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Protocol for studying racial/ethnic disparities in depression care using joint information from participant surveys and administrative claims databases: an observational cohort study

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ABSTRACT

Introduction Current evidence indicates that older racial/ethnic minorities encounter disparities in depression care. Because late-life depression is common and confers major adverse health consequences, it is imperative to reduce disparities in depression care. Thus, the primary objectives of this protocol are to: (1) quantify racial/ethnic disparities in depression treatment and (2) identify and quantify the magnitude of these disparities accountable for by a multifactorial combination of patient, provider and healthcare system factors.

Methods and analysis Data will be derived from the Vitamin D and Omega-3 Trial-Depression Endpoint Prevention (VITAL-DEP) study, a late-life depression prevention ancillary study to the VITAL trial. A total of 25 871 men and women, aged 50+ and 55+ years, respectively, were randomised in a 2×2 factorial randomised trial of heart disease and cancer prevention to receive vitamin D and/or fish oil for 5 years starting from 2011. Most participants were aged 65+ years old at randomisation. Medicare claims data for over 19 000 VITAL/VITAL-DEP participants were linked to conduct our study.

The major study outcomes are depression treatment (*antidepressant use and/or receipt of psychotherapy services*) and adherence to medication treatment (*antidepressant adherence and acceptability*). The National Academy of Medicine framework for studying racial disparities was leveraged to select patient-level, provider-level and healthcare system-level variables and to address their potential roles in depression care disparities. Blinder-Oaxaca regression decomposition methods will be implemented to quantify and identify correlates of racial/ethnic disparities in depression treatment and adherence.

Ethics and dissemination This study received Institutional Review Board (IRB) approval from the Partners Healthcare (PHS) IRB, protocol# 2010P001881. We plan to disseminate our results through publication of manuscripts patient engagement activities, such as study newsletters regularly sent out to VITAL participants, and presentations at scientific meetings.

Trial registration number NCT01696435.

Strengths and limitations of this study

► Linking cohort questionnaire (Vitamin D and Omega-3 Trial-Depression Endpoint Prevention (VITAL)/VITAL-Depression Endpoint Prevention (DEP)) and Medicare databases is a novel strategy to overcome the inherent limitations of each database and maximise their strengths to study depression care in real-world conditions.

► Results of the proposed study will elucidate the magnitude of racial/ethnic disparities in depression treatment and antidepressant medication adherence as well as the correlates of these disparities among older adults.

► There is a high representation (30%) of racial and ethnic minorities (ie, Black, Hispanic, Asian and other racial/ethnic groups) in this linked dataset to facilitate quantification of racial/ethnic disparities in depression care.

► Notable potential determinants of racial/ethnic disparities in depression care, such as bias, prejudice, discrimination and provider uncertainty, cannot be readily identified from the linked VITAL-DEP/Medicare dataset.

► Diagnoses based on claims data are vulnerable to coding and administrative errors at the Medicare data source.

BACKGROUND

Current evidence indicates that older racial/ethnic minorities, especially Blacks and Hispanics, encounter disparities in depression care. Because late-life depression is common and confers major adverse health consequences,[1 2] it is imperative to reduce disparities, which include under-diagnosis,[3] lower rates of receiving prescribed medication, lower likelihood of outpatient mental health visits, and differences in quality of treatment and outcomes.[4–6] Such potential

disparities[7 8] are concerning, given evidence pointing toward higher current depression burden,[9–12] symptom severity[11] and depression-related role dysfunction[13] among older minorities. Thus, a critical task is to identify the major potential drivers of racial/ethnic disparities in depression care—including those disparities related to diagnosis, treatment and/or treatment adherence. Also, older Black and Hispanic adults appear to have higher prevalence and incidence of dementia than non-Hispanic Whites,[14 15] and depression has emerged as an important risk factor for dementia.[16] Thus, the downstream sequelae of disparities in depression care for older minorities may include greater vulnerability to dementing illness.

The National Academy of Medicine (NAM) developed a working definition of disparities in healthcare as 'racial or ethnic differences in the quality of healthcare that are not due to access-related factors or clinical needs, preferences, and appropriateness of intervention'.[17] Numerous challenges limit the ability of investigators to determine potential sources of disparities in depression care. First, both definition and implementation of the disparities concept within population-based settings have been barriers to date. Second, implementation of the NAM definition has been challenged by the lack of databases that comprehensively capture the many potential sources of disparities.[18] Third, beyond lack of adequate data, the implementation of the NAM definition also requires the application of specific statistical models that allow for the quantification and identification of correlates of disparities.[18]

The existing evidence base regarding racial/ethnic disparities in depression pharmacotherapy has been derived from single source population-based survey data[19–22] and administrative claims data[19–23] that do not fully capture many potentially important sources of disparities. The NAM working definition of healthcare disparities grouped the major sources of disparities into: clinical appropriateness/need and patients' preferences; healthcare providers' biases, prejudices and uncertainty in clinical communication and decision-making; operation of healthcare system factors.[17] Published studies on racial/ethnic disparities in antidepressant treatment did not fully account for most of these sources of disparities.[18–25] The majority of these studies were conducted using population-based survey data, relied on self-reported antidepressant use, and lacked information on provider, prescriber as well as healthcare system characteristics.[19–22 25] The only study based on Medicaid claims data, including antidepressant use information based on filled prescriptions, was limited by lack of detailed information on sociodemographic, behavioural and lifestyle factors[23]; yet, many such factors are known correlates of disparities. None of these studies assessed the role of diet and/or lifestyle factors (eg, dietary pattern and nutrient intakes, physical activity, alcohol consumption, smoking behaviour, etc) as potential correlates. Yet, such factors may be determinants of treatment need since they have been associated with depression among older adults[26]; diet may be an especially important determinant of depression outcomes among older Blacks.[24]

No single data source, to date, has contained adequate information to facilitate the full characterisation and quantification of racial/ethnic disparities in depression care and to extend our understanding of the correlates of these disparities. One solution to the above-noted challenges is to link population-based survey databases that capture comprehensive data on sociodemographic, behavioural, diet, health and lifestyle factors with administrative claims data that capture information on prescription medications, healthcare utilisation factors, and prescriber and provider characteristics.

