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Neuropsychiatric comorbidities in adults with phenylketonuria: A retrospective cohort study

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ABSTRACT

Adults with phenylketonuria (PKU) may experience neurologic and psychiatric disorders, including intellectual disability, anxiety, depression, and neurocognitive dysfunction. Identifying the prevalence and prevalence ratios of these conditions will inform clinical treatment. This nested, case-controlled study used International Classification of Diseases, Ninth Revision (ICD-9) codes from the MarketScan® insurance claims databases from 2006 to 2012 and healthcare claims data for US-based employer and government-sponsored health plans. Prevalence and prevalence ratio calculations of neuropsychiatric comorbidities for adults (≥20 years old) with PKU were compared with two groups [diabetes mellitus (DM) and general population (GP)] matched by age, gender, geographic location, and insurance type. Age cohorts (i.e., 20–29, 30–39, 40–49, 50–59, 60–69, and 70+ years, and a combined subset of 20–39) were used to stratify data. The PKU cohort experienced significantly higher rates of several comorbid neurologic, psychiatric and developmental conditions. Compared to GP, PKU was associated with significantly higher prevalence for numerous neuropsychiatric conditions, most notably for intellectual disability (PR = 7.9, 95% CI: 6.4–9.9), autism spectrum disorder (PR = 6.1, 95% CI: 3.6–10.4), Tourette/tic disorders (PR = 5.4, 95% CI: 2.1–14.1), and eating disorders (4.0, 95% CI: 3.2–5.0). Rates of fatigue/malaise, epilepsy/convulsions, sleep disturbance, personality disorders, phobias, psychosis, and migraines among those with PKU exceeded rates for the GP but were comparable to those with DM, with significantly lower rates of concomitant disorders occurring in younger, compared to older, adults with PKU. Lifelong monitoring and treatment of co-occurring neuropsychiatric conditions are important for effective PKU management.

1. Introduction

Phenylketonuria (PKU) is an inherited deficiency in the phenylalanine hydroxylase (PAH) enzyme caused by one of >950 gene variants [1]. These variants can result in a mildly, moderately, or severely defective PAH enzyme with subsequent benign, slightly elevated, or severely elevated blood phenylalanine (Phe), respectively. Newborn screening for PKU was initiated in the 1960′s in the U.S. after the development of an assay to detect blood Phe [2]. Since then, newborn screening and early initiation of treatment with a Phe-restricted diet and Phe-free medical foods have successfully ameliorated or prevented severe neurological and neurocognitive impairments [3–4].

Phenylalanine is an essential amino acid that is present in most natural protein foods. Dietary treatment recommendations for PKU are designed to promote physical growth and normal neurocognitive development [5]. Even with Phe-restrictive dietary recommendations for all age groups, evidence suggests that PKU management with diet alone has resulted in sub-optimal outcomes, including deficits in neurocognitive and psychosocial metrics, quality of life measures, nutritional deficits, and brain pathology [6]. Current treatment guidelines, based upon available clinical research, indicate that individuals with PKU should maintain lifelong metabolic control with blood Phe levels between 120 and 360 μmol/L, which is typically achieved by strict adherence to a Phe-restricted diet and dietary supplementation with Phe-free amino acid fortified medical foods [7–9].

Abbreviations: PKU, Phenylketonuria; PAH, Phenylalanine hydroxylase; Phe, Phenylalanine; DM, Diabetes Mellitus; GP, General population; OCD, Obsessive Compulsive Disorder; GMC, General Medical Condition; ADD/ADHD, Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder; PR, Prevalence ratio; ICD-9, International Classification of Diseases, Ninth Revision.

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Maintaining a Phe-restricted diet that ensures blood Phe levels within recommended guidelines represents a significant burden on quality of life, and adherence is a major medical problem [10]. With limited therapeutic alternatives, many adults with PKU are not adherent to dietary treatment and their blood Phe exceeds the recommended range. For example, Walter et al. found that a majority of adolescents and young adults were not adherent with recommendations for the monitoring and control of blood Phe [11] and, in a recent survey, Brown et al. reported that more than half (51.7%) of respondents were having difficulty managing their PKU, including the maintenance of a Phe-restricted diet [12]. In addition, Berry et al. estimated that 71% of adults with PKU in the US between the ages of 19 and 45 years, who were diagnosed by newborn screen, are not actively treated by a metabolic clinic [13]. This lack of clinical follow-up is presumed to be an interaction of multiple factors and may, in part, reflect the impact of the continuing evolution of treatment practices and guidelines since the initiation of newborn screening. Difficulties accessing metabolic centers and/or lack of insurance coverage also likely contribute to the nonadherence of treatment recommendations. The National PKU Alliance, a patient and caregiver organization focused on supporting the management of PKU, may help to improve lifelong care of these individuals [12].

