Predictors of Clinically Significant Depression Symptoms as Determined by PHQ-9

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Background: Depression is a debilitating and potentially life-threatening mental illness that is very common. Thus, finding predictors of depression is of paramount importance. This study examined household size, high sensitivity C-reactive protein, and select dietary nutrients for possible links to depression.

Methods: Data from the 2017-2018 cycle of the National Health and Nutrition Examination Survey (NHANES) was used. Depression was determined based on a PHQ-9 score of 10 or above. Of the 9,254 participants in the overall survey, 4,692 were included in this study. The **survey** package was used in R to account for the study design and sample weights. Household size 7+ was combined with household size 6 due to low cell size.

Results: No nutrients were included in the final model due to lack of significance at the univariate level. HSCRP had a p-value of 0.022 in a univariate model and p-value of 0.053 in the final model. Household size had an overall p-value of less than 0.001 in the final model, and household sizes of 4 and 5 had p-values below 0.05.

Conclusion: HSCRP was not statistically significant in the final model, and the difference in the p-value between the univariate model and the final model is most likely explained by the inclusion of BMI in the final model. Household size was found to have an overall statistically significant effect in the final model, with household sizes 4 and 5 in particular having lower odds of depression than a single-person household. Therefore, it may be worthwhile to inform young adults that people who live with 3 or 4 other people are less likely to be depressed.

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1.0 Introduction

Depression is a serious mental illness that affected 8.1% of American adults between 2013 and 2016[1]. It is characterized by overwhelming sadness, loss of interest in activities, feelings of worthlessness, hopelessness, and often thoughts of death or suicide. Severe depression is thought to be a factor in more than half of all suicides[2], which is the 10th leading cause of death in the United States[3].

Depression is associated with biological as well as sociological factors. High-sensitivity C-reactive protein, or HSCRP, is a substance found in blood plasma that functions as an indicator of inflammation and is predictive of cardiovascular disease[5]. Previous studies have found mixed results[6,7] on whether it is associated with depression. We are interested in this possible association because it would provide incentive for further research into the relationship between depression and inflammation. Some common nutrients are also thought to be associated with depression[8], while others have been found to have little or no association[9]. Household size, particularly when defined as living alone, has been shown to be associated with depression in prior studies[4]. However, these studies usually only include elderly adults and do not examine specific household sizes.

This study will examine several predictors in an attempt to find an association with depression. The predictors involved are household size and HSCRP. We attempt to evaluate the role of household size across all adults in the United States and determine which particular household sizes are most protective against depression. We will also run preliminary analyses on several nutrients – chloride, iron, phosphorus, potassium, sodium, and calcium – to determine if

further investigation is warranted. Finally, depression is thought to vary by age[10], gender[10], BMI[11], and race[12], so these variables will be included to control for confounding.

2.0 Methods

2.1 Participants

The dataset comes from the 2017-2018 edition of NHANES (National Health and Nutrition Examination Survey) published online by the CDC. NHANES began in the 1960s to monitor the health of people of all ages in the United States. The selection process is made up of four stages and begins by grouping counties in the country into 15 different geographical categories and selecting a county from each category. Each county is further divided into census blocks or combinations of blocks, 20-24 of which are selected, and roughly 30 households within each group are chosen. In the fourth stage, one or more individuals from each household are chosen to take part in the study.

The first component of NHANES is a verbal interview, which every participant in the study takes part in. During this part of the study, the participants provide information such as occupation and medical history. After the interview comes the examination in the Mobile Examination Center (MEC) where the interviewers take bodily measures such as weight and blood pressure, as well as blood and urine samples with the patient's consent.

In order to protect confidentiality, the CDC does not include the true strata and primary sampling units in the NHANES dataset. Instead, they include masked variance units to approximate the true design variance estimates. It is recommended to take these masked variance units into account when performing analyses on NHANES data, along with sampling weights for each participant. The purpose of the weights is to inflate the sample to be more representative of the population being studied, which in the case of NHANES is the entire population of the United

States. The two weights offered by NHANES are WTINT2YR and WTMEC2YR. A value for WTINT2YR is assigned to every participant in NHANES, but WTMEC2YR is only assigned to participants who undergo the MEC portion of the survey.

