It is illegal to post this copyrighted PDF on any website. Understanding the Relationship Between Depression Symptom Severity and Health Care Costs for Patients With Treatment-Resistant Depression

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ABSTRACT

Objective: To examine whether measures of depression symptom severity could improve understanding of health care costs for patients with major depressive disorder (MDD) or treatment-resistant depression (TRD) from the health plan perspective.

Methods: In this retrospective cohort study within an integrated health system, cohorts consisted of 2 mutually exclusive groups: (1) adults with TRD based on a standard treatment algorithm and (2) adults with MDD, but no TRD, identified through *ICD-9/10-CM* codes. Depression severity was measured using the Patient Health Questionnaire-9 (PHQ-9). Patterns of health care resource utilization (HRU) and costs were compared between the TRD and MDD groups overall and within the groups at different symptom levels. A general linear model with a γ distribution and log link for cost outcomes, logistic regression for binary outcomes, and negative binomial regression for count outcomes were used.

Results: Patients with TRD (n = 24,534) had greater comorbidity than those in the MDD group (n = 17,628). Mean age in the TRD group was 52.8 years versus 48.2 for MDD (P < .001). Both groups were predominantly female (TRD: 72.8% vs MDD: 66.9%; P < .001). Overall, the TRD group had greater costs than the MDD group, with 1.23 times (95% Cl, 1.21–1.26; P < .001) greater total cost on average over 1 year following index date. Within both groups, those with severe symptoms had greater total mean (SD) costs (TRD: moderate: \$12,429 [\$23,900] vs severe: \$13,344 [\$22,895], P < .001; low: \$12,220 [\$31,864] vs severe: \$13,344 [\$22,895], P < .001; MDD: moderate: \$8,899 [\$20,755] vs severe: \$10,098 [\$22,853]; P < .001; low: \$8,752 [\$25,800] vs severe: \$10,098 [\$22,853], P < .001).

Conclusions: MDD and TRD impose high costs for health systems, with increasing costs as PHQ-9 symptom severity rises. Better understanding of subgroups with different symptom levels could improve clinical care by helping target interventions.

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Health Research, 3800 North Interstate, Portland, OR 97227 (frances.lynch@kpchr.org). A n estimated 17.3 million adults—about 7.1% of adults in the US experienced at least one major depressive disorder (MDD) episode in 2016,^{1,2} and recurrence is common.² About 30% of persons with MDD also experience treatment-resistant depression (TRD) that does not respond to evidence-based treatment, defined as 2 or more consecutive treatments with 2 different antidepressant medications, used for sufficient length and at an adequate dose.^{3,4} Multiple studies⁵⁻¹⁵ have shown that MDD and TRD are linked to higher costs. In addition, MDD and TRD are associated with problems in functioning, employment, and risk of suicide, which leads to additional burden to patients, families and communities.¹⁻³

Cost studies of TRD typically use diagnostic data to categorize patients; however, this approach does not account for variation in symptoms within diagnostic categories. Patients diagnosed with MDD may have symptoms ranging from low to very severe; this is not reflected in diagnosis codes. The use of patient-reported outcomes presents an opportunity to study the economic impact of depression from a new perspective. The Patient Health Questionnaire-9 (PHQ-9)¹⁶ is becoming widely used in clinical care for depression and provides information on symptom severity. A few studies have begun to integrate the PHQ-9 into analyses of outcomes for patients with MDD and TRD,^{15,17-23} including examining patterns of health resource utilization (HRU)^{15,17,19-22} and cost.^{15,17,20} To date, the only studies that have examined cost and depression symptoms have used self-report surveys of symptoms and service use, and these have not included data on clinical diagnoses or health care utilization or cost based on claims or electronic health records (EHRs).

Our objective was to examine whether including measures of depression symptom severity (PHQ-9 scores) could improve understanding of patterns of HRU and costs. We conducted our study within a sample of patients who are clinically identified as having MDD and a subsample of patients who also met criteria for TRD based on an algorithm using EHR and pharmacy data from the health system perspective.

METHODS

Data come from Kaiser Permanente Northwest (KPNW), an integrated health system providing health care to about 633,000 individuals in Oregon and Washington. Data are It is illegal to post this copyri Clinical Points

- Most studies of health care costs for persons with treatment-resistant depression use diagnoses to group people but do not take into consideration the level of symptoms patients are experiencing.
- Understanding the ongoing level of symptoms patients are experiencing can help to better focus resources on persons who are currently most in need.

from the Center for Health Research data warehouse. We estimated costs using the standardized relative resource cost algorithm (SRRCA)²⁴ and internal health plan data, with the exception of pharmacy dispensing, for which we used the approximate retail value. In addition, we included data from the PHQ-9,¹⁶ a patient questionnaire that has been used extensively since 2010 at KPNW both as a screening tool and to monitor treatment outcomes.

This study was reviewed and approved by the KPNW Institutional Review Board.

Study Design

We conducted a retrospective cohort study consisting of 2 mutually exclusive groups: (1) adults with MDD who met criteria for TRD and (2) adults with MDD, but no TRD (hereafter MDD). The study window was January 2014–December 2017. Because the focus of this study was to examine the impact of depression symptoms on HRU and cost, all subjects were required to have at least 2 PHQ-9 scores during the study window. Our study followed subjects for 12 months after their index date.

We included adults aged 18 years and over who had health plan eligibility during the study period and at least 1 system contact per year. We excluded persons with severe mental disorders (bipolar disorder, dementia, schizophrenia) and persons currently being treated for cancer (based on cancer tumor registry) because these disorders are very costly (See Supplementary Table 1).

The TRD group included adults who had at least 1 diagnosis of MDD (*ICD-9-CM*: 296.2x, 296.3x or *ICD-10-CM*: F32.X, F33.0–F33.2) and had received 2 courses of antidepressant treatment with an adequate dose and duration followed by an additional medication change (indicating that 2 prior treatments failed) within the study window. This definition is based on similar definitions in the literature and on national guidelines for adequate dose and duration.⁶ The index date for the TRD group was the first date when they met the TRD definition during the study window.

The MDD group included adults who had at least 1 MDD diagnosis but who never met the definition of TRD within the study window. The index date for the MDD group was the first MDD diagnosis received during the study window.

Outcomes

Outcomes included HRU and cost. The primary outcome was total all-cause health system cost for 1 year following index date. We also explored total mental health cost, total

Table 1. Comparison of EHR-Derived Characteristics of the Study Population by Group^a

	TRD	Non-TRD MDD	Р
Characteristic	(n=24,534)	(n=17,628)	Value
Age, mean (SD), y	52.8 (15.9)	48.2 (17.9)	<.001
Male	27.2	33.1	<.001
Race/ethnicity			<.001
Hispanic	4.2	7.3	<.001
White/Caucasian	95.0	90.9	<.001
Black/African American	1.9	4.2	<.001
Asian	1.5	3.0	<.001
American Indian/Alaska Native	1.3	1.4	.366
Hawaiian/Pacific Islander	0.5	0.7	.002
Other	0.4	0.6	.031
Insurance type			<.001
Commercial	64.2	61.1	<.001
Medicare	33.9	25.3	<.001
Medicaid	2.0	13.6	<.001
Household income, mean (SD),			
US \$			
< 50,000	38.7 (17.0)	39.9 (17.2)	<.001
50,000–99,999	33.4 (10.0)	33.1 (10.1)	.002
100,000 or more	28.0 (16.0)	27.0 (16.1)	<.001
Education level, mean (SD)			
High school or less	32.4 (14.5)	32.8 (14.8)	.020
Some college/	55.9 (9.6)	55.6 (9.9)	<.001
undergraduate degree			
Graduate/postgraduate/	11.6 (9.3)	11.7 (9.4)	.640
professional degree			
Anxiety disorder	68.2	58.1	<.001
Attention-deficit/hyperactivity	11.9	8.0	<.001
disorder			
Autism spectrum disorder	0.4	0.5	.031
Eating disorder	4.1	3.3	<.001
Other psychosis	3.4	2.8	.001
Overweight/obese	49.3	41.2	<.001
Substance abuse disorder	27.9	26.8	.013
Possibly self-inflicted injury	0.7	0.5	.001
Self-inflicted injury	1.5	1.2	.004
Myocardial infarction	8.4	7.9	.068
Congestive heart failure	7.7	5.7	<.001
Peripheral vascular disease	21.2	14.8	<.001
Cerebrovascular disease	14.3	12.8	<.001
Chronic pulmonary disease	40.3	33.9	< .001
Connective tissue/rheumatic	4.7	2.9	<.001
disease			
Pentic ulcer disease	8.8	67	< 001
Mild liver disease	13.0	10.5	< .001
Diabetes without chronic	23.2	19.4	< .001
complications/mild to	23.2	12.4	1.001
moderate			
Moderate or severe liver disease	0.8	0.6	.074
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values are snown as percentages u	Iness otherwise		
disorder TRD - treatment-resistant	iti record, MDL	= major depressi	ve
u_{1}			

mental health pharmacy cost, and total depression care cost for 1 year following index date. We obtained depression symptom rating scores on the PHQ-9,¹⁶ which measures persistence and severity of depression symptoms. Scores of 0 to 4 (low) indicate few or no depression symptoms, scores of 5–14 (moderate) indicate mild to moderate depression, and scores of 15+ (inclusive of 15; severe) indicate significant depression symptoms. We used the mean score from available PHQ-9 scores to assign subjects to these 3 groupings.

