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Prevalence of comorbid conditions among adult patients diagnosed with phenylketonuria

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ABSTRACT

Background: Phenylalanine hydroxylase (PAH) deficiency, otherwise known as phenylketonuria (PKU), is an inborn error of metabolism that requires treatment to be initiated in the newborn period and continued throughout life. Due to the challenges of treatment adherence and the resulting cumulative effects of high and labile blood phenylalanine, PKU exerts a significant burden of disease. Retrospective studies using large databases allow for unique perspectives on comorbidities associated with rare diseases. An evaluation of co-morbidities across various organ systems is warranted to understand the disease burden in adult patients.

Objectives: The aim of this insurance claim-based observational study was to assess the prevalence of comorbid conditions across various organ systems (e.g. dermatological, renal, respiratory, gastrointestinal, hematological, and others) among adult PKU patients compared with matched controls from the general population.

Methods: This retrospective, case-controlled study selected patients from United States insurance claims databases from 1998 to 2014 using International Classification of Diseases, Ninth Revision (ICD-9) codes for diagnosis of PKU. The date of first diagnosis during the study period was index date and this was not necessarily the first time the patient was diagnosed with PKU. Cases were matched with a 1:5 ratio with general population (non-PKU controls) on age, sex, race, geographic location, duration of time in the database and insurance type. Prevalence and prevalence ratio (PR) calculations for comorbidities across various organ systems among adults ($\geq$20 years old) with PKU were compared with the general population (non-PKU controls). The conditions were selected based on complications associated with PKU and feedback from clinicians treating PKU patients.

Results: A total of 3691 PKU patients and 18,455 matched, non-PKU controls were selected, with an average age of 35 years. The mean healthcare costs incurred by the PKU patients during baseline, were approximately 4 times that of the controls ($4141 vs $1283; $p < .0001$). The prevalence rates of comorbidities across various organ systems during the follow-up period were significantly higher for those with PKU than in the control group. After adjusting for baseline characteristics, the adjusted prevalence ratios (PR) of 15 conditions studied (asthma, alopecia, urticaria, gallbladder disease, rhinitis, esophageal disorders, anemia, overweight, GERD, eczema, renal insufficiency, osteoporosis, gastritis/esophagitis and kidney calculus) were all above PR = 1.24 and significantly higher for the PKU cohort ($p \leq .001$). The highest adjusted PR were for renal insufficiency with hypertension (PR [95% CI]: 2.20 [1.60–3.00]; $p < .0001$) and overweight (PR [95%CI]: 2.06 [1.85–2.30]; $p < .0001$).

Conclusions: The prevalence of selected comorbidities across several organ systems is significantly higher among PKU patients than for general population controls. Regular screening for common co-morbidities may be warranted as part of PKU management.

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1. Introduction

Phenylalanine hydroxylase (PAH) deficiency, otherwise known as phenylketonuria (PKU), is the most frequent of the neurologically impacted inborn errors of amino acid metabolism [1]. In the US population, incidence of PKU is approximately 1 in 12,707 live births [2]. PAH deficiency is an autosomal-recessive disorder resulting from mutations in the PAH gene. These mutations result in an impaired ability of the enzyme to metabolize the essential amino acid, phenylalanine (Phe), to tyrosine (Tyr), leading to the accumulation of Phe in blood and tissues [3]. Allelic variation in the PKU population results in a broad spectrum of severity of PAH dysfunction and thus a wide range of clinical manifestations [4].

American College of Medical Genetics and Genomics (ACMG) guidelines recommend maintaining blood Phe concentrations within the range of 120–360 μmol/L in individuals of all ages, using any safe combination of therapeutic approaches [5]. These guidelines recommend that treatment is initiated as early as possible within the first two weeks of life and continued for life [5]. Adherence to Phe-restricted diet is challenging, and tends to diminish with age [6], resulting in increased blood Phe concentrations and neuropsychiatric and neurocognitive symptoms [6–8]. Recently it has been reported that > 60% of adolescents and 70% of adult PKU patients have uncontrolled blood Phe, with concentrations exceeding the upper limit of ACMG target range (360 μmol/L) [6].

The accumulation of Phe in blood, brain, and other tissues leads to a wide spectrum of disorders throughout life [5]. Among adult PKU patients, neurologic, neurocognitive, and neuropsychiatric deficits exceed general population estimates, and lowering blood Phe concentrations in these individuals may reduce some of these complications [9]. A recent retrospective study by Bilder et al., utilizing insurance claims databases, concluded that rates of neuropsychiatric comorbid conditions were significantly higher for adult PKU patients compared with matched non-PKU controls from the general adult population [10].

