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Covariates of depression and high utilizers of healthcare: Impact on resource use and costs

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ABSTRACT

Objective: To characterize healthcare costs, resource use, and treatment patterns of survey respondents with a history of depression who are high utilizers (HUds) of healthcare and to identify factors associated with high utilization.

Methods: Adults with two or more depression diagnoses identified from the HealthCore Integrated Research Database were invited to participate in the CODE study, which links survey data with 12-month retrospective claims data. Patient surveys provided data on demographics, general health, and symptoms and/or comorbidities associated with depression. Similar clinical conditions also were identified from the medical claims. Factors associated with high utilization were identified using logistic regression models.

Results: Of 3132 survey respondents, 1921 were included, 193 of whom were HUds (defined as those who incurred the top 10% of total all-cause costs in the preceding 12 months). Mean total annual healthcare costs were eightfold greater for HUds than for non-HUds ($US56,145 vs. $US6,954; $p < .0001$). HUds incurred more inpatient encounters ($p < .0001$) and emergency department ($p = .01$) and physician office visits ($p < .0001$). Similar findings were observed for mental healthcare costs/resource use. HUds were prescribed twice as many medications (total mean: 16.86 vs. 8.32; psychotropic mean: 4.11 vs. 2.61; both $p < .0001$). HUds reported higher levels of depression severity, fatigue, sleep difficulties, pain, high alcohol consumption, and anxiety. Predictors of becoming a HUd included substance use, obesity, cardiovascular disease, comorbidity severity, psychiatric conditions other than depression, and pain.

Conclusion: Focusing on pain, substance use, and psychiatric conditions beyond depression may be effective approaches to reducing high costs in patients with depression.

1. Introduction

Healthcare decision makers are beginning to pay greater attention to the relatively small group of high utilizers (HUs) who consume a disproportionate amount of healthcare resources. For instance, using Medicaid data, 5% of beneficiaries, termed 'super-utilizers', accounted for 54% of total expenditure in 2008 [1].

Studies focusing on HUs frequently report an association between high resource utilization, healthcare costs, and depression [2]. HUs with depression or in partial remission were found to incur more office visits and days hospitalized than those without depression [3]. HU populations have been used to evaluate the effectiveness of screening programs and treatments for depression [4–6]. Von Korff et al. [7] investigated the association between disability and depression among HUs and concluded, "Depressed high utilizers of medical care are an important group to study because they are often afflicted by severe chronic medical conditions and account for a share of healthcare resource consumption disproportionate to their numbers." Depression is also cited as a comorbidity in other high utilization populations, including those with diabetes [8], spinal cord injury [9], advanced cancer [10], chronic musculoskeletal pain [11], and post-traumatic stress disorder [12]. Yet the relative impact of symptoms associated with depression or other covariates on healthcare utilization and cost in HUs has not been well studied. Potentially this is because data sources with quality cost data, such as administrative claims, lack clinical severity information, and comprehensive cost data are challenging to collect longitudinally in survey research.

Unlike most previous studies of high utilization [2,3,13], which included heterogeneous populations and were conducted retrospectively, in the current study we adapted the general definition of HUs by focusing on utilization in a subpopulation of HUs with depression (HUd), using a retrospective/prospective design. A HUd is defined in this study as a person with depression whose all-cause total costs place him/her in the top decile of this study's cost distribution.

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The aim of this study is to describe treatment patterns, characteristics, and outcomes among survey respondents who are HUds and compare them with non-HUds using administrative claims. Using total costs allows for a comprehensive definition of HUds along multiple dimensions of healthcare resources. The study also seeks to determine factors affecting high utilization.

2. Methods

The data reported here are from the CO-morbidities and Symptoms of DEpression (CODE) study, which utilized a retrospective/prospective fixed-cohort repeated-measures design in which initial and 6-month patient survey data were linked to 24 months of administrative claims data (±12 months from the initial survey date). The source for the claims data was the HealthCore Integrated Research Database (HIRD), which contains medical, pharmacy, and enrollment information for patients from a large commercially insured population from 14 geographically-diverse US health plans. Medical data are collected from physician and facility claims (containing diagnoses and procedure codes) and are integrated with outpatient pharmacy claims (captured by national drug codes) for all plan members. Coverage includes health maintenance organizations, point of service, preferred provider organizations, and fee-for-service plans. A central institutional review board approved the CODE protocol and all survey-related materials. All patient data were handled in compliance with US Health Insurance Portability and Accountability Act of 1996 regulations.

The CODE survey sample was identified from medical claims in the HIRD from 1 June 2009 through 31 May 2010 and comprised patients with at least two distinct medical claims with a primary diagnosis code for depression using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) (Appendix A) (Fig. 1). Eligible patients were aged 18–64 years and continuously enrolled in their health plan for ≥12 months with both medical and pharmacy benefits. Patients with at least one medical claim during the study period for bipolar disorder or schizophrenia were ineligible.

Survey recruitment (1 January 2011 through 9 February 2011) ended when the target enrollment goal of at least 3000 patients was attained. Eligible patients were mailed invitations to participate, along with a study description. Patients could call directly or wait to be contacted to opt in or out of the study. Once verbal informed consent was received, respondents were screened for further eligibility and offered the option