High blood Phe leads to both acute and chronic neuropsychiatric symptoms [7–9]. Impairment in psychiatric, behavioral, and neurocognitive function often reflect the timing, duration, and intensity of Phe exposure in addition to the emotional burden of having a chronic disorder [14–19]. Because newborn screening was not implemented before the early-to-mid 1960′s, majority of adults with PKU > 55 years of age reflect 'late diagnosed' individuals who did not have the opportunity for early diagnosis. In addition, because treatment targets have tightened over the proceeding decades, younger aged cohorts (e.g., individuals with PKU < 40 years of age) would more likely be expected to have maintained treatment for life, had increased opportunity for continuous treatment, and, subsequently, may have less comorbidity compared to older cohorts (e.g., individuals with PKU ≥ 40 years old). Indeed, studies published in the last 15 years of individuals with PKU, who were clinically managed from birth, have demonstrated intellectual abilities predominantly in the normal range [20–21]. However, even with continuous clinical management, neuropsychological, psychosocial, academic, and/or neuropsychiatric impairments have been observed in clinically treated cohorts [22–24].

Studies of adult outcomes associated with early-treated PKU have identified increased rates of symptoms and impairment related to mood, anxiety, hyperactivity/inattention, and executive functioning [24–29]. Burton et al. found that 53% of adults with PKU screened positive for the presence of clinically significant psychiatric symptoms [30]. Unlike the general population and other studies of chronic illness, the age of individuals with PKU is positively correlated with the presence and intensity of psychiatric symptoms [16]. Even with early treatment, PKU in adulthood has also been associated with recurrent headaches, neurological signs, seizures, and tremor, to a greater degree in those with a history of early discontinuation of treatment [31–35]. More contemporary studies have reported modest rates of seizures and/or tremor in this population [36–37].

The purpose of the current study is to investigate the prevalence and prevalence ratios (PR) of neuropsychiatric disorders in a large, population-based sample of adults with PKU. This study uses an insurance claims database to: (1) measure the prevalence of neuropsychiatric disorders in adults with PKU and (2) determine the PRs of these conditions when compared to matched cohorts within the general population (GP) and adults with diabetes mellitus (DM). DM is a chronic disorder that also includes dietary intake restrictions and frequent blood monitoring for routine management.

2. Methods

This retrospective cohort study used three MarketScan® Research Databases which provided healthcare claims data for US-based employer and government-sponsored health plans for the years 2006 to 2012. These databases did not include claims for uninsured individuals. Diagnoses were based on the International Classification of Diseases, Ninth Revision (ICD-9), Clinical Modification (CM) Codes. During this timeframe, ICD-9-CM was the official system of assigning codes to diagnoses associated with hospital utilization in the United States (http://www.cdc.gov/nchs/icd/icd9cm.htm). Individuals were identified using at least 1 PKU claim in the years 1995 to 2012. To be included in this study, individuals in the database must have been ≥20 years of age in 2006 to prevent inclusion of presumptive positive individuals who may have been miscoded during the newborn screening period and reflect diagnostic codes used during adulthood.

Adults with PKU (ICD-9 code 270.1) were matched for age, gender, geographic region (Northeast, Midwest, South, West) and insurance type (commercial, Medicare, Medicaid) to both diabetes mellitus (DM) and general population (GP) cohorts, achieving approximately 1:2 and 1:6 ratios, respectively. Patients with DM were identified with at least one claim of ICD-9 code 250 and all related 250 sub codes (Diabetes Mellitus Type 1 or Type 2) and zero concomitant claims of PKU. The GP cohort was drawn from the complete data set, excluding claims of PKU. These groups were stratified by age (i.e., 20–29, 30–39, 40–49, 50–59, 60–69, and 70+ years. The combined subset of 20–39 year olds was analyzed to provide evaluation of outcomes of an adult cohort most likely to have had PKU diagnosed at birth through newborn screening, early-initiation of dietary treatment, and increased likelihood of having had the opportunity for "early and continuous treatment" rather than merely "early treatment" for PKU [38].

2.1. Statistical analyses

Patients with an ICD-9 diagnostic code 270.1 (Phenylketonuria - PKU) in the MarketScan® Research Databases were included in the PKU cohort analysis. Only adjudicated data up to and including 2012 were included. A prevalence ratio (PR) was used to compare comorbidity prevalence between the PKU, DM, and GP cohorts. Because the PR across age cohorts did not follow a normal distribution, corresponding 95% confidence intervals (CI) for each PR were based on the natural log of each comparison. Statistical differences for prevalence rates among and between age groups were determined by Chi-square analysis. An alpha level of 0.05 was assumed for all statistical tests.

2.2. Prevalence of neuropsychiatric disorders

Neuropsychiatric diagnoses were assessed by ICD-9 codes (Supplemental File 1) on database claims for study cohorts and included attention-deficit hyperactivity disorder (ADD/ADHD), alcohol dependency, anxiety, autism spectrum disorder, bipolar disorder, depression, eating disorder, epilepsy and convulsion, fatigue and malaise, intellectual disability, migraine and headache, movement disorders, Parkinson's, tremor, obsessive-compulsive disorder (OCD), pain disorder, personality disorder, and Tourette syndrome/tic disorder among others. Disorders included in the study were pre-defined by the authors based on PKU comorbidities reported in the medical literature and clinical experience. The corresponding ICD-9 codes for each disorder were defined by at least 2 experts familiar with ICD-9 coding for neuropsychiatric diagnoses.