There have been a few published reports of somatic comorbidities among PKU patients, such as renal impairment, proteinuria, arterial hypertension, and obesity [11–13]. However, a more comprehensive evaluation of comorbidities across various organ systems is warranted, especially in adult patients. This real-world insurance claims-based study aimed to evaluate the prevalence of comorbid medical conditions among adult PKU patients compared with a matched non-PKU control group from the general population.

2. Methods

2.1. Data sources

This retrospective, observational, insurance claims-based study utilized data from three United States (US) MarketScan® research databases: Commercial Claims and Encounters (Commercial) Database, Medicare Supplemental Coordination of Benefits (Medicare) Database, and the Medicaid Multistate Database. These databases contain all of the inpatient, outpatient, and outpatient prescription drug experience for the beneficiaries while they were enrolled in the health-plan.

All database records were de-identified and fully compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and the study did not involve the collection, use, or transmittal of individually identifiable data. Hence, Institutional Review Board (IRB) approval to conduct this study was not necessary.

2.2. Study design and population

The study included individuals with PKU and without PKU presenting in the database any time between January 1, 1998 through October 31, 2014 (Commercial and Medicare Supplemental Databases); and between January 1, 2000 and June 30, 2014 (Multi-State Medicaid Database).

2.3. PKU cohort

Individuals aged ≥20 years with a diagnosis of PKU (ICD-9-CM 270.1) during the study period and no diagnosis of other specified disorders of amino acid metabolism (ICD-9-CM 270.8) at any time were selected for this study. The first date of the first claim with a PKU diagnosis during the study period was considered as the index date. This was done to prevent inclusion of individuals who may have been miscoded or not confirmed to have PKU during the newborn screening period and to reflect an adult population that has PKU.

2.4. Non-PKU controls

Individuals aged ≥20 years with no history of diagnosed PKU (ICD-9-CM 270.1) during the study period were selected as potential controls. Individuals with diagnosis of other specified disorders of amino acid metabolism (ICD-9-CM 270.8) at any time were excluded from control cohort. Individuals with prescription claim(s) for sapropterin at any time were also excluded from the control group. The index date for controls was randomly assigned to align with the PKU cases' index dates. This control group was selected from the same claims database.

For both individuals with PKU and non-PKU controls, the baseline period was 90 days prior to the index date, and the follow-up period began at the index date and continued until the individual was no longer enrolled in the database with a minimum of 30-days of follow-up.

2.5. Matching

Adults with PKU were directly matched to non-PKU controls based on age, sex, geographical region (Northeast, Midwest, South, West), race, index-year, insurance type (commercial, Medicare, or Medicaid) and length of time of continuous enrollment in the database during follow-up. Among the group of controls that matched to each case, controls were randomly selected with a ratio of five controls for each case.

2.6. Outcomes

The frequency of 35 selected comorbid conditions were evaluated during the baseline period. These conditions were selected based on complications associated with PKU and feedback from clinicians treating PKU patients. The comorbid conditions included chronic sinusitis, COPD, cellulitis, rosacea, vitiligo, osteoarthritis/osteoarthrosis, fractures, systemic lupus erythematosus, rheumatoid arthritis and collagen vascular diseases, psoriasis and parapsoriasis, colitis/enteritis, diverticulosis/diverticulitis of GI tract, diarrhea, irritable bowel syndrome, pancreatitis; bleeding disorders, iron metabolism disorder, neutropenia and leukopenia, non-melanoma skin cancer, benign neoplasms of the skin, melanoma, gastrointestinal cancers, genitourinary cancer, breast cancer, lung cancer, hematologic cancer, head and neck cancer, neurological cancer, hepatoma, female bleeding conditions, overweight and underweight.

A final set of 15 comorbid conditions was selected based on a known association with PKU and presence in a sufficient number of cases to ensure adequate sample size for covariate analyses: dermatitis and eczema, alopecia and baldness, asthma, allergic and chronic rhinitis, osteoporosis, calculus of kidney, renal insufficiency with hypertension, renal insufficiency without hypertension, esophageal disorders, gastroesophageal reflux disease (GERD), gastritis and esophagitis, gallbladder diseases (gallstones, cholecystitis), anemia, overweight, urticaria. The prevalence of these comorbid conditions was assessed during the variable follow-up period.

2.7. Other covariates

Demographics measured on the index date were, age, sex, geographical location (US Census division) urban/rural residence, payer and index year.