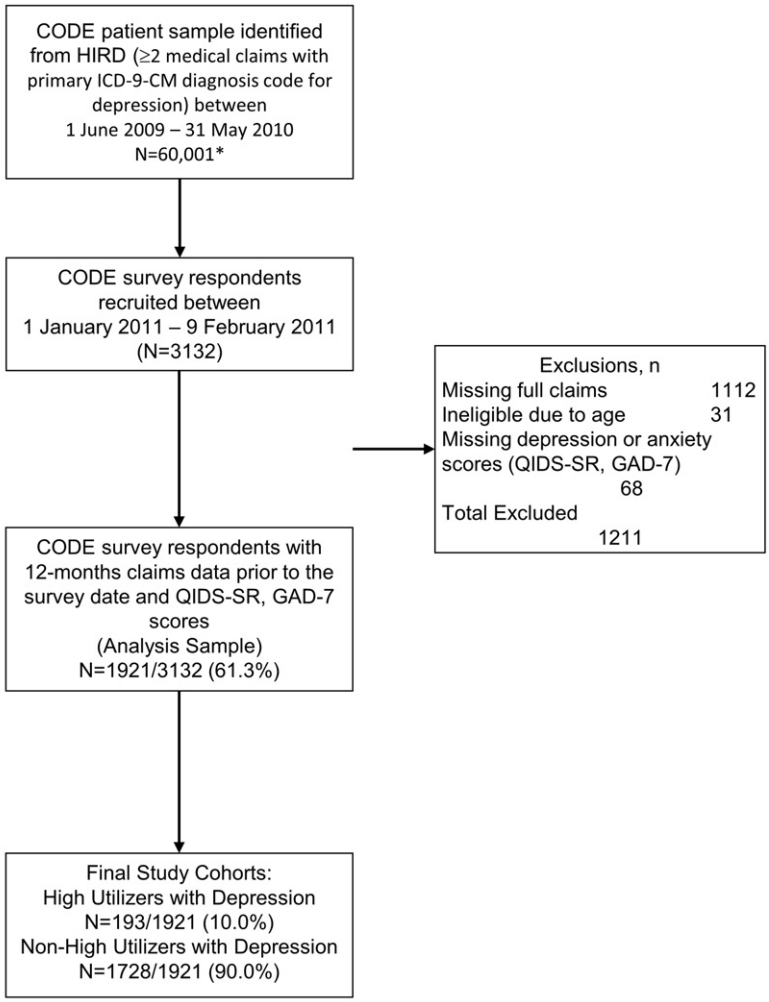


Fig. 1. Derivation of final study cohorts.

of completing the survey by telephone with an interviewer or via the internet. Patients were considered unavailable after six contact attempts. The survey required approximately 30 min, and respondents were compensated $US35 for their time. After survey completion, respondents' survey and claims data were linked. No major differences in demographic characteristics between full respondents (completed initial and six-month surveys) and partial respondents (completed only initial survey) were apparent (data not shown).

The current analysis utilizes data from the initial survey for respondents with non-missing depression and anxiety survey scores and complete medical and pharmacy claims (n = 1921; 61.3% of the initial 3132 survey respondents) (Fig. 1).

Groups of interest were established based on the distribution of all-cause total costs in the 12 months prior to the survey date. Patients in the top 10% of costs were identified as HUds and were evaluated against the remaining participants (non-HUds).

2.1. Measures

The CODE survey collected respondent information on demographics, general health, and the presence and severity of depression as well as symptoms and/or comorbidities often associated with depression, including pain, fatigue, anxiety, sleep difficulty, and heavy alcohol use (Appendix B). Demographics included race and ethnicity, body mass index (BMI), marital status, education, employment status, and family income level. General health was measured using the 12-item General Health Questionnaire (GHQ-12) (range 0–36) [14] and through lifestyle measures of smoking status, diet (poor to healthy), activity, and sexual functioning.

Variables of interest from the administrative claims data were specified for the 12-month period prior to the survey date. Demographic variables available from the claims included sex, age, geographic region of residence, and insurance plan type.

Provider specialty (primary care physician [family or general practitioner, internal medicine physician, or obstetrician/gynecologist], psychiatrist, non-physician, and other/unknown/missing) was defined based on pre-period medical claims for the primary depression diagnosis when available or by the prescriber specialty of the most recent antidepressant prescription fill.

Clinical conditions, including depressive disorders, anxiety, fatigue/sleep-related conditions, pain disorders, alcohol use disorders, other substance use conditions, sexual dysfunction, memory loss, other psychiatric conditions, diabetes, cardiovascular disease, thyroid disorders, obesity, cancer, and cerebrovascular disease, were derived from the presence of ICD-9-CM diagnosis codes (Appendix A) in any medical inpatient or outpatient or emergency department claim. Mental health-related utilization and costs were based on claims that contained ICD-9-CM and CPT codes in any position that were related to mental health (Appendix C). Comorbidity severity was measured using the Quan-Charlson Comorbidity Index (QCI) [23].

Healthcare resource utilization and costs (inflation-adjusted to $US, year 2012 values) were categorized based on the presence of claims for each medical component (inpatient hospitalizations, ED visits, physician office visits, other outpatient visits) and pharmacy. Overall all-cause healthcare utilization and costs as well as mental health-related utilization and costs are reported. Any use of select psychotropic medications was identified using standard measures of adherence. Length of therapy (LOT) was defined as the number of days with the presence of a medication prescription fill and was capped at 365 days. The medication possession ratio (MPR) was defined as LOT divided by 365 days (i.e. length of the 12-month period of interest). An MPR ≥ 80% is typically deemed a good indication of adherence [24].

2.2. Statistics

Cohort characteristics were summarized and compared using chi-squared or Fisher's exact tests for categorical variables and *t*-tests for continuous variables. Cost variables were compared using Wilcoxon–Mann–Whitney tests to account for distribution skewness. The conclusions were the same; therefore, *t*-test results are reported for consistency. Two-sided 0.05 significance levels were used without multiplicity adjustment due to the nature of this exploratory study.

Logistic regression modeling was used to assess the relationship between patient factors, including symptoms associated with depression and the likelihood of being a HUd. Development of the primary model was guided by our objective to illuminate associations with survey-specific measures. Therefore, utilization and cost variables, as well as claims-based variables with domains that overlapped those of survey-based variables, were excluded from the primary model. Additional models were explored that 1) used stepwise model selection rather than a manually selected model; 2) included additional claims-based variables; 3) dichotomized continuous measures for simplicity; and 4) included interactions between measures of depression (16-Item Quick Inventory of Depressive Symptomatology [QIDS]) and anxiety [Generalized Anxiety Disorder scale [GAD-7]). Goodness of fit was assessed using the Akaike information criterion [25], c statistics [26], and the Hosmer-Lemeshow test [26]. Odds ratios (ORs) and 95% confidence intervals were computed for all covariates in the final model.

