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Sex Differences in the Association between Depression, Anxiety, and Type 2 Diabetes Mellitus

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Abstract

Background—Depression and anxiety have been inconsistently associated with diabetes. Sex differences in the biological and behavioral correlates of these forms of distress could partially explain these inconsistencies. We investigated sex-specific associations between depression/anxiety symptomatology and diabetes in two separate samples.

Methods—The First National Health and Nutrition Examination Survey (NHANES) enrolled 3,233 participants aged 25–74 years from 1971–1974. Depression and anxiety symptoms were measured via General Well Being schedule subscales. Incident diabetes over 17 years was defined by: i) death certificate; ii) participant self-report; or iii) healthcare facility discharge. The Detroit Neighborhood Health Study (DNHS) enrolled 1,054 participants aged 18 years or older, from 2008–2010. The Patient Health Questionnaire-9 and Generalized Anxiety Disorder-7 assessed depression and anxiety. Participants' self-reported physician diagnosed prevalent diabetes.

Results—In NHANES the RR [95%CI] for incident diabetes among men with high vs. low anxiety symptoms was 0.85 [0.56–1.29] and among women 2.19 [1.17–4.09], P for interaction=0.005. Risk ratios (RRs) comparing high vs. low depressive symptoms for men and women were 0.69 [0.43–1.10] and 2.11 [1.06–4.19], P for interaction=0.007. In DNHS, the RRs for prevalent diabetes comparing those with high vs. low anxiety symptoms were 0.24 [0.02–2.42]

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Conflicts of Interest

The authors declare no conflicts of interest.

for men and 1.62[0.61–4.32] for women, P for interaction=<0.001 while RRs for depression were 1.30[0.46–3.68] for men and 2.32[1.10–4.89] for women, P for interaction=0.16.

Conclusion—In two separate samples, depressive symptoms were related to increased diabetes risk among women but not men. While less robust, findings for anxiety were differentially associated with diabetes by sex.

Keywords

Depression; Anxiety; Diabetes; Mental Health; Epidemiology; Sex

INTRODUCTION

Depression and anxiety have been linked to increased risk of incident diabetes in several previous studies with most research focusing specifically on diabetes risk as it relates to depression (1,2,3,4,5,6,7,8,9,10,11,12,13,14,15). Two previous meta-analyses have summarized the current longitudinal literature and concluded that higher baseline depression levels are associated with a statistically significant increase in incident diabetes rates, although both reports also observed heterogeneity of associations across studies (16,17). One possible source of heterogeneity is differential strength of association between depression and diabetes by sex, although this possibility could not be explored because surprisingly few studies have reported sex-specific results. Only 1 of 9 studies analyzed by Knol et al. and 2 of 13 studies analyzed by Mezuk et al. included sex-specific results; in both meta-analyses, measures of association were pooled for the meta-analysis. Therefore, little is known about the potential for sex differences in these associations. Furthermore, most studies have focused on depression, and despite findings that other cardiometabolic diseases are also associated with anxiety, few studies exist considering anxiety in relation to diabetes risk (13,14).

Exploring whether depression and/or anxiety are differentially related to diabetes risk among men as compared with women is justified for at least four reasons. First, sex is an easily identifiable characteristic, simplifying risk stratification for clinical and public health purposes. Second, there is precedent for sex-specific diabetes risk in regard to several other factors including obesity, sex hormones, infection and inflammation (18,19,20,21,22,23). Differences of this nature underlie the NIH policy requiring the inclusion of women in human studies beginning in 1993 and in preclinical cell and animal studies beginning in 2014 (24). Third, a sex-specific relationship between mental health and diabetes is biologically plausible. For example, women tend to have higher levels of psychosocial risk than men (e.g., lower levels of education and income, more likely to be a single parent), which could exacerbate effects of distress (25,26). Moreover, other research has demonstrated that effects on disease risk are often stronger in women. Some work has suggested that the heightened effects are due in part to a stronger effect of psychosocial risk factors on risk of overweight and obesity in women as compared with men (25). This may be because men and women cope with depression and anxiety differently (27,28,29,30,31) and these coping mechanisms, in turn, influence diet, physical activity and ultimately adiposity and diabetes risk. It has also been suggested that sexually dimorphic biological responses to stress could influence diabetes-risk in men and women differently (31). For