2.3. Sensitivity analyses and estimation of error

To include as many individual records as possible, data were analyzed without restricting total enrollment time in the database. A sensitivity analysis was then performed for individuals with no minimum enrollment time in the database and those with a minimum of six, twelve, and eighteen months of total enrollment time in the database. In addition, an analysis of the individuals meeting all inclusion criteria with 2 or more PKU diagnosis codes (270.1) in the database between 1995 and 2012 were evaluated.

Table 1
Mean age and number of individuals in phenylketonuria, diabetes mellitus and general population cohorts matched for age, gender, and insurance type.

	PKU cohort[a]	DM cohort[b]	GP cohort[c]
Patients, n	3714	7060	22,726
Mean age, years	38.5	38.1	41.3
Age cohorts			
Mean age ± SD, n (%)			
20–29	25 ± 2.8, 1297 (35%)	25 ± 2.8, 2399 (34%)	25 ± 2.8, 6613 (29%)
30–39	34 ± 2.8, 945 (25%)	34 ± 2.8, 1935 (27%)	34 ± 2.9, 5368 (24%)
40–49	44 ± 2.9, 593 (16%)	44 ± 2.9, 1152 (16%)	44 ± 2.8, 4079 (18%)
50–59	54 ± 3.0, 525 (14%)	54 ± 2.9, 1022 (14%)	54 ± 2.9, 3494 (15%)
60–69	63 ± 2.6, 222 (6%)	63 ± 2.5, 403 (6%)	63 ± 2.5, 1867 (8%)
70–79	73 ± 2.6, 86 (2%)	74 ± 2.8, 100 (1%)	74 ± 2.7, 760 (3%)
80+	84 ± 3.7, 46 (1%)	85 ± 3.2, 49 (1%)	86 ± 3.8, 545 (2%)
Gender, n (%)			
Male	1410 (38.0)	2719 (38.5)	8992 (39.6)
Female	2304 (62.0)	4341 (61.5)	13,734 (60.4)
Insurance, n (%)			
Employer	2841 (76.5)	5722 (81.0)	15,274 (67.2)
Government	873 (23.5)	1338 (19.0)	7452 (32.8)

[a] Patients with phenylketonuria (ICD-9 diagnostic code 270.1).
[b] Patients with diabetes mellitus type 1 or type 2 (ICD-9 code 250 and all related 250 sub codes).
[c] General population patients.

3. Results

3.1. Population characteristics

A total of 3714 individuals with PKU were identified within the claims database and matched for age, gender, geographic location and insurance type to 7060 individuals with DM and 22,726 individuals in the GP (Table 1). The majority of the individuals were ≤40 years of age with a similar mean age across, and within, age-grouped cohorts. Females outnumbered males by 1.6 times in each cohort. The majority of individuals were commercially insured.

3.2. Estimated prevalence and prevalence ratios of medical diagnoses for overall adult cohort with PKU

Table 2 compares adults with PKU with those in DM and GP cohorts matched by age, gender, geographical location and insurance type. Prevalence of comorbidities in the PKU cohort is significantly higher than the GP cohort for all neuropsychiatric diagnoses investigated except multiple sclerosis, substance abuse, and alcohol dependency. Disorders with particularly high prevalence ratios (PR ≥ 4.0) associated with PKU, when compared to GP are intellectual disability, autism spectrum disorder, Tourette/tic disorders, and eating disorders.

When compared to the DM cohort, the PR associated with PKU is significantly higher for intellectual disabilities, autism spectrum disorder, eating disorders, OCD, Tourette/tic disorder, behavior/conduct disorder, cognitive and/or personality changes secondary to a general medical condition, and dementia. When compared to PKU, DM is associated with a higher prevalence for bipolar disorder, substance abuse, and alcohol dependency.

Table 2
Estimated prevalence and prevalence ratios for medical diagnoses for individuals with phenylketonuria compared to matched cohorts with diabetes mellitus and the general population.