3. Results

Of the 1921 study patients, 193 (10%) were classified as HUds and 1728 (90%) as non-HUds.

Table 1
Annual costs for depressed patients: high utilizers of healthcare with depression (HUds) vs. non-HUds.

Annual healthcare costs	HUds	Non-HUds	P-value
	n = 193	n = 1728	
All-cause			
Total medical	45,436 (± 42,002)	4,322 (± 4456)	<.0001
Inpatient	19,144 (± 26,672)	446 (± 2068)	<.0001
Emergency department	1,856 (± 7237)	307 (± 1085)	0.0034
Physician office	4,574 (± 5900)	1,557 (± 1537)	<.0001
Primary care physician	933 (± 3524)	300 (± 432)	0.0135
Psychiatrist	303 (± 820)	236 (± 717)	0.2778
Non-physician	772 (± 1601)	474 (± 1032)	0.0124
Others (incl. missing, unknown)	2,567 (± 4442)	546 (± 928)	<.0001
Outpatient	19,603 (± 31,033)	2,013 (± 2983)	<.0001
Pharmacy	10,709 (± 11,371)	2,632 (± 3013)	<.0001
Total	56,145 (± 40,886)	6,954 (± 5649)	<.0001
Mental health related			
Total medical	12,943 (± 19,838)	1,377 (± 2092)	<.0001
Inpatient	7,663 (± 14,753)	209 (± 1274)	<.0001
Emergency department	511 (± 2216)	65 (± 430)	0.0058
Physician office	1,468 (± 2752)	898 (± 1328)	0.0050
Primary care physician	242 (± 2169)	77 (± 305)	0.2919
Psychiatrist	301 (± 819)	235 (± 716)	0.2811
Non-physician	649 (± 1566)	441 (± 1028)	0.0733
Others (incl. missing, unknown)	275 (± 813)	145 (± 537)	0.0310
Outpatient	3,177 (± 11,434)	205 (± 818)	0.0004
Outpatient psychiatric services[a]	1,198 (± 7905)	97 (± 447)	0.0545
Pharmacy	2,671 (± 3488)	1,238 (± 1845)	<.0001
Total	15,614 (± 20,651)	2,615 (± 2922)	<.0001

Data are presented as mean ± standard deviation unless otherwise indicated.

[a] Includes psychiatric diagnostic evaluation, psychotherapy (individual, group, family), psychiatric services or procedures (including pharmacotherapy, narcosynthesis, biofeedback training, hypnotherapy, electroconvulsive therapy, etc.), suicide risk assessment, psychiatric treatment (home visit).

3.1. Costs

Costs were significantly higher for HUds than for non-HUds across all medical and pharmacy cost components. An eightfold difference in total annual healthcare costs (medical plus pharmacy) was found between HUds and non-HUds (Table 1). Total medical annual healthcare costs (excluding pharmacy) were tenfold higher in HUds than in non-HUds. Inpatient and outpatient encounters each accounted for approximately 40% of costs for HUds. Inpatient costs were 40-fold higher in the HUd group than in the non-HUd group, and other disparities between the two groups were seen for costs related to outpatient visits (tenfold higher) and pharmacy (fourfold higher). Total mental health-related costs were also sixfold higher in HUds, with a ninefold disparity in medical mental health-related annual costs.

3.2. Resource utilization

Table 2 illustrates the disparities in resource utilization between the two cohorts. For example, the 60% rate of inpatient encounters for HUds was approximately ninefold higher than the 6.6% rate for non-HUds ($p < .0001$). HUds made more visits to the ED, physician offices, and any other outpatient site.

Results were similar for mental health-related resource utilization, with HUds having more inpatient encounters, ED visits, physician office visits, other outpatient visits, and outpatient psychiatric service visits. Among those with inpatient encounters, HUds were hospitalized for twice as long as non-HUds.

HUds were generally prescribed more psychotropic (mean number of drugs: 4.11 ± 2.67 vs. 2.61 ± 1.74, $p < .0001$) and total medications (mean number: 16.86 ± 7.97 vs. 8.32 ± 5.42, $p < .0001$) than non-HUds. HUds were prescribed more tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and other antidepressants, whereas both groups used selective serotonin reuptake inhibitors and bupropion to a similar extent. Antidepressant exposure was longer (mean LOT 275.52 ± 84.03 days vs. 249.33 ± 97.22 days, $p = .0003$) and adherence was greater (50.26% vs. 37.15%, $p = .0029$) among HUds.

HUds were more likely to be prescribed second-generation antipsychotics, hypnotics/sedatives, anxiolytics, and benzodiazepines (Table 2), including short/intermediate-acting ($p = .0064$) or long-acting ($p < .0001$) formulations; no differences in usage were observed between groups for mood-stabilizing anticonvulsants or lithium. HUds also were prescribed more medicine combinations than non-HUds, including co-administration of an antidepressant with a second-generation antipsychotic or benzodiazepine.

Table 2
Resource utilization and treatment for depressed patients: high utilizers of healthcare with depression (HUds) vs. non-HUds.

