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Eeshwar Kaushik Chandrasekar Date

Glycemic Contributions to Depressive Outcomes:
National Health and Nutrition Examination Surveys, 2005-2012

By

Eeshwar Kaushik Chandrasekar
Master of Public Health

Global Epidemiology

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Glycemic Contributions to Depressive Outcomes: National Health and Nutrition Examination Surveys, 2005-2012

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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in Global Epidemiology
2015

Abstract

Glycemic Contributions to Depressive Outcomes:
National Health and Nutrition Examination Surveys, 2005-2012
By Eeshwar Kaushik Chandrasekar

To address limited national data exploring the factors that contribute to depressive outcomes among individuals with diabetes, we developed regression models to estimate the independent associations between glycemic categories (normal glycemia, prediabetes, diabetes) and depressive outcomes in the United States. We used data from 21,618 adults surveyed in the 2005-2012 National Health and Nutrition Examination Surveys, a nationally representative sample of non-institutionalized US civilians. Diabetes was classified based on self-reporting a physician diagnosis of diabetes or measured A1C $\geq$ 6.5% ($\geq$48mmol/mol). Individuals without a diagnosis of diabetes, but whose AIC was 5.7-6.4% (39 to 47mmol/mol) were classified as having pre-diabetes and those with AIC < 5.7% (<39mmol/mol) were classified as having normal glycemic status. We used the PHQ-9 screening questionnaire to determine prevalence and odds of 'Clinically Significant Depressive Symptoms' (CSDS) [PHQ-9 score $\geq$ 10 or antidepressant use] and 'Major Depressive Syndrome' [PHQ-9 score $\geq$12] (MDS). We calculated prevalence of CSDS and MDS standardized to the 2000 US census population, and used multivariate regression models to quantify the independent associations between glycemic categories and both depressive outcomes. The age standardized prevalence of CSDS in 2005-2008 was 15.2% [14.0-16.4], 15.9% [13.4-18.7], and 26.2% [21.2-31.9] for individuals with normal glycemia, pre-diabetes, and diabetes, respectively. For MDS, the age-standardized prevalence was 1.0% [0.7-1.3], 1.5% [0.9-2.5], and 2.6% [1.3-4.9] for the three glycemic groups, respectively. There were no significant changes in either CSDS or MDS prevalence between 2005-2008 and 2009-2012 in either crude or age-standardized estimates. While having diabetes was associated with two-fold higher odds of depressive outcomes in crude models, having diabetes was independently associated with a 25% greater odds of CSDS in adjusted models. The association between diabetes and depressive symptoms suggests a need to further integrate depression screening and treatment into routine diabetes management.

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Introduction

Diabetes mellitus is a growing health concern in the United States, affecting 29.1 million Americans [1]. A 2001 meta-analysis by Anderson et al, summarizing 20 cross-sectional reports, showed that depression affects upwards of 25% of patients with diabetes [2]. However, these estimates were derived from a small number of studies, of which many were not population based, and often times the study methodologies were inconsistent. Having comorbid diabetes and depression is associated with poorer adherence to diabetes medications and an increased risk for diabetes complications [3, 4]. Additionally, comorbid depression nearly doubles the risk of all-cause mortality in individuals with type 2 diabetes [5, 6]. Not only does comorbid diabetes and depression have negative health implications, but it also provides a tremendous strain on the healthcare system; individuals affected by both conditions experience double the healthcare costs compared to individuals with diabetes alone [7]. However, approximately two thirds of patients with both conditions are neither identified nor treated for depression [8].

There is conflicting evidence on the direction of the diabetes depression comorbidity. In nationally representative sample populations from England, Demakakos et al found that depressive symptoms, measured using the Center for Epidemiological Studies-Depression scale, were associated with a 60% higher risk of developing type 2 diabetes, even after accounting for sociodemographic, lifestyle, and clinical variables [9]. However, longitudinal studies from the US suggest the opposite direction, reporting that diabetes is associated with a 30% higher risk of developing depression in a cohort of female nurses [10]. While studies report an association between glycemic status and depression, few recent studies have considered this relationship in nationally representative samples

using the Patient Health Questionnaire-9 screening tool. Moreover, no studies, to our knowledge, have explored the independent associations of either diabetes or pre-diabetes, compared to people with normal glycemia, with depressive outcomes in a nationally representative sample of the United States. In this report, we analyze the associations of glycemic status with depressive outcomes in two independent cross-sectional waves of the National Health and Nutrition Examination Surveys.

Research Design and Methods

Data Sources:

Data for this analysis were compiled from the 2005-2012 National Health and Nutrition Examination Surveys (NHANES). This survey is a repeated cross-sectional survey representing the non-institutionalized civilian population of the United States. NHANES is conducted by the National Center for Health Statistics (NCHS) of the United States Centers for Disease Control and Prevention (CDC) in independent 2-year cycles. Data were collected through household surveys followed by physical examinations and interviews. Full survey details, including sampling designs, are published elsewhere [11]. For this analysis, we combined the 2005-2008 survey waves and the 2009-2012 survey waves in order to increase sample size and provide more reliable estimates when comparing our two time periods of interest [12]. Response rates were between 75 and 78 percent for all survey waves [13]. The un-weighted sample sizes (representing US civilian population in millions in parentheses) were 9,528 (191.9 million) and 10,132 (198.5 million) for the 2005-2008 and 2009-2012 time periods, respectively.

Definitions:

Outcomes

Depressive symptoms were assessed using the nine-item Patient Health Questionnaire (PHQ-9), a screening tool that ascertains frequency of depressive thoughts or behaviors in the previous 2 weeks. Each of the 9 questions are ranked from 1 to 3, with 3 being the maximum. Individuals scoring $\geq$ 10 or self-reporting use of antidepressants

were classified as having clinically significant depressive symptoms (CSDS). A score of ≥ 10 on the PHQ-9 has been shown to have 77% sensitivity and 94% specificity to the clinical diagnosis of major depression [14]. We also used a more stringent definition of 'Major Depressive Syndrome' (MDS) represented by responding 'More than half the days' to either of the first two questions of the PHQ-9 ["Little interest or pleasure in doing things" or "Feeling down, depressed, or hopeless in, doing things"] and at least five of the remaining seven questions (composite score ≥ 12).

