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Estimated prevalence of moderate to severely elevated total homocysteine levels in the United States: A missed opportunity for diagnosis of homocystinuria?

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ABSTRACT

Classical homocystinuria (HCU) is a genetic disorder caused by mutations in the cystathionine beta synthase gene, which results in impaired metabolism of the sulfur-bearing amino acid homocysteine and its accumulation in blood and tissues. Classical HCU can be detected via newborn screening in the United States, but the test is widely acknowledged to miss many patients. While severely elevated homocysteine levels (> 100 μmol /L) frequently lead to a classical HCU diagnosis, intermediate levels (> 30 to 100 μmol /L), though linked to many of the known complications of HCU, are not always recognized as associated with HCU. We aimed to identify and describe potentially undiagnosed classical HCU patients using a nationally-representative database of administrative claims and laboratory results. We estimated the national prevalence of patients with homocysteine > 30 μmol /L, and compared their demographic and clinical characteristics to those of patients with homocysteine levels ≤30 μmol/L. Among 57,580 patients with a homocysteine test result, 1.8% had a value > 30 μmol /L. Patients with homocysteine > 30 μmol /L were more frequently diagnosed with hypothyroidism (39.2% vs. 20.7%, $p < .001$) and renal disease (9.7% vs. 5.5%, $p < .001$), and were more likely to have a prescription for an anxiolytic/antidepressant (44.5% vs. 38.9%), opioid (58.4% vs. 53.1%), steroid (46.4% vs. 42.5%), or thyroid hormone (38.8% vs. 18.8%), compared to patients with homocysteine ≤30 μmol /L (all $p < .05$). Both groups were equally likely to have a diagnosis of homocystinuria or another disorder of sulfur-bearing amino acid metabolism (3.8% vs. 4.0%, $p = .752$). The age-adjusted national prevalence of homocysteine > 30 μmol /L was estimated at 33,068 (95% CI: 1033 - 35,104). These findings suggest that thousands of people in the US may be living with intermediate to severely elevated homocysteine levels and may require further evaluation for the presence of classical HCU.

1. Introduction

Hyperhomocysteinemia has been classified into moderate, intermediate, and severe types, based on the level of tHcy in the blood, with moderate levels generally defined as 15 to 30 μmol/L, intermediate as greater than 30 to 100 μmol /L, and severe as greater than 100 μmol/L [1]. Classical HCU is a rare inherited genetic disorder caused by mutations in the CBS gene resulting in impaired metabolism of homocysteine and the accumulation of homocysteine and its related metabolites in urine, tissues, and plasma [2]. Diagnostically, classical HCU has been associated in the literature with severely elevated tHcy [3].

Complications of HCU have a variable presentation and can include ocular deficits, skeletal abnormalities, developmental delays/intellectual disability, and vascular abnormalities including thromboembolism [4]. Numerous studies have reported an association between intermediate elevations of tHcy and many of the abnormalities common to classical HCU [5–9], prompting the question of whether classical HCU has been underdiagnosed and misdiagnosed based on an overly narrow definition of relevant tHcy levels.

The majority of prevalence estimates for classical homocystinuria

Abbreviations: CBS, cystathionine beta synthase; HCU, homocystinuria; MTHFR, methylenetetrahydrofolate reductase; tHcy, total homocysteine

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are based upon newborn screening results. In the US, newborn screening for classical HCU is based on detection of increased methionine, a precursor to homocysteine, rather than tHcy itself, at an age when methionine levels may not be elevated yet in newborns with HCU [10–12]. It is widely acknowledged that this methodology is imperfect at best and may miss the majority of patients [3,13,14]. Patients missed during newborn screening may be detected later after they present with one or more symptoms or comorbidities indicative of HCU and confirmed with tHcy testing. As symptom manifestation, severity, and progression can vary between patients and mimic other disease states, there are significant risks of misdiagnosis and delayed diagnosis.

