orthopedic surgery), (2) muscular (weakness, gross motor delay, abnormal gait, cramps, and impaired mobility), (3) constitutional/metabolic (failure to thrive, fatigue, and short stature), (4) neurologic (craniosynostosis), (5) dental (early loss of primary teeth, teeth malocclusion, irregular teeth, loss of permanent/adult teeth, top dentures, and poor dentition), (6) renal (hypercalcemia/hypercalciuria/hyperphosphatemia, nephrocalcinosis, and nephrolithiasis), (7) pain (musculoskeletal pain and generalized body pain), (8) rheumatic (ectopic calcifications, chondrocalcinosis, calcific periarthritis, and arthralgia), and (9) respiratory (respiratory failure, pneumonia). The distribution of manifestations was reported out of the total number of manifestations extracted from the studies and was presented by age (pediatric or adult) and by setting (general clinical populations versus selected clinical settings, both inpatient and outpatient). Results were reported descriptively.

Classification of comorbid diagnoses

All reported comorbid diagnoses, including potential misdiagnoses, were extracted if available. We coded comorbid diagnoses by the highest category in the International Classification of Diseases 11th Revision: musculoskeletal system or connective tissue (which included autoimmune rheumatic diseases); immune system; skin; nervous system; circulatory system; genitourinary system; blood or blood-forming organs; respiratory system; endocrine, nutritional, or metabolic diseases; mental, behavioral, or neurodevelopmental disorders; neoplasms; developmental anomalies; factors influencing health status or contact with health services; extension codes: histopathology, osseous and chondromatous neoplasms, benign; and symptoms, signs, or clinical findings not elsewhere classified. Comorbidities among patients were quantified in a similar manner to clinical manifestations; results were reported descriptively.

Results

Search results

A summary of search results is provided in Online Resource 2. A total of 27 studies were included (Fig. 1). Fifteen studies focused on general clinical populations, including 7 studies in pediatric patients [20–26], 5 in adults [27–31], 2 in patients of any age that did not report results by age group [32, 33], and 1 that had stratified data for both

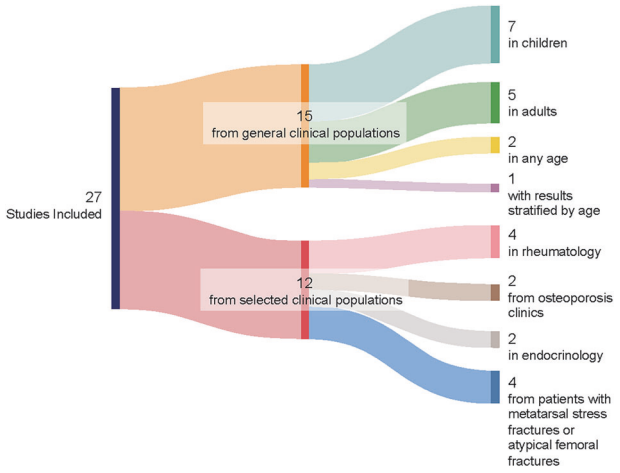


Fig. 1 Overview of studies included in the analysis

children and adults [34] (Table 1; Online Resources 3–5). Of the 27 included studies, 12 focused on selected clinical populations, including 4 studies in a rheumatology setting [7, 12, 35, 36], 2 in an osteoporosis setting [14, 37], 2 in an endocrinology setting [38, 39], and 4 that included patients screened for HPP because of atypical femoral fractures or metatarsal stress fractures [40–43] (Table 2; Online Resources 6, 7). The definition of an HPP case varied across studies and included persistently low ALP activity with or without elevated substrates, presence of *ALPL* variant(s), and manifestations of HPP, depending on study design and data availability. The definition of an HPP case, as determined within each study, is summarized in Tables 1 and 2.

Frequency of persistently low ALP activity

Among children and adults from a general clinical population, the frequency of persistently low ALP activity ranged from 0.03% to 3.8% [21–23, 25, 26, 28, 29, 31–34] (Table 1). This range reflects heterogeneous ALP lower-limit thresholds, varying definitions of "persistently low" ALP activity, and inconsistent exclusion of secondary causes of low ALP across studies. In select clinical populations, the frequency of persistently low ALP activity was 0.3% to 1.2% in rheumatology [12, 35, 36], 0.4% to 0.5% in osteoporosis [14, 37], 0.2% in 1 study in endocrinology [38], and 2.6% to 9.7% among patients with atypical femoral fractures [40, 42] (Table 2). Definitions of the lower limit of normal for ALP activity used in each study varied and are presented in Tables 1 and 2; recommended age- and sex-specific reference ranges are shown in Online Resource 8. Of note, 1 study from a rheumatology clinic in patients with fibromyalgia reported that 9.3% of patients had low ALP activity [7]; however, this estimate was not comparable to the frequency in the other studies from rheumatology populations owing to the inclusion of patients who had either low or normal ALP activity. Additionally, no further investigations of ALP substrates, genetic testing, or manifestations of HPP were conducted in this study.

Frequency of potential HPP in the study populations and among patients with persistently low ALP activity

The frequency of potential HPP in the overall study populations and among those with persistently low ALP is presented in Tables 1 and 2. The frequencies within the study populations varied based on the definition of potential HPP used in the studies. In children, 1 study that relied only on clinical symptoms had the highest frequency of potential HPP (0.3%) [23]. In adults, a study that required persistently low ALP and elevated substrates had the highest frequency (0.5%), followed by studies that did not include genetic confirmation (0.02–0.03%), those with *ALPL* variants with or without symptoms (0.02%), and a study with both clinical and genetic confirmation of cases (0.01%) [28–31, 34]. In the osteoporosis setting, the highest frequency of potential HPP was observed in the study that did not assess specific HPP signs and symptoms (0.04%), and in the rheumatology setting, the highest frequency was observed when genetic confirmation was with or without the presence of specific HPP signs and symptoms (0.6%) [35, 37].

Among patients with persistently low ALP activity from general clinical populations, the frequency of potential HPP based on clinical symptoms only ranged from 22.6% to 38.1% [23, 29] (Table 1). The frequency of potential HPP based on genetic testing among patients with persistently low ALP with or without clinical symptoms varied from 8.3% to 45.8% [21, 24]. Of note, in this high estimate, the ALP cutoff may have been too high for some of the older children, and not all patients had overt manifestations of HPP [24] (Table 1). When the case definition was based on genetic testing and clinical symptoms, the proportion ranged from no patients identified in a small study of only ~2500 children to 20.0% [25, 34]. The estimates from studies in the general clinical population with the lowest risk of bias ranged from 10.4% to 26.2% [25, 31, 32, 34] (Fig. 2a).

