PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Biological and Clinical Correlates of the Patient Health Questionnaire-9: Exploratory Cross-Sectional Analyses of the Baseline Health Study
AUTHORS	Califf, Robert; Wong, Celeste; Doraiswamy, Murali; Hong, David; Miller, David; Mega, Jessica

VERSION 1 – REVIEW

REVIEWER	Li, Changqiang The Affiliated Hospital of Southwest Medical University, Department of Dermatology
REVIEW RETURNED	26-Jul-2021

GENERAL COMMENTS	The author performed a cross-sectional analysis of 2365 participants from the Baseline Health Study (BHS), assessed the relationship between the PHQ-9 at intake and other measurements intended to assess biological factors, markers of disease, and health status, and come to the conclusion that PHQ-9 scores are related to multiple demographic, vital sign, and clinical measures that indicate poor physical status. The idea is novel, the structure of the manuscript is reasonable and its conclusions have important clinical value. I think the manuscript is suitable for the BMJ Open. I have two questions: 1. I feel confused if PHQ-9 can represent depression since PHQ-9 is a self-rating depression scale. If the score exceeds a certain threshold, whether other scales or diagnostic criteria are needed to assess the severity of depression? 2.There is often a certain correlation between anxiety and depression. When the author explains that PHQ-9 can assess the depression status of patients, how does the author rule out the biased effect of the patient's possible anxiety state on the results?

REVIEWER	Otten, Danielle University Medical Center of the Johannes Gutenberg University Mainz, Department of Psychosomatic Medicine and Psychotherapy
REVIEW RETURNED	06-Aug-2021

GENERAL COMMENTS	This is an interesting manuscript in which the relationship between depression measured by PHQ-9 and biological factors, markers of disease and health status is examined.

	Abstract It is written that BHS data confirm relationships between PHQ-9 and measures of chronic disease, psychological well-being, social well-being, socioeconomic status, and poor physical performance. However, it seems like psychological well-being and social well-being were not included in this study. If this is the case, this part of the sentence needs to be removed from the abstract. Otherwise, please add in your manuscript how psychological and social well/being were measured and in which models these aspects were examined. Research question/ study objective The study objective is defined, but the research question is very broad. The knowledge gap is not completely clear. Why is a multidimensional phenotyping approach important? More in depth theory on the existing associations between depression and biological and clinical factors should be included in the introduction. Results - Table 1, Table 2, eTable 2: For some groups the sample size is very small (e.g., subgroups race, several medical disorders). It is therefore questionable whether significant effects are meaningful. A relationship may appear to be present even though none exists. - It was not mentioned whether the covariates (e.g., age, sex) included in the LASSO models are significantly associated to PHQ-9. This should be included in the results. Many studies have shown that associations between depression and physical health differ for men and women. This should be addressed in the discussion. - Why were asthma, backache, memory change, body image concerns and sleep apnea further examined (see eFigure 1) when other factors were shown to be stronger related to higher PHQ-9 scores? Discussion In the discussion it is stated that PHQ-9 scores align less with cardiovascular disease, cancer, and more other organ-focused conditions. Literature suggests that depression and cancer as well as depression and cardiovascular diseases commonly co-occur. In this study, diseases were individually included (e.g., coronary artery disease, peripheral vascular disorder) instead of combining similar types of diseases (e.g., cardiovascular disease). This makes comparisons with previous studies that often combine similar types of diseases, difficult.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
We thank the reviewer for commending the novelty and clinical value.

1. I feel confused if PHQ-9 can represent depression since PHQ-9 is a self-rating depression scale...whether other scales or diagnostic criteria are needed to assess the severity of depression?

The PHQ-9 is a self-rated scale, but has been validated in numerous prior studies against psychiatric diagnostic interviews and clinician scales, such as HAM-D, and is shown to have high sensitivity and specificity at the cut-offs of 10 or 11. Furthermore, PHQ-9 cut-offs for mild, moderate, and severe depression have also been validated against standard clinician scales. In our study, 98% of research participants with PHQ-9 >10 scores also endorsed depressed mood and/or loss of interest, which are the core criterion for a diagnosis of major depressive disorder, suggesting they likely had clinical depression. Lastly, there was also a high correlation with loss of functioning. We have now added a statement in the Discussion that even though the PHQ-9 is a validated screening instrument, the absence of psychiatric interviews is a potential limitation.

2. There is often a certain correlation between anxiety and depression. When the author explains that PHQ-9 can assess the depression status of patients, how does the author rule out the biased effect of the patient's possible anxiety state on the results?
The PHQ9 has greater specificity for depression than anxiety, but we do agree that these are highly comorbid conditions. We agree it is important for clinicians to consider these as comorbid conditions; therefore, we have added a sentence in the Discussion about this potential bias or contextual factor.