	Phenylketonuria (PKU)		Diabetes mellitus		General population controls		PKU/diabetes prevalence ratio		PKU/general prevalence ratio	
Category	N	%	N	%	N	%	PR[d]	95% CI	PR[d]	95% CI
Total patients	3714	100%	7060	100%	22,726	100%				
Intellectual disabilities	179	4.8	51	0.7	138	0.6	6.7*	(4.9–9.1)	7.9*	(6.4–9.9)
Autism spectrum disorder	27	0.7	10	0.1	27	0.1	5.1*	(2.5–10.6)	6.1*	(3.6–10.4)
Tourette/Tic disorders	8	0.2	4	0.1	9	0.0	3.8*	(1.1–12.6)	5.4*	(2.1–14.1)
Eating disorders	128	3.4	135	1.9	195	0.9	1.8*	(1.4–2.3)	4.0*	(3.2–5.0)
OCD[a]	40	1.1	32	0.5	63	0.3	2.4*	(1.5–3.8)	3.9*	(2.6–5.8)
Behavior/conduct	76	2.0	67	0.9	127	0.6	2.2*	(1.6–3.0)	3.7*	(2.8–4.9)
Fatigue & malaise	54	1.5	77	1.1	133	0.6	1.3	(0.9–1.9)	2.5*	(1.8–3.4)
Movement disorders/Parkinson's/tremors	285	7.7	471	6.7	746	3.3	1.2	(1.0–1.3)	2.3*	(2.0–2.7)
Epilepsy & convulsions	194	5.2	338	4.8	515	2.3	1.1	(0.9–1.3)	2.3*	(2.0–2.7)
Cognitive and/or personality changes secondary to GMC[b]	137	3.7	181	2.6	386	1.7	1.4*	(1.2–1.8)	2.2*	(1.8–2.6)
Sleep disturbances	534	14.4	1011	14.3	1578	6.9	1.0	(0.9–1.1)	2.1*	(1.9–2.3)
Personality disorders	55	1.5	88	1.2	171	0.8	1.2	(0.9–1.7)	2.0*	(1.5–2.7)
Psychosis/schizophrenia	138	3.7	239	3.4	461	2.0	1.1	(0.9–1.3)	1.8*	(1.5–2.2)
ADD/ADHD[c]	79	2.1	117	1.7	280	1.2	1.3	(1.0–1.7)	1.7*	(1.3–2.2)
Anxiety	581	15.6	994	14.1	2091	9.2	1.1	(1.0–1.2)	1.7*	(1.6–1.9)
Phobias	23	0.6	51	0.7	81	0.4	0.9	(0.5–1.4)	1.7*	(1.1–2.8)
Migraine & headache	313	8.4	578	8.2	1134	5.0	1.0	(0.9–1.2)	1.7*	(1.5–1.9)
Depression	723	19.5	1490	21.1	2683	11.8	0.9	(0.9–1.0)	1.6*	(1.5–1.8)
Dementia	130	3.5	180	2.5	503	2.2	1.4*	(1.1–1.7)	1.6*	(1.3–1.9)
Pain disorders	2408	64.8	4604	65.2	10,009	44.0	1.0	(1.0–1.0)	1.5*	(1.4–1.5)
Bipolar disorder	151	4.1	365	5.2	657	2.9	0.8*	(0.7–0.9)	1.4*	(1.2–1.7)
Multiple sclerosis	17	0.5	49	0.7	74	0.3	0.7	(0.4–1.1)	1.4	(0.8–2.4)
Substance abuse	90	2.4	247	3.5	516	2.3	0.7*	(0.5–0.9)	1.1	(0.9–1.3)
Alcohol dependency	72	1.9	201	2.8	458	2.0	0.7*	(0.5–0.9)	1.0	(0.8–1.2)

* $p < 0.05$.
[a] OCD, Obsessive Compulsive Disorder.
[b] GMC, General Medical Condition.
[c] ADD/ADHD, Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder.
[d] PR, prevalence ratio.

Table 3
Estimated prevalence and prevalence ratio for diagnoses among 20- to 39-year-old cohort with phenylketonuria compared to diabetes mellitus and general population cohorts matched by age, gender, geographical location and insurance carrier.

	Phenylketonuria (PKU)		Diabetes mellitus		General population controls		PKU/diabetes prevalence ratio		PKU/general prevalence ratio	
Category	N	%	N	%	N	%	PR[d]	95% CI	PR[d]	95% CI
Total patients	2242	100%	4334	100%	11,981	100%				
Tourette/Tic disorders	6	0.3	3	0.1	5	0.0	3.9	(0.92–16.13)	6.8*	(2.06–22.1)
Autism spectrum disorder	15	0.7	9	0.2	15	0.1	3.2*	(1.4–7.29)	5.2*	(2.52–10.53)
Eating disorders	59	2.6	71	1.6	67	0.6	1.6*	(1.15–2.24)	4.7*	(3.32–6.64)
Intellectual disabilities	43	1.9	31	0.7	65	0.5	2.7*	(1.74–4.08)	3.6*	(2.43–5.21)
OCD[b]	21	0.9	24	0.6	35	0.3	1.7*	(1.02–2.87)	3.2*	(1.89–5.56)
Cognitive and/or personality changes secondary to GMC[c]	30	1.3	61	1.4	51	0.4	1.0	(0.66–1.38)	3.1*	(1.99–4.88)
Behavior/conduct	30	1.3	52	1.2	60	0.5	1.1	(0.77–1.62)	2.7*	(1.73–4.14)
Movement disorders/Parkinson's/tremors	73	3.3	160	3.7	167	1.4	0.9	(0.71–1.09)	2.3*	(1.79–3.08)
Fatigue & malaise	22	1.0	41	1.0	54	0.5	1.0	(0.69–1.55)	2.2*	(1.33–3.57)
Phobias	16	0.7	35	0.8	46	0.4	0.9	(0.57–1.36)	1.9*	(1.06–3.29)
Dementia	13	0.6	35	0.8	38	0.3	0.7	(0.45–1.13)	1.8	(0.97–3.4)
Sleep disturbances	202	9.0	470	10.8	587	4.9	0.8*	(0.74–0.93)	1.8*	(1.58–2.14)
ADD/ADHD[a]	64	2.9	93	2.2	203	1.7	1.3*	(1.04–1.69)	1.7*	(1.28–2.23)
Psychosis/schizophrenia	40	1.8	105	2.4	128	1.1	0.7*	(0.57–0.95)	1.7*	(1.17–2.37)
Anxiety	309	13.8	599	13.8	1053	8.8	1.0	(0.91–1.1)	1.6*	(1.39–1.76)
Depression	366	16.3	854	19.7	1217	10.2	0.8*	(0.76–0.9)	1.6*	(1.44–1.79)
Migraine & headache	194	8.7	399	9.2	657	5.5	0.9	(0.83–1.06)	1.6*	(1.35–1.84)
Epilepsy & convulsions	54	2.4	203	4.7	182	1.5	0.5*	(0.42–0.63)	1.6*	(1.17–2.14)
Pain disorders	1286	57.4	2585	59.6	4605	38.4	1.0*	(0.93–0.99)	1.5*	(1.43–1.56)
Personality disorders	22	1.0	57	1.3	86	0.7	0.7	(0.53–1.04)	1.4	(0.85–2.17)
Multiple sclerosis	6	0.3	22	0.5	23	0.2	0.5*	(0.3–0.95)	1.4	(0.58–3.49)
Bipolar disorder	83	3.7	235	5.4	347	2.9	0.7*	(0.58–0.8)	1.3*	(1.01–1.61)
Substance abuse	47	2.1	167	3.9	288	2.4	0.5*	(0.45–0.66)	0.9	(0.64–1.19)
Alcohol dependency	26	1.2	113	2.6	183	1.5	0.4*	(0.35–0.56)	0.8	(0.5–1.14)