The frequency of potential HPP among patients with persistently low ALP was 46.4% to 56.5% in outpatient rheumatology [12, 35] and 6.0% in a study of hospitalized rheumatology and internal medicine patients [36] (Table 2). The frequency was 57.1% to 87.5% in osteoporosis [14, 37], and 3.9% to 17.7% in endocrinology [38, 39]. Among rheumatology and osteoporosis outpatients with persistently low ALP activity, the frequency of HPP with *ALPL* variants from studies with the lowest risk of bias was considerably higher than in the general clinical population,

Table 1 Potential HPP identified in studies of ALP screening algorithms in general clinical populations

Case definition	ALP LLN, U/L	Persistently low ALP, *n* (%)	Elevated substrate(s), *n/N* (%)	Category of manifestations reported	*ALPL* variant detected, *n/N* (%)	Cases, *N*	Frequency in study population, %	Frequency in patients with persistently low ALP, %
Children								
Pers. ↓ALP[b] + HPP signs/sx	Deeb and Elfatih [23], Abu Dhabi, United Arab Emirates–Study population *N* = 2890 patients aged <18 y w/ ≥ 2 ALP tests							
	Limitations & risk of bias: Small sample size; did not exclude secondary causes of persistently low ALP; no genetic or ALP substrate testing; risk of bias score[a]: 1							
	Age- and sex-specific LLN	21 (0.73)[b]	NR	Skeletal, respiratory, renal	NA	8[c]	0.277[d]	38.1[b,c]
Pers. ↓ALP + ↑ALP sub + *ALPL* var +/− HPP signs/sx	Bayramli et al. [21], Istanbul, Turkey–Study population *N* = 93,162 patients aged <18 y w/≥1 ALP test							
	Limitations & risk of bias: Did not exclude secondary causes of persistently low ALP; 3 patients did not have overt HPP signs/sx; risk of bias score[a]: 2							
	Age- and sex-specific LLN	60 (0.06)[b,e]	7/37 (18.9) elevated PLP and/or PEA	Constitutional-metabolic, dental, skeletal	5/7 (71.4)	5	0.005	8.3
	Buyukyilmaz et al. [22], Ankara, Turkey–Study population *N* = 5779 patients aged <19 y with any low ALP record							
	Limitations & risk of bias: Study population was restricted to patients with any low ALP (no overall N of patients tested); 7 patients did not have overt HPP signs and symptoms; risk of bias score[a]: 3							
	Age- and sex-specific LLN	103 (1.78)[b]	13/16 (81.3)	Neurologic, constitutional/metabolic, dental, muscular, renal, respiratory, skeletal	16/22 (72.7)	16	0.277	15.5
	Gurevich (2020) [24], Beer Sheva, Israel–Study population N = NR patients aged <18 y w/≥1 ALP test							
	Limitations & risk of bias: No study population N; same ALP LLN used for all children <18 y, which may be too high for older children; 3 patients did not have overt HPP signs/sx; risk of bias score[a]: 2							
	<100	24 (NR)	11/11 (100) elevated PLP	Pain, dental, skeletal, neurologic, constitutional- metabolic, renal	11/12 (91.7)	11	NR	45.8
	Saraff et al. [26], Birmingham, UK–Study population *N* = 62,285 patients aged <16 y w/≥1 ALP test							
	Limitations & risk of bias: Did not exclude secondary causes of persistently low ALP; same ALP LLN used for all children <16 y, which may be too high for older children; 1 patient (aged 4 y) described as asymptomatic; risk of bias score[a]: 3							
	<100	18 (0.03)[b]	2/4 (50.0) elevated PLP and PEA	Muscular, skeletal	2/2 (100)	2	0.003	11.1[b]
Pers. ↓ALP + *ALPL* var + HPP signs/sx	Araci et al. [20], Izmir, Turkey–Study population N = NR patients 0–23 y w/≥2 ALP tests							
	Limitations & risk of bias: No study population N; ALP LLN overly restrictive for children; risk of bias score[a]: 2							
	<40	126 (NR)	NR	Skeletal, dental, constitutional-metabolic	4/30 (13.3)	4	NR	3.2
Pers. ↓ALP + ↑ALP sub + *ALPL* var + HPP signs/sx	Held et al. [25], Freiburg, Germany–Study population *N* = 6731 patients aged <18 y w/≥1 ALP test							
	Risk of bias score[a]: 4							
	Age- and sex-specific LLN	5 0.07	11/30 (36.7) elevated PLP, PEA, and/or PPi	Constitutional-metabolic	3/4 (75.0)	1	0.015	20.0
	García-Fontana et al. [34], Granada, Spain–Study population *N* = 2507 patients aged <20 y w/≥2 ALP tests							
	Limitations & risk of bias: Sample size very limited; risk of bias score[a]: 3							
	Age-specific LLN	23 0.92	2/8 (25.0) elevated PLP	NA	0/8 (0.0)	0	0	0
Adults								
↓ALP + ↑ALP sub	Schmidt et al. [30], Geesthacht, Germany–Study population N = NR patients aged >18 y with 6,918,126 ALP records							
	Limitations & risk of bias: No study population N; persistently low ALP, HPP signs/sx. or genetic testing not assessed; assumes measurements represent individuals; risk of bias score[a]: 1							
	<30	NR	210/3447 (6.1) elevated PLP	NR	NA	210[c]	0.516[c,d]	NR
Pers. ↓ALP + HPP signs/sx	Maman et al. [29], Paris, France–*N* = 48,755 adult hospitalized patients w/ ≥ 1 ALP test							
	Limitations & risk of bias: Limited generalizability as study population includes hospitalized patients; no genetic or substrate testing; risk of bias score[a]: 2							
	<30	62 (0.13)	NR	Skeletal, rheumatic, dental	NA	14[c,f]	0.029[c]	22.6[c]
	Fujiwara et al. [28], Okayama, Japan–Study population *N* = 50,136 inpatients and outpatients aged ≥18 y with ≥2 ALP records							
	Limitations & risk of bias: No genetic or substrate (PLP or PEA) testing; Risk of bias score[a]: 3							
	≤35–40, depending on age and sex	38 (0.08)	NR	Pain, muscle, constitutional-metabolic	NA	12[c]	0.024[c]	31.6[c]

Table 1 (continued)