Resource utilization	HUds n = 193	Non-HUds n = 1728	P-value
All-cause utilization			
Any inpatient encounters	116 (60.1)	114 (6.6)	<.0001
Length of stay of those with hospitalizations	10.24 (± 11.96)	4.07 (± 5.24)	<.0001
Length of stay of total population	6.16 (± 10.53)	0.27 (± 1.68)	<.0001
Any emergency department visits	76 (39.38)	291 (16.84)	<.0001
# of emergency department visits	1.09 (± 4.56)	0.22 (± 0.63)	0.01
Any physician office visits	192 (99.48)	1711 (99.02)	1.0000
# of physician office visits	27.8 (± 23.45)	14.98 (± 13.84)	<.0001
Any other outpatient visits	193 (100)	1,596 (92.36)	<.0001
# of other outpatient visits	27.91 (± 20.09)	8.39 (± 9.85)	<.0001
Mental health-related utilization			
Any inpatient encounters	75 (38.86)	66 (3.82)	<.0001
Length of stay of those with hospitalizations	11.16 (± 12.95)	4.85 (± 6.53)	0.0003
Length of stay of total population	4.34 (± 9.72)	0.19 (± 1.57)	<.0001
Any emergency department visits	36 (18.65)	84 (4.86)	<.0001
# of emergency department visits	0.38 (± 1.78)	0.05 (± 0.25)	0.0120
Any physician office visits	172 (89.12)	1,551 (89.76)	0.7823
# of physician office visits	13.6 (± 21.66)	9.8 (± 12.93)	0.0177
Any other outpatient visits	104 (53.89)	584 (33.8)	<.0001
# of other outpatient visits	4.54 (± 11.28)	1.06 (± 3.35)	<.0001
Any outpatient psychiatric services	70 (36.27)	411 (23.78)	0.0001
# of visits involving outpatient psychiatric services	2.9 (± 8.51)	0.79 (± 2.87)	0.0008
Medication utilization			
Antidepressants			
Any antidepressant			
Selective serotonin reuptake inhibitors	92 (47.67)	864 (50)	0.5389
Serotonin-norepinephrine reuptake inhibitors	81 (41.97)	421 (24.36)	<.0001
Bupropion	54 (27.98)	426 (24.65)	0.3114
Tricyclics	26 (13.47)	90 (5.21)	<.0001
Other antidepressants	52 (26.94)	293 (16.96)	0.0006
Second generation antipsychotic utilization	55 (28.5)	174 (10.07)	<.0001
Second generation antipsychotic + antidepressant	52 (26.94)	154 (8.91)	<.0001
Mood-stabilizing anticonvulsants	5 (2.59)	19 (1.1)	0.0851
Lithium	3 (1.55)	16 (0.93)	0.4292
Hypnotics/sedatives	62 (32.12)	313 (18.11)	<.0001
Any benzodiazepine	109 (56.48)	662 (38.31)	0.0005
Anxiolytics	119 (61.66)	734 (42.48)	<.0001
Any antidepressant + benzodiazepine	85 (44.04)	487 (28.18)	<.0001

Data are presented as n (%) or mean ± standard deviation.

3.3. Demographic and clinical characteristics

HUds and non-HUds shared some similar demographic characteristics (Table 3). More than three-quarters of respondents in both groups were female. Most were middle aged (45–64 years), although HUds were significantly older on average than non-HUds. More than 90% of both groups were Caucasian/White and most were married, had a significant other or domestic partner, or were living with another person. A significant difference in geographic region was observed, with HUds being more likely to live in the Northeast and West regions than non-HUds. HUds were less likely to be employed full-time and more likely to be disabled, retired, or unemployed. Educational status and family income were similar for both groups. Additionally, a greater proportion of HUds were seeing primary care physicians or psychiatrists than non-HUds, whereas non-HUds were more likely to be treated by non-physicians.

Clinical differences were apparent between the two groups (Table 4). HUds had more severe depression than non-HUds, as indicated by significantly higher mean scores on the QIDS-self-report

HUds reported higher levels of fatigue than non-HUds, with increased scores on the mean Fatigue Associated with Depression Questionnaire (FAsD) total, impact, and experience subscales. Sleep difficulties were also more common in HUds, as indicated by higher scores on the Athens Insomnia Scale (AIS). Similar trends were found in the claims data, with HUds also more likely to have fatigue/sleep-related diagnoses.

GAD-7 patient-reported anxiety severity levels were elevated in HUds compared with non-HUds (Table 4), as was the percentage of patients with claims for anxiety (67.88% vs. 60.07%, $p = 0.0351$). Yet, the presence of diagnoses of GAD (HUd vs. non-HUd: 15.03% vs. 11.17%, $p = .1119$), post-traumatic stress disorder (4.15% vs. 2.72%, $p = .2602$) or other anxiety disorders (37.31 vs. 36.57%, $p = .8414$) from the claims did not differ between groups.

Mean pain severity as measured by Brief Pain Inventory (BPI) was higher in HUds, and more than 92% of HUds had claims for pain disorders compared with 59% of non-HUds ($p < .0001$).

HUds had poorer self-reported general health, based on higher GHQ-12 scores, and more comorbidity, as indicated by higher mean QCI scores. Previous diagnoses of diabetes, cardiovascular disease, thyroid disorders, cancer, cerebrovascular disease, memory loss,

Table 3
Demographics: high utilizers of healthcare with depression (HUds) vs. non-HUds.

	HUds	Non-HUds	P-value
	n = 193	n = 1728	
Female	149 (77.2)	1333 (77.14)	0.9838
Age (years)	49.27 (± 11)	46.18 (± 11.65)	0.0004
Geographic region			0.0383
Northeast	38 (19.69)	264 (15.28)	
South	31 (16.06)	410 (23.73)	
Midwest	48 (24.87)	491 (28.41)	
West	74 (38.34)	541 (31.31)	
Unknown	2 (1.04)	22 (1.27)	
Health plan type			
Health Maintenance Organization/Point of Service	32 (16.58)	430 (24.88)	
Preferred Provider Organization	125 (64.77)	1071 (61.98)	
Others	36 (18.65)	227 (13.14)	0.0004
Race and ethnicity			0.3700
Caucasian/white	179 (92.75)	1569 (90.8)	
Others	14 (7.25)	159 (9.2)	
Marital status			0.0105
Married or partnered	113 (58.55)	986 (57.06)	
Single, separated, divorced or widowed	77 (39.9)	740 (42.82)	
Others	3 (1.55)	2 (0.12)	
Educational status			0.1044
High school or less	39 (20.21)	294 (17.01)	
College	117 (60.62)	1032 (59.72)	
Graduate	36 (18.65)	401 (23.21)	
Other	1 (0.52)	1 (0.06)	
Employment status			<0.0001
Employed full-time	51 (26.42)	847 (49.02)	
Employed part-time or self	46 (23.83)	343 (19.85)	
Homemaker	23 (11.92)	192 (11.11)	
Student	2 (1.04)	54 (3.13)	
Disabled, retired, unemployed	71 (36.79)	292 (16.9)	
Family income			0.5076
Less than $25,000	25 (12.95)	214 (12.38)	
$25,000–$99,999	109 (56.48)	1017 (58.85)	
$100,000 and greater	40 (20.73)	377 (21.82)	
Don't know/refused	19 (9.84)	120 (6.94)	
Most recent antidepressant prescribing/treating physician specialty			0.0227
Primary care physician	73 (37.82)	616 (35.65)	
Psychiatrist	74 (38.34)	622 (36.00)	
Non-physician	21 (10.88)	268 (15.51)	
Others	8 (4.15)	25 (1.45)	
Missing/unknown	17 (8.81)	197 (11.40)	