Thus, in this protocol, we describe an approach to investigating racial/ethnic disparities in depression care by joining questionnaire survey data from over 19 000 participants in a large US randomised trial with their linked Medicare claims data. Our overall objective is to measure racial/ethnic disparities in depression care based on clinical diagnosis and treatment utilisation for depression and to explore the sources of these disparities. Specifically, we aim to: (1) quantify racial/ethnic disparities in depression treatment and (2) identify and quantify the magnitude of these disparities and determine the contributions of patient, provider and healthcare system factors to disparities.

METHODS/DESIGN
Data sources
Participants are members of the Vitamin D and Omega-3 Trial-Depression Endpoint Prevention (VITAL-DEP) study, a late-life depression prevention ancillary study[27] to the VITAL (NCT01169259) trial.[28–31] These include 25 871 men and women, aged 50+ and 55+ years, respectively, enrolled in a long-term 2×2 factorial randomised trial of heart disease and cancer prevention using vitamin D and/ or fish oil; participants were randomised starting in 2011. Most participants are aged 65+ years (mean age=67 years; range=50–100 years old at randomisation). Consistent with prior work[32] as well as other large-scale, high-quality studies[33–35] of older adults, we designed VITAL-DEP to detect cases of depression using Boolean classification of *depressive symptoms, diagnosis and/or treatment* data. S*ymptoms* are ascertained annually via the Patient Health Questionnaire-8 (PHQ-8),[36 37] which has high sensitivity and specificity for clinical depression (defined as PHQ-8 score ≥10),[36] validity for identifying depression,[38] and cross-cultural validity among diverse, community-based older adults.[39–41] On the annual questionnaires, all participants are asked global questions on prior history or past-year clinical *diagnosis* and medication and/or counselling *treatment* of depression. All questionnaires were self-administered, therefore, participants were required to be able to read and write in English, although it was not required that English be their first or primary language.

Medicare claims data
To date, the following Medicare (Centers for Medicare and Medicaid Services (CMS)) datasets have been retrieved (2011–2016): MedPar/Inpatient, Outpatient
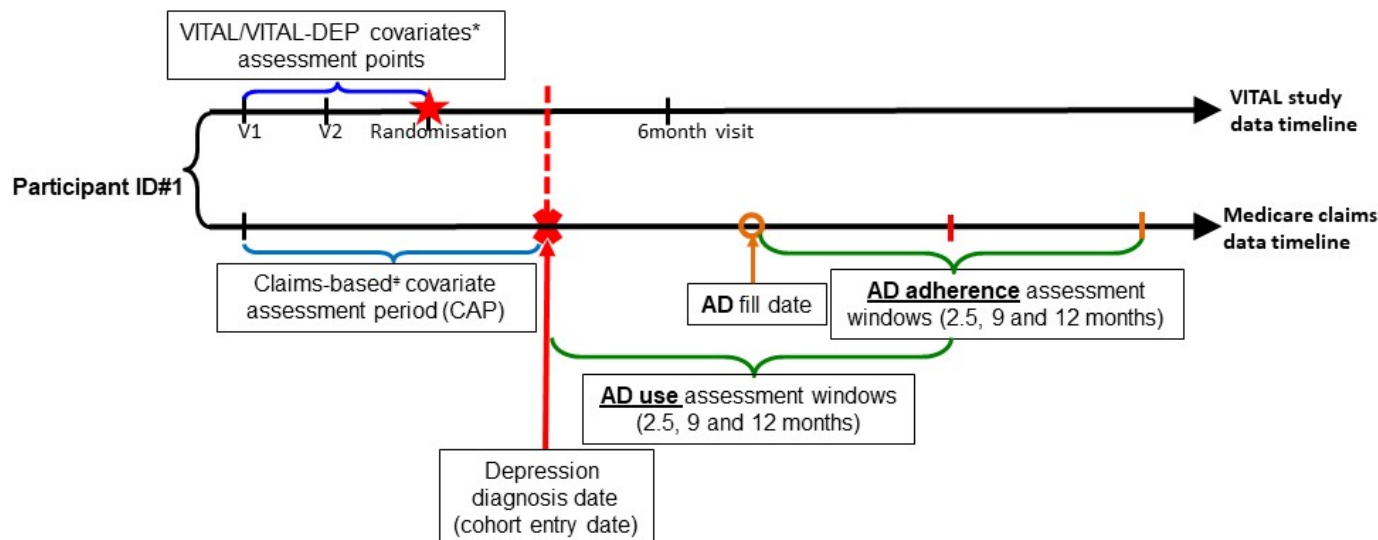
Figure 1 Schematic of study design for analysing the VITAL/DEP-Medicare claims linked dataset. *VITAL-DEP, Vitamin D and Omega-3 Trial-Depression Endpoint Prevention. Depression diagnosis, identified from Medicare (parts A/B) claims data will serve as the index date. ‡Claims-based baseline covariates (healthcare access and utilisation, characteristics of provider, characteristics of first antidepressant (AD) prescription filled and so on) will be defined within the 180 days prior to the cohort entry date. VITAL/VITAL-DEP baseline covariates will be defined from the most recent questionnaire date prior (randomisation and/or pre-randomisation visits): depression and mood assessment scores, demographics, socioeconomic, lifestyle and so on. V1, first pre-randomisation visit; V2, second pre-randomisation visit; V3, data of randomisation; AD, antidepressant.