Recent research using administrative claims data estimated the prevalence of HCU in the US to be ~1 in 10,000 people [15]. This is substantially higher than prior estimates of 1 in 100,000–200,000 people [16–18] and may well reflect the insufficiency of current newborn screening methods. Although there are multiple disease states that are accompanied by tHcy elevations, few other than classical HCU give rise to intermediate to severe tHcy levels [3]. Of note, after the introduction of folic acid fortification in the United States, folate status and MTHFR polymorphisms became less prevalent causes of intermediate and severe tHcy levels, compared to pre-fortification years [3,19]. In this study, we describe the demographic and clinical characteristics of a national sample of patients who underwent tHcy testing and estimate the prevalence of patients in the US with intermediate to severely elevated tHcy levels (hyperhomocysteinemia). Intermediate to severe elevations in homocysteine levels may represent opportunities for the identification of previously undiagnosed homocystinuria patients.

2. Materials and methods

2.1. Study design and data sources

This observational retrospective analysis utilized US administrative claims data from IBM® MarketScan® Research Databases. The Commercial and Medicare databases contain enrollment data and health insurance claims across the continuum of care (e.g., inpatient, outpatient, outpatient pharmacy) for their respective covered populations, and together form a nationally-representative sample of insured individuals living in the US. The Commercial database includes data from large employers and health plans across the US who provide private healthcare coverage for employees, their spouses, and dependents under a variety of fee-for-service, preferred provider organizations, and capitated health plans. The Medicare database contains the healthcare experience of individuals with Medicare supplemental insurance paid for by employers. Both the Medicare-covered portion of (represented as Coordination of Benefits Amount) and the employer-paid portion are included in this database. The Lab Database contains laboratory test results for a subset of patients contained in the Commercial and Medicare databases and the laboratory results data are linked to the MarketScan claims data with approximately 8.4 million covered lives between 2006 and 2016. The lab data are contributed by large national medical laboratories that conduct testing of specimens collected in outpatient settings; therefore, no inpatient laboratory results are included in the Lab Database. The Commercial, Medicare and Lab databases have been linked and so all patients included in the current analysis are unique patients with no duplicate patients.

The MarketScan Research Databases were accessed via IBM MarketScan Treatment Pathways®, an online analytic interface that allows users to query the databases to identify patients with specific diagnoses, test results, procedures, and other clinical events, as well as to quantify healthcare resource use and costs. All study cohorts and variables were created and analyzed using the Treatment Pathways tool.

2.2. Study population

The study population consists of commercially-insured patients who underwent tHcy testing between January 1, 2006 and March 31, 2016 (study period). Patients with any result in the Lab database for tHcy testing in serum or plasma (LOINC 13965–9) during the study period were included. Patients were stratified based on the value of the first tHcy test result in the time period: ≤30 μmol/L or > 30 μmol/L.

2.3. Outcomes

Demographic characteristics were assessed on the date of the first eligible tHcy test and included age group (0–17, 18–34, 35–44, 45–54, 55–64, 65+), sex, geographic region (Northeast, North Central, South, West, unknown), and urban/rural residency.

The percentage of patients diagnosed with HCU or another disorder of sulfur-bearing amino acid metabolism at any time during their enrollment in the MarketScan databases was assessed by identifying International Classification of Diseases, 9th and 10th revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes on healthcare claims. Additionally, we assessed the percentage of patients who had an ICD-9 or ICD-10 diagnosis code for conditions commonly associated with HCU and the percentage of patients with at least one outpatient pharmacy claim for medications used to treat conditions commonly associated with HCU, at any time during the study period. Medications were identified using American Hospital Formulary Service (AHFS) therapeutic class categories. Assessed comorbid conditions included anxiety/depression, hyperlipidemia, hypertension, hypothyroidism, joint/limb pain, renal disease, and vitamin D deficiency. Assessed medication classes included antihypertensives, anxiolytics/antidepressants, folic acid and other B vitamins, lipid-lowering medications, non-opioid pain medications, opioids, steroids, thyroid hormones, and vitamin D.