Data are presented as n (%) or mean ± standard deviation.

and other psychiatric conditions were more prominent in HUds. Although a previous diagnosis of obesity was three times more common in HUds than in non-HUds, no between-group difference in mean BMI was observed.

The mean Alcohol Consumption Scale score was higher in HUds than in non-HUds. No between-group difference was observed in the percentage of heavy drinkers; however, these data were missing for more HUds than non-HUds (30.6% vs. 22.1%; p = .008). HUds were more likely to have diagnoses for alcohol use disorders or dependence or other substance use conditions.

For lifestyle factors, a decline in normal activity levels and change in sexual functioning were reported more frequently in HUds than in non-HUds. However, no between-group differences were found in smoking or having a fair/poor diet.

3.4. Factors associated with being a HUd

Several factors associated with being a HUd were identified. Of the primary conditions of interest (self-reported symptoms from the survey), only pain (p = .0037) was found to be associated with being a HUd. Clinically significant levels of depression (as indicated by moderate QIDS scores), anxiety, fatigue, sleep disruption, or general health were not associated when considering all factors.

Respondents with pain were almost 74% more likely to be HUds, where "presence of pain" was defined as scores ≥4 on the 1–10 scale. In an alternative model, where the full pain score range was used as a covariate, a one-point increase on the scale was associated with a 13.7% increased chance of being a HUd (p = .0385). Both approaches suggest a marked association between pain and increased healthcare costs.

Fig. 2 shows the strongest association was a 'use of other substances' diagnosis; individuals falling into this category had more than a fivefold increased risk of being a HUd. HUds were also associated with having diagnoses of obesity, cardiovascular disease, high comorbidity severity, other psychiatric conditions, and pain. Diagnoses of sexual dysfunction or memory loss or medical conditions such as cancer, cerebrovascular disease, or thyroid dysfunction were not associated with being a HUd when all other factors were considered.

Several factors present at the initial assessment were associated with less risk of being a HUd (Fig. 2). These included holding a full-time job, having diabetes, and being from Mid-Western or Southern US regions. The effects of sex, age, marital status, or higher education were not significant.

Model goodness of fit and significance of survey-based associated factors did not differ between models where factors were chosen manually compared with models chosen via automatic stepwise selection or when dichotomous or continuous variables were used. No statistically significant relationship was observed between depression and anxiety when interaction terms were included.

4. Discussion

In a cohort of patients with a history of depression identified from a large administrative claims database with self-reported depression ratings and linked survey and administrative claims data, costs and resource utilization for HUds (whose all-cause total costs fell within the top decile of cost distribution), were compared with findings for non-HUds. Mean total healthcare costs for HUds were eightfold higher than those for non-HUds, with higher expenditures attributed to more inpatient stays, outpatient encounters, ED use, and physician visits. Similar findings were found for mental healthcare, with a sixfold increase in total costs among HUds. HUds used twice as many medications as non-HUds, including more prescriptions for psychotropic medications, serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants, second-generation antipsychotics, hypnotics/sedatives, benzodiazepines, and anxiolytics.

We examined the data to see whether characteristics other than healthcare utilization levels distinguished HUds from non-HUds. We found patients with a history of depression in the CODE study who became HUds tended to be older, less likely to be employed full time, and more likely to be disabled, retired, or unemployed. They were also more likely to be residents of Northeastern or Western US regions than non-HUs. Univariate analyses showed that the higher healthcare utilization of these patients was associated with a range of characteristics, including more severe depression, fatigue, anxiety, pain, memory loss, other psychiatric conditions, or sleep difficulties, as well as comorbidities such as obesity, diabetes, cardiovascular disease, thyroid disorders, cancer, and cerebrovascular disease. HUds were more likely to use or be dependent upon alcohol or other substances, although the presence of heavy drinking was not found to be a significant determinant. Smoking or maintaining a poor diet did not portend high utilization, although declines in normal activity levels and changes in sexual functioning were more common in HUds.

Multivariate analyses were performed to identify covariates of depression that were indicative of future high utilization. Using a logistic regression model, the strongest predictor of becoming a HUd

Table 4
Clinical characteristics, comorbidities, lifestyle, and wellness variables at initial assessment: high utilizers of healthcare with depression (HUds) vs. non-HUds.