SAF (Standard Analytic Files), Carrier files and Part D files. Currently, we have successfully linked over 19 000 VITAL/VITAL-DEP participants with their corresponding Medicare claims data between 2011 and 2016. Informed consent was obtained from participants to link the survey data with their Medicare claims data using Social Security Numbers, date of birth and sex. We will extract Medicare variables for each year 2011–2016 from the MedPar/ Inpatient, Outpatient SAF, Part D Drug Event and Carrier files, which provide extensive information on healthcare access and utilisation, hospitalisations, other medical conditions, number of visits, visit type and provider variables (specialty, setting, type, location/region). Diagnosis of depression will be identified in CMS data through a previously validated algorithm[42] using a combination of International Classification of Diseases (ICD)-9 (or their ICD-10 equivalent) codes: *296.20–296.26, 296.30–296.36, 300.4, 311, 296.5, 296.6, 296.82, 296.90, 309.0, 309.1 and 309.28.* This validated algorithm has a 99.55% specificity and 91.06% positive predictive value for a combination of ICD-9 codes and a 99.43% specificity and 89.47% positive predictive value for a combination of ICD-10 codes. In addition, Part D Event files will furnish National Drug Codes (NDC), fill dates and quantity dispensed.

Study design and participant selection

A cohort of participants with depression diagnosis will be created from the VITAL/VITAL-DEP-Medicare claims dataset (figure 1). Depression diagnosis will be defined from Medicare Parts A/B claims data using validated ICD codes (online supplementary appendix A). Claims data, rather than VITAL-DEP depression assessment data, will be used for cohort derivation since Outpatient SAF and Part

D antidepressant prescription data are tied to the claims-based clinical diagnosis of depression. For both study objectives, analysis will be restricted to depression diagnoses recorded after the date a participant was randomised in VITAL through to end of claims data availability (ie, 2016 or earlier). For example, in figure 1, Participant #1 had depression diagnosis sometime between date of randomisation and 6-month VITAL questionnaire follow-up (FU) time. This diagnosis qualifies as the cohort entry date for Participant #1 and will serve as an anchor date to define covariates and start of FU for outcomes, as explained in later sections of this protocol. An individual can contribute more than one episode as long as they have distinct depression diagnoses that meet the inclusion and exclusion criteria as detailed below. Among those with a depression diagnosis, a depression episode will be defined by leveraging the pre and postdepression diagnosis PHQ-8 scores measured at annual visits in the VITAL/VITAL-DEP survey. First, we will calculate the reliable change index (RCI) to measure the magnitude and direction of change in depression symptoms between predepression and postdepression PHQ-8 scores. The RCI measures change that is not due to random measurement error alone.[43] RCI will be calculated as the difference between any two annual PHQ-8 scores divided by the SE of this difference.[43 44] RCI >1.96 indicates a reliable increase; RCI <−1.96 indicates a reliable decrease; RCI between 1.96 and −1.96 indicates no significant change in depression symptoms.[43] Among participants with a reliable decrease in depressive symptoms, *a depression episode will be considered resolved if the next PHQ-8 score measured after the depression diagnosis date is <5;* patients with PHQ-8 scores<5 are considered to have no/minimal current symptoms.[45]

A new episode will be considered to have commenced if, subsequent to the time point when previous episode was considered resolved, another claims-based depression diagnosis is recorded and/or PHQ-8 score ≥5 is observed during subsequent FU visits.

Inclusion criteria
Inclusion criteria in this analysis are: (1) successful linkage of participants' Medicare claims data; (2) depression diagnosis recorded in Medicare claims data (Parts A/B).

Exclusion criteria
Eligible participants must have at least 180 days of continuous Medicare (Part A/B) enrolment (ie, continuous coverage without any gaps or with gaps <7 days) prior to the first recorded depression diagnosis postrandomisation—to allow for uniform assessment of covariates from claims data. Additional health plan continuous enrolment period requirements after the index depression diagnosis are specified using standard pharmacoepidemiology methods, as detailed in the FU for outcomes and Outcomes assessment sections of this protocol.

Patient and public involvement
Patients and the general public were not involved with the conception of this study analytic protocol. However, the selection of our study outcomes is driven by patient and provider challenges in deciding treatment choices for depression. Decisions made by patients and physicians/clinicians regarding depression care are largely influenced by concerns around acceptability and adherence to antidepressants. Racial and ethnic minorities may be less likely to use antidepressants and/or adhere to antidepressants due to various social, cultural, clinical or other factors. Thus, the proposed study may yield new data and insights regarding the drivers of disparities in the use and selection of different antidepressants. Data that will be generated after the implementation of the study protocol described here will be shared with participants through periodic newsletters sent out to VITAL participants.

FU for outcomes
FU for utilisation of treatment will be defined based on clinical practice guidelines.[46] Hence, three FU windows of observation will be constructed to correspond with the acute (the first 12 weeks of FU after the index depression diagnosis following diagnosis), continuation (the next 20 weeks after acute phase during FU) and maintenance (the next 20 weeks after the continuation phase) phases.[46] The acute phase is essential to clinical remission and functional improvement; the continuation phase is aimed at eliminating residual symptoms, restoring prior levels of functioning and preventing relapse/recurrence.[32] To ensure all patients have the same length of observation periods for utilisation of treatment, eligible participants will be required to have a minimum continuous enrolment in Medicare equivalent to the length of each phase of treatment, that is, 12 (84 days), 32 (224 days) and 52 (364 days) weeks, respectively.