example, there is evidence that the interplay between mental health, inflammation and the hypothalamic-pituitary-adrenal (HPA) axis may differ by sex with women showing greater dysregulation, and both inflammation and HPA axis dysregulation have been linked to insulin resistance and diabetes (32,30,33,31). Finally, if depression and/or anxiety contributed differentially to diabetes risk, it could help explain the similarity in sex-specific diabetes prevalence estimates (34,35) despite the fact that men have a higher prevalence of traditional cardiometabolic risk factors (36). Higher prevalence (or stronger influence) of novel risk factors among women might counter-balance the influence of traditional risk factors on T2D prevalence throughout the lifecourse.

We investigate sex differences in the association of depression or anxiety symptoms with risk of both incident and prevalent diabetes using a nationally-representative sample of diabetes-free adults enrolled in the First National Health and Nutrition Examination Survey (NHANES I) and Its Epidemiological Follow-Up Study (NHEFS). While data collection were completed in NHEFS in 1992, we do not anticipate that the relationships under study would alter significantly in the intervening period, and in fact findings are informative for a substantial population of older adults currently at risk. However, to ensure findings remain relevant today and to address the lack of racial diversity in NHANES, we also assess the relationship between depression and anxiety symptomatology and prevalent diabetes in a separate population-based sample of adults enrolled in the Detroit Neighborhood Health Study (DNHS).

METHODS

NHANES I was a national probability sample of the non-institutionalized U.S. population aged 1–74 years, conducted during 1971–1974. NHEFS was a longitudinal study of 14,407 NHANES I participants initially 25–74 years of age who completed a medical examination (37,23). NHEFS includes four longitudinal follow-up studies in 1982–1984, 1986, 1987 and 1992. Ninety-six percent of the study population was successfully traced through the 1992 follow-up. Death certificates were sought for all deceased participants. 3,555 NHANES participants who were administered the General Well-Being (GWB) Schedule, a baseline diabetes questionnaire and received at least one follow-up interview were eligible for the present analysis. Among these, participants were excluded due to missing covariates, prevalent diabetes or a participant's report of "other" for race (due to low sample size), yielding a final sample of 3,233.

Detroit Neighborhood Health Study

The Detroit Neighborhood Health Study (DNHS) is a longitudinal cohort of adults in Detroit, Michigan (38). Participants were selected by dual-frame probability design, using list-assisted random-digit-dial as well as telephone numbers obtained from U.S. Postal Service Delivery Sequence Files. Wave 1 was conducted from 2008–2009 and enrolled 1,547 participants. Wave 2 included 1,054. Wave 1 participants who were reinterviewed one year later (1050 included presently).

Assessment of Depression and Anxiety Symptomatology

In NHANES, depressive and anxious symptoms were measured using the General Well-Being Schedule (GWB), a validated measure with known psychometric properties (39,40). Participants were assessed during NHANES I by trained interviewers. Two of six GWB subscales were used in these analyses: cheerful versus depressed mood (General Well-Being Schedule Depression subscale, GWB-D) and relaxed versus tense/anxious (General Well-Being Schedule Anxiety subscale, GWB-A). The GWB-D and GWB-A each yield subscale scores ranging from 0 to 25, with low values indicating more depressive or anxious symptoms. GWB-A and GWB-D subscale scores were used to categorize participants into sex-specific tertiles of anxiety and depression. In sensitivity analyses, we also categorized participants according to clinical cut points in which scale scores of 0 to 12 indicated high, 13 to 18 indicated moderate, and 19 to 25 indicated low symptomatology, as previously described (41,4). The overall GWB has sound psychometric properties (42,40).

In DNHS, depression and anxiety symptoms were measured in Wave 1 using DSM IV symptomatology criteria collected via modified versions of the Patient Health Questionnaire (PHQ-9) and The Generalized Anxiety Disorder Questionnaire (GAD-7). Depression symptom scores from the PHQ-9 scale were used to categorize participants into three groups according to clinically validated cut-off points (0, 1–2, 3+). Similarly, GAD-7 symptom scores were used to categorize participants into three groups (0–9, 10–14, 15+) according to clinical cut-off points (43). Clinical reappraisal using clinician interviews in this sample showed good concordance between the measures and diagnoses using the Structured Clinical Interview for DSM-IV (SCID)(38).