Statistical Analysis

The goal was to explore whether adding symptom information to HRU and cost analyses improves our understanding regarding patterns of HRU and cost for

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^aRisk ratio (and 95% Cl) measured as the exponentiated coefficient of TRD (relative to MDD) from γ regression, controlling for demographics (sex, age, race/ethnicity, poverty status), type of insurance (private, Medicaid/Medicare), comorbid physical health disorders (eg, diabetes), and behavioral health conditions (eg, substance use disorder). Abbreviations: ED = emergency department, MDD = major depressive disorder (only), MH = mental health, Rx=prescription, TRD = treatment-resistant depression.

persons. First, we compared HRU and cost for the TRD group to those for the MDD group overall and for different types of HRU/cost categories. Doing so allows comparison with recently published analyses. Next, we compared annual rates of HRU and cost within each group (TRD, MDD) based on level of symptoms (low, moderate, severe) to examine whether increasing levels of symptoms result in increased HRU and/or cost within each group. Baseline characteristics between groups were compared using χ^2 tests for categorical variables and ANOVAs for continuous variables. We used logistic regression for binary outcomes and negative binomial regression for count outcomes. Cost data are often not normally distributed, and after testing several specifications we selected general linear regression with a γ distribution and log link.^{25,26}

In all regression models, we included covariates likely to influence cost including demographics (sex, age, race/ ethnicity, poverty status), type of insurance (private, Medicaid/Medicare) comorbid physical health disorders (eg, diabetes), and behavioral health conditions (eg, substance use disorder).

RESULTS

During the study period, 24,534 patients met study criteria for TRD; 17,628 patients met study criteria for MDD, but never met criteria for TRD (see Supplementary Figure 1). The majority of study subjects meeting criteria for TRD and MDD were female (72.8% and 66.9%, respectively). Patients experiencing TRD were significantly older compared to the MDD group (mean age = 52.8 years vs 48.2 years; P < .001) and were more likely to be non-Hispanic White (95% compared to 91%; P < .001). For most other demographic

measures, the two groups were relatively similar (Table 1). The comorbidity burden was higher for patients with TRD, with higher rates of nearly all examined physical and mental health conditions (Table 1). We also examined differences in included compared to excluded participants (Supplementary Table 2).

Depression Symptoms

The pattern of depression symptom severity scores and individual item scores on the PHQ-9 was similar for the TRD and MDD groups, with the TRD group having modestly higher severity scores within each level (Supplementary Figure 2). In both groups, the majority of observations fell in the moderate severity range (TRD: 69%; MDD: 66%; see supplementary Table 4.1.a).

Comparison of HRU and Cost Overall for TRD and MDD

Figure 1 presents relative risk ratios comparing costs for TRD and MDD. The TRD group had significantly greater costs in all categories, with total all-cause costs 1.23 times greater than MDD (95% CI, 1.21–1.26). The TRD group also had significantly greater use of several expensive services including inpatient stays (odds ratio [OR] = 1.09; 95% CI, 1.02–1.17), ED visits (OR=1.09; 95% CI, 1.03–1.14), and outpatient visits (OR=1.42; 95% CI, 1.15–1.74). Tables reporting descriptive statistics and ORs or incident rate ratios (IRRs) associated with comparisons between the groups are available in Supplementary Tables 3.a and 3.b.

Patterns of HRU and Cost by Symptom

HRU. Figure 2 presents differences in the OR for any use of HRU by group (TRD, MDD) and by depression symptom severity. We compared 3 levels of symptom severity (severe







vs low, severe vs moderate, moderate vs low). The following comparisons were always significantly different for both TRD and MDD groups, with more severe symptoms always having significantly greater OR compared to lower severity: any MH ED visit, number of MH ED visits, any MH outpatient visit, number of MH outpatient visits, and any psychotherapy visit. Patients with greater symptom severity were more likely to have greater numbers of MH-related outpatient visits, including psychotherapy visits. In several categories, results were mixed. For example, the odds of any MH inpatient visit were significantly higher only when comparing the most severe patients in the TRD group with those in the lower severity groups. Of note, use of any MH prescription medication was not significantly different for any of the TRD group comparisons; for the MDD group, it was significant only for the severe compared to moderate and severe compared to low-severity groups. Detailed reporting of HRU for each group, and the OR/IRR associated with comparisons, is available in Supplementary Tables 4.1.a and 4.1.b.

Costs. Figure 3 summarizes the costs for the TRD and MDD groups by symptom severity. For both the TRD and MDD groups, those with more severe symptoms had greater total all-cause costs. For the TRD group, differences in total all-cause cost were significantly different between the severe and moderate (mean [SD] total cost: TRD moderate \$12,429

\$23,900], TRD severe \$13,344 P < .001) and the severe and low levels of symptoms (mean [SD] total all-cause cost: TRD low: \$12,220 [\$31,864], TRD severe: \$13,344 [\$22,895]; *P*<.001). For the MDD group, the pattern was similar, with total allcause cost significantly different between the severe and moderate (MDD moderate: \$8,899 [\$20,755], MDD severe: \$10,098 [\$22,853]; P < .001) and severe and low (MDD low: \$8,752 [\$25,800], MDD severe: \$10,098 [\$22,853]; P<.001). For 3 of the subcategories of costs, greater symptom severity was always significantly associated with higher costs (total MH costs, MH ED cost, total outpatient MH cost). Symptom severity was also associated with several non-mental health care cost categories. For other categories, the pattern was mixed. Detailed reporting of costs by subcategory and group and the relevant ratios associated with comparisons between the groups is available in Supplementary Tables 4.2.a, 4.2.b, and 5.

DISCUSSION

We found that the TRD group had significantly greater costs compared to the MDD group in all major categories. Within each group (TRD, MDD), greater severity of depression symptoms based on PHQ-9 scores was associated with higher levels of total cost. For most subcategories of costs and HRU, greater levels of symptoms were associated with greater use or cost, but not all results were significant. In general, differences in costs associated with more severe symptoms were driven by greater mental health costs. However, in some cases, non-mental health medical costs were also greater in groups with more severe depression symptoms.

Most previous studies have used claims data to estimate the economic burden of TRD.⁵⁻¹² These studies have reported higher costs for persons with TRD compared to persons with MDD and to persons without depression. Sussman and colleagues²⁷ reported mean annual health care costs of \$9,890 for TRD and \$6,848 for MDD, and Amos and colleagues⁶ reported that persons with TRD cost \$6,709 more than those with MDD and \$9,917 more than persons without MDD. Our results are similar to these, with patients with TRD costing on average 23% more than patients with MDD. Together, these results document the heavy burden of

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It is illegal to post this copyrighted BDE Figure 3. Unadjusted Annual Costs by Type of Cost and Symptom Level



both MDD and TRD in terms of patient, payer, and health system; increased HRU; and higher costs.

While these results are compelling, studies using claims data are limited. A key limitation is that estimates are based solely on clinical diagnoses and pharmacy records. These studies do not take into account the level of symptoms that patients may be experiencing. As health systems have increasingly begun to use patient-reported outcomes such as the PHQ-9 in regular care, the possibility of incorporating symptoms into the understanding of depression burden is increasing. One recent study, by Voelker and colleagues,²⁰ used an EHR/claims dataset that included PHQ-9 data and examined the odds of having inpatient encounters by symptom severity. The study found that increasing levels of symptoms led to increasing risk of all-cause and MDDrelated hospitalizations. Two other reports have used data from the 2013 US National Health and Wellness Survey, which included self-reported depression assessment using the PHQ-9 and self-reported service use data.¹⁵ Both reports also define TRD using PHQ-9 data. Chow and colleagues¹⁵ reported that health care costs were \$6,053, \$7,604, and \$10,611, respectively, for 3 PHQ-9–defined symptom groups (low, moderate, and severe) for persons with TRD. Using the same data, Singer and colleagues²¹ reported annual costs of \$8,145 for persons with MDD and moderately severe symptoms, \$15,321 for persons with TRD with moderately severe symptoms, \$11,680 for persons with MDD with severe symptoms, and \$19,592 for persons with TRD with severe symptoms. Our results, using clinical diagnoses, EHR data, and PHQ-9 data collected as part of clinical care, follow a similar pattern. However, whereas these studies are subject to recall bias, as patients reported diagnoses and

HRU, our study does not have such limitations. The current study confirms and amplifies earlier work that depended on patient self-report of diagnoses, symptoms, and HRU.

We sought to combine EHR and claims data with patientreported PHQ-9 data to refine our understanding of the economic burden of depression. Our results suggest that there is considerable variation in the level of symptoms in persons identified as having TRD or MDD. We also found that costs vary by symptom level in both patients with TRD and those with MDD, with costs rising as severity increases. Similar to previous studies that have used EHR/claims data to estimate the burden of TRD and MDD, we controlled for covariates including demographic data and clinically defined comorbidities. The current study adds to previous work by examining how level of depression symptoms impacts HRU and cost. We find that TRD status is a stronger driver of costs, with symptoms playing a significant, but secondary role. For example, the TRD group with the lowest symptom severity has higher costs than the highest severity MDD group.