The unadjusted national prevalence of tHcy > 30 μmol/L was estimated by calculating the number of patients per 1000 in the MarketScan databases with a tHcy test result > 30 μmol/L and then applying the MarketScan rate per 1000 to the overall US population on July 1, 2016 [20]. We then calculated the number of patients per 1000 in each age group in the MarketScan databases with a tHcy test result > 30 μmol/L, applied those rates to US age group populations, and summed those age group projections to estimate the age-adjusted national prevalence.

3. Results

3.1. Patient selection and tHcy levels

Of the 8.4 million patients included in the Lab Database, 57,580 patients (0.7%) had at least one tHcy test (valid result > 0) during the study period, and the mean (SD) tHcy level was 10.4 (12.1) μmol/L. Among these 57,580 patients, the first tHcy test result during the study period was > 30 μmol/L for 1014 (1.8%) unique patients. These patients were considered to have intermediate to severely elevated tHcy [1]. The mean (SD) tHcy level among patients with > 30 μmol/L tHcy was 75.3 (57.2) μmol/L, and the median was 74.0 μmol/L. Among the 56,566 patients (98.2%) whose first tHcy test value during the study period was ≤30 μmol/L, the mean (SD) tHcy level was 9.3 (3.7) μmol/L and the median was 8.7 μmol/L.

3.2. Demographic characteristics

Patients with a tHcy test result had a mean (SD) age of 47.6 (13.8) years at the time of their first eligible tHcy test (median age = 49 years). Patients with elevated tHcy were slightly younger than those with tHcy ≤30 (46.7 [12.9] vs. 47.6 [13.8] years, $p = .04$; Table 1). The proportion of tested patients who had tHcy > 30 μmol/L was, however, similar across all age groups (0–17: 1.6%; 18–34: 1.8%;

Table 1
Demographic characteristics of patients with a total homocysteine (tHcy) test result between January 1, 2006 and March 31, 2016.

	All Patients	tHcy ≤30 μmol/L	tHcy > 30 μmol/L	p-value[a]
	N = 57,580	*N* = 56,566	*N* = 1014	
Age group, N (%)				
0–17	1353 (2.3%)	1331 (2.4%)	22 (2.2%)	0.702
18–34	8855 (15.4%)	8700 (15.4%)	155 (15.3%)	0.934
35–44	11,278 (19.6%)	11,053 (19.5%)	225 (22.2%)	0.035
45–54	16,351 (28.4%)	16,037 (28.4%)	314 (31.0%)	0.067
55–64	16,420 (28.5%)	16,158 (28.6%)	262 (25.8%)	0.057
65+	3323 (5.8%)	3287 (5.8%)	36 (3.6%)	0.002
Sex, N (%)				
Male	21,911 (38.1%)	21,576 (38.1%)	335 (33.0%)	0.001
Female	35,669 (61.9%)	34,990 (61.9%)	679 (67.0%)	0.001
Geographic region, N (%)				
Northeast	18,949 (32.9%)	18,837 (33.3%)	112 (11.0%)	< 0.001
North Central	9883 (17.2%)	9736 (17.2%)	147 (14.5%)	0.023
South	23,748 (41.2%)	23,041 (40.7%)	707 (69.7%)	< 0.001
West	4991 (8.7%)	4943 (8.7%)	48 (4.7%)	< 0.001
Unknown	9 (< 0.1%)	9 (< 0.1%)	0 (0.0%)	0.688
Urban/rural residence, N (%)				
Urban	54,508 (94.7%)	53,581 (94.7%)	927 (91.4%)	< 0.001
Rural	3064 (5.3%)	2977 (5.3%)	87 (8.6%)	< 0.001
Unknown	8 (< 0.1%)	8 (< 0.1%)	0 (0.0%)	0.705

[a] Chi-squared tests compared patients with tHcy ≤30 μmol/L to patients with tHcy > 30 μmol/L.