Clinical characteristics	HUds	Non-HUds	P-value
	n = 193	n = 1728	
Depression severity (QIDS-SR score)	10.23 (± 5.68)	8.73 (± 4.79)	0.0005
Clinically significant depression — yes	144 (74.61)	1,221 (70.66)	0.2509
Fatigue			
FAsD experience subscale	3.13 (± 1.03)	2.77 (± 0.97)	<.0001
FAsD experience — yes	91 (47.15)	537 (31.08)	<.0001
FAsD impact subscale	2.69 (± 1.1)	2.37 (± 1.01)	<.0001
FAsD total score	2.92 (± 0.99)	2.59 (± 0.91)	<.0001
Average 24 hour pain score (BPI)	3.72 (±2.56)	2.46 (± 2.41)	<.0001
Clinically significant pain — yes	109 (56.48)	577 (33.39)	<.0001
Sleep disruption (AIS)	8.44 (± 4.85)	7.16 (± 4.62)	0.0003
Clinically significant sleep disruption — yes	130 (67.36)	1,046 (60.53)	0.0649
Anxiety (GAD-7)	7.98 (± 5.71)	7.04 (± 5.41)	0.0233
Clinically significant GAD — yes	93 (48.19)	679 (39.29)	0.0169
Alcohol Consumption Scale[a]	10.1 (± 1.96)	9.37 (± 2.36)	<0.0001
Heavy drinking — yes[b]	12 (6.22)	125 (7.23)	0.6029
General health (GHQ-12)	16.01 (± 7.38)	14.15 (± 6.37)	0.0009
QCI comorbid score	1.85 (± 2.36)	0.4 (± 0.87)	<.0001
Diagnoses			
Alcohol use or dependence	11 (5.7)	38 (2.2)	0.0075
Other substance use conditions	18 (9.33)	32 (1.85)	<.0001
Sexual dysfunction, erectile dysfunction	4 (2.07)	11 (0.64)	0.0556
Memory loss	6 (3.11)	13 (0.75)	0.0084
Other psychiatric conditions	55 (28.5)	299 (17.3)	0.0001
Fatigue/Sleep-related diagnoses[c]	112 (58.03)	558 (32.29)	<.0001
Pain disorders	178 (92.23)	1024 (59.26)	<.0001
Diabetes mellitus	39 (20.21)	168 (9.72)	<.0001
Cardiovascular disease	33 (17.1)	60 (3.47)	<.0001
Thyroid disorders	56 (29.02)	293 (16.96)	<.0001
Obesity	35 (18.13)	111 (6.42)	<.0001
Cancer	29 (15.03)	54 (3.13)	<.0001
Cerebrovascular disease	18 (9.33)	30 (1.74)	<.0001
Lifestyle and wellness variables			
Current smoker	25 (12.95)	224 (12.96)	0.9970
Fair/poor diet	60 (31.09)	521 (30.15)	0.7880
Decrease in normal activity levels	116 (60.1)	706 (40.86)	<.0001
Change (+/-) in sexual functioning	73 (37.82)	516 (29.86)	0.0203
BMI	28.07 (± 6.37)	28.36 (± 7.25)	0.5564

Data are presented as n (%) or mean ± standard deviation.
AIS = Athens Insomnia Scale; BPI = Brief Pain Inventory; BMI = Body Mass Index; FAsD = Fatigue Associated with Depression Questionnaire; GAD-7 = Generalized Anxiety Disorder scale; GHQ = General Health Questionnaire; QCI = Quan-Charlson Comorbidity Index; QIDS-SR = Quick Inventory of Depressive Symptomatology (Self-Report).
[a] Alcohol Consumption Scale scores were available for 134 (69.43%) of HUds and 1347 (77.95%) of non-HUds.
[b] Heavy drinking was assessed with the Alcohol Consumption Scale and defined as ≥5 alcoholic drinks for males and ≥4 alcoholic drinks for females in a single day [22]. Note that these data were missing for more HUds than non-HUds (30.6% vs. 22.1%; p = .008).
[c] Fatigue/sleep related diagnoses included any claims for chronic fatigue syndrome, general fatigue symptoms, anemia, insomnia, hypersomnia, and other sleep disturbances.

was 'use of other substances', followed by obesity, cardiovascular disease, comorbidity severity, other psychiatric conditions, and pain. Using this adjusted model, moderate depression, anxiety, fatigue, sexual dysfunction, memory loss, sleep disturbance, and general health were not associated with becoming a HUd.

Interestingly, findings from the model suggested that several variables were associated with less risk of becoming a HUd, including holding a full-time job, having diabetes, and living in the mid-western or southern US. Serious medical conditions, including cancer and cerebrovascular disease, were not associated with being a HUd. The impact of some of these clinical conditions may be modified due to overlap with the QCI comorbidity index, obesity, and/or their relatively low prevalence in this cohort.

These findings are similar in part to a comprehensive literature review that reported all non-genetic factors predictive of or associated with response to depression therapy [27]. In that study, anxiety and pain contributed to worse antidepressant treatment outcomes. In the STAR*D study, comorbid anxiety was associated with poorer response to depression treatment, as well as increased rates of adverse events, psychiatric hospitalizations, and suicide attempts [28].

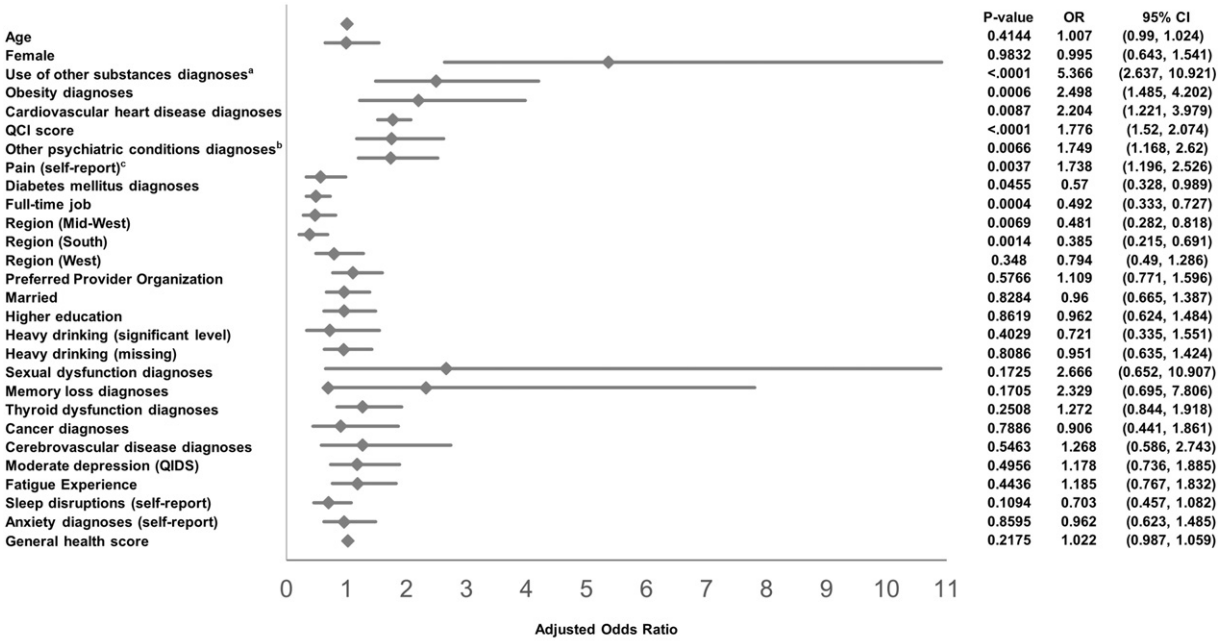
Two studies evaluated the impact of substance abuse on treatment response and found mixed results. In a large case study of over 4000 patients, comorbid substance abuse increased the risk of depression relapse and recurrence [29], whereas in a randomized clinical trial of over 600 patients with chronic depression or double depression, neither substance abuse nor anxiety was associated with treatment response [30].