Case definition	ALP LLN, U/L	Persistently low ALP, *n* (%)	Elevated substrate(s), *n/N* (%)	Category of manifestations reported	*ALPL* variant detected, *n/N* (%)	Cases, *N*	Frequency in study population, %	Frequency in patients with persistently low ALP, %
Pers. ↓ALP + *ALPL*var +/− HPP signs/sx	Tornero et al. [31], Madrid, Spain–Study population *N* = 231,805 adults with ≥2 ALP tests							
	Limitations & risk of bias: 6 patients did not have overt signs and symptoms of HPP; risk of bias score[a]: 4							
	<35	396 (0.17)	NR	Pain, skeletal, dental, muscle, rheumatic	40/85 (47.1)	40	0.017	10.4[g]
Pers. ↓ALP + *ALPL* var + HPP signs/sx	Calmarza et al. [27], Aragon, Spain–Study population N = NR patients aged ≥18 y w/≥1 ALP test							
	Limitations & risk of bias: No study population N; isk of bias score[a]: 3							
	<30	21 (NR)	7/12 (58.3) elevated PLP	Constitutional-metabolic, pain, dental, skeletal, rheumatic, muscular	10/12 (83.3)	10[h]	NR	NR
Pers. ↓ALP + ↑ALP sub + *ALPL* var + HPP signs/sx	García-Fontana et al. [34], Granada, Spain–Study population *N* = 76,083 adults w/ ≥ 1 ALP test							
	Limitations & risk of bias: More up-to-date data presented in González-Cejudo; risk of bias score[a]: 4							
	≤40	56 (0.07)	10/16 (62.5) elevated PLP	Skeletal, rheumatic, dental	7/16 (43.8)	7	0.009	12.5
All ages								
Pers. ↓ALP + *ALPL* var +/− HPP signs/sx	González-Cejudo et al. [32], Granada, Spain–Study population *N* = 64,013 tertiary care patients with ≥1 ALP test							
	Limitations & risk of bias: 4 patients did not have overt signs and symptoms; Risk of bias score[a]: 4							
	Age- and sex-specific LLN	61 (0.10)	20/24 (83.3) elevated PLP	Fractures, dental	16/20 (80.0)	16[i]	0.025	26.2
Pers. ↓ALP[b] +/− ↑ALP sub + *ALPL* var + HPP signs/sx	İnci et al. [33], Ankara, Turkey—*N* = 30,000 inpatients or outpatients with ≥2 ALP records							
	Limitations & risk of bias: Did not exclude secondary causes of persistently low ALP; risk of bias score[a]: 3							
	Age- and sex-specific LLN	1132 (3.77)[b]	5/8 (62.5) elevated PLP or PEA	Children: skeletal, renal, dental, constitutional-metabolic, neurologic; Adults: rheumatic, pain, dental, skeletal	8/37 (21.6)	8	0.027	0.7[b]

ALP alkaline phosphatase, *HPP* hypophosphatasia, *LLN* lower limit of normal, *NA* not available, *NR* not reported, *PEA* phosphoethanolamine, *Pers* persistently, *PLP* pyridoxal 5'-phosphate, *PPi* inorganic pyrophosphate, *sub* substrate(s), *sx* symptoms, *var* variant, *y* years

[a]Each study was assigned 1 point for each category of: (1) generalizability (appropriate study population and a reported denominator), (2) appropriate ALP activity cutoff for age and sex, (3) assessment of HPP-related manifestations, and (4) *ALPL* or substrate (PLP, PEA, or PPi) testing, with the highest quality studies receiving all 4 points

[b]Secondary causes of low ALP activity not excluded

[c]Not genetically confirmed

[d]Calculated as (number of ALP activity <30 U/L) × (percentage of elevated PLP)/total number of ALP activity measurement) = 585,287 × 6.1%/6,918,126

[e]Calculated based on authors' assumption that if all 122 had participated in ALP testing, the same proportion would have persistently low ALP: (37/75) × 122 = 60

[f]Cases enumerated by authors of this manuscript based on persistently low ALP and signs/symptoms of HPP described in Table 1 of source study

[g]Of 383 patients who could be contacted for further study

[h]Restricted to genetically confirmed cases

[i]Three patients had no signs and symptoms, and 1 patient did not have an *ALPL* variant but had elevated PLP and signs and symptoms of HPP

ranging from 46.4% to 87.5% among the studies with low risk of bias [12, 14, 35, 37] (Fig. 2a). In a small study of patients with atypical femoral fractures, Kimura et al. identified 1 of 38 patients to have persistently low ALP (2.6%) and determined this patient to be a potential case of HPP [40]. In another study in 72 patients with atypical femoral fractures, Tsiantouli et al. identified 7 (9.7%) patients with persistently low ALP, 1 (14.3%) of whom had signs and symptoms of HPP and was heterozygous for an *ALPL* variant; however, only 3 of the 7 patients were genetically tested [42].

Total prevalence of HPP in the general population

A total of 4 studies in the general clinical population met all of the predetermined criteria for calculating total prevalence: Tornero et al. [31], Held et al. [25], García-Fontana et al. [34], and González-Cejudo, et al. [32]. As the study by González-Cejudo et al. was conducted in the same population as the study by García-Fontana et al. and provided more up-to-date data, we excluded the study by García-Fontana et al. from the estimation of total prevalence (Fig. 2b, Online Resource 9). Tornero et al. considered 40 adults to have potential HPP

Table 2 Overview of studies from selected clinical populations: osteoporosis, rheumatology, endocrinology, and patients with atypical femoral and metatarsal fractures