35–44: 2.0%; 45–54: 1.9%; 55–64: 1.6%; 65+: 1.1%; data not shown), suggesting an underlying lifelong genetic condition contributing to a constant percentage of patients with elevated tHcy levels across age groups. Overall, the majority of patients (61.9%) were female, and patients with elevated tHcy were more likely to be female than those with tHcy levels ≤30 (67% vs. 62% female, $p < .001$). Among all patients with a tHcy test result, most lived in the southern (41.2%) or northeastern (32.9%) region of the US and 94.7% lived in urban areas. However, more patients with elevated tHcy lived in the south (69.7% vs. 40.7%, $p < .001$) and in a rural area (8.6% vs. 5.3%, $p < .001$), compared with those who had tHcy levels ≤30 μmol/L.

3.3. Clinical characteristics

The presence of various diagnoses commonly associated with classical HCU, as well as medications used to treat those conditions, was assessed throughout patients' entire enrollment history in the MarketScan databases that overlapped with the study period (January 1, 2006 through March 31, 2016; Table 2). Patients with elevated tHcy levels were significantly more likely than those with tHcy ≤30 μmol/L to have an antianxiety or antidepressant medication (44.5% vs. 38.9%, $p < .001$), opioids (58.4% vs. 53.1%, $p = .001$), or steroids (46.4% vs. 42.5%, $p = .014$). Patients with elevated tHcy were significantly more likely than those with tHcy levels ≤30 μmol/L to have a diagnosis of hypothyroidism (39.2% vs. 20.7%, $p < .001$) or a prescription for a thyroid hormone medication (38.8% vs. 18.8%, $p < .001$) during the study period. They were also significantly more likely to have a diagnosis of renal disease (9.7% vs. 5.5%, $p < .001$). Interestingly, patients with elevated tHcy were slightly less likely than those with tHcy levels ≤30 μmol/L to have a diagnosis of hyperlipidemia (47.8% vs 53.9%, $p < .001$), hypertension (42.3% vs 45.4%, $p = .047$), or stroke or other thrombosis (13.4% vs. 16.8%, $p < .01$), though they were more likely to have a prescription for an antihypertensive medication (43.1% vs. 39.5%, $p = .021$). Patients with a tHcy test result > 30 μmol/L were significantly more likely to have a prescription for folic acid or another B vitamin (11.3% vs. 9.5%, $p = .049$) or vitamin D (14.2% vs. 11.3%, $p = .004$) compared with patients who had tHcy levels ≤30 μmol/L. Notably, the rate of diagnosis of HCU or another disorder of sulfur-bearing amino acid metabolism was similar in patients with tHcy levels > 30 μmol/L and those with levels ≤30 μmol/L (3.8% vs. 4.0%, $p = .75$).

3.4. National prevalence of elevated tHcy

Estimates of the unadjusted age-specific prevalence, and age-adjusted prevalence of individuals with tHcy levels > 30 μmol/L in the US on July 1, 2016 are shown in Table 3. The estimated unadjusted total prevalence of elevated tHcy was 39,108 (95% CI: 36,701–41,515) and the age-adjusted prevalence was 31,466 (95% CI: 29,529–33,403). Nearly half (47%) of the age-adjusted cases were between 45 and 64 years old.

4. Discussion

This study identified and described a sample of patients with elevated tHcy levels. Few disease states give rise to intermediate to severe tHcy elevations other than classical HCU [3], especially since folic acid fortification of the food supply was introduced in the United States in 1998. Since then, the contribution of folate deficiency and MTHFR polymorphisms to intermediate and severe tHcy levels has decreased [3,19]. However, it is still likely that some of the elevations in tHcy observed here are attributable to other conditions, such as MTHFR defects and vitamin B_{12} deficiency, which were not examined in this study. Elevated tHcy levels are also associated with hypothyroidism and renal disease, and as expected, those diagnoses were assigned to almost half of the patients. Hypothyroidism, however, is generally associated with moderate elevations in tHcy (> 15 and < 30 μmol/L), rather than the intermediate to severe levels examined in this study [21–23], and less than 10% of study patients with tHcy > 30 had any claims with a diagnosis of renal disease. Additionally, more than half of patients with intermediate to severely elevated tHcy had at least 1 diagnosis indicative of cardiovascular disease (hyperlipidemia, hypertension, myocardial infarction, or stroke/thrombosis). Though the mechanisms of the relationship are still being investigated, there is evidence that elevated tHcy is a cause, rather than an effect, of cardiovascular disease [24]. Notably, a low percentage of patients with elevated tHcy were assigned a diagnosis of classical HCU or another disorder of sulfur-bearing amino acid metabolism, and the rates of these diagnoses were similar in patients with tHcy levels > 30 μmol/L and those with levels ≤30 μmol/L.