In a previous analysis of CODE study data, one-third of patients with survey and complete claims data had significant levels of fatigue [31]. Patients with fatigue incurred higher total healthcare costs, used more healthcare resources, and reported increased severity of depression, pain, sleep difficulty, and anxiety. The current results suggest that although fatigue is an important covariate of depression and is more common in HUds, its presence may not be predictive of becoming a HUd.

Our results suggest that an effective approach to reduce the likelihood of patients with depression becoming HUds, thereby reducing high healthcare utilization and the resulting costs, would be to focus on several specific and modifiable patient characteristics, such as the use of other substances, pain, and the presence of psychiatric conditions other than depression. Obesity, cardiovascular disease, and comorbidity severity appear to be other red flags for future high healthcare utilization and may also be good targets for early and effective intervention.

4.1. Limitations

Several limitations should be considered when interpreting these findings. The prospective/retrospective hybrid study design offers an efficient and effective method to examine outcomes by augmenting survey data with administrative claims data; however, typical limitations of prospective and retrospective observational research are present. Self-reported symptoms were assessed at a single time point, whereas costs were observed over 12 months preceding the survey; hence, the association between symptoms and costs may differ with alternative time periods. Claims data are collected for the purpose of payment and not for research. Medication use identifies that prescriptions were filled but lacks information on whether the drug was ingested or if additional medications were taken, including over-the-counter drugs, drugs paid for by the individual, or drugs provided through office samples. Medical diagnostic codes, including those for comorbid medical conditions, may be incorrectly coded, undercoded, incomplete, or included as rule-out criteria. This is especially true with depression, which has been known to be under-reported in claims [32]. Participants were identified as having at least two distinct medical claims for depression in a large US commercial database, rather than through structured diagnostic interviews. However, respondents answered a self-reported question regarding whether they had been told by a physician that they had depression, and completed the QIDS-SR, which has been shown to correlate strongly with the HAM-D and other clinician-rated scales [16]. Nevertheless, our depression identification algorithm has not been validated. In addition, survey results were based on respondents' self-report and could not be independently verified through clinical documentation; thus, their accuracy may be subject to self-report and recall biases. Although no major differences in demographic characteristics between full respondents and partial respondents were identified in the limited data available from the claim forms, differences beyond the data collected may have existed; it was not, however, possible to quantify this. It is also possible that individuals with other diagnoses, such as primary psychotic disorders, were included in the study. As patients were identified based on prior claims, the duration and course of depression was variable. In some cases, patients reported no symptoms of depression during the survey. Participants therefore included



Abbreviations: QCI: Quan-Charlson Comorbidity Index; QIDS: 16-item Quick Inventory of Depressive Symptomatology

[a] Use of other substances diagnoses primarily refers to the use of drugs other than alcohol, including Schedule I and Schedule II drugs (codes V65.42 [counseling on substance use and abuse], 977.9 [unspecified drug or medical substance], and 304.xx [drug dependence]).

[b] Other psychiatric conditions diagnoses refer to conditions other than depression, including manic disorders and psychosis.

[c] Presence of pain defined as scores ≥4 on the 1–10 scale.

Fig. 2. Factors associated with being a high utilizer of healthcare in depressed patients. Abbreviations: QCI: Quan–Charlson Comorbidity Index; QIDS: 16-item Quick Inventory of Depressive Symptomatology [a]Use of other substances diagnoses primarily refers to the use of drugs other than alcohol, including Schedule I and Schedule II drugs (codes V65.42 [counseling on substance use and abuse], 977.9 [unspecified drug or medical substance], and 304.xx [drug dependence]). [b]Other psychiatric conditions diagnoses refer to conditions other than depression, including manic disorders and psychosis. [c]Presence of pain defined as scores ≥4 on the 1–10 scale.

patients in remission, those being managed through treatment, and, possibly, those who were incorrectly diagnosed. Importantly, the study was limited to the determination of the resource utilization and direct costs of care of HUds, and may not be generalizable to all HUs of healthcare. Since only individuals and/or their dependents with employer-provided commercial health insurance were included, the results may not generalize to other populations such as uninsured individuals, Medicaid or Medicare recipients, or individuals in non-US countries with alternative healthcare systems. In addition, the population includes a predominance of Caucasians compared to the general US population; hence, the study does not purport to provide insights into the potential contribution of race or ethnicity to outcomes. Information not available in claims data or through self-report could impact study outcomes, such as certain clinical and disease-specific parameters.

Costs were detailed from a payers' perspective and do not include the entire cost of depression [33,34]. For the regression model, the sample size was too small to replicate in test samples.

5. Conclusions

Not all depressed patients will become HUds of healthcare. The results of this unique prospective/retrospective hybrid study design confirm that residual symptoms of depression or specific comorbidities add to the economic burden of illness and highlight the importance of treating patients to full resolution of all depression symptoms. HUds have more severe depression symptoms, and are more likely to manifest fatigue, sleep disturbance, anxiety, pain, substance use, and have certain comorbidities than non-HUds. However, our results suggest only some of these variables (e.g. use of other substances, obesity, cardiovascular disease, comorbidity burden, other psychiatric illnesses other than depression, and pain) may be associated with becoming a HUd. Until genotypic differentiation can adequately distinguish subgroups in understanding the relationship between depression and healthcare costs, identification of factors associated with high utilization may help focus therapeutic efforts to mitigate high healthcare utilization and costs in depressed patients more effectively.