Case definition	ALP LLN, U/L	Persistently Low ALP, *n* (%)	Elevated substrate levels, *n/N* (%)	Category of manifestations reported	*ALPL* variant detected, *n/N*, (%)	Cases, *N*	Frequency in study population, %	Frequency in patients with persistently low ALP, %
Osteoporosis								
Pers. ↓ALP[a] + *ALPL* var	Alonso et al. [37], Edinburgh, UK–Study population $N = 3285$ adults with ≥1 ALP test							
	Limitations & risk of bias: Did not exclude secondary causes of low ALP; risk of bias score[a]: 3							
	≤40	16 (0.49%)[b]	NR	NR	14/16 (87.5)	14[c]	0.43%	87.5[b]
Pers. ↓ALP + *ALPL* var +/− HPP signs/sx	Ng et al. [14], Melbourne, Australia–Study population $N = 1839$ adults with ≥1 ALP test							
	Limitations & risk of bias: Did not exclude secondary causes of low ALP; risk of bias score[a]: 3							
	≤30	7 (0.38%)[b]	5/6[c] (83.3) elevated PLP	Skeletal, dental	3/3 (100)	4	0.22%	57.1[b,d]
Rheumatology								
N/A	Injean et al. [7], California, USA–Study population $N = 611$ adults with fibromyalgia and low/normal ALP							
	Limitations & risk of bias: Did not exclude secondary causes of low ALP, no genetic or substrate testing; risk of bias score[a]: 1							
	<37	57 (9.33%)[b]	NR	NA	NR	NR	NA	NR
Pers. ↓ALP + *ALPL* var +/− HPP signs/sx	Karakostas et al. [35], Bonn, Germany—Study population $N = 2289$ adults with ≥1 ALP test							
	Quality score[a]: 4							
	<35	28 (1.22%)	NR	Skeletal, dental	13/19 (68.4)	13	0.57%	46.4
Pers. ↓ALP + MSK signs/sx +	Feurstein et al. [12], Vienna, Austria–Study population $N = 9522$ adults with ≥1 ALP test							
	Risk of bias score[a]: 4							
	≤40	23 (0.24%)–73 (0.77%)[e] with MSK symptoms	NR	Skeletal, rheumatic, muscle, pain, dental	13/23 (56.5)	13	0.14%	56.5[b]
Pers. ↓ALP + ≥3 HPP signs/sx + *ALPL* var	Larid et al. [36], France–Study population $N = 56{,}321$ hospitalized adults with ≥2 ALP tests							
	Limitations & risk of bias: Mix of hospitalized internal medicine and rheumatology patients, difficult to generalize; risk of bias score[a]: 3							
	<35	182 (0.32%)	NR	Skeletal, dental, rheumatic	11/18 (61.1)	11	0.02%	6
Endocrinology								
Pers. ↓ALP + HPP signs/sx	Quinn et al. [39], New York, US–Study population N = NR patients (all ages) with ≥1 ALP test							
	Limitations & risk of bias: No study population N; did not exclude secondary causes of low ALP; no genetic testing; risk of bias score[a]: 1							
	≤40	259 (NR)[b]	3/4 (75.0) elevated PLP	Pain, rheumatic, skeletal, muscular, renal, dental, constitutional-metabolic	NR	10[f]	NR	3.9[b]
Pers. ↓ALP + *ALPL* var + HPP signs/sx	Hepp et al. [38], Copenhagen, Denmark–Study population $N = 26{,}121$ adults with ≥2 ALP tests							
	Limitations & risk of bias: Did not exclude secondary causes of low ALP; risk of bias score[a]: 3							
	≤35	51 (0.20%)[b]	NR	Pain, skeletal, muscle, dental	13/24 (54.2)	9	0.03%	17.6[b]

Table 2 (continued)

Case definition	ALP LLN, U/L	Persistently Low ALP, *n* (%)	Elevated substrate levels, *n/N* (%)	Category of manifestations reported	*ALPL* variant detected, *n/N*, (%)	Cases, *N*	Frequency in study population, %	Frequency in patients with persistently low ALP, %
Atypical Femoral Fractures (Orthopedics)								
Subtrochanteric FF + Pers. ↓ALP + HPP signs/sx	Kimura et al. [40], Tokyo, Japan–Study population *N* = 38 patients ≥15 y admitted with subtrochanteric femoral fracture							
	Limitations & risk of bias: Retrospective chart review only; no genetic or substrate testing; risk of bias score: NA							
	<38 U/L (or <95 U/L for 15-y-old male)	1 (2.63%)	NR	Skeletal	NR	1[f]	2.63%	100
AFF+ Pers. ↓ALP + *ALPL* var	Zhou et al. [43], The Netherlands–Study population *N* = 60 patients with AFF and ≥1 ALP test							
	Risk of bias score[a]: NA							
	<40 U/L	NR	2/2 (100) elevated PLP and/or PEA	Skeletal, constitutional-metabolic	2/60 (3.3)	2	3.33%	NR
AFF + Pers. ↓ALP + HPP signs/sx + *ALPL* var	Tsiantouli et al. [42], Geneva, Switzerland–Study population *N* = 72 hospitalized adults with AFF and ≥1 ALP							
	Limitations & risk of bias: Did not exclude secondary causes of persistently low ALP; only 3/7 eligible patients genetically tested; risk of bias score[a]: NA							
	≤40 U/L	7 (9.72%)[b]	0/2 (0.0) elevated PLP	Skeletal, constitutional-metabolic, pain, renal, neurologic	1/3 (33.3)	1	1.39%	14.3[b]
Metatarsal Stress Fractures (Podiatry)								
MSF + ↓ALP + *ALPL* var	Koehler et al. [41], Ohio, US—Study population *N* = 937 patients ≥18 y with metatarsal stress fractures and ≥1 ALP test							
	Limitations & risk of bias: Persistently low ALP not assessed; risk of bias score[a]: NA							
	<38 before and <32 after June 24, 2013	NR	NR	Fractures, dental, pain, constitutional-metabolic	2/8 (25.0)	2	0.21%	NR

AFF atypical femoral fracture, *ALP* alkaline phosphatase, *FF* femoral fracture, *HPP* hypophosphatasia, *LLN* lower limit of normal, *MSF* metatarsal stress fracture, *MSK* musculoskeletal, *NA* not available, *NR* not reported, *PEA* phosphoethanolamine, *PLP* pyridoxal 5'-phosphate, *PPi* inorganic pyrophosphate, *sub* substrate(s), *sx* symptoms, *var* variant

[a]Each study was assigned 1 point for each category of: (1) generalizability (appropriate study population and a reported denominator), (2) appropriate ALP activity cutoff for age and sex, (3) assessment of HPP-related manifestations, and (4) *ALPL* or substrate (PLP, PEA, or PPi) testing, with the highest quality studies receiving all 4 points

[b]Secondary causes of low ALP activity not excluded

[c]One elevated PLP level was in the context of vitamin B_6 supplementation

[d]One additional HPP case was diagnosed in the group without persistently low ALP