Incident Diabetes in NHANES

Incident diabetes was defined by: i) death certificate: International Classification of Diseases, Ninth Revision (ICD)-9 code in the range of 250.0–250.9, or diabetes otherwise listed on the death certificate; ii) self-reported physician diagnosis requiring pharmacological treatment: participants reporting physician diagnosed diabetes and dietary intervention but not pharmacological intervention were not considered to have developed incident diabetes to enhance outcome specificity; or iii) health care facility stay with diabetes discharge diagnosis.

Prevalent Diabetes in DNHS

Diabetes status was determined via self-report of physician-diagnosed diabetes in Wave 2 (~one year after depression and anxiety assessments). Given the short follow-up time between waves 1 and 2, all diabetes cases are assumed to be prevalent at wave 1 (38).

Risk Factor Data Collection

In NHANES, potential confounding (or mediating) variables related to diabetes risk and/or indicative of healthy lifestyle were collected during the baseline evaluation including age, race (African American, or White), poverty index (total household income in the numerator and total income necessary to maintain the family on a nutritionally adequate food plan in the denominator; values>1 indicate incomes above poverty), education level (<high school, high school graduate, >high school education), post-menopausal status (self-report complete

cessation of menstruation), body mass index (BMI, weight in kilograms divided by height in meters squared based on in-person measures), physical activity and smoking status (current, former, never) as previously described (23). Similarly, DNHS covariables assessed include age, gender, race, employment, marital status, education, binge drinking (five or more drinks on a single drinking occasion in the past month for men; four or more for women) and cigarette smoking (any lifetime smoking). BMI data were not available in DNHS.

Statistical analysis

Survey procedures in SAS version 9.3 and SAS-callable SUDAAN version 10 were used for analyses. The NHANES and DNHS samples were analyzed separately. Our main results are based on the NHANES sample because these data were longitudinal and provide clarity regarding temporality of exposure-outcome relationships while DNHS results provide an alternative and valuable cohort with which to compare NHANES findings and reduce the potential for false-positive findings.

In each sample, we performed the following specific analyses. First, distributions of several potential diabetes risk factors were presented according to sex and category of symptomatology (defined above). Chi-square and ANOVA tests were conducted to determine statistical significance of variation in risk factors according to both depression and anxiety symptomatology.

Next, we used multivariable regression models to regress the probability of either incident diabetes (NHANES) or prevalent diabetes (DNHS) across categories of depression or anxiety; main effects regressions were performed separately for depression and anxiety symptoms. Additional regression models assessed associations in sex subgroups. Finally, formal tests for interaction were performed using an interaction model which included variables for sex, depression or anxiety symptoms and a sex*depression or anxiety symptom interaction term; in our interaction model, we operationalized depression and anxiety symptom level as an ordinal variable in tertiles.

PROC RLOGIST in SUDAAN was used to account for the stratification, clustering and sample weights used in both NHANES and DNHS and to obtain multivariable adjusted risk ratios from fitted logistic regression models by obtaining point estimates of model-adjusted risk ratios (RR) as functions of average marginal predictions (44). Results from crude and adjusted regression models are presented to provide clarity regarding confounding.

RESULTS

NHANES

In the NHANES sample, participants were 52% female, 86% White, and 14% African American. Mean age±standard deviation (STD) at baseline was 49±14 years. The cumulative incidence of diabetes was 9.2% (n=298 cases) during an average follow-up time of 17 years and the risk was higher among men (11%) than among women (8%), P<0.01. Death certificates were the lone source of incident diabetes determination for only 2 cases and 40% of cases were confirmed by >one source (Table 1). There was no evidence that diabetes ascertainment differed by gender (Table 1).