There are several limitations to our study. The study is not generalizable to all health systems, as data came from only one system. We used inclusion/exclusion criteria that were necessary to allow us to accurately estimate costs, but these restrictions may not reflect the experience of a broader population. We were limited to including patients who had at least 2 PHQ-9 scores; doing so meant that some potential study subjects with TRD or MDD were not included, and this was a greater limitation for the MDD group.

Although the PHQ-9 is increasingly used in both screening and care management, there are likely biases in who gets screened or followed with the PHQ-9, and this may

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It is illegal to post this cop have biased the sample to more severe patients. Althoug patients with PHQ-9 data are similar to the larger full sample of patients identified with MDD and TRD in terms of their demographic characteristics, there could be unobserved differences in those who have PHQ-9 data. To make the study comparable to earlier work,¹⁵ we chose to use a 3-level categorization of the PHQ-9 data rather than the 5-level categorization and thus may have missed some differences in health care costs related to the expanded categories. We controlled directly for known differences between the TRD and MDD groups that would likely confound our estimates using widely accepted regression methods. Our methods for confounding control are similar to other methods such as propensity score modeling, especially given the large sample size; however, adjustment is limited to observable confounders. Like in previous studies of TRD using EHR/claims data to study costs, coding errors in claims or diagnoses could have occurred that allowed errors in inclusion/exclusion. We were not able to include a comparison group of persons with PHQ-9 scores who had neither MDD nor TRD. We considered this possibility but were concerned that persons with at least 2 PHQ-9 scores without any MDD diagnosis might have other unobserved characteristics that led providers to screen them. This study also did not include indirect costs of depression.⁶

Despite these limitations, the current study has several strengths. To our knowledge, it is the first that has combined EHR data, claims data, and PHQ-9 data collected during routine patient care. This perspective likely more closely reflects routine care compared to studies that have obtained data through patient surveys only. In addition, the study includes a large sample of patients, allowing detailed comparisons of HRU and costs and the ability to control **ghted PDF on any website**. for important covariates. Finally, the study uses recent data and thus provides an update to previous work on the cost of TRD and MDD.

Health systems are increasingly screening for depression with the PHQ-9 and similar measures, but there are large differences between systems, with some systems implementing widespread screening and others offering very limited screening.²² The data from the current study come from a health system in which providers do not have specific incentives to record depression symptoms in a particular way. However, some types of insurance or organizations might encourage providers to adjust scores to allow patients to receive specific treatments. As screening rates increase, future research will be able to extend our results. In particular, there may be opportunities to include more representative samples and to follow patients longitudinally to examine how patterns of HRU and cost are impacted as symptoms change.

CONCLUSION

Use of patient-reported depression symptoms can provide a more nuanced understanding of the clinical and economic burden of depression. This additional information about the burden of TRD and MDD, and subgroups of patients with different levels of symptoms within these groups, could aid in planning of clinical care by helping to target interventions to the persons most in need. Large health systems are in the unique position to manage patients with depression across the continuum of symptom severity. Research conducted in real-world settings can provide important insight to improve our understanding of the value of treatments for TRD and MDD.

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Potential conflicts of interest: Dr Pesa is an employee of Janssen Scientific Affairs, LLC, and a Johnson & Johnson stockholder. Dr Chow was an employee of Janssen Scientific Affairs, LLC, during the study operation and is a Johnson & Johnson stockholder. Drs Lynch and Dickerson and Ms O'Keeffe-Rosetti are employees of the Center for Health Research at Kaiser Permanente, a nonprofit health care research organization that has received research grants from Janssen Scientific Affairs, LLC, to conduct this study.

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See supplementary material for this article at PSYCHIATRIST.COM.



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Supplementary Material

- Article Title: Understanding the Relationship Between Depression Symptom Severity and Health Care Costs for Patients With Treatment-Resistant Depression
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Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Excluded Mental Health conditions

Diagnosis Class	ICD9_CD ¹	ICD10_CD ²
Bipolar Spectrum Disorder	296.7X	F31.70
Dementia	290.0	F03.90
Dementia	780.93	R41.X
Schizophrenia Spectrum Disorder	295.XX	F20.XX
Schizophrenia Spectrum Disorder	295.70	F25.X
Mood disorder due to known physiological condition	293.X	F06.3X
Cyclothymic disorder	301.13	F34.0

- 1. International Classification of Diseases, Ninth Revision (ICD-9)
- 2. International Classification of Diseases, Tenth Revision (ICD-10)

Supplementary Table 2. Comparison of Analysis Sample with Those Excluded because too few PHQ-9s.¹

	Analysis San (N=42,162	nple)	Excluded b/c ≤ (N=18,34	<i>p</i> -value	
	Mean or %	SD	Mean or %	SD	
Age	50.9	16.9	49.3	17.2	<.001
Male	29.7%		33.8%		<.001
Race/ethnicity					<.001
Hispanic	5.5%		5.1%		.034
White/Caucasian	93.3%		92.6%		.002
Black/African American	2.9%		2.7%		.372
Asian	2.1%		2.9%		<.001
American Indian/Alaska Native	1.4%		1.1%		.007
Hawaiian/Pacific Islander	0.6%		0.6%		.636
Other	0.5%		0.6%		.035
InsuranceType					<.001
Commercial	62.9%		72.3%		<.001
Medicare	30.3%		21.9%		<.001
Medicaid	6.8%		5.8%		<.001
Household Income: <\$50,000	39.2	17.1	37.8	16.8	<.001
Household Income: \$50,000-99,999	33.3	10.1	33.0	10.1	.020

Household Income: \$100,000 or more	27.6	16.1	29.2	16.5	<.00
High School or less	32.6	14.6	30.4	14.7	<.00
Some College/Undergraduate degree	55.8	9.7	56.5	9.4	<.00
Graduate/Post-graduate/Professional degree	11.6	9.3	13.0	10.0	<.00
Anxiety Disorder	64.0%		43.9%		<.00
Attention Deficit Disorder	10.3%		6.1%		<.00
Autism Spectrum Disorder	0.5%		0.3%		.00
Conduct/Disruptive behavior/Opp. Defiant	0.5%		0.5%		.83
Eating Disorder	3.8%		2.1%		<.00
Other Psychosis	3.2%		2.2%		<.00
Overweight/Obese	45.9%		33.3%		<.00
Substance Abuse Disorder	27.5%		19.9%		<.00
Possibly Self-Inflicted Injury	0.6%		0.2%		<.00
Self-Inflicted Injury	1.4%		0.7%		<.00
Myocardial infarction	8.2%		6.2%		<.00
Congestive heart failure	6.8%		5.5%		<.00
Peripheral vascular disease	18.5%		12.0%		<.00
Cerebrovascular disease	13.7%		11.7%		<.00
Chronic Pulmonary Disease	37.6%		27.5%		<.00
Connective tissue/rheumatic disease	3.9%		2.4%		<.00
Peptic ulcer disease	7.9%		5.2%		<.00
Mild liver disease	11.9%		7.7%		<.00
Diabetes without chronic complications/mild to moderate	21.6%		13.8%		<.00
Moderate or severe liver disease	0.7%		0.5%		.00

1. Patient Health Questionnaire 9

	TRD	3	Non-TRD	MDD ⁴		TRD com	pared to M	DD
	Mean or %	SD	Mean or %	SD	OR / IRR	Lower 95% Cl	Upper 95% Cl	<i>p</i> -value
All Services								
Any Inpatient Stay: Total (%)	11.1%		9.1%		1.09	1.02	1.17	.014
Number of Inpatient Stays: Total (mean)	0.16	0.58	0.13	0.52	1.08	1.00	1.16	.036
Number of Inpatient Days: Total (mean)	0.80	4.08	0.61	3.34	1.08	0.97	1.20	.151
Any ED Visit: Total (%)	28.3%		26.4%		1.09	1.03	1.14	.001
Number of ED Visits: Total (Mean)	0.58	1.56	0.60	1.85	1.03	0.99	1.08	.161
Any Outpatient Visit: Total (%)	99.1%		98.4%		1.42	1.15	1.74	.001
Number of Outpatient Visits: Total (Mean)	22.53	22.51	17.99	20.78	1.11	1.09	1.13	<.001
Any Other (Telephone, Email) Visit: Total (%)	98.6%		97.1%		1.64	1.41	1.91	<.001
Number of Other Visits: Total (Mean)	20.20	22.59	15.87	20.57	1.15	1.13	1.17	<.001
Any MH Medication	96.0%		72.7%		8.97	8.33	9.67	<.001
With a mental health diagnosis								
Any Inpatient Stay: (%)	10.2%		7.9%		1.14	1.06	1.23	<.001
Number of Inpatient Stays: (mean)	0.15	0.55	0.11	0.47	1.14	1.06	1.23	.001
Number of Inpatient Days: (mean)	0.73	3.79	0.52	3.07	1.16	1.04	1.30	.009
Any ED Visit: (%)	14.7%		13.8%		1.10	1.04	1.18	.002
Number of ED Visits: (Mean)	0.26	0.97	0.28	1.20	1.06	1.00	1.13	.067
Any Outpatient Visit: (%)	89.1%		82.7%		1.57	1.48	1.67	<.001
Number of Outpatient Visits: (Mean)	5.58	11.16	4.72	12.49	1.10	1.07	1.13	<.001
Any Other (Telephone, Email) Visit: (%)	46.4%		35.1%		1.51	1.44	1.58	<.001
Number of Other Visits: (Mean)	1.05	1.80	0.71	1.48	1.37	1.33	1.42	<.001
With a mental health specialty provider								
Any Inpatient Stay: (%)	10.2%		7.9%		1.14	1.06	1.23	.001
Number of Inpatient Stays: (mean)	0.15	0.55	0.11	0.47	1.14	1.05	1.22	.001
Number of Inpatient Days: (mean)	0.73	3.79	0.52	3.07	1.16	1.04	1.29	.010
Any Outpatient Visit: (%)	89.5%		83.4%		1.56	1.47	1.66	<.001
Number of Outpatient Visits: (Mean)	6.02	11.95	5.13	13.06	1.09	1.07	1.12	<.001
Any Other (Telephone, Email) Visit: (%)	60.3%		50.7%		1.37	1.31	1.43	<.001
Number of Other Visits: (Mean)	3.11	6.47	2.26	6.12	1.25	1.21	1.29	<.001
With a depression diagnosis								
Any Inpatient Stay: (%)	8.3%		5.9%		1.25	1.15	1.36	<.001

