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Longitudinal association between diabetes and cognitive decline: The National Health and Aging Trends Study

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Abstract

Type II diabetes mellitus (DM) is associated with increased risk of dementia; however, few studies have examined the longitudinal association between DM and cognitive outcomes in large nationally representative cohorts. We investigated these associations in 7605 participants enrolled in the National Health and Aging Trends Study, a nationally representative prospective study of Medicare beneficiaries 65, from 2011 to 2015. Participants or proxy respondents reported DM and dementia diagnosis, and participants completed immediate and delayed recall word list learning tests and the Clock Drawing Test. In multivariable-adjusted generalized linear mixed models, baseline DM diagnosis was associated with decline on immediate and delayed word recall and the Clock Drawing Test. In Cox proportional hazards models, DM also predicted incident dementia in older age groups at baseline. These findings further support the notion that DM is associated with cognitive outcomes, suggesting that treatment and prevention of DM may reduce the risk of these outcomes. However, more studies are needed to better understand whether DM treatments affect this relationship.

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Keywords

Dementia; Diabetes; Cognitive decline; Epidemiology

1. Introduction

Dementia is a major public health issue. One meta-analysis found that approximately 5% of adults over the age of 60 have dementia in the United States (Prince et al., 2013), and it is estimated that over a six-year period there will be 3.4 million new cases of dementia and 4.8 million people will develop cognitive impairment (Plassman et al., 2011). Alzheimer's disease (AD), the most common cause of dementia, cost the country \$214 billion in 2014 (Alzheimer's Association, 2014). As there is no cure for dementia, intervening on modifiable risk factors may be the most effective route for reducing dementia prevalence and burden. Indeed, it has been suggested that a quarter of dementia cases could be prevented by treating and addressing modifiable risk factors for dementia (Barnes & Yaffe, 2011).

Nearly 30% of older adults have type II diabetes mellitus (DM), and it is estimated that an additional 50% of older adults are pre-diabetic (i.e., in the prodromal stage of DM) (American Diabetes Association, 2013). The prolonged hyperglycemic and hyperinsulemic states in DM may contribute to cognitive decline. For instance, it has been shown that hyperinsulemia is detrimental to the otherwise positive effects that normal levels of insulin have on cognition (Cholerton, Baker, & Craft, 2013). Further, insulin receptors are concentrated in the hippocampus and medial frontal cortex, suggesting that chronically high levels of insulin might affect memory performance (Cholerton, Baker, & Craft, 2011; Craft, 2006). Although there is evidence for an association between insulin resistance and AD (Cholerton et al., 2011; Gasparini, Netzer, Greengard, & Xu, 2002), the link between DM and AD continues to be explored.

Evidence suggests that DM is associated with increased risk of cognitive impairment (Cukierman, Gerstein, & Williamson, 2005), neurodegeneration (Verdile, Fuller, & Martins, 2015), and dementia (Vagelatos & Eslick, 2013), potentially through prolonged hyperglycemia and hyperinsulinemia (Launer, 2005). Although past studies have investigated the association between DM and dementia, or DM and cognitive decline, few have examined the association of DM with both dementia and cognitive decline over time in an older, nationally representative cohort (Elias et al., 1997; Irie et al., 2008; Peila, Rodriguez, & Launer, 2002). Here, we investigated the association between DM and cognitive test performance and dementia over a five-year period in a large, nationally representative sample of adults 65 years old and older – the National Health and Aging Trends Study (NHATS). Our previous work in NHATS showed that DM was cross-sectionally associated with poorer performance on cognitive tests, but not dementia diagnosis (Wennberg et al., 2014). In this longitudinal study we hypothesized that DM would predict incident dementia diagnosis and decline in cognitive performance over time, above and beyond what might be expected with age.

2. Methods

2.1. Participants

This study included participants from NHATS, a nationally representative prospective cohort of Medicare beneficiaries 65 years old and older. The design incorporated oversamples of non-Hispanic Black and older age groups (Montaquila, Freedman, Edwards, & Kasper, 2012). Nursing home residents and those in non-nursing home residential care were not included in the present study. NHATS is conducted by the Johns Hopkins Bloomberg School of Public Health and is supported by funding from the National Institute on Aging (U01AG032947). This analysis used data from participants recruited in Round 1 (5/1/2011–11/30/2011; N = 8245), and followed in Rounds 2 (5/1/2012–11/30/2012; N = 7075), 3 (5/1/2013–11/30/2013; N = 5799), 4 (5/1/2014–11/30/2014; N = 4737), and 5 (5/1/2015–11/30/2015; N = 4152) of NHATS (Fig. 1).