Reviewer: 2
This is an interesting manuscript in which the relationship between depression measured by PHQ-9 and biological factors, markers of disease and health status is examined.
We thank the reviewer for this positive comment.

It is written that BHS data confirm relationships between PHQ-9 and measures of chronic disease, psychological well-being, social well-being, socioeconomic status, and poor physical performance. However, it seems like psychological well-being and social well-being were not included in this study. If this is the case, this part of the sentence needs to be removed from the abstract. Otherwise, please add in your manuscript how psychological and social well/being were measured and in which models these aspects were examined
We have removed that part of the sentence from the abstract and have added a sentence to the Methods section stating that patient-reported outcomes (including psychological and social well-being measures) were excluded from the models to minimize less interpretable findings. These measures, including those related to socioeconomic status, are deeply explored in a recently published manuscript that was referenced in this manuscript, which is now updated to include the published reference.

Research question/ study objective
The knowledge gap is not completely clear. Why is a multidimensional phenotyping approach important?
Most previous studies have been limited in the number of dimensions that could be examined. We believe that the ability to evaluate so many dimensions is important to obtain a holistic view of a condition like depression.

While prior studies have looked at associations between depression and specific diseases (e.g., anxiety, addictions, cardiac disease, stroke) few have examined effects on whole body using a combination of symptom, psychometric, wearable, laboratory, and physiological measures in a sample that is representative of the population. Furthermore, few studies have examined the link between these issues and socioeconomic status. This approach is crucial to understand how depression impacts every aspect of a person's health and well-being, how other factors impact depression, and how to develop appropriate interventions. Our study illustrates the value of deep phenotyping to convey the highly interlinked nature of mental, physical, and socioeconomic status. We have added text to the Discussion to stress this point.

Results

- Table 1, Table 2, eTable 2: For some groups the sample size is very small (e.g., subgroups race, several medical disorders). It is therefore questionable whether significant effects are meaningful. A relationship may appear to be present even though none exists.

Since the manuscript is exploratory in nature, we have chosen not to rely solely on p-values to decide relevance to research or clinical interpretation. Instead, we have reported the values so that those who read the manuscript can form their opinions with as much data as possible. Follow-up studies will be important to clarify these issues.

- It was not mentioned whether the covariates (e.g., age, sex) included in the LASSO models are significantly associated to PHQ-9. This should be included in the results.

We included additional tables in the supplementary material with the estimates of each non-zero coefficient that remained in each LASSO model and a sentence in the Results section indicating this. Although inferential statistics for LASSO regression have been proposed (https://statweb.stanford.edu/~tibs/ftp/covtest.pdf), they are still under development and not implemented in standard statistical packages. Thus, standard errors, confidence intervals or p-values are not presented since it remains challenging to compute and interpret those measures when using LASSO regression, especially for the zero estimates. We chose to use LASSO for developing our "adjustment" models to estimate a covariate-adjusted effect for all other candidate variables displayed in Figures 1-5 and eTables 8-12.

Many studies have shown that associations between depression and physical health differ for men and women. This should be addressed in the discussion.

We agree that, on average, the men and women have different relationships and we have now emphasized this point in the discussion.

- Why were asthma, backache, memory change, body image concerns and sleep apnea further examined (see eFigure 1) when other factors were shown to be stronger related to higher PHQ-9 scores?

These were felt to be representative and common conditions that would be of interest to the readers. We also clarified in the Results section that these were a sample of conditions to demonstrate the interrelationships between demographic and socioeconomic risk factors, as well as PHQ-9 score.

Discussion

In the discussion it is stated that PHQ-9 scores align less with cardiovascular disease, cancer, and more other organ-focused conditions. Literature suggests that depression and cancer as well as depression and cardiovascular diseases commonly co-occur. In this study, diseases were individually included (e.g., coronary artery disease, peripheral vascular disorder) instead of combining similar types of diseases (e.g., cardiovascular disease). This makes comparisons with previous studies that often combine similar types of diseases, difficult.

We included diseases individually since that is the most precise way to measure impacts on specific diseases.

Per the Reviewers request, we re-ran analyses by pooling all CVD diseases and found the pooled CVD variable to be a significant predictor of PHQ-9, consistent with prior literature reports. However, we believe our more detailed analyses reported in the paper reveals additional insights as to how individual diseases relate to PHQ-9.

VERSION 2 – REVIEW

REVIEWER	Otten, Danielle University Medical Center of the Johannes Gutenberg University Mainz, Department of Psychosomatic Medicine and Psychotherapy
REVIEW RETURNED	03-Dec-2021

GENERAL COMMENTS	Dear authors, thank you very much for addressing my remarks and adapt your manuscript accordingly. I have no further comments.