Number of Inpatient Stays: (mean)	0.11	0.46	0.08	0.37	1.26	1.15	1.37	<.001
Number of Inpatient Days: (mean)	0.56	3.38	0.36	2.35	1.29	1.14	1.46	<.001
Any ED Visit: (%)	8.0%		7.2%		1.12	1.03	1.22	.007
Number of ED Visits: (Mean)	0.12	0.53	0.11	0.60	1.11	1.02	1.21	.018
Any Outpatient Visit: (%)	78.7%		71.8%		1.39	1.33	1.46	<.001
Number of Outpatient Visits: (Mean)	3.58	6.12	2.74	5.07	1.15	1.12	1.18	<.001
Any Other (Telephone, Email) Visit: (%)	32.2%		24.0%		1.43	1.37	1.50	<.001
Number of Other Visits: (Mean)	0.59	1.21	0.39	0.92	1.43	1.37	1.49	<.001
With a depression diagnosis and a mental health provide	er							
Any Inpatient Stay: (%)	0.1%		0.1%		na	na	na	.356
Number of Inpatient Stays: (mean)	0.00	0.03	0.00	0.04	na	na	na	.409
Number of Inpatient Days: (mean)	0.01	0.31	0.01	0.44	na	na	na	.998
Any ED Visit: (%)	0.0%		0.1%		na	na	na	.392
Number of ED Visits: (Mean)	0.00	0.02	0.00	0.03	na	na	na	.587
Any Outpatient Visit: (%)	32.9%		27.5%		1.06	1.02	1.12	.009
Number of Outpatient Visits: (Mean)	2.05	5.71	1.58	4.78	1.13	1.07	1.19	<.001
Any Other (Telephone, Email) Visit: (%)	13.3%		7.8%		1.45	1.35	1.56	<.001
Number of Other Visits: (Mean)	0.25	0.88	0.13	0.62	1.56	1.45	1.69	<.001
With any mental health diagnosis any setting								
Any Psychotherapy Visit: (%)	25.8%		26.1%		0.78	0.75	0.82	<.001
Number of Psychotherapy Visits: (Mean)	2.06	6.38	1.81	5.44	0.97	0.91	1.04	.407
With any mental health diagnosis specialty setting								
Any Psychotherapy Visit: (%)	26.7%		27.0%		0.79	0.75	0.83	<.001
Number of Psychotherapy Visits: (Mean)	2.16	6.58	1.91	5.61	0.97	0.91	1.03	.384
With a depression diagnosis any setting								
Any Psychotherapy Visit: (%)	20.6%		21.2%		0.78	0.74	0.83	.000
Number of Psychotherapy Visits: (Mean)	1.38	4.60	1.23	4.04	0.99	0.92	1.06	.762
With a depression diagnosis specialty setting								
Any Psychotherapy Visit: (%)	20.6%		21.2%		0.78	0.74	0.82	<.001
Number of Psychotherapy Visits: (Mean)	1.36	4.56	1.22	4.03	0.98	0.92	1.06	.647
 Regression models include the following covar (private, Medicaid/Medicare), comorbid physi use disorder). 	iates: demo cal health di	graphics isorders ((gender, ag e.g., diabet	e, race/et es) and be	hnicity, p havioral	overty stat health con	tus), type of ditions (e.g	finsurance g., substance

2. Participants observed for a minimum of 1 year.

Supplementary Table 3.b. Adjusted ¹ comparison of health	upplementary Table 3.b. Adjusted ¹ comparison of health care costs by group and type of cost for one year ² following index date													
	TR	D	Non-TRI	D MDD		TRD co	mpared to MDD							
	Mean	SD	Mean	SD	В	Lower 95% Cl	Upper 95% Cl	<i>p</i> -value						
All Costs														
Total Cost	12,562	24,934	9071	22089	1.23	1.21	1.26	<.001						
Inpatient Costs: Total	3,402	15,688	2394	12750	1.15	1.08	1.22	<.001						
ED Costs: Total	671	2,488	594	2,364	1.13	1.07	1.18	<.001						
Outpatient Costs: Total	3,891	4,422	3,070	3,931	1.14	1.11	1.16	<.001						
Other Costs (telephone, email): Total	308	363	252	343	1.10	1.08	1.12	<.001						
Total RX Cost	3,433	11,063	2,098	11,835	1.58	1.53	1.62	<.001						
Total MH RX Cost	688	1,666	278	1,153	2.58	2.49	2.66	<.001						
Costs with mental health diagnosis														
Total Cost: With MH DX	5,013	16,355	3,632	13,871	1.19	1.15	1.24	<.001						
Inpatient Costs: With MH DX	3,095	14,495	2,050	11,647	1.22	1.15	1.30	<.001						
ED Costs: With MH DX	267	1,447	245	1,453	1.20	1.14	1.26	<.001						
Outpatient Costs: With MH DX	1,196	2,083	969	2,063	1.13	1.10	1.17	<.001						
Other Costs (telephone, email): With MH DX	18	33	13	28	1.30	1.26	1.34	<.001						
Costs with mental health diagnosis and specialty setting														
Total Cost: With MH Provider & DX	5,835	16,583	4,008	14,100	1.31	1.27	1.35	<.001						
Inpatient Costs: With MH Provider & DX	3,095	14,495	2,051	11,647	1.22	1.15	1.30	<.001						
ED Costs: With MH Provider & DX	271	1,466	252	1,474	1.19	1.13	1.25	<.001						
Outpatient Costs: With MH Provider & DX	1,231	2,120	1,004	2,112	1.13	1.10	1.16	<.001						
Other Costs (telephone, email): With MH Provider & DX	50	105	39	102	1.18	1.14	1.22	<.001						
Costs with depression diagnosis														
Total Cost: With Depression DX	3,568	13,732	2,347	10,823	1.26	1.21	1.31	<.001						
Inpatient Costs: With Depression DX	2,397	12,795	1,455	9,480	1.32	1.24	1.40	<.001						
ED Costs: With Depression DX	86	615	72	540	1.26	1.20	1.32	<.001						
Outpatient Costs: With Depression DX	805	1,589	603	1,265	1.18	1.14	1.22	<.001						
Other Costs (telephone, email): With Depression DX	10	22	7	17	1.32	1.28	1.36	<.001						

1. Regression models include the following covariates: demographics (gender, age, race/ethnicity, poverty status), type of insurance (private, Medicaid/Medicare), comorbid physical health disorders (e.g., diabetes) and behavioral health conditions (e.g., substance use disorder).