Outcomes assessment
The major study outcomes are depression treatment (*antidepressants use and receipt of psychotherapy services*) and adherence to antidepressant treatment (*adherence to antidepressants and acceptability of antidepressants*).

Depression treatment
The use of pharmacological agents with or without psychotherapy services will be assessed over a period of 12 months, encompassing both the acute and continuation phases of depression treatment, after the first recorded depression diagnosis during the study period (figure 1).

a. Antidepressant use
Records of prescription medication fills from Medicare Part D data will be queried to determine fills of at least one antidepressant prescription up to 365 days after the index depression diagnosis (figure 1). Antidepressants will be grouped by therapeutic classes (online supplementary appendix B) and according to treatment guidelines based on the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for pharmacological treatment of depression (online supplementary appendix C): *first line* (comprising of selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitor); *second line* (comprising of tricyclic antidepressants, monoamine oxidase inhibitors, monoamine oxidase B inhibitors (MAOB-I) and others); *third line* (comprising of mostly MAOB-Is) antidepressants. This will allow us to assess whether there are racial/ethnic differences in the prescription of antidepressants according to clinical guidelines. In a sensitivity analysis, we will also assess the use of other non-antidepressant psychotropic medications: for example, typical and atypical antipsychotics, mood stabilisers, stimulants, antianxiety and sedative/hypnotic agents and others. In addition to identifying whether or not a patient filled a prescription, we will also measure the Daily Defined Dose (DDD) of each filled prescription.[47] The DDD will be calculated, in accordance with WHO's Collaborating Centre for Drug Statistics Methodology, as the assumed average maintenance dose per day for a drug that is used for its main indication in adults. This metric will allow us to compare the total consumption of antidepressants by classes and between racial/ethnic groups independent of the cost (out-of-pocket), package size and strength of individual antidepressants.

b. Psychotherapy
Current Procedural Terminology codes (online supplementary appendix D) will be used to define receipt of psychotherapy services. Any records of psychotherapy (with or without Evaluation and Management services), individual or group-based, will be considered as utilisation of psychotherapy services. The unique counts of psychotherapy services received during FU will also be captured.

Adherence to treatment

Adherence to psychotherapy cannot be measured accurately with claims data because of lack of information on the length of the intended duration of psychotherapy treatment in claims data. Therefore, only adherence to antidepressants will be assessed.

a. Adherence to antidepressants

Adherence is a measure of the extent to which patients are taking their medications.[48] Prescription fill information will be assessed from Medicare Part D files and unique medications will be identified based on NDC. The goal is to assess whether patients had medication supply to cover each day during the prespecified FU windows specified above. Therefore, a medication 'supply diary' will be created for each patient by linking all observed prescription fills within the therapeutic class of the index medication based on the dispensing date and the days' supply of prescriptions. The supply diary will begin from the first fill of the index medication and continue until the end of FU (84, 224 and 364 days, respectively). Given that antidepressants are grouped into three categories according to the CANMAT guidelines, fills of any agents within a specific line of therapy will be considered exchangeable. However, any remaining supply of the initial agent after switching to a different one will be truncated and not counted towards the total days of supply.[49] Among patients who do not switch to any other medications but may have accumulated excess supply, only a maximum of 180 days of excess supply will be allowed.[50] This will help address potential stockpiling behaviours whereby patients may make early refills while still in possession of previous ones. Based on the computed supply diaries, adherence will be calculated as the proportion of days covered (PDC) during the FU windows as: the number of days covered divided by 84, 224 and 365 days, respectively, for adherence within the acute, continuation and maintenance phases of treatment. PDC, calculated from prescription fill claims data, is a validated measure of adherence and persistence to medications, especially among patients with repeated fills.[51 52]

b. Acceptability of antidepressants

In addition to measuring adherence, we will also assess patients' acceptability of antidepressants. There is currently no consensus on the operational definition of acceptability based on prescription fill records. Therefore, we propose to measure acceptability as the premature discontinuation of an antidepressant before the end of a specified treatment phase.[53] Discontinuation will be operationally defined as a >30-day gap after the date on which a patient would have used up their last filled prescription (based on the days' supply of this last prescription).

Assessment of potential correlates of disparities in depression treatment

Correlates of disparities in antidepressant use and adherence will be assessed from both VITAL/VITAL-DEP

questionnaires (self-administered) and Medicare claims data. Information on numerous sociodemographic (eg, education level, household income, etc), lifestyle/behavioural (eg, nutrient intakes and dietary patterns, smoking behaviour, alcohol consumption, leisure-time physical activity, etc), health (eg, self-rated health, physical function, bodily pain, medical comorbidities, etc), and depression diagnosis-related factors and other VITAL/VITAL-DEP study variables will be assessed from questionnaires (table 1A). Since questionnaire data are captured and updated annually at time points which may not align with the depression cohort entry dates of participants in our study protocol, the VITAL/VITAL-DEP questionnaire administration time point closest but prior to an individual's depression cohort entry date will be used to measure these variables (figure 1). A combination of ICD codes, Healthcare Procedure Codes and NDCs will be used to define claims-based variables (online supplementary appendix D).

Clinical appropriateness/need and preferences

The clinical appropriateness and needs for antidepressant treatment will be captured from the index depression diagnosis factors, self-reported depressive symptom level based on PHQ-8 scores, use of other psychiatric medications (online supplementary appendix B) and health status (psychiatric comorbidities and other chronic comorbidities). Demographic, lifestyle/behavioural and health factors (eg, age, sex, smoking, physical activity, physical function, pain, medical comorbidity and others) that have been associated with depression[26] will also be included in the analysis as markers of clinical appropriateness and need. All patient-level clinical appropriateness variables are listed in table 1A.

