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Biological and Clinical Correlates of the Patient Health Questionnaire-9

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BMJ

ORIGINAL RESEARCH

Biological and Clinical Correlates of the Patient Health Questionnaire-9

Running title: Biological and Clinical Correlates of PHQ-9

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ABSTRACT

Objectives: The most common screening tool for depression is the Patient Health Questionnaire-9 (PHQ-9). We assessed the relationship between the PHQ-9 at intake and other measurements intended to assess biological factors, markers of disease, and health status.

Design, setting, and participants: We performed a cross-sectional analysis of 2365 participants from the Baseline Health Study (BHS), a prospective cohort of adults selected to represent major demographic groups in the United States. Participants underwent deep phenotyping on demographic, clinical, laboratory, functional, and imaging findings.

Importance: Despite extensive research on the clinical implications of the PHQ-9, data are limited on the relationship between PHQ-9 scores and other measures of health and disease; this study seeks to better understand this relationship.

Interventions: None.

Main outcomes and measures: Cross-sectional measures of medical illnesses, gait, balance strength, activities of daily living, imaging, and laboratory tests.

Results: Higher PHQ-9 scores were associated with female sex, younger participants, and those with compromised physical status and chronic conditions. Within physical health, increasing PHQ-9 score was associated with a higher frequency of many comorbidities and active symptoms.

Conclusions: BHS data confirm findings in the literature regarding the relationship between PHQ-9 and measures of chronic disease, psychological well-being, social well-being, socioeconomic status, and poor physical performance. Our study highlights how even subthreshold depressive symptoms (measured by PHQ-9) may serve as an entree into a variety of

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individual- and population-level concerns that demand more attention. Furthermore, our findings

underscore that depression should be considered a comorbidity in common disease.

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT03154346

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ARTICLE SUMMARY

Strengths and limitations of this study

- This study included deep phenotyping on demographic, clinical, laboratory, functional, and imaging findings of 2365 participants from the Baseline Health Study (BHS).

- This study provides important data on the relationship between PHQ-9 scores and other measures of health and disease.

- The cross-sectional nature of this study limits our ability to assess the time course of these findings; however, follow-up is currently accruing.

- People with significant depression are less likely to volunteer, thereby limiting the breadth of depression observed in this study.

- The study population is generally representative of adult age, sex, race, and ethnicity, but it is not a fully representative sample of the population.

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Depression is a complex, chronic condition that affects hundreds of millions of people worldwide.[1] Bidirectional relationships have been reported between depression and many chronic illnesses[2]; however, most studies have focused on specific conditions, such as diabetes, stroke, or congestive heart failure, as opposed to a multidimensional deep phenotyping approach. Findings from previous studies highlight the need to more fully characterize the relationship between depression and physical health. Furthermore, it would be helpful to better understand whether these relationships exist only above a certain threshold or across the entire continuum.

The most common screening tool for depression is the Patient Health Questionnaire-9 (PHQ-9), whose operating characteristics are well known[3] and have been validated in a variety of contexts.[4,5] Despite extensive research on the clinical and behavioral implications of PHQ-9,[6,7] the results of this questionnaire are often used in a dichotomous manner (e.g., cut-off of 10) without evaluating the full relationship between PHQ-9 scores and measures of health and disease.

The Baseline Health Study (BHS)[8] is a prospective cohort study of an adult population selected to represent major demographic groups in the U.S. In BHS, deep phenotyping of numerous demographic, clinical, laboratory, functional, and imaging findings is coupled with ongoing longitudinal follow-up. The purpose of our study was to assess the relationship between the entire spectrum of depression, measured by PHQ-9, and a broad array of measurements intended to assess health status.

METHODS

The Baseline Health Study

BHS methods have been previously described,[8,9] including entry and exclusion criteria, the

institutional review board and participant consent procedures, the data collection scheme, and

key components of study procedures. Additional details of the effects of social determinants on

health in the BHS study have been previously reported.[9] BHS is enrolling a large number of

participants, beginning with intensive measurement of the first 2502 people (the deeply

phenotyped cohort) in whom a large volume of multimodal data are collected. Four clinical BHS

sites in the U.S. have begun enrollment.

The participants were enrolled through a virtual online registry with selection of

participants for the deep phenotyping cohort included in this report using an algorithm intended

to produce a representative sample of U.S. adult age, race, and ethnicity. People in good health

and with medical conditions were included and the sampling method was designed to over-

represent people at risk of heart disease or cancer. The PHQ-9 in this report was collected at the

initial study visit in person or online.

A pre-BHS pilot study, which tested clinical assessment workflows, was conducted in

200 healthy participants prior to initiation of the primary study. BHS is funded by Verily (San

Francisco, CA) and is managed in collaboration with Stanford University (Stanford, CA), Duke

University (Durham, NC), and the California Health and Longevity Institute (Westlake Village,

CA) with enrolling sites in Durham, NC; Kannapolis, NC; Los Angeles, CA; and Palo Alto, CA.

The extended studies have governance approaches specific to the needs of each study. Herein,

we examine a cross-sectional analysis of the first BHS time point PHQ-9 scores.

Statistical methods

The statistical methods used in this manuscript have been described previously.[9] Distributional measures; medians and 25th, 75th percentiles for continuous variables; and counts and percentages for categorical variables were computed and summarized across each of 5 PHQ-9 severity groups[3] (0, 1–4, 5–9, 10–14, >14), divided by convention to be consistent with prior studies. The Cochran-Armitage trend test for binomial variables,[10,11] and the Spearman rank correlation test for continuous variables[12] or categorical variables that are ordinal in nature (e.g., education and income), were used to test for linear trend across severity group. Multiple tests were not adjusted for, given the exploratory nature of this study. Subsequent studies with pre-planned hypotheses are needed to confirm results.

Penalized regression using the least absolute shrinkage and selection operator (LASSO) was conducted to model physical, phenotypic, and symptom factors that could predict the PHQ-9 score (logarithm of PHQ-9 + 1). Data were randomly split into a training set (approximately 70% of the data), which was used to build the models, and an independent test set, which was used to evaluate model performance. The final linear model was trained on the full training set, retaining all predictors with coefficients not equal to zero, and was evaluated on the held-aside test set.

Since inference rather than prediction is the goal of this analysis, we considered 5 sets of sequential "adjustment" models, consisting of smaller-to-larger covariate lists that were entered into a LASSO regression model. The LASSO-predicted values resulting from each of the 5 models were used to estimate a covariate-adjusted effect for all other candidate variables. Separate regressions for *each* of the candidate variables that are not included in a given model were performed to obtain coefficients and confidence intervals (i.e., only the LASSO-predicted value and the candidate variable to be evaluated were included in each model).

The LASSO adjustment models comprise the following covariates: 1) Model 1: age, sex, and age × sex interaction; 2) Model 2: variables from Model 1, plus race and ethnicity, socioeconomic-related variables (highest education completed, household income, marital status, employment status, and health insurance), and behavioral-related variables (smoking status, pack-years smoked, and the Alcohol Use Disorders Identification Test-Consumption [AUDIT-C] sum score); 3) Model 3: variables from Model 2 plus medical conditions except mental health disorder diagnoses or disorders directly related to mental health or depression (major depressive disorder, generalized anxiety disorder, attention deficit hyperactivity disorder, post-traumatic stress disorder, bipolar disorder, alcohol abuse, drug abuse, and concussion or loss of consciousness); 4) Model 4: variables from Model 3, plus symptoms and allergies, except those symptoms that are directly related to mental health or depression (i.e., nervousness, mood changes, fatigue, lack of energy, change in sleep patterns, change in appetite, and difficulty concentrating); and 5) Model 5: variables from Model 4, plus all physical health metrics. The key variables included in each covariate model can be found in **eTable 1**.

Since LASSO regression techniques require an input dataset with complete data, missing data were addressed using iterative regression-based imputation, where predictors were first grouped by data type, then the groups were rank-ordered by the most missing to the least missing data. The rank of the whole group was based on the amount of missingness of the majority (≥50%) of the fields within that group), and then at each imputation step, the grouped predictors were used in a regression model to predict the missing data. The PHQ-9 score was imputed in the last step along with other patient-reported outcome scores and, therefore, all 2502 participants were included in the LASSO models.

To summarize key model findings adjusted for known demographic and socioeconomic-related risk factors of PHQ-9, 4 groups were created based on the LASSO-predicted value using Model 1 (age, sex, and age × sex interaction) and Model 2 (race, ethnicity, socioeconomic-related variables and health behaviors). For both models, "high risk" was defined as the top 50% of the predicted value, while "low risk" was defined as the bottom 50% of the predicted value. The 2 risk groups from each model were combined to create the following 4 groups: 1) high risk Model 1 + high risk Model 2; 2) high risk Model 1 + low risk Model 2; 3) low risk Model 1 + high risk Model 2; and 4) low risk Model 1 + low risk Model 2.

Patient and public involvement statement

From the beginning, BHS has used participant and community engagement methods. Participants have been involved in feedback sessions, and return of results is a commitment of the project. Community meetings have also been held to assure broad feedback on the goals and conduct of the project.

RESULTS

The relationship between the PHQ-9 score and key demographic characteristics and vital signs is shown in **Table 1**. Younger participants, women, people of color, and those of Hispanic ethnicity had higher PHQ-9 scores. While no difference was observed in blood pressure or temperature, higher PHQ-9 scores were found in participants with higher resting heart rates, larger body mass index, greater waist circumference, and higher respiratory rates.

PHQ-9 scores as a function of medical history and symptoms are shown in **Table 2** and **eTable 2**. As expected, participants with other chronic conditions, particularly gastroesophageal

reflux disease, anxiety, and asthma, had higher PHQ-9 scores. A history of diagnosed depression

was highly correlated with elevated PHQ-9. Various symptoms were evident in participants with

higher PHQ-9 scores, with musculoskeletal, mood, and anxiety symptoms proving particularly

prominent.

Table 3 demonstrates the relationship between measures of physical performance and

PHQ-9; differences in 6-minute walk distance, handgrip strength, leg balance, chair stand, and

mean steps are particularly associated with higher PHQ-9.

The interplay of higher PHQ-9 score predictors based on the LASSO regression is shown

in Figure 1. Model performance was similar between the training and test sets for each model

(Model 1: R^2 = 0.032 vs. 0.035; Model 2: R^2 = 0.117 vs. 0.112; Model 3: R^2 = 0.167 vs. 0.133;

Model 4: R^2 = 0.247 vs. 0.228; and Model 5: R^2 = 0.270 vs. 0.240, respectively). Regardless of

adjustment factors, memory change, tension, shortness of breath, and indicators of

musculoskeletal symptoms are related to higher PHQ-9 scores (Models 1–3). Further details of

the LASSO analysis are included in the supplementary materials (eTables 3–7). Tension,

memory change, and back pain consistently remain in the models after adjustment. When

medical conditions, symptoms, and allergies are taken into account, indicators of obesity (body

mass index, waist circumference) and lack of physical fitness are the most significant predictors

of PHQ-9 score. When physical performance is also factored into the adjustment, laboratory

values are only weakly associated with PHQ-9 scores.

eFigure 1 presents the distribution of PHQ-9 according to other health conditions. The

inter-relationships are clear across this spectrum of measures, emphasizing the importance of

understanding all 3 dimensions when designing interventions.

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DISCUSSION

Our study reinforces previous observations regarding the relationship between PHQ-9 and measures of chronic disease, psychological distress, and poor physical performance. While these findings are not surprising, they highlight how PHQ-9 is an entree into a variety of individual- and population-level concerns that demand more attention. Contextual awareness is critically important when the PHQ-9 is used in clinical practice[13] as recommended by the U.S. Preventive Services Task Force[14] for screening within a health system or for public health assessment.

This analysis cannot answer questions of cause and effect since it is cross-sectional. The PHQ-9 and detailed serial measures of biological, clinical, behavioral, and social function will be assessed in the ongoing BHS longitudinal study; the bi-directional relationship between the PHQ-9 and these multiple measures will be particularly interesting, as few studies have collected this amount of detail in a diverse population. This measurement depth of demographic, clinical, biological, and behavioral issues offers an opportunity to better understand how different aspects of distress track similarly or differently over time.

An important aspect of our examination is how the binary division of PHQ-9 into labels of depression or "not depression" leaves significant content unattended. While the division of PHQ-9 scores at 10 provides good discrimination with regard to a clinical diagnosis of Major Depressive Disorder,[3,6,7] the gradient between a score of 0 and 10 contains relevant information about distress levels. Such a finding is not novel,[15] but a reminder that singular focus on a binary classification tends to obscure important information. For example, demographic data demonstrate how females and younger participants had higher PHQ-9 scores, yet whether this

finding represents a different approach to revealing concerns or more significant distress is unclear.

The higher scores associated with elevated heart rates, body mass index, and abdominal girth were expected and consistent with previous literature. In general, PHQ-9 scores aligned with musculoskeletal or central and peripheral nervous system disorders,[16,17] but less with cardiovascular disease, cancer, and other more organ-focused conditions. The previously widely-reported association with obesity and diabetes was confirmed in our study.[18-21] We found low PHQ-9 scores in a small, but noticeable proportion of the population with a previous diagnosis of depression, which could represent diagnostic errors, inaccurate reporting of medical history, or recovery from a previous episode of depression.

The profound relationship between PHQ-9 score and a host of common symptoms[22-26] is also expected, but the continuous nature of the relationship with PHQ-9 score and the depth of the relationships raise many issues that need further exploration. Significant predictors of PHQ-9 scores include a wide range of concerns encompassing neurological disease, musculoskeletal disease,[27,28] and psychological distress. A particularly notable finding is the progressive and highly significant relationship between reported memory loss and PHQ-9 score. Among people with PHQ-9 scores of 0, only 1.9% reported memory change, while among those with PHQ-9 scores >15, memory change was reported in 34%.

Finally, participants with higher PHQ-9 scores had impaired physical functioning, as indicated by a host of measurements, including daily steps, 6-minute walk distance, ability to balance on one leg, or propensity to exert a strong grip. Multiple previous studies have shown that depression and physical functioning are inter-related[29–34] and that interventions to increase physical activity can improve depression status.[35,36] Nevertheless, the overall picture of this study

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highlights the need for multimodal intervention to enable people with social disadvantages and physical comorbidities to improve physical function.

Limitations

This study has some limitations. First, the cross-sectional nature of the study limits our ability to assess the time course of these findings; however, follow-up is currently accruing. The time course of chronic disease and symptom progression in relation to the PHQ-9 will be of interest. Second, people with significant depression are probably less likely to volunteer, thereby limiting the breadth of depression observed in this study; BHS participants are volunteers from selected sites who express willingness to share data. Finally, the population is generally representative of adult age, sex, race, and ethnicity, but it is not a fully representative sample of the population; the differences between those who volunteer for digital technology studies and the general population are well-known.[37] We also lack detailed information on depression treatment, which is a potentially modifying factor.

Conclusions

PHQ-9 scores are related to multiple demographic, vital sign, and clinical measures that indicate poor physical status. BHS data provide a comprehensive picture of numerous interactive factors influencing PHQ-9 scores, thereby demonstrating how focusing on one chief complaint in hopes of improving depression status is likely futile, given that many common symptoms and physical limitations are profoundly integrated with depression status. The close association with symptoms often considered somatic raises a practical issue for clinical practice, and this is evident across the entire spectrum of PHQ-9 scores. When a high PHQ-9 score or other indicator

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of depression brings someone to the attention of a clinician, contextual awareness is critically

important to provide an effective clinical intervention. When someone has significant

neurological or musculoskeletal symptoms, assessment for depression should be a routine

consideration. The complex associations across biological, clinical, behavioral, and social factors

stress the need for holistic evaluation of depression for individuals, as well as patient

populations.

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Conflict of interest disclosures

Califf: Employee of Verily Life Sciences and Google Health; Board member for Cytokinetics,

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Wong: Employee of Verily Life Sciences.

Doraiswamy: Consulting fees from Verily Life Sciences, Neuronix, Apollo Health, VitaKey,

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Hong: Research funding from NIMH; Consulting for Little Otter.

Miller: Employee of and holds stock in Verily Life Sciences.

Mega: Employee of Verily Life Sciences.

Author contributions

Califf: Dr. Califf had full access to all of the data in the study and takes responsibility for the

integrity of the data and the accuracy of the data analysis. Dr. Califf contributed to the

conception and design of the study, the data analysis, the data interpretation, the manuscript

drafting, and the critical revision of the manuscript.

Wong: Dr. Wong contributed to the conception and design of the study, data interpretation, the

manuscript drafting, and the critical revision of the manuscript.

Doraiswamy: Dr. Doraiswamy contributed to the data interpretation, the manuscript drafting,

and the critical revision of the manuscript.

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Miller: Dr. Miller contributed to the conception and design of the study, data interpretation, the

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Mega: Dr. Mega contributed to the conception and design of the study, the supervision, data

acquisition, data interpretation, the manuscript drafting, and the critical revision of the

manuscript.

Data sharing statement

The study is committed to access to the study data for qualified investigators from the global

community after testing the process within the diverse investigator communities of the

participating institutions. Please see the following article for more information: Arges K,

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National Trends Survey, 2003–2018. J Cancer Surviv. 2021;15(1):87–98.

Table 1. Demographics: PHQ-9 score

	PHQ-9 0 (N=484)	PHQ-9 1-4 (N=1086)	PHQ-9 5-9 (N=518)	PHQ-9 10-14 (N=184)	PHQ-9 15+ (N=93)
Age, median (25th, 75th)*	53.6 (36.7, 66.1)	51.7 (37.0, 66.5)	47.6 (32.7, 60.7)	42.8 (31.2, 55.1)	42.4 (32.1, 54.2)
Female sex*	227 (46.9)	622 (57.3)	299 (57.7)	108 (58.7)	62 (66.7)
Race					
Black	80 (16.5)	153 (14.1)	82 (15.8)	31 (16.8)	19 (20.4)
White	294 (60.7)	731 (67.3)	323 (62.4)	110 (59.8)	57 (61.3)
Asian†	64 (13.2)	113 (10.4)	47 (9.1)	15 (8.2)	5 (5.4)
NHOPI	7 (1.4)	11 (1)	7 (1.4)	2 (1.1)	0 (0.0)
American Indian or Alaska Native	4 (0.8)	8 (0.7)	11 (2.1)	3 (1.6)	1 (1.1)
Other†	35 (7.2)	70 (6.4)	48 (9.3)	23 (12.5)	11 (11.8)
Ethnicity					
Hispanic	54 (11.2)	108 (9.9)	69 (13.3)	26 (14.1)	13 (14.0)
Site					
Los Angeles	94 (19.4)	194 (17.9)	111 (21.4)	35 (19)	21 (22.6)
Durham	99 (20.5)	196 (18.0)	102 (19.7)	40 (21.7)	25 (26.9)
Kannapolis	100 (20.7)	226 (20.8)	105 (20.3)	41 (22.3)	28 (30.1)
Palo Alto †	191 (39.5)	470 (43.3)	200 (38.6)	68 (37.0)	19 (20.4)

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Systolic BP, median (25th, 75th), mm Hg	123.0 (112.5, 133.1)	122.0 (112.0, 132.5)	123.0 (112.5, 133.5)	119.5 (109.9, 132.0)	122.5 (115.5, 130.5)
Diastolic BP, median (25th, 75th), mm Hg	75.5 (69.0, 82.0)	75.0 (68.0, 82.0)	76.0 (70.0, 83.5)	74.0 (68.9, 81.1)	77.5 (71.5, 84.0)
Body mass index, median (25th, 75th), kg/m2*	26.5 (23.7, 29.9)	26.1 (22.9, 31.0)	28.0 (24.5, 33.2)	29.1 (25.1, 34.7)	30.0 (25.4, 38.8)
Waist circumference, median (25th, 75th), cm*	91.0 (81.0, 100.1)	88.9 (78.7, 101.6)	93.0 (81.3, 105.4)	96.5 (82.0, 111.8)	96.5 (81.6, 112.5)
Heart rate, median (25th, 75th), beats/min*	65.0 (58.0, 72.0)	66.0 (59.0, 73.0)	67.0 (60.0, 77.0)	70.0 (61.8, 80.0)	75.0 (65.0, 82.0)
Respiratory rate, median (25th, 75th), breaths/min*	16.0 (14.0, 16.0)	16.0 (14.0, 16.0)	16.0 (14.0, 17.0)	16.0 (14.0, 18.0)	16.0 (16.0, 18.0)
Oxygen saturation, median (25th, 75th), %†	99.0 (98.0, 100.0)	99.0 (98.0, 100.0)	99.0 (98.0, 100.0)	99.0 (97.0, 100.0)	98.0 (97.0, 100.0)

Data shown are no. (%), unless otherwise indicated.

BP, blood pressure; NHOPI, Native Hawaiians and other Pacific Islanders; PHQ-9, Patient Health Questionnaire-9.

P-values for trend were calculated with the use of Spearman Correlation or Cochrane-Armitage tests, where appropriate.

*P-value for trend <0.0001.

†P-value for trend <0.01

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Table 2. Medical history: PHQ-9 score

	PHQ-9 0 (N=484)	PHQ-9 1-4 (N=1086)	PHQ-9 5-9 (N=518)	PHQ-9 10-14 (N=184)	PHQ-9 15+ (N=93)
Alcohol use disorder*	1 (0.2)	20 (1.8)	12 (2.3)	7 (3.8)	6 (6.5)
Fibromyalgia*	2 (0.4)	10 (0.9)	11 (2.1)	7 (3.8)	6 (6.5)
Gallbladder disorder†	18 (3.7)	57 (5.2)	32 (6.2)	14 (7.6)	8 (8.6)
Bipolar disorder*	3 (0.6)	9 (0.8)	12 (2.3)	9 (4.9)	8 (8.6)
PTSD*	8 (1.7)	14 (1.3)	15 (2.9)	21 (11.4)	9 (9.7)
Hypercholesterolemia	68 (14.0)	127 (11.7)	70 (13.5)	19 (10.3)	9 (9.7)
Irritable bowel disorder†	9 (1.9)	60 (5.5)	34 (6.6)	7 (3.8)	10 (10.8)
COPD with emphysema*	5 (1.0)	19 (1.7)	22 (4.2)	12 (6.5)	10 (10.8)
Sleep apnea	38 (7.9)	101 (9.3)	63 (12.2)	19 (10.3)	11 (11.8)
ADHD*	15 (3.1)	50 (4.6)	33 (6.4)	25 (13.6)	11 (11.8)
Diabetes type 2†	45 (9.3)	109 (10.0)	62 (12.0)	32 (17.4)	14 (15.1)
Pneumonia	30 (6.2)	85 (7.8)	40 (7.7)	12 (6.5)	15 (16.1)
Osteoarthritis	76 (15.7)	216 (19.9)	118 (22.8)	33 (17.9)	17 (18.3)
Asthma*	46 (9.5)	157 (14.5)	79 (15.3)	39 (21.2)	19 (20.4)
Migraine*	29 (6.0)	134 (12.3)	77 (14.9)	31 (16.8)	19 (20.4)
GERD*	64 (13.2)	176 (16.2)	106 (20.5)	40 (21.7)	23 (24.7)
Hypertension	122 (25.2)	297 (27.3)	144 (27.8)	51 (27.7)	26 (28.0)
Anxiety*	13 (2.7)	98 (9.0)	109 (21.0)	55 (29.9)	34 (36.6)
Depression*	16 (3.3)	93 (8.6)	110 (21.2)	63 (34.2)	55 (59.1)
Hay fever	26 (5.4)	78 (7.2)	36 (6.9)	19 (10.3)	3 (3.2)
Discharge†	19 (3.9)	64 (5.9)	44 (8.5)	18 (9.8)	8 (8.6)
Hemorrhoids†	22 (4.5)	69 (6.4)	40 (7.7)	17 (9.2)	9 (9.7)
Itching skin *	19 (3.9)	81 (7.5)	50 (9.7)	30 (16.3)	10 (10.8)
Sinus pain *	18 (3.7)	77 (7.1)	58 (11.2)	21 (11.4)	10 (10.8)
Urgency *	13 (2.7)	69 (6.4)	46 (8.9)	23 (12.5)	10 (10.8)
Excessive belching or passing of gas *	24 (5.0)	84 (7.7)	54 (10.4)	29 (15.8)	13 (14.0)
Ear ringing†	38 (7.9)	101 (9.3)	59 (11.4)	23 (12.5)	13 (14.0)
Dryness *	35 (7.2)	113 (10.4)	68 (13.1)	39 (21.2)	14 (15.1)
Heartburn *	27 (5.6)	94 (8.7)	70 (13.5)	42 (22.8)	15 (16.1)
Dry mouth *	27 (5.6)	84 (7.7)	64 (12.4)	28 (15.2)	16 (17.2)

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Constipation *	22 (4.5)	98 (9.0)	64 (12.4)	48 (26.1)	17 (18.3)
Numbness or loss of sensation *	17 (3.5)	54 (5.0)	38 (7.3)	19 (10.3)	17 (18.3)
Easy bruising or bleeding[†]	39 (8.1)	130 (12.0)	68 (13.1)	22 (12.0)	18 (19.4)
Cramping*	14 (2.9)	62 (5.7)	45 (8.7)	18 (9.8)	18 (19.4)
Frequency of urination *	33 (6.8)	90 (8.3)	73 (14.1)	34 (18.5)	19 (20.4)
Runny nose[†]	70 (14.5)	210 (19.3)	116 (22.4)	44 (23.9)	20 (21.5)
Swelling in calves, legs, or feet *	15 (3.1)	62 (5.7)	49 (9.5)	31 (16.8)	20 (21.5)
Coughing up sputum *	12 (2.5)	62 (5.7)	56 (10.8)	27 (14.7)	20 (21.5)
Floaters[†]	55 (11.4)	160 (14.7)	81 (15.6)	28 (15.2)	21 (22.6)
Pain or stiffness in neck *	32 (6.6)	128 (11.8)	72 (13.9)	49 (26.6)	22 (23.7)
Diarrhea *	24 (5.0)	99 (9.1)	70 (13.5)	31 (16.8)	22 (23.7)
Night sweats *	22 (4.5)	88 (8.1)	65 (12.5)	25 (13.6)	22 (23.7)
Lightheadedness *	11 (2.3)	62 (5.7)	53 (10.2)	37 (20.1)	22 (23.7)
Cough *	36 (7.4)	98 (9.0)	83 (16.0)	41 (22.3)	23 (24.7)
Tingling or numbness in extremities *	35 (7.2)	101 (9.3)	74 (14.3)	36 (19.6)	23 (24.7)
Leg cramps *	31 (6.4)	103 (9.5)	55 (10.6)	31 (16.8)	23 (24.7)
Shortness of breath with exercise *	11 (2.3)	59 (5.4)	68 (13.1)	37 (20.1)	23 (24.7)
Joint pain or swelling*	42 (8.7)	140 (12.9)	81 (15.6)	45 (24.5)	25 (26.9)
Sleeping pattern changes *	21 (4.3)	126 (11.6)	78 (15.1)	47 (25.5)	25 (26.9)
Tingling or pins and needles *	30 (6.2)	91 (8.4)	75 (14.5)	36 (19.6)	25 (26.9)
Appetite changes *	9 (1.9)	36 (3.3)	35 (6.8)	25 (13.6)	26 (28.0)
Heat or cold intolerance *	17 (3.5)	85 (7.8)	65 (12.5)	36 (19.6)	27 (29.0)
Shortness of breath *	8 (1.7)	51 (4.7)	57 (11.0)	34 (18.5)	27 (29.0)
Bloating *	26 (5.4)	104 (9.6)	61 (11.8)	41 (22.3)	29 (31.2)
Body image concerns *	9 (1.9)	40 (3.7)	46 (8.9)	33 (17.9)	29 (31.2)
Nasal stuffiness *	70 (14.5)	218 (20.1)	141 (27.2)	53 (28.8)	30 (32.3)
Urination at night *	69 (14.3)	172 (15.8)	105 (20.3)	43 (23.4)	30 (32.3)
Muscle or joint pain*	71 (14.7)	225 (20.7)	142 (27.4)	61 (33.2)	31 (33.3)
Memory change*	9 (1.9)	52 (4.8)	55 (10.6)	41 (22.3)	32 (34.4)
Headache*	28 (5.8)	151 (13.9)	104 (20.1)	44 (23.9)	38 (40.9)
Fatigue*	10 (2.1)	129 (11.9)	113 (21.8)	65 (35.3)	38 (40.9)

Stiffness*	76 (15.7)	267 (24.6)	121 (23.4)	63 (34.2)	39 (41.9)
Backache*	43 (8.9)	183 (16.9)	148 (28.6)	63 (34.2)	39 (41.9)
Nervousness*	4 (0.8)	46 (4.2)	51 (9.8)	39 (21.2)	43 (46.2)
Mood change*	6 (1.2)	36 (3.3)	60 (11.6)	42 (22.8)	44 (47.3)
Difficulty concentrating*	8 (1.7)	58 (5.3)	74 (14.3)	54 (29.3)	50 (53.8)
Neck or low back pain*	73 (15.1)	264 (24.3)	185 (35.7)	73 (39.7)	51 (54.8)
Tension*	10 (2.1)	84 (7.7)	86 (16.6)	44 (23.9)	51 (54.8)
Lack of energy*	6 (1.2)	92 (8.5)	115 (22.2)	74 (40.2)	53 (57.0)

Data presented as no. (%).
ADHD, attention deficit hyperactivity disorder; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; PHQ-9, Patient Health Questionnaire-9; PTSD, post-traumatic stress disorder.
P-values for trend were calculated with the use of Spearman Correlation or Cochrane-Armitage tests, where appropriate.
*P-value for trend <0.0001.
†P-value for trend <0.01.