2. Participants observed for a minimum of 1 year.

Supplementary Table 4.1.a. Unadjusted description of healthcare resource use by group, depression symptom level and type of service for 1-year ¹ post index date															
			TRE)					Non-TRD	MDD	/IDD				
					Modera	ately					Modera	ately			
	Non-Mi	nimal	Mild-Mo	derate	Severe to	Severe	Non-Mi	nimal	Mild-Mo	derate	Severe to	Severe			
	(N=3,2	45)	(N=17,0	009)	(N=4,3	08)	(N=3,1	.47)	(N=11,	583)	(N=2,9	24)			
	Mean or		Mean or		Mean or		Mean or		Mean or		Mean or				
Description	%	SD	%	SD	%	SD	%	SD	%	SD	%	SD			
Any Service															
Any Inpatient Stay: Total (%)	11.3%		11.1%		11.2%		9.2%		8.9%		9.5%				
Number of Inpatient Stays: Total (mean)	0.16	0.54	0.16	0.58	0.17	0.63	0.12	0.42	0.13	0.51	0.14	0.64			
Number of Inpatient Days: Total (mean)	0.79	6.13	0.80	3.72	0.81	3.44	0.57	2.82	0.59	3.09	0.73	4.56			
Any ED Visit: Total (%)	23.9%		28.0%		33.1%		20.0%		25.8%		35.3%				
Number of ED Visits: Total (Mean)	0.47	1.68	0.56	1.47	0.75	1.77	0.41	1.51	0.57	1.78	0.88	2.37			
Any Outpatient Visit: Total (%)	99.4%		99.1%		99.0%		98.6%		98.3%		98.3%				
Number of Outpatient Visits: Total (Mean)	21.01	20.92	22.40	22.42	24.22	23.87	16.82	18.73	17.87	19.53	19.74	26.74			
Any Other (Telephone, Email) Visit: Total (%)	98.6%		98.5%		98.7%		96.6%		97.0%		98.1%				
Number of Other Visits: Total (Mean)	17.79	19.79	20.00	22.52	22.78	24.52	13.90	17.44	15.72	20.53	18.57	23.41			
With a mental health diagnosis															
Any Inpatient Stay: (%)	10.4%		10.2%		10.2%		7.9%		7.7%		8.6%				
Number of Inpatient Stays: (mean)	0.14	0.49	0.15	0.55	0.16	0.60	0.10	0.36	0.11	0.46	0.13	0.62			
Number of Inpatient Days: (mean)	0.71	5.32	0.72	3.54	0.75	3.31	0.48	2.48	0.50	2.76	0.67	4.48			
Any ED Visit: (%)	10.8%		14.1%		20.0%		9.0%		13.0%		22.3%				
Number of ED Visits: (Mean)	0.18	0.99	0.24	0.88	0.39	1.24	0.15	0.85	0.26	1.14	0.49	1.66			
Any Outpatient Visit: (%)	86.7%		89.0%		91.2%		76.5%		82.9%		88.6%				
Number of Outpatient Visits: (Mean)	3.67	8.57	5.39	11.03	7.76	12.90	3.07	9.33	4.55	10.10	7.13	20.87			
Any Other (Telephone, Email) Visit: (%)	36.9%		46.1%		54.7%		22.9%		35.6%		46.3%				
Number of Other Visits: (Mean)	0.69	1.27	1.02	1.74	1.47	2.27	0.41	1.05	0.69	1.42	1.11	1.96			
With a mental health diagnosis and specialty															
care															
Any Inpatient Stay: (%)	10.4%		10.2%		10.2%		7.9%		7.7%		8.6%				
Number of Inpatient Stays: (mean)	0.14	0.49	0.15	0.55	0.16	0.60	0.10	0.36	0.11	0.46	0.13	0.62			
Number of Inpatient Days: (mean)	0.71	5.32	0.72	3.54	0.75	3.31	0.48	2.48	0.50	2.76	0.67	4.48			
Any Outpatient Visit: (%)	87.4%		89.4%		91.5%		77.3%		83.5%		89.2%				
Number of Outpatient Visits: (Mean)	3.97	9.05	5.80	11.79	8.44	13.97	3.30	9.74	4.97	10.80	7.73	21.33			
Any Other (Telephone, Email) Visit: (%)	48.5%		60.0%		70.6%		33.8%		51.5%		65.4%				
Number of Other Visits: (Mean)	1.69	3.54	2.87	6.03	5.09	8.95	1.14	3.24	2.15	5.98	3.90	8.32			
With a depression diagnosis															
Any Inpatient Stay: (%)	8.6%		8.2%		8.1%		6.2%		5.6%		6.8%				
Number of Inpatient Stays: (mean)	0.11	0.43	0.11	0.46	0.12	0.50	0.07	0.30	0.07	0.35	0.10	0.48			
Number of Inpatient Days: (mean)	0.58	5.16	0.55	3.09	0.56	2.73	0.33	1.72	0.33	2.14	0.48	3.49			
Any ED Visit: (%)	5.8%		7.5%		11.5%		4.6%		6.6%		12.5%				
Number of ED Visits: (Mean)	0.08	0.63	0.10	0.46	0.19	0.70	0.06	0.32	0.10	0.59	0.21	0.80			
Any Outpatient Visit: (%)	75.0%		78.7%		81.5%		65.6%		71.8%		78.7%				
Number of Outpatient Visits: (Mean)	2.23	3.54	3.47	5.81	5.03	8.20	1.79	3.32	2.75	4.95	3.75	6.65			
Any Other (Telephone, Email) Visit: (%)	24.0%		32.2%		38.8%		14.5%		24.4%		32.7%				

Number of Other Visits: (Mean)	0.35	0.77	0.57	1.18	0.82	1.51	0.21	0.59	0.38	0.89	0.61	1.26
With a depression diagnosis and specialty care												
Any Inpatient Stay: (%)	0.0%		0.1%		0.2%		0.0%		0.1%		0.3%	
Number of Inpatient Stays: (mean)	0.00	0.02	0.00	0.03	0.00	0.05	0.00	0.02	0.00	0.03	0.00	0.07
Number of Inpatient Days: (mean)	0.00	0.14	0.01	0.21	0.03	0.62	0.00	0.05	0.01	0.30	0.04	0.90
Any ED Visit: (%)	0.0%		0.0%		0.0%		0.0%		0.0%		0.1%	
Number of ED Visits: (Mean)	0.00	0.00	0.00	0.01	0.00	0.05	0.00	0.02	0.00	0.03	0.00	0.04
Any Outpatient Visit: (%)	21.7%		32.3%		43.8%		16.4%		28.0%		37.3%	
Number of Outpatient Visits: (Mean)	0.92	3.19	1.95	5.44	3.27	7.68	0.80	3.02	1.60	4.68	2.32	6.33
Any Other (Telephone, Email) Visit: (%)	8.2%		12.8%		19.5%		4.1%		7.3%		13.8%	
Number of Other Visits: (Mean)	0.13	0.51	0.23	0.85	0.41	1.15	0.06	0.36	0.12	0.56	0.27	0.94
With a mental health diagnosis												
Any Psychotherapy Visit: (%)	14.0%		25.6%		35.4%		15.8%		26.8%		34.1%	
Number of Psychotherapy Visits: (Mean)	1.03	4.51	1.98	6.10	3.12	8.25	1.06	4.27	1.88	5.42	2.37	6.44
Any Psychotherapy Visit: (%)	15.2%		26.5%		36.3%		16.4%		27.8%		35.1%	
Number of Psychotherapy Visits: (Mean)	1.11	4.67	2.08	6.33	3.24	8.39	1.13	4.48	1.97	5.59	2.51	6.63
With a depression diagnosis												
Any Psychotherapy Visit: (%)	9.6%		20.5%		29.4%		12.0%		22.0%		28.1%	
Number of Psychotherapy Visits: (Mean)	0.55	2.56	1.34	4.42	2.16	6.11	0.67	2.87	1.27	4.00	1.65	5.10
Any Psychotherapy Visit: (%)	9.6%		20.5%		29.3%		12.0%		22.0%		28.0%	
Number of Psychotherapy Visits: (Mean)	0.54	2.53	1.32	4.38	2.14	6.05	0.66	2.86	1.26	3.98	1.64	5.10
 Participants observed for a minimum of TRD is treatment resistant depression non-TRD MDD is major depressive disor 	1 year. der, but not	TRD										