Mean±STD GWB scores for anxiety and depressive symptoms were 18.2±5.0 and 18.6±4.3. Men had higher (indicating less symptomatology) mean scores±standard error (SE) than women for anxiety and depressive symptoms: anxiety symptoms=18.5±0.2 vs. 17.5±0.2 (P<0.0001) and depressive symptoms=19.3±0.2 vs. 18.1±0.2 (P<0.0001). Increased anxiety symptoms (3rd vs. 1st tertile) was associated with an average age that was 4 years younger among men (P<0.0001) and 2 years younger among women (P<0.001). This trend was similar for depressive symptoms among women while, in contrast, men with higher depression symptomatology were three years older than men with lower symptomatology (Tables S1 and S2, Supplemental Digital Content 1). Among men, both increased depression and anxiety symptomatology were weakly associated with decreased BMI although the trends were not statistically significant (Tables S1 and S2). The reverse was true among women: BMI was increased by 1.5 kg/m^2 (P<0.001) among women with high vs. low anxiety symptomatology and BMI increased by 2.2 kg/m^2 (p<0.001) when comparing women with high vs. low depression symptomatology (Tables S1 and S2). Finally, higher symptomatology for depression and anxiety were both associated with being a current smoker and having lower physical activity levels in men and women (Supplemental Tables S1 and S2).

Anxiety Symptoms, Depressive Symptoms and Incident Diabetes in NHANES

After multivariable adjustment, including age, race, education, smoking status, BMI and physical activity, there were no associations between anxiety or depressive symptoms and diabetes development among the full sample. The RRs for incident diabetes were as follows: High vs. low anxiety symptoms RR=1.07[0.69,1.67]; high vs. low depressive symptoms RR=1.06[0.59,1.90].

In sex specific analyses and after adjustment for age, race, education, smoking status, BMI and physical activity, 3rd tertile (vs. 1st) anxiety symptomatology was associated with increased diabetes risk among women: RR=2.19[1.17–4.09], p for trend=0.01. In contrast, high anxiety was non-significantly associated with lower diabetes risk among men: RR=0.85[0.56–1.28], p for trend=0.49 (p for sex interaction=0.005, Table 2). Similarly, 3rd tertile depression symptomatology (vs. 1st) was associated with increased diabetes risk among women but non-significantly lower risk among men (Table 3): RR among women=2.11[1.06–4.19], P for trend=0.03; RR among men=0.69[0.43–1.10], p for trend=0.12 (p for sex interaction=0.007). Results were unchanged among women in models additionally adjusting for postmenopausal status (data not shown).

DNHS General Characteristics

Participants were 53% female, 88% African American. Mean age±STD was 54±16 years. Characteristics of DNHS participants according to either depression or anxiety status are presented in Tables S3 and S4, Supplemental Digital Content 1.

The prevalence of diabetes in the sample was 18.3 % (n=192 cases) and was higher among women (20.3%) than men (15.3%), p=0.04. Mean±STD scores for GAD-7 and PHQ-9 were 3.8±5.1and 1.5±2.1 respectively. In contrast to NHANES, women had higher (indicating

less symptomatology) mean±STDERR scores than men for GAD-7 (4.2±5.1 vs. 3.3±4.9, P<0.001) and PHQ-9 (1.7±2.2 vs. 1.2±2.0, P<0.0001).

Anxiety Symptoms, Depressive Symptoms and Prevalent Diabetes in DNHS

In the full DNHS sample, multivariable adjusted RRs for prevalent diabetes according to anxiety and depressive symptoms were as follows: High vs. low anxiety symptoms RR=1.24[0.47–3.26]; High vs. low depressive symptoms RR=1.78[1.01–3.14]. The RRs for high (vs. low) anxiety symptomatology predicting prevalent diabetes among men and women, respectively were: 0.24[0.02,2.42] and 1.62[0.61,4.32]; p for interaction<0.001. The RRs for high (vs. low) depression symptomatology predicting prevalent diabetes among men and women, respectively were: 1.30[0.46,3.68] and 2.32[1.10,4.89]; p for interaction=0.16. Additional sex-specific results are presented in Table 4.

DISCUSSION

We report sex differences in the relationship between depression and anxiety symptoms and incident diabetes during 20 years of follow-up. Risk for incident diabetes was consistently higher among women, but not men, with more depressive symptoms. While less robust, the relationship between anxiety symptoms and diabetes also differed by sex. These differences were not explained by sex differences in putative diabetes risk factors and were largely consistent across measures of both depression and anxiety.