Table 3. Physical Functioning: PHQ-9 Score

	PHQ-9 0 (N=484)	PHQ-9 1-4 (N=1086)	PHQ-9 5-9 (N=518)	PHQ-9 10-14 (N=184)	PHQ-9 15+ (N=93)
6-minute walk*	485.5 (444.0, 543.2)	480.0 (431.7, 530.3)	465.0 (422.0, 517.6)	460.1 (403.8, 511.9)	443.0 (391.2, 492.4)
30-second chair stand*	15.0 (12.0, 18.0)	14.0 (12.0, 17.0)	13.0 (11.0, 16.0)	13.0 (10.0, 16.0)	12.0 (10.0, 15.0)
Mean leg balance time†	60.0 (23.5, 60.0)	55.0 (21.4, 60.0)	50.5 (14.0, 60.0)	49.5 (11.0, 60.0)	44.0 (12.5, 60.0)
10-meter walk speed*	2.0 (1.8, 2.2)	2.0 (1.8, 2.2)	2.0 (1.6, 2.1)	1.8 (1.5, 2.0)	1.8 (1.5, 2.0)
Handgrip†	35.8 (27.8, 44.4)	32.5 (26.3, 42.5)	32.3 (26.4, 42.8)	33.4 (25.6, 40.7)	30.0 (22.0, 39.7)
Sit-rise score	8.0 (6.0, 9.0)	8.0 (6.0, 9.0)	8.0 (6.0, 9.0)	8.0 (6.0, 9.0)	7.5 (5.0, 9.0)
EF at rest, %	59.0 (55.8, 60.5)	58.8 (55.9, 60.5)	59.2 (56.1, 60.5)	59.2 (56.0, 61.4)	58.9 (56.0, 60.9)
Mean steps in first 30 days*	8398.0 (6560.6, 10709.6)	8172.2 (6220.6, 10335.7)	7666.7 (5128.2, 9862.5)	7008.4 (4673.5, 9821.8)	6498.1 (4684.1, 9044.5)
Coronary calcium score†	0.0 (0.0, 33.9)	0.0 (0.0, 42.6)	0.0 (0.0, 8.8)	0.0 (0.0, 7.1)	0.0 (0.0, 1.9)
FEV1/FVC	0.8 (0.7, 0.8)	0.8 (0.7, 0.8)	0.8 (0.7, 0.8)	0.8 (0.7, 0.8)	0.8 (0.7, 0.8)
ABI †	1.1 (1.1, 1.2)	1.1 (1.1, 1.2)	1.1 (1.1, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)

Data presented as median (25th, 75th percentile).
ABI, ankle brachial index; EF, ejection fraction; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PHQ-9, Patient Health Questionnaire.
P-values for trend were calculated with the use of Spearman Correlation or Cochrane-Armitage tests, where appropriate.
*P-value for trend <0.01.
†P-value for trend <0.001

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FIGURE LEGENDS

Figure 1. Top 30 Regression Coefficients

Top 30 regression coefficients for: A) model 1; B) model 2; C) model 3; D) model 4; E) model 5.

Top 30 Regression Coefficients for Model 1

Adjusted by Age and Sex

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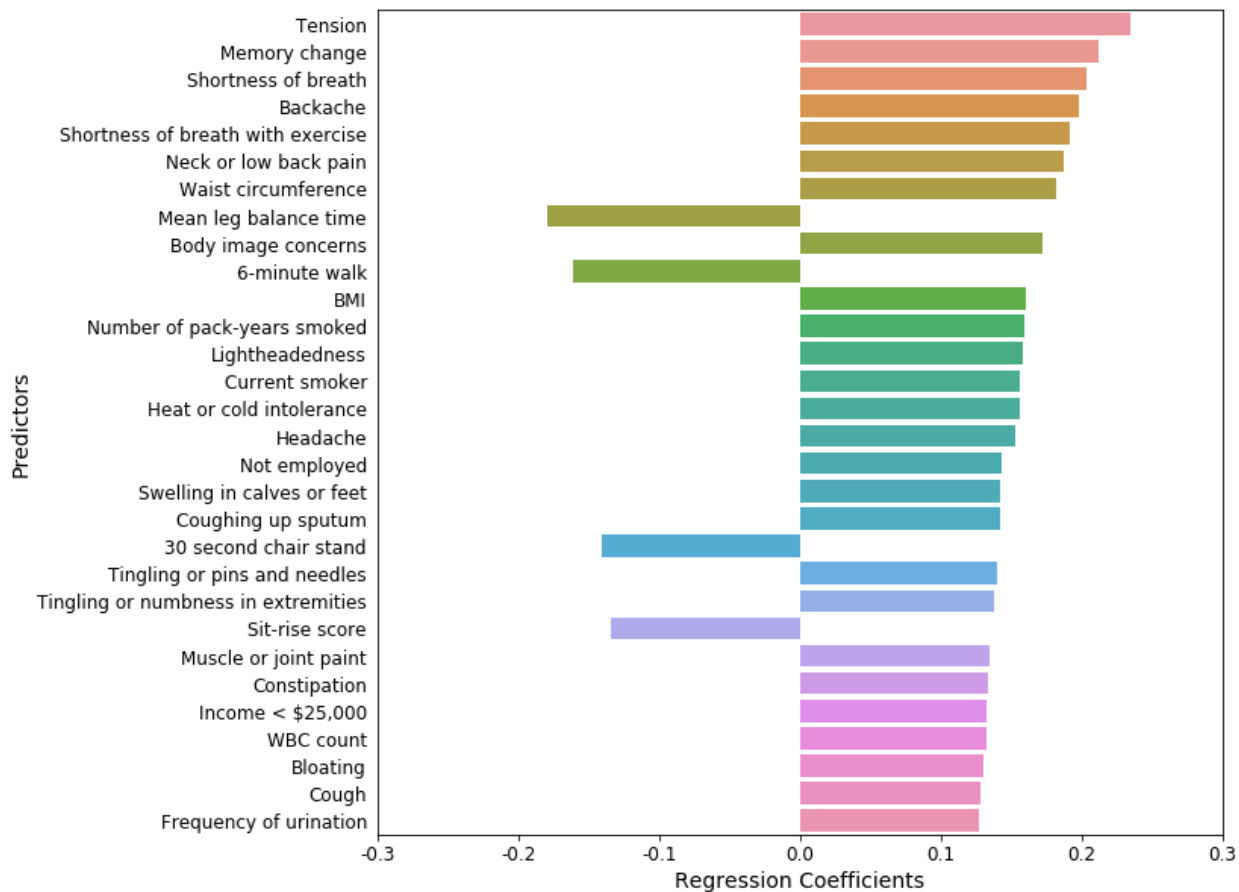
Top 30 Regression Coefficients for Model 2

Adjusted by Age, Sex, SES and Health Behavior

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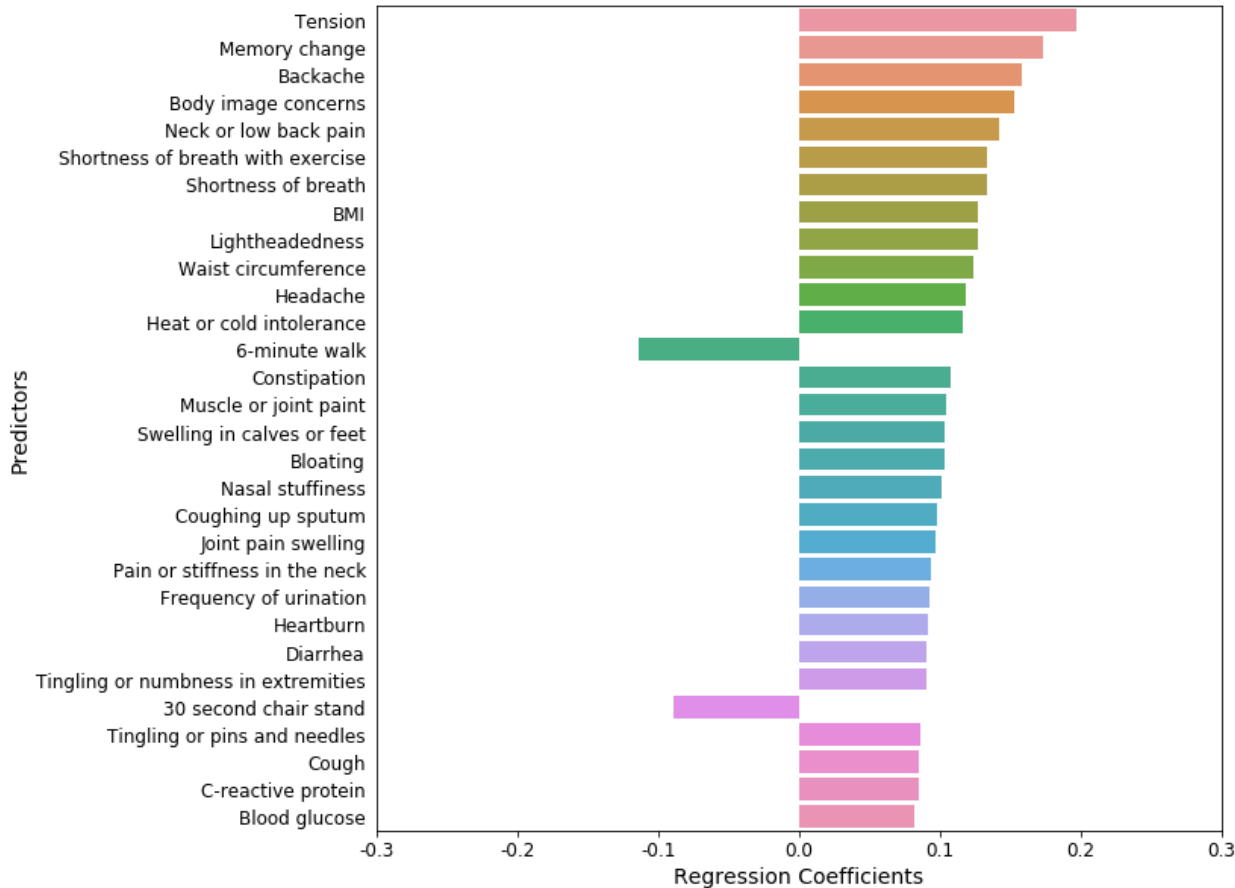
Top 30 Regression Coefficients for Model 3

Adjusted by Age, Sex, SES, Health Behavior, and Medical Conditions
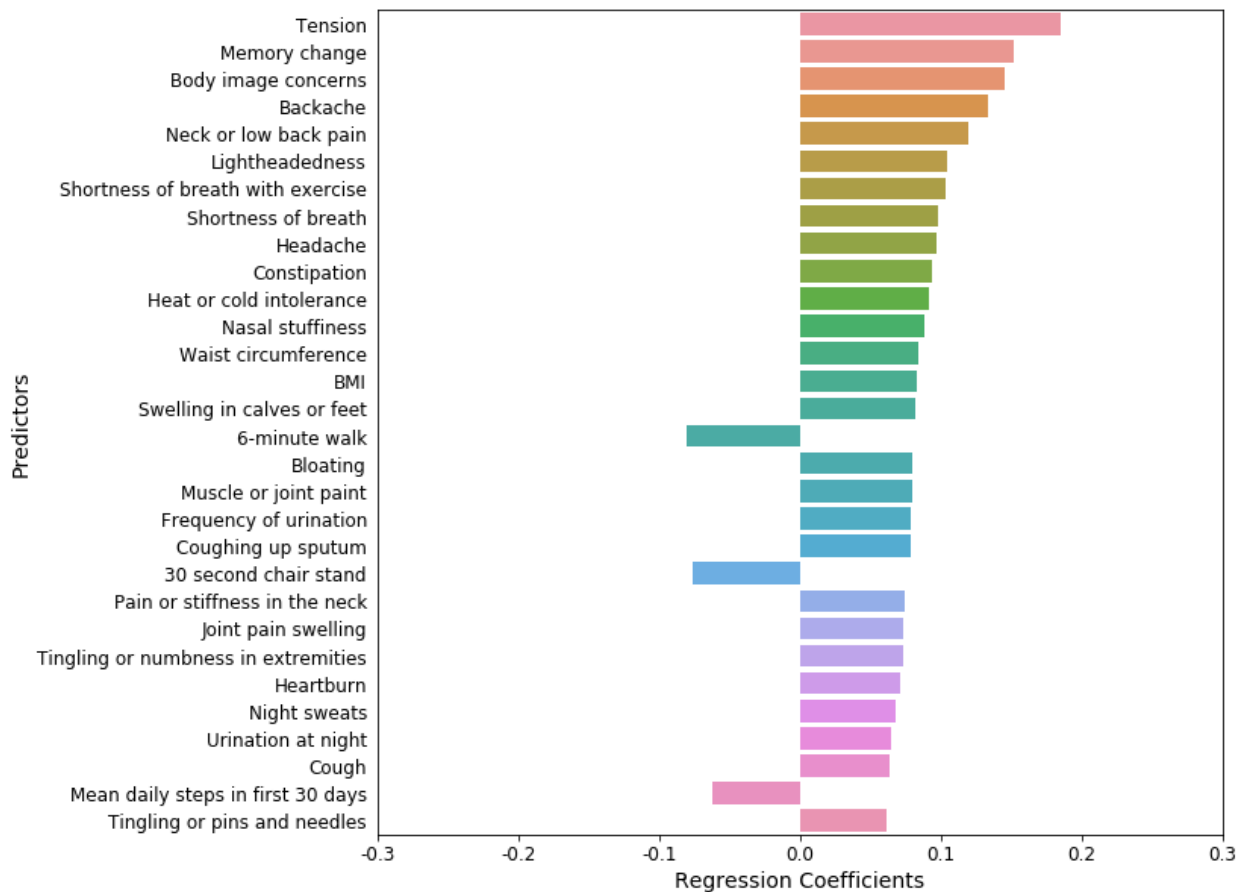
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Top 30 Regression Coefficients for Model 4

Adjusted by Age, Sex, SES, Health Behavior, Medical Conditions, Symptoms and Allergies

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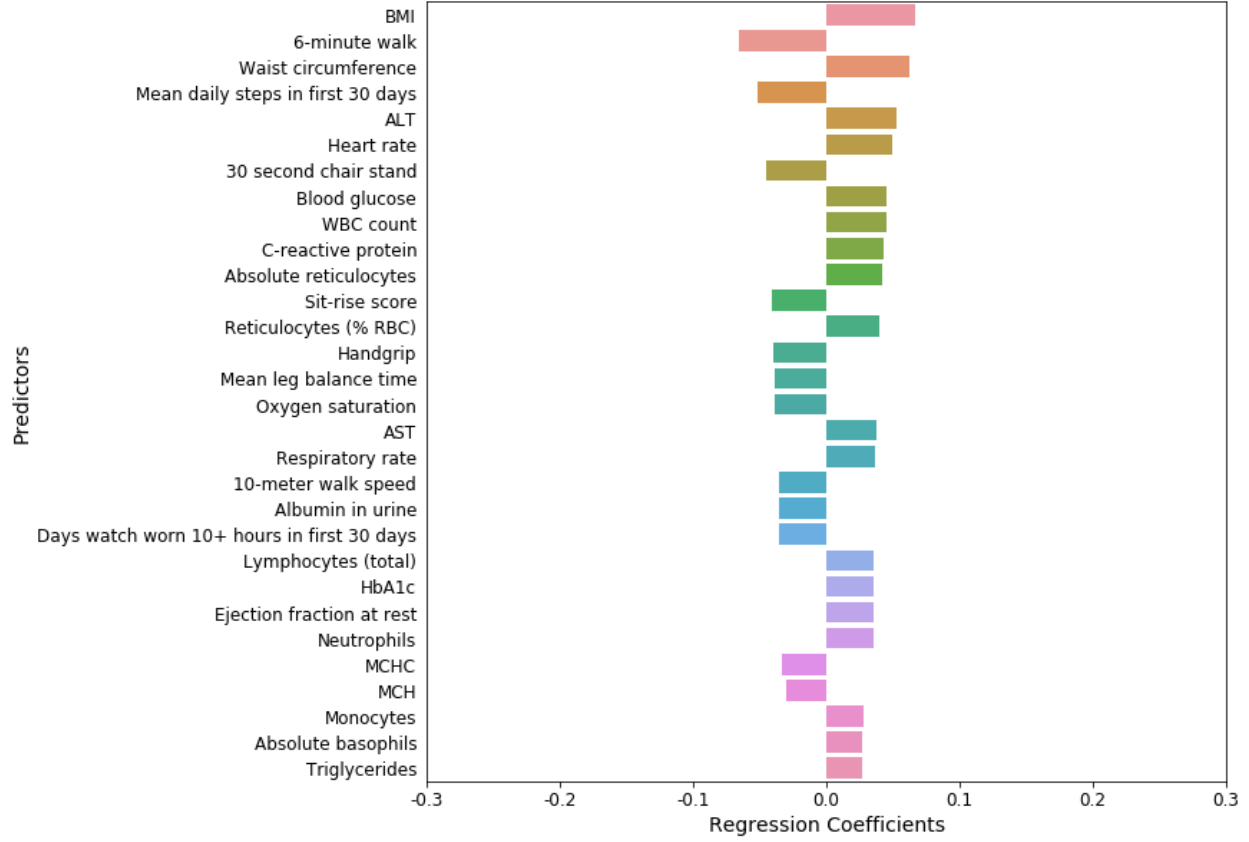
Top 30 Regression Coefficients for Model 5

Adjusted by Age, Sex, SES, Health Behavior, Medical Conditions, Symptoms, Allergies, and Physical Function

1

SUPPLEMENTAL MATERIAL

2

eTable 1. Key Variables Included in Each LASSO Covariate Model

Variables	Model 1	Model 2	Model 3	Model 4	Model 5
Age,sex and age × sex interaction (Supplemental Table 1.1)	✓	✓	✓	✓	✓
Race and ethnicity (Supplemental Table 1.1)		✓	✓	✓	✓
Socioeconomic-related variables (Supplemental Table 1.6)		✓	✓	✓	✓
Behavioral-related behaviors (Supplemental Tables 1.1 and 1.6)		✓	✓	✓	✓
Medical conditions *not* related to mental health / depression (Supplemental Table 1.3)			✓	✓	✓
Symptoms and allergies *not* related to mental health / depression (Supplemental Table 1.3)				✓	✓
Physical health metrics (Table Supplemental Tables 1.2 and 1.7)					✓
Standard labs (Supplemental Table 1.5)					

eTable 2. Additional Medical History: PHQ-9 Scores

	0 (N=484)	1–4 (N=1086)	5–9 (N=518)	10–14 (N=184)	15+ (N=93)
Nonmelanoma skin cancer	12 (2.5)	42 (3.9)	18 (3.5)	3 (1.6)	0 (0.0)*
Osteoporosis	11 (2.3)	47 (4.3)	17 (3.3)	3 (1.6)	0 (0.0)*
Benign prostatic hyperplasia	22 (4.5)	44 (4.1)	17 (3.3)	3 (1.6)	0 (0.0)*
Melanoma skin cancer	11 (2.3)	23 (2.1)	5 (1.0)	0 (0.0)	0 (0.0)*
Prostate cancer	12 (2.5)	17 (1.6)	6 (1.2)	1 (0.5)	0 (0.0)*
Diabetes type 1	3 (0.6)	12 (1.1)	4 (0.8)	3 (1.6)	0 (0.0)
Macular degeneration	2 (0.4)	20 (1.8)	4 (0.8)	4 (2.2)	0 (0.0)
TIA	7 (1.4)	9 (0.8)	3 (0.6)	3 (1.6)	0 (0.0)
Hepatitis B	6 (1.2)	10 (0.9)	4 (0.8)	3 (1.6)	0 (0.0)
Coronary artery disease	11 (2.3)	44 (4.1)	13 (2.5)	6 (3.3)	1 (1.1)
Hashimoto's disease	8 (1.7)	22 (2.0)	11 (2.1)	3 (1.6)	1 (1.1)
Goiter	7 (1.4)	12 (1.1)	3 (0.6)	0 (0.0)	1 (1.1)
Hemorrhoids	11 (2.3)	44 (4.1)	18 (3.5)	4 (2.2)	1 (1.1)
Hypothyroidism	42 (8.7)	93 (8.6)	40 (7.7)	9 (4.9)	2 (2.2)
Glaucoma	14 (2.9)	29 (2.7)	10 (1.9)	6 (3.3)	2 (2.2)
Psoriasis	10 (2.1)	16 (1.5)	11 (2.1)	8 (4.3)	2 (2.2)
Peptic ulcer	5 (1.0)	22 (2.0)	13 (2.5)	4 (2.2)	2 (2.2)
Diverticulosis	8 (1.7)	29 (2.7)	10 (1.9)	5 (2.7)	2 (2.2)
Peripheral vascular disorder	1 (0.2)	15 (1.4)	8 (1.5)	2 (1.1)	2 (2.2)
Atrial fibrillation	4 (0.8)	17 (1.6)	1 (0.2)	1 (0.5)	2 (2.2)
Colon polyps	53 (11.0)	113 (10.4)	52 (10.0)	12 (6.5)	3 (3.2)
Arrhythmia	20 (4.1)	69 (6.4)	27 (5.2)	8 (4.3)	3 (3.2)
Tinnitus	31 (6.4)	52 (4.8)	35 (6.8)	6 (3.3)	3 (3.2)
Hearing Loss	29 (6.0)	75 (6.9)	26 (5.0)	12 (6.5)	3 (3.2)
Gout	14 (2.9)	29 (2.7)	14 (2.7)	5 (2.7)	3 (3.2)
Diverticulitis	3 (0.6)	20 (1.8)	17 (3.3)	3 (1.6)	3 (3.2)
Headaches	6 (1.2)	18 (1.7)	13 (2.5)	3 (1.6)	3 (3.2)
Epilepsy	5 (1.0)	19 (1.7)	12 (2.3)	5 (2.7)	3 (3.2)
Breast cancer	8 (1.7)	20 (1.8)	9 (1.7)	1 (0.5)	3 (3.2)
Myocardial infarction	6 (1.2)	19 (1.7)	11 (2.1)	1 (0.5)	3 (3.2)
Osteopenia	22 (4.5)	62 (5.7)	22 (4.2)	1 (0.5)	3 (3.2)
Stroke	5 (1.0)	12 (1.1)	9 (1.7)	1 (0.5)	3 (3.2)
Drug abuse*	5 (1.0)	14 (1.3)	5 (1.0)	13 (7.1)	4 (4.3)
Pulmonary embolism	4 (0.8)	17 (1.6)	7 (1.4)	3 (1.6)	4 (4.3)
Nonalcoholic fatty liver disease	5 (1.0)	17 (1.6)	16 (3.1)	3 (1.6)	4 (4.3)
Hepatitis C†	5 (1.0)	8 (0.7)	3 (0.6)	8 (4.3)	4 (4.3)
Cataracts	61 (12.6)	167 (15.4)	63 (12.2)	16 (8.7)	5 (5.4)
Kidney or bladder stones	36 (7.4)	66 (6.1)	18 (3.5)	13 (7.1)	5 (5.4)

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Concussions	19 (3.9)	62 (5.7)	35 (6.8)	13 (7.1)	5 (5.4)
Rheumatoid arthritis†	4 (0.8)	13 (1.2)	12 (2.3)	4 (2.2)	6 (6.5)

P-values for trend were calculated with the use of Spearman Correlation or Cochrane-Armitage tests, where appropriate.
*P-value for trend <0.0001.
†P-value for trend <0.01.