[e]ALP levels not evaluated prospectively

[f]Not genetically confirmed

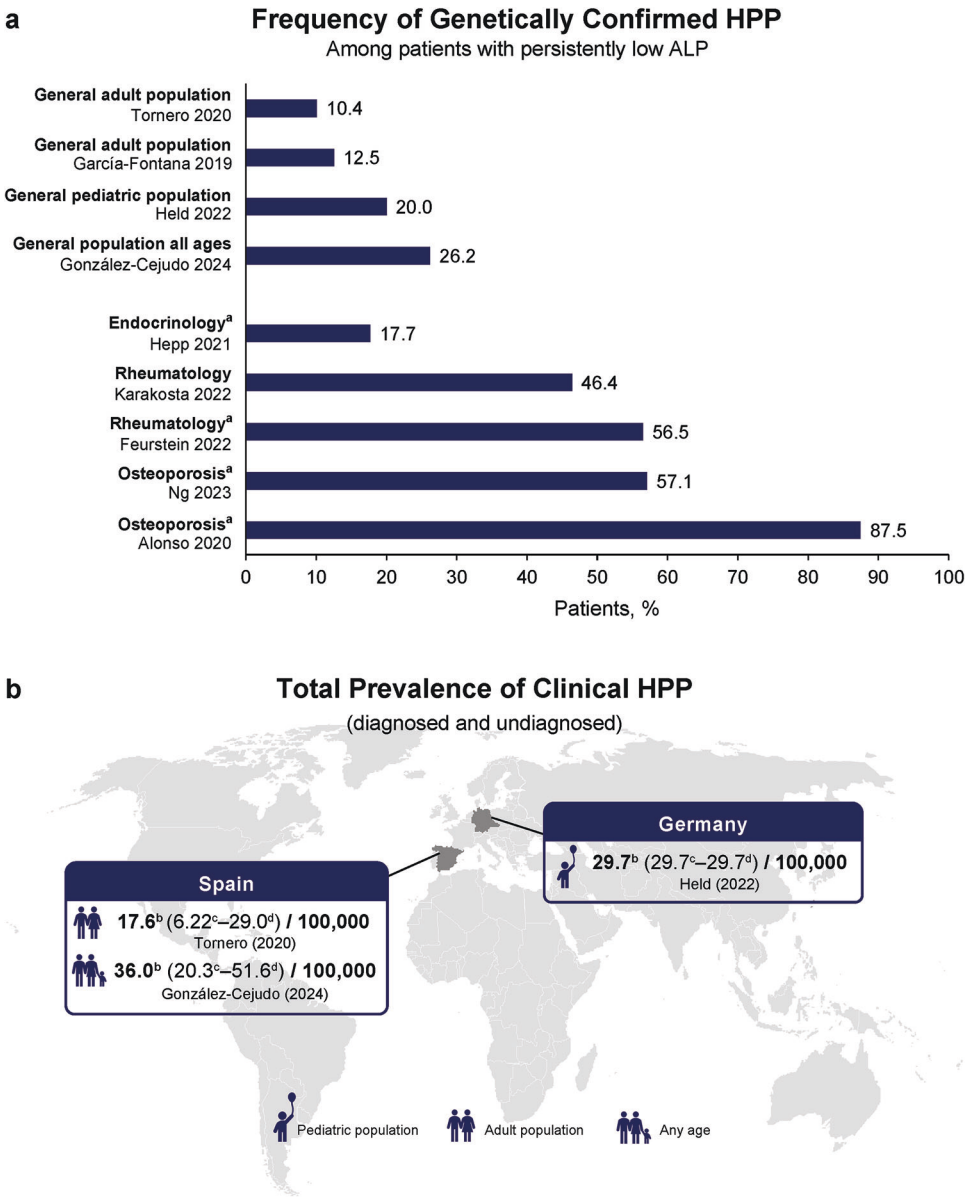


Fig. 2 Overview of (**a**) frequency of genetically confirmed HPP among patients with persistently low ALP activity in general and selected populations [12, 14, 25, 31, 32, 34, 35, 37, 38], and **b** total prevalence of clinical HPP (diagnosed and undiagnosed) estimated from studies in general clinical populations deemed to have lowest risk of bias based on predetermined criteria [25, 31, 32]. [a]Indicates secondary causes of low ALP were not excluded from denominator. Only studies with appropriate ALP LLN for age and sex with *ALPL* variant(s) were included. [b]Prevalence per 100,000 population (midpoint). [c]Low estimate per 100,000 population (assumes all cases identified). [d]High estimate per 100,000 population (assumes same rate of positivity within the persistently low ALP population not tested for *ALPL* variants/ALP substrates). ALP alkaline phosphatase, HPP hypophosphatasia, LLN lower limit of normal

[31]; however, we excluded 6 adults who had no signs or symptoms of HPP, as well as 11 adults who reported pain as their only symptom and had no family history of HPP. This left 23 patients with HPP based on signs and symptoms and *ALPL* variant(s). ALP substrate testing was not performed. Held et al. considered 1 patient to have potential HPP [25]; however, we included 1 additional patient with musculoskeletal pain, elevated PLP and PEA, and a positive *ALPL* test result. González-Cejudo et al. reported 16 potential cases of HPP based on positive *ALPL* testing [32]; however, we excluded 4 patients who did not have reported signs and symptoms of HPP and included 1 additional patient with calcifying tendonitis of the shoulder and elevated PLP but negative *ALPL* testing findings, resulting in 13 cases. From these studies, the total prevalence of HPP may range from ~17.6 to 36.0 per 100,000 population based on the midpoint identified in each study (Fig. 1b, Online Resource 9).

Manifestations of HPP in children and adults

HPP manifestations were reported in 24 of the 27 studies [12, 14, 20–29, 31–36, 38–43]. Among 51 children with 73 reported manifestations, the most frequently reported manifestations were skeletal (27% of all reported manifestations; most frequently bone deformity and fractures), constitutional/metabolic (18%; most frequently short stature and failure to thrive) dental (14%), renal (11%; hypercalcemia/hypercalciuria/hyperphosphatemia, nephrocalcinosis, and nephrolithiasis), neurologic (11%; most frequently cerebral seizures and craniosynostosis), muscular (10%;