The observed patterns in NHANES were similar to those in a separate cohort of participants enrolled in the Detroit Neighborhood Health Study, which is an important strength of this report. Although the DNHS analysis considers prevalent diabetes, the observation of consistent trends in both DNHS and NHANES minimizes the potential for false-positive, chance findings in regard to the observed sex interaction. Moreover, the potential for biases related to age, period or cohort effects are reduced because NHANES and DNHS are two distinctly different study samples with enrollment times separated by thirty years. The high prevalence of African American participants in DNHS increases the generalizability of the finding as African Americans were underrepresented in the NHANES I sample. Although the DNHS sex by depression interaction was not statistically significant, the sample size was much lower in DNHS relative to NHANES where the interaction was significant; nevertheless, the sex by anxiety interaction was statistically significant in DNHS (and NHANES).

Both depression and anxiety have been previously linked to diabetes risk but to our knowledge, this is the first study to show clear sex-specific findings in two separate population-based cohorts. Interestingly, a previous report regarding depression and diabetes was published from NHANES noting evidence for stronger results among women, but sex specific results were not presented and sex by anxiety interactions also were not tested (4). Moreover, that analysis included 3,081 participants who did not receive a baseline diabetes questionnaire raising the possibility that reverse causality might explain their observed findings (i.e., unascertained baseline diabetes actually preceded, and caused, depression but was mistakenly determined to be incident). Our current report restricts the analysis to individuals who received a baseline diabetes questionnaire.

Examining the potential for sex interactions is important as it has been hypothesized that stress and poor mental health might portend different health outcomes for women than men (27,29,30,31). Several possible explanations exist, such as sex differences in coping mechanisms or differential biological responses to depression or anxiety including inflammatory response and/or hypothalamic-pituitary-adrenal (HPA) axis dysregulation.

It has been shown that men and women often display different coping styles in responses to stress and distress that might contribute to differential diabetes risk factor profiles. For example, men tend to distract themselves from mood by becoming aggressive and participating in activities while women are more likely to ruminate, decrease physical activity and eat more (45,27,29,46). Mikolajczyk and colleagues report that females – but not males – with depressive symptoms are more likely to consume sweets and fast foods but less likely to consume fruits/vegetables (47). Sex differences of this nature could therefore lead to increased adiposity among women but not men. The current results from NHANES provide modest support for this notion as small BMI increases (~10%) were observed among women with anxiety or depression symptoms but not among men. Nevertheless, the qualitative evidence for BMI mediation (or confounding) was modest in the NHANES data, as the results were not meaningfully changed after BMI adjustment.

Alternatively, depression and anxiety are possible sources of hypothalamic-pituitary-adrenal (HPA) axis dysregulation (31) and there is evidence that HPA axis abnormalities can lead to insulin resistance (48). HPA axis functioning is also known to differ by sex and these differences emerge during the lifecourse around the same time that depression and anxiety prevalence begins to show sex-specific patterns (31), although it remains unknown whether these patterns are causally linked.

Differential inflammatory response to psychopathology is another possible explanation for the observed sex differences. Psychopathology has been hypothesized as a contributor to the establishment of a chronic pro-inflammatory state and inflammation is strongly associated with both insulin resistance and diabetes development. Several previous studies have found inflammatory stimuli such as adipose tissue (49), dietary constituents (50), environmental pollutants (51) and chronic infections (52,53,54) to be related to insulin resistance and/or diabetes risk. Interestingly, there are also data to suggest that women have an exaggerated inflammatory response to experimentally induced psychological stress while men’s inflammatory responses are blunted (30).

It is also possible that bias could have contributed to the apparently null (or possibly inverse) associations observed among men. One possible scenario is differential ascertainment of diabetes status dependent on both sex and depression or anxiety symptoms. Men with depressive or anxiety symptoms (vs. those with low levels) might have underreported their diabetes while women with depressive or anxiety symptoms over reported diabetes. However, the differential ascertainment would need to be substantial to change the direction of the association from positive to inverse. It would also require, at minimum, incident diabetes in NHANES to have been less frequently identified by self-report among men than women and the evidence for this was weak. Diagnostic bias is another possible explanation assuming men with less depressive or anxious symptomatology and women with more

symptomatology were more likely have undiagnosed baseline diabetes. If this were to occur the undiagnosed baseline diabetes would subsequently become diagnosed and incorrectly believed to be incident (23) and this would happen differentially by sex and depressive or anxiety symptoms. However, Knol et al. report that the role of undetected baseline diabetes on study results was minimal (16). Moreover, the prevalence of undiagnosed diabetes among U.S. adults during a similar time period (1976–1980) has been shown to be very low (2%)(55) which also reduces the likelihood for diagnostic bias to explain results.