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eTable 3. LASSO Regression Results: Model 1

Variable	Estimate	P-value	CI 25%	CI 75%
Tension	0.2344	< 0.0001	0.2026	0.2661
Memory change	0.2119	< 0.0001	0.1801	0.2437
Shortness of breath	0.2033	< 0.0001	0.1714	0.2352
Backache	0.1974	< 0.0001	0.1655	0.2293
Shortness of breath with exercise	0.1914	< 0.0001	0.1594	0.2233
Neck or low back pain	0.1869	< 0.0001	0.1549	0.2189
Waist circumference	0.1814	< 0.0001	0.1480	0.2149
Mean leg balance time	-0.1796	< 0.0001	-0.2172	-0.1420
Body image concerns	0.1726	< 0.0001	0.1403	0.2049
6-minute walk	-0.1608	< 0.0001	-0.1932	-0.1284
BMI	0.1604	< 0.0001	0.1282	0.1926
Number of pack-years smoked	0.1590	< 0.0001	0.1258	0.1922
Lightheadedness	0.1576	< 0.0001	0.1254	0.1899
Current smoker	0.1561	< 0.0001	0.1238	0.1884
Heat or cold intolerance	0.1560	< 0.0001	0.1238	0.1882
Headache	0.1532	< 0.0001	0.1205	0.1859
Not employed	0.1434	< 0.0001	0.1111	0.1757
Swelling in calves or feet	0.1421	< 0.0001	0.1098	0.1745
Coughing up sputum	0.1416	< 0.0001	0.1093	0.1739
30 second chair stand	-0.1407	< 0.0001	-0.1732	-0.1081
Tingling or pins and needles	0.1403	< 0.0001	0.1079	0.1727
Tingling or numbness in extremities	0.1373	< 0.0001	0.1049	0.1697
Sit-rise score	-0.1345	< 0.0001	-0.1714	-0.0975
Muscle or joint paint	0.1343	< 0.0001	0.1019	0.1668
Constipation	0.1334	< 0.0001	0.1010	0.1657
Income < $25,000	0.1325	< 0.0001	0.1001	0.1650
WBC count	0.1322	< 0.0001	0.0998	0.1647
Bloating	0.1305	< 0.0001	0.0979	0.1631
Cough	0.1276	< 0.0001	0.0952	0.1601
Frequency of urination	0.1274	< 0.0001	0.0945	0.1603
Nasal stuffiness	0.1259	< 0.0001	0.0934	0.1583
COPD with emphysema	0.1228	< 0.0001	0.0901	0.1555
Joint pain swelling	0.1225	< 0.0001	0.0899	0.1550
Heartburn	0.1215	< 0.0001	0.0890	0.1540
Pain or stiffness in the neck	0.1206	< 0.0001	0.0881	0.1531
Stiffness	0.1194	< 0.0001	0.0868	0.1520
Mean daily steps in first 30 days	-0.1176	< 0.0001	-0.1503	-0.0848
Heart rate	0.1165	< 0.0001	0.0835	0.1495
Urination at night	0.1158	< 0.0001	0.0823	0.1492
HbA1c	0.1144	< 0.0001	0.0813	0.1476
Diarrhea	0.1138	< 0.0001	0.0812	0.1463
10-meter walk speed	-0.1137	< 0.0001	-0.1463	-0.0810
Blood glucose	0.1136	< 0.0001	0.0808	0.1463
Oxygen saturation	-0.1118	< 0.0001	-0.1458	-0.0777

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Dry mouth	0.1117	< 0.0001	0.0791	0.1444
Night sweats	0.1110	< 0.0001	0.0784	0.1435
C-reactive protein	0.1084	< 0.0001	0.0759	0.1409
Urgency	0.1080	< 0.0001	0.0751	0.1410
Monocytes	0.1075	< 0.0001	0.0742	0.1408
Neutrophils	0.1072	< 0.0001	0.0747	0.1398
Numbness or loss of sensation	0.1055	< 0.0001	0.0729	0.1380
GERD	0.1004	< 0.0001	0.0675	0.1334
Itching skin	0.0971	< 0.0001	0.0645	0.1297
Excessive belching or passing of gas	0.0957	< 0.0001	0.0631	0.1283
Respiratory rate	0.0944	< 0.0001	0.0618	0.1270
Leg cramps	0.0933	< 0.0001	0.0606	0.1260
Urine specific gravity	0.0931	< 0.0001	0.0605	0.1257
Albumin in urine	-0.0928	< 0.0001	-0.1261	-0.0595
Dryness	0.0926	< 0.0001	0.0600	0.1252
Absolute basophils	0.0925	< 0.0001	0.0598	0.1251
Uninsured	0.0924	< 0.0001	0.0597	0.1250
Cramping	0.0920	< 0.0001	0.0592	0.1248
Osteoarthritis	0.0917	< 0.0001	0.0568	0.1267
Lymphocytes (total)	0.0883	< 0.0001	0.0554	0.1213
Sleep apnea	0.0877	< 0.0001	0.0541	0.1213
ALT	0.0848	< 0.0001	0.0522	0.1175
Married	-0.0848	< 0.0001	-0.1188	-0.0508
Sinus pain	0.0838	< 0.0001	0.0511	0.1164
HDL	-0.0835	< 0.0001	-0.1161	-0.0509
Creatinine (urine)	0.0811	< 0.0001	0.0484	0.1138
Reticulocytes (% RBC)	0.0803	< 0.0001	0.0475	0.1131
Triglycerides	0.0800	< 0.0001	0.0471	0.1128
Fibromyalgia	0.0798	< 0.0001	0.0472	0.1125
Asthma	0.0796	< 0.0001	0.0469	0.1123
Former smoker	0.0791	< 0.0001	0.0454	0.1127
Absolute reticulocytes	0.0786	< 0.0001	0.0458	0.1114
Diabetes type 2	0.0780	< 0.0001	0.0448	0.1111
Urine reaction pH	-0.0762	< 0.0001	-0.1095	-0.0430
Migraines	0.0753	< 0.0001	0.0425	0.1081
Hypertension	0.0749	< 0.0001	0.0397	0.1102
Runny nose	0.0738	< 0.0001	0.0411	0.1065
Vitamin D	-0.0732	< 0.0001	-0.1067	-0.0397
Easy bruising or bleeding	0.0719	< 0.0001	0.0390	0.1049
High school or less education	0.0706	< 0.0001	0.0379	0.1033
Floaters	0.0701	< 0.0001	0.0370	0.1033
Discharge	0.0698	< 0.0001	0.0372	0.1025
Ear ringing	0.0671	< 0.0001	0.0338	0.1003
Hemorrhoids (symptom)	0.0649	0.0001	0.0320	0.0977
Days watch worn 10+ hours in first 30 days	-0.0639	0.0002	-0.0976	-0.0301
Asian race	-0.0636	0.0002	-0.0964	-0.0307
Absolute eosinophils	0.0632	0.0002	0.0304	0.0960
Seasonal allergies	0.0626	0.0002	0.0299	0.0954
Medication allergies	0.0612	0.0003	0.0283	0.0941
Irritable bowel disorder	0.0585	0.0005	0.0258	0.0912

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Hepatitis C	0.0579	0.0005	0.0252	0.0907
Rheumatoid arthritis	0.0572	0.0006	0.0244	0.0900
Systolic blood pressure	0.0566	0.0017	0.0212	0.0920
Diverticulitis	0.0561	0.0008	0.0232	0.0890
Uric acid	0.0538	0.0019	0.0199	0.0876
Magnesium	-0.0537	0.0013	-0.0865	-0.0209
MCHC	-0.0533	0.0015	-0.0861	-0.0205
Handgrip	-0.0514	0.0021	-0.0842	-0.0187
Gallbladder disease	0.0488	0.0036	0.0160	0.0816
MCH	-0.0465	0.0065	-0.0799	-0.0130
AST	0.0443	0.0080	0.0116	0.0771
Epilepsy	0.0427	0.0106	0.0100	0.0755
Food allergies	0.0424	0.0112	0.0096	0.0752
Diastolic blood pressure	0.0420	0.0124	0.0091	0.0748
Pneumonia	0.0403	0.0163	0.0074	0.0732
Nonalcoholic fatty liver disease	0.0403	0.0159	0.0075	0.0731
Ejection fraction at rest	0.0403	0.0161	0.0075	0.0731
Non-seasonal allergies	0.0393	0.0189	0.0065	0.0722
Serum creatinine	0.0388	0.0239	0.0051	0.0725
Protein (serum)	-0.0381	0.0299	-0.0725	-0.0037
Cataracts	0.0368	0.0513	-0.0002	0.0737
Pulmonary embolism	0.0359	0.0321	0.0031	0.0688
Peripheral vascular disease	0.0344	0.0401	0.0016	0.0673
Hay fever	0.0342	0.0413	0.0014	0.0671
Stroke	0.0337	0.0450	0.0008	0.0667
MCV	-0.0331	0.0529	-0.0666	0.0004
Diverticulosis	0.0324	0.0541	-0.0006	0.0655
Arrhythmia	0.0324	0.0584	-0.0012	0.0659
Gout	0.0323	0.0570	-0.0010	0.0655
Myocardial infarction	0.0317	0.0606	-0.0014	0.0649
Cholesterol	-0.0305	0.0685	-0.0633	0.0023
Platelets	0.0303	0.0783	-0.0034	0.0640
LDL	-0.0301	0.0726	-0.0630	0.0028
Peptic ulcer	0.0300	0.0730	-0.0028	0.0628
Hypercholesterolemia	0.0297	0.0879	-0.0044	0.0638
Goiter	-0.0290	0.0836	-0.0618	0.0039
Coronary artery disease	0.0287	0.0959	-0.0051	0.0625
Chloride	-0.0268	0.1096	-0.0596	0.0060
Neutrophil lymphocyte ratio	0.0266	0.1156	-0.0065	0.0597
Basophils (% WBC)	0.0258	0.1242	-0.0071	0.0587
Chronic headaches	0.0258	0.1236	-0.0070	0.0586
Nonmelanoma skin cancer	0.0233	0.1738	-0.0103	0.0569
Hearing loss	0.0229	0.1869	-0.0111	0.0568
MPV	0.0224	0.1802	-0.0104	0.0552
AUDIT-C sum score	-0.0219	0.1897	-0.0547	0.0109
Benign prostatic hyperplasia	0.0218	0.2273	-0.0136	0.0571
Eosinophils (% WBC)	0.0216	0.2001	-0.0114	0.0545
Hypothyroidism	-0.0213	0.2064	-0.0544	0.0118
Macular degeneration	0.0209	0.2140	-0.0121	0.0540
Left ventricular mass index	0.0197	0.2623	-0.0147	0.0541
Hemoglobin	-0.0181	0.2868	-0.0515	0.0153

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RBC count	0.0180	0.2814	-0.0148	0.0508
Psoriasis	0.0170	0.3108	-0.0158	0.0497
Lymphocytes (% WBC)	-0.0166	0.3270	-0.0499	0.0166
Kidney or bladder stones	-0.0159	0.3448	-0.0490	0.0171
Glaucoma	0.0157	0.3547	-0.0175	0.0489
Hemorrhoids	0.0152	0.3649	-0.0177	0.0482
Coronary calcium score	0.0144	0.4287	-0.0213	0.0502
Other race	0.0131	0.4445	-0.0204	0.0466
Colon polyps	0.0120	0.4975	-0.0227	0.0467
Breast cancer	0.0118	0.4826	-0.0211	0.0446
Melanoma skin cancer	-0.0117	0.4889	-0.0450	0.0215
Sodium	-0.0117	0.4856	-0.0446	0.0212
Calcium	-0.0115	0.4909	-0.0443	0.0213
Hashimotos Disease	-0.0108	0.5175	-0.0436	0.0220
Transient ischemic attack	-0.0087	0.6029	-0.0417	0.0242
Osteopenia	-0.0076	0.6521	-0.0408	0.0256
Atrial fibrillation	0.0075	0.6601	-0.0258	0.0407
Neutrophil segments (% WBC)	0.0071	0.6714	-0.0257	0.0399
Total neutrophils (% WBC)	0.0071	0.6714	-0.0257	0.0399
TSH	0.0069	0.6786	-0.0259	0.0397
Potassium	-0.0060	0.7193	-0.0390	0.0269
Hematocrit	-0.0049	0.7722	-0.0383	0.0285
Monocytes (% WBC)	0.0041	0.8177	-0.0305	0.0386
Osteoporosis	-0.0039	0.8192	-0.0369	0.0292
GFR MDRD	0.0030	0.8737	-0.0343	0.0403
Tinnitus	0.0029	0.8627	-0.0304	0.0362
Diabetes type 1	-0.0027	0.8707	-0.0356	0.0301
Hispanic ethnicity	-0.0023	0.8914	-0.0360	0.0314
Hepatitis B	-0.0022	0.8963	-0.0351	0.0307
Prostate cancer	-0.0009	0.9575	-0.0348	0.0329
Black race	0.0004	0.9790	-0.0325	0.0334

eTable 4. LASSO Regression Results: Model 2

Variable	Estimate	P-value	CI 25%	CI 75%
Tension	0.1970	< 0.0001	0.1659	0.2282
Memory change	0.1732	< 0.0001	0.1423	0.2040
Backache	0.1585	< 0.0001	0.1273	0.1898
Body image concerns	0.1527	< 0.0001	0.1216	0.1837
Neck or low back pain	0.1419	< 0.0001	0.1105	0.1733
Shortness of breath with exercise	0.1336	< 0.0001	0.1019	0.1652
Shortness of breath	0.1329	< 0.0001	0.1011	0.1646
BMI	0.1269	< 0.0001	0.0958	0.1581
Lightheadedness	0.1268	< 0.0001	0.0955	0.1581
Waist circumference	0.1235	< 0.0001	0.0925	0.1545
Headache	0.1188	< 0.0001	0.0871	0.1505
Heat or cold intolerance	0.1159	< 0.0001	0.0845	0.1472
6-minute walk	-0.1139	< 0.0001	-0.1451	-0.0827
Constipation	0.1078	< 0.0001	0.0766	0.1391
Muscle or joint paint	0.1044	< 0.0001	0.0732	0.1356
Swelling in calves or feet	0.1036	< 0.0001	0.0723	0.1349
Bloating	0.1036	< 0.0001	0.0721	0.1351
Nasal stuffiness	0.1014	< 0.0001	0.0702	0.1326
Coughing up sputum	0.0978	< 0.0001	0.0663	0.1293
Joint pain swelling	0.0971	< 0.0001	0.0659	0.1282
Pain or stiffness in the neck	0.0937	< 0.0001	0.0623	0.1250
Frequency of urination	0.0927	< 0.0001	0.0615	0.1238
Heartburn	0.0913	< 0.0001	0.0599	0.1227
Diarrhea	0.0903	< 0.0001	0.0589	0.1216
Tingling or numbness in extremities	0.0900	< 0.0001	0.0586	0.1214
30 second chair stand	-0.0893	< 0.0001	-0.1207	-0.0580
Tingling or pins and needles	0.0859	< 0.0001	0.0543	0.1176
Cough	0.0855	< 0.0001	0.0539	0.1170
C-reactive protein	0.0847	< 0.0001	0.0534	0.1161
Blood glucose	0.0819	< 0.0001	0.0506	0.1131
Night sweats	0.0811	< 0.0001	0.0497	0.1125
Stiffness	0.0806	< 0.0001	0.0492	0.1119
Mean leg balance time	-0.0777	< 0.0001	-0.1090	-0.0464
HbA1c	0.0772	< 0.0001	0.0460	0.1084
Heart rate	0.0771	< 0.0001	0.0450	0.1092
Urination at night	0.0770	< 0.0001	0.0458	0.1082
ALT	0.0751	< 0.0001	0.0439	0.1063
Mean daily steps in first 30 days	-0.0745	< 0.0001	-0.1058	-0.0432
Urgency	0.0743	< 0.0001	0.0430	0.1055
Excessive belching or passing of gas	0.0739	< 0.0001	0.0426	0.1052
GERD	0.0727	< 0.0001	0.0414	0.1039
10-meter walk speed	-0.0721	< 0.0001	-0.1035	-0.0407
Dry mouth	0.0718	< 0.0001	0.0404	0.1032

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Asthma	0.0715	< 0.0001	0.0403	0.1028
Sleep apnea	0.0711	< 0.0001	0.0397	0.1024
Itching skin	0.0682	< 0.0001	0.0368	0.0997
Sit-rise score	-0.0663	< 0.0001	-0.0978	-0.0348
WBC count	0.0653	< 0.0001	0.0327	0.0979
MCH	-0.0653	< 0.0001	-0.0965	-0.0340
Sinus pain	0.0652	< 0.0001	0.0338	0.0966
Urine specific gravity	0.0651	< 0.0001	0.0338	0.0965
Respiratory rate	0.0646	< 0.0001	0.0332	0.0960
Absolute reticulocytes	0.0634	< 0.0001	0.0319	0.0948
Leg cramps	0.0632	< 0.0001	0.0319	0.0945
Dryness	0.0622	0.0001	0.0307	0.0937
Numbness or loss of sensation	0.0615	0.0001	0.0299	0.0930
Creatinine (urine)	0.0611	0.0001	0.0297	0.0925
Cramping	0.0602	0.0002	0.0284	0.0920
Reticulocytes (% RBC)	0.0601	0.0002	0.0286	0.0916
Oxygen saturation	-0.0597	0.0002	-0.0910	-0.0284
Albumin in urine	-0.0581	0.0003	-0.0894	-0.0268
Migraines	0.0581	0.0003	0.0266	0.0896
MCV	-0.0578	0.0003	-0.0891	-0.0266
Osteoarthritis	0.0561	0.0005	0.0247	0.0876
Seasonal allergies	0.0556	0.0005	0.0243	0.0868
HDL	-0.0534	0.0009	-0.0848	-0.0220
Hemorrhoids (symptom)	0.0528	0.0009	0.0215	0.0841
Fibromyalgia	0.0525	0.0011	0.0211	0.0840
Lymphocytes (total)	0.0518	0.0015	0.0198	0.0838
Runny nose	0.0515	0.0013	0.0201	0.0828
Irritable bowel disorder	0.0513	0.0013	0.0200	0.0826
Ear ringing	0.0498	0.0019	0.0184	0.0811
Vitamin D	-0.0497	0.0023	-0.0816	-0.0178
Days watch worn 10+ hours in first 30 days	-0.0495	0.0023	-0.0813	-0.0177
COPD with emphysema	0.0488	0.0027	0.0170	0.0807
Food allergies	0.0483	0.0025	0.0170	0.0796
MCHC	-0.0483	0.0025	-0.0797	-0.0170
Hypertension	0.0479	0.0030	0.0162	0.0795
Urine reaction pH	-0.0473	0.0031	-0.0787	-0.0160
Triglycerides	0.0470	0.0033	0.0156	0.0783
Monocytes	0.0465	0.0037	0.0151	0.0779
Neutrophils	0.0462	0.0049	0.0140	0.0785
Serum creatinine	0.0460	0.0044	0.0143	0.0777
Uric acid	0.0460	0.0043	0.0144	0.0775
Diabetes type 2	0.0456	0.0044	0.0143	0.0769
AST	0.0447	0.0052	0.0134	0.0760
Discharge	0.0446	0.0054	0.0132	0.0760
Non-seasonal allergies	0.0445	0.0053	0.0132	0.0759
Diverticulitis	0.0432	0.0069	0.0119	0.0745
Floaters	0.0421	0.0084	0.0108	0.0734
Absolute basophils	0.0417	0.0098	0.0101	0.0734
Ejection fraction at rest	0.0415	0.0094	0.0102	0.0729
Easy bruising or bleeding	0.0354	0.0272	0.0040	0.0667
Medication allergies	0.0345	0.0311	0.0031	0.0658

Epilepsy	0.0318	0.0471	0.0004	0.0631
Systolic blood pressure	0.0316	0.0505	-0.0001	0.0632
Chloride	-0.0308	0.0544	-0.0621	0.0006
Nonalcoholic fatty liver disease	0.0303	0.0578	-0.0010	0.0617
Arrhythmia	0.0299	0.0629	-0.0016	0.0614
RBC count	0.0296	0.0641	-0.0017	0.0610
Kidney or bladder stones	-0.0288	0.0721	-0.0601	0.0026
Chronic headaches	0.0285	0.0746	-0.0028	0.0599
Rheumatoid arthritis	0.0280	0.0808	-0.0034	0.0594
Hay fever	0.0279	0.0815	-0.0035	0.0592
Benign prostatic hyperplasia	0.0274	0.0946	-0.0047	0.0596
Cholesterol	-0.0267	0.0947	-0.0581	0.0046
Absolute eosinophils	0.0265	0.0983	-0.0049	0.0580
Diverticulosis	0.0262	0.1013	-0.0051	0.0576
Goiter	-0.0261	0.1034	-0.0574	0.0053
Magnesium	-0.0258	0.1099	-0.0574	0.0058
Gout	0.0255	0.1116	-0.0059	0.0569
LDL	-0.0246	0.1238	-0.0560	0.0067
Hepatitis C	0.0239	0.1373	-0.0076	0.0554
Diastolic blood pressure	0.0232	0.1467	-0.0081	0.0546
Peripheral vascular disease	0.0230	0.1508	-0.0084	0.0543
Hypercholesterolemia	0.0227	0.1598	-0.0089	0.0543
Hemoglobin	-0.0225	0.1601	-0.0540	0.0089
Nonmelanoma skin cancer	0.0212	0.1869	-0.0103	0.0528
MPV	0.0211	0.1861	-0.0102	0.0525
Hearing loss	0.0210	0.1924	-0.0106	0.0527
Hypothyroidism	-0.0209	0.1930	-0.0523	0.0106
Handgrip	-0.0205	0.2025	-0.0522	0.0111
Pulmonary embolism	0.0194	0.2246	-0.0119	0.0508
Cataracts	0.0186	0.2549	-0.0134	0.0507
Glaucoma	0.0186	0.2477	-0.0129	0.0501
Sodium	-0.0167	0.2976	-0.0480	0.0147
Pneumonia	0.0166	0.3007	-0.0148	0.0479
Potassium	-0.0153	0.3403	-0.0466	0.0161
Macular degeneration	0.0140	0.3806	-0.0173	0.0454
Protein (serum)	-0.0139	0.3870	-0.0454	0.0176
Stroke	0.0133	0.4058	-0.0181	0.0447
Hemorrhoids	0.0132	0.4094	-0.0182	0.0446
Coronary artery disease	0.0123	0.4424	-0.0191	0.0438
Basophils (% WBC)	0.0118	0.4593	-0.0195	0.0432
Hematocrit	-0.0117	0.4667	-0.0431	0.0198
Psoriasis	0.0109	0.4946	-0.0204	0.0423
Myocardial infarction	0.0104	0.5153	-0.0210	0.0418
Eosinophils (% WBC)	0.0104	0.5158	-0.0210	0.0418
Peptic ulcer	0.0102	0.5244	-0.0212	0.0416
Breast cancer	0.0101	0.5287	-0.0213	0.0414
Neutrophil lymphocyte ratio	0.0100	0.5337	-0.0214	0.0413
Melanoma skin cancer	-0.0099	0.5384	-0.0414	0.0216
Calcium	-0.0098	0.5396	-0.0412	0.0215
Transient ischemic attack	-0.0090	0.5746	-0.0404	0.0224
Coronary calcium score	-0.0085	0.6007	-0.0401	0.0232

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Left ventricular mass index	0.0082	0.6113	-0.0234	0.0398
Gallbladder disease	0.0081	0.6131	-0.0234	0.0397
TSH	0.0081	0.6117	-0.0232	0.0395
Tinnitus	0.0081	0.6138	-0.0234	0.0397
Osteoporosis	-0.0081	0.6139	-0.0395	0.0233
GFR MDRD	0.0075	0.6465	-0.0247	0.0398
Colon polyps	0.0074	0.6490	-0.0244	0.0391
Hashimotos Disease	-0.0073	0.6467	-0.0387	0.0240
Neutrophil segments (% WBC)	-0.0072	0.6530	-0.0386	0.0242
Total neutrophils (% WBC)	-0.0072	0.6530	-0.0386	0.0242
Platelets	0.0059	0.7162	-0.0261	0.0380
Atrial fibrillation	0.0056	0.7273	-0.0259	0.0371
Osteopenia	-0.0046	0.7748	-0.0361	0.0269
Diabetes type 1	0.0039	0.8093	-0.0275	0.0352
Lymphocytes (% WBC)	0.0038	0.8133	-0.0276	0.0351
Hepatitis B	0.0030	0.8507	-0.0284	0.0344
Monocytes (% WBC)	0.0030	0.8543	-0.0288	0.0348
Prostate cancer	0.0030	0.8543	-0.0287	0.0347

eTable 5. LASSO Regression Results: Model 3

Variable	Estimate	P-value	CI 25%	CI 75%
Tension	0.1847	< 0.0001	0.1543	0.2152
Memory change	0.1511	< 0.0001	0.1207	0.1816
Body image concerns	0.1457	< 0.0001	0.1154	0.1760
Backache	0.1336	< 0.0001	0.1026	0.1645
Neck or low back pain	0.1191	< 0.0001	0.0881	0.1501
Lightheadedness	0.1047	< 0.0001	0.0739	0.1355
Shortness of breath with exercise	0.1028	< 0.0001	0.0713	0.1343
Shortness of breath	0.0976	< 0.0001	0.0657	0.1294
Headache	0.0967	< 0.0001	0.0655	0.1280
Constipation	0.0932	< 0.0001	0.0627	0.1238
Heat or cold intolerance	0.0918	< 0.0001	0.0609	0.1227
Nasal stuffiness	0.0880	< 0.0001	0.0574	0.1185
Waist circumference	0.0834	< 0.0001	0.0528	0.1141
BMI	0.0829	< 0.0001	0.0517	0.1142
Swelling in calves or feet	0.0816	< 0.0001	0.0508	0.1124
6-minute walk	-0.0801	< 0.0001	-0.1111	-0.0491
Bloating	0.0795	< 0.0001	0.0484	0.1106
Muscle or joint paint	0.0791	< 0.0001	0.0484	0.1098
Frequency of urination	0.0786	< 0.0001	0.0482	0.1091
Coughing up sputum	0.0781	< 0.0001	0.0471	0.1090
30 second chair stand	-0.0762	< 0.0001	-0.1068	-0.0455
Pain or stiffness in the neck	0.0745	< 0.0001	0.0438	0.1053
Joint pain swelling	0.0735	< 0.0001	0.0428	0.1041
Tingling or numbness in extremities	0.0729	< 0.0001	0.0420	0.1037
Heartburn	0.0712	< 0.0001	0.0404	0.1021
Night sweats	0.0681	< 0.0001	0.0373	0.0988
Urination at night	0.0642	< 0.0001	0.0337	0.0946
Cough	0.0631	< 0.0001	0.0320	0.0941
Mean daily steps in first 30 days	-0.0620	< 0.0001	-0.0926	-0.0313
Tingling or pins and needles	0.0616	0.0001	0.0304	0.0928
Diarrhea	0.0609	0.0001	0.0298	0.0919
C-reactive protein	0.0604	0.0001	0.0296	0.0913
Urgency	0.0601	0.0001	0.0295	0.0906
Blood glucose	0.0594	0.0001	0.0288	0.0901
Stiffness	0.0591	0.0002	0.0284	0.0899
Leg cramps	0.0588	0.0002	0.0282	0.0893
Mean leg balance time	-0.0565	0.0003	-0.0870	-0.0260
ALT	0.0560	0.0003	0.0254	0.0865
Dryness	0.0556	0.0004	0.0250	0.0863
Heart rate	0.0550	0.0006	0.0234	0.0866
Itching skin	0.0548	0.0005	0.0240	0.0856
Excessive belching or passing of gas	0.0547	0.0005	0.0240	0.0854

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Sit-rise score	-0.0526	0.0008	-0.0831	-0.0220
Sinus pain	0.0525	0.0008	0.0219	0.0832
10-meter walk speed	-0.0525	0.0008	-0.0833	-0.0217
Oxygen saturation	-0.0506	0.0012	-0.0811	-0.0201
HbA1c	0.0499	0.0014	0.0193	0.0805
Respiratory rate	0.0495	0.0016	0.0187	0.0802
Ejection fraction at rest	0.0465	0.0028	0.0160	0.0771
WBC count	0.0462	0.0045	0.0144	0.0781
Absolute reticulocytes	0.0462	0.0033	0.0154	0.0770
Reticulocytes (% RBC)	0.0461	0.0034	0.0153	0.0770
Dry mouth	0.0456	0.0038	0.0148	0.0765
Albumin in urine	-0.0456	0.0034	-0.0761	-0.0151
Numbness or loss of sensation	0.0441	0.0052	0.0132	0.0751
Ear ringing	0.0422	0.0068	0.0116	0.0727
Food allergies	0.0418	0.0072	0.0113	0.0724
MCH	-0.0413	0.0084	-0.0720	-0.0106
Runny nose	0.0389	0.0128	0.0083	0.0695
Cramping	0.0389	0.0147	0.0076	0.0701
Hemorrhoids (symptom)	0.0386	0.0134	0.0080	0.0691
Days watch worn 10+ hours in first 30 days	-0.0385	0.0149	-0.0696	-0.0075
Handgrip	-0.0379	0.0150	-0.0685	-0.0074
MCHC	-0.0378	0.0156	-0.0684	-0.0072
Urine specific gravity	0.0361	0.0222	0.0052	0.0669
Absolute basophils	0.0352	0.0255	0.0043	0.0660
Urine reaction pH	-0.0351	0.0243	-0.0657	-0.0046
Monocytes	0.0350	0.0253	0.0043	0.0657
Lymphocytes (total)	0.0350	0.0283	0.0037	0.0663
Triglycerides	0.0347	0.0262	0.0041	0.0654
Discharge	0.0345	0.0273	0.0039	0.0652
MCV	-0.0338	0.0306	-0.0645	-0.0032
Neutrophils	0.0331	0.0390	0.0017	0.0645
Floaters	0.0330	0.0342	0.0025	0.0636
Creatinine (urine)	0.0325	0.0397	0.0015	0.0635
AST	0.0319	0.0404	0.0014	0.0625
Serum creatinine	0.0311	0.0465	0.0005	0.0618
Seasonal allergies	0.0288	0.0650	-0.0018	0.0595
Easy bruising or bleeding	0.0272	0.0821	-0.0035	0.0578
Vitamin D	-0.0269	0.0928	-0.0583	0.0045
Medication allergies	0.0258	0.0977	-0.0047	0.0564
Uric acid	0.0247	0.1137	-0.0059	0.0552
Non-seasonal allergies	0.0237	0.1300	-0.0070	0.0543
HDL	-0.0229	0.1470	-0.0540	0.0081
Hemoglobin	-0.0229	0.1427	-0.0535	0.0077
Chloride	-0.0219	0.1590	-0.0525	0.0086
Protein (serum)	-0.0213	0.1737	-0.0520	0.0094
Systolic blood pressure	0.0186	0.2348	-0.0121	0.0492
Hay fever	0.0173	0.2677	-0.0133	0.0478
MPV	0.0154	0.3227	-0.0152	0.0460
Absolute eosinophils	0.0147	0.3473	-0.0160	0.0455
Hematocrit	-0.0147	0.3474	-0.0453	0.0159
Basophils (% WBC)	0.0140	0.3691	-0.0166	0.0446