* $p < 0.05$.
[a] ADD/ADHD, Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder.
[b] OCD, Obsessive Compulsive Disorder.
[c] GMC, General Medical Condition.
[d] PR, prevalence ratio.

3.3. Prevalence and prevalence ratio of medical diagnoses for 20- to 39-year-old cohorts

Table 3 describes the comparison between adults aged 20 to 39 years with PKU, DM, and the GP. This age cohort coincides with birth after the initiation of newborn screening and is more likely to have had opportunities for continuous PKU treatment and/or recommendations to maintain a Phe-restricted diet for life.

Compared to the GP cohort in this age range, the PR for the PKU group is significantly higher for 19 of the neuropsychiatric and neurocognitive comorbid conditions. The PKU and GP cohort do not differ significantly for five comorbid conditions.

Compared to the DM cohort in this age group, the PR for the PKU group is significantly higher for five conditions: autism spectrum disorder, eating disorders, intellectual disabilities, ADD/ADHD, and OCD. The PR for the PKU cohort is significantly lower than the DM cohort for 9 conditions, and the two cohorts are similar in PR for 10 conditions.

3.4. Prevalence of intellectual disabilities as a function of age

Rates of intellectual disability for adults with PKU are significantly higher overall (4.8% vs. 0.6%, $p < 0.0001$) when compared to the matched GP cohort. Fig. 1 shows significantly higher rates of intellectual disability for the PKU cohort compared to the GP cohort for all age groups ($p < 0.0001$).

Fig. 1 shows that rates of intellectual disability among adults with PKU compared to DM are significantly higher in cohorts 40–49, 50–59, and 60–69 years of age ($p < 0.0001$) and cohorts 20–29, 30–39, and 70+ years of age ($p = 0.002$). Rates of intellectual disability do not differ significantly between any of the GP and DM cohort age groups.

3.5. Prevalence of anxiety as a function of age

Rates of anxiety disorders are significantly higher in the overall adult PKU cohort compared to the GP cohort (15.6% vs. 9.2%, $p = 0.0001$). Fig. 2 shows that rates of anxiety among adults with PKU compared to the GP differ significantly for cohorts 20–29, 30–39, 40–49, 50–59, and 60–69 years of age ($p < 0.0001$); and the cohort 70+ years of age ($p = 0.003$).

Rates of anxiety disorders are significantly higher in the overall adult PKU cohort compared to DM (15.6% vs. 14.1%, $p = 0.03$), and significantly higher rates of anxiety disorders are associated with PKU compared to DM in the following age cohorts: 40–49 years of age (21.3% vs. 16.6%, $p = 0.017$) and 60–69 years of age (14.9% vs. 8.2%, $p = 0.009$).

3.6. Prevalence of depression as a function of age

Rates of depression are significantly higher in the overall adult PKU cohort compared to the GP cohort (19.5% vs. 11.8%, $p < 0.0001$). Fig. 3 shows significantly higher rates of depression for the PKU cohort compared to the GP cohort for the following age groups: 20–29, 30–39, 40–49, and 50–59 years ($p < 0.0001$); 60–69 years ($p = 0.0004$); and 70+ years ($p = 0.0001$).

PR for depression is significantly lower for the overall adult PKU cohort compared to the DM cohort (19.5% vs. 21.1%; $p = 0.046$). Rates of depression associated with PKU compared to DM are also significantly lower in the 20–29 year-old cohort ($p = 0.008$), though the remaining PKU versus DM age group comparisons do not differ significantly.