Healthcare providers' biases, prejudices and uncertainty in clinical communication and decision-making

These factors are not explicitly captured in the data both VITAL-DEP and Medicare claims data. Therefore, other provider–patient relationship factors will be measured. Detailed definitions of these factors are provided in tables 1B and 1C and will include: proportion of racial/ethnic minority patients who are treated by a provider, proportion of patients initiated on a first line antidepressant agent and proportion of patients referred to psychotherapy.

Operation of healthcare system/environment factors

Factors relating to how healthcare systems are organised and financed, and the availability of services, were identified by the NAM to be predictive of disparities. We focused on healthcare systems' organisational (drug on formulary and dispensed as written), policy (requirement of prior authorisation, drug coverage status, low-income subsidy for antidepressants) and financial (out-of-pocket spending and copay) factors that could exert influence on the use of antidepressants (tables 1B and 1C).

Table 1A	List of variables to be included in the analysis		
	VITAL-DEP*	**Claims†**	**Variable assessment period**
Vital study			
Randomisation group			VITAL data measurement point closest to index depression diagnosis date
Vitamin D₃	X		
Placebo	X		
Pill compliance	X		VITAL data measurement point closest to index depression diagnosis date
Past month—days missed	X		
Side effects	X		VITAL data measurement point closest to index depression diagnosis date
Stomach upset or pain	X		
Nausea	X		
Constipation	X		
Diarrhoea	X		
Skin rash	X		
Colds or URI	X		
Influenza-like symptoms	X		
Frequent nosebleeds	X		
Easy bruising	X		
Blood in urine	X		
GI bleeding	X		
Bad taste in mouth	X		
Patient-level characteristics			
Demographics			VITAL data measurement point closest to index depression diagnosis date
Race/ethnicity	X		
Age	X		
Sex	X		
Level of education	X		
Marital status	X		
Employment status	X		
Household income	X		VITAL data measurement point closest to index depression diagnosis date
Geographic region/state	X		VITAL data measurement point closest to index depression diagnosis date
Lifestyle and psychosocial factors			VITAL data measurement point closest to index depression diagnosis date
Smoking status	X		
Alcohol use	X		
Diet (Healthy Eating Index)	X		
Physical activity	X		

Table 1A Continued

	VITAL-DEP*	Claims†	Variable assessment period
Lost 5 lbs. or more in past 2 years	X		
Body mass index	X		
Limitation in daily activity	X		
Independence in living	X		
Dietary supplement intake			VITAL data measurement point closest to index depression diagnosis date
Vitamin D	X		
Fish oil (incl. krill, cod liver at YR 2)	X		
Other supplmt. Containing Omega-3	X		
Calcium	X		
Multivitamins	X		
Vitamin A	X		
Any other supplements	X		
Depression diagnosis-related factors			VITAL data measurement point closest to index depression diagnosis date
Mood and depression scores (PHQ-8)	X		
Self-reported depression diagnosis	X		
Self-reported core depressive symptoms, 2 weeks	X		
Self-reported depression treatment, medications and/or counselling	X		
Depression diagnoses, in CMS		Refer to online supplementary file for codes	From V3 date to end* of claims data
Date of depression diagnosis, in CMS		Refer to online supplementary file for codes	
Other mental health disorders		Refer to online supplementary file for codes	180 days prior to index depression diagnosis date (inclusive)
Dementia		Refer to online supplementary file for codes	
Delirium/psychotic disorder		Refer to online supplementary file for codes	
Mood and anxiety		Refer to online supplementary file for codes	
Schizophrenia		Refer to online supplementary file for codes	
Manic disorder		Refer to online supplementary file for codes	
Bipolar disorder		Refer to online supplementary file for codes	
Attention deficit disorder		Refer to online supplementary file for codes	
Intellectual disabilities		Refer to online supplementary file for codes	
Chronic comorbidities		Refer to online supplementary file for codes	180 days prior to index depression diagnosis date (inclusive)

Continued

Table 1A Continued

	VITAL-DEP*	Claims†	Variable assessment period
Coronary artery diseases	X	Refer to online supplementary file for codes	
Myocardial infarction	X	Refer to online supplementary file for codes	
Valvular heart disease	X	Refer to online supplementary file for codes	
Heart failure	X	Refer to online supplementary file for codes	
Stroke	X	Refer to online supplementary file for codes	
Peripheral artery disease	X	Refer to online supplementary file for codes	
Chronic obstructive pulmonary disease	X	Refer to online supplementary file for codes	
Asthma	X	Refer to online supplementary file for codes	
Hypertension	X	Refer to online supplementary file for codes	
Diabetes mellitus	X	Refer to online supplementary file for codes	
End-stage renal disease	X	Refer to online supplementary file for codes	
Macular degeneration	X	Refer to online supplementary file for codes	
Parkinson disease	X	Refer to online supplementary file for codes	
Dementia	X	Refer to online supplementary file for codes	
Cancer	X	Refer to online supplementary file for codes	
AIDS	X	Refer to online supplementary file for codes	
Traumatic brain injury		Refer to online supplementary file for codes	
Combined comorbidity score (mean)			
Prior medication use (please provide flags (1/0) for each class of medication listed below and the unique drug names (character variable) as a separate variable)			180 days prior to index depression diagnosis date (inclusive)
Psychiatric medications		Refer to online supplementary appendix B for codes	
Antidepressants		Refer to online supplementary appendix B for codes	
1. First-generation agents		Refer to online supplementary appendix B for codes	
2. Second-generation agents		Refer to online supplementary appendix B for codes	
3. Third-generation agents		Refer to online supplementary appendix B for codes	