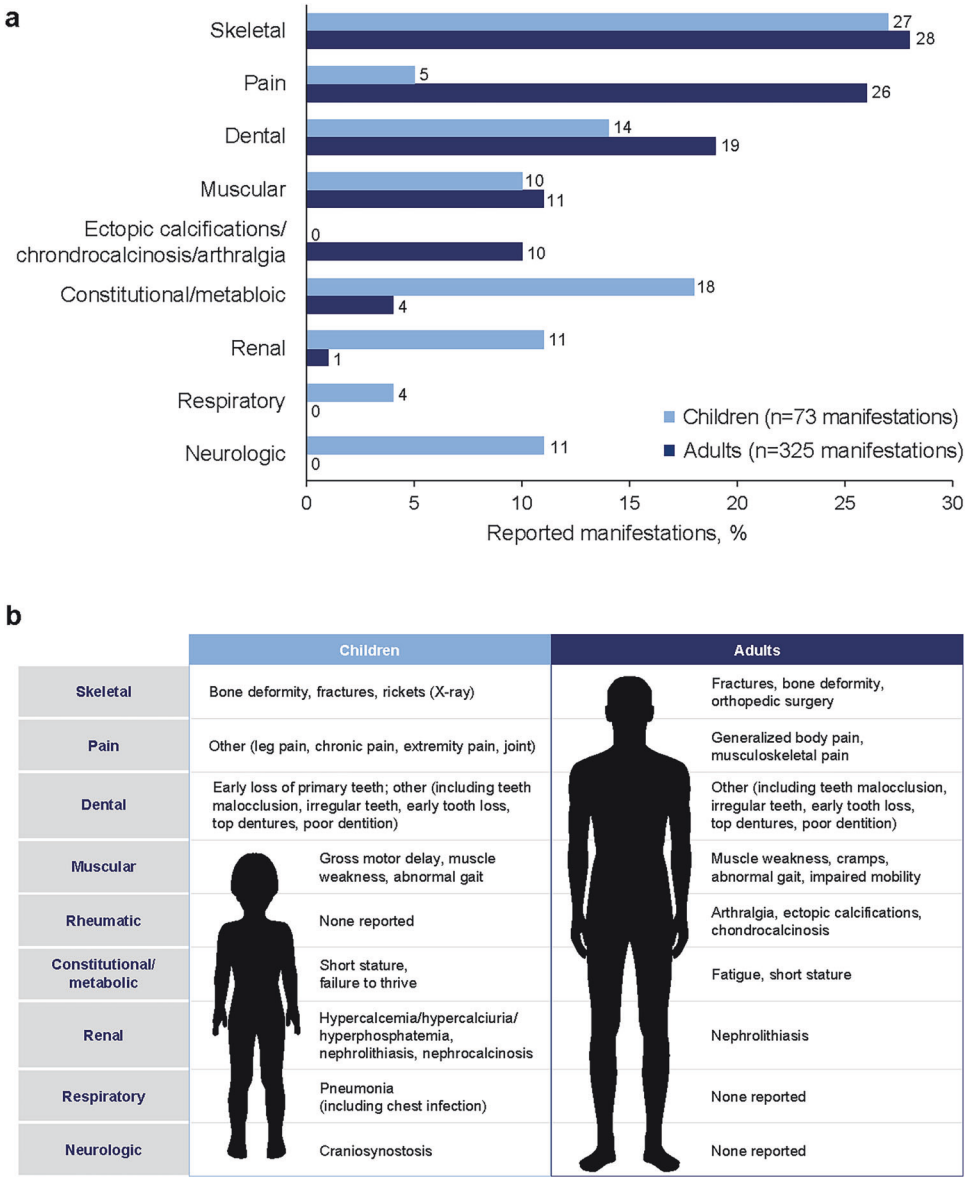


Fig. 3 Overview of (**a**) distribution of reported HPP manifestations among children and adults (cumulative frequencies) in general and select clinical populations and **b** reported signs and symptoms of HPP among children and adults. HPP, hypophosphatasia

most frequently gross motor delay, abnormal gait, and muscle weakness), pain (5%), and respiratory (4%) (Fig. 3a). Among 158 adults with 325 manifestations reported, the most common were skeletal (28%; most frequently fractures), pain (26%; most frequently musculoskeletal), dental (19%), muscular (11%; mainly muscle weakness), rheumatic (10%; arthralgia, ectopic calcifications, and chondrocalcinosis), constitutional-metabolic (4%; mainly fatigue). Specific manifestations reported among children and adults are shown in Fig. 3b and patient-level results are presented in Online Resources 3, 4, 6, and 7.

Comorbid diagnoses

Comorbid diagnoses, including initial diagnoses and potential misdiagnoses were reported in 6 studies in pediatric populations [20–23, 26, 32] (21 comorbid diagnoses among 37 children) and in 9 studies in adult populations [12, 14, 29, 32–35, 38, 39] (156 comorbid diagnoses among 89 adults; Fig. 4). The most common comorbid diagnoses among children were diseases of the nervous system (19.0% of all comorbidities); diseases of the digestive system (19.0%); developmental anomalies (19.0%); endocrine, nutritional, or metabolic diseases (9.5%); and diseases of the musculoskeletal system or connective tissue (9.5%; Fig. 4a). Among adults, the most common comorbid diagnoses were diseases of the musculoskeletal system or connective tissue (66.7%); diseases of the immune system (7.7%); and endocrine, nutritional, or metabolic diseases (6.4%; Fig. 4b). Frequent comorbid musculoskeletal diseases among adults included osteoporosis, osteopenia, osteoarthritis, fibromyalgia, and rheumatoid arthritis