3.7. Adults with 1 PKU diagnosis code compared to adults with 2 + PKU diagnosis codes

The prevalence and PRs for individuals with a minimum 6 month enrollment, 12 month enrollment, and 18 month enrollment in the

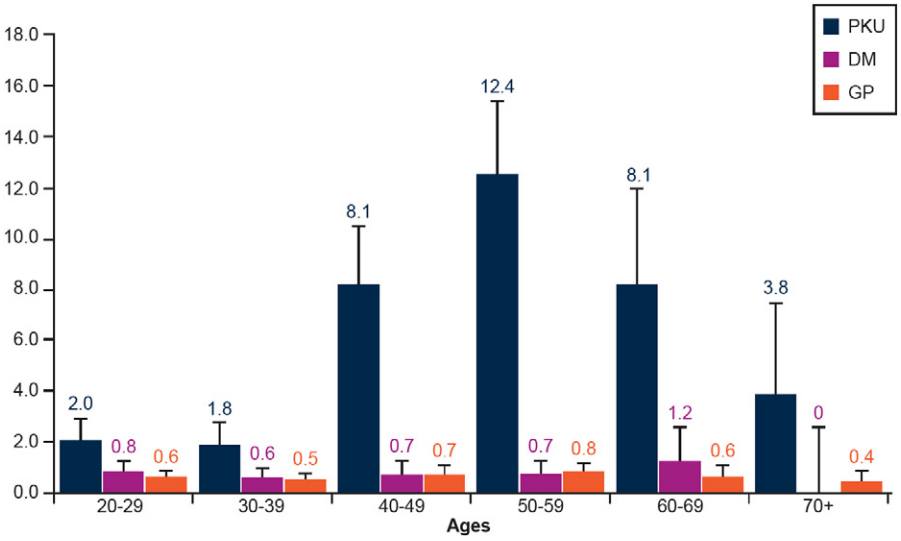

Fig. 1. Prevalence of intellectual disability among adults with phenylketonuria (PKU), diabetes mellitus (DM), and within the general population (GP)[a]. Error bar depicts the upper 95% confidence interval.

database are comparable for all diagnostic conditions. When adults with a single PKU diagnostic code (N = 2676) are compared to individuals with two or more PKU diagnostic codes (N = 1038), prevalence data for 10 of the 24 comorbid conditions differ significantly (Supplemental File 2), revealing significantly higher rates of intellectual disabilities, epilepsy/convulsions, ADD/ADHD, OCD & autism spectrum disorders but significantly lower rates of substance abuse, pain disorders, sleep disturbances, fatigue/malaise in adults with ≥2 PKU codes compared to those with only a single PKU code.

4. Discussion

The findings of the current study suggest that PKU is associated with a significantly higher prevalence for multiple comorbid neuropsychiatric and developmental conditions when compared to adults in the general population or adults treated for diabetes. When matched for general demographic variables, including age, gender, geographical location and type of insurance, adults with PKU were more likely to have diagnoses of intellectual disability, autism spectrum disorder, Tourette/tic disorders, eating disorders and behavior/conduct disorder than adults in the general population, and had higher rates of a range of other conditions or disorders as well. Significant differences in prevalence rates between the PKU and general population persisted even after the sample was restricted to younger adults (aged 20–39 years) who were most likely to have been diagnosed with PKU at birth, treated throughout childhood, and had opportunities for continuous treatment along with recommendations to remain on treatment throughout life. The substantial effect of the initiation of newborn screening and early and continuous treatment for individuals with PKU is readily apparent in the lower prevalence of numerous comorbid neurological and neurocognitive impairments in the youngest PKU subgroup (20–39 years old) when compared to the overall PKU cohort.

Current findings reveal that, across all analyzed age groups, adults with PKU have an increased risk for intellectual disabilities. While a large body of research suggests that the majority of early and continuously treated individuals with PKU perform within the normal range of intellectual functioning, clinical investigations have found an inverse relationship between blood Phe and intellectual performance [8,10] and individuals with PKU generally have lower cognitive functioning when compared to matched control groups [22,39] and sibling controls [40]. Similarly, although occurring at a very low rate, the prevalence for autism spectrum disorder, which has previously been associated with