Exposures

To categorize glycemic status, we combined self-reported diagnosis with A1C levels. Individuals were classified as having diabetes if they answered "yes" to the question "Have you ever been told by a doctor that you have diabetes or sugar diabetes" or if their A1C ≥ 6.5% (≥48mmol/mol). Individuals not reporting a diagnosis of diabetes with AIC 5.7 – 6.4% (39 to 47mmol/mol) were classified as having pre-diabetes and those with AIC < 5.7 (<39mmol/mol) were classified as having normal glycemic status.

Other covariates

We included a series of variables in our analysis in order to control for confounding. Sociodemographic variables included age (18-44, 45-64, and ≥ 65 years), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican-American, and Other), gender, poverty to income ratio (PIR: ratio of family income to federal poverty thresholds, specific to family size, state, and year), and education (< High School vs ≥ High School). Clinical variables considered in this analysis were obesity (BMI ≥ 30kg/m^2) and history of

cardiovascular disease (defined as self-reported history of stroke, myocardial infarction, coronary heart disease, or congestive heart failure). Behavioral variables included self-reported smoking (currently smoking and smoked at least 100 cigarettes in lifetime vs not) and heavy alcohol consumption (≥ 15 drinks per week for males or ≥ 8 drinks per week for females). Finally, access variables included health insurance, number of hospital visits in the past 12 months (0, 1-3, 4+ visits), and usual place of care (yes vs no usual place of care).

Statistical Analysis:

We described the social, demographic, and clinical characteristics of individuals in each glycemic category for the 2005-2008 and 2009-2012 sample populations. Initial comparisons of descriptive covariates by survey wave were assessed using Wald F tests. Differences in distributions of covariates between glycemic groups provided justification to control for these covariates in multivariate adjusted analyses. We calculated prevalence estimates age-standardized to the 2000 US census population and compared differences between 2005-2008 and 2009-2012 using a T-test. To examine independent associations of glycemic status with depressive outcomes, a multivariable logistic regression model was used to compute adjusted odds ratios of CSDS and MDS for 2005-2008 and 2009-2012. We fit three nested regression models: unadjusted, adjusted for sociodemographic variables, and additional adjustment for clinical, behavior, and access variables.

We used SAS-callable Sudaan 11.0.1 software (RTI International, Research Triangle Park, NC) to account for complex multistage sampling and to produce weighted

estimates. All reported confidence intervals are 95% confidence intervals, unless otherwise noted. P values <0.05 were considered statistically significant.

Results

Table 1 describes selected characteristics for the US population aged 18 and older for each time period stratified by glycemic status. Consistent with previous research, our samples show that persons with diabetes were older, more likely to be Non-Hispanic Black, Mexican-American, or Other Race, and have less than a high school education. Moreover, individuals with diabetes generally had lower income, were more likely to be obese, and a greater proportion of them had a history of cardiovascular disease. In both time periods, we observed individuals with diabetes reporting lower levels of self-reported smoking and heavy alcohol use. Nearly two thirds of persons with diabetes had four or more healthcare visits in the past year, compared to less than one-third among individuals with normal glycemic status. Finally, more individuals with diabetes reported having a place of care than other glycemic groups.

Appendix Table 1A compares characteristics of each glycemic group between 2005-2008 and 2009-2012. In the total population, there was no change in age, gender, or education distributions between 2005-2008 and 2009-2012; however, PIR decreased in the PIR ≥ 3 category from 51.1% to 48.3% and increased in the PIR < 1 category from 13.0% to 16.4% ($p=0.02$), suggesting an overall decrease in income. Self-reported smoking also decreased significantly from 23.6% in 2005-2008 to 20.0% in 2009-2012 ($p<0.01$). The only significant change among individuals with normal glycemic status was a decline in self-reported smoking, from 24.2% to 19.6% ($p<0.01$). Among individuals with pre-diabetes, the percentage of individuals falling in the PIR < 1.0 category increased from 12.0% to 15.6% ($p=0.03$). Additionally, access to healthcare declined, as the percentage of individuals with health insurance dropped from 84.6% to 79.7% ($p<0.01$) and the percent

of individuals reporting no usual place of care increased from 10.4% to 13.1% (p=0.05). Among individuals with diabetes, the percentage of persons having a history of cardiovascular disease decreased from 26.2% in 2005-2008 to 22.2% in 2009-2012 (p=0.05).

Figure 1A shows the age-standardized prevalence of CSDS for the US population aged 18 and older. In 2005-2008, the prevalence of CSDS was 15.2% [14.0-16.4], 15.9% [13.4-18.7], and 26.2% [21.2-31.9] for individuals with normal glycemic status, pre-diabetes, and diabetes, respectively. These estimates stayed relatively constant in 2009-2012 wave, with prevalence of 16.2% [14.7-17.9], 17.7% [15.5-20.3], and 25.5% [21.7-29.6] for the three glycemic groups.

Figure 1B shows the age-standardized prevalence of MDS. In 2005-2008, the prevalence of MDS was 1.0% [0.7-1.3], 1.3% [0.8-2.2], and 1.5% [1.0-2.2] for the normal, pre-diabetes, and diabetes glycemic groups. These estimates increased slightly to 1.2% [0.9-1.5], 2.1% [1.3-3.2], and 3.4% [2.0-5.6]; however, none of the changes for either depressive outcome were significant between 2005-2008 and 2009-2012 for any glycemic group in either crude or age-standardized estimates.

Table 2 shows adjusted odds ratios for CSDS. The association between pre-diabetes and CSDS was not significantly different from the relationship between normal glycemic status and CSDS in either time period. In models that only considered glycemic status, the odds of CSDS were 1.93 [1.64-2.26] times greater and 1.72 [1.39 – 2.13] times greater for individuals with diabetes than people with normal glycemic status in 2005-2008 and 2009-2012. After controlling for sociodemographic variables, individuals with diabetes had 1.86 [1.54-2.25] and 1.65 [1.32 – 2.08] times greater odds of CSDS than individuals with normal

glycemic status for 2005-2008 and 2009-2012, respectively. In both time periods, individuals aged 45-64 had higher odds of CSDS, at 1.64 [1.46-1.86] times and 1.44 [1.16-1.79] times that of individuals in the 18-44 age group, respectively. Gender had the strongest association with CSDS in this model; women had twice the odds of reporting CSDS compared to males in both periods. Interestingly, Non-Hispanic Blacks, Mexican-Americans, and Other Race categories all had a significantly lower odds of having CSDS compared to non-Hispanic Whites. While education was not associated with CSDS, PIR showed a consistent inverse association with the odds of CSDS. Compared to their highest-income peers, individuals in the lowest income group had more than double the odds of CSDS.