As overall measures of disease burden and general health status the following were evaluated during the baseline period: the number of unique 3-digit ICD-9 codes, the number of unique NDC codes and the Deyo Charlson Comorbidity Index (DCI) [14]. DCI is an aggregate measure of comorbidity expressed as a numeric score based on the presence of select diagnoses for various conditions. A higher score denotes a higher burden from comorbid conditions. The mean overall total healthcare costs during the baseline period were computed as another measure of general health and economic burden. The 35 selected comorbid conditions were also measured during the baseline period.

The use of medications such as analgesics and antipyretics, anti-anemia drugs, antihypertensives, antiplatelets, asthma/chronic obstructive pulmonary disease (COPD) drugs, bisphosphonates, anti-diabetics, GI agents, statins, and thyroid hormones, were also assessed during the baseline period. These medications were selected based on their use in treating potential complications associated with having PKU, as well as the treatment of the most frequent comorbidities in this population.

2.8. Statistical analyses

During the variable follow-up period, frequency (N, %) and prevalence rate per 100 person years (PY) of comorbid conditions were reported for the PKU group and for the matched control group. The occurrence of the comorbid conditions was calculated accounting for the fact that the person-time contributed by each patient during the follow-up period was varied (i.e. patients were followed as long as they were continuously enrolled in the database). The prevalence ratios (PR) and 95% confidence intervals (CI) were calculated comparing the PKU population to the control population. An alpha level of 0.05 was assumed for all statistical tests.

Multivariate analyses (15 models) were performed comparing the prevalence rates for the 15 selected conditions (listed above) for individuals with PKU vs matched non-PKU controls. Data were adjusted for the following characteristics: age, sex, health insurance payer, race, geographic region, index year, years of eligibility, baseline clinical characteristics such as DCI, all-cause healthcare costs, comorbid conditions and concomitant medications. The models were generalized linear models with Poisson error, log link, and the logarithm of exposure (time at risk for the outcome) as an offset.

3. Results

3.1. Participant selection and demographics

A total of 3691 individuals with a diagnosis of PKU met criteria for inclusion in this study. A total of 18,455 individuals without PKU were selected as matched controls from among 98,230,450 potential subjects included in the databases. (Fig. 1).

The average age of the study population was approximately 35 years (34.6 years PKU; 34.9 years controls), and 63.7% were female. The majority of participants (70.5%) were commercially insured and had continuous enrollment for an average of 2.5 years post-index date. (Table 1).

3.2. Baseline clinical

All measures of general health status at baseline indicated that non-PKU controls were healthier than those with a diagnosis of PKU. Individuals with PKU had a higher number of unique diagnoses (3.39 vs. 1.87) and concomitant medications (2.80 vs. 1.73) compared with the non-PKU controls (both $p < .0001$). In addition, the mean DCI score was significantly higher for those with PKU than for non-PKU controls (0.20 vs 0.09; $p < .0001$). The mean healthcare costs incurred by those with PKU at baseline were approximately 4 times that of the controls ($4141 vs $1283; $p < .0001$). (Table 2).

A higher proportion of those with PKU had prescriptions across all of the medication types assessed compared with the non-PKU controls ($P < .05$). (Table 2) In both the PKU and control populations, respectively, analgesics and antipyretics (19% and 14%), followed by anti-hypertensives (15% and 9%), were the most commonly used concomitant medications during baseline. A total of 35 selected comorbidities were assessed during the baseline period. The most common comorbid conditions during the baseline period were female bleeding disorders (PKU: 5.28%; Control: 3.51%), COPD (PKU: 1.3%; Control: 0.57%), benign skin cancers (PKU: 1.46%; Control: 0.93%) and chronic sinusitis (PKU: 1.03%; Control: 0.81%). When compared with matched non-PKU controls, the baseline comorbidity burden was higher for individuals with PKU. (Table 3).

3.3. Estimated prevalence and prevalence ratios of comorbidities

Prevalence rates of the 15 comorbidities included in analyses of the follow-up period were assessed per 100 PY. The comorbidities with > 5 events per 100 PY in the PKU cohort were allergic and chronic rhinitis (7.03), esophageal disorders (5.56), anemia (5.46), overweight (5.35), GERD (5.23), and dermatitis and eczema (5.15). Overall unadjusted event rates per 100 PY for each of the 15 comorbidities were significantly higher for the PKU patients than the matched non-PKU controls. (Table 4).