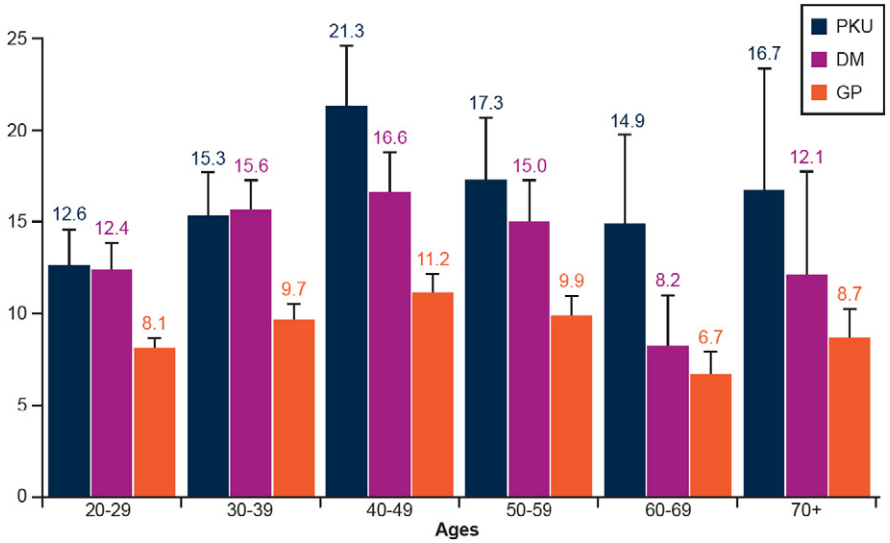

Fig. 2. Prevalence of anxiety disorders for adults with phenylketonuria (PKU), diabetes mellitus (DM), and general population (GP)[a]. [a] Error bar depicts the upper 95% confidence interval.

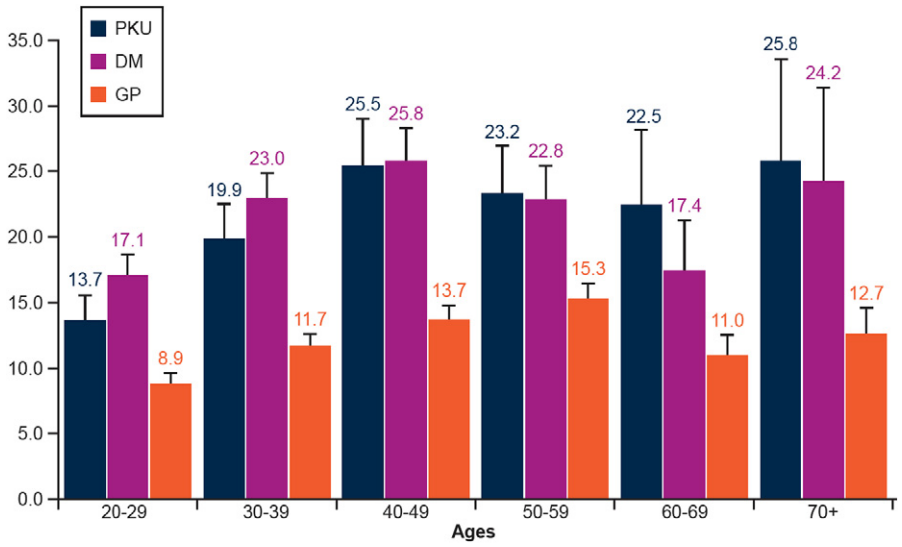

Fig. 3. Prevalence of depression among adults with phenylketonuria (PKU), diabetes mellitus (DM), and in the general population (GP)[a]. [a] Error bar depicts the upper 95% confidence interval.

late diagnosed/untreated PKU [41–43], was found to be higher in adults with PKU than in the general population, even in the youngest 20 to 39 year old subgroup. This discrepancy may reflect the impact of treatment history, which was not available for this study. Thus, we cannot exclude the possibility that some of the adults 20 to 39 years old had untreated PKU, a late diagnosis, or were treatment non-adherent. This finding supports the critical importance of monitoring early treatment carefully. Autism spectrum disorder characteristics may also be more common than previously considered based on findings within this population-based cohort of young to middle-aged adults with early-treated PKU. The presence of co-occurring intellectual disability and/or autism spectrum disorder increases susceptibility to neuropsychiatric conditions and hinders the identification of these conditions because of their associated limitations in verbal communication [44–45]. The degree to which co-occurring intellectual disability and autism spectrum disorder may impact other neuropsychiatric comorbidity found in this study is an important consideration, particularly for older cohorts who were less likely to have early- and/or continuously-treated PKU.

Neuropsychological sequelae associated with PKU have been attributed to biological mechanisms. These include direct toxicity from hyperphenylalaninemia [46], impaired transport of large neutral amino acids across the blood-brain barrier (i.e., tryptophan [serotonin precursor] and tyrosine [dopamine precursor]) [47–48], subsequent neurotransmitter depletion (e.g., dopamine, serotonin) [49–52], reduced volume of specific brain structures [33], the toxic effects of high Phe levels on white matter [53–56], and decreased functional connectivity of neural networks [57]. The contributions of these various phenomena to the neuropsychiatric symptoms and cognitive impairments associated with PKU are unclear and merit further study.

PKU and DM are chronic disorders that include dietary intake restrictions and blood monitoring as core features of management. Although significantly exceeding that of the GP, the prevalence of fatigue/malaise, epilepsy/convulsions, sleep disturbance, and migraines in the DM cohort are comparable to adults with PKU, with these findings persisting for fatigue/malaise and migraines in the younger cohorts. Koch et al. also reported the presence of recurrent headaches and lethargy in early-treated adults who participated in the initial PKU collaborative study [3] while DM Type 1 and Type 2 have been associated with neuropathy [58–59], cardiovascular disease [58–59], cerebrovascular disease [58–59], and renal disease [60].