The fully adjusted models, controlling for sociodemographic, clinical, behavior, and access variables, were inconsistent between the two waves. Adjusted for all other factors, persons with diabetes had a 1.25 [1.02-1.54] times higher odds of CSDS than individuals with normal glycemic status in the first wave; however, this stronger association was not statistically evident in the 2009-2012 time period. While there was a higher odds of CSDS among individuals aged 45-64 in both time periods, individuals in the oldest age group had significantly lower odds of CSDS in 2005-2008. Race/ethnicity and PIR showed nearly identical associations with CSDS to the previous model, with non-Hispanic Whites and the lowest PIR group experiencing nearly twice the odds of CSDS compared to other racial/ethnic groups and the wealthiest PIR category in both time periods. Obesity and history of cardiovascular disease were associated with higher odds of CSDS in both time periods. While smoking was associated with 50% higher odds of CSDS in both waves, heavy alcohol use was not related to CSDS in both waves. Number of

healthcare visits in the past year showed the strongest association with odds of CSDS, with individuals having 4+ healthcare visits in the previous year having 5.34 [3.74-7.64] and 3.50 [2.63-4.67] times greater odds for the two waves, respectively.

Table 3 shows unadjusted and adjusted relationships between glycemic status and MDS. Estimates varied greatly between the two time periods. Having diabetes was associated with a two-fold higher odds of MDS in the crude model in 2009-2012, but was insignificant with addition of covariates in all other models. Like CSDS, we found much lower odds of MDS among the oldest age group after sociodemographic variables were included in 2005-2008. Mexican Americans and Other races had a significantly lower odds of developing MDS compared to non-Hispanic Whites in 2005-2008, but not in 2009-2012. The associations with PIR were much more pronounced for MDS than CSDS. Individuals in the lowest PIR category (living below the poverty level) had 9.95 [4.68 – 21.168] and 8.17 [4.32 – 15.26] greater odds of MDS than individuals with PIR $\geq$ 3.

In the fully adjusted models, individuals aged 65+ had 80% lower odds of MDS compared to individuals aged 18-44. Females had more than double the odds of MDS than males in 2005-2008, but the estimate ceased to be significant in 2009-2012. PIR continued to have a strong association with MDS. Individuals in the lowest income groups had 6.34 [2.76-14.57] and 8.11 [4.35-15.10] times the odds of MDS compared to individuals in the highest income group for the two years, respectively. The association with obesity was only significant in the second time period; however, history of cardiovascular disease was associated with more than double the odds of MDS in both time periods. As observed for CSDS, the odds of MDS among individuals with 4+ healthcare visits in the past year was 5.24 [2.35 – 11.66] times greater than individuals who had 0 visits.

Conclusion

As diabetes rates continue to grow in the United States, the number of individuals with comorbid depression is of growing concern. Our age-standardized prevalence estimates were consistent with findings by Roy and Lloyd, that the prevalence of depressive symptoms were roughly twice as high among individuals with diabetes compared with normal glycemic status [15]. While their analysis was systematic, they did not explore the independent associations of glycemic status after controlling for covariates. Using a sample representing U.S. civilians, we found that having diabetes is associated with a nearly two-fold higher odds of CSDS in unadjusted models of two independent samples. Our odds ratio estimate is consistent with the 2001 meta-analysis by Anderson et al., suggesting that the odds of depressive symptoms among individuals with diabetes compared to normal glycemic status has stayed relatively constant in the past decade [2]. In fully adjusted models, we found that having diabetes was associated with a 25% higher odds of CSDS. Our data regarding associations between glycemic status and MDS were conflicting in our two time periods, with one period suggesting no difference and the other suggesting a two-fold higher odds. To our knowledge, this is the first study using a nationally representative sample to examine the individual contribution of glycemic status to depressive outcomes. Additionally, our analysis identified demographic subgroups that may benefit from integrated care programs to screen for and manage both diabetes and depressive symptoms.

Our analysis controlled for many variables confounding the relationship between glycemic status and depressive outcomes. While number of hospital visits in the past year provided consistently large odds ratios, it is difficult to disentangle the directionality of this

association. It may be that individuals who have depressive symptoms seek medical services as a means of coping; however, individuals attending hospitals due to recurrent illnesses may also become more depressed. More pronounced in this analysis was the association of PIR with MDS, even in fully adjusted models. The relationship between income and mental health has been well studied, with a recent estimates by Sareen et al showing the OR of individuals with household income less than $19,999 associated with 1.44 times greater odds of major depression compared to those with income greater than $70,000 [16]. The association in our analysis was more pronounced, with odds of MDS being 6 and 8 times higher for individuals in the lowest PIR group compared to the highest in 2005-2008 and 2009-2012, respectively. Given the frequency of NHANES survey collection, our analysis falls just around the 'Great Recession of 2008', the second greatest economic recession in the United States. Though historical trends in the US suggest that suicides, an extreme depressive outcome, increased during times of economic recession, our results suggest that the prevalence of depressive symptoms did not change meaningfully in the general US population, in either crude or age-standardized estimates between 2005-2008 and 2009-2012 [17]. Our descriptive characteristics show some signs of the recession, including lower reported income as well as health access in the second wave, which was most prominent in individuals with pre-diabetes [Table 1A]. The higher odds of MDS, 6.3 in 2005-2008 and 8.1 in 2009-2012, for PIR in adjusted models could be due, in part, to additional financial strain from the economic recession; however, further studies should explore this interplay accounting for additional variables (e.g., employment status) that more adequately capture the economic recession in nationally representative data.