The weights are calculated starting with the base weight, which is the reciprocal of an individual's probability of being selected. This base weight is then adjusted for nonresponse, which could be an individual choosing not to participate in the study whatsoever, or in the case of the MEC weight, an individual who participated in the interview but not the MEC portion. The third step is post-stratification, in which the weights are adjusted to add up to the population counts of various demographic groups.

2.2 PHQ-9

The outcome variable used in this study is based on the individual's PHQ-9 score. PHQ-9 is a series of 9 questions from the Patient Health Questionnaire (PHQ) used to assess depression. The specific questions that make up the questionnaire are shown in Figure 1. Photograph credits to Greenspace Health[15].

		Not at all	Several days	More than half the days	Nearly every day
1.	Little interest or pleasure in doing things	0	1	2	3
2.	Feeling down, depressed, or hopeless	0	1	2	3
3.	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4.	Feeling tired or having little energy	0	1	2	3
5.	Poor appetite or overeating	0	1	2	3
6.	Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7.	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8.	Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9.	Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Figure 1 Example PHQ-9

The overall score is calculated by summing up the responses to the 9 questions. A score of 10 or above generally indicates clinical depression[13].

2.3 Data Management

The particular NHANES files and variables used are detailed in Table 1.

Table 1 Files and Variables

File Name	Variables
BIOPRO_J	SEQN, LBXSCLSI, LBDSIRSI, LBDSPHSI, LBXSKSI, LBXSNASI, LBDSCASI
BMX_J	SEQN, BMXBMI
DEMO_J	SEQN, RIDAGEYR, RIDRETH3, RIAGENDR, WTMEC2YR, DMDHHSIZ, SDMVPSU, SDMVSTRA
DPQ_J	All except DPQ100
HSCRP_J	SEQN, LBXHSCRP

BIOPRO_J is the standard biochemistry profile. We were interested in blood levels of chloride, iron, phosphorus, potassium, sodium, and calcium, respectively corresponding to the variable names in Table 1. All nutrients are measured in millimoles per liter except for iron which is measured in micromoles per liter. SEQN is the participant's ID, which we used later on to merge the datasets into one.

BMX_J contains the individuals' body measures. We were only interested in BMI from this file.

DEMO_J includes the demographic variables. From this file, we made use of age, race, gender, sample weight, household size, primary sampling unit, and stratum. Because every person in the subset we are using participated in the MEC portion, we chose to use the MEC weights (WTMEC2YR) instead of the interview weights.

DPQ_J contains the responses to the individual PHQ-9 questions. We used every question except for DPQ100 ("difficulty these problems have caused") because it is not traditionally included in the score.

HSCRP_J contains the amount of HSCRP measured in milligrams per liter. This amount was standardized by subtracting the mean and dividing by the standard deviation in order to facilitate a more meaningful interpretation.

The overall survey includes 9,254 total participants but only 4,692 have data for all variables used in our analysis. This is largely because people of all ages are included in NHANES, but the mental health aspect of the survey is only conducted on participants who are at least 18 years of age. Therefore, the population of this analysis is United States residents who are at least 18 years of age.

The statistical software R was used for all data management and analysis. We began by importing the aforementioned files in Table 1 into separate datasets in R. We manually computed the individuals' PHQ-9 scores by adding up their responses to the individual questions. Individuals with missing data for any of the questions were excluded, along with those having a 7 or a 9 as a response because they correspond to "Refused" and "Don't know" respectively. In total, 58.2% of the participants who took part in the MEC had complete PHQ-9 data. Finally, we merged the separate datasets by SEQN, selecting only the variables mentioned in Table 1, and then removed any entries with missing values.

2.4 Analysis

As mentioned in Section 2.2, a PHQ-9 score of 10 or above has been shown to be a successful indicator of clinical depression[13]. We therefore used this value to classify individuals as depressed or not depressed (coded as 1 or 0 respectively in R) and treated the outcome as binary. Because the outcome is binary, we made use of logistic regression. The formula for logistic regression is as follows:

$$logit(P) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n$$

In the above equation, P represents the probability of being depressed, and the parameter β_0 is the constant. The interpretation of the remaining β parameters depends on the nature of the input. For instance, if x_1 is continuous, then β_1 is the log odds ratio of depression for a one-unit increase in x_1. If x_1 is a dummy variable for a categorical predictor, then β_1 is the log odds ratio of depression for the level associated with x_1 versus the reference level.