Continued

Table 1A Continued

	VITAL-DEP*	Claims†	Variable assessment period
Stimulants		Refer to online supplementary appendix B for codes	
Antipsychotics		Refer to online supplementary appendix B for codes	
Mood stabilisers		Refer to online supplementary appendix B for codes	
Antianxiety agents		Refer to online supplementary appendix B for codes	
First-generation (typical) antipsychotics		Refer to online supplementary appendix B for codes	
Second-generation (atypical) antipsychotics		Refer to online supplementary appendix B for codes	
Other psychotropic		Refer to online supplementary appendix B for codes	
Number of unique psychiatric medications (mean)		Total counts of unique psychiatric medications filled	
Index prescription filled			
Antidepressants		Refer to online supplementary appendix B for codes	During follow-up‡
1. First-generation agents		Refer to online supplementary appendix B for codes	
2. Second-generation agents		Refer to online supplementary appendix B for codes	
3. Third-generation agents		Refer to online supplementary appendix B for codes	
Stimulants		Refer to online supplementary appendix B for codes	
Antipsychotics		Refer to online supplementary appendix B for codes	
Mood stabilisers		Refer to online supplementary appendix B for codes	
Antianxiety agents		Refer to online supplementary appendix B for codes	
First-generation (typical) antipsychotics		Refer to online supplementary appendix B for codes	
Second-generation (atypical) antipsychotics		Refer to online supplementary appendix B for codes	
Other psychotropic		Refer to online supplementary appendix B for codes	
Characteristics of index prescription filled			On index prescription filled date
Prescription type—brand vs generic		From Medicare Part D files	
Days' supply		From Medicare Part D files	
Quantity dispensed		From Medicare Part D files	
Patient out-of-pocket spending on index fill		From Medicare Part D files	
Dispensed as written		From Medicare Part D files	
Low-income subsidy for index drug		From Medicare Part D files	
Drug coverage status		From Medicare Part D files	

Continued

Table 1A Continued

	VITAL-DEP*	Claims†	Variable assessment period
Healthcare utilisation and healthcare system-related		From MedPAR, Inpatient, Outpatient, Carrier files	180 days prior to index depression diagnosis date (inclusive)
Visit with psychiatrist in the past		From MedPAR, Inpatient, Outpatient, Carrier files	
Use of psychotherapy services		From MedPAR, Inpatient, Outpatient, Carrier files	
Number of physician office visits (unique counts)		From MedPAR, Inpatient, Outpatient, Carrier files	
Number of hospitalisations (mean)		From MedPAR, Inpatient, Outpatient, Carrier files	
Psychiatric related		From MedPAR, Inpatient, Outpatient, Carrier files	
Number of unique prescribers		Counts of number of unique prescribers who wrote any prescription for participants in the study cohort. Each prescriber with a unique ID is counted once from Medicare Part D files	
Number of unique providers		Counts of number of unique providers who wrote any prescription for participants in the study cohort. Each provider with a unique ID is counted once from MedPAR, Inpatient, Outpatient, Carrier files	
Visit with both psychiatrist and PCP in prior 180 days		Flag for patients who had at least one visit with both a psychiatrist and PCP in prior 180 days. This information will be assessed from MedPAR, Inpatient, Outpatient, Carrier files	
Copay/coinsurance associated with office visit during depression diagnosis		The sum of the copay and coinsurance associated with the depression diagnosis. This information will be assessed from MedPAR, Inpatient, Outpatient, Carrier files	
Number of unique pharmacies		Counts of different unique pharmacies where patient filled any medication. Each pharmacy with a unique ID is counted once. This information will be assessed from Medicare Part D files	
Provider characteristics			Index depression diagnosis date
Provider type and place of service		From MedPAR, Inpatient, Outpatient, Carrier files	
Psychiatrist-Office		From MedPAR, Inpatient, Outpatient, Carrier files	
Psychiatrist-Other		From MedPAR, Inpatient, Outpatient, Carrier files	
Nurse practitioner		From MedPAR, Inpatient, Outpatient, Carrier files	
Hospital		From MedPAR, Inpatient, Outpatient, Carrier files	
PCP-Office		From MedPAR, Inpatient, Outpatient, Carrier files	

Continued

Table 1A Continued

	VITAL-DEP*	Claims†	Variable assessment period
PCP-Other		From MedPAR, Inpatient, Outpatient, Carrier files	
Geographic location of provider		From MedPAR, Inpatient, Outpatient, Carrier files	Index depression diagnosis date
Northeast		From MedPAR, Inpatient, Outpatient, Carrier files	
South		From MedPAR, Inpatient, Outpatient, Carrier files	
Midwest		From MedPAR, Inpatient, Outpatient, Carrier files	
West		From MedPAR, Inpatient, Outpatient, Carrier files	

*VITAL-DEP variables will be assessed at the closest study visit prior to date of index depression diagnosis.
†Claims-based covariates will be assessed during the 6-month period prior to date of index depression diagnosis.
‡Follow-up duration (in days)=index date–first of (date of death, disenrolment, or end of available data).
CMS, Centers for Medicare and Medicaid Services; PCP, primary care physician; PHQ, Patient Health Questionnaire; VITAL-DEP, Vitamin D and Omega-3 Trial-Depression Endpoint Prevention.