While many subgroups were affected by depressive outcomes, the odds of CSDS and MDS were especially worrisome among individuals with history of cardiovascular conditions and among women, each associated with nearly a two-fold higher odds of depressive outcomes. Individuals with one chronic condition are more likely to develop other conditions, which is associated with even higher odds of experiencing depressive outcomes [18]. The finding among women is of particular concern since studies suggest children of severely depressed mothers have 2.5 times the risk of becoming depressed themselves [19]. While the literature suggests crude odds of depression is greater among Non-Hispanic Blacks and Mexican Americans, our findings suggested that these race/ethnicity groups are associated with a 40-50% lower odds of depression after accounting for glycemic status, sociodemographic, clinical, behavior, and access variables. Our estimates are consistent with findings from Dunlop et al, but we provide a more accurate assessment of health care utilization since we included number of healthcare visits in our multivariate analyses [20]. Targeted screening and counseling for depressive symptoms in these high risk populations could help identify and address undiagnosed cases of CSDS and MDS.

Our study findings must be accepted in light of several limitations. First, the NHANES is a repeated cross-sectional study, meaning we do not have longitudinal data at the individual level. This limits our ability to observe individual level changes and directionality of our covariates in relation to their effect on glycemic status and depressive outcomes. For example, while we identified a strong association between PIR and depressive outcomes, we could not discern which factor preceded the other. Second, while we attempted to control for a variety of covariates, our analysis could not consider all of

the covariates associated with the exposure and outcome, given the complex and multifactorial onset of depressive symptoms [Figure 2, Figure 3]. For example, our analysis did not include awareness of diabetes, which Mezuk et al. found to be associated with 4.3-times greater odds of depression [21]. Finally, our selection of variables allows for potential collinearity since there may be assocations between covariates. It is plausible that number of health care visits is correlated with history of cardiovascular conditions, which could have led to inaccurate estimates for the odds-ratios of both covariates.

However, our study also had several strengths. A major strength of this study is that NHANES is a large, nationally representative sample of the US non-institutionalized population, reducing the chance of selection bias. Moreover, protocols and measures of assessment followed a standardized protocol during all survey waves which allowed for appropriate comparisons between our survey waves. Finally, our measures of exposures and depressive outcomes were from objectively collected data, increasing the validity of measurements in this analysis,

In summary, our results show the individual contribution of glycemic status in nationally representative samples of the US. While having diabetes was associated with a two-fold higher odds of depressive outcomes in crude models, other factors may mediate the odds of depressive symptoms too as fully adjusted models showed that independent of all these other factors, diabetes status was associated with a 25% higher odds of CSDS. Improved screening for depression among individuals with diabetes and high risk populations, including women and individuals with multiple chronic conditions, could help identify and address cases of CSDS and MDS that may otherwise be undiagnosed. The

association between diabetes and depressive symptoms suggests a need to further integrate depression screening and treatment into routine diabetes management.

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E.K.C, M.K.A, and K.M.B developed the study concept. E.K.C. conducted the statistical analyses and wrote the manuscript. M.K.A., K.M.B., and K.M.V.N. guided the analysis and edited the manuscript. E.K.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the analysis.

Table 1 - Selected characteristics by Glycemic Status in US adults aged 18 and older, NHANES 2005-2012

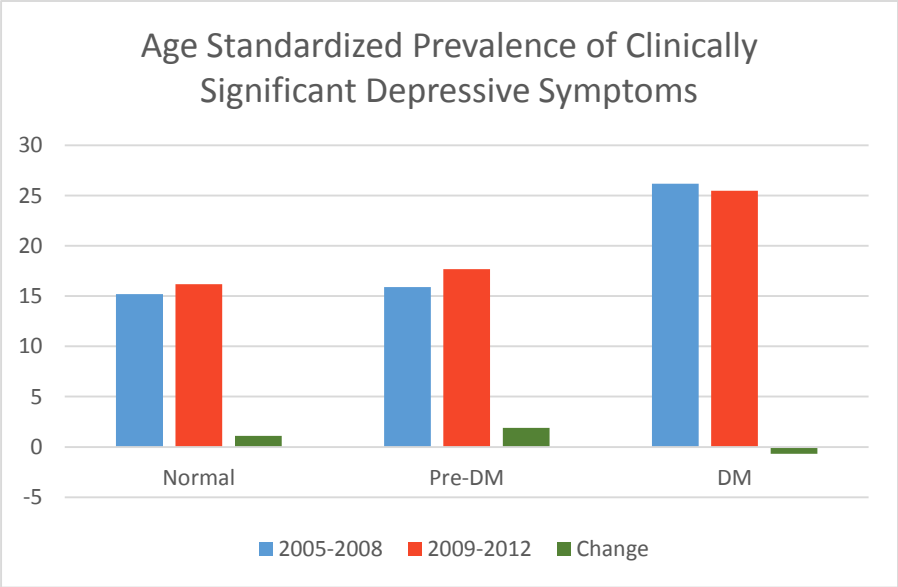
	2005-2008				2009-2012			
Glycemic Status	Normal	Pre-Diabetes	Diabetes	p-value	Normal	Pre-Diabetes	Diabetes	p-value
Age group (years), %				**0.00**				**0.00**
18-44	59.6 (1.2)	22.9 (1.6)	15.6 (1.6)		60.9 (1.5)	27.2 (1.2)	15.5 (1.3)	
45-64	30.6 (1.0)	47.7 (1.5)	48.4 (1.4)		30.3 (1.1)	45.9 (1.3)	48.6 (1.3)	
65+	9.8 (0.7)	29.4 (1.5)	36.0 (1.5)		8.8 (0.6)	26.9 (1.4)	35.9 (1.3)	
Female, %	51.7 (1.5)	51.0 (1.4)	51.8 (1.8)	0.87	51.6 (0.6)	52.9 (1.0)	47.1 (1.0)	0.10
Race/ethnicity, %				**0.00**				**0.00**
Non-Hispanic White	72.0 (2.1)	65.1 (3.2)	61.7 (3.9)		69.0 (2.5)	62.4 (3.1)	56.9 (3.1)	
Non-Hispanic Black	9.3 (1.2)	16.8 (2.2)	18.8 (2.2)		9.4 (1.1)	15.6 (1.9)	17.3 (2.2)	
Mexican American	13.2 (1.2)	11.8 (1.4)	13.6 (1.8)		14.6 (1.8)	14.6 (2.0)	16.3 (2.8)	
Other	5.5 (0.6)	6.4 (1.1)	5.9 (1.2)		7.0 (0.7)	7.5 (1.0)	9.5 (1.3)	
Education (< HS), %	16.5 (1.1)	23.1 (1.5)	29.3 (1.6)	**0.00**	14.3 (1.0)	22.3 (1.3)	28.3 (1.9)	**0.00**
PIR, %				**0.00**				**0.00**
<1.0	13.7 (0.8)	12.4 (1.0)	15.4 (1.5)		16.7 (1.3)	16.0 (1.0)	18.9 (1.7)	
1.0-2.9	34.0 (1.4)	41.1 (2.2)	45.7 (1.9)		33.6 (1.2)	39.1 (1.9)	43.7 (1.8)	
>=3.0	52.3 (1.8)	46.5 (2.4)	38.9 (2.3)		49.7 (1.7)	44.9 (2.2)	37.4 (2.2)	
Obese (BMI >= 30), %	25.1 (0.9)	45.0 (1.4)	60.0 (1.7)	**0.00**	25.9 (0.9)	41.5 (1.8)	63.9 (1.9)	**0.00**
History of Cardiovascular Disease*, %	4.7 (0.4)	12.1 (0.9)	26.2 (1.4)	**0.00**	4.1 (0.3)	11.1 (1.0)	22.2 (1.4)	**0.00**
Self Reported Smoking, %	23.8 (1.0)	24.4 (1.5)	17.8 (1.4)	**0.01**	19.5 (0.9)	22.6 (1.4)	17.1 (1.0)	**0.00**
Heavy Alcohol use, %	9.7 (0.6)	6.0 (0.9)	4.0 (0.7)	**0.00**	10.8 (0.6)	6.0 (0.6)	5.5 (0.7)	**0.00**
Health Insurance, %	80.3 (1.1)	84.8 (1.1)	87.5 (1.2)	**0.00**	80.5 (1.0)	80.0 (1.0)	84.7 (1.1)	**0.00**
Number of helathcare visits in past year, %				**0.00**				**0.00**
0	18.0 (0.6)	12.8 (1.0)	5.8 (0.9)		17.1 (0.7)	13.6 (1.0)	7.5 (1.2)	
1 to 3	49.5 (0.6)	44.4 (1.5)	28.6 (1.6)		50.9 (0.6)	47.9 (1.2)	28.5 (1.7)	
4+	32.5 (0.7)	42.9 (1.3)	65.6 (1.8)		32.0 (0.6)	38.5 (1.5)	64.0 (1.3)	
No usual place of care, %	15.9 (0.8)	10.5 (0.9)	5.1 (0.9)	**0.00**	15.2 (0.7)	12.8 (1.0)	6.7 (1.0)	**0.00**