Consistent with previous studies, rates of depression and anxiety are significantly higher among adults with PKU and DM when compared to the GP [15,61–63] perhaps in part reflecting a combination of neurobiological factors as well as the psychosocial impact and stress of living with, and managing, a chronic medical condition. A pediatric comparison study of PKU and Type 1 DM also found higher than expected rates of depression, anxiety, and physical complaints associated with both disorders [14]. When comparing adults with PKU to those with DM, the current study demonstrated a significantly higher prevalence of anxiety disorders associated with PKU overall and within two age cohorts while depressive disorders was significantly more common overall and within one age cohort among adults with DM. Future studies that provide in-person assessments of adults with PKU and DM are merited to understand what components of these conditions may contribute to differences in the experience of anxiety and depression between these two groups.

A high prevalence of disordered eating symptomatology was previously described in a comparison study between adolescents and young adult females with early-treated PKU and Type I DM with comparable rates demonstrated by both groups [18]. In contrast, current findings indicate a higher prevalence of eating disorders associated with PKU when compared to DM. The discrepancy in studies' findings may reflect differences between study designs, including individual ascertainment versus use of claims database, assessment of disordered eating symptomatology, sample size, age/gender distribution, and DM type. The dietary management of Type 1 DM approximates PKU more than Type 2 DM, while a large majority of adults in our DM cohort had Type 2 DM.

To our knowledge, this is the largest study examining neuropsychiatric diagnoses in the PKU population conducted to date. While these Marketscan data are representative of a commercially insured population, there are limitations. Some of the limitations relate to the nature of database claims, which are subject to coding errors, miscoding (for the purpose of rule-out rather than actual disease), and under-coding. This database did not include information regarding treatment for the uninsured (e.g., individuals without health insurance, those receiving pro-bono medical care, or those who directly paid their medical and/or mental health providers). There were approximately 50.0 to 48.6 million uninsured individuals in the United States between 2010 and 2011 [64], which precedes our 2012 inclusion end date for this study. The recent implementation of universal health care coverage in the United States occurred after the study's inclusion period ended. The inherent absence of adults without insurance in this analysis is a clear limitation to its generalizability because access to medical and mental health care services and treatment is limited by the absence of insurance coverage [65]. Although Berry et al. estimated that >70% of adults 19–45 years

of age with PKU were no longer seen in a metabolic clinic [13], PKU may be captured among their billing codes from other healthcare provider visits, particularly if PKU relates to the chief complaint or medical decision making surrounding the medical visit. The measured prevalence of intellectual disability (0.6%) and autism spectrum disorder (0.1%) in our GP cohort is less than previously established rates (1.5% and 1.2%, respectively) using population-based education and health records [66–67]. This discrepancy may reflect the limitations of using medical billing codes to study developmental conditions for which assessment and treatment are generally not reimbursed or are performed primarily through the public education system. Thus, prevalence ratios measured for these conditions are likely underestimated across our adult cohorts and merit further investigation within population-based samples specifically ascertained for intellectual disability and/or autism spectrum disorder. Furthermore, PKU treatment history (early, late, or untreated) and even current treatment status and Phe levels are not available for consideration in interpreting current study results. The claims database analysis included individuals with at least one PKU code because our data revealed considerably higher comorbidity rates among individuals when limiting the cohort to those with two or more codes, suggesting a bias toward individuals who are seen more frequently, possibly as a result of higher comorbidity. Although use of a claims-based data may have included miscoded individuals, it is also inclusive of healthier individuals, further supporting a conservative methodology. With regards to participant demographics, the claims data selected for this study are skewed toward younger females (there are approximately 1.6 times as many females as males in each of the three pre-defined PKU, GP, and DM cohorts in the database) that may reflect increased medical care utilization by women [68]. Women of reproductive age with PKU also face concerns surrounding maternal PKU syndrome that may prompt increased access to healthcare [69].

Lifelong management of PKU is recommended by the 2014 American College of Medical Genetics and Genomics clinical practice guidelines [7]; however, prior studies suggest that many individuals with PKU experience a deterioration of care (e.g., dietary adherence, blood Phe control, and clinic attendance) during transition from adolescence to adulthood [11,13,34]. Given the low incidence of PKU, psychiatrists and psychologists may not be aware of the neuropsychiatric comorbidities associated with this disorder [70]. A number of neurocognitive and psychological tests, and regular mental health monitoring, have been recommended for individuals with PKU [5,7,9]. Improving awareness about common neuropsychiatric comorbidity experienced by adults with PKU may facilitate monitoring, detection, and treatment of these disorders in this population.

5. Conclusions

This study highlights, on a population-based level, a marked reduction in the prevalence of intellectual disabilities and other neurologic and psychiatric conditions coinciding temporally with the initiation of newborn screening and the evolution of treatment practices and guidelines. Despite these successes, findings of this study also demonstrate increased risk for multiple neuropsychiatric conditions among adults with PKU that is comparable to, or in excess of, those experienced by adults with DM, another chronic disorder that includes dietary intake restrictions and blood monitoring as core features of management. These results support the inclusion of neuropsychiatric screening into the routine care of adults with PKU and access to mental health professionals who can assist with diagnosis, monitoring and management of concomitant conditions and disease burden associated with PKU.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ymgme.2017.03.002.

Disclosures

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