Data analysis plan

The primary focus of the analysis is to quantify racial/ethnic disparity based on the NAM definition of disparities and to identify the correlates of any observed disparities in antidepressant use, receipt of psychotherapy services, antidepressant adherence and acceptability of antidepressant treatment. Although racial/ethnic disparities will be assessed between non-Hispanic Whites and each distinct racial/ethnic minority group, we will have more statistical power to measure disparities between non-Hispanic Whites versus Blacks, Hispanics and Other minority groups (combined). Descriptive analysis will be

Table 1B List of variables to be defined at the prescriber-level

Variable	Definition	Variable assessment period
Unique prescriber ID (CCW_PRSCRBR_ID)	Unique prescriber IDs associated with index medication prescriptions in the eligible patient cohort	Index prescription fill date
Total number of patients initiated on an antidepressant by this prescriber	Total number of times this unique prescriber ID shows up in the cohort as the initiating prescriber for any antidepressants during study period*	Start to end of claims data
Percent racial/ethnic minority patients seen by provider during entire study period	(Total number of Black, Hispanic, Asian or other racial/ethnic minority patients with any medical claim with this provider during entire study period)/ (Total number of patients with any medical claim with this provider during entire study period*)	Start to end of claims data
Total number of SSRI users initiated by this prescriber	Total number of times this unique prescriber ID shows up in the cohort as the initiating prescriber for SSRI users during study period*	Start to end of claims data
Prescriber preference for SSRIs	(Total number of SSRI users)/(Total number of all antidepressant users)	Start to end of claims data
Percent racial/ethnic minority patients prescribed SSRIs by prescriber during entire study period	(Total number of Black, Hispanic, Asian or other racial/ethnic minority patients initiated on SSRI by the prescriber during entire study period)/(Total number of patients initiated on an antidepressant by this prescriber during entire study period*)	Start to end of claims data
Total number of patients ordered to receive psychotherapy service by this prescriber	Total number of patients ordered to receive psychotherapy service by this prescriber during study period*	Start to end of claims data

*Study period: start to end of claims data.
SSRI, selective serotonin reuptake inhibitors.

Table 1C List of variables to be defined at the provider level

Variable	Definition	Variable assessment period
Unique provider ID (**PRVDR_NUM**)	Identified by unique provider ID on the depression diagnosis claim	Antidepressant index date3
Facility type/specialty (**FAC_TYPE**)	Identify the facility type or specialty associated with the index prescription	Antidepressant index date
Healthcare service type (**AT_PHYSN_SPCLTY_CD**)	For each provider, identify the healthcare service type, for example, primary care physician, specialist, allied health provider, etc	Antidepressant index date
Place of service (**SRVC_LOC_NPI_NUM**)	For each provider, identify the place of service (eg, office, inpatient hospital, emergency room, etc)	Antidepressant index date
Proportion receiving psychotherapy services	(Total number of depression patients receiving psychotherapy services)/(Total cohort)	Start to end of claims data
Proportion of racial/ethnic minority patients prescribed antidepressant by provider	(Total number of Black, Hispanic, Asian or other racial/ethnic minority participants prescribed antidepressants)/(Total number of antidepressant users)	Start to end of claims data

used to further characterise disparities affecting each specific racial/ethnic minority group (Black, Hispanic, Asian and other racial/ethnic groups).

Identification of correlates of racial/ethnic disparity in depression treatment

Blinder-Oaxaca (BO) regression decomposition methods will be implemented to identify the correlates of racial disparities in depression treatment and adherence.[54 55] BO methods have been widely used in health disparity research[56–63] including the assessment of racial/ethnic disparities in antidepressant use[59] and psychotherapy.[58] Unlike traditional regression methods, the BO regression decomposition method not only measures the disparity in the outcome variables (antidepressant use, receipt of psychotherapy services, adherence and acceptability) but it decomposes the observed disparity into two portions of explained and unexplained disparities.

To implement the BO model, separate models including each set of variables grouped according to the NAM's classification of sources of disparities will be implemented to assess their role as a pathway for racial/ethnic disparities in the outcomes specified in this protocol. We will begin with a reduced covariate model to measure the influence of participant-level clinical appropriateness/need and preferences variables. Cook *et al* proposed excluding measures of socioeconomic status (SES) from this reduced covariate model to allow for the capture of racial differences by SES in the observed racial disparity effect.[18] Because of the tight correlation between race/ethnicity and SES, adjusting for the latter would cancel out or obscure some of the variation in estimates due to race/ethnicity that are of particular interest in our study.[18] This type of reduced model has been previously implemented to measure healthcare racial/ethnic disparities as defined by the NAM.[18] Next, healthcare provider-level variables will be added to the first model to assess changes in disparities due to these higher-level factors.

Lastly, the role of the healthcare system/environment will be evaluated by adding variables measured at this level to the previous model that contained both participant and provider-level variables. An extended version of the BO technique developed by Jann has flexibility to model binary, count and continuous outcomes.[64] This extended version, available in Stata as Oaxaca, also has a cluster command to allow for clustering of patients at the provider/prescriber and healthcare system/environmental levels.[64]

Prespecified secondary and sensitivity analysis
Subgroup of participants with new-onset depression

To examine whether racial/ethnic differences exist in utilisation, treatment and adherence for ongoing versus initial depression episodes, the primary analysis will be repeated among a subcohort of participants with new-onset depression (ie, incidence, or first occurrence, of depression). Preliminary data indicate that ~1500 incident late-life depression cases will have accrued during the FU period of this study.