The **survey** package in R was used to create the weighted logistic models. The first step was to specify the survey design using the **svydesign** function. Because 8,704 participants in NHANES are assigned a value for WTMEC2YR, all 8,704 of these participants had to be included in the survey design object in order to use the weights properly, even though only 4,692 participants were included in the analysis. We set the **id** argument of **svydesign** to ~SDMVPSU (primary sampling unit), the **strata** argument to ~SDMVSTRA (stratum), the **weights** argument to ~WTMEC2YR, and the **nest** argument to true because the values of SDMVPSU are not unique. We then used the **subset** function to select only the 4,692 participants who had data for all the variables used in the analysis. Finally, we used the **svyglm** function to fit the model, with the **family** argument set to quasi-binomial() for logistic regression.

We first examined the dataset, looking at weighted distributions of demographic variables and descriptive statistics of continuous variables. We ran univariate models for the six dietary nutrients to determine which if any to add to the final model based on whether or not the nutrient was statistically significant in the univariate model. These univariate models included age, gender, and race to control for confounding. The final model consisted of household size and HSCRP from *a priori* interest, along with age, gender, race, and BMI as potential confounders. After fitting the final model, we examined the variance inflation factors (VIF) to check for collinearity.

3.0 Results

The sample was well-balanced between genders, with 51.26% of the unweighted sample and 51.53% of the weighted sample being female. In terms of the outcome, 8.38% of the weighted sample met the threshold for clinical depression. Figure 2 shows that over 50% of the weighted sample was contained in household sizes 2 and 3, while a household of 7 or more people had the lowest percentage at 3.34%. Because of this, sizes of 6 and 7+ were combined into a single category of 6+.

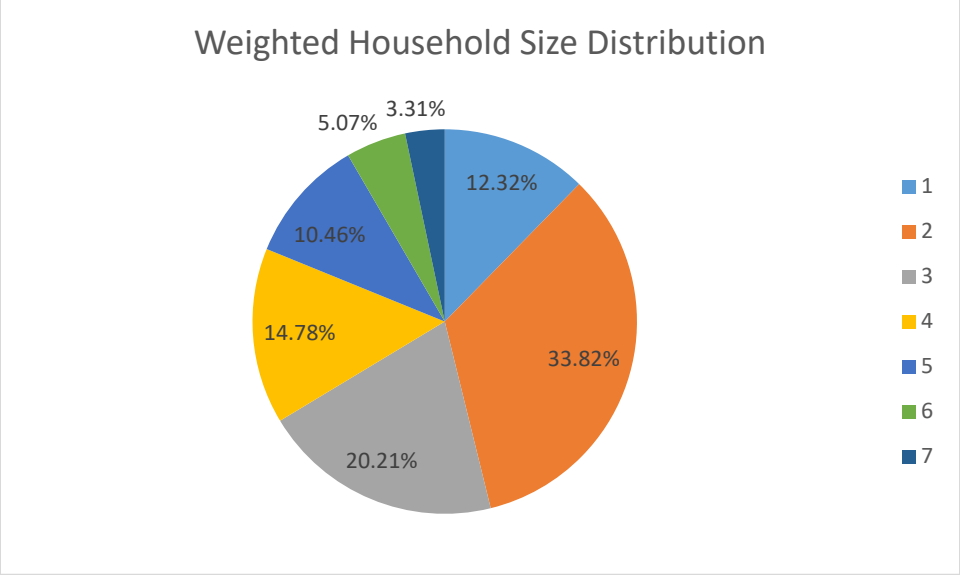

Figure 2 Household Size Distribution

Figure 3 shows the weighted prevalence of depression by household size. Interestingly, the prevalence was not monotonically increasing nor decreasing, as the largest and smallest households had the highest weighted percentage.