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Coronary calcium score	-0.0118	0.4500	-0.0426	0.0189
RBC count	0.0109	0.4830	-0.0196	0.0415
LDL	-0.0105	0.5007	-0.0411	0.0201
GFR MDRD	-0.0087	0.5884	-0.0402	0.0228
Diastolic blood pressure	0.0087	0.5775	-0.0219	0.0393
Neutrophil lymphocyte ratio	0.0079	0.6135	-0.0227	0.0384
Sodium	-0.0077	0.6218	-0.0383	0.0229
Calcium	-0.0056	0.7179	-0.0362	0.0249
Cholesterol	-0.0054	0.7296	-0.0360	0.0252
Monocytes (% WBC)	0.0038	0.8106	-0.0271	0.0346
Neutrophil segments (% WBC)	-0.0035	0.8244	-0.0340	0.0271
Total neutrophils (% WBC)	-0.0035	0.8244	-0.0340	0.0271
Platelets	0.0031	0.8456	-0.0280	0.0342
Left ventricular mass index	-0.0026	0.8673	-0.0333	0.0280
TSH	0.0025	0.8751	-0.0281	0.0330
Eosinophils (% WBC)	0.0023	0.8824	-0.0283	0.0329
Lymphocytes (% WBC)	0.0014	0.9280	-0.0292	0.0320
Potassium	-0.0008	0.9588	-0.0314	0.0298
Magnesium	-0.0005	0.9745	-0.0316	0.0306

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eTable 6. LASSO Regression Results: Model 4

Variable	Estimate	P-value	CI 25%	CI 75%
BMI	0.0664	< 0.0001	0.0369	0.0960
6-minute walk	-0.0661	< 0.0001	-0.0955	-0.0368
Waist circumference	0.0618	< 0.0001	0.0326	0.0910
Mean daily steps in first 30 days	-0.0522	0.0004	-0.0813	-0.0232
ALT	0.0520	0.0004	0.0230	0.0809
Heart rate	0.0491	0.0012	0.0195	0.0787
30 second chair stand	-0.0458	0.0023	-0.0752	-0.0164
Blood glucose	0.0454	0.0022	0.0164	0.0745
WBC count	0.0454	0.0028	0.0157	0.0751
C-reactive protein	0.0431	0.0040	0.0137	0.0724
Absolute reticulocytes	0.0413	0.0054	0.0122	0.0705
Sit-rise score	-0.0408	0.0058	-0.0697	-0.0118
Reticulocytes (% RBC)	0.0401	0.0071	0.0109	0.0692
Handgrip	-0.0399	0.0070	-0.0688	-0.0109
Mean leg balance time	-0.0390	0.0083	-0.0679	-0.0100
Oxygen saturation	-0.0385	0.0091	-0.0675	-0.0096
AST	0.0374	0.0112	0.0085	0.0663
Respiratory rate	0.0367	0.0138	0.0075	0.0659
10-meter walk speed	-0.0362	0.0154	-0.0654	-0.0069
Albumin in urine	-0.0361	0.0146	-0.0651	-0.0071
Days watch worn 10+ hours in first 30 days	-0.0360	0.0157	-0.0653	-0.0068
Lymphocytes (total)	0.0354	0.0181	0.0060	0.0648
HbA1c	0.0352	0.0177	0.0061	0.0643
Ejection fraction at rest	0.0351	0.0173	0.0062	0.0641
Neutrophils	0.0350	0.0200	0.0055	0.0644
MCHC	-0.0341	0.0212	-0.0631	-0.0051
MCH	-0.0301	0.0428	-0.0592	-0.0010
Monocytes	0.0282	0.0577	-0.0009	0.0572
Absolute basophils	0.0270	0.0702	-0.0022	0.0562
Triglycerides	0.0267	0.0716	-0.0023	0.0557
Urine reaction pH	-0.0265	0.0734	-0.0554	0.0025
MCV	-0.0223	0.1333	-0.0513	0.0068
Sodium	-0.0220	0.1359	-0.0510	0.0069
Chloride	-0.0211	0.1537	-0.0500	0.0079
Serum creatinine	0.0203	0.1701	-0.0087	0.0492
MPV	0.0189	0.2015	-0.0101	0.0478
Potassium	-0.0185	0.2097	-0.0475	0.0104
Urine specific gravity	0.0179	0.2308	-0.0114	0.0473
Vitamin D	-0.0166	0.2713	-0.0462	0.0130
Systolic blood pressure	0.0165	0.2654	-0.0125	0.0455
LDL	-0.0158	0.2837	-0.0448	0.0131
Protein (serum)	-0.0145	0.3256	-0.0435	0.0145
RBC count	0.0144	0.3285	-0.0145	0.0434

Creatinine (urine)	0.0140	0.3518	-0.0154	0.0434
Basophils (% WBC)	0.0119	0.4208	-0.0171	0.0408
Left ventricular mass index	-0.0114	0.4391	-0.0404	0.0175
Uric acid	0.0111	0.4506	-0.0178	0.0401
Coronary calcium score	-0.0108	0.4681	-0.0398	0.0183
TSH	0.0102	0.4912	-0.0188	0.0391
Hemoglobin	-0.0095	0.5236	-0.0385	0.0196
Magnesium	-0.0074	0.6195	-0.0366	0.0218
Diastolic blood pressure	0.0064	0.6651	-0.0226	0.0354
Eosinophils (% WBC)	-0.0057	0.7011	-0.0346	0.0233
GFR MDRD	-0.0054	0.7173	-0.0349	0.0241
Neutrophil lymphocyte ratio	0.0053	0.7185	-0.0236	0.0343
Calcium	-0.0049	0.7398	-0.0339	0.0240
Platelets	0.0039	0.7947	-0.0254	0.0331
Cholesterol	-0.0034	0.8172	-0.0324	0.0256
HDL	-0.0027	0.8565	-0.0322	0.0267
Monocytes (% WBC)	0.0025	0.8652	-0.0266	0.0317
Absolute eosinophils	0.0017	0.9082	-0.0274	0.0309
Lymphocytes (% WBC)	0.0015	0.9192	-0.0275	0.0305
Neutrophil segments (% WBC)	-0.0013	0.9307	-0.0302	0.0277
Total neutrophils (% WBC)	-0.0013	0.9307	-0.0302	0.0277
Hematocrit	-0.0011	0.9413	-0.0301	0.0279

eTable 7. LASSO Regression Results: Model 5

Variable	Estimate	P-value	CI 25%	CI 75%
AST	0.0382	0.0087	0.0096	0.0667
ALT	0.0352	0.0162	0.0065	0.0638
HDL	0.0312	0.0383	0.0017	0.0607
Serum creatinine	0.0220	0.1313	-0.0066	0.0506
LDL	-0.0212	0.1460	-0.0497	0.0074
Blood glucose	0.0207	0.1606	-0.0082	0.0497
MCHC	-0.0199	0.1747	-0.0486	0.0088
Basophils (% WBC)	0.0183	0.2085	-0.0102	0.0469
Chloride	-0.0183	0.2099	-0.0468	0.0103
MPV	0.0181	0.2145	-0.0105	0.0467
Sodium	-0.0179	0.2203	-0.0464	0.0107
Absolute basophils	0.0170	0.2479	-0.0119	0.0460
Protein (serum)	-0.0169	0.2471	-0.0455	0.0117
MCH	-0.0148	0.3137	-0.0437	0.0140
Potassium	-0.0143	0.3259	-0.0429	0.0143
GFR MDRD	-0.0138	0.3535	-0.0430	0.0154
Lymphocytes (total)	0.0133	0.3748	-0.0160	0.0425
Platelets	-0.0127	0.3923	-0.0417	0.0164
WBC count	0.0125	0.4143	-0.0175	0.0424
Monocytes	0.0121	0.4122	-0.0168	0.0409
C-reactive protein	0.0104	0.4880	-0.0190	0.0398
Monocytes (% WBC)	0.0103	0.4818	-0.0185	0.0391
HbA1c	0.0101	0.4930	-0.0188	0.0391
MCV	-0.0101	0.4933	-0.0388	0.0187
TSH	0.0100	0.4930	-0.0186	0.0386
Albumin in urine	-0.0096	0.5130	-0.0383	0.0192
Magnesium	0.0095	0.5205	-0.0195	0.0385
Uric acid	-0.0080	0.5827	-0.0366	0.0206
RBC count	0.0073	0.6161	-0.0213	0.0359
Urine reaction pH	-0.0073	0.6185	-0.0360	0.0214
Neutrophil segments (% WBC)	-0.0072	0.6205	-0.0358	0.0214
Total neutrophils (% WBC)	-0.0072	0.6205	-0.0358	0.0214
Absolute reticulocytes	0.0069	0.6408	-0.0222	0.0361
Neutrophils	0.0068	0.6483	-0.0226	0.0363
Absolute eosinophils	-0.0064	0.6635	-0.0352	0.0224
Calcium	0.0062	0.6691	-0.0224	0.0348
Vitamin D	0.0057	0.7024	-0.0237	0.0352
Lymphocytes (% WBC)	0.0057	0.6944	-0.0229	0.0343
Reticulocytes (% RBC)	0.0057	0.7017	-0.0235	0.0349
Triglycerides	0.0055	0.7075	-0.0233	0.0343
Eosinophils (% WBC)	-0.0047	0.7449	-0.0333	0.0238
Hemoglobin	-0.0047	0.7481	-0.0334	0.0240

Cholesterol	-0.0033	0.8231	-0.0319	0.0254
Urine specific gravity	-0.0029	0.8465	-0.0321	0.0263
Neutrophil lymphocyte ratio	-0.0009	0.9488	-0.0295	0.0276
Creatinine (urine)	0.0006	0.9663	-0.0285	0.0298
Hematocrit	0.0000	0.9974	-0.0286	0.0287

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eFigure 1A. Distribution of PHQ-9 Across Risk Groups by Asthma

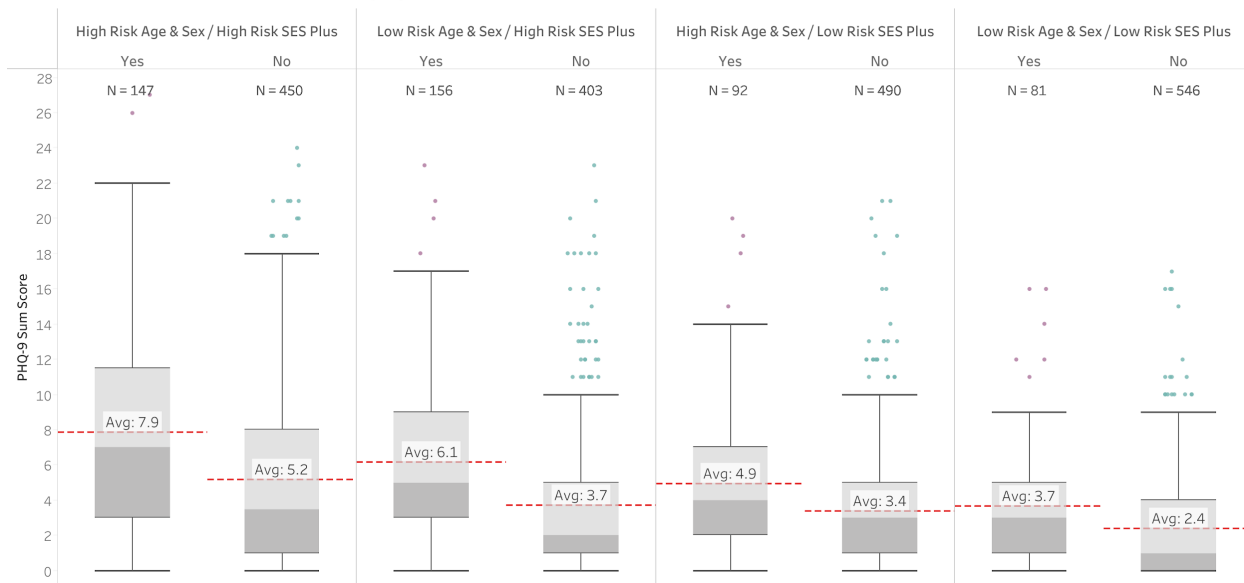Distribution of PHQ-9 across Risk Group by Asthma
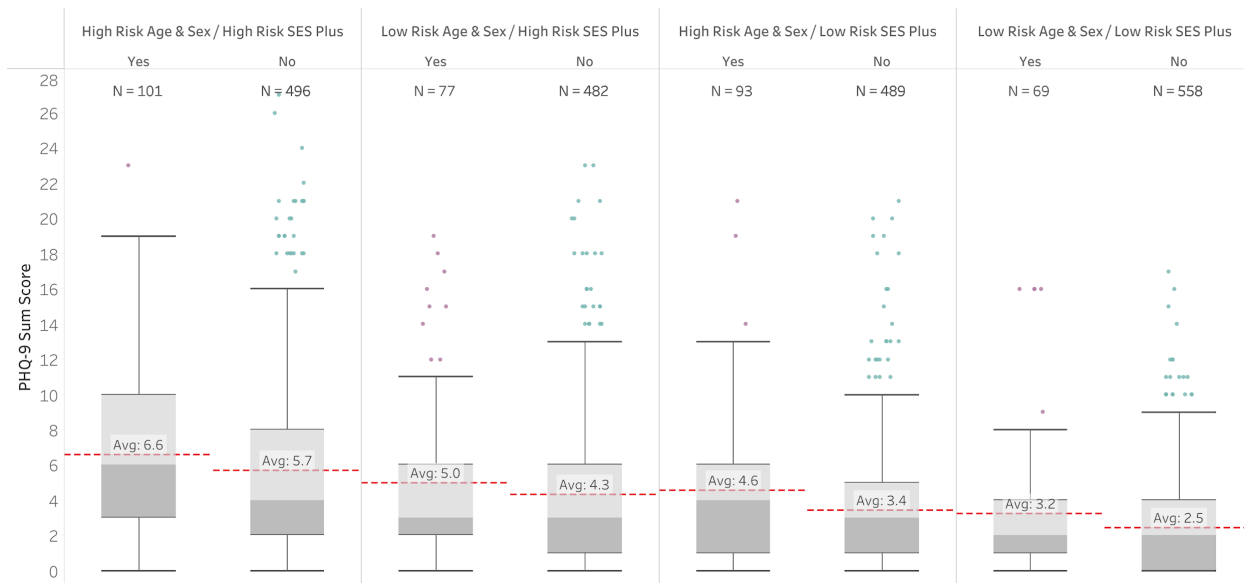
eFigure 1B. Distribution of PHQ-9 Across Risk Groups by Backache

Distribution of PHQ-9 across Risk Group by Backache

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eFigure 1C. Distribution of PHQ-9 Across Risk Groups by Memory Change

Distribution of PHQ-9 across Risk Group by Memory Change

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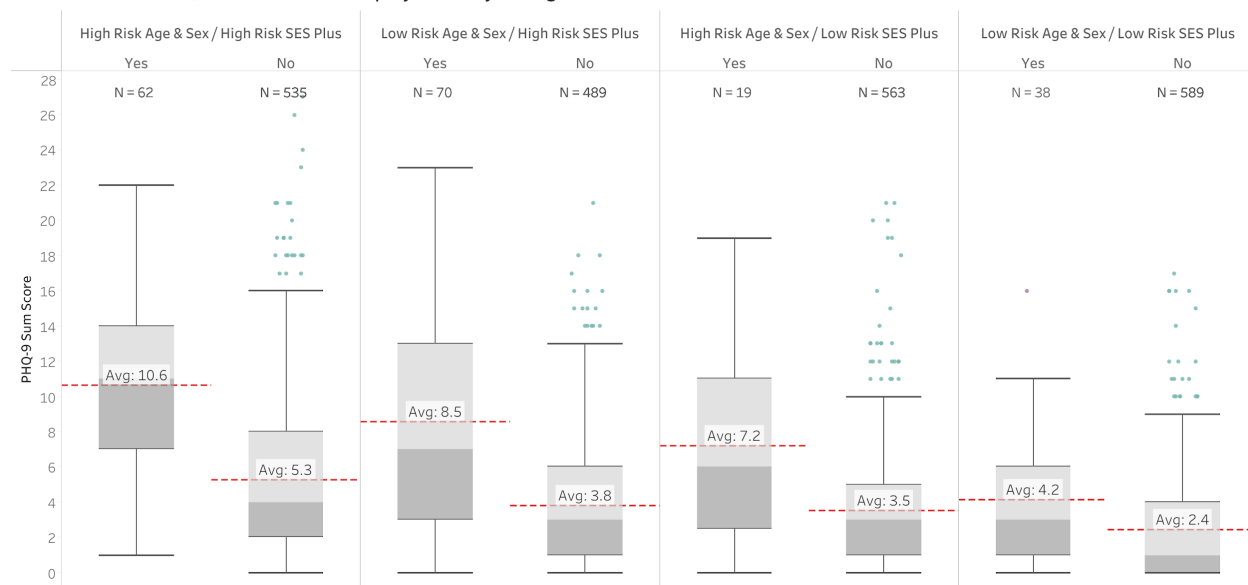
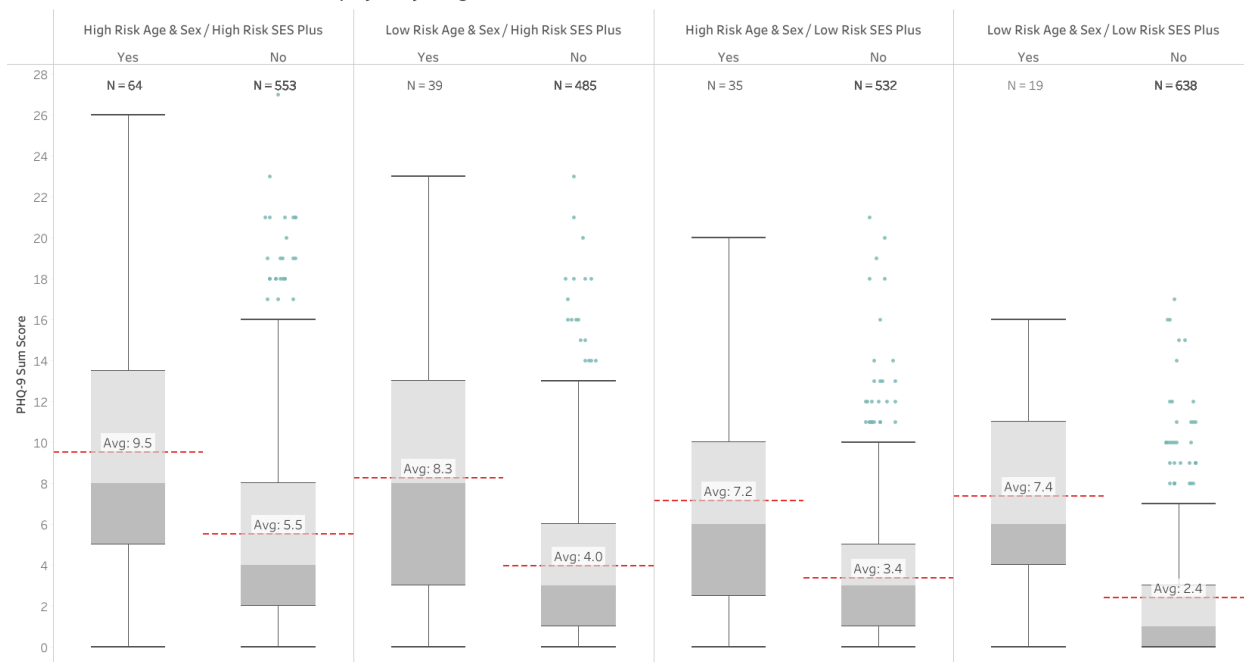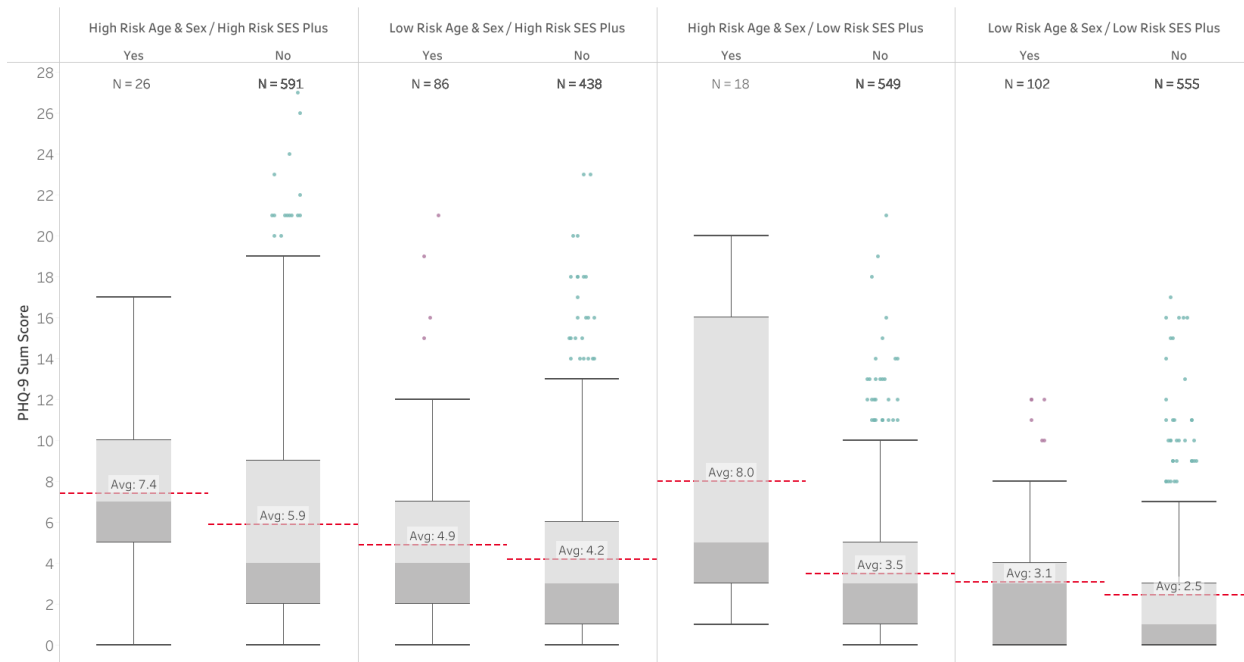## eFigure 1D. Distribution of PHQ-9 Across Risk Groups by Body Image Concerns

Distribution of PHQ-9 across Risk Group by Body Image Concerns

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eFigure 1E. Distribution of PHQ-9 Across Risk Groups by Sleep Apnea

Distribution of PHQ-9 across Risk Group by Sleep Apnea

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	7-9
		(*c*) Explain how missing data were addressed	7-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7-9
		(*e*) Describe any sensitivity analyses	n/a

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,10
		(b) Give reasons for non-participation at each stage	9,10
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10
		(b) Indicate number of participants with missing data for each variable of interest	9,10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9,10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9,10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10
		(*b*) Report category boundaries when continuous variables were categorized	9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a

Discussion

Key results	18	Summarise key results with reference to study objectives	11-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Biological and Clinical Correlates of the Patient Health Questionnaire-9: Exploratory Cross-Sectional Analyses of the Baseline Health Study

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ORIGINAL RESEARCH

Biological and Clinical Correlates of the Patient Health Questionnaire-9: Exploratory

Cross-Sectional Analyses of the Baseline Health Study

Running title: Biological and Clinical Correlates of PHQ-9

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Text word count: 2827

Abstract word count: 300

2

Key words: Patient Health Questionnaire-9; measures of health and disease; effective clinical

intervention

ABSTRACT

Objectives: We assessed the relationship between the Patient Health Questionnaire-9 (PHQ-9) at intake and other measurements intended to assess biological factors, markers of disease, and health status.

Design, setting, and participants: We performed a cross-sectional analysis of 2365 participants from the Baseline Health Study (BHS), a prospective cohort of adults selected to represent major demographic groups in the United States. Participants underwent deep phenotyping on demographic, clinical, laboratory, functional, and imaging findings.

Importance: Despite extensive research on the clinical implications of the PHQ-9, data are limited on the relationship between PHQ-9 scores and other measures of health and disease; we sought to better understand this relationship.

Interventions: None.

Main outcomes and measures: Cross-sectional measures of medical illnesses, gait, balance strength, activities of daily living, imaging, and laboratory tests.

Results: Compared with lower PHQ-9 scores, higher scores were associated with female sex (46.9 to 66.7%), younger participants (53.6 to 42.4 years), and compromised physical status (higher resting heart rates [65 vs. 75 bpm], larger body mass index [26.5 to 30 kg/m2], greater waist circumference [91 to 96.5 cm]) and chronic conditions, including gastroesophageal reflux disease (13.2 to 24.7%) and asthma (9.5 to 20.4%) (p<0.0001). Increasing PHQ-9 score was associated with a higher frequency of comorbidities (migraines [6 to 20.4%]) and active symptoms (leg cramps [6.4 to 24.7%], mood change [1.2 to 47.3%], lack of energy [1.2 to 57%]) (p<0.0001). After adjustment for relevant demographic, socioeconomic, behavioral, and medical characteristics, we found that memory change, tension, shortness of breath, and indicators of

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musculoskeletal symptoms (backache and neck pain) are related to higher PHQ-9 scores

(p<0.0001).

Conclusions: Our study highlights how: 1) even subthreshold depressive symptoms (measured

by PHQ-9) may be indicative of several individual- and population-level concerns that demand

more attention; and 2) depression should be considered a comorbidity in common disease.

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT03154346

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ARTICLE SUMMARY

Strengths and limitations of this study

- This study included deep phenotyping on demographic, clinical, laboratory, functional, and imaging findings of 2365 participants from the Baseline Health Study (BHS).

- This study provides important data on the relationship between PHQ-9 scores and other measures of health and disease.

- The cross-sectional nature of this study limits our ability to assess the time course of these findings; however, follow-up is currently accruing.

- People with significant depression are less likely to volunteer, thereby limiting the breadth of depression observed in this study.

- The study population is generally representative of adult age, sex, race, and ethnicity, but it is not a fully representative sample of the population.

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INTRODUCTION

Depression is a complex, chronic condition that affects hundreds of millions of people worldwide.[1] Bidirectional relationships have been reported between depression and many chronic illnesses[2]; however, most studies have focused on specific conditions, such as diabetes, stroke, or congestive heart failure, as opposed to a multidimensional deep phenotyping approach. Findings from previous studies highlight the need to more fully characterize the relationship between depression and physical health.[3–5] Furthermore, it would be helpful to better understand whether these relationships exist only above a certain threshold or across the entire continuum.

The most common screening tool for depression is the Patient Health Questionnaire-9 (PHQ-9), whose operating characteristics are well known[6] and have been validated in a variety of contexts.[7,8] Despite extensive research on the clinical and behavioral implications of PHQ-9,[9,10] the results of this questionnaire are often used in a dichotomous manner (e.g., cut-off of 10) without evaluating the full relationship between PHQ-9 scores and measures of health and disease.

The Baseline Health Study (BHS)[11] is a prospective cohort study of an adult population selected to represent major demographic groups in the U.S. In BHS, deep phenotyping of numerous demographic, clinical, laboratory, functional, and imaging findings is coupled with ongoing longitudinal follow-up. The purpose of our study was to assess the relationship between the entire spectrum of depression, measured by PHQ-9, and a broad array of measurements intended to assess health status.

METHODS

The Baseline Health Study

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BHS methods have been previously described,[11–13] including entry and exclusion criteria, the institutional review board and participant consent procedures, the data collection scheme, and key components of study procedures. Briefly, BHS (ClinicalTrials.gov Identifier: NCT03154346) was approved by the Western Institutional Review Board, Inc. (Puyallup, WA; protocol number is 2017-BL-001). All research participants gave written, informed consent prior to participation.