After adjusting for baseline characteristics, the adjusted prevalence ratios (PRs) of the 15 selected conditions were significantly higher for the PKU cohort ($p \leq .001$) and all of the PRs were > 1.24. Renal insufficiency with hypertension (PR [95% CI]: 2.20 [1.60–3.00]; $p < .0001$) and overweight (PR [95%CI]: 2.06 [1.85–2.30]; $p < .0001$) had the highest adjusted PR among PKU patients compared with the matched controls. In addition, several GI-related conditions had statistically significant PR > 1.3 (gallbladder diseases PR [95%CI]: 1.31 [1.08–1.58]; GERD 1.44 [1.29–1.60]; other esophageal disorders 1.45 [1.30–1.61]; gastritis and esophagitis 1.57 [1.39–1.76]). (Fig. 2).

4. Discussion

This retrospective study used insurance claims data to assess comorbid conditions across multiple organ systems in adult patients with PKU compared with non-PKU controls from the general population. Our results demonstrate that the comorbidity burden in adult PKU patients is higher than that observed in the general population with similar demographic and clinical characteristics. This was demonstrated by higher prevalence of comorbid conditions in the PKU group compared with the controls and also through an increase in overall disease burden among PKU patients, as measured by the number of unique 3-digit ICD-9 codes, the number of unique number of NDC codes, DCI scores and the overall total healthcare costs during the baseline period.

Although the etiology for many of the symptoms associated with PKU are still under investigation, the clinical manifestations of PKU are considered to be related to either elevated blood Phe levels or the requisite Phe-restricted, diet low in intact protein [15]. High blood Phe may be associated with biological mechanisms that are related to increased risk of other diseases such as obesity, renal disease, metabolic dysfunction, and cardiovascular complications [16–20]. For example, high Phe levels have been associated with arterial stiffness, which impacts risks of cardiovascular disease [21]. In addition, adherence to a PKU diet has been shown to be associated with factors known to contribute to obesity, such as lower levels of satiety, reduced thermic effect of feeding and post prandial fat oxidation [[22,23] NEY]. Other studies