Data presented are weighted percentages (standard error) unless otherwise noted. P-values were calculated from a Wald F Test at significance level of 0.05.

* History of congestive heart failure, coronary heart disease, heart attack, or stroke.

Figure 1. Prevalence of Depressive Outcomes by Glycemic Category Standardized to 2000 US Census

A) Clinically Significant Depressive Symptoms



B) Major Depressive Syndrome

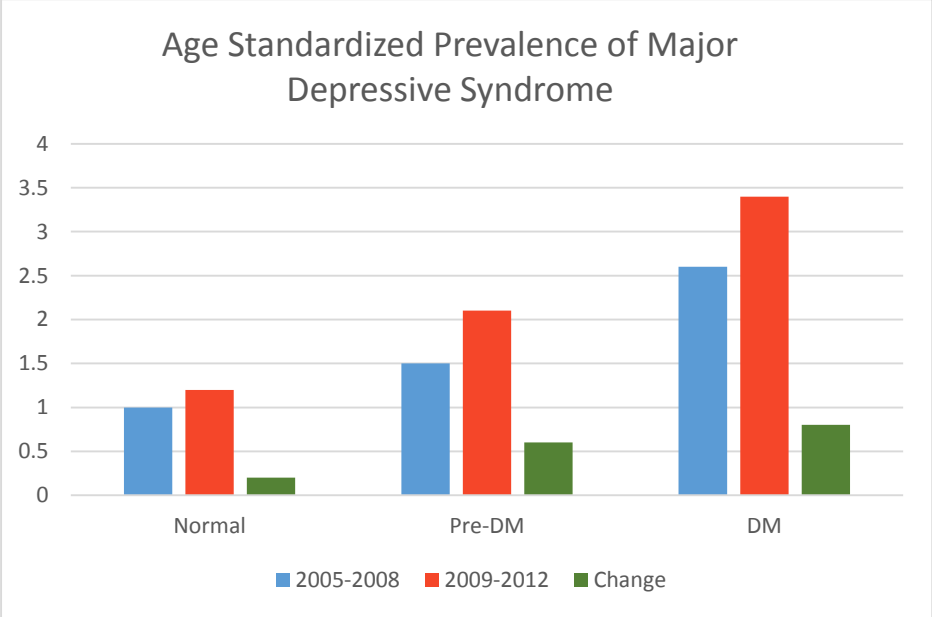


Table 2. Adjusted Odds Ratios for CSDS associated with Glycemic Status and Other Factors