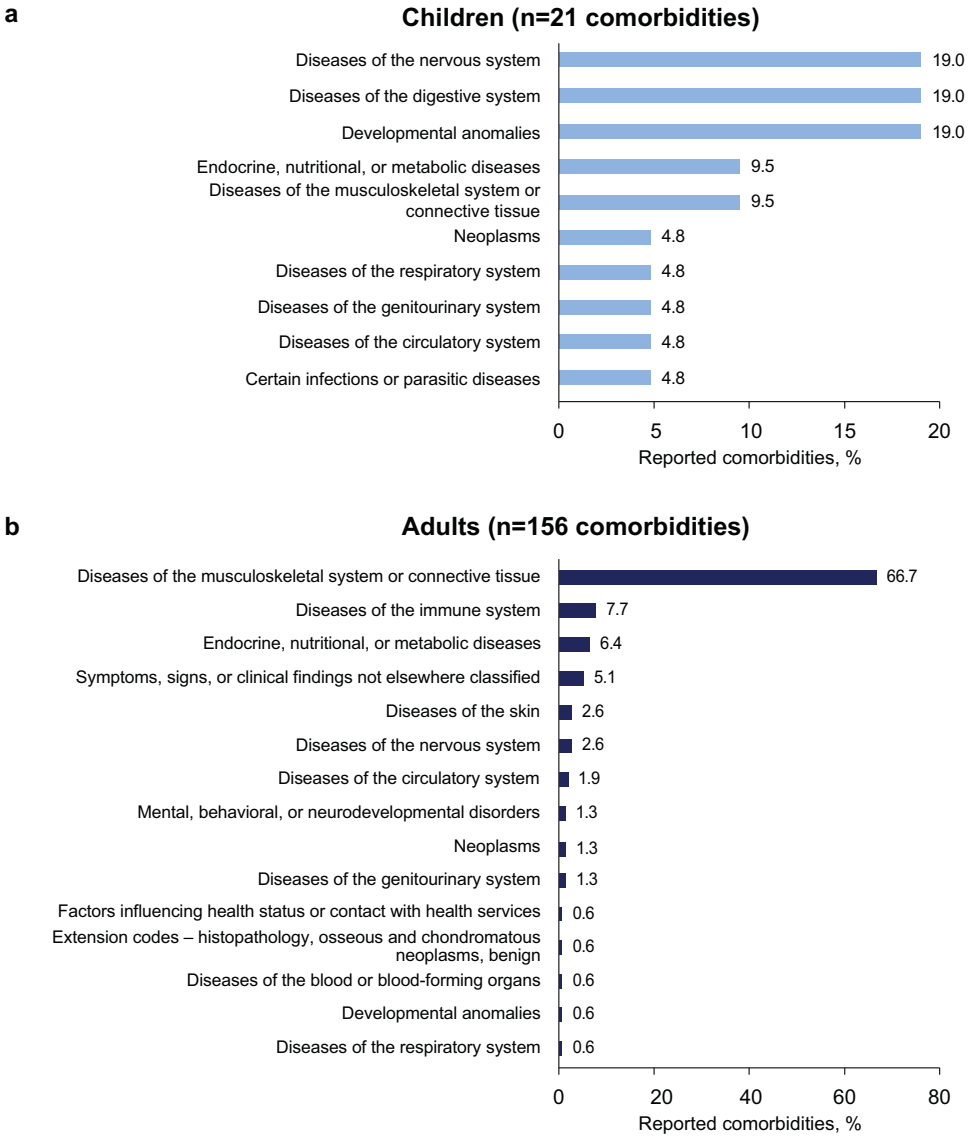


Fig. 4 Distribution of comorbidities among (**a**) children and **b** adults with HPP in general and select clinical populations with comorbidities reported. HPP hypophosphatasia

(Online Resources 4–6). Patient-level comorbidities among children and adults are listed in Online Resources 3–6.

Discussion

This systematic literature review identified an increasing number of studies implementing ALP-based screening algorithms to identify HPP. Nearly all studies identified undiagnosed cases of HPP, highlighting a need for better awareness of the implications of low ALP activity. In many of the original reports, authors noted that the frequency of HPP was higher than expected, particularly in rheumatology and osteoporosis settings. Importantly, the widespread lack of clinician attention to ALP values below the normal range, compared with the routine evaluation of elevated ALP, continues to be a major contributor to missed HPP diagnoses.

Comorbid or initial diagnoses often include the symptoms for which patients with HPP first seek medical care. Musculoskeletal diseases were the most frequently reported initial or comorbid diagnoses, which may explain why the frequency of HPP was approximately 2-fold higher in rheumatology clinics than in the general population

[12, 35]. As musculoskeletal pain is an indication of many rheumatologic disorders, such as seronegative rheumatoid arthritis, osteoarthritis, calcium pyrophosphate deposition disease, and fibromyalgia [12], rheumatologists should consistently screen for persistently low ALP to avoid delayed or incorrect diagnoses.

The high frequency of HPP diagnosis in osteoporosis clinics, where older adults are often treated, indicates that diagnostic delay and delays in treatment for HPP may be common [14, 37]. Misdiagnosis can lead to the use of contraindicated treatments that may harm patients, such as antiresorptive therapies that may increase the risk of atypical femoral fractures [37]. Physicians need to be aware of the types of fractures that may indicate HPP, such as metatarsal fractures and atypical femoral fractures [6], and perform additional assessments for patients with these hallmark manifestations. Additionally, nonskeletal manifestations should not be overlooked in these patients, especially considering that musculoskeletal pain is frequently reported by patients with HPP and is a minor diagnostic criterion for HPP per recent guidelines [17, 44].

Diagnostic guidelines for HPP specify measures of ALP activity as an obligate criterion, while substrate measurements or genetic testing are major criteria for diagnosis [17, 44, 45]. It is important to note that genetic testing is not a mandatory criterion. HPP can be diagnosed based on a combination of low ALP activity, elevated substrate concentrations, and clinical manifestations when a genetic test is unavailable or inconclusive. However, in the absence of genetic testing when clinical symptoms are limited, HPP can be underdiagnosed, as suggested by the elevated levels of ALP substrates found in a greater number of patients with genetic testing or clinical manifestations of HPP compared with patients with genetic testing and manifestations. While variations in study design and HPP diagnostic criteria made it challenging to compare HPP frequencies across studies, in general, the highest frequencies were observed among studies requiring only clinical manifestations, elevated substrates, or only genetic confirmation.

Our analysis of the total prevalence of HPP was exploratory, as it required several assumptions: (1) patients with ALP test results are representative of the general population, including those who had multiple ALP tests performed, and (2) those not genetically tested could have tested positive at the same rate as those tested. In countries with universal healthcare, where ALP testing is routinely ordered during physical exams, it may be reasonable to assume that the ALP-tested population is similar to the general population. Given that only a low proportion of eligible patients with persistently low ALP were further screened in the studies by González-Cejudo et al. and Tornero et al., it is reasonable to expect that not all cases were identified by these investigators [31, 32]. However, it is also possible that patients who were symptomatic or had a family history of HPP were more likely to consent to genetic testing, leading to inflated midpoint prevalence estimates. Despite these limitations, our estimation of total prevalence points directionally to a large contrast with the diagnosed prevalence of HPP of ~3 per 100,000 population determined from US electronic health records and suggests that as few as 1 in 10 patients with HPP are diagnosed [46]. A steady increase in the diagnosed prevalence of HPP from 2016 to 2023, identified by Fang et al., likely coincides with an increasing awareness of HPP [46]. However, even with this recent increase in diagnoses, HPP remains classified as a rare disease, and further studies are needed to quantify the total prevalence.

Manifestations of HPP, both skeletal and nonskeletal, were commonly reported in the studies reviewed here, yet certain HPP manifestations reported in the Global HPP Registry were not reported in any of the publications. For example, in the Global HPP Registry, osteomalacia as determined by biopsy was reported in 4.0% of children and 0.9% of adults, and respiratory failure was noted in 22.5% of children and 0.5% of adults [19, 47]. In comparison, osteomalacia and respiratory failure were not reported in any of the studies included in this review. These differences may reflect survivor bias in respiratory failure and underreporting of osteomalacia due to limited use of bone biopsy in clinical practice. Chronic bone pain and chronic muscle pain were also not reported separately, likely owing to difficulty in distinguishing between bone and muscle pain and because both may coexist with variable frequency and intensity.

The most common comorbid diagnoses among adults were related to the musculoskeletal system and connective tissue, which should prompt physicians to measure ALP activity in patients with these disorders. Musculoskeletal and connective tissue conditions are commonly associated with misdiagnoses of HPP, including osteoarthritis and fibromyalgia. Bone mineral density is typically normal or even elevated, particularly in the lumbar spine, in patients with HPP [16]. However, in populations such as postmenopausal women, osteoporosis may occur concomitantly with HPP.