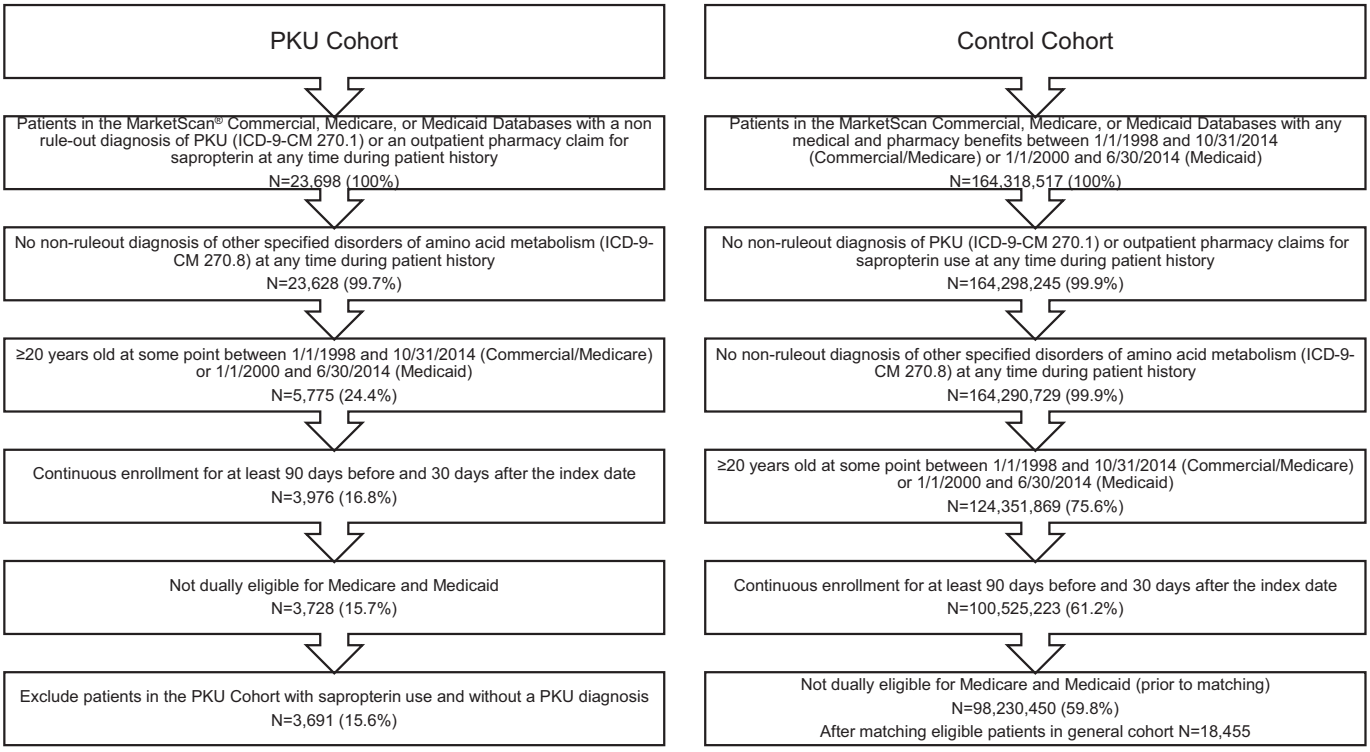

Fig. 1. Patient selection.

Table 1
Baseline demographics.

Demographic characteristics	PKU	Matched control	P-value
	N = 3691	N = 18,455	
Age (Mean, SD)	34.6 (14.3)	34.9 (14.2)	0.198
Sex (%, N)			1.000
Male	1341 (36.3%)	6705 (36.3%)	
Female	2350 (63.7%)	11,750 (63.7%)	
Payer* (N, %)			1.000
Commercial	2604 (70.5%)	13,020 (70.5%)	
Medicare	173 (4.7%)	865 (4.7%)	
Medicaid	914 (24.8%)	4570 (24.8%)	
Race (N, %)			1.000
White (Medicaid only)	582 (15.8%)	2910 (15.8%)	
Black (Medicaid only)	203 (5.5%)	1015 (5.5%)	
Other known (Medicaid only)	90 (2.4%)	450 (2.4%)	
Unknown (Medicaid only)	39 (1.1%)	195 (1.1%)	
Unknown (Commercial and Medicare only)	2777 (75.2%)	13,885 (75.2%)	
Geographic Region* (N, %)			1.000
Northeast (Commercial and Medicare only)	524 (14.20%)	2620 (14.20%)	
North Central (Commercial and Medicare only)	607 (16.45%)	3035 (16.45%)	
South (Commercial and Medicare only)	1033 (27.99%)	5165 (27.99%)	
West (Commercial and Medicare only)	528 (14.31%)	2640 (14.31%)	
Unknown (Commercial and Medicare only)	85 (2.30%)	425 (2.30%)	
Unknown (Medicaid only)	914 (24.76%)	4570 (24.76%)	
Length of Continuous Enrollment (Mean, SD days)	1035.2 (1046.3)	1027.9 (1050.6)	0.697

Table 2
Baseline clinical characteristics.

Clinical characteristics	PKU	Matched control	P-value
	N = 3691	N = 18,455	
General Health Status			
Count of Unique Three-Digit ICD-9-CM Codes (Mean, SD)	3.39 (4.43)	1.87 (2.93)	< 0.0001*
Count of Unique Medications (Mean, SD)	2.80 (3.85)	1.73 (2.78)	< 0.0001*
Deyo-Charlson Comorbidity Index (DCI) (Mean, SD)	0.20 (0.73)	0.09 (0.49)	< 0.0001*
Baseline Healthcare Costs (Mean, SD)	$4141.40 ($11,916.60)	$1283.29 ($5941.89)	< 0.0001*
Concomitant Medications (N, %)			
Analgesics and antipyretics	714 (19.34%)	2517 (13.64%)	< 0.0001*
Antihypertensives	551 (14.93%)	1705 (9.24%)	< 0.0001*
GI agents	305 (8.26%)	818 (4.43%)	< 0.0001*
Asthma/COPD drugs	294 (7.97%)	951 (5.15%)	< 0.0001*
Statins	205 (5.55%)	752 (4.07%)	0.0001*
Antidiabetics	190 (5.15%)	333 (1.80%)	< 0.0001*
Thyroid hormones	129 (3.49%)	533 (2.89%)	0.0481*
Bisphosphonates	27 (0.73%)	107 (0.58%)	0.278
Antiplatelets	29 (0.79%)	81 (0.44%)	0.006*
Antianemia drugs	22 (0.60%)	42 (0.23%)	0.0001*

* $p < .05$.

have shown low bone mineral density among PKU patients, which contributes to an elevated risk of skeletal fragility and potentially, osteoporosis [24]. Depression along with other neuropsychological and executive functioning deficits occur at a higher frequency in PKU patients and are also associated with poor health and other comorbid conditions, such as obesity [9,10,12].