Additional details of the effects of social determinants on health in the BHS study have been previously reported.[12] BHS is enrolling a large number of participants, beginning with intensive measurement of the first 2502 people (the deeply phenotyped cohort) in whom a large volume of multimodal data are collected. Four clinical BHS sites in the U.S. have begun enrollment.

The participants were enrolled through a virtual online registry with selection of participants for the deep phenotyping cohort included in this report using an algorithm intended to produce a representative sample of U.S. adult age, race, and ethnicity. People in good health and with medical conditions were included and the sampling method was designed to over-represent people at risk of heart disease or cancer. The PHQ-9 in this report was collected at the initial study visit in person or online.

A pre-BHS pilot study, which tested clinical assessment workflows, was conducted in 200 healthy participants prior to initiation of the primary study. BHS is funded by Verily (San Francisco, CA) and is managed in collaboration with Stanford University (Stanford, CA), Duke University (Durham, NC), and the California Health and Longevity Institute (Westlake Village, CA) with enrolling sites in Durham, NC; Kannapolis, NC; Los Angeles, CA; and Palo Alto, CA.

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The extended studies have governance approaches specific to the needs of each study. Herein, we examine a cross-sectional analysis of the first BHS time point PHQ-9 scores.

Statistical methods

The statistical methods used in this manuscript have been described previously.[12] Distributional measures; medians and 25th, 75th percentiles for continuous variables; and counts and percentages for categorical variables were computed and summarized across each of 5 PHQ-9 severity groups[6] (0, 1–4, 5–9, 10–14, >14), divided by convention to be consistent with prior studies. The Cochran-Armitage trend test for binomial variables,[13,14] and the Spearman rank correlation test for continuous variables[15] or categorical variables that are ordinal in nature (e.g., education and income), were used to test for linear trend across severity group. Multiple tests were not adjusted for, given the exploratory nature of this study. Subsequent studies with pre-planned hypotheses are needed to confirm results.

Penalized regression using the least absolute shrinkage and selection operator (LASSO) was conducted to model physical, phenotypic, and symptom factors that could predict the PHQ-9 score (logarithm of PHQ-9 + 1). Data were randomly split into a training set (approximately 70% of the data), which was used to build the models, and an independent test set, which was used to evaluate model performance. The final linear model was trained on the full training set, retaining all predictors with coefficients not equal to zero, and was evaluated on the held-aside test set.

Since inference rather than prediction is the goal of this analysis, we considered 5 sets of sequential "adjustment" models, consisting of smaller-to-larger covariate lists that were entered into a LASSO regression model. The LASSO-predicted values resulting from each of the 5 models were used to estimate a covariate-adjusted effect for all other candidate variables.

Separate regressions for *each* of the candidate variables that are not included in a given model were performed to obtain coefficients and confidence intervals (i.e., only the LASSO-predicted value and the candidate variable to be evaluated were included in each model).

The LASSO adjustment models comprise the following covariates: 1) Model 1: age, sex, and age × sex interaction; 2) Model 2: variables from Model 1, plus race and ethnicity, socioeconomic-related variables (highest education completed, household income, marital status, employment status, and health insurance), and behavioral-related variables (smoking status, pack-years smoked, and the Alcohol Use Disorders Identification Test-Consumption [AUDIT-C] sum score); 3) Model 3: variables from Model 2 plus medical conditions except mental health disorder diagnoses or disorders directly related to mental health or depression (major depressive disorder, generalized anxiety disorder, attention deficit hyperactivity disorder, post-traumatic stress disorder, bipolar disorder, alcohol abuse, drug abuse, and concussion or loss of consciousness); 4) Model 4: variables from Model 3, plus symptoms and allergies, except those symptoms that are directly related to mental health or depression (i.e., nervousness, mood changes, fatigue, lack of energy, change in sleep patterns, change in appetite, and difficulty concentrating); and 5) Model 5: variables from Model 4, plus all physical health metrics. Patient-reported outcomes, including measures of anxiety, psychological and social well-being (e.g., General Anxiety Disorder-7, World Health Organization Disability Assessment Schedule, and Satisfaction with Life), and self-reported medical conditions and symptoms related to mental health or depression, have been reported[6] and were excluded from these analyses to enable a focus on physical and medical findings. In preliminary analyses, higher PHQ-9 score was associated with female sex, age, and the age by sex interaction, confirming the well-established relationship between depression, sex, and age,[16] thereby informing our decision to include age

and sex in all models. The key variables included in each covariate model can be found in

eTable 1.

Since LASSO regression techniques require an input dataset with complete data, missing

data were addressed using iterative regression-based imputation, where predictors were first

grouped by data type, then the groups were rank-ordered by the most missing to the least missing

data. The rank of the whole group was based on the amount of missingness of the majority

(≥50%) of the fields within that group), and then at each imputation step, the grouped predictors

were used in a regression model to predict the missing data. The PHQ-9 score was imputed in the

last step along with other patient-reported outcome scores and, therefore, all 2502 participants

were included in the LASSO models.

To summarize key model findings adjusted for known demographic and socioeconomic-

related risk factors of PHQ-9, 4 groups were created based on the LASSO-predicted value using

Model 1 (age, sex, and age × sex interaction) and Model 2 (race, ethnicity, socioeconomic-

related variables and health behaviors). For both models, "high risk" was defined as the top 50%

of the predicted value, while "low risk" was defined as the bottom 50% of the predicted value.

The 2 risk groups from each model were combined to create the following 4 groups: 1) high risk

Model 1 + high risk Model 2; 2) high risk Model 1 + low risk Model 2; 3) low risk Model 1 +

high risk Model 2; and 4) low risk Model 1 + low risk Model 2.

Patient and public involvement statement

From the beginning, BHS has used participant and community engagement methods. Participants

have been involved in feedback sessions, and return of results is a commitment of the project.

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Community meetings have also been held to assure broad feedback on the goals and conduct of the project.

RESULTS

The relationship between the PHQ-9 score and key demographic characteristics and vital signs is shown in **Table 1**. Younger participants, women, people of color, and those of Hispanic ethnicity had higher PHQ-9 scores. While no difference was observed in blood pressure or temperature, higher PHQ-9 scores were found in participants with higher resting heart rates, larger body mass index, greater waist circumference, and higher respiratory rates.

PHQ-9 scores as a function of medical history and symptoms are shown in **Table 2** and **eTable 2**. As expected, participants with other chronic conditions, particularly gastroesophageal reflux disease, anxiety, and asthma, had higher PHQ-9 scores. A history of diagnosed depression was highly correlated with elevated PHQ-9. Various symptoms were evident in participants with higher PHQ-9 scores, with musculoskeletal, mood, and anxiety symptoms proving particularly prominent.

Table 3 demonstrates the relationship between measures of physical performance and PHQ-9; differences in 6-minute walk distance, handgrip strength, leg balance, chair stand, and mean steps are particularly associated with higher PHQ-9.

The covariates resulting from each LASSO model are shown in **eTables 3–7**. All other variables that are not presented in those tables are set to zero by the LASSO regression and thereby excluded from the final adjustment models. Age remained a top predictor in all models. Where health behaviors and measures of socioeconomic status were included (i.e., Models 2–5), smoking status and employment, insurance, and marital status also remained in the models as

significant predictors. When medical conditions were added (i.e., Models 3–5), respiratory-

related conditions such as asthma remained in the models, and when symptoms were added (i.e,

Models 4 and 5), tension, body image concerns, and memory change remained in the models as

top predictors. Model performance was similar between the training and test sets for each model

(Model 1: R^2 = 0.032 vs. 0.035; Model 2: R^2 = 0.117 vs. 0.112; Model 3: R^2 = 0.167 vs. 0.133;

Model 4: R^2 = 0.247 vs. 0.228; and Model 5: R^2 = 0.270 vs. 0.240, respectively).

The interplay of higher PHQ-9 score predictors based on the LASSO regression

adjustment models is shown in **Figures 1–5**. Regardless of adjustment factors included in the

models, memory change, tension, shortness of breath, and indicators of musculoskeletal

symptoms are significantly related to higher PHQ-9 scores (Models 1–3). Further details of the

LASSO analysis are included in the supplementary materials (**eTables 8–12**). Tension, memory

change, and back pain consistently remain in the models after adjustment. When medical

conditions, symptoms, and allergies are taken into account, indicators of obesity (body mass

index, waist circumference) and lack of physical fitness are the most significant predictors of

PHQ-9 score. When physical performance is also factored into the adjustment, laboratory values

are only weakly associated with PHQ-9 scores.

eFigures 1–5 present the distribution of PHQ-9 according to a sample of other health conditions, such as asthma, sleep apnea and body image concerns, after adjustment for known demographic and socioeconomic-related risk factors of PHQ-9. The inter-relationships are clear across this spectrum of measures, emphasizing the importance of understanding all 3 dimensions when designing interventions.

DISCUSSION

Our study reinforces previous observations regarding the relationship between PHQ-9 and measures of chronic disease and poor physical performance in addition to the critical importance of social factors and psychological distress, previously published.[12] While these findings are not surprising, they highlight how PHQ-9 is an entree into a variety of individual- and population-level concerns that demand more attention. Contextual awareness is critically important when the PHQ-9 is used in clinical practice[17] as recommended by the U.S. Preventive Services Task Force[18] for screening within a health system or for public health assessment.

This analysis cannot answer questions of cause and effect since it is cross-sectional. The PHQ-9 and detailed serial measures of biological, clinical, behavioral, and social function will be assessed in the ongoing BHS longitudinal study; the bi-directional relationship between the PHQ-9 and these multiple measures will be particularly interesting, as few studies have collected this amount of detail in a diverse population. This measurement depth of demographic, clinical, biological, and behavioral issues offers an opportunity to better understand how different aspects of distress track similarly or differently over time.

An important aspect of our examination is how the binary division of PHQ-9 into labels of depression or "not depression" leaves significant content unattended. While the division of

PHQ-9 scores at 10 provides good discrimination with regard to a clinical diagnosis of Major

Depressive Disorder,[6,9,10] the gradient between a score of 0 and 10 contains relevant information

about distress levels. Such a finding is not novel,[19] but a reminder that singular focus on a binary

classification tends to obscure important information. For example, demographic data

demonstrate how females and younger participants had higher PHQ-9 scores, yet whether this

finding represents a different approach to revealing concerns or more significant distress is

unclear.

The higher scores associated with elevated heart rates, body mass index, and abdominal

girth were expected and consistent with previous literature. In general, PHQ-9 scores aligned

with musculoskeletal or central and peripheral nervous system disorders,[20,21] but less with

cardiovascular disease, cancer, and other more organ-focused conditions. The previously widely-

reported association with obesity and diabetes was confirmed in our study.[22-25] We found low

PHQ-9 scores in a small, but noticeable proportion of the population with a previous diagnosis of

depression, which could represent diagnostic errors, inaccurate reporting of medical history, or

recovery from a previous episode of depression.

The profound relationship between PHQ-9 score and a host of common symptoms[26–30] is

also expected, but the continuous nature of the relationship with PHQ-9 score and the depth of

the relationships raise many issues that need further exploration. Significant predictors of PHQ-9

scores include a wide range of concerns encompassing neurological disease, musculoskeletal

disease,[31,32] and psychological distress. A particularly notable finding is the progressive and

highly significant relationship between reported memory loss and PHQ-9 score. Among people

with PHQ-9 scores of 0, only 1.9% reported memory change, while among those with PHQ-9

scores >15, memory change was reported in 34%.

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Finally, participants with higher PHQ-9 scores had impaired physical functioning, as indicated by a host of measurements, including daily steps, 6-minute walk distance, ability to balance on one leg, or propensity to exert a strong grip. Multiple previous studies have shown that depression and physical functioning are inter-related[33–38] and that interventions to increase physical activity can improve depression status.[39,40] Nevertheless, the overall picture of this study highlights the need for multimodal intervention to enable people with social disadvantages and physical comorbidities to improve physical and psychological function.

Limitations

This study has some limitations. First, the cross-sectional nature of the study limits our ability to assess the time course of these findings; however, follow-up is currently accruing. The time course of chronic disease and symptom progression in relation to the PHQ-9 will be of interest. Second, people with significant depression are probably less likely to volunteer, thereby limiting the breadth of depression observed in this study; BHS participants are volunteers from selected sites who express willingness to share data. Third, the population is generally representative of adult age, sex, race, and ethnicity, but it is not a fully representative sample of the population; the differences between those who volunteer for digital technology studies and the general population are well-known.[41] Fourth, we acknowledge the high comorbidity of depression and anxiety, which is a potential bias; psychological comorbidities are important contextual factors to consider when assessing depression. We also lack detailed information on depression treatment, which is a potentially modifying factor. Finally, even though the PHQ-9 is a validated screening instrument, our study did not include psychiatric interviews.

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Conclusions

PHQ-9 scores are related to multiple demographic, vital sign, and clinical measures that indicate poor physical status. BHS data provide a comprehensive picture of numerous interactive factors influencing PHQ-9 scores, thereby demonstrating how focusing on one chief complaint in hopes of improving depression status is likely futile, given that many common symptoms and physical limitations are profoundly integrated with depression status. The close association with symptoms often considered somatic raises a practical issue for clinical practice, and this is evident across the entire spectrum of PHQ-9 scores. When a high PHQ-9 score or other indicator of depression brings someone to the attention of a clinician, contextual awareness is critically important to provide an effective clinical intervention. When someone has significant neurological or musculoskeletal symptoms, assessment for depression should be a routine consideration. The complex associations across biological, clinical, behavioral, and social factors stress the need for holistic evaluation of depression for individuals, as well as patient populations.

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disorders.

Hong: Research funding from NIMH; Consulting for Little Otter.

Miller: Employee of and holds stock in Verily Life Sciences.

Mega: Employee of Verily Life Sciences.

Author contributions

Califf: Dr. Califf had full access to all of the data in the study and takes responsibility for the

integrity of the data and the accuracy of the data analysis. Dr. Califf contributed to the

conception and design of the study, the data analysis, the data interpretation, the manuscript

drafting, and the critical revision of the manuscript.

Wong: Dr. Wong contributed to the conception and design of the study, data interpretation, the

manuscript drafting, and the critical revision of the manuscript.

Doraiswamy: Dr. Doraiswamy contributed to the data interpretation, the manuscript drafting,

and the critical revision of the manuscript.

Hong: Dr. Hong contributed to the data interpretation, the manuscript drafting, and the critical

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Miller: Dr. Miller contributed to the conception and design of the study, data interpretation, the

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Mega: Dr. Mega contributed to the conception and design of the study, the supervision, data

acquisition, data interpretation, the manuscript drafting, and the critical revision of the

manuscript.

Data Sharing Statement

The Baseline Study data will be available to qualified researchers for exploratory analysis after

the data are adequately curated and initial planned primary manuscripts are written. Qualified

external researchers will be able to apply through applications reviewed by the Proposal Review

and Publications Committee and Scientific Executive Committee.

Ethics Statement

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This study involves human participants and was approved by an Ethics Committee(s) or

Institutional Board(s):

Approved by: wcg IRB

Work order #: 1-1379515-1

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Table 1. Demographics: PHQ-9 score

	PHQ-9 0 (N=484)	PHQ-9 1-4 (N=1086)	PHQ-9 5-9 (N=518)	PHQ-9 10-14 (N=184)	PHQ-9 15+ (N=93)
Age, median (25th, 75th)*	53.6 (36.7, 66.1)	51.7 (37.0, 66.5)	47.6 (32.7, 60.7)	42.8 (31.2, 55.1)	42.4 (32.1, 54.2)
Female sex*	227 (46.9)	622 (57.3)	299 (57.7)	108 (58.7)	62 (66.7)
Race					
Black	80 (16.5)	153 (14.1)	82 (15.8)	31 (16.8)	19 (20.4)
White	294 (60.7)	731 (67.3)	323 (62.4)	110 (59.8)	57 (61.3)
Asian†	64 (13.2)	113 (10.4)	47 (9.1)	15 (8.2)	5 (5.4)
NHOPI	7 (1.4)	11 (1)	7 (1.4)	2 (1.1)	0 (0.0)
American Indian or Alaska Native	4 (0.8)	8 (0.7)	11 (2.1)	3 (1.6)	1 (1.1)
Other†	35 (7.2)	70 (6.4)	48 (9.3)	23 (12.5)	11 (11.8)
Ethnicity					
Hispanic	54 (11.2)	108 (9.9)	69 (13.3)	26 (14.1)	13 (14.0)
Site					
Los Angeles	94 (19.4)	194 (17.9)	111 (21.4)	35 (19)	21 (22.6)
Durham	99 (20.5)	196 (18.0)	102 (19.7)	40 (21.7)	25 (26.9)
Kannapolis	100 (20.7)	226 (20.8)	105 (20.3)	41 (22.3)	28 (30.1)
Palo Alto †	191 (39.5)	470 (43.3)	200 (38.6)	68 (37.0)	19 (20.4)

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Systolic BP, median (25th, 75th), mm Hg	123.0 (112.5, 133.1)	122.0 (112.0, 132.5)	123.0 (112.5, 133.5)	119.5 (109.9, 132.0)	122.5 (115.5, 130.5)
Diastolic BP, median (25th, 75th), mm Hg	75.5 (69.0, 82.0)	75.0 (68.0, 82.0)	76.0 (70.0, 83.5)	74.0 (68.9, 81.1)	77.5 (71.5, 84.0)
Body mass index, median (25th, 75th), kg/m2*	26.5 (23.7, 29.9)	26.1 (22.9, 31.0)	28.0 (24.5, 33.2)	29.1 (25.1, 34.7)	30.0 (25.4, 38.8)
Waist circumference, median (25th, 75th), cm*	91.0 (81.0, 100.1)	88.9 (78.7, 101.6)	93.0 (81.3, 105.4)	96.5 (82.0, 111.8)	96.5 (81.6, 112.5)
Heart rate, median (25th, 75th), beats/min*	65.0 (58.0, 72.0)	66.0 (59.0, 73.0)	67.0 (60.0, 77.0)	70.0 (61.8, 80.0)	75.0 (65.0, 82.0)
Respiratory rate, median (25th, 75th), breaths/min*	16.0 (14.0, 16.0)	16.0 (14.0, 16.0)	16.0 (14.0, 17.0)	16.0 (14.0, 18.0)	16.0 (16.0, 18.0)
Oxygen saturation, median (25th, 75th), %†	99.0 (98.0, 100.0)	99.0 (98.0, 100.0)	99.0 (98.0, 100.0)	99.0 (97.0, 100.0)	98.0 (97.0, 100.0)

Data shown are no. (%), unless otherwise indicated.
BP, blood pressure; NHOPI, Native Hawaiians and other Pacific Islanders; PHQ-9, Patient Health Questionnaire-9.
P-values for trend were calculated with the use of Spearman Correlation or Cochrane-Armitage tests, where appropriate.
*P-value for trend <0.0001.
†P-value for trend <0.01

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Table 2. Medical history: PHQ-9 score

	PHQ-9 0 (N=484)	PHQ-9 1-4 (N=1086)	PHQ-9 5-9 (N=518)	PHQ-9 10-14 (N=184)	PHQ-9 15+ (N=93)
Alcohol use disorder*	1 (0.2)	20 (1.8)	12 (2.3)	7 (3.8)	6 (6.5)
Fibromyalgia*	2 (0.4)	10 (0.9)	11 (2.1)	7 (3.8)	6 (6.5)
Bipolar disorder*	3 (0.6)	9 (0.8)	12 (2.3)	9 (4.9)	8 (8.6)
PTSD*	8 (1.7)	14 (1.3)	15 (2.9)	21 (11.4)	9 (9.7)
COPD with emphysema*	5 (1.0)	19 (1.7)	22 (4.2)	12 (6.5)	10 (10.8)
ADHD*	15 (3.1)	50 (4.6)	33 (6.4)	25 (13.6)	11 (11.8)
Asthma*	46 (9.5)	157 (14.5)	79 (15.3)	39 (21.2)	19 (20.4)
Migraine*	29 (6.0)	134 (12.3)	77 (14.9)	31 (16.8)	19 (20.4)
GERD*	64 (13.2)	176 (16.2)	106 (20.5)	40 (21.7)	23 (24.7)
Anxiety*	13 (2.7)	98 (9.0)	109 (21.0)	55 (29.9)	34 (36.6)
Depression*	16 (3.3)	93 (8.6)	110 (21.2)	63 (34.2)	55 (59.1)
Itching skin *	19 (3.9)	81 (7.5)	50 (9.7)	30 (16.3)	10 (10.8)
Sinus pain *	18 (3.7)	77 (7.1)	58 (11.2)	21 (11.4)	10 (10.8)
Urgency *	13 (2.7)	69 (6.4)	46 (8.9)	23 (12.5)	10 (10.8)
Excessive belching or passing of gas *	24 (5.0)	84 (7.7)	54 (10.4)	29 (15.8)	13 (14.0)
Dryness *	35 (7.2)	113 (10.4)	68 (13.1)	39 (21.2)	14 (15.1)
Heartburn *	27 (5.6)	94 (8.7)	70 (13.5)	42 (22.8)	15 (16.1)
Dry mouth *	27 (5.6)	84 (7.7)	64 (12.4)	28 (15.2)	16 (17.2)
Constipation *	22 (4.5)	98 (9.0)	64 (12.4)	48 (26.1)	17 (18.3)
Numbness or loss of sensation *	17 (3.5)	54 (5.0)	38 (7.3)	19 (10.3)	17 (18.3)
Cramping*	14 (2.9)	62 (5.7)	45 (8.7)	18 (9.8)	18 (19.4)
Frequency of urination *	33 (6.8)	90 (8.3)	73 (14.1)	34 (18.5)	19 (20.4)
Swelling in calves, legs, or feet *	15 (3.1)	62 (5.7)	49 (9.5)	31 (16.8)	20 (21.5)
Coughing up sputum *	12 (2.5)	62 (5.7)	56 (10.8)	27 (14.7)	20 (21.5)
Pain or stiffness in neck *	32 (6.6)	128 (11.8)	72 (13.9)	49 (26.6)	22 (23.7)
Diarrhea *	24 (5.0)	99 (9.1)	70 (13.5)	31 (16.8)	22 (23.7)
Night sweats *	22 (4.5)	88 (8.1)	65 (12.5)	25 (13.6)	22 (23.7)
Lightheadedness *	11 (2.3)	62 (5.7)	53 (10.2)	37 (20.1)	22 (23.7)

Cough [*]	36 (7.4)	98 (9.0)	83 (16.0)	41 (22.3)	23 (24.7)
Tingling or numbness in extremities [*]	35 (7.2)	101 (9.3)	74 (14.3)	36 (19.6)	23 (24.7)
Leg cramps [*]	31 (6.4)	103 (9.5)	55 (10.6)	31 (16.8)	23 (24.7)
Shortness of breath with exercise [*]	11 (2.3)	59 (5.4)	68 (13.1)	37 (20.1)	23 (24.7)
Joint pain or swelling[*]	42 (8.7)	140 (12.9)	81 (15.6)	45 (24.5)	25 (26.9)
Sleeping pattern changes [*]	21 (4.3)	126 (11.6)	78 (15.1)	47 (25.5)	25 (26.9)
Tingling or pins and needles [*]	30 (6.2)	91 (8.4)	75 (14.5)	36 (19.6)	25 (26.9)
Appetite changes [*]	9 (1.9)	36 (3.3)	35 (6.8)	25 (13.6)	26 (28.0)
Heat or cold intolerance [*]	17 (3.5)	85 (7.8)	65 (12.5)	36 (19.6)	27 (29.0)
Shortness of breath [*]	8 (1.7)	51 (4.7)	57 (11.0)	34 (18.5)	27 (29.0)
Bloating [*]	26 (5.4)	104 (9.6)	61 (11.8)	41 (22.3)	29 (31.2)
Body image concerns [*]	9 (1.9)	40 (3.7)	46 (8.9)	33 (17.9)	29 (31.2)
Nasal stuffiness [*]	70 (14.5)	218 (20.1)	141 (27.2)	53 (28.8)	30 (32.3)
Urination at night [*]	69 (14.3)	172 (15.8)	105 (20.3)	43 (23.4)	30 (32.3)
Muscle or joint pain[*]	71 (14.7)	225 (20.7)	142 (27.4)	61 (33.2)	31 (33.3)
Memory change[*]	9 (1.9)	52 (4.8)	55 (10.6)	41 (22.3)	32 (34.4)
Headache[*]	28 (5.8)	151 (13.9)	104 (20.1)	44 (23.9)	38 (40.9)
Fatigue[*]	10 (2.1)	129 (11.9)	113 (21.8)	65 (35.3)	38 (40.9)
Stiffness[*]	76 (15.7)	267 (24.6)	121 (23.4)	63 (34.2)	39 (41.9)
Backache[*]	43 (8.9)	183 (16.9)	148 (28.6)	63 (34.2)	39 (41.9)
Nervousness[*]	4 (0.8)	46 (4.2)	51 (9.8)	39 (21.2)	43 (46.2)
Mood change[*]	6 (1.2)	36 (3.3)	60 (11.6)	42 (22.8)	44 (47.3)
Difficulty concentrating[*]	8 (1.7)	58 (5.3)	74 (14.3)	54 (29.3)	50 (53.8)
Neck or low back pain[*]	73 (15.1)	264 (24.3)	185 (35.7)	73 (39.7)	51 (54.8)
Tension[*]	10 (2.1)	84 (7.7)	86 (16.6)	44 (23.9)	51 (54.8)
Lack of energy[*]	6 (1.2)	92 (8.5)	115 (22.2)	74 (40.2)	53 (57.0)

Data presented as no. (%).
ADHD, attention deficit hyperactivity disorder; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; PHQ-9, Patient Health Questionnaire-9; PTSD, post-traumatic stress disorder.
P-values for trend were calculated with the use of Spearman Correlation or Cochrane-Armitage tests, where appropriate.
*P-value for trend <0.0001.

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Table 3. Physical Functioning: PHQ-9 Score

	PHQ-9 0 (N=484)	PHQ-9 1-4 (N=1086)	PHQ-9 5-9 (N=518)	PHQ-9 10-14 (N=184)	PHQ-9 15+ (N=93)
6-minute walk*	485.5 (444.0, 543.2)	480.0 (431.7, 530.3)	465.0 (422.0, 517.6)	460.1 (403.8, 511.9)	443.0 (391.2, 492.4)
30-second chair stand*	15.0 (12.0, 18.0)	14.0 (12.0, 17.0)	13.0 (11.0, 16.0)	13.0 (10.0, 16.0)	12.0 (10.0, 15.0)
Mean leg balance time†	60.0 (23.5, 60.0)	55.0 (21.4, 60.0)	50.5 (14.0, 60.0)	49.5 (11.0, 60.0)	44.0 (12.5, 60.0)
10-meter walk speed*	2.0 (1.8, 2.2)	2.0 (1.8, 2.2)	2.0 (1.6, 2.1)	1.8 (1.5, 2.0)	1.8 (1.5, 2.0)
Handgrip†	35.8 (27.8, 44.4)	32.5 (26.3, 42.5)	32.3 (26.4, 42.8)	33.4 (25.6, 40.7)	30.0 (22.0, 39.7)
Sit-rise score	8.0 (6.0, 9.0)	8.0 (6.0, 9.0)	8.0 (6.0, 9.0)	8.0 (6.0, 9.0)	7.5 (5.0, 9.0)
EF at rest, %	59.0 (55.8, 60.5)	58.8 (55.9, 60.5)	59.2 (56.1, 60.5)	59.2 (56.0, 61.4)	58.9 (56.0, 60.9)
Mean steps in first 30 days*	8398.0 (6560.6, 10709.6)	8172.2 (6220.6, 10335.7)	7666.7 (5128.2, 9862.5)	7008.4 (4673.5, 9821.8)	6498.1 (4684.1, 9044.5)
Coronary calcium score†	0.0 (0.0, 33.9)	0.0 (0.0, 42.6)	0.0 (0.0, 8.8)	0.0 (0.0, 7.1)	0.0 (0.0, 1.9)
FEV1/FVC	0.8 (0.7, 0.8)	0.8 (0.7, 0.8)	0.8 (0.7, 0.8)	0.8 (0.7, 0.8)	0.8 (0.7, 0.8)
ABI †	1.1 (1.1, 1.2)	1.1 (1.1, 1.2)	1.1 (1.1, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)

Data presented as median (25th, 75th percentile).
ABI, ankle brachial index; EF, ejection fraction; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PHQ-9, Patient Health Questionnaire.
P-values for trend were calculated with the use of Spearman Correlation or Cochrane-Armitage tests, where appropriate.
*P-value for trend <0.01.
†P-value for trend <0.001

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FIGURE LEGENDS

Figure 1. Top 30 Factors Associated with PHQ-9 Score Adjusted by Age, Sex, and Age by Sex Interaction

LASSO regression model 1 comprised age, sex, and age by sex interaction. The LASSO-predicted value was used to estimate a covariate-adjusted effect for all other candidate variables.