	2005-2008						2009-2012					
	Model 1	P	Model 2	P	Model 3	P	Model 1	P	Model 2	P	Model 3	P
Glycemic status (Ref=Normal)		**0.00**		**0.00**		**0.00**		**0.00**		**0.00**		0.76
PreDM	1.07 (0.91-1.26)		1.05 (0.89-1.24)		0.88 (0.74-1.05)		1.16 (0.97-1.39)		1.11 (0.92-1.35)		0.96 (0.79-1.18)	
DM	1.93 (1.64-2.26)		1.86 (1.54-2.25)		1.25 (1.02-1.54)		1.72 (1.39-2.13)		1.65 (1.32-2.08)		1.08 (0.85-1.37)	
Sociodemographic												
Age (Ref=18-44 years)				**0.00**		**0.00**				**0.00**		**0.00**
45-64			1.64 (1.46-1.86)		1.49 (1.30-1.71)				1.44 (1.16-1.79)		1.40 (1.11-1.76)	
65+			0.94 (0.75-1.18)		0.67 (0.52-0.87)				0.98 (0.82-1.18)		0.84 (0.67-1.04)	
Gender (Ref=Male)				**0.00**		**0.00**				**0.00**		**0.00**
Female			2.48 (2.16-2.86)		2.15 (1.84-2.50)				2.05 (1.79-2.36)		1.86 (1.58-2.18)	
Race/Ethnicity (Ref=Non-Hispanic White)				**0.00**		**0.00**				**0.00**		**0.00**
Non-Hispanic Black			0.46 (0.37-0.56)		0.49 (0.39-0.61)				0.56 (0.47-0.66)		0.54 (0.45-0.66)	
Mexican American			0.49 (0.40-0.61)		0.65 (0.52-0.80)				0.50 (0.41-0.61)		0.63 (0.51-0.77)	
Other			0.40 (0.25-0.65)		0.42 (0.26-0.69)				0.44 (0.34-0.58)		0.52 (0.38-0.71)	
Education (Ref= < HS)				0.08		0.12				0.10		0.30
≥ HS			0.83 (0.66-1.03)		0.83 (0.65-1.05)				0.83 (0.67-1.04)		0.89 (0.71-1.12)	
PIR (Ref = ≥ 3.0)				**0.00**		**0.00**				**0.00**		**0.01**
< 1.0			2.22 (1.87-2.63)		2.07 (1.74-2.47)				2.32 (1.84-2.92)		1.98 (1.59-2.47)	
1.0-2.9			1.55 (1.35-1.79)		1.54 (1.34-1.78)				1.57 (1.20-2.04)		1.49 (1.17-1.89)	
Clinical												
Obesity (Ref=Not Obese)						**0.03**						**0.00**
Obese					1.22 (1.02-1.46)						1.50 (1.24-1.81)	
Cardivascular conditions (Ref=None)						**0.00**						**0.00**
History Cardiovascular Disease					1.58 (1.35-1.86)						1.59 (1.26-2.01)	
Behaviors												
Current Smoking (Ref=Not)						**0.00**						**0.00**
Currently Smoking					1.56 (1.29-1.89)						1.85 (1.54-2.24)	
Heavy Alcohol (Ref= No)						0.13						0.28
Yes					1.27 (0.93-1.72)						1.18 (0.87-1.60)	
Access												
Health Insurance (Ref=Insurance)						0.85						0.40
No Insurance					1.02 (0.83-1.25)						0.91 (0.72-1.14)	
Number helathcare visits in past year (Ref=0)						**0.00**						**0.00**
1-3					2.21 (1.60-3.04)						1.78 (1.32-2.39)	
4+					5.34 (3.74-7.64)						3.50 (2.63-4.67)	
Place of Care (Ref=Has Place of Care)						0.13						**0.04**
No Usual Place of Care					0.77 (0.55-1.08)						0.74 (0.55-0.99)	

P Values Calculated from Wald F-Tests at significance level of 0.05.

Table 3. Adjusted Odds Ratios for MDS associated with Glycemic Status and Other Factors

	2005-2008						2009-2012					
	Model 1	P	Model 2	P	Model 3	P	Model 1	P	Model 2	P	Model 3	P
Glycemic status (Ref=Normal)		0.29		0.80		0.35		**0.01**		0.09		0.81
PreDM	1.32 (0.75-2.34)		1.27 (0.63-2.56)		1.06 (0.52-2.16)		1.42 (0.83-2.40)		1.32 (0.71-2.46)		1.21 (0.67-2.21)	
DM	1.50 (0.88-2.59)		1.15 (0.58-2.28)		0.63 (0.30-1.34)		2.19 (1.39-3.46)		1.84 (1.06-3.18)		1.04 (0.57-1.88)	
Sociodemographic												
Age (Ref=18-44 years)				**0.00**		**0.00**				**0.00**		**0.00**
45-64			1.62 (0.90-2.93)		1.36 (0.73-2.55)				1.51 (0.99-2.32)		1.30 (0.81-2.07)	
65+			0.21 (0.06-0.71)		0.16 (0.04-0.63)				0.27 (0.11-0.65)		0.19 (0.07-0.48)	
Gender (Ref=Male)				**0.00**		**0.00**				0.14		0.56
Female			2.86 (1.56-4.41)		2.39 (1.45-3.95)				1.30 (0.91-1.86)		1.13 (0.75-1.71)	
Race/Ethnicity (Ref=Non-Hispanic White)				**0.04**		0.22				0.19		0.93
Non-Hispanic Black			1.06 (0.56-2.01)		1.27 (0.69-2.36)				1.10 (0.75-1.62)		1.07 (0.72-1.59)	
Mexican American			0.63 (0.27-0.49)		1.04 (0.49-2.21)				0.71 (0.45-1.13)		0.95 (0.59-1.53)	
Other			0.21 (0.05-0.89)		0.27 (0.07-1.12)				0.63 (0.27-1.46)		0.86 (0.41-1.78)	
Education (Ref= < HS)				0.34		0.42				0.10		0.14
≥ HS			0.78 (0.46-1.32)		0.81 (0.48-1.36)				0.57 (0.29-1.12)		0.60 (0.30-1.12)	
PIR (Ref = ≥ 3.0)				**0.00**		**0.00**				**0.00**		**0.00**
< 1.0			9.95 (4.68-21.17)		6.34 (2.76-14.57)				8.17 (4.32-15.26)		8.11 (4.35-15.10)	
1.0-2.9			5.75 (2.79-11.86)		4.81 (2.34-9.89)				3.55 (1.92-6.54)		3.82 (2.00-7.28)	
Clinical												
Obesity (Ref=Not Obese)						0.43						**0.00**
Obese					1.22 (0.74-1.99)						2.27 (1.52-3.39)	
Cardiovascular conditions (Ref=None)						**0.02**						**0.00**
History Cardiovascular Disease					2.38 (1.19-4.75)						2.07 (1.29-3.32)	
Behaviors												
Current Smoking (Ref=Not)						**0.00**						0.23
Currently Smoking					2.70 (1.79-4.08)						1.21 (0.89-1.65)	
Heavy Alcohol (Ref= No)						0.30						**0.02**
Yes					0.63 (0.26-1.52)						2.01 (1.10-3.68)	
Access												
Health Insurance (Ref=Insurance)						0.56						0.28
No Insurance					0.86 (0.51-1.45)						1.22 (0.85-1.74)	
Number helathcare visits in past year (Ref=0)						**0.00**						**0.00**
1 to 3					1.17 (0.61-2.25)						0.64 (0.23-1.76)	
4+					5.24 (2.35-11.66)						1.40 (0.47-4.15)	
Place of Care (Ref=Has Place of Care)						0.52						**0.04**
No Usual Place of Care					0.76 (0.32-1.78)						0.46 (0.22-0.95)	

P Values Calculated from Wald F-Tests at significance level of 0.05.