The current study found higher prevalence of comorbid conditions that were also noted in a review by MacLeod et al. where approximately one third of PKU subjects have total plasma homocysteine concentrations that exceed the 97th percentile, suggesting an increased risk for thrombosis, atherosclerosis and stroke [7]. In addition, there was also a reduced absorption and utilization of calcium, phosphorus and vitamin D leading to low bone mass (i.e. osteopenia, osteoporosis and fractures), especially in adults [7]. A study by Hennermann et al. of 67 adults

Table 3
Baseline comorbidities by system class.

Comorbidities (N, %)	PKU	Matched control	P-value
	N = 3691	N = 18,455	
Respiratory			
COPD	48 (1.30%)	105 (0.57%)	< 0.0001*
Chronic sinusitis	38 (1.03%)	150 (0.81%)	0.190
Skin			
Cellulitis	35 (0.95%)	124 (0.67%)	0.070
Rosacea	7 (0.19%)	20 (0.11%)	0.197
Vitiligo	2 (0.05%)	2 (0.01%)	0.132
Bone & joint			
Osteoarthritis/osteoarthrosis	74 (2.00%)	179 (0.97%)	< 0.0001*
Fractures	36 (0.98%)	137 (0.74%)	0.142
Autoimmune			
Systemic lupus erythematosus	10 (0.27%)	18 (0.10%)	0.018*
Rheumatoid arthritis and collagen vascular diseases	10 (0.27%)	63 (0.34%)	0.496
Psoriasis and parapsoriasis	14 (0.38%)	32 (0.17%)	0.012*
GI			
Diarrhea	27 (0.73%)	111 (0.60%)	0.359
Colitis/enteritis	25 (0.68%)	101 (0.55%)	0.338
Diverticulosis/diverticulitis of GI tract	15 (0.41%)	42 (0.23%)	0.050
Irritable bowel syndrome	15 (0.41%)	39 (0.21%)	0.028*
Pancreatitis	10 (0.27%)	10 (0.05%)	0.001*
Hematological			
Bleeding disorder	11 (0.30%)	18 (0.10%)	0.005*
Neutropenia and leukopenia	4 (0.11%)	16 (0.09%)	0.762
Cancers			
Benign neoplasms of the skin	54 (1.46%)	171 (0.93%)	0.003*
Breast cancer	7 (0.30%)	40 (0.34%)	0.744
GU cancer	11 (0.30%)	45 (0.24%)	0.550
Female GU cancer	4 (0.17%)	12 (0.10%)	0.325
Male GU cancer	5 (0.37%)	23 (0.34%)	0.801
GU cancer (both males and females)	2 (0.05%)	10 (0.05%)	1.000
Non-melanoma skin cancer	10 (0.27%)	28 (0.15%)	0.110
Hematologic cancer	10 (0.27%)	13 (0.07%)	0.002*
Ears, nose, throat cancer	4 (0.11%)	5 (0.03%)	0.048*
Melanoma	4 (0.11%)	8 (0.04%)	0.125
GI cancer	2 (0.05%)	15 (0.08%)	0.755
Neurological cancer	2 (0.05%)	6 (0.03%)	0.628
Hepatoma	0 (0.00%)	1 (0.01%)	1.000
Lung cancer	1 (0.03%)	7 (0.04%)	1.000
Miscellaneous			
Female bleeding	124 (5.28%)	413 (3.51%)	< 0.0001*
Underweight	0 (0.00%)	1 (0.01%)	1.000

* $p < .05$.

Table 4
Unadjusted prevalence rates of comorbid conditions.

Condition	PKU (N = 3691)		Matched control (N = 18,455)		P-value[a]
	Events	Rate/100PY	Events	Rate/100PY	
Dermatitis and eczema	468	5.15	1731	3.70	< 0.0001
Alopecia and baldness	61	0.59	181	0.35	0.0003
Asthma	396	4.27	1287	2.67	< 0.0001
Allergic and chronic rhinitis	611	7.03	2247	4.96	< 0.0001
Osteoporosis	125	1.24	399	0.79	< 0.0001
Calculus of kidney	155	1.54	435	0.86	< 0.0001
Renal insufficiency with hypertension	78	0.76	109	0.21	< 0.0001
Renal insufficiency without hypertension	320	3.33	855	1.72	< 0.0001
Esophageal disorders	503	5.56	1516	3.19	< 0.0001
GERD	477	5.23	1449	3.03	< 0.0001
Gastritis and esophagitis	402	4.35	1150	2.38	< 0.0001
Gallbladder diseases (gallstones, cholecystitis)	153	1.52	477	0.94	< 0.0001
Anemia	498	5.46	1550	3.26	< 0.0001
Overweight	492	5.35	1109	2.25	< 0.0001
Urticaria	205	2.08	603	1.20	< 0.0001