BMI, body mass index; LASSO, least absolute shrinkage and selection operator; PHQ-9, Patient Health Questionnaire-9; WBC, white blood cell

Figure 2. Top 30 Factors Associated with PHQ-9 Score Adjusted by Age, Sex, Age by Sex Interaction, Race, Ethnicity, Socioeconomic Status and Health Behaviors

LASSO regression model 2 comprised age, sex, age by sex interaction, race, ethnicity, socioeconomic status and health behaviors. The LASSO-predicted value was used to estimate a covariate-adjusted effect for all other candidate variables.

BMI, body mass index; LASSO, least absolute shrinkage and selection operator; PHQ-9, Patient Health Questionnaire-9

Figure 3. Top 30 Factors Associated with PHQ-9 Score Adjusted by Age, Sex, Age by Sex Interaction, Race, Ethnicity, Socioeconomic Status, Health Behaviors, and Medical Conditions

LASSO regression model 3 comprised age, sex, age by sex interaction, race, ethnicity, socioeconomic status, health behaviors, and medical conditions (except mental health disorder diagnoses or disorders directly related to mental health or depression). The LASSO-predicted value was used to estimate a covariate-adjusted effect for all other candidate variables.

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BMI, body mass index; LASSO, least absolute shrinkage and selection operator; PHQ-9, Patient

Health Questionnaire-9

Figure 4. Top 30 Factors Associated with PHQ-9 Score Adjusted by Age, Sex, Age by Sex

Interaction, Race, Ethnicity, Socioeconomic Status, Health Behaviors, Medical Conditions,

Symptoms, and Allergies

LASSO regression model 4 comprised age, sex, age by sex interaction, race, ethnicity,

socioeconomic status, health behaviors, medical conditions (except mental health disorder

diagnoses or disorders directly related to mental health or depression), symptoms (except those

that are directly related to mental health or depression), and allergies. The LASSO-predicted

value was used to estimate a covariate-adjusted effect for all other candidate variables.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index;

HbA1c, hemoglobin A1c; LASSO, least absolute shrinkage and selection operator; MCH, mean

corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PHQ-9, Patient

Health Questionnaire-9; RBC, red blood cell; WBC, white blood cell

Figure 5. Top 30 Factors Associated with PHQ-9 Score Adjusted by Age, Sex, Age by Sex

Interaction, Race, Ethnicity, Socioeconomic Status, Health Behaviors, Medical Conditions,

Symptoms, Allergies, and Physical Function

LASSO regression model 5 comprised age, sex, age by sex interaction, race, ethnicity,

socioeconomic status, health behaviors, medical conditions (except mental health disorder

diagnoses or disorders directly related to mental health or depression), symptoms (except those

that are directly related to mental health or depression), allergies, and physical function. The

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LASSO-predicted value was used to estimate a covariate-adjusted effect for all other candidate variables.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LASSO, least absolute shrinkage and selection operator; LDL, low density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MDRD, modification of diet in renal disease; MPV, mean platelet volume; pH, potential hydrogen; PHQ-9, Patient Health Questionnaire-9; RBC, red blood cell; TSH, thyroid-stimulating hormone; WBC, white blood cell

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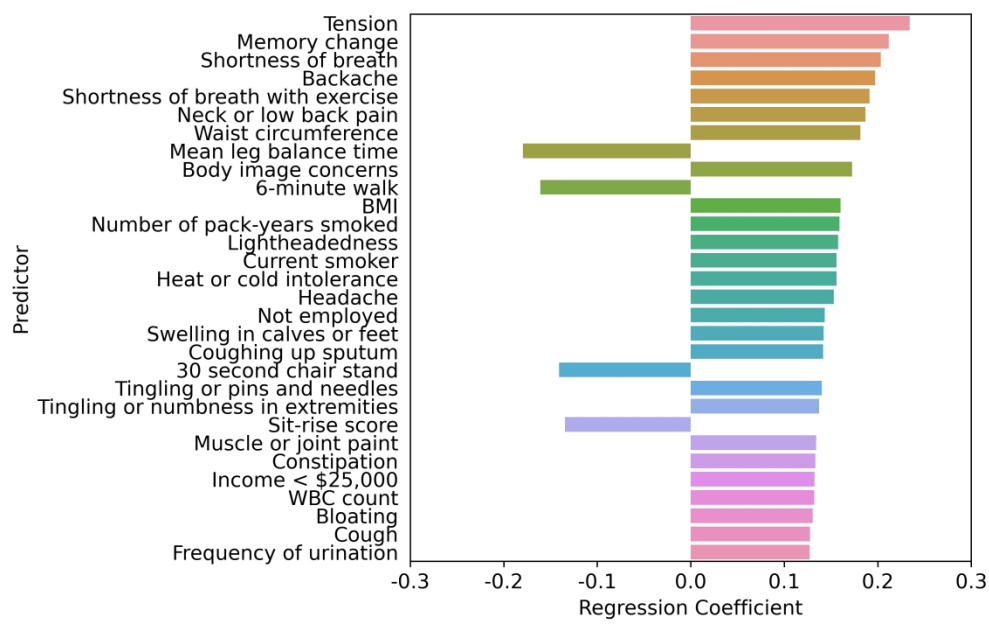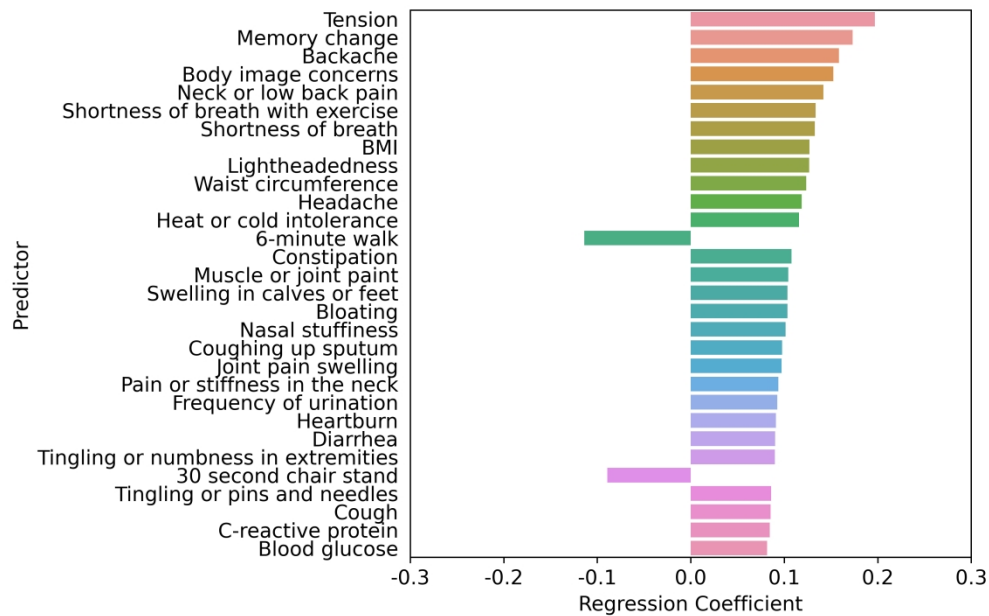
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SUPPLEMENTAL MATERIAL

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eTable 1. Key Variables Included in Each LASSO Covariate Model

Variables	Model 1	Model 2	Model 3	Model 4	Model 5
Age, sex and age × sex interaction	✓	✓	✓	✓	✓
Race and ethnicity		✓	✓	✓	✓
Socioeconomic-related variables		✓	✓	✓	✓
Behavioral-related behaviors		✓	✓	✓	✓
Medical conditions *not* related to mental health / depression			✓	✓	✓
Symptoms and allergies *not* related to mental health / depression				✓	✓
Physical health metrics					✓
Standard labs					

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eTable 2. Additional Medical History: PHQ-9 Scores

	0 (N=484)	1–4 (N=1086)	5–9 (N=518)	10–14 (N=184)	15+ (N=93)
Nonmelanoma skin cancer	12 (2.5)	42 (3.9)	18 (3.5)	3 (1.6)	0 (0.0)*
Osteoporosis	11 (2.3)	47 (4.3)	17 (3.3)	3 (1.6)	0 (0.0)*
Benign prostatic hyperplasia	22 (4.5)	44 (4.1)	17 (3.3)	3 (1.6)	0 (0.0)*
Melanoma skin cancer	11 (2.3)	23 (2.1)	5 (1.0)	0 (0.0)	0 (0.0)*
Prostate cancer	12 (2.5)	17 (1.6)	6 (1.2)	1 (0.5)	0 (0.0)*
Diabetes type 1	3 (0.6)	12 (1.1)	4 (0.8)	3 (1.6)	0 (0.0)
Macular degeneration	2 (0.4)	20 (1.8)	4 (0.8)	4 (2.2)	0 (0.0)
TIA	7 (1.4)	9 (0.8)	3 (0.6)	3 (1.6)	0 (0.0)
Hepatitis B	6 (1.2)	10 (0.9)	4 (0.8)	3 (1.6)	0 (0.0)
Coronary artery disease	11 (2.3)	44 (4.1)	13 (2.5)	6 (3.3)	1 (1.1)
Hashimoto's disease	8 (1.7)	22 (2.0)	11 (2.1)	3 (1.6)	1 (1.1)
Goiter	7 (1.4)	12 (1.1)	3 (0.6)	0 (0.0)	1 (1.1)
Hemorrhoids	11 (2.3)	44 (4.1)	18 (3.5)	4 (2.2)	1 (1.1)
Hypothyroidism	42 (8.7)	93 (8.6)	40 (7.7)	9 (4.9)	2 (2.2)
Glaucoma	14 (2.9)	29 (2.7)	10 (1.9)	6 (3.3)	2 (2.2)
Psoriasis	10 (2.1)	16 (1.5)	11 (2.1)	8 (4.3)	2 (2.2)
Peptic ulcer	5 (1.0)	22 (2.0)	13 (2.5)	4 (2.2)	2 (2.2)
Diverticulosis	8 (1.7)	29 (2.7)	10 (1.9)	5 (2.7)	2 (2.2)
Peripheral vascular disorder	1 (0.2)	15 (1.4)	8 (1.5)	2 (1.1)	2 (2.2)
Atrial fibrillation	4 (0.8)	17 (1.6)	1 (0.2)	1 (0.5)	2 (2.2)
Colon polyps	53 (11.0)	113 (10.4)	52 (10.0)	12 (6.5)	3 (3.2)
Arrhythmia	20 (4.1)	69 (6.4)	27 (5.2)	8 (4.3)	3 (3.2)
Tinnitus	31 (6.4)	52 (4.8)	35 (6.8)	6 (3.3)	3 (3.2)
Hearing Loss	29 (6.0)	75 (6.9)	26 (5.0)	12 (6.5)	3 (3.2)
Gout	14 (2.9)	29 (2.7)	14 (2.7)	5 (2.7)	3 (3.2)
Diverticulitis	3 (0.6)	20 (1.8)	17 (3.3)	3 (1.6)	3 (3.2)
Headaches	6 (1.2)	18 (1.7)	13 (2.5)	3 (1.6)	3 (3.2)
Epilepsy	5 (1.0)	19 (1.7)	12 (2.3)	5 (2.7)	3 (3.2)
Breast cancer	8 (1.7)	20 (1.8)	9 (1.7)	1 (0.5)	3 (3.2)
Myocardial infarction	6 (1.2)	19 (1.7)	11 (2.1)	1 (0.5)	3 (3.2)
Osteopenia	22 (4.5)	62 (5.7)	22 (4.2)	1 (0.5)	3 (3.2)
Stroke	5 (1.0)	12 (1.1)	9 (1.7)	1 (0.5)	3 (3.2)
Drug abuse*	5 (1.0)	14 (1.3)	5 (1.0)	13 (7.1)	4 (4.3)
Pulmonary embolism	4 (0.8)	17 (1.6)	7 (1.4)	3 (1.6)	4 (4.3)
Nonalcoholic fatty liver disease	5 (1.0)	17 (1.6)	16 (3.1)	3 (1.6)	4 (4.3)
Hepatitis C†	5 (1.0)	8 (0.7)	3 (0.6)	8 (4.3)	4 (4.3)
Cataracts	61 (12.6)	167 (15.4)	63 (12.2)	16 (8.7)	5 (5.4)
Kidney or bladder stones	36 (7.4)	66 (6.1)	18 (3.5)	13 (7.1)	5 (5.4)

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Concussions	19 (3.9)	62 (5.7)	35 (6.8)	13 (7.1)	5 (5.4)
Rheumatoid arthritis†	4 (0.8)	13 (1.2)	12 (2.3)	4 (2.2)	6 (6.5)
Gallbladder disorder†	18 (3.7)	57 (5.2)	32 (6.2)	14 (7.6)	8 (8.6)
Hypercholesterolemia	68 (14.0)	127 (11.7)	70 (13.5)	19 (10.3)	9 (9.7)
Irritable bowel disorder†	9 (1.9)	60 (5.5)	34 (6.6)	7 (3.8)	10 (10.8)
Sleep apnea	38 (7.9)	101 (9.3)	63 (12.2)	19 (10.3)	11 (11.8)
Diabetes type 2†	45 (9.3)	109 (10.0)	62 (12.0)	32 (17.4)	14 (15.1)
Pneumonia	30 (6.2)	85 (7.8)	40 (7.7)	12 (6.5)	15 (16.1)
Osteoarthritis	76 (15.7)	216 (19.9)	118 (22.8)	33 (17.9)	17 (18.3)
Hypertension	122 (25.2)	297 (27.3)	144 (27.8)	51 (27.7)	26 (28.0)
Hay fever	26 (5.4)	78 (7.2)	36 (6.9)	19 (10.3)	3 (3.2)
Discharge†	19 (3.9)	64 (5.9)	44 (8.5)	18 (9.8)	8 (8.6)
Hemorrhoids†	22 (4.5)	69 (6.4)	40 (7.7)	17 (9.2)	9 (9.7)
Ear ringing†	38 (7.9)	101 (9.3)	59 (11.4)	23 (12.5)	13 (14.0)
Easy bruising or bleeding†	39 (8.1)	130 (12.0)	68 (13.1)	22 (12.0)	18 (19.4)
Runny nose†	70 (14.5)	210 (19.3)	116 (22.4)	44 (23.9)	20 (21.5)
Floaters†	55 (11.4)	160 (14.7)	81 (15.6)	28 (15.2)	21 (22.6)

Data shown are no. (%), unless otherwise indicated.
P-values for trend were calculated with the use of Spearman Correlation or Cochrane-Armitage tests, where appropriate.
*P-value for trend <0.0001.
†P-value for trend <0.01.

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eTable 3. Estimates of the Non-Zero Coefficients from LASSO Model 1

Variable	Estimate
Age	-0.152
Age x sex	0.063

LASSO regression model 1 comprised age, sex, and age by sex interaction. Variables with zero estimates are not shown.

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eTable 4. Estimates of the Non-Zero Coefficients from LASSO Model 2

Variable	Estimate
Age	-0.167
Current smoker	0.103
Not employed	0.096
Black race	-0.076
Age x sex	0.074
Former smoker	0.061
Number of pack-years smoked	0.058
Income < $25,000	0.057
Asian race	-0.042
Uninsured	0.032
Married	-0.025
AUDIT-C score	-0.012
High school or less education	0.009
Other race	0.005
Hispanic ethnicity	0.003

LASSO regression model 2 comprised age, sex, age by sex interaction, race, ethnicity, socioeconomic status and health behaviors.
Variables with zero estimates are not shown.
AUDIT-C, Alcohol Use Disorders Identification Test-Concise; LASSO, least absolute shrinkage and selection operator.

eTable 5. Estimates of the Non-Zero Coefficients from LASSO Model 3

Variable	Estimate
Age	-0.194
Current smoker	0.106
Not employed	0.065
Former smoker	0.054
Uninsured	0.049
COPD with emphysema	0.048
Asthma	0.048
Sleep apnea	0.048
Fibromyalgia	0.038
Married	-0.037
GERD	0.036
Age x sex	0.035
Kidney or bladder stones	-0.032
Osteoarthritis	0.03
Asian race	-0.029
Hypertension	0.028
Epilepsy	0.027
Irritable bowel disorder	0.025
Diverticulitis	0.024
Pulmonary embolism	0.023
Migraines	0.023
Black race	-0.02
Chronic headaches	0.017
Hepatitis C	0.017
Income < $25,000	0.016
Diabetes type 2	0.015
Cataracts	0.011
Osteoporosis	-0.011
Goiter	-0.011
Rheumatoid arthritis	0.01
Psoriasis	0.01
Nonmelanoma skin cancer	0.009
Number of pack-years smoked	0.009
Hypothyroidism	-0.009
Arrhythmia	0.008
Glaucoma	0.008
Female	0.006
Nonalcoholic fatty liver disease	0.006
Prostate cancer	-0.003

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Hypercholesterolemia	0.002

LASSO regression model 3 comprised age, sex, age by sex interaction, race, ethnicity, socioeconomic status, health behaviors, and medical conditions (except mental health disorder diagnoses or disorders directly related to mental health or depression). Variables with zero estimates are not shown.
COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; LASSO, least absolute shrinkage and selection operator.

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eTable 6. Estimates of the Non-Zero Coefficients from LASSO Model 4

Variable	Estimate
Age	-0.14
Tension	0.095
Body image concerns	0.085
Current smoker	0.071
Not employed	0.06
Memory change	0.059
Uninsured	0.042
Asthma	0.041
Shortness of breath	0.039
Backache	0.037
Sleep apnea	0.037
Former smoker	0.035
Lightheadedness	0.034
Kidney or bladder stones	-0.026
Married	-0.025
Neck or low back pain	0.022
Black race	-0.021
Coughing up sputum	0.019
Osteoarthritis	0.019
Headache	0.017
Food allergies	0.016
Diverticulitis	0.015
Cataracts	0.014
Constipation	0.014
Asian race	-0.014
Shortness of breath with exercise	0.012
Hypothyroidism	-0.012
Fibromyalgia	0.011
Epilepsy	0.011
GERD	0.011
Migraines	0.011
Joint pain swelling	0.009
COPD with emphysema	0.009
Heat or cold intolerance	0.009
Pulmonary embolism	0.009
Bloating	0.009
Diabetes type 2	0.007
Swelling in calves or feet	0.007
Irritable bowel disorder	0.007

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Nasal stuffiness	0.007
Pneumonia	0.004
Nonmelanoma skin cancer	0.004
Hypertension	0.004
Psoriasis	0.002
Cough	0.002
Chronic headaches	0.002
Hepatitis C	0.001
Prostate cancer	-0.001

LASSO regression model 4 comprised age, sex, age by sex interaction, race, ethnicity, socioeconomic status, health behaviors, medical conditions (except mental health disorder diagnoses or disorders directly related to mental health or depression), symptoms (except those that are directly related to mental health or depression), and allergies. Variables with zero estimates are not shown. COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; LASSO, least absolute shrinkage and selection operator.

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eTable 7. Estimates of the Non-Zero Coefficients from LASSO Model 5

Variable	Estimate
Age	-0.148
Tension	0.094
Body image concerns	0.077
Current smoker	0.068
Memory change	0.062
Not employed	0.051
Waist circumference	0.049
Black race	-0.042
Asthma	0.038
6-minute walk	-0.037
Uninsured	0.036
Backache	0.035
Days watch worn 10+ hours in first 30 days	-0.032
Lightheadedness	0.031
BMI	0.031
Former smoker	0.031
Shortness of breath	0.029
Kidney or bladder stones	-0.026
Sleep apnea	0.025
Neck or low back pain	0.022
Coughing up sputum	0.021
Cataracts	0.02
Mean daily steps in first 30 days	-0.019
Constipation	0.018
Married	-0.017
Ejection fraction at rest	0.016
Food allergies	0.016
Osteoarthritis	0.015
Heart rate	0.015
Hypothyroidism	-0.015
Coronary calcium score	-0.015
Heat or cold intolerance	0.013
Headache	0.013
Irritable bowel disorder	0.013
Diverticulitis	0.012
Handgrip	-0.012
Bloating	0.011
Nonmelanoma skin cancer	0.01
Migraines	0.01

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Asian race	-0.01
AUDIT-C	0.009
Joint pain swelling	0.009
Epilepsy	0.009
Pneumonia	0.008
COPD with emphysema	0.007
Pulmonary embolism	0.007
Respiratory rate	0.007
Gallbladder disease	-0.007
Nasal stuffiness	0.006
30 second chair stand	-0.005
GERD	0.004
Discharge	-0.004
Shortness of breath with exercise	0.002
Fibromyalgia	0.002
Colon polyps	0.002
Arrhythmia	0.001
Goiter	-0.001

LASSO regression model 5 comprised age, sex, age by sex interaction, race, ethnicity, socioeconomic status, health behaviors, medical conditions (except mental health disorder diagnoses or disorders directly related to mental health or depression), symptoms (except those that are directly related to mental health or depression), allergies, and physical function. Variables with zero estimates are not shown.
AUDIT-C, Alcohol Use Disorders Identification Test-Concise; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; LASSO, least absolute shrinkage and selection operator.

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eTable 8. LASSO Regression Results: Model 1

Variable	Estimate	P-value	CI 25%	CI 75%
Tension	0.2344	< 0.0001	0.2026	0.2661
Memory change	0.2119	< 0.0001	0.1801	0.2437
Shortness of breath	0.2033	< 0.0001	0.1714	0.2352
Backache	0.1974	< 0.0001	0.1655	0.2293
Shortness of breath with exercise	0.1914	< 0.0001	0.1594	0.2233
Neck or low back pain	0.1869	< 0.0001	0.1549	0.2189
Waist circumference	0.1814	< 0.0001	0.1480	0.2149
Mean leg balance time	-0.1796	< 0.0001	-0.2172	-0.1420
Body image concerns	0.1726	< 0.0001	0.1403	0.2049
6-minute walk	-0.1608	< 0.0001	-0.1932	-0.1284
BMI	0.1604	< 0.0001	0.1282	0.1926
Number of pack-years smoked	0.1590	< 0.0001	0.1258	0.1922
Lightheadedness	0.1576	< 0.0001	0.1254	0.1899
Current smoker	0.1561	< 0.0001	0.1238	0.1884
Heat or cold intolerance	0.1560	< 0.0001	0.1238	0.1882
Headache	0.1532	< 0.0001	0.1205	0.1859
Not employed	0.1434	< 0.0001	0.1111	0.1757
Swelling in calves or feet	0.1421	< 0.0001	0.1098	0.1745
Coughing up sputum	0.1416	< 0.0001	0.1093	0.1739
30 second chair stand	-0.1407	< 0.0001	-0.1732	-0.1081
Tingling or pins and needles	0.1403	< 0.0001	0.1079	0.1727
Tingling or numbness in extremities	0.1373	< 0.0001	0.1049	0.1697
Sit-rise score	-0.1345	< 0.0001	-0.1714	-0.0975
Muscle or joint pain	0.1343	< 0.0001	0.1019	0.1668
Constipation	0.1334	< 0.0001	0.1010	0.1657
Income < $25,000	0.1325	< 0.0001	0.1001	0.1650
WBC count	0.1322	< 0.0001	0.0998	0.1647
Bloating	0.1305	< 0.0001	0.0979	0.1631
Cough	0.1276	< 0.0001	0.0952	0.1601
Frequency of urination	0.1274	< 0.0001	0.0945	0.1603
Nasal stuffiness	0.1259	< 0.0001	0.0934	0.1583
COPD with emphysema	0.1228	< 0.0001	0.0901	0.1555
Joint pain swelling	0.1225	< 0.0001	0.0899	0.1550
Heartburn	0.1215	< 0.0001	0.0890	0.1540
Pain or stiffness in the neck	0.1206	< 0.0001	0.0881	0.1531
Stiffness	0.1194	< 0.0001	0.0868	0.1520
Mean daily steps in first 30 days	-0.1176	< 0.0001	-0.1503	-0.0848
Heart rate	0.1165	< 0.0001	0.0835	0.1495
Urination at night	0.1158	< 0.0001	0.0823	0.1492
HbA1c	0.1144	< 0.0001	0.0813	0.1476
Diarrhea	0.1138	< 0.0001	0.0812	0.1463
10-meter walk speed	-0.1137	< 0.0001	-0.1463	-0.0810
Blood glucose	0.1136	< 0.0001	0.0808	0.1463
Oxygen saturation	-0.1118	< 0.0001	-0.1458	-0.0777
Dry mouth	0.1117	< 0.0001	0.0791	0.1444
Night sweats	0.1110	< 0.0001	0.0784	0.1435
C-reactive protein	0.1084	< 0.0001	0.0759	0.1409
Urgency	0.1080	< 0.0001	0.0751	0.1410
Monocytes	0.1075	< 0.0001	0.0742	0.1408
Neutrophils	0.1072	< 0.0001	0.0747	0.1398
Numbness or loss of sensation	0.1055	< 0.0001	0.0729	0.1380
GERD	0.1004	< 0.0001	0.0675	0.1334

Itching skin	0.0971	< 0.0001	0.0645	0.1297
Excessive belching or passing of gas	0.0957	< 0.0001	0.0631	0.1283
Respiratory rate	0.0944	< 0.0001	0.0618	0.1270
Leg cramps	0.0933	< 0.0001	0.0606	0.1260
Urine specific gravity	0.0931	< 0.0001	0.0605	0.1257
Albumin in urine	-0.0928	< 0.0001	-0.1261	-0.0595
Dryness	0.0926	< 0.0001	0.0600	0.1252
Absolute basophils	0.0925	< 0.0001	0.0598	0.1251
Uninsured	0.0924	< 0.0001	0.0597	0.1250
Cramping	0.0920	< 0.0001	0.0592	0.1248
Osteoarthritis	0.0917	< 0.0001	0.0568	0.1267
Lymphocytes (total)	0.0883	< 0.0001	0.0554	0.1213
Sleep apnea	0.0877	< 0.0001	0.0541	0.1213
ALT	0.0848	< 0.0001	0.0522	0.1175
Married	-0.0848	< 0.0001	-0.1188	-0.0508
Sinus pain	0.0838	< 0.0001	0.0511	0.1164
HDL	-0.0835	< 0.0001	-0.1161	-0.0509
Creatinine (urine)	0.0811	< 0.0001	0.0484	0.1138
Reticulocytes (% RBC)	0.0803	< 0.0001	0.0475	0.1131
Triglycerides	0.0800	< 0.0001	0.0471	0.1128
Fibromyalgia	0.0798	< 0.0001	0.0472	0.1125
Asthma	0.0796	< 0.0001	0.0469	0.1123
Former smoker	0.0791	< 0.0001	0.0454	0.1127
Absolute reticulocytes	0.0786	< 0.0001	0.0458	0.1114
Diabetes type 2	0.0780	< 0.0001	0.0448	0.1111
Urine reaction pH	-0.0762	< 0.0001	-0.1095	-0.0430
Migraines	0.0753	< 0.0001	0.0425	0.1081
Hypertension	0.0749	< 0.0001	0.0397	0.1102
Runny nose	0.0738	< 0.0001	0.0411	0.1065
Vitamin D	-0.0732	< 0.0001	-0.1067	-0.0397
Easy bruising or bleeding	0.0719	< 0.0001	0.0390	0.1049
High school or less education	0.0706	< 0.0001	0.0379	0.1033
Floaters	0.0701	< 0.0001	0.0370	0.1033
Discharge	0.0698	< 0.0001	0.0372	0.1025
Ear ringing	0.0671	< 0.0001	0.0338	0.1003
Hemorrhoids (symptom)	0.0649	0.0001	0.0320	0.0977
Days watch worn 10+ hours in first 30 days	-0.0639	0.0002	-0.0976	-0.0301
Asian race	-0.0636	0.0002	-0.0964	-0.0307
Absolute eosinophils	0.0632	0.0002	0.0304	0.0960
Seasonal allergies	0.0626	0.0002	0.0299	0.0954
Medication allergies	0.0612	0.0003	0.0283	0.0941
Irritable bowel disorder	0.0585	0.0005	0.0258	0.0912
Hepatitis C	0.0579	0.0005	0.0252	0.0907
Rheumatoid arthritis	0.0572	0.0006	0.0244	0.0900
Systolic blood pressure	0.0566	0.0017	0.0212	0.0920
Diverticulitis	0.0561	0.0008	0.0232	0.0890
Uric acid	0.0538	0.0019	0.0199	0.0876
Magnesium	-0.0537	0.0013	-0.0865	-0.0209
MCHC	-0.0533	0.0015	-0.0861	-0.0205
Handgrip	-0.0514	0.0021	-0.0842	-0.0187
Gallbladder disease	0.0488	0.0036	0.0160	0.0816
MCH	-0.0465	0.0065	-0.0799	-0.0130
AST	0.0443	0.0080	0.0116	0.0771
Epilepsy	0.0427	0.0106	0.0100	0.0755