References

1. Centers for Disease Control and Prevention, *National Diabetes Statistics Report, 2014*. 2014, Department of Health and Human Services: Atlanta, GA, USA.
2. Anderson, R.J., et al., *The prevalence of comorbid depression in adults with diabetes: a meta-analysis.* Diabetes Care, 2001. **24**(6): p. 1069-78.
3. Lin, E.H., et al., *Relationship of depression and diabetes self-care, medication adherence, and preventive care.* Diabetes Care, 2004. **27**(9): p. 2154-60.
4. de Groot, M., et al., *Association of depression and diabetes complications: a meta-analysis.* Psychosom Med, 2001. **63**(4): p. 619-30.
5. Sullivan, M.D., et al., *Depression predicts all-cause mortality: epidemiological evaluation from the ACCORD HRQL substudy.* Diabetes Care, 2012. **35**(8): p. 1708-15.
6. Egede, L.E., P.J. Nietert, and D. Zheng, *Depression and all-cause and coronary heart disease mortality among adults with and without diabetes.* Diabetes Care, 2005. **28**(6): p. 1339-45.
7. Ciechanowski, P.S., W.J. Katon, and J.E. Russo, *Depression and diabetes: impact of depressive symptoms on adherence, function, and costs.* Arch Intern Med, 2000. **160**(21): p. 3278-85.
8. Katon, W.J., *The comorbidity of diabetes mellitus and depression.* Am J Med, 2008. **121**(11 Suppl 2): p. S8-15.
9. Demakakos, P., M.B. Pierce, and R. Hardy, *Depressive symptoms and risk of type 2 diabetes in a national sample of middle-aged and older adults: the English longitudinal study of aging.* Diabetes Care, 2010. **33**(4): p. 792-7.
10. Pan, A., et al., *Bidirectional association between depression and type 2 diabetes mellitus in women.* Arch Intern Med, 2010. **170**(21): p. 1884-91.
11. Centers for Disease Control and Prevention. *National Health and Nutrition Examination Surveys*. 2014; Available from: http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm.
12. Centers for Disease Control and Prevention. *Analytic Note Regarding 2007-2010 Survey Design Changes and Combining Data Across other Survey Cycles*. Available from: http://www.cdc.gov/nchs/data/nhanes/analyticnote_2007-2010.pdf.
13. Centers for Disease Control and Prevention. *NHANES Response Rates and Population Tools*. 2013; Available from: http://www.cdc.gov/nchs/nhanes/response_rates_cps.htm.
14. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure.* J Gen Intern Med, 2001. **16**(9): p. 606-13.
15. Roy, T. and C.E. Lloyd, *Epidemiology of depression and diabetes: a systematic review.* J Affect Disord, 2012. **142 Suppl**: p. S8-21.
16. Sareen, J., et al., *Relationship between household income and mental disorders: findings from a population-based longitudinal study.* Arch Gen Psychiatry, 2011. **68**(4): p. 419-27.
17. Luo, F., et al., *Impact of business cycles on US suicide rates, 1928-2007.* Am J Public Health, 2011. **101**(6): p. 1139-46.
18. Schellevis, F.G., et al., *Comorbidity of chronic diseases in general practice.* J Clin Epidemiol, 1993. **46**(5): p. 469-73.
19. Hammen, C., et al., *Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder.* Arch Gen Psychiatry, 1990. **47**(12): p. 1112-7.
20. Dunlop, D.D., et al., *Racial/ethnic differences in rates of depression among preretirement adults.* Am J Public Health, 2003. **93**(11): p. 1945-52.

21. Mezuk, B., et al., *Is ignorance bliss? Depression, antidepressants, and the diagnosis of prediabetes and type 2 diabetes.* Health Psychol, 2013. **32**(3): p. 254-63.

Table 1A - Selected characteristics by Glycemic Status in US adults aged 18 and older, NHANES 2005-2012