Supplementary Table 4.1.b. Ad	pplementary Table 4.1.b. Adjusted ¹ comparison of health care use by group, depression symptom level, and type of service for one year ² follow																							
						TF	RD ³											Non-TR	D MDD ⁴					
	Sever	e compar	ed to Moo	lerate	Se	vere com	pared to N	1ild	Moo	lerate con	npared to	Mild	Sever	re compar	ed to Moo	derate	Se	vere comp	oared to N	ſild	Мос	lerate con	pared to	Mild
		Lower 95%	Upper 95%	p-	OR /	Lower 95%	Upper 95%	p-	OR /	Lower 95%	Upper 95%	p-	OR /	Lower 95%	Upper 95%	p-	OR /	Lower 95%	Upper 95%	p-	OR /	Lower 95%	Upper 95%	p-
Description		CI ⁷	CI	value		CI	CI	value		CI	CI	value		CI	CI	value	inter	CI	CI	value		CI	CI	value
Any Service							1			1	1	I	1			1					LI			
Any Inpatient Stay: Total (%)	1.13	1.01	1.26	0.02	1.18	1.01	1.37	0.02	1.04	0.92	1.18	0.40	1.05	0.91	1.22	0.54	1.04	0.87	1.26	0.54	0.99	0.86	1.15	0.62
Number of Inpatient Stays: Total (mean)	1.19	1.07	1.33	0.00	1.25	1.08	1.45	0.00	1.05	0.93	1.19	0.45	1.12	0.97	1.29	0.13	1.22	1.01	1.48	0.03	1.10	0.95	1.27	0.22
Number of Inpatient Days: Total (mean)	1.20	1.02	1.42	0.03	1.19	0.95	1.49	0.13	0.99	0.82	1.19	0.91	1.24	0.99	1.55	0.06	1.28	0.97	1.69	0.08	1.04	0.83	1.28	0.75
Any ED Visit: Total (%)	1.26	1.17	1.36	0.00	1.53	1.38	1.71	0.00	1.22	1.11	1.33	0.57	1.39	1.27	1.53	0.00	1.86	1.64	2.10	0.00	1.33	1.20	1.48	0.56
Number of ED Visits: Total (Mean)	1.30	1.21	1.39	0.00	1.48	1.34	1.64	0.00	1.14	1.05	1.24	0.00	1.32	1.21	1.44	0.00	1.69	1.51	1.90	0.00	1.28	1.16	1.41	0.00
Any Outpatient Visit: Total (%)	0.94	0.66	1.36	0.73	0.92	0.53	1.62	0.73	0.98	0.60	1.60	0.91	1.09	0.78	1.53	0.49	1.18	0.75	1.83	0.49	1.08	0.76	1.53	0.97
Number of Outpatient Visits: Total (Mean)	1.13	1.10	1.16	0.00	1.23	1.18	1.28	0.00	1.08	1.05	1.12	0.00	1.11	1.07	1.15	0.00	1.23	1.18	1.29	0.00	1.11	1.07	1.15	0.00
Any Other (Telephone, Email) Visit: Total (%)	1.27	0.93	1.73	0.06	1.48	0.98	2.23	0.06	1.16	0.84	1.61	0.73	1.72	1.27	2.33	0.00	2.37	1.67	3.36	0.00	1.37	1.09	1.73	0.28
Number of Other Visits: Total (Mean)	1.17	1.14	1.21	0.00	1.30	1.25	1.36	0.00	1.11	1.08	1.15	0.00	1.18	1.13	1.22	0.00	1.37	1.31	1.44	0.00	1.17	1.12	1.21	0.00
With a mental health diagnosis	5																							
Any Inpatient Stay: (%)	1.11	0.99	1.25	0.05	1.15	0.98	1.35	0.05	1.04	0.91	1.18	0.46	1.10	0.94	1.28	0.24	1.10	0.91	1.34	0.24	1.01	0.86	1.17	0.46
Number of Inpatient Stays: (mean)	1.19	1.06	1.33	0.00	1.25	1.07	1.46	0.01	1.05	0.92	1.19	0.48	1.19	1.02	1.38	0.03	1.31	1.07	1.60	0.01	1.10	0.94	1.29	0.23
Number of Inpatient Days: (mean)	1.21	1.02	1.44	0.03	1.19	0.94	1.51	0.15	0.98	0.81	1.19	0.84	1.34	1.06	1.71	0.01	1.36	1.01	1.83	0.04	1.01	0.80	1.28	0.91
Any ED Visit: (%)	1.40	1.28	1.54	0.00	1.76	1.53	2.03	0.00	1.26	1.11	1.42	0.00	1.58	1.42	1.77	0.00	2.06	1.76	2.42	0.00	1.30	1.13	1.50	0.00
Number of ED Visits: (Mean)	1.46	1.33	1.60	0.00	1.74	1.51	2.00	0.00	1.19	1.06	1.35	0.00	1.58	1.41	1.77	0.00	2.17	1.84	2.56	0.00	1.38	1.20	1.58	0.00
Any Outpatient Visit: (%)	1.29	1.14	1.45	0.00	1.65	1.42	1.92	0.00	1.28	1.14	1.44	0.00	1.51	1.33	1.71	0.00	2.20	1.90	2.55	0.00	1.46	1.33	1.61	0.00
Number of Outpatient Visits: (Mean)	1.33	1.29	1.38	0.00	1.85	1.76	1.95	0.00	1.39	1.33	1.45	0.00	1.36	1.29	1.43	0.00	1.94	1.82	2.07	0.00	1.43	1.36	1.50	0.00
Any Other (Telephone, Email) Visit: (%)	1.26	1.18	1.35	0.00	1.66	1.51	1.83	0.00	1.32	1.22	1.42	0.49	1.42	1.31	1.55	0.00	2.40	2.14	2.69	0.00	1.69	1.54	1.85	0.01
Number of Other Visits: (Mean)	1.32	1.25	1.38	0.00	1.75	1.63	1.89	0.00	1.33	1.25	1.42	0.00	1.43	1.33	1.53	0.00	2.18	1.98	2.40	0.00	1.52	1.41	1.65	0.00
With a mental health diagnosis	and sett	ing		1	1	I		1			1			I	I	1		I		T	1			
Any Inpatient Stay: (%)	1.11	0.99	1.25	0.05	1.15	0.98	1.35	0.05	1.04	0.91	1.18	0.46	1.10	0.94	1.28	0.24	1.10	0.91	1.34	0.24	1.01	0.86	1.17	0.46
Number of Inpatient Stays: (mean)	1.19	1.06	1.33	0.00	1.25	1.07	1.46	0.01	1.05	0.92	1.19	0.48	1.19	1.02	1.38	0.03	1.31	1.07	1.60	0.01	1.10	0.94	1.29	0.23
Number of Inpatient Days: (mean)	1.21	1.02	1.44	0.03	1.19	0.94	1.51	0.15	0.98	0.81	1.19	0.84	1.34	1.06	1.71	0.01	1.36	1.01	1.83	0.04	1.01	0.80	1.28	0.91
Any Outpatient Visit: (%)	1.40	1.28	1.54	0.00	1.76	1.53	2.03	0.00	1.26	1.11	1.42	0.18	1.58	1.42	1.77	0.00	2.06	1.76	2.42	0.00	1.30	1.13	1.50	0.05
Number of Outpatient Visits: (Mean)	1.46	1.33	1.60	0.00	1.74	1.51	2.00	0.00	1.19	1.06	1.35	0.00	1.58	1.41	1.77	0.00	2.17	1.84	2.56	0.00	1.38	1.20	1.58	0.00

Any Other (Telephone, Email) Visit: (%)	1.29	1.14	1.45	0.00	1.65	1.42	1.92	0.00	1.28	1.14	1.44	0.97	1.51	1.33	1.71	0.00	2.20	1.90	2.55	0.00	1.46	1.33	1.61	0.73
Number of Other Visits: (Mean)	1.33	1.29	1.38	0.00	1.85	1.76	1.95	0.00	1.39	1.33	1.45	0.00	1.36	1.29	1.43	0.00	1.94	1.82	2.07	0.00	1.43	1.36	1.50	0.00
With a depression diagnosis																								
Any Inpatient Stay: (%)	1.08	0.95	1.23	0.19	1.11	0.93	1.32	0.19	1.02	0.89	1.18	0.58	1.21	1.02	1.43	0.09	1.13	0.91	1.40	0.09	0.93	0.79	1.11	0.06
Number of Inpatient Stays: (mean)	1.16	1.02	1.31	0.02	1.19	1.00	1.42	0.05	1.03	0.89	1.18	0.71	1.29	1.08	1.53	0.00	1.31	1.05	1.64	0.02	1.02	0.85	1.22	0.84
Number of Inpatient Days: (mean)	1.14	0.94	1.38	0.17	1.06	0.81	1.38	0.68	0.93	0.75	1.15	0.48	1.45	1.10	1.91	0.01	1.51	1.07	2.13	0.02	1.04	0.80	1.36	0.75
Any ED Visit: (%)	1.51	1.35	1.69	0.00	1.87	1.56	2.24	0.00	1.24	1.06	1.46	0.08	1.71	1.49	1.96	0.00	2.18	1.77	2.69	0.00	1.28	1.06	1.54	0.02
Number of ED Visits: (Mean)	1.58	1.40	1.78	0.00	1.82	1.51	2.19	0.00	1.15	0.98	1.35	0.09	1.67	1.43	1.94	0.00	2.35	1.88	2.94	0.00	1.41	1.16	1.71	0.00
Any Outpatient Visit: (%)	1.27	1.16	1.38	0.00	1.68	1.50	1.89	0.00	1.33	1.21	1.45	0.51	1.47	1.33	1.62	0.00	2.04	1.81	2.30	0.00	1.39	1.28	1.52	0.46
Number of Outpatient Visits: (Mean)	1.39	1.34	1.45	0.00	2.10	1.98	2.22	0.00	1.51	1.43	1.58	0.00	1.34	1.27	1.41	0.00	1.97	1.84	2.11	0.00	1.47	1.40	1.56	0.00
Any Other (Telephone, Email) Visit: (%)	1.27	1.19	1.36	0.00	1.81	1.63	2.01	0.00	1.42	1.30	1.55	0.07	1.45	1.32	1.58	0.00	2.60	2.28	2.96	0.00	1.80	1.61	2.01	0.01
Number of Other Visits: (Mean)	1.36	1.28	1.45	0.00	2.08	1.90	2.29	0.00	1.53	1.41	1.66	0.00	1.54	1.42	1.68	0.00	2.63	2.33	2.96	0.00	1.70	1.54	1.88	0.00
With a depression diagnosis ar	nd special	ty setting																						
Any Inpatient Stay: (%)	2.24	0.99	5.06	0.04	5.56	0.70	44.37	0.04	2.48	0.32	18.89	0.93	3.24	1.32	7.93	0.01	7.35	0.91	59.52	0.01	2.27	0.28	18.10	0.77
Number of Inpatient Stays: (mean)	2.12	0.91	4.94	0.08	6.06	0.73	50.49	0.10	2.86	0.36	22.49	0.32	3.39	1.42	8.12	0.01	7.69	0.96	61.34	0.05	2.27	0.29	17.98	0.44
Number of Inpatient Days: (mean)	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Any ED Visit: (%)	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Number of ED Visits: (Mean)	1.50	1.39	1.61	0.00	2.34	2.10	2.60	0.00	1.56	1.43	1.71	0.50	1.57	1.43	1.72	0.00	2.80	2.46	3.19	0.00	1.79	1.60	1.99	0.09
Any Outpatient Visit: (%)	1.49	1.37	1.62	0.00	2.96	2.62	3.35	0.00	1.99	1.80	2.20	0.00	1.47	1.31	1.65	0.00	2.85	2.46	3.30	0.00	1.94	1.73	2.17	0.00
Number of Outpatient Visits: (Mean)	1.53	1.40	1.67	0.00	2.28	1.96	2.65	0.00	1.49	1.30	1.71	0.80	2.02	1.77	2.31	0.00	3.37	2.72	4.17	0.00	1.67	1.37	2.02	0.13
Any Other (Telephone, Email) Visit: (%)	1.65	1.49	1.82	0.00	2.77	2.36	3.25	0.00	1.68	1.46	1.93	0.00	2.23	1.91	2.60	0.00	3.66	2.93	4.57	0.00	1.64	1.35	1.99	0.00
Number of Other Visits: (Mean)	2.24	0.99	5.06	0.04	5.56	0.70	44.37	0.04	2.48	0.32	18.89	0.93	3.24	1.32	7.93	0.01	7.35	0.91	59.52	0.01	2.27	0.28	18.10	0.77
All psychotherapy																								
Any Psychotherapy Visit: (%)	1.37	1.27	1.48	0.00	2.40	2.13	2.70	0.00	1.75	1.58	1.94	0.00	1.38	1.26	1.52	0.00	2.39	2.09	2.73	0.00	1.73	1.55	1.93	0.01
Number of Psychotherapy Visits: (Mean)	1.36	1.20	1.54	0.00	2.71	2.29	3.22	0.00	1.99	1.73	2.29	0.00	1.14	0.99	1.32	0.07	2.10	1.75	2.52	0.00	1.84	1.60	2.11	0.00
Any mental health diagnosis																								
Any Psychotherapy Visit: (%)	1.38	1.28	1.49	0.00	2.52	2.23	2.85	0.00	1.83	1.64	2.04	0.00	1.38	1.26	1.52	0.00	2.38	2.08	2.72	0.00	1.72	1.54	1.92	0.01
Number of Psychotherapy Visits: (Mean)	1.35	1.22	1.50	0.00	2.52	2.18	2.92	0.00	1.86	1.65	2.10	0.00	1.14	1.01	1.29	0.03	1.99	1.70	2.32	0.00	1.74	1.55	1.97	0.00
Any mental health diagnosis																								
and specialty setting																								
Any Psychotherapy Visit: (%)	1.37	1.27	1.48	0.00	2.40	2.13	2.70	0.00	1.75	1.58	1.94	0.00	1.38	1.26	1.52	0.00	2.39	2.09	2.73	0.00	1.73	1.55	1.93	0.01
Number of Psychotherapy Visits: (Mean)	1.35	1.22	1.49	0.00	2.42	2.10	2.80	0.00	1.80	1.60	2.02	0.00	1.13	1.01	1.27	0.04	1.94	1.67	2.26	0.00	1.72	1.53	1.94	0.00
Any depression diagnosis																								
Any Psychotherapy Visit: (%)	1.44	1.34	1.56	0.00	3.11	2.71	3.56	0.00	2.15	1.90	2.44	0.00	1.41	1.28	1.56	0.00	2.62	2.27	3.03	0.00	1.86	1.65	2.09	0.00
Number of Psychotherapy Visits: (Mean)	1.39	1.24	1.56	0.00	3.09	2.62	3.65	0.00	2.23	1.94	2.55	0.00	1.23	1.08	1.41	0.00	2.38	2.00	2.82	0.00	1.93	1.69	2.20	0.00
Mental Health Medication																								