Of the 1170 participants who participated in Round 1, but not Round 2, 503 of them died, 853 refused to participate, and 38 could not be located. Between Round 2 and Round 3, 523 participants died, 568 refused to participate, and 26 could not be located. Between Round 3 and Round 4, 426 participants died, 407 refused to participate, and 30 could not be located. By Round 5, 3856 living participants were continuing from Round 1 (296 died between Round 4 and 5; 176 refused to participate; 2 could not be located). At each round, proxy respondents were asked if the study participant could attempt the cognitive testing (i.e., “There are a few questions that I would like to ask subject person so that the study can better understand memory in people {his/her} age. Some may be hard to answer, but it is important to the study that we ask these. May I speak to subject person and ask {him/her} a few questions?”). This information is missing if the proxy respondent did not agree to cognitive testing (in Round 1: 336; Round 2: 298; Round 3: 534; Round 4: 255; Round 5: 237). At Round 1, two participants or proxy respondents replied “don’t know” to the DM diagnosis question. Additionally, there were small numbers (< 5 cases) at each subsequent round who did not know if they had been diagnosed with dementia. Participants who did not know if they had been diagnosed with dementia but did complete cognitive testing were included in analyses.

Participants or proxy respondents completed an in-person interview. Informed consent was obtained from each participant or proxy respondent. Proxy respondents were used in the event that the sample person was unable to answer the questions themselves (e.g., dementia, due to a language barrier). In Rounds 1, 2, and 4, each, 7% of participants had a proxy respondent. In Round 3, 6% had a proxy and in Round 5, 13% had a proxy. Proxies were generally spouses or children of the participants. This study included 7605 people with complete data for DM diagnosis and cognitive test performance or dementia diagnosis.

2.2. Measures

2.2.1. DM and dementia—At each visit, participants or proxy respondents reported whether “a doctor ever told you that you had diabetes” or “dementia or Alzheimer’s disease.” Response options were “yes,” “no,” or “don’t know.” Participants with a response of “don’t know” to the dementia question were excluded from the analyses.

2.2.2. Cognitive testing—NHATS participants also completed cognitive tests at each Round. They completed an episodic memory test from the CERAD battery, a 10-item word-list memory task, with immediate and delayed recall (Morris et al., 1989). Participants were asked to recall the words immediately after they were presented, and after a delay of approximately five minutes. The total number of words recalled immediately and after a delay was the participant's score (refusals or 'don't know' responses were coded as missing). Participants also completed the Clock Drawing Test (Wolf-Klein, Silverstone, Levy, & Brod, 1989), a test of visuospatial ability and executive function, in which they were given a sheet of paper with circle on it and asked to draw a clock face with the time as "10 after 11." Participants had 120 seconds to complete the task. The test was scored according to standard criteria on a scale ranging from 0 ("not recognizable as a clock") to 5 ("accurate depiction of a clock") (Shulman, Gold, Cohen, & Zuccherro, 1993).

2.2.3. Other measures—Participants or proxies provided information about a number of other medical conditions (e.g., heart disease, lung disease, heart attack, hypertension, osteoporosis, arthritis, stroke, and cancer), by responding to a similar stem question described above for the DM and dementia status. Participants or proxies also reported participants' sex, age (which were collected in 5-year strata: 65–69 years, 70–74 years, 75–79 years, 80–84 years, 85–89 years, and 90+ years); race (White, non-Hispanic; Black, non-Hispanic; Hispanic; or other); years of education, which we coded as less than high school, high school, or more than high school; height and weight, which were used to calculate body mass index (BMI) in kg/m². Participants completed the two-item Patient Health Questionnaire (PHQ-2) (Kroenke, Spitzer, & Williams, 2003) and the two-item Generalized Anxiety Disorder Scale (GAD) (Wild et al., 2013), which were used to measure depressive and anxiety symptoms.

2.3. Statistical analyses

All analyses were conducted using round-varying survey weights to create nationally representative estimates; additionally, by weighting the analyses we took into account differential probabilities of selection and nonresponse. We used chi-square and *t*-tests to compare baseline participant characteristics.