[a] All conditions $p < .05$.

reported renal impairment, proteinuria, and arterial hypertension in patients with PKU [17]. Diets high in amino acids also lead to greater renal workload and potential for reduced kidney function [23]. The present study confirms this finding, with the adult PKU patients demonstrating twice the likelihood of having renal insufficiency with hypertension, after adjusting for baseline factors. Other studies have reported a high concurrence of PKU diagnosis and obesity [11–13,25,26]. Our findings suggest that after adjusting for baseline characteristics, adult PKU patients were twice as likely to be overweight than the general population. A case series study of 30 PKU patients found 21 different comorbid conditions across a variety of organ systems among the 30 patients studied, with autoimmune and gastrointestinal conditions being among the most common [27]. Although direct comparisons with the current study are limited since this small case series study did not have a control group, the current analysis also found elevated prevalence of some autoimmune and gastrointestinal disorders (eg. GERD).

The few anecdotal reports on patients with managed PKU have conflicting conclusions on whether the elevated risk of low bone mineral density (BMD) results primarily from elevated blood Phe or the requisite Phe-restricted diet [16,18,20]. In the current analysis, adult PKU patients had a higher risk of developing osteoporosis compared with the general population. As we were not able to assess adherence to diet nor the degree of blood Phe control, the impact of these factors on BMD could not be confirmed.

A role for adherence to diet is also supported by evidence that patients who remain on diet, and thus have been able to achieve lower blood Phe levels, have fewer comorbidities and fewer physician visits for non-PKU reasons than those who discontinue diet in adolescence or adulthood (15–25 years of age) [28].

Extrapolation of these study outcomes to the general PKU population should be performed cautiously, as the female patients outnumbered the males by 1.8 times in this PKU population; this is similar to the previous insurance claims PKU study [10]. This could be due to increased access to and utilization of healthcare by females [29] or to the recommendation that females of reproductive age be screened for risks associated with maternal PKU [5].

The mean age of the PKU patients in this study is approximately 35 years of age, which likely represents a population of PKU patients who were diagnosed through newborn screening. A population of adults at a later stage in life (e.g. late-diagnosed as they were born prior to the implementation of widespread newborn screening) may present with a different constellation of comorbid conditions. Information about severity of PKU, degree of control of blood Phe, or the metabolic phenotype of PKU were not available for this study, hence the impact of these factors on the prevalence of comorbid conditions could not be assessed. As with all studies based on insurance claims databases, this investigation is comprised of commercial, Medicare and Medicaid insured populations, and thus the results may not be generalizable to the uninsured PKU population. In addition, prior studies have shown that > 70% of the adult PKU patients fail to access treatment regularly, and hence these data may not accurately estimate the true prevalence of these comorbidities in the PKU population [2]. It is also possible that patients with PKU have more contact with medical personnel than the controls due to their frequent visits for dietary and metabolic follow-up and therefore are more likely to be identified with screened comorbid conditions by high blood pressure, overweight, and abnormalities on routine laboratory tests and this may contribute to explain the higher PR for some of the conditions.