Any MH Medication	1.02	0.86	1.21	0.51	0.86	0.67	1.11	0.51	0.85	0.68	1.05	0.21	1.28	1.15	1.41	0.00	1.44	4 1.27	1.62	0.00	1.13	1.03	1.23	0.09
1. Regression model	s include	the follo	owing co	ovariates:	demogr	aphics (g	gender, a	ge, race/	ethnicity	y, povert	ty status)	, type of	insuran	ce (privat	e, Medic	aid/Me	dicare), comorbic	l physica	health	disorders	s (e.g., dia	abetes) a	and
behavioral health	conditio	ns (e.g.,	substand	ce use dis	order).																			
2. Participants obser	ved for a	i minimu	ım of 1 y	/ear.																				
3. TRD is treatment i	3. TRD is treatment resistant depression																							
4. non-TRD MDD is r	najor dep	oressive	disorder	r, but not	TRD																			
5. OR is odds ratio	5. OR is odds ratio																							
6. IRR is incident rate	6. IRR is incident rate ratio																							
7. Cl is confidence in	terval																							

			D ²			Non-TRD MDD ³							
	Non-M	linimal	Mild-M	oderate	Mode Seve Sev	rately re to ere	Non-N	/inimal	M Mod	ild- erate	Moderately Severe to Severe		
	(N=3	,245)	(N=17,009)		(N=4	,308)	(N=3	3,147)	(N=1	1,583)	(N=2,924)		
Descriptions	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
All Costs													
Total Cost	12,220	31,864	12,429	23,900	13,344	22,895	8,752	25,800	8,899	20,755	10,098	22,853	
Inpatient Costs	3 <i>,</i> 548	21,942	3,434	15,006	3,169	12,307	2,301	10,837	2,352	12,343	2,659	15,860	
ED Costs	572	2,822	659	2,428	792	2,446	483	2,812	573	2,161	798	2,583	
Outpatient Costs	3,621	4,316	3,852	4,306	4,246	4,906	2,791	3,878	3,066	3,845	3,388	4,290	
Costs with mental health diagnosis													
Total Cost	4,547	19,407	4,986	16,245	5,473	14,113	3,033	10,944	3,529	13,677	4,686	17,039	
Inpatient Costs	3,205	18,637	3,132	14,235	2,865	11,672	1,957	9,819	1,990	11,176	2,387	14,847	
ED Costs	198	1,525	255	1,423	369	1,476	158	1,606	223	1,253	427	1,923	
Outpatient Costs	888	1,613	1,169	2,024	1,539	2,532	690	1,560	946	1,905	1,360	2,908	
Medication costs													
Total RX Cost	3 <i>,</i> 500	15,271	3,339	9,736	3,754	12,160	2,402	20,479	1,993	8 <i>,</i> 998	2,186	8,575	
Total MH RX Cost	606	1,700	652	1,551	893	2,024	195	695	259	1,050	446	1,763	