The DNHS prevalent diabetes findings might have been biased by differential response patterns to mental health questionnaires in which truly anxious or depressed men with diabetes were less likely to respond to questionnaires about their anxiety and/or depressive symptoms accurately. While we cannot rule out this possibility, it is important to note that the incidence data from NHANES are not susceptible to this bias as diabetes determinations were made prospectively and ~75% of diabetes cases were confirmed via death certificates or hospitalization records. Because the DNHS data report on prevalent diabetes, it is also possible that reverse causality (e.g., diabetes status preceded and potentially caused depressive symptoms as opposed to the reverse) might explain those findings. This potential is supported by conclusions of a two separate meta-analyses that found depression incidence to be increased among individuals with vs. without diabetes (17,56).

The current analyses did not account for potential confounding by antidepressant/antianxiety medications and future research that addresses this limitation will be important. In addition, while the lack of BMI information in DNHS is an important limitation, the lack of meaningful attenuation of results after BMI adjustment in NHANES suggests that baseline adiposity might not be a strong confounder.

We have found higher levels of anxiety and depression symptomatology to be positively related to incident diabetes among women but not among men where findings were inverse but did not reach statistical significance. These results arise from a population-based sample of US adults who were followed longitudinally for 20 years in NHANES. The patterns observed in NHANES were also apparent in a separate cohort of adults enrolled in DNHS. While our current findings do not allow for definitive causal conclusions, they are biologically plausible and supported by research showing other diabetes risk factors to have sex-specific patterns. Future studies that can minimize the potential for diagnostic bias are necessary. Additional research exploring biological plausibility of these findings such as sex differences in diabetes risk phenotype or biological response to anxiety and depression will be informative. If sex differential truly exists in the association between depression or anxiety and diabetes, it has important implications for public health screening as well as clinical risk stratification and treatment decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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R.T.D. conceptualized the analysis, obtained and analyzed the data, drafted the manuscript; S.G. helped analyze the data and write the manuscript; S.S. provided critical review and editing of the manuscript; K.M.K. helped analyze the data and provided critical review and editing of the manuscript; A.E.A. made DNHS data available and provided critical review and editing of the manuscript; P.C.C. provided critical review and editing of the manuscript; S.G. made DNHS data available and provided critical review and editing of the manuscript; M.U. made DNHS data available and provided critical review and editing of the manuscript; K.C.K. made DNHS data available, conceptualized the analysis and provided critical review and editing of the manuscript; L.D.K. conceptualized the analysis and provided critical review and editing of the manuscript;

Abbreviations

BMI	Body mass index
DNHS	Detroit Neighborhood Health Study
NHANES I	First National Health and Nutrition Examination Survey
GAD-7	Generalized Anxiety Disorder Questionnaire
GWB	General Well-Being
HPA	Hypothalamic-pituitary-adrenal
NEFS	National Epidemiological Follow-Up Study
PHQ-9	Patient Health Questionnaire

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Table 1

Sources of Incident Diabetes Classification

Source(s)	Women # (%)	Men # (%)	Combined # (%)
One Source	81 (62%)	96 (57%)	177 (60%)
Self-report Interview	35 (27%)	36 (21%)	71 (24%)
Facility Discharge	45 (35%)	59 (35%)	104 (35%)
Death Certificate	1 (0.8%)	1 (0.6%)	2 (0.7%)
Two Sources	40 (31%)	59 (35%)	99 (33%)
Self-report Interview & Facility Discharge	28 (22%)	45 (27%)	73 (24%)
Self-report Interview & Death Certificate	2 (2%)	2 (1%)	4 (1%)
Death Certificate & Facility Discharge	10 (8%)	12 (7%)	22 (7%)
Three Sources	9 (7%)	13 (8%)	22 (7%)
Total	168 (100%)	130 (100%)	298 (100%)

The First National Health and Nutrition Examination Survey and Its Epidemiologic Follow-up Study, 1971–74 through 1992 (n=298 Incident Diabetes Mellitus Cases; Cumulative Incidence = 9.2%)

Table 2

Risk Ratios for Incident Diabetes by Category of Baseline Level of Anxiety Symptoms According to the General Well-Being Schedule