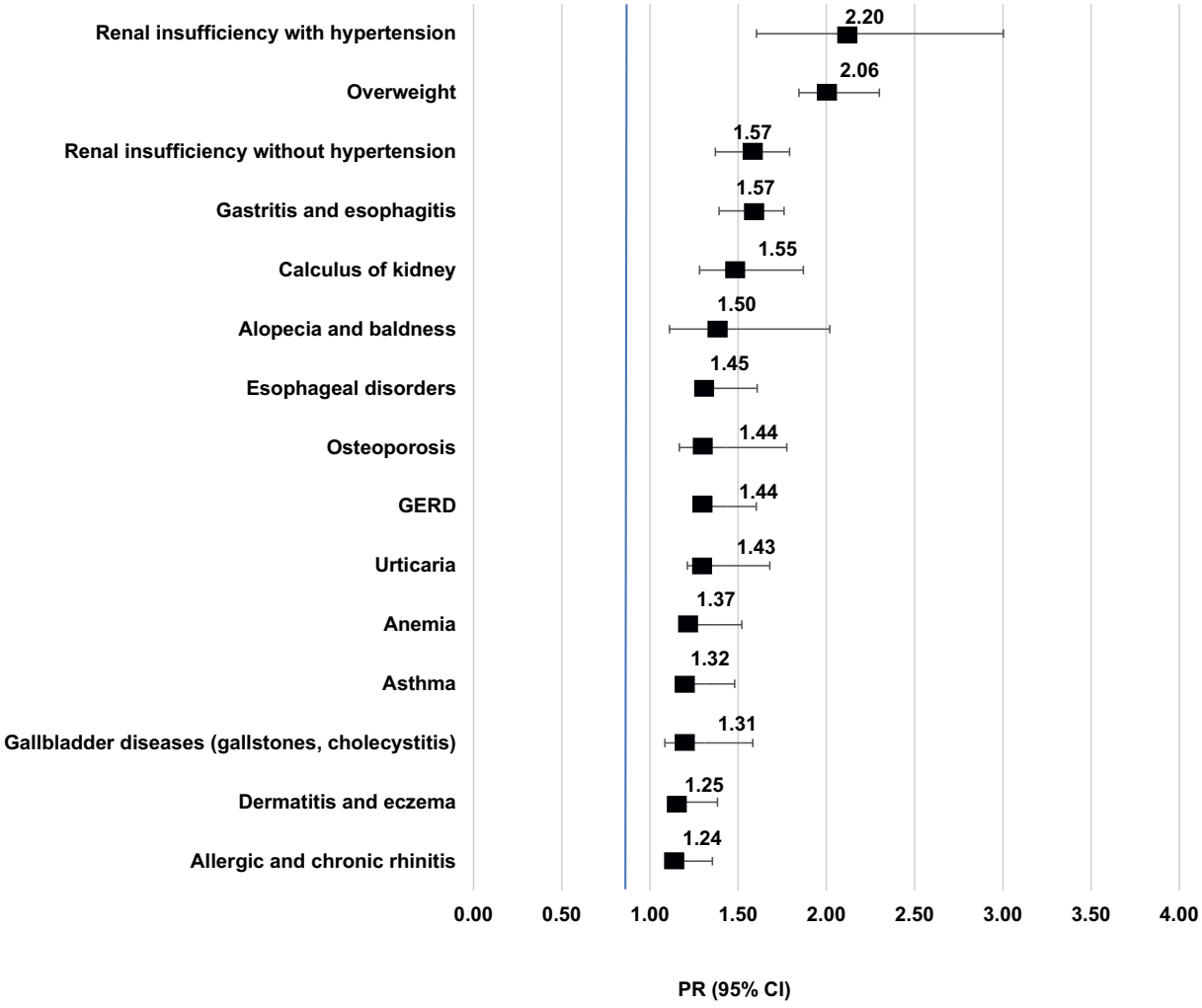

Fig. 2. Adjusted prevalence ratio (PR) of comorbid conditions in PKU patients compared with non-PKU controls.

5. Conclusions

The cumulative deleterious effects of high blood Phe in patients with PKU justifies the clinical practice guideline recommendations for lifelong management to control blood Phe [5,24]. Although potential pathogenic mechanisms remain to be fully elucidated, this study indicates that the prevalence of comorbidities across several organ systems is significantly higher for individuals with PKU compared with controls from the general population. These results suggest that the prevailing understanding of the clinical manifestations of PKU may be incomplete, and that the burden of illness may extend beyond neurologic, neurocognitive, and neuropsychiatric manifestations. Regular screening for somatic comorbidities, including monitoring of body weight and renal function, may be warranted as part of PKU management. Additional sources of care for adult PKU patients should be developed since adult clinics are not routinely available and many PKU patients continue to be seen by pediatric providers, who may not be as familiar with adult onset conditions. Additional studies on PKU-related comorbidities and their etiologies are warranted, especially for adult patients.

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Conflict of interest

BioMarin Pharmaceutical Inc provided funding to conduct this study and for medical writing support for the production of this manuscript. Joshua Lilienstein, Ignacio Alvarez, and Elaina Jurecki are employees and shareholders of Biomarin Pharmaceuticals Inc. Debra Irwin and Gilwan Kim are employees of Truven Health Analytics, an IBM company, contracted by BioMarin to conduct this study.

BKB and HL are investigators on BioMarin sponsored clinical trials. SW has received honararia from BioMarin as a consultant. DI, EJ and GK contributed to the design, data acquisition, analysis of this data. All authors were involved in the interpretation of data, writing and critical review of the manuscript. All authors have reviewed and approved the contents of this manuscript in accordance to the International Committee of Medical Journal Editors guidelines.

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