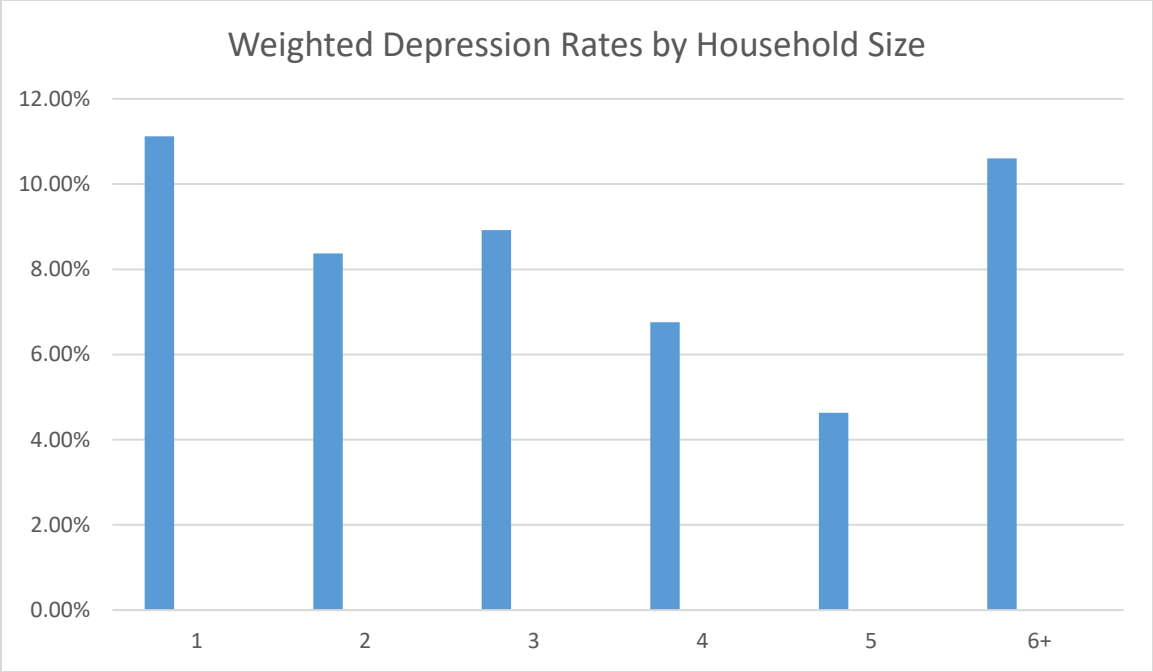

Figure 3 Depression by Household Size

Table 2 shows the descriptive statistics for all continuous variables. The nutrients with higher levels of concentration in the body tended to have higher standard deviations, which is not surprising because the percent difference from the mean decreases as the mean increases if the deviation is held constant. Additionally, the weights only had a slight effect on the means and medians because the weighted values were very close to the unweighted values.

Table 2 Descriptive Statistics for Continuous Variables

Variable	Mean	Weighted Mean	Standard Deviation	Minimum	Lower Quartile	Median	Weighted Median	Upper Quartile	Maximum
PHQ-9 Score	3.23	3.14	4.21	0	0	2	2	5	25
Age (years)	49.71	47.42	18.36	18	34	51	47	64	80
Chloride (mmol/L)	101.09	100.99	2.80	84	99	101	101	103	117
Iron (umol/L)	15.71	16.02	6.47	2.1	11.3	14.90	15.2	19.20	85.3
Phosphorus (mmol/L)	1.15	1.16	0.17	0.61	1.03	1.16	1.16	1.26	3.1
Potassium (mmol/L)	4.08	4.10	0.36	2.8	3.8	4.1	4.1	4.3	6.6
Sodium (mmol/L)	140.3	140.23	2.75	121	139	140	140	142	151
Calcium (mmol/L)	2.32	2.32	0.09	1.6	2.28	2.32	2.32	2.38	2.77
HSCRP (mg/L)	4.04	3.81	7.51	0.11	0.88	1.95	1.83	4.43	138.81
BMI (kg/m^2)	29.84	29.78	7.43	14.8	24.7	28.6	28.6	33.6	86.2

Every continuous variable was tested separately as a predictor for depression in univariate logistic models, and the results are listed in Table 3. Age, BMI, and standardized HSCRP were included only for the sake of completeness because they were included in the final model regardless of statistical significance. Because the six nutrients that were tested all had p-values above 0.05, none of them were added to the final model.