Patients with elevated tHcy were more likely than those with lower tHcy levels to have one or more prescriptions for medications used to treat conditions associated with classical HCU, including folic acid and other B vitamins and antihypertensives. Elevated tHcy was also associated with a greater prevalence of anxiolytic and antidepressant medications, which is consistent with evidence of high rates of anxiety, depression, and related disorders among classical HCU patients [25,26]. While patients with elevated tHcy levels were more likely than those with lower tHcy levels to have a prescription for folic acid and other B vitamins (11.3% vs 9.5%), most patients were not being prescribed therapeutics to address their elevated tHcy levels.

This is the first study to estimate the US prevalence of tHcy levels elevated at levels similar to those observed in patients with classical HCU. The estimated age-adjusted prevalence of 33,068 people in the US (~1 in 10,000) with tHcy levels > 30 μmol/L is consistent with a recent analysis estimating that ~31,000 people in the US have classical HCU

Table 2
Clinical characteristics of patients with a total homocysteine (tHcy) test result between January 1, 2006 and March 31, 2016.

	All Patients	tHcy ≤30 μmol/L	tHcy > 30 μmol/L	p-value[a]
	N = 57,580	N = 56,566	N = 1014	
Diagnoses, N (%)				
Anxiety/depression	18,929 (32.9%)	18,594 (32.9%)	335 (33.0%)	0.911
Homocystinuria or other disorder of sulfur-bearing amino acid metabolism	2326 (4.0%)	2287 (4.0%)	39 (3.8%)	0.752
Hyperlipidemia	30,987 (53.8%)	30,502 (53.9%)	485 (47.8%)	< 0.001
Hypertension	26,135 (45.4%)	25,706 (45.4%)	429 (42.3%)	0.047
Hypothyroidism	12,129 (21.1%)	11,732 (20.7%)	397 (39.2%)	< 0.001
Myocardial infarction	2203 (3.8%)	2157 (3.8%)	46 (4.5%)	0.234
Renal disease	3237 (5.6%)	3139 (5.5%)	98 (9.7%)	< 0.001
Stroke or other thrombosis	9660 (16.8%)	9524 (16.8%)	136 (13.4%)	0.004
Vitamin D deficiency	10,988 (19.1%)	10,776 (19.1%)	212 (20.9%)	0.136
Medications, N (%)				
Antihypertensives	22,797 (39.6%)	22,360 (39.5%)	437 (43.1%)	0.021
Anxiolytics/antidepressants	22,462 (39.0%)	22,011 (38.9%)	451 (44.5%)	< 0.001
Folic acid and other B vitamins	5494 (9.5%)	5379 (9.5%)	115 (11.3%)	0.049
Lipid-lowering medications	18,908 (32.8%)	18,598 (32.9%)	310 (30.6%)	0.121
Opioids	30,644 (53.2%)	30,052 (53.1%)	592 (58.4%)	0.001
Other cardiovascular medications	8106 (14.1%)	7964 (14.1%)	142 (14.0%)	0.946
Other pain medications	28,256 (49.1%)	27,746 (49.1%)	510 (50.3%)	0.432
Steroids	24,515 (42.6%)	24,045 (42.5%)	470 (46.4%)	0.014
Thyroid hormones	11,007 (19.1%)	10,614 (18.8%)	393 (38.8%)	< 0.001
Vitamin D	6524 (11.3%)	6380 (11.3%)	144 (14.2%)	0.004

[a] Chi-squared tests compared patients with tHcy ≤30 μmol/L to patients with tHcy > 30 μmol/L.

Table 3
Projected prevalence of elevated total homocysteine (> 30 μmol/L) in the United States.