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Food allergies	0.0424	0.0112	0.0096	0.0752
Diastolic blood pressure	0.0420	0.0124	0.0091	0.0748
Pneumonia	0.0403	0.0163	0.0074	0.0732
Nonalcoholic fatty liver disease	0.0403	0.0159	0.0075	0.0731
Ejection fraction at rest	0.0403	0.0161	0.0075	0.0731
Non-seasonal allergies	0.0393	0.0189	0.0065	0.0722
Serum creatinine	0.0388	0.0239	0.0051	0.0725
Protein (serum)	-0.0381	0.0299	-0.0725	-0.0037
Cataracts	0.0368	0.0513	-0.0002	0.0737
Pulmonary embolism	0.0359	0.0321	0.0031	0.0688
Peripheral vascular disease	0.0344	0.0401	0.0016	0.0673
Hay fever	0.0342	0.0413	0.0014	0.0671
Stroke	0.0337	0.0450	0.0008	0.0667
MCV	-0.0331	0.0529	-0.0666	0.0004
Diverticulosis	0.0324	0.0541	-0.0006	0.0655
Arrhythmia	0.0324	0.0584	-0.0012	0.0659
Gout	0.0323	0.0570	-0.0010	0.0655
Myocardial infarction	0.0317	0.0606	-0.0014	0.0649
Cholesterol	-0.0305	0.0685	-0.0633	0.0023
Platelets	0.0303	0.0783	-0.0034	0.0640
LDL	-0.0301	0.0726	-0.0630	0.0028
Peptic ulcer	0.0300	0.0730	-0.0028	0.0628
Hypercholesterolemia	0.0297	0.0879	-0.0044	0.0638
Goiter	-0.0290	0.0836	-0.0618	0.0039
Coronary artery disease	0.0287	0.0959	-0.0051	0.0625
Chloride	-0.0268	0.1096	-0.0596	0.0060
Neutrophil lymphocyte ratio	0.0266	0.1156	-0.0065	0.0597
Basophils (% WBC)	0.0258	0.1242	-0.0071	0.0587
Chronic headaches	0.0258	0.1236	-0.0070	0.0586
Nonmelanoma skin cancer	0.0233	0.1738	-0.0103	0.0569
Hearing loss	0.0229	0.1869	-0.0111	0.0568
MPV	0.0224	0.1802	-0.0104	0.0552
AUDIT-C sum score	-0.0219	0.1897	-0.0547	0.0109
Benign prostatic hyperplasia	0.0218	0.2273	-0.0136	0.0571
Eosinophils (% WBC)	0.0216	0.2001	-0.0114	0.0545
Hypothyroidism	-0.0213	0.2064	-0.0544	0.0118
Macular degeneration	0.0209	0.2140	-0.0121	0.0540
Left ventricular mass index	0.0197	0.2623	-0.0147	0.0541
Hemoglobin	-0.0181	0.2868	-0.0515	0.0153
RBC count	0.0180	0.2814	-0.0148	0.0508
Psoriasis	0.0170	0.3108	-0.0158	0.0497
Lymphocytes (% WBC)	-0.0166	0.3270	-0.0499	0.0166
Kidney or bladder stones	-0.0159	0.3448	-0.0490	0.0171
Glaucoma	0.0157	0.3547	-0.0175	0.0489
Hemorrhoids	0.0152	0.3649	-0.0177	0.0482
Coronary calcium score	0.0144	0.4287	-0.0213	0.0502
Other race	0.0131	0.4445	-0.0204	0.0466
Colon polyps	0.0120	0.4975	-0.0227	0.0467
Breast cancer	0.0118	0.4826	-0.0211	0.0446
Melanoma skin cancer	-0.0117	0.4889	-0.0450	0.0215
Sodium	-0.0117	0.4856	-0.0446	0.0212
Calcium	-0.0115	0.4909	-0.0443	0.0213
Hashimotos Disease	-0.0108	0.5175	-0.0436	0.0220
Transient ischemic attack	-0.0087	0.6029	-0.0417	0.0242
Osteopenia	-0.0076	0.6521	-0.0408	0.0256
Atrial fibrillation	0.0075	0.6601	-0.0258	0.0407

Neutrophil segments (% WBC)	0.0071	0.6714	-0.0257	0.0399
Total neutrophils (% WBC)	0.0071	0.6714	-0.0257	0.0399
TSH	0.0069	0.6786	-0.0259	0.0397
Potassium	-0.0060	0.7193	-0.0390	0.0269
Hematocrit	-0.0049	0.7722	-0.0383	0.0285
Monocytes (% WBC)	0.0041	0.8177	-0.0305	0.0386
Osteoporosis	-0.0039	0.8192	-0.0369	0.0292
GFR MDRD	0.0030	0.8737	-0.0343	0.0403
Tinnitus	0.0029	0.8627	-0.0304	0.0362
Diabetes type 1	-0.0027	0.8707	-0.0356	0.0301
Hispanic ethnicity	-0.0023	0.8914	-0.0360	0.0314
Hepatitis B	-0.0022	0.8963	-0.0351	0.0307
Prostate cancer	-0.0009	0.9575	-0.0348	0.0329
Black race	0.0004	0.9790	-0.0325	0.0334

LASSO regression model 1 comprised age, sex, and age by sex interaction. The LASSO-predicted value was used to estimate a covariate-adjusted effect for all other candidate variables shown.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUDIT-C, Alcohol Use Disorders Identification Test-Concise; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; GERD, gastroesophageal reflux disease; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LASSO, least absolute shrinkage and selection operator; LDL, low density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MDRD, modification of diet in renal disease; RBC, red blood cells; TSH, thyroid-stimulating hormone; WBC, white blood cells.

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eTable 9. LASSO Regression Results: Model 2

Variable	Estimate	P-value	CI 25%	CI 75%
Tension	0.1970	< 0.0001	0.1659	0.2282
Memory change	0.1732	< 0.0001	0.1423	0.2040
Backache	0.1585	< 0.0001	0.1273	0.1898
Body image concerns	0.1527	< 0.0001	0.1216	0.1837
Neck or low back pain	0.1419	< 0.0001	0.1105	0.1733
Shortness of breath with exercise	0.1336	< 0.0001	0.1019	0.1652
Shortness of breath	0.1329	< 0.0001	0.1011	0.1646
BMI	0.1269	< 0.0001	0.0958	0.1581
Lightheadedness	0.1268	< 0.0001	0.0955	0.1581
Waist circumference	0.1235	< 0.0001	0.0925	0.1545
Headache	0.1188	< 0.0001	0.0871	0.1505
Heat or cold intolerance	0.1159	< 0.0001	0.0845	0.1472
6-minute walk	-0.1139	< 0.0001	-0.1451	-0.0827
Constipation	0.1078	< 0.0001	0.0766	0.1391
Muscle or joint pain	0.1044	< 0.0001	0.0732	0.1356
Swelling in calves or feet	0.1036	< 0.0001	0.0723	0.1349
Bloating	0.1036	< 0.0001	0.0721	0.1351
Nasal stuffiness	0.1014	< 0.0001	0.0702	0.1326
Coughing up sputum	0.0978	< 0.0001	0.0663	0.1293
Joint pain swelling	0.0971	< 0.0001	0.0659	0.1282
Pain or stiffness in the neck	0.0937	< 0.0001	0.0623	0.1250
Frequency of urination	0.0927	< 0.0001	0.0615	0.1238
Heartburn	0.0913	< 0.0001	0.0599	0.1227
Diarrhea	0.0903	< 0.0001	0.0589	0.1216
Tingling or numbness in extremities	0.0900	< 0.0001	0.0586	0.1214
30 second chair stand	-0.0893	< 0.0001	-0.1207	-0.0580
Tingling or pins and needles	0.0859	< 0.0001	0.0543	0.1176
Cough	0.0855	< 0.0001	0.0539	0.1170
C-reactive protein	0.0847	< 0.0001	0.0534	0.1161
Blood glucose	0.0819	< 0.0001	0.0506	0.1131
Night sweats	0.0811	< 0.0001	0.0497	0.1125
Stiffness	0.0806	< 0.0001	0.0492	0.1119
Mean leg balance time	-0.0777	< 0.0001	-0.1090	-0.0464
HbA1c	0.0772	< 0.0001	0.0460	0.1084
Heart rate	0.0771	< 0.0001	0.0450	0.1092
Urination at night	0.0770	< 0.0001	0.0458	0.1082
ALT	0.0751	< 0.0001	0.0439	0.1063
Mean daily steps in first 30 days	-0.0745	< 0.0001	-0.1058	-0.0432
Urgency	0.0743	< 0.0001	0.0430	0.1055
Excessive belching or passing of gas	0.0739	< 0.0001	0.0426	0.1052
GERD	0.0727	< 0.0001	0.0414	0.1039
10-meter walk speed	-0.0721	< 0.0001	-0.1035	-0.0407
Dry mouth	0.0718	< 0.0001	0.0404	0.1032
Asthma	0.0715	< 0.0001	0.0403	0.1028
Sleep apnea	0.0711	< 0.0001	0.0397	0.1024
Itching skin	0.0682	< 0.0001	0.0368	0.0997
Sit-rise score	-0.0663	< 0.0001	-0.0978	-0.0348
WBC count	0.0653	< 0.0001	0.0327	0.0979
MCH	-0.0653	< 0.0001	-0.0965	-0.0340
Sinus pain	0.0652	< 0.0001	0.0338	0.0966
Urine specific gravity	0.0651	< 0.0001	0.0338	0.0965

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Respiratory rate	0.0646	< 0.0001	0.0332	0.0960
Absolute reticulocytes	0.0634	< 0.0001	0.0319	0.0948
Leg cramps	0.0632	< 0.0001	0.0319	0.0945
Dryness	0.0622	0.0001	0.0307	0.0937
Numbness or loss of sensation	0.0615	0.0001	0.0299	0.0930
Creatinine (urine)	0.0611	0.0001	0.0297	0.0925
Cramping	0.0602	0.0002	0.0284	0.0920
Reticulocytes (% RBC)	0.0601	0.0002	0.0286	0.0916
Oxygen saturation	-0.0597	0.0002	-0.0910	-0.0284
Albumin in urine	-0.0581	0.0003	-0.0894	-0.0268
Migraines	0.0581	0.0003	0.0266	0.0896
MCV	-0.0578	0.0003	-0.0891	-0.0266
Osteoarthritis	0.0561	0.0005	0.0247	0.0876
Seasonal allergies	0.0556	0.0005	0.0243	0.0868
HDL	-0.0534	0.0009	-0.0848	-0.0220
Hemorrhoids (symptom)	0.0528	0.0009	0.0215	0.0841
Fibromyalgia	0.0525	0.0011	0.0211	0.0840
Lymphocytes (total)	0.0518	0.0015	0.0198	0.0838
Runny nose	0.0515	0.0013	0.0201	0.0828
Irritable bowel disorder	0.0513	0.0013	0.0200	0.0826
Ear ringing	0.0498	0.0019	0.0184	0.0811
Vitamin D	-0.0497	0.0023	-0.0816	-0.0178
Days watch worn 10+ hours in first 30 days	-0.0495	0.0023	-0.0813	-0.0177
COPD with emphysema	0.0488	0.0027	0.0170	0.0807
Food allergies	0.0483	0.0025	0.0170	0.0796
MCHC	-0.0483	0.0025	-0.0797	-0.0170
Hypertension	0.0479	0.0030	0.0162	0.0795
Urine reaction pH	-0.0473	0.0031	-0.0787	-0.0160
Triglycerides	0.0470	0.0033	0.0156	0.0783
Monocytes	0.0465	0.0037	0.0151	0.0779
Neutrophils	0.0462	0.0049	0.0140	0.0785
Serum creatinine	0.0460	0.0044	0.0143	0.0777
Uric acid	0.0460	0.0043	0.0144	0.0775
Diabetes type 2	0.0456	0.0044	0.0143	0.0769
AST	0.0447	0.0052	0.0134	0.0760
Discharge	0.0446	0.0054	0.0132	0.0760
Non-seasonal allergies	0.0445	0.0053	0.0132	0.0759
Diverticulitis	0.0432	0.0069	0.0119	0.0745
Floaters	0.0421	0.0084	0.0108	0.0734
Absolute basophils	0.0417	0.0098	0.0101	0.0734
Ejection fraction at rest	0.0415	0.0094	0.0102	0.0729
Easy bruising or bleeding	0.0354	0.0272	0.0040	0.0667
Medication allergies	0.0345	0.0311	0.0031	0.0658
Epilepsy	0.0318	0.0471	0.0004	0.0631
Systolic blood pressure	0.0316	0.0505	-0.0001	0.0632
Chloride	-0.0308	0.0544	-0.0621	0.0006
Nonalcoholic fatty liver disease	0.0303	0.0578	-0.0010	0.0617
Arrhythmia	0.0299	0.0629	-0.0016	0.0614
RBC count	0.0296	0.0641	-0.0017	0.0610
Kidney or bladder stones	-0.0288	0.0721	-0.0601	0.0026
Chronic headaches	0.0285	0.0746	-0.0028	0.0599
Rheumatoid arthritis	0.0280	0.0808	-0.0034	0.0594
Hay fever	0.0279	0.0815	-0.0035	0.0592
Benign prostatic hyperplasia	0.0274	0.0946	-0.0047	0.0596
Cholesterol	-0.0267	0.0947	-0.0581	0.0046

Absolute eosinophils	0.0265	0.0983	-0.0049	0.0580
Diverticulosis	0.0262	0.1013	-0.0051	0.0576
Goiter	-0.0261	0.1034	-0.0574	0.0053
Magnesium	-0.0258	0.1099	-0.0574	0.0058
Gout	0.0255	0.1116	-0.0059	0.0569
LDL	-0.0246	0.1238	-0.0560	0.0067
Hepatitis C	0.0239	0.1373	-0.0076	0.0554
Diastolic blood pressure	0.0232	0.1467	-0.0081	0.0546
Peripheral vascular disease	0.0230	0.1508	-0.0084	0.0543
Hypercholesterolemia	0.0227	0.1598	-0.0089	0.0543
Hemoglobin	-0.0225	0.1601	-0.0540	0.0089
Nonmelanoma skin cancer	0.0212	0.1869	-0.0103	0.0528
MPV	0.0211	0.1861	-0.0102	0.0525
Hearing loss	0.0210	0.1924	-0.0106	0.0527
Hypothyroidism	-0.0209	0.1930	-0.0523	0.0106
Handgrip	-0.0205	0.2025	-0.0522	0.0111
Pulmonary embolism	0.0194	0.2246	-0.0119	0.0508
Cataracts	0.0186	0.2549	-0.0134	0.0507
Glaucoma	0.0186	0.2477	-0.0129	0.0501
Sodium	-0.0167	0.2976	-0.0480	0.0147
Pneumonia	0.0166	0.3007	-0.0148	0.0479
Potassium	-0.0153	0.3403	-0.0466	0.0161
Macular degeneration	0.0140	0.3806	-0.0173	0.0454
Protein (serum)	-0.0139	0.3870	-0.0454	0.0176
Stroke	0.0133	0.4058	-0.0181	0.0447
Hemorrhoids	0.0132	0.4094	-0.0182	0.0446
Coronary artery disease	0.0123	0.4424	-0.0191	0.0438
Basophils (% WBC)	0.0118	0.4593	-0.0195	0.0432
Hematocrit	-0.0117	0.4667	-0.0431	0.0198
Psoriasis	0.0109	0.4946	-0.0204	0.0423
Myocardial infarction	0.0104	0.5153	-0.0210	0.0418
Eosinophils (% WBC)	0.0104	0.5158	-0.0210	0.0418
Peptic ulcer	0.0102	0.5244	-0.0212	0.0416
Breast cancer	0.0101	0.5287	-0.0213	0.0414
Neutrophil lymphocyte ratio	0.0100	0.5337	-0.0214	0.0413
Melanoma skin cancer	-0.0099	0.5384	-0.0414	0.0216
Calcium	-0.0098	0.5396	-0.0412	0.0215
Transient ischemic attack	-0.0090	0.5746	-0.0404	0.0224
Coronary calcium score	-0.0085	0.6007	-0.0401	0.0232
Left ventricular mass index	0.0082	0.6113	-0.0234	0.0398
Gallbladder disease	0.0081	0.6131	-0.0234	0.0397
TSH	0.0081	0.6117	-0.0232	0.0395
Tinnitus	0.0081	0.6138	-0.0234	0.0397
Osteoporosis	-0.0081	0.6139	-0.0395	0.0233
GFR MDRD	0.0075	0.6465	-0.0247	0.0398
Colon polyps	0.0074	0.6490	-0.0244	0.0391
Hashimotos Disease	-0.0073	0.6467	-0.0387	0.0240
Neutrophil segments (% WBC)	-0.0072	0.6530	-0.0386	0.0242
Total neutrophils (% WBC)	-0.0072	0.6530	-0.0386	0.0242
Platelets	0.0059	0.7162	-0.0261	0.0380
Atrial fibrillation	0.0056	0.7273	-0.0259	0.0371
Osteopenia	-0.0046	0.7748	-0.0361	0.0269
Diabetes type 1	0.0039	0.8093	-0.0275	0.0352
Lymphocytes (% WBC)	0.0038	0.8133	-0.0276	0.0351
Hepatitis B	0.0030	0.8507	-0.0284	0.0344
Monocytes (% WBC)	0.0030	0.8543	-0.0288	0.0348

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| Prostate cancer | 0.0030 | 0.8543 | -0.0287 | 0.0347 |

LASSO regression model 2 comprised age, sex, age by sex interaction, race, ethnicity, socioeconomic status and health behaviors.
The LASSO-predicted value was used to estimate a covariate-adjusted effect for all other candidate variables shown.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; GERD, gastroesophageal reflux disease; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LASSO, least absolute shrinkage and selection operator; LDL, low density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MDRD, modification of diet in renal disease; RBC, red blood cells; TSH, thyroid-stimulating hormone; WBC, white blood cells.

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eTable 10. LASSO Regression Results: Model 3

Variable	Estimate	P-value	CI 25%	CI 75%
Tension	0.1847	< 0.0001	0.1543	0.2152
Memory change	0.1511	< 0.0001	0.1207	0.1816
Body image concerns	0.1457	< 0.0001	0.1154	0.1760
Backache	0.1336	< 0.0001	0.1026	0.1645
Neck or low back pain	0.1191	< 0.0001	0.0881	0.1501
Lightheadedness	0.1047	< 0.0001	0.0739	0.1355
Shortness of breath with exercise	0.1028	< 0.0001	0.0713	0.1343
Shortness of breath	0.0976	< 0.0001	0.0657	0.1294
Headache	0.0967	< 0.0001	0.0655	0.1280
Constipation	0.0932	< 0.0001	0.0627	0.1238
Heat or cold intolerance	0.0918	< 0.0001	0.0609	0.1227
Nasal stuffiness	0.0880	< 0.0001	0.0574	0.1185
Waist circumference	0.0834	< 0.0001	0.0528	0.1141
BMI	0.0829	< 0.0001	0.0517	0.1142
Swelling in calves or feet	0.0816	< 0.0001	0.0508	0.1124
6-minute walk	-0.0801	< 0.0001	-0.1111	-0.0491
Bloating	0.0795	< 0.0001	0.0484	0.1106
Muscle or joint paint	0.0791	< 0.0001	0.0484	0.1098
Frequency of urination	0.0786	< 0.0001	0.0482	0.1091
Coughing up sputum	0.0781	< 0.0001	0.0471	0.1090
30 second chair stand	-0.0762	< 0.0001	-0.1068	-0.0455
Pain or stiffness in the neck	0.0745	< 0.0001	0.0438	0.1053
Joint pain swelling	0.0735	< 0.0001	0.0428	0.1041
Tingling or numbness in extremities	0.0729	< 0.0001	0.0420	0.1037
Heartburn	0.0712	< 0.0001	0.0404	0.1021
Night sweats	0.0681	< 0.0001	0.0373	0.0988
Urination at night	0.0642	< 0.0001	0.0337	0.0946
Cough	0.0631	< 0.0001	0.0320	0.0941
Mean daily steps in first 30 days	-0.0620	< 0.0001	-0.0926	-0.0313
Tingling or pins and needles	0.0616	0.0001	0.0304	0.0928
Diarrhea	0.0609	0.0001	0.0298	0.0919
C-reactive protein	0.0604	0.0001	0.0296	0.0913
Urgency	0.0601	0.0001	0.0295	0.0906
Blood glucose	0.0594	0.0001	0.0288	0.0901
Stiffness	0.0591	0.0002	0.0284	0.0899
Leg cramps	0.0588	0.0002	0.0282	0.0893
Mean leg balance time	-0.0565	0.0003	-0.0870	-0.0260
ALT	0.0560	0.0003	0.0254	0.0865
Dryness	0.0556	0.0004	0.0250	0.0863
Heart rate	0.0550	0.0006	0.0234	0.0866
Itching skin	0.0548	0.0005	0.0240	0.0856
Excessive belching or passing of gas	0.0547	0.0005	0.0240	0.0854
Sit-rise score	-0.0526	0.0008	-0.0831	-0.0220
Sinus pain	0.0525	0.0008	0.0219	0.0832
10-meter walk speed	-0.0525	0.0008	-0.0833	-0.0217
Oxygen saturation	-0.0506	0.0012	-0.0811	-0.0201
HbA1c	0.0499	0.0014	0.0193	0.0805
Respiratory rate	0.0495	0.0016	0.0187	0.0802
Ejection fraction at rest	0.0465	0.0028	0.0160	0.0771
WBC count	0.0462	0.0045	0.0144	0.0781

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Absolute reticulocytes	0.0462	0.0033	0.0154	0.0770
Reticulocytes (% RBC)	0.0461	0.0034	0.0153	0.0770
Dry mouth	0.0456	0.0038	0.0148	0.0765
Albumin in urine	-0.0456	0.0034	-0.0761	-0.0151
Numbness or loss of sensation	0.0441	0.0052	0.0132	0.0751
Ear ringing	0.0422	0.0068	0.0116	0.0727
Food allergies	0.0418	0.0072	0.0113	0.0724
MCH	-0.0413	0.0084	-0.0720	-0.0106
Runny nose	0.0389	0.0128	0.0083	0.0695
Cramping	0.0389	0.0147	0.0076	0.0701
Hemorrhoids (symptom)	0.0386	0.0134	0.0080	0.0691
Days watch worn 10+ hours in first 30 days	-0.0385	0.0149	-0.0696	-0.0075
Handgrip	-0.0379	0.0150	-0.0685	-0.0074
MCHC	-0.0378	0.0156	-0.0684	-0.0072
Urine specific gravity	0.0361	0.0222	0.0052	0.0669
Absolute basophils	0.0352	0.0255	0.0043	0.0660
Urine reaction pH	-0.0351	0.0243	-0.0657	-0.0046
Monocytes	0.0350	0.0253	0.0043	0.0657
Lymphocytes (total)	0.0350	0.0283	0.0037	0.0663
Triglycerides	0.0347	0.0262	0.0041	0.0654
Discharge	0.0345	0.0273	0.0039	0.0652
MCV	-0.0338	0.0306	-0.0645	-0.0032
Neutrophils	0.0331	0.0390	0.0017	0.0645
Floaters	0.0330	0.0342	0.0025	0.0636
Creatinine (urine)	0.0325	0.0397	0.0015	0.0635
AST	0.0319	0.0404	0.0014	0.0625
Serum creatinine	0.0311	0.0465	0.0005	0.0618
Seasonal allergies	0.0288	0.0650	-0.0018	0.0595
Easy bruising or bleeding	0.0272	0.0821	-0.0035	0.0578
Vitamin D	-0.0269	0.0928	-0.0583	0.0045
Medication allergies	0.0258	0.0977	-0.0047	0.0564
Uric acid	0.0247	0.1137	-0.0059	0.0552
Non-seasonal allergies	0.0237	0.1300	-0.0070	0.0543
HDL	-0.0229	0.1470	-0.0540	0.0081
Hemoglobin	-0.0229	0.1427	-0.0535	0.0077
Chloride	-0.0219	0.1590	-0.0525	0.0086
Protein (serum)	-0.0213	0.1737	-0.0520	0.0094
Systolic blood pressure	0.0186	0.2348	-0.0121	0.0492
Hay fever	0.0173	0.2677	-0.0133	0.0478
MPV	0.0154	0.3227	-0.0152	0.0460
Absolute eosinophils	0.0147	0.3473	-0.0160	0.0455
Hematocrit	-0.0147	0.3474	-0.0453	0.0159
Basophils (% WBC)	0.0140	0.3691	-0.0166	0.0446
Coronary calcium score	-0.0118	0.4500	-0.0426	0.0189
RBC count	0.0109	0.4830	-0.0196	0.0415
LDL	-0.0105	0.5007	-0.0411	0.0201
GFR MDRD	-0.0087	0.5884	-0.0402	0.0228
Diastolic blood pressure	0.0087	0.5775	-0.0219	0.0393
Neutrophil lymphocyte ratio	0.0079	0.6135	-0.0227	0.0384
Sodium	-0.0077	0.6218	-0.0383	0.0229
Calcium	-0.0056	0.7179	-0.0362	0.0249
Cholesterol	-0.0054	0.7296	-0.0360	0.0252
Monocytes (% WBC)	0.0038	0.8106	-0.0271	0.0346
Neutrophil segments (% WBC)	-0.0035	0.8244	-0.0340	0.0271
Total neutrophils (% WBC)	-0.0035	0.8244	-0.0340	0.0271

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Platelets	0.0031	0.8456	-0.0280	0.0342
Left ventricular mass index	-0.0026	0.8673	-0.0333	0.0280
TSH	0.0025	0.8751	-0.0281	0.0330
Eosinophils (% WBC)	0.0023	0.8824	-0.0283	0.0329
Lymphocytes (% WBC)	0.0014	0.9280	-0.0292	0.0320
Potassium	-0.0008	0.9588	-0.0314	0.0298
Magnesium	-0.0005	0.9745	-0.0316	0.0306

LASSO regression model 3 comprised age, sex, age by sex interaction, race, ethnicity, socioeconomic status, health behaviors, and medical conditions (except mental health disorder diagnoses or disorders directly related to mental health or depression). The LASSO-predicted value was used to estimate a covariate-adjusted effect for all other candidate variables shown.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GFR, glomerular filtration rate; GERD, gastroesophageal reflux disease; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LASSO, least absolute shrinkage and selection operator; LDL, low density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MDRD, modification of diet in renal disease; RBC, red blood cells; TSH, thyroid-stimulating hormone; WBC, white blood cells.