3. non-TRD MDD is major depressive disorder, but not TRD

Supplementary Table 4.	2.b. Ad	justed ¹ co	ompariso	n of hea	alth care	e costs by	group, d	epressio	n sympt	tom leve	l, and typ	e of cost	for one	e year ² fo	llowing ir	ndex dat	e							
	TRD ³																	Non-TR	D MDD ⁴					
	Severe compared to Moderate					Severe compared to Mild			Mod	lerate co	mpared to	o Mild	Severe compared to Moderate				Severe compared to Mild				Mod	lerate coi	npared to	o Mild
	OR ⁵	Lower	Upper	p -	OR	Lower	Upper	p-	OR	Lower	Upper	p-	OR	Lower	Upper	p -	OR	Lower	Upper	p -	OR	Lower	Upper	p-
.	/	95%	95%	value	/	95%	95%	value	/	95%	95%	value	/	95%	95%	value	/	95%	95%	value	/	95%	95%	value
Description	IRR®	CI'	CI		IKK	CI	CI		IKK	CI	CI		IKK	CI	CI		IRK	CI	CI		IKK	CI	CI	
All Costs	1.10	1.12	1.24		4.24	4.45	1.20	0.00	4.05	1.01	1.00	0.02	4.22	4 4 7	4.20	0.00	4 25	4.4.0	4.22	0.00	4.05	1.00	4 00	
	1.16	1.12	1.21	0.00	1.21	1.15	1.28	0.00	1.05	1.01	1.09	0.02	1.23	1.17	1.28	0.00	1.25	1.18	1.33	0.00	1.05	1.00	1.09	0.05
Inpatient Costs	1.11	1.01	1.23	0.04	1.07	0.93	1.23	0.35	0.99	0.88	1.10	0.79	1.35	1.19	1.52	0.00	1.22	1.04	1.44	0.01	1.06	0.94	1.19	0.34
ED Costs	1.26	1.16	1.36	0.00	1.44	1.28	1.62	0.00	1.18	1.07	1.29	0.00	1.23	1.12	1.36	0.00	1.64	1.44	1.88	0.00	1.30	1.18	1.44	0.00
Outpatient Costs	1.15	1.11	1.18	0.00	1.24	1.19	1.30	0.00	1.07	1.03	1.11	0.00	1.12	1.07	1.1/	0.00	1.25	1.18	1.33	0.00	1.13	1.08	1.1/	0.00
(telephone email)	1.22	1.18	1.26	0.00	1.40	1.34	1.47	0.00	1.15	1.11	1.19	0.00	1.22	1.17	1.27	0.00	1.44	1.36	1.52	0.00	1.19	1.14	1.23	0.00
Total RX Cost	1.17	1.12	1.22	0.00	1.17	1.10	1.24	0.00	1.00	0.95	1.05	0.98	1.21	1.14	1.29	0.00	1.03	0.94	1.12	0.52	0.77	0.72	0.82	0.00
With any mental health	diagno	sis																						
Total Cost	1.23	1.16	1.30	0.00	1.32	1.21	1.43	0.00	1.11	1.04	1.18	0.00	1.42	1.32	1.52	0.00	1.64	1.48	1.81	0.00	1.21	1.13	1.30	0.00
Inpatient Costs	1.12	1.01	1.24	0.03	1.04	0.90	1.21	0.56	0.97	0.87	1.08	0.60	1.41	1.24	1.59	0.00	1.27	1.08	1.50	0.00	1.02	0.91	1.14	0.77
ED Costs	1.38	1.27	1.50	0.00	1.63	1.45	1.84	0.00	1.24	1.14	1.36	0.00	1.62	1.47	1.79	0.00	2.72	2.39	3.10	0.00	1.45	1.32	1.60	0.00
Outpatient Costs	1.26	1.20	1.32	0.00	1.61	1.50	1.72	0.00	1.25	1.18	1.31	0.00	1.32	1.24	1.41	0.00	1.81	1.66	1.98	0.00	1.33	1.25	1.42	0.00
Other Costs (telephone, email)	1.35	1.29	1.42	0.00	1.86	1.73	1.99	0.00	1.36	1.29	1.43	0.00	1.43	1.35	1.52	0.00	2.10	1.94	2.28	0.00	1.47	1.39	1.56	0.00
Mental health diagnosis	and sn	ecialty se	otting																					<u> </u>
Total Cost	1.24	1.18	1.30	0.00	1.32	1.23	1.41	0.00	1.09	1.03	1.15	0.00	1.42	1.33	1.51	0.00	1.67	1.53	1.82	0.00	1.22	1.15	1.30	0.00
Innatient Costs	1 12	1 01	1 23	0.03	1 04	0.90	1 21	0.56	0.97	0.87	1.09	0.61	1 40	1 24	1 58	0.00	1 27	1.08	1 50	0.00	1 02	0.91	1 1 5	0.74
FD Costs	1 36	1 25	1 48	0.00	1.57	1 39	1 77	0.00	1 1 9	1.08	1 30	0.00	1.10	1 46	1.30	0.00	2.76	2.00	3 15	0.00	1 48	1 34	1.13	0.00
Outpatient Costs	1.27	1.21	1.33	0.00	1.62	1.51	1.73	0.00	1.24	1.18	1.31	0.00	1.33	1.25	1.41	0.00	1.82	1.67	1.98	0.00	1.34	1.26	1.42	0.00
Other Costs	1.27	1.21	1.55	0.00	1.02	1.51	1.75	0.00	1.2 1	1.10	1.51	0.00	1.55	1.25	1.11	0.00	1.02	1.07	1.50	0.00	1.01	1.20	1.12	0.00
(telephone, email	1.62	1.54	1.70	0.00	2.51	2.33	2.70	0.00	1.53	1.45	1.62	0.00	1.64	1.54	1.75	0.00	2.81	2.58	3.06	0.00	1.68	1.58	1.79	0.00
With a depression Diagr	nosis																-							
Total Cost	1.21	1.14	1.29	0.00	1.30	1.18	1.42	0.00	1.10	1.02	1.18	0.01	1.44	1.33	1.56	0.00	1.65	1.48	1.85	0.00	1.23	1.14	1.33	0.00
Inpatient Costs	1.03	0.93	1.14	0.56	0.94	0.81	1.08	0.37	0.94	0.84	1.05	0.27	1.49	1.32	1.68	0.00	1.32	1.12	1.56	0.00	1.04	0.92	1.16	0.54
ED Costs	1.61	1.49	1.74	0.00	1.91	1.70	2.16	0.00	1.22	1.12	1.33	0.00	1.53	1.40	1.68	0.00	2.27	1.97	2.62	0.00	1.29	1.18	1.41	0.00
Outpatient Costs	1.30	1.23	1.37	0.00	1.75	1.62	1.90	0.00	1.32	1.25	1.41	0.00	1.30	1.21	1.39	0.00	1.82	1.65	2.00	0.00	1.34	1.25	1.44	0.00
Other Costs (telephone, email)	1.38	1.31	1.44	0.00	2.10	1.96	2.25	0.00	1.51	1.43	1.60	0.00	1.53	1.44	1.62	0.00	2.45	2.27	2.65	0.00	1.54	1.45	1.63	0.00
Medication Cost			1	I			1	I			1		I			1	I		1					L
Total MH RX Cost	1.31	1.25	1.37	0.00	1.40	1.31	1.50	0.00	1.04	0.99	1.09	0.16	1.42	1.32	1.53	0.00	1.73	1.57	1.91	0.00	1.22	1.14	1.31	0.00
1. Regression mc	delsing	clude the	following	g covaria	tes: den	nographic	cs (gendei	r, age, rad	ce/ethn	icity, pov	erty statu	us), type	ofinsur	ance (priv	vate, Med	icaid/Me	edicare)	, comorb	id physica	al health	disorde	rs (e.g., d	iabetes) a	and

behavioral health conditions (e.g., substance use disorder).

2. Participants observed for a minimum of 1 year.

3. TRD is treatment resistant depression

4. non-TRD MDD is major depressive disorder, but not TRD

5. OR is odds ratio

6. IRR is incident rate ratio

7. Cl is confidence interval

Supplementary Table 5. Regression Output from Total All-Cause Cost Model.

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF ¹
Deviance	42E3	57903.9334	1.3743
Scaled Deviance	42E3	49593.3845	1.1771
Pearson Chi-Square	42E3	161194.3624	3.8259
Scaled Pearson X2	42E3	138059.2566	3.2768
Log Likelihood		-426804.5559	
Full Log Likelihood		-426804.5559	
AIC (smaller is better)		853651.1117	
AICC (smaller is better)		853651.1337	
BIC (smaller is better)		853832.7415	

Algorithm converged.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter	DF	Estimate	Standard Error	Wald 95% Conf	idence Limits	Wald Chi-Square	Pr > ChiSq
Intercept	1	8.3383	0.0377	8.2644	8.4121	48973.2	<.0001
PHQ ² -Level 1	1	-0.0479	0.0152	-0.0776	-0.0182	10.00	0.0016
PHQ-Level 3	1	0.1671	0.0144	0.1388	0.1954	134.06	<.0001
PHQ-Level 2	0	0.0000	0.0000	0.0000	0.0000		

Analysis Of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald 95% Con	fidence Limits	Wald Chi-Square	Pr > ChiSq
TRD	1	1	0.2088	0.0113	0.1866	0.2310	339.40	<.0001
TRD	0	0	0.0000	0.0000	0.0000	0.0000		
Age		1	0.0049	0.0004	0.0040	0.0058	120.55	<.0001
Male		1	0.0037	0.0117	-0.0192	0.0266	0.10	0.7523
Race ³	AS	1	-0.1421	0.0380	-0.2166	-0.0677	14.00	0.0002
Race	BA	1	0.1002	0.0328	0.0358	0.1646	9.31	0.0023
Race	HP	1	-0.1437	0.0725	-0.2858	-0.0016	3.93	0.0475
Race	IN	1	0.0895	0.0471	-0.0028	0.1818	3.61	0.0574
Race	от	1	-0.0228	0.0838	-0.1871	0.1414	0.07	0.7854
Race	UN	1	-0.1640	0.0327	-0.2281	-0.0999	25.13	<.0001
Race	WН	0	0.0000	0.0000	0.0000	0.0000		
Ethnicity	Ν	1	0.0688	0.0323	0.0055	0.1321	4.54	0.0332
Ethnicity	UN	1	-0.0475	0.0314	-0.1090	0.0140	2.29	0.1298
Ethnicity	н	0	0.0000	0.0000	0.0000	0.0000		
Charlson		1	0.2725	0.0046	0.2635	0.2814	3566.63	<.0001
Anxiety		1	0.2379	0.0125	0.2134	0.2624	360.84	<.0001
Substance ⁴		1	0.6410	0.0262	0.5896	0.6924	597.55	<.0001
Enrollment		1	-0.0000	0.0000	-0.0001	0.0001	0.18	0.6737
Medicaid		1	0.4184	0.0221	0.3750	0.4618	357.15	<.0001

Analysis Of Maximum Likelihood Parameter Estimates

Parameter	DF	Estimate	Standard Error	Wald 95% Conf	idence Limits	Wald Chi-Square	Pr > ChiSq
Medicare	1	0.3483	0.0152	0.3186	0.3780	527.24	<.0001
Scale	1	0.8565	0.0051	0.8465	0.8666		

Note: The scale parameter was estimated by maximum likelihood.

1. DF is degrees of freedom; 2. Patient Health Questionnaire 9

3. Race categories are abbreviated as AS, Asian; BA, Black; HP, Hawaiian/Pacific Islander; IN, American Indian/Alaska Native; OT, Other;

UN, Unknown; WH, White; N, Non-Hispanic; 4. Substance is substance use disorder.

Supplementary Figure 1. Patient Flow Diagram



1. No MDD is no diagnosis of major depressive disorder in the study period.

2. MDD diagnosis is one or more major depressive diagnosis during the study period. 3. TRD is treatment resistant depression.

4. MDD Only is major depressive disorder, but no TRD.

Supplementary Figure 2. Distribution of Depression Symptom Severity by Diagnostic Group