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Competing interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare that Douglas Faries and Rebecca Robinson are employees of, and minor shareholders in, Eli Lilly and Company. Judith Stephenson and Michael Grabner are employees of HealthCore Inc., which received funding to carry out this work from Eli Lilly and Company. Swetha Rao Palli was an employee of HealthCore Inc. at the time of the study.

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Appendix A. Medical codes for selected diagnoses

	ICD-9-CM codes
Psychiatric conditions	
Depression	296.2x, 296.3x, 300.4x
Alcohol use disorders or dependence	303.xx, 305.0x
Other substance use conditions	V65.42, 977.9, 304.xx
Sexual dysfunction, Erectile dysfunction	799.81, 302.71, 302.72
Memory loss	780.93
Bipolar disorder	296.0x, 296.1x or 296.4x-296.9x
Schizophrenia	295.xx
Other psychiatric conditions	290.xx to 316.xx, V40.x, excluding the following: 295.0x to 295.9x, 299.0x, 299.9x, 302.6x, 307.59, 309.83, 312.1x, 312.2x, 312.81, 312.9x, 313.xx, 314.9x, 315.35; 296.xx, 298.xx, 300.xx, 302.71, 303.xx to 305.xx, 309.0x, 309.1x, 311.xx, 309.81
Fatigue/Sleep Related Diagnoses (including chronic fatigue syndrome, general fatigue symptoms, anemia, insomnia, hypersomnia, other sleep disturbance)	780.71, 780.70, 780.79, 300.5x, 280.xx to 284.xx, 780.51, 780.52, 307.41, 307.42, 327.0x, 780.53, 780.54, 307.43, 307.44, 327.1x, 327.20 to 327.23, 327.29, 327.3x to 327.8x, 780.50, 780.55 to 780.59, 786.03
Pain disorders (including back pain, fibromyalgia, and other pain)	720.xx, 721.2x to 721.9x, 722.1x to 722.3x, 722.5x, 722.6x, 722.70, 722.72, 722.73, 722.80, 722.82, 722.83, 722.90, 722.92, 722.93, 724.xx, 729.1x, 780.96, 338.xx, 307.80, 053.1x, 250.6x, 307.8x, 323.xx, 335.20, 335.34, 336.9x, 337.1x, 337.2x, 338.3x, 339.xx, 340.xx, 341.xx, 346.0x to 346.9x, 350.xx, 351.xx, 353.xx to 356.xx, 357.2x, 358.xx, 524.6x, 577.1x, 696.xx, 714.xx, 715.xx, 719.xx, 720.xx, 721.0x to 722.4x, 722.71, 722.81, 722.91, 723.1x, 724.4x, 728.0x, 729.0x, 729.2x, 729.5x, 784.0x, 786.5x, 789.xx, 733.99, 733.14, 780.71, 820.8x, 820.9x, 951.4x, 952.xx, 953.4x, 955.5x to 955.7x; Procedure code: 88.81
Comorbidities	
Diabetes mellitus	250.xx
Cardiovascular disease	410.xx to 414.xx, 440.xx, 441.xx, 443.9x
Thyroid disorders	241.xx to 246.xx
Obesity	278.0x, V85.3, V85.4
Cancer	140.xx to 172.xx, 174.xx to 208.xx, 238.6x
Cerebrovascular disease, prior transient ischemic attack, stroke	362.34, 430.xx to 438.xx , V12.54

Appendix B. Patient-reported symptom severity survey scales

Symptom	Scale	Range (*higher scores = greater severity*)	Cut-points: significant symptom level
Depression	Quick Inventory of Depressive Symptomatology, 16 item (QIDS-SR) [15,16]	0–27	QIDS-SR > 5
Fatigue	Fatigue Associated with Depression (FAsD) Questionnaire, including total, experience, and impact scales [17,18]	1–5 (*items averaged for each scale*)	FAsD Experience score > 3.2
Anxiety	Generalized Anxiety Disorder scale, 7 items (GAD-7) [19]	0–21	GAD-7 ≥8
Insomnia	Athens Insomnia Scale (AIS) [20]	0–24	AIS ≥6
Pain	Average pain within the last 24 h using the single item on the Brief Pain Inventory (BPI) Short Form [21]	1–10	≥4 on single item of BPI

Appendix B (*continued*)

Symptom	Scale	Range (*higher scores = greater severity*)	Cut-points: significant symptom level
Heavy alcohol use	Measured by the Alcohol Consumption Scale [22]	1–11	Cut-point measure for heavy drinking: ≥5 alcoholic drinks for males and ≥4 alcoholic drinks for females in a single day and/or pre-period diagnoses for alcohol-use disorder or alcohol dependence (303.xx, 305.0x)

Appendix C. Codes for mental health-related utilization and costs

	Codes
Medical claims	
All psychiatric conditions/services (except bipolar disorder, schizophrenia, those related to childhood conditions)	ICD-9: 290.xx–316.xx, V40.x, V65.42, 799.81, 780.93, 977.9x *excluding* [295.0x–295.9x, 299.0x, 299.9x, 302.6x, 307.59, 309.83, 312.1x, 312.2x, 312.81, 312.9x, 313.xx, 314.9x and 315.35] CPT: 90801–90802, 90804–90809, 90810–90815, 90816–90829, 90845–90857, 90862–90899, 90901–90911, 99510, 4066F
Pharmacy claims	
Anxiolytics, Antidepressants, Second Generation Anti-psychotics, Hypnotics/Sedatives/Antihistamines	GPI: 57x, 58x, 59x, 60x, 61x, 6250405010x, 6299x, 72100010x

GPI = generic product identifier.

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