Table 3 Univariate Models

Nutrient	Coefficient	p-value
Chloride	-0.021	0.513
Iron	-0.024	0.079
Phosphorus	0.126	0.785
Potassium	-0.143	0.579
Sodium	-0.007	0.818
Calcium	-0.789	0.468
HSCRP	0.082	0.022*
BMI	0.016	0.097
Age	-0.005	0.242

Table 4 shows the results of the final model. Once again, the two main covariates of interest were household size and HSCRP. While every coefficient of household size was negative, statistical significance was found only in sizes of 4 and 5. An overall Wald test for all coefficients of household size resulted in a statistically significant p-value of less than 0.001. The coefficient for standardized HSCRP decreased from 0.082 in the univariate model to 0.068 and was no longer statistically significant.

Table 4 Final Model

Variable	Coefficient	Odds Ratio	p-value
Intercept	-2.267	--	<0.001*
Household Size = 2	-0.352	0.703	0.130
Household Size = 3	-0.419	0.658	0.078
Household Size = 4	-0.762	0.467	<0.001*
Household Size = 5	-1.104	0.332	0.003*
Household Size = 6+	-0.255	0.775	0.152*
HSCRP	0.068	1.070	0.053
Gender = Female	0.397	1.487	0.031*
Age	-0.010	0.990	0.051
BMI	0.014	1.014	0.162
Race – Other Hispanic	0.329	1.389	0.261
Race – Non-Hispanic White	0.067	1.069	0.842
Race – Non-Hispanic Black	0.067	1.069	0.791
Race – Non-Hispanic Asian	-0.398	0.671	0.141
Race – Other	0.909	2.483	0.039*

Because BMI is thought[7] to confound the relationship between HSCRP and depression, we refit the model without BMI and compared. When BMI was removed, the coefficient for standardized HSCRP increased to 0.087, which equates to an odds ratio of 1.09, and became statistically significant with a p-value of 0.013 (data not shown).

Table 5 shows the generalized variance inflation factors for the final model. The recommended approach[14] for interpreting these values is to adjust the GVIF by the degrees of freedom by raising the GVIF to the power of the reciprocal of the degrees of freedom times two. We can then square this adjusted GVIF and apply the regular VIF cutoff of 10. None of these squared values were above 10 so collinearity is not a concern.

Table 5 Generalized Variance Inflation Factors

Variable	GVIF	Degrees of Freedom (df)	GVIF adjusted by df	Adjusted GVIF squared
Household Size	102.665	5	1.589	2.525
HSCRP	8.541	1	2.922	8.541
Gender	3.816	1	1.953	3.816
Age	3.732	1	1.932	3.732
BMI	4.359	1	2.088	4.359
Race	150.223	5	1.651	2.725

4.0 Discussion and Conclusion

The main strength of this study is the inclusion of the sampling weights. The weight variable signifies the number of people in the United States who are represented by the particular individual. Because the sum of the weights of the participants in our subset is over 200 million, we can think of our results as coming from a sample of over 200 million people, which should equate to low sampling error, high statistical power, and good representation of the national population.

A major limitation of this study is that it is cross-sectional. Because all measurements are taken at the same time, there is no way to know which exposure preceded which outcome, and thus we cannot make any claims about causation.

The main predictors of interest in this study were household size and HSCRP. Because household size is a categorical variable with six levels, the model uses a household size of 1 as the reference group and compares it against the remaining five levels. We are able to say that household size has a statistically significant association with depression because the overall Wald test had a p-value of less than 0.001. Additionally, all five coefficients of household size were negative, which corroborates prior research that has found living alone to be associated with higher rates of depression[4]. Household sizes of 4 and 5 in particular had statistically significantly lower odds of depression than single-person households. From a public health standpoint, this finding may justify encouraging young people to cultivate romantic relationships that lead to cohabitation and childbearing.

While there is some literature to suggest that increased HSCRP is associated with depression[6], other studies found no such link when BMI was taken into account[7], which echoes

our findings. BMI acts as a confounder in this context because higher BMI is associated with increases in both depression (through body image issues) and HSCRP (through adipose tissue creating HSCRP). It should be noted that our results do not necessarily prove that there is no association between HSCRP and depression that is independent of BMI.

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