	U.S. population[a]	Projected U.S. Prevalence of tHcy > 30 on 4/1/2016 N (95% CI)
All ages	323,127,513	39,108 (36,701 - 41,515)
Age groups		
0–11	48,632,077	682 (259–1105)
12–17	25,010,208	672 (292–1052)
18–24	30,843,811	1487 (972–2003)
25–34	44,677,243	3857 (3175 - 4538)
35–44	40,470,156	5683 (4941 - 6426)
45–54	42,786,679	7541 (6720 - 8363)
55–64	41,463,144	8172 (7182 - 9162)
65–74	28,630,330	3068 (1866 - 4271)
75–84	14,233,534	1107 (340–1874)
85+	6380,331	798 (105–1701)
Age-adjusted prevalence		33,068 (31,033 - 35,104)

[a] Estimates of the U.S. resident population on 7/1/2016.

based on ICD-10 diagnostic codes [15]. Both estimates are in line with prevalence reports using genetic analysis [3,27], and significantly higher than previously published estimates of the US prevalence of classical HCU [16–18].

The majority of patients with elevated tHcy in this study were middle-aged or older adults. While some of the patients identified in this study were born before the wide adoption of newborn screening for HCU in the US, it is widely acknowledged that such screening has severe limitations. Within each age decile of patients in this study, a remarkably similar percentage of patients had tHcy > 30 μmol/L, ranging from 1.08% to 2.0% of patients tested. This suggests that a tHcy value above 30 μmol/L is not just a condition of aging, but rather has other causes which may include genetic disorders. The lower prevalence of younger patients in this study may simply reflect the older age at which tHcy testing is routinely conducted. Given that classical HCU is a congenital condition, these data suggest the existence of a population of patients who have lived with manifestations of undiagnosed HCU for decades. This is consistent with the hypothesis that there is a substantial cohort of individuals with classical HCU symptoms that are misdiagnosed or underdiagnosed until later decades of life [28]. Routine homocysteine testing may allow for earlier diagnosis and adherence to treatment guidelines [29] for patients at risk of classical HCU and disorders of sulfur metabolism.

4.1. Limitations

This study was limited to only those individuals with commercial health coverage or private Medicare supplemental coverage, and those for whom outpatient lab results were provided by one of the large national medical laboratories that contribute to the MarketScan Lab Database. Results of this analysis may not be generalizable to individuals with other insurance or without health insurance coverage, or those with tHcy tests that were not conducted by one of the contributing laboratories. There is also the potential for misclassification of diagnoses or other study outcomes due to the limitations of claims data. Since the ICD-9-CM coding system did not have a specific code for HCU, we used the general code for disturbances of sulfur-bearing amino acid metabolism (ICD-9-CM 270.4) to identify an HCU diagnosis on claims prior to October 1, 2015 (the date of ICD-10 implementation with a specific code for HCU [E72.11]). Therefore, it is possible that some patients who had only the ICD-9 diagnosis code during the study period had one of the other disorders for which that code was used. However, this would imply that the rate of HCU diagnoses among these patients is even lower than what we report. Additionally, only tHcy levels obtained during patients' enrollment in the MarketScan Lab database between 1/1/2006 and 3/31/2016 were assessed, and only each patient's first tHcy test value in that time period was used in this study. Any temporal differences in tHcy levels that may exist within patients or across the whole sample were not captured in this study.

5. Conclusions

An estimated 33,068 people in the US are living with tHcy levels > 30 μmol/L. These findings support other recent findings that the national prevalence of HCU may be much higher than estimates from newborn screening results. Patients with elevated tHcy levels warrant further evaluation of their hyperhomocysteinemia, including screening for classical HCU.

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Ethics approval and informed consent.

All study data were accessed with protocols compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 regulations (HIPAA). As all databases used in the study are fully de-identified and compliant with the HIPPA, informed consent was not required, and this study was exempted from Institutional Review Board approval.

Availability of data

The data that support the findings of this study are available from IBM Watson Health, but restrictions apply. These data were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of IBM Watson Health.

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