Potential effects of dynamic antidepressant treatment patterns

Because of the dynamic nature of depression care with antidepressants, patients tend to have multiple episodes of treatment. In sensitivity analysis, episodes of depression care will be assessed and defined for participants without records of antidepressant prescription fills within the acute treatment window after the first recorded diagnosis during the study period. For this subgroup, a subsequent depression diagnosis will be considered as a new episode of depression care if the diagnosis date was recorded outside the acute phase treatment window. To allow for accurate assessment, eligible participants will be required to have at least 12 weeks of continuous Medicare coverage. Antidepressant use and predepression diagnosis covariates will be assessed during each episode of treatment using the same criteria specified in the

main analysis. The list of covariates will be updated for potential time-varying covariates for each newly defined episode of care. The within-person variation in antidepressant use and adherence across different episodes of care will be accounted for through the implementation of generalised linear mixed models.

Potential confounding by severity of depression

Given that decreased utilisation of antidepressants is warranted in some cases because of lower symptom severity or in cases of depression diagnoses that are not specifically related to major depressive disorder (eg, adjustment disorder, depression not otherwise specified, etc), we will restrict the analysis to the subset of patients with an indication for antidepressants based on records of major depression diagnosis codes: ICD-9 codes: 296.2, 296.3; ICD-10 codes: F32.0-F32.5, F32.9, F33.0-F33.4, F33.9.

Power calculations

The final number of participants with clinically diagnosed depression will be determined after the creation of the study cohort as described in earlier sections. Based on preliminary data, we expect approximately 4000 prevalent and 1500 incident depression cases, with ~30% minority participation (ie, of Black, Hispanic, Asian and other racial/ethnic group participants). These sample sizes will be sufficient for the purposes of the descriptive and predictive analyses proposed for Aim 1. For estimation of racial/ethnic differences in levels of adherence to antidepressants (Aim 2), the total number of antidepressant users will be known after cohort creation and assessment of antidepressant use. Assuming a conservative estimate that 50% of all diagnosed cases are using antidepressants, we are likely to identify ~2000 users (1400 Whites, 600 minorities) among prevalent cases. This assumption appears conservative based on preliminary data in VITAL-DEP: among those who self-report diagnosis of depression, the percentage who report antidepressant treatment is ~60%, even among Asians/Pacific Islanders, who self-report the lowest treatment rates. Kales *et al*[65] reported a 0.61 standardised mean difference of adherence rates between Whites and African-Americans. Based on these assumptions, we would have 80% statistical power (0.05 type I error) to detect comparable or slightly smaller effect sizes (mean differences).

DISCUSSION

Results of the proposed study will elucidate the magnitude of racial/ethnic disparities in antidepressant treatment and adherence as well as the correlates of these disparities among older adults. These data will be critical for the formulation of targeted interventions that are responsive to multifactorial factors driving racial disparities in depression care.

Linking the VITAL/VITAL-DEP and Medicare databases is a novel strategy to overcome the inherent limitations of each database and maximise their strengths to study depression care in real-world conditions. Preliminary work using questionnaire data provides assurance that information from this study cohort can be leveraged to address race/ethnic differences in depression care. First, there is excellent minority representation. Among 25 871 randomised participants, there were nearly 5000 prevalent depression cases at randomisation (68% non-Hispanic White, 23% Black, 4% Hispanic, 1% Asian/Pacific Islander, 1% Native American/Alaska Native, 3% other/more than one race). Annual FU rates have been >95%, and new depression cases are accruing during FU at ~17/1000 person-years. At baseline, all minority groups had higher symptom burden of the core feature of anhedonia, compared with non-Hispanic Whites; Black, Hispanic and Native American participants had higher burden of depressed mood and neurovegetative symptoms.

Potential limitations and plans for mitigation

Diagnoses based on medical claims are vulnerable to coding and administrative errors at the Medicare data source. To address this limitation, we will augment claims-based diagnoses with depression information from VITAL-DEP questionnaires. We also use rigorous programming procedures to ensure reproducibility, with verification of coding protocols by independent programmers, when utilising both CMS and VITAL/VITAL-DEP data. While pharmacy claims are generally considered to be accurate sources of information on medication use, the exact timing of non-adherence to medications cannot always be precisely determined. Our data do not contain information on reasons for antidepressant discontinuation; thus, our definition of discontinuation could potentially misclassify patients as having discontinued using antidepressants when the decision was a deliberate one taken by the patient and his/her provider. One way to mitigate such potential misclassification would be to restrict the sample for analysis to patients with major depression diagnosis codes, as long-term antidepressant use is typically recommended for these patients. Since this study relies on Medicare Part D data, the results may not be generalisable to older adults without such a health coverage benefit; thus, we will interpret findings with caution. Because VITAL participants were required to be able to read and write in English, our results may not generalisable to segments of the population for whom disparities may be driven in part by linguistic isolation. Despite the wealth of data in the VITAL-DEP/CMS linked dataset, we are still not able to perfectly adapt the NAM definition of racial/ethnic disparities due to the lack of pertinent variables such as bias, prejudice, uncertainty and the race, age and gender of prescribers. Collection among VITAL/VITAL-DEP participants of a validated perceived discrimination scale is currently underway; this information on participants' own reports of experiencing discrimination could inform how well we are able to capture the possibility of bias/prejudices affecting patients' care when

using the provider characteristics as proxies. Although this study design is strengthened by data collected as part of the VITAL trial, it is possible that participation in the trial itself could potentially influence behaviour with regard to medication adherence. Finally, we acknowledge the limitation that we are unable to capture with high granularity other forms of depression care not captured in questionnaire or CMS data, such as faith-based care. However, participants were asked on the VITAL questionnaires every year whether they had received 'medications and/or counselling' for depression. This is specifically a separate question from asking about SSRI antidepressants and was worded so that it would encompass more than traditional outpatient psychotherapy services. We used the term counselling, not psychotherapy, as we recognised that some participants may receive counselling services from pastors, spiritual advisors or elders, or others outside the professional outpatient mental health setting.

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