This review had several limitations. First, key parameters, such as source populations and screening approaches, differed between studies, which made direct comparisons difficult. Variations in ranges of ALP activity, age of study populations, inclusion of substrate (PLP or PEA) or genetic testing, and criteria for the number of ALP measurements contribute to the heterogeneity of the studies and interpretation of results. For example, Araci et al. reported a lower HPP frequency among children with persistently low ALP activity than in other reported studies in children that may be attributable to the overly stringent ALP cutoff of <40 U/L [20]. Other studies in children typically used cutoffs adjusted by age and sex,

which are appropriate because the lower limit of normal ALP activity in children may be higher depending on the child's age and sex [18]. Importantly, the types of HPP signs and symptoms, as well as comorbidities, were not systematically captured or reported in all studies and likely were underreported. In addition, 3 of the studies included cases with *ALPL* VUS, which may eventually be reclassified as nonpathogenic [12, 31, 32]. The number of patients with *ALPL* VUS was small and likely had minimal impact on the estimated frequency of HPP. Furthermore, an assessment of the first 100 reclassified *ALPL* variants of uncertain significance in the Johannes Kepler University *ALPL* variant database determined that 11 were pathogenic and 62 were likely pathogenic, suggesting it is more likely that VUS cases will be reclassified as pathogenic or likely pathogenic [48]. The summary of the frequency of HPP in the study populations was challenged by the varying case definitions, but the frequency of cases decreased with increased diagnostic criteria, which was expected.

This analysis was additionally limited by studies inconsistently excluding known secondary causes of low ALP, which led to different population denominators. Studies that did not exclude secondary causes of low ALP may be more prone to false-positive results. We acknowledge as well that the frequency of low ALP in osteoporosis settings and among patients with atypical femoral fractures may be complicated by the use of antiresorptive medication among these patients, which can lower ALP values. While all studies in these select populations noted this limitation, one reported that at least 87.5% of patients receiving bisphosphonates had low serum ALP values measured before bisphosphonate initiation [37].

This review highlights the importance of ALP screening in populations in which HPP is included in the differential diagnosis. ALP screening is an accessible first step toward HPP identification and, in some countries, is consistently performed in children and as part of the comprehensive metabolic panel in adults [49]. Clinicians often investigate ALP values that are higher than the upper limit of normal, suspecting liver or gastrointestinal diseases, calcium or vitamin D deficiency, or side effects of other treatments [49]. The challenge, however, is to increase physician awareness of the implications of low ALP activity and the proper protocol for testing. Physicians should use reference ranges adjusted by age and sex when testing ALP in children. Two recent publications noted that in about half of the laboratory tests in children, reference ranges were inappropriate [50, 51]. Furthermore, physicians should be aware that fractures can transiently raise ALP values, in which case physicians who suspect HPP should look to historical ALP measurements [49].

When low ALP activity is identified, clinicians should first look for secondary causes of low ALP, including endocrine or hematologic conditions or the use of certain medication classes, among other factors known to lower ALP [45, 52]. If no secondary causes are found, HPP should be included in the differential diagnosis. Laboratory screening for ALP activity over time (excluding other causes of low ALP), substrate testing (ensuring elevated PLP is not caused by vitamin B_6 supplementation), and genetic screening should be considered for a diagnosis of HPP among patients presenting with hallmark clinical features. Such features, as reported in the Global HPP Registry, include skeletal manifestations, premature loss of deciduous teeth, pain, and muscular and rheumatic symptoms [13]. Screening for HPP among patients with concomitant disorders, particularly osteoporosis, is essential before treatment is started, as bisphosphonates worsen hypomineralization and may increase the risk of atypical femoral fractures among patients with HPP [53,54].

Conclusion

In almost all cases, further clinical evaluation and investigation in populations with persistently low ALP activity identified patients with undiagnosed HPP, indicating that the diagnosed prevalence of HPP likely underestimates the total prevalence. The frequency of HPP was especially high in select clinical populations, such as those in rheumatology, osteoporosis, or endocrinology settings, and those with atypical femoral fractures. These findings should be a call to action for practitioners to investigate low ALP activity in the absence of known causes of manifestations associated with HPP and consider a diagnosis of this disease.

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Data availability Alexion, AstraZeneca Rare Disease, will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://www.alexionclinicaltrialtransparency.com/data-requests.

Conflict of interest Valentin S Schäfer has received honoraria for lectures from: AbbVie, Novartis, Bristol Myers Squibb, Chugai, Celgene, Medac, Sanofi, Lilly, Hexal, Pfizer, Janssen, Roche, Shire, Onkowissen, Royal College London, Boehringer-Ingelheim, UCB, Fresenius, and GSK; has served as a consultant/advisor for Novartis, Chugai, AbbVie, Celgene, Sanofi, Lilly, Hexal, Pfizer, Amgen, BMS, Roche, Gilead, Medac, Boehringer-Ingelheim, and Alexion; and has received research support from The German Federal Ministry of Education and Research (BMBF), the State of North Rhine-Westphalia, the Medical Faculty of the University of Bonn, the University of Bonn, the German Society for Rheumatology (DGRh), Novartis, Roche, Lilly, Boehringer-Ingelheim, Celgene, Alexion, Hexal, Medac, and Butterfly IQ. Jessica Hinman reports consulting fees from Alexion, AstraZeneca Rare Disease. Katie Moss has received conference sponsorship from AbbVie, Alexion, UCB, Novartis, Kyowa Kirin, Lilly, Pfizer, and Internis; received honoraria for lectures from Alexion and UCB; and served as a consultant advisor for Alexion and UCB. Julia F Charles has received support for investigator-initiated research from Alexion and advisory board participation from Alexion and Kyowa Kirin; has a membership in the Nutrition Advisory Panel for the California Prune Board; and has received author royalties/fees for work on Merck Manuals and UpToDate. Jonathan D Adachi has received honoraria from Alexion, Amgen, Organon, and Sandoz; has served on an advisory board for Amgen, Organon, and Sandoz; has contributed to research for CIHR; and has served as an advisor for Osteoporosis Canada. Andrea J Singer has served as a consultant/advisor for Agnovos, Amgen, Astellas, Bayer, Echolight, and UCB and has received honoraria for speaking/teaching from Alexion, Amgen, Astellas, Kyowa Kirin, and Radius Health. Vrinda Saraff has received honoraria for speaking/teaching from Alexion, Kyowa Kirin, and Sandoz. Asma Deeb declares no conflicts of interest. Fatih Süheyl Ezgü declares no conflicts of interest. Fumio Otsuka reports speaker honoraria from Novo Nordisk, MSD, Kyowa Kirin, and Tsumura. Liliana-Georgiana Wegmann is a former employee of and owns stock/options in AstraZeneca Rare Disease. Shona Fang is an employee of Alexion, AstraZeneca Rare Disease, and may hold stock or stock options with AstraZeneca. Carolina Tornero reports receiving personal fees from Alexion, Amgen, UCB, Gedeon Richter, and Grünenthal and grants from Alexion Pharmaceuticals, and has served on advisory boards for Alexion and UCB–Amgen.

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