	MEN (n=1,544)			WOMEN (n=1,689)			
Gender-Specific Tertiles							
Model*	Low Symptomatology (22–25)† Crude Incidence 74/534 (14%)	Moderate Symptomatology (18–21)† Crude Incidence 41/494 (8%)	High Symptomatology (1–17)† Crude Incidence 53/516 (10%)	Low Symptomatology (21–25)† Crude Incidence 32/548 (6%)	Moderate Symptomatology (17–20)† Crude Incidence 36/532 (7%)	High Symptomatology (0–16)† Crude Incidence 62/609 (10%)	P-value for interaction‡
1.	1.0	0.70 (0.45,1.08)	0.74 (0.50,1.11)	1.0	1.67 (0.94,2.97)	2.30 (1.31,4.04)	<0.001
2.	1.0	0.79 (0.56,1.27)	0.85 (0.56,1.27)	1.0	1.78 (0.98,3.23)	2.31 (1.27,4.19)	0.002
3.§	1.0	0.78 (0.49,1.24)	0.85 (0.56,1.28)	1.0	1.81 (0.99,3.30)	2.19 (1.17,4.09)	0.005
Uniform Clinical Cut-Points							
Model*	Low Symptomatology (19–25)† Crude Incidence 109/939 (12%)	Moderate Symptomatology (13–18)† Crude Incidence 45/440 (10%)	High Symptomatology (0–12)† Crude Incidence 14/165 (8%)	Low Symptomatology (19–25)† Crude Incidence 52/809 (6%)	Moderate Symptomatology (13–18)† Crude Incidence 40/590 (7%)	High Symptomatology (0–12)† Crude Incidence 38/290 (13%)	P-value for interaction‡
1.	1.0	0.89 (0.57,1.38)	0.68 (0.32,1.42)	1.0	1.33 (0.73,2.40)	2.15 (1.24,3.74)	0.007
2.	1.0	0.95 (0.61,1.49)	0.72 (0.33,1.58)	1.0	1.36 (0.74,2.52)	2.02 (1.11,3.65)	0.009
3.‖	1.0	0.94 (0.61,1.44)	0.70 (0.32,1.55)	1.0	1.42 (0.78,2.61)	1.72 (0.86,3.44)	0.029

The First National Health and Nutrition Examination Survey and Its Epidemiologic Follow-up Study, 1971–74 through 1992 (n=3,233) with Anxiety Defined using (a) Gender-Specific Tertiles and (b) Uniform Clinical Cut-points

*Model 1: Crude; Model 2: Adjusted for age, race, education; Model 3: Model 2 + smoking status, BMI & physical activity level

†Range of GWB-Anxiety scores within categories of symptomatology

‡P-value for interaction with ordinal GWB-Anxiety interaction term

§P-value for linear trend among Men = 0.49 & Women = 0.01

‖P-value for linear trend among Men = 0.32 & Women = 0.08

Table 3

Risk Ratios for Incident Diabetes by Category of Baseline Level of Depressive Symptoms According to the General Well-Being Schedule

	MEN (n=1,544)			WOMEN (n=1,689)			
Gender-Specific Tertiles							
Model*	Low Symptomatology (18–22)† Crude Incidence 68/546 (12%)	Moderate Symptomatology (19–21)† Crude Incidence 46/452 (10%)	High Symptomatology (0–18)† Crude Incidence 54/546 (10%)	Low Symptomatology (21–25)† Crude Incidence 29/574 (5%)	Moderate Symptomatology (17–20)† Crude Incidence 42/559 (8%)	High Symptomatology (0–16)† Crude Incidence 59/556 (11%)	P-value for interaction‡
1.	1.0	0.74 (0.45,1.23)	0.75 (0.48,1.15)	1.0	1.54 (0.87,2.74)	2.45 (1.39,4.31)	0.003
2.	1.0	0.79 (0.48,1.30)	0.70 (0.45,1.10)	1.0	1.52 (0.84,2.75)	2.32 (1.27,4.22)	0.001
3.§	1.0	0.72 (0.41,1.25)	0.69 (0.43,1.10)	1.0	1.46 (0.77,2.80)	2.11 (1.06,4.19)	0.007
Uniform Clinical Cut-points							
Model*	Low Symptomatology (19–25)† Crude Incidence 114/998 (11%)	Moderate Symptomatology (13–18)† Crude Incidence 43/455 (9%)	High Symptomatology (0–12)† Crude Incidence 11/91 (6%)	Low Symptomatology (19–25)† Crude Incidence 58/876 (7%)	Moderate Symptomatology (13–18)† Crude Incidence 50/629 (8%)	High Symptomatology (0–12)† Crude Incidence 22/184 (12%)	P-value for interaction‡
1.	1.0	0.80 (0.53,1.19)	1.09 (0.53,2.25)	1.0	1.09 (0.63,1.87)	2.09 (1.11,3.91)	0.089
2.	1.0	0.75 (0.49,1.14)	0.90 (0.44,1.86)	1.0	1.04 (0.60,1. 83)	1.77 (0.88,3.57)	0.051
3.||	1.0	0.79 (0.51,1.22)	0.82 (0.38,1.78)	1.0	1.06 (0.59,1.90)	1.32 (0.55,3.17)	0.15