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eTable 11. LASSO Regression Results: Model 4

Variable	Estimate	P-value	CI 25%	CI 75%
BMI	0.0664	< 0.0001	0.0369	0.0960
6-minute walk	-0.0661	< 0.0001	-0.0955	-0.0368
Waist circumference	0.0618	< 0.0001	0.0326	0.0910
Mean daily steps in first 30 days	-0.0522	0.0004	-0.0813	-0.0232
ALT	0.0520	0.0004	0.0230	0.0809
Heart rate	0.0491	0.0012	0.0195	0.0787
30 second chair stand	-0.0458	0.0023	-0.0752	-0.0164
Blood glucose	0.0454	0.0022	0.0164	0.0745
WBC count	0.0454	0.0028	0.0157	0.0751
C-reactive protein	0.0431	0.0040	0.0137	0.0724
Absolute reticulocytes	0.0413	0.0054	0.0122	0.0705
Sit-rise score	-0.0408	0.0058	-0.0697	-0.0118
Reticulocytes (% RBC)	0.0401	0.0071	0.0109	0.0692
Handgrip	-0.0399	0.0070	-0.0688	-0.0109
Mean leg balance time	-0.0390	0.0083	-0.0679	-0.0100
Oxygen saturation	-0.0385	0.0091	-0.0675	-0.0096
AST	0.0374	0.0112	0.0085	0.0663
Respiratory rate	0.0367	0.0138	0.0075	0.0659
10-meter walk speed	-0.0362	0.0154	-0.0654	-0.0069
Albumin in urine	-0.0361	0.0146	-0.0651	-0.0071
Days watch worn 10+ hours in first 30 days	-0.0360	0.0157	-0.0653	-0.0068
Lymphocytes (total)	0.0354	0.0181	0.0060	0.0648
HbA1c	0.0352	0.0177	0.0061	0.0643
Ejection fraction at rest	0.0351	0.0173	0.0062	0.0641
Neutrophils	0.0350	0.0200	0.0055	0.0644
MCHC	-0.0341	0.0212	-0.0631	-0.0051
MCH	-0.0301	0.0428	-0.0592	-0.0010
Monocytes	0.0282	0.0577	-0.0009	0.0572
Absolute basophils	0.0270	0.0702	-0.0022	0.0562
Triglycerides	0.0267	0.0716	-0.0023	0.0557
Urine reaction pH	-0.0265	0.0734	-0.0554	0.0025
MCV	-0.0223	0.1333	-0.0513	0.0068
Sodium	-0.0220	0.1359	-0.0510	0.0069
Chloride	-0.0211	0.1537	-0.0500	0.0079
Serum creatinine	0.0203	0.1701	-0.0087	0.0492
MPV	0.0189	0.2015	-0.0101	0.0478
Potassium	-0.0185	0.2097	-0.0475	0.0104
Urine specific gravity	0.0179	0.2308	-0.0114	0.0473
Vitamin D	-0.0166	0.2713	-0.0462	0.0130
Systolic blood pressure	0.0165	0.2654	-0.0125	0.0455
LDL	-0.0158	0.2837	-0.0448	0.0131
Protein (serum)	-0.0145	0.3256	-0.0435	0.0145
RBC count	0.0144	0.3285	-0.0145	0.0434
Creatinine (urine)	0.0140	0.3518	-0.0154	0.0434
Basophils (% WBC)	0.0119	0.4208	-0.0171	0.0408
Left ventricular mass index	-0.0114	0.4391	-0.0404	0.0175
Uric acid	0.0111	0.4506	-0.0178	0.0401
Coronary calcium score	-0.0108	0.4681	-0.0398	0.0183
TSH	0.0102	0.4912	-0.0188	0.0391
Hemoglobin	-0.0095	0.5236	-0.0385	0.0196
Magnesium	-0.0074	0.6195	-0.0366	0.0218

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Diastolic blood pressure	0.0064	0.6651	-0.0226	0.0354
Eosinophils (% WBC)	-0.0057	0.7011	-0.0346	0.0233
GFR MDRD	-0.0054	0.7173	-0.0349	0.0241
Neutrophil lymphocyte ratio	0.0053	0.7185	-0.0236	0.0343
Calcium	-0.0049	0.7398	-0.0339	0.0240
Platelets	0.0039	0.7947	-0.0254	0.0331
Cholesterol	-0.0034	0.8172	-0.0324	0.0256
HDL	-0.0027	0.8565	-0.0322	0.0267
Monocytes (% WBC)	0.0025	0.8652	-0.0266	0.0317
Absolute eosinophils	0.0017	0.9082	-0.0274	0.0309
Lymphocytes (% WBC)	0.0015	0.9192	-0.0275	0.0305
Neutrophil segments (% WBC)	-0.0013	0.9307	-0.0302	0.0277
Total neutrophils (% WBC)	-0.0013	0.9307	-0.0302	0.0277
Hematocrit	-0.0011	0.9413	-0.0301	0.0279

LASSO regression model 4 comprised age, sex, age by sex interaction, race, ethnicity, socioeconomic status, health behaviors, medical conditions (except mental health disorder diagnoses or disorders directly related to mental health or depression), symptoms (except those that are directly related to mental health or depression), and allergies. The LASSO-predicted value was used to estimate a covariate-adjusted effect for all other candidate variables shown.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GFR, glomerular filtration rate; GERD, gastroesophageal reflux disease; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LASSO, least absolute shrinkage and selection operator; LDL, low density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MDRD, modification of diet in renal disease; RBC, red blood cells; TSH, thyroid-stimulating hormone; WBC, white blood cells.

eTable 12. LASSO Regression Results: Model 5

| Variable	Estimate	P-value	CI 25%	CI 75%
AST	0.0382	0.0087	0.0096	0.0667
ALT	0.0352	0.0162	0.0065	0.0638
HDL	0.0312	0.0383	0.0017	0.0607
Serum creatinine	0.0220	0.1313	-0.0066	0.0506
LDL	-0.0212	0.1460	-0.0497	0.0074
Blood glucose	0.0207	0.1606	-0.0082	0.0497
MCHC	-0.0199	0.1747	-0.0486	0.0088
Basophils (% WBC)	0.0183	0.2085	-0.0102	0.0469
Chloride	-0.0183	0.2099	-0.0468	0.0103
MPV	0.0181	0.2145	-0.0105	0.0467
Sodium	-0.0179	0.2203	-0.0464	0.0107
Absolute basophils	0.0170	0.2479	-0.0119	0.0460
Protein (serum)	-0.0169	0.2471	-0.0455	0.0117
MCH	-0.0148	0.3137	-0.0437	0.0140
Potassium	-0.0143	0.3259	-0.0429	0.0143
GFR MDRD	-0.0138	0.3535	-0.0430	0.0154
Lymphocytes (total)	0.0133	0.3748	-0.0160	0.0425
Platelets	-0.0127	0.3923	-0.0417	0.0164
WBC count	0.0125	0.4143	-0.0175	0.0424
Monocytes	0.0121	0.4122	-0.0168	0.0409
C-reactive protein	0.0104	0.4880	-0.0190	0.0398
Monocytes (% WBC)	0.0103	0.4818	-0.0185	0.0391
HbA1c	0.0101	0.4930	-0.0188	0.0391
MCV	-0.0101	0.4933	-0.0388	0.0187
TSH	0.0100	0.4930	-0.0186	0.0386
Albumin in urine	-0.0096	0.5130	-0.0383	0.0192
Magnesium	0.0095	0.5205	-0.0195	0.0385
Uric acid	-0.0080	0.5827	-0.0366	0.0206
RBC count	0.0073	0.6161	-0.0213	0.0359
Urine reaction pH	-0.0073	0.6185	-0.0360	0.0214
Neutrophil segments (% WBC)	-0.0072	0.6205	-0.0358	0.0214
Total neutrophils (% WBC)	-0.0072	0.6205	-0.0358	0.0214
Absolute reticulocytes	0.0069	0.6408	-0.0222	0.0361
Neutrophils	0.0068	0.6483	-0.0226	0.0363
Absolute eosinophils	-0.0064	0.6635	-0.0352	0.0224
Calcium	0.0062	0.6691	-0.0224	0.0348
Vitamin D	0.0057	0.7024	-0.0237	0.0352
Lymphocytes (% WBC)	0.0057	0.6944	-0.0229	0.0343
Reticulocytes (% RBC)	0.0057	0.7017	-0.0235	0.0349
Triglycerides	0.0055	0.7075	-0.0233	0.0343
Eosinophils (% WBC)	-0.0047	0.7449	-0.0333	0.0238
Hemoglobin	-0.0047	0.7481	-0.0334	0.0240
Cholesterol	-0.0033	0.8231	-0.0319	0.0254
Urine specific gravity	-0.0029	0.8465	-0.0321	0.0263
Neutrophil lymphocyte ratio	-0.0009	0.9488	-0.0295	0.0276
Creatinine (urine)	0.0006	0.9663	-0.0285	0.0298
Hematocrit	0.0000	0.9974	-0.0286	0.0287

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LASSO regression model 5 comprised age, sex, age by sex interaction, race, ethnicity, socioeconomic status, health behaviors, medical conditions (except mental health disorder diagnoses or disorders directly related to mental health or depression), symptoms (except those that are directly related to mental health or depression), allergies, and physical function. The LASSO-predicted value was used to estimate a covariate-adjusted effect for all other candidate variables shown.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate; GERD, gastroesophageal reflux disease; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LASSO, least absolute shrinkage and selection operator; LDL, low density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MDRD, modification of diet in renal disease; RBC, red blood cells; TSH, thyroid-stimulating hormone; WBC, white blood cells.

eFigure 1. Distribution of PHQ-9 Score Across Risk Groups by Asthma

Risk groups were created based on the LASSO-predicted value using LASSO Model 1 (age, sex, age x sex interaction) and Model 2 (race, ethnicity, socioeconomic-related variables and health behaviors). "High risk" was defined as the top 50% of the predicted value, while "low risk" was defined as the bottom 50% of the predicted value.
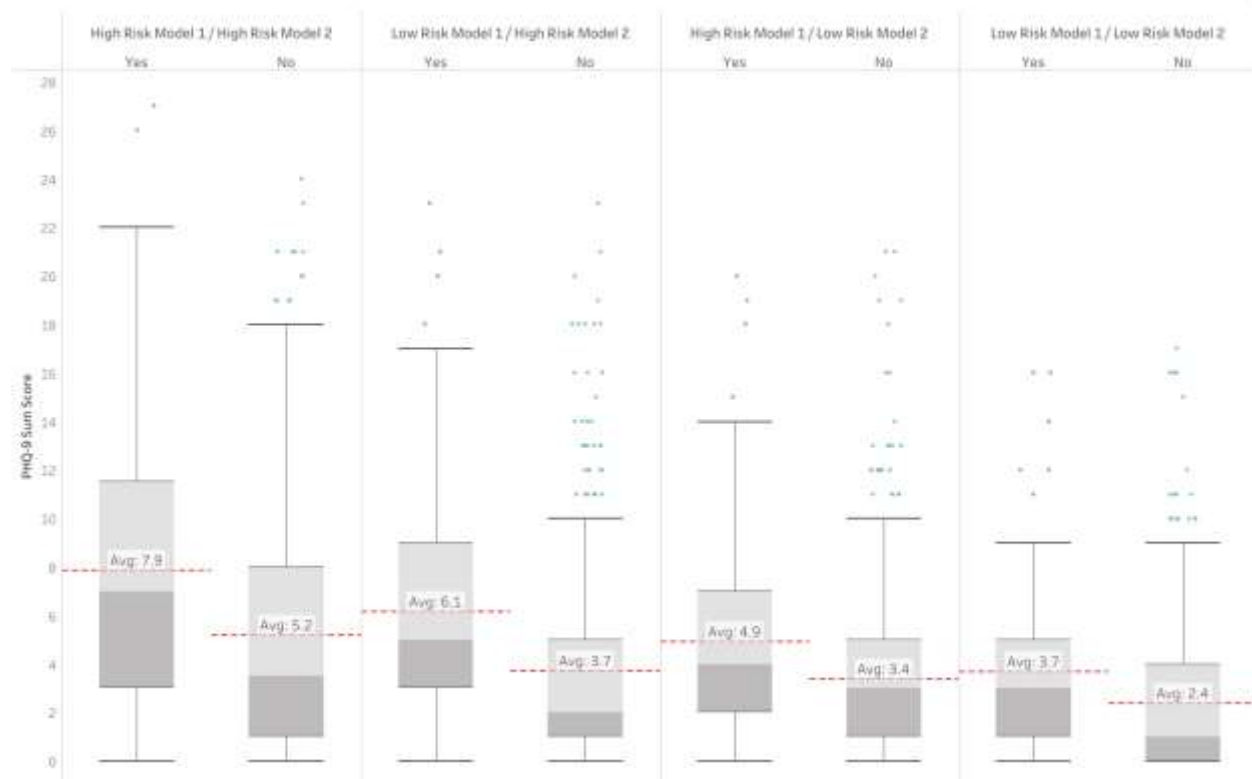LASSO, least absolute shrinkage and selection operator; PHQ-9, Patient Health Questionnaire-9.
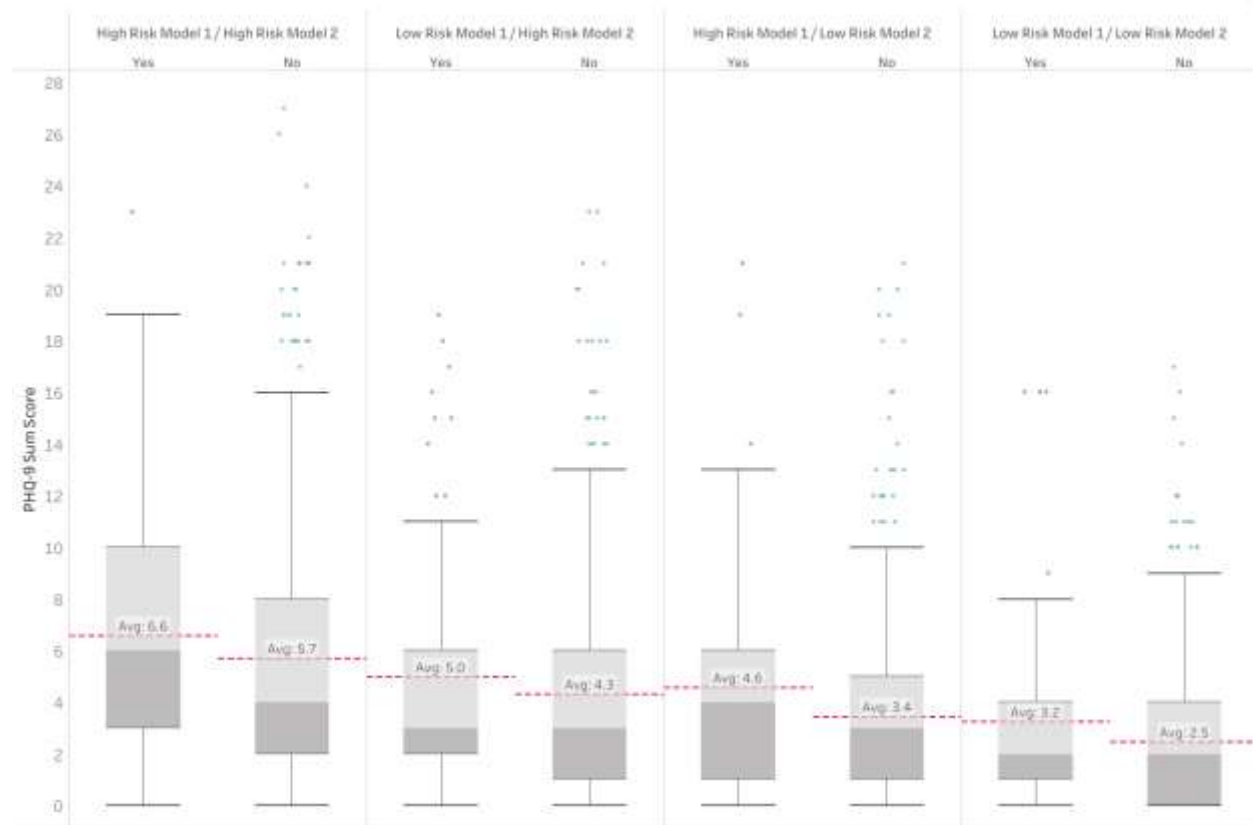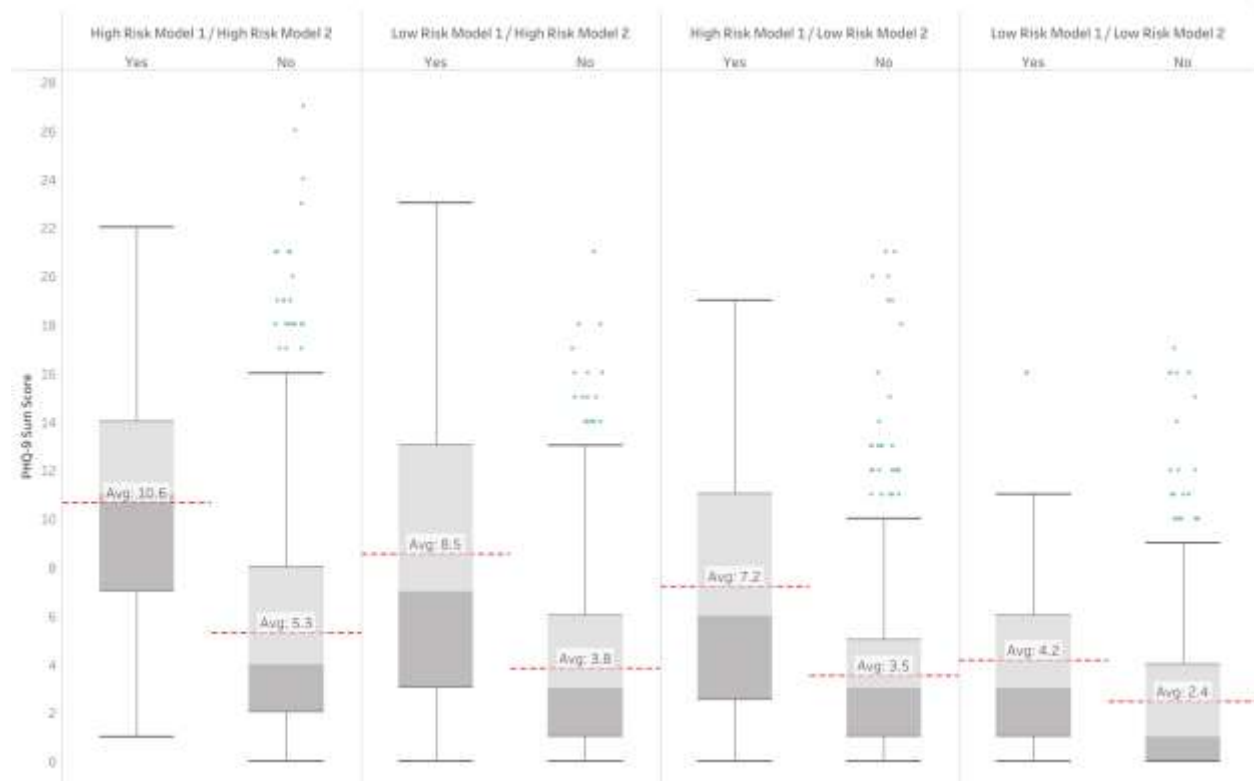
eFigure 2. Distribution of PHQ-9 Score Across Risk Groups by Backache
Risk groups were created based on the LASSO-predicted value using LASSO Model 1
(age, sex, age x sex interaction) and Model 2 (race, ethnicity, socioeconomic-related
variables and health behaviors). "High risk" was defined as the top 50% of the predicted
value, while "low risk" was defined as the bottom 50% of the predicted value.
LASSO, least absolute shrinkage and selection operator; PHQ-9, Patient Health
Questionnaire-9.

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eFigure 3. Distribution of PHQ-9 Score Across Risk Groups by Memory Change
Risk groups were created based on the LASSO-predicted value using LASSO Model 1
(age, sex, age x sex interaction) and Model 2 (race, ethnicity, socioeconomic-related
variables and health behaviors). "High risk" was defined as the top 50% of the predicted
value, while "low risk" was defined as the bottom 50% of the predicted value.
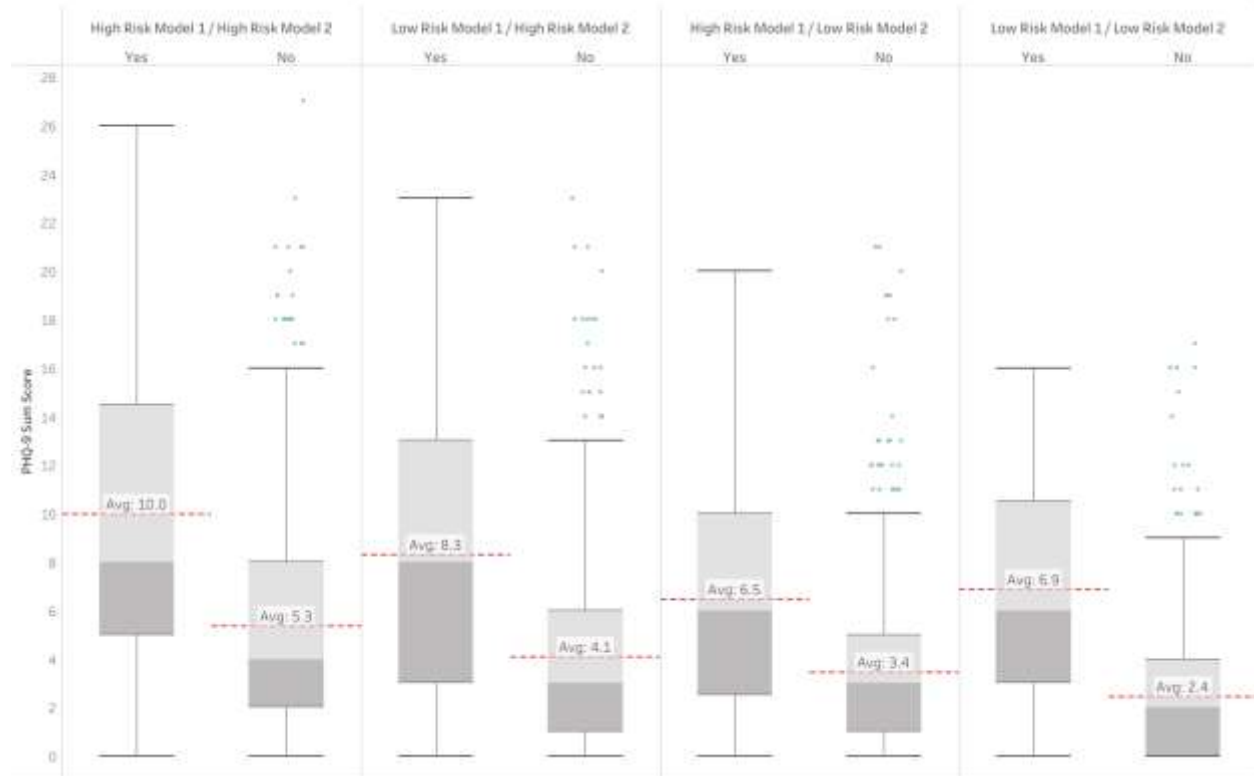LASSO, least absolute shrinkage and selection operator; PHQ-9, Patient Health
Questionnaire-9.

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eFigure 4. Distribution of PHQ-9 Score Across Risk Groups by Body Image Concerns
Risk groups were created based on the LASSO-predicted value using LASSO Model 1 (age, sex, age x sex interaction) and Model 2 (race, ethnicity, socioeconomic-related variables and health behaviors). "High risk" was defined as the top 50% of the predicted value, while "low risk" was defined as the bottom 50% of the predicted value.
LASSO, least absolute shrinkage and selection operator; PHQ-9, Patient Health Questionnaire-9.

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eFigure 5. Distribution of PHQ-9 Score Across Risk Groups by Sleep Apnea
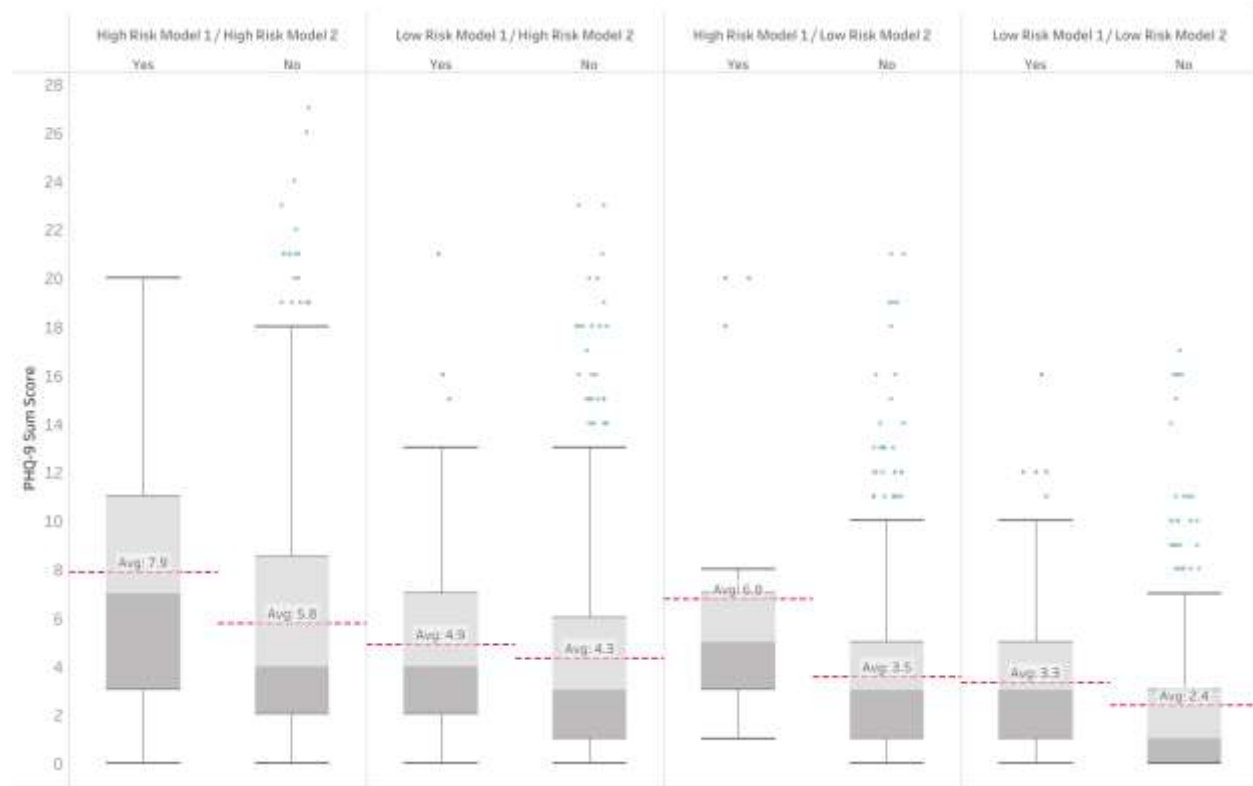Risk groups were created based on the LASSO-predicted value using LASSO Model 1 (age, sex, age x sex interaction) and Model 2 (race, ethnicity, socioeconomic-related variables and health behaviors). "High risk" was defined as the top 50% of the predicted value, while "low risk" was defined as the bottom 50% of the predicted value.
LASSO, least absolute shrinkage and selection operator; PHQ-9, Patient Health Questionnaire-9.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-11
Bias	9	Describe any efforts to address potential sources of bias	7-11
Study size	10	Explain how the study size was arrived at	7-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-11
		(*b*) Describe any methods used to examine subgroups and interactions	7-11
		(*c*) Explain how missing data were addressed	7-11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7-11
		(*e*) Describe any sensitivity analyses	n/a

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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-13
		(b) Give reasons for non-participation at each stage	11-13
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-13
		(b) Indicate number of participants with missing data for each variable of interest	11-13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11-13
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11-13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	11-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a

Discussion

Key results	18	Summarise key results with reference to study objectives	13-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15,16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15,16

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.