	Normal Glycemic			Pre-Diabetes			Diabetes		
Survey Cycle	2005-2008	2009-2012		2005-2008	2009-2012		2005-2008	2009-2012	
(Population size in millions)	(149.8)	(144.4)	p-value	(34.9)	(49.0)	p-value	(21.5)	(24.5)	p-value
Age group (years), %			0.52			0.11			0.99
18-44	58.8 (1.2)	60.3 (1.5)		22.7 (1.6)	27.0 (1.2)		15.4 (1.6)	15.5 (1.3)	
45-64	31.2 (1.0)	30.7 (1.2)		47.8 (1.5)	46.0 (1.3)		48.5 (1.4)	48.6 (1.3)	
65+	10.0 (0.7)	9.0 (0.6)		29.5 (1.5)	26.9 (1.4)		36.1 (1.5)	35.9 (1.3)	
Female, %	51.1 (0.6)	51.0 (0.6)	0.90	51.2 (1.5)	53.1 (1.1)	0.31	51.8 (1.8)	49.0 (1.6)	0.24
Race/ethnicity, %			0.37			0.65			0.17
Non-Hispanic White	73.7 (2.1)	70.6 (2.4)		66.2 (3.2)	63.7 (3.1)		61.8 (3.9)	56.9 (3.1)	
Non-Hispanic Black	8.8 (1.1)	8.9 (1.0)		15.7 (2.1)	14.9 (1.8)		18.8 (2.2)	17.3 (2.2)	
Mexican American	12.2 (1.2)	13.7 (1.8)		11.6 (1.4)	14.0 (2.0)		13.5 (1.8)	16.3 (2.8)	
Other	5.3 (0.6)	6.9 (0.8)		6.5 (1.1)	7.3 (1.0)		5.9 (1.3)	9.5 (1.3)	
Education (< HS), %	16.4 (1.1)	14.3 (1.0)	0.15	23.1 (1.5)	22.3 (1.3)	0.68	29.3 (1.6)	28.3 (1.9)	0.70
PIR, %			0.07			**0.03**			0.26
<1.0	12.9 (0.8)	16.3 (1.3)		12.0 (1.0)	15.6 (1.0)		15.2 (1.4)	18.8 (1.7)	
1.0-2.9	33.4 (1.4)	32.7 (1.3)		40.9 (2.2)	39.0 (2.0)		45.6 (1.9)	43.8 (1.8)	
>=3.0	53.7 (1.8)	51.0 (1.7)		47.1 (2.4)	45.3 (2.2)		39.2 (2.3)	37.4 (2.2)	
Obese (BMI >= 30), %	26.8 (1.0)	27.9 (1.0)	0.43	45.4 (1.4)	42.1 (1.7)	0.14	60.6 (1.7)	64.2 (1.9)	0.16
History of Cardiovascular Disease*, %	4.8 (0.4)	4.2 (0.3)	0.21	12.1 (0.9)	11.2 (1.0)	0.50	26.2 (1.4)	22.2 (1.4)	**0.05**
Self Reported Smoking, %	24.2 (1.0)	19.6 (1.0)	**<0.01**	24.4 (1.5)	22.7 (1.4)	0.40	17.8 (1.4)	17.1 (1.0)	0.66
Heavy Alcohol use, %	9.9 (0.6)	10.9 (0.7)	0.24	6.0 (0.9)	6.1 (0.6)	0.94	3.9 (0.7)	5.5 (0.7)	0.14
Health Insurance, %	79.1 (1.2)	78.9 (1.1)	0.89	84.6 (1.1)	79.7 (1.0)	**<0.01**	87.4 (1.2)	84.7 (1.1)	0.10
Number of helathcare visits in past year, %			0.33			0.10			0.47
0	18.9 (0.6)	18.2 (0.8)		12.8 (1.0)	13.6 (1.0)		5.8 (0.9)	7.5 (1.2)	
1 to 3	48.6 (0.7)	50.1 (0.7)		43.9 (1.6)	47.5 (1.3)		28.6 (1.7)	28.6 (1.7)	
4+	32.5 (0.8)	31.7 (0.7)		43.4 (1.4)	38.9 (1.5)		65.6 (1.9)	63.9 (1.3)	
No usual place of care, %	17.1 (0.9)	16.4 (0.7)	0.60	10.4 (0.9)	13.1 (1.0)	**0.05**	5.2 (0.9)	6.8 (1.1)	0.25

Data presented are weighted percentages (standard error) unless otherwise noted. P-values were calculated from a Wald F Test.

* History of .congestive heart failure, coronary heart disease, heart attack, or stroke.

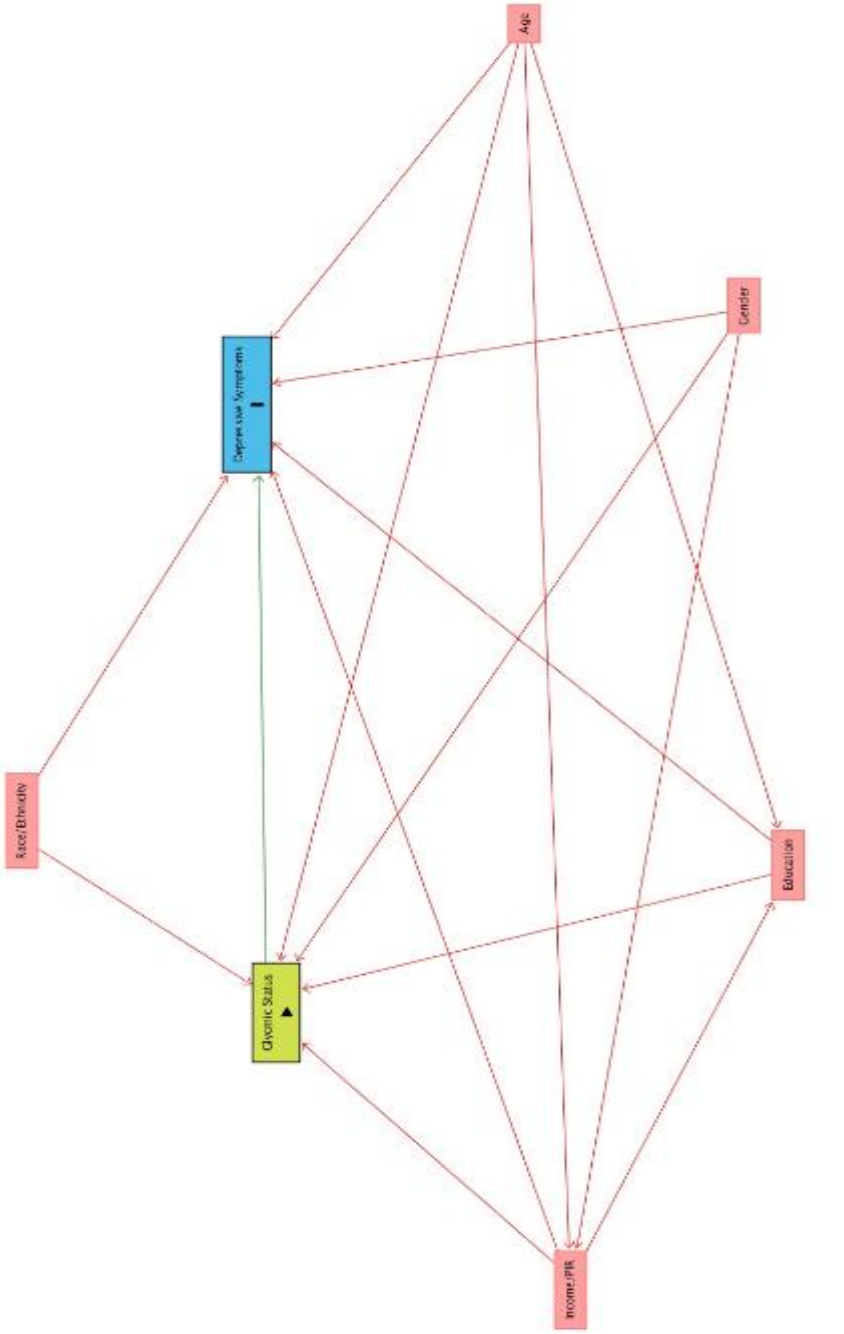


Figure 2: Directional Acyclic Graphs – Sociodemographic

Figure 3: Directional Acyclic Graphs – Full Model