The First National Health and Nutrition Examination Survey and Its Epidemiologic Follow-up Study, 1971–74 through 1992 (n=3,233) with Depression Defined using (a) Gender-Specific Tertiles and (b) Uniform Clinical Cut-points

*Model 1: Crude; Model 2: Adjusted for age, race, education, smoking status; Model 3: Model 2 + BMI & physical activity level

†Range of GWB-Depression scores within categories of symptomatology

‡P-value for interaction with ordinal depression interaction term.

§P-value for linear trend among Men = 0.12 & Women= 0.03

||P-value for linear trend among Men = 0.30 & Women = 0.50

Table 4

Risk Ratios for Prevalent Diabetes by Category of Baseline Level of Generalized Anxiety (GAD-7) or Depression (PHQ-9) Symptomatology

	MEN (n=425)			WOMEN (n=625)			
ANXIETY SYMPTOMS							
Model*	Low Symptomatology (0–9)† Diabetes Prevalence 59/373 (16%)	Moderate Symptomatology (10–14)† Diabetes Prevalence 4/30 (13%)	High Symptomatology (15+)† Diabetes Prevalence 2/22 (9%)	Low Symptomatology (0–9)† Diabetes Prevalence 111/519 (21%)	Moderate Symptomatology (10–14)† Diabetes Prevalence 5/69 (7%)	High Symptomatology (15+)† Diabetes Prevalence 11/37 (30%)	P–value for interaction‡
1.	1.0	0.97 (0.31,3.00)	0.12 (0.02,0.60)	1.0	0.23 (0.05,0.96)	1.80 (0.84,3.86)	0.14
2.§	1.0	1.27 (0.25,6.49)	0.24 (0.02,2.42)	1.0	0.15 (0.04,0.59)	1.62 (0. 61,4.32)	<0.001
DEPRESSION SYMPTOMS							
	Low Symptomatology (0)† Diabetes Prevalence 42/261 (16%)	Moderate Symptomatology (1–2)† Diabetes Prevalence 11/80 (14%)	High Symptomatology (3+)† Diabetes Prevalence 12/84 (14%)	Low Symptomatology (0)† Diabetes Prevalence 48/275 (17%)	Moderate Symptomatology (1–2)† Diabetes Prevalence 36/169 (21%)	High Symptomatology (3+)† Diabetes Prevalence 43/181 (24%)	P-value for interaction‡
1.	1.0	1.16 (0.44,3.09)	0.74 (0.31,1.78)	1.0	1.21 (0.61,2.40)	1.48 (0.85,2.59)	0.23
2.||	1.0	1.01 (0.31,3.29)	1.30 (0.46,3.68)	1.0	1.91 (0.90,4.06)	2.32 (1.10,4.89)	0.16

The Detroit Neighborhood Health Study, 2008–2010 (n=1,050)

*Mode 1: Crude; Model 2: adjusted for age, race, marital status, employment status, education level, lifetime depression or lifetime GAD, smoking status, and binge drinking

†Range of generalized anxiety disorder (GAD)-7 or patient health questionnaire (PHQ)-9 scores within categories of symptomatology according to clinical cut-points

‡P-value for interaction with ordinal depression interaction term.

§P-values for linear trend for anxiety in model 2 among Men: 0.70 & Women: 0.93

||P-values for linear trend using for depression in model 2 among Men: 0.75 & Women: 0.02