We used survey-weighted multivariable-adjusted generalized linear mixed models to investigate the association between baseline DM diagnosis and change in cognitive test performance over 5 Rounds. We specified random intercepts, unstructured covariance structure, and the "RANDOM" option to adjust for within-subject effects. To investigate the association between baseline DM diagnosis and risk of developing dementia during follow-up, we used survey-weighted multivariable-adjusted Cox proportional hazards models. Model 1 was adjusted for baseline age, sex, education, race, baseline depressive and anxiety symptoms, baseline BMI, and baseline medical conditions (i.e., heart attack, heart disease, hypertension, and stroke). Model 2 included the same covariates as Model 1; however, in Model 2 we excluded participants who reported stroke at Round 1. This latter sensitivity analysis was conducted because DM is a risk factor for stroke, which is associated with poorer cognitive outcomes and risk of dementia (Lu, Lin, & Kuo, 2009).

Additional sensitivity analyses were conducted to determine whether osteoporosis, pulmonary disease, arthritis, and cancer were confounders and whether age, education, and sex were effect modifiers in the association between DM and cognitive outcomes. All analyses were conducted using SAS 9.4 (SAS Institute, Inc. Cary, NC).

3. Results

This study included 7605 participants from NHATS with complete DM data at Round 1, and complete dementia or cognitive test data at Rounds 1–4, or 5. At baseline, over half of the participants were between 65 and 74 years old, over half were female, approximately 80% were White, and half had education beyond high school (Table 1). Approximately one-quarter of participants reported a DM diagnosis at Round 1. Those with a DM diagnosis at Round 1 were significantly different from those without a DM diagnosis. DM patients were younger, were more likely to be male and a race other than White, had a lower level of education, higher BMI, and were more likely to report depression and anxiety symptoms. Additionally, participants reporting DM were more likely to report a history of heart attack, heart disease, hypertension, pulmonary disease, and stroke.

In multivariable-adjusted generalized linear mixed models baseline DM diagnosis was associated with declining cognitive test performance. In Model 1 (adjusted for baseline age, sex, education, race, baseline depression and anxiety symptoms, baseline BMI, and baseline medical conditions), we found that DM diagnosis at Round 1 was associated with declining performance on the immediate ($B = -0.21$; 95% CI $-0.26, -0.15$) and delayed ($B = -0.21$; 95% CI $-0.31, -0.16$) word recall tests, and the Clock Drawing Test ($B = -0.11$, 95% CI $-0.18, -0.04$) over Rounds 1–5 (Table 2). DM diagnosis at baseline was associated with recalling 0.21 fewer words on the immediate recall test across the 5 Rounds. In Model 2, which excluded participants with history of incident stroke, we again found that DM was associated with declining performance on the immediate ($B = -0.11$, 95% CI $-0.28, -0.15$) and delayed ($B = -0.23$; 95% CI $-0.31, -0.15$) word recall and Clock Drawing ($B = -0.10$; 95% CI $-0.18, -0.03$) tests. These results indicate that DM at Round 1 is significantly associated with declining cognitive test performance over a period of five years.

Results from survival analyses showed that baseline DM diagnosis was not associated with risk of incident dementia over a period of 5 years in either Model 1 (HR = 1.14; 95% CI 0.83, 1.57) or Model 2 (HR = 1.21; 95% CI 0.85, 1.73), among all participants.

In sensitivity analyses, we investigated whether additionally adjusting for osteoporosis, pulmonary disease, arthritis, and cancer affected the association between baseline DM and cognitive test performance or incidence of dementia, but found that it did not (results not shown). Further, we investigated the interaction between DM and age, DM and education, and DM and sex, to determine whether these variables modified the association between DM and cognitive outcomes. There was no evidence of interaction between DM and either sex or education (results not shown). We observed evidence of an interaction ($p < 0.05$) between DM and age, and therefore stratified analyses by age group. In generalized linear mixed models, the association between DM and decline in immediate and delayed word recall was primarily driven by participants aged 65–79 and 85–89 years old, whereas the association

between DM and decline in performance on the Clock Drawing Test was primarily driven by those aged 65–69 (Table 2). These patterns were similar in models both including and excluding participants with history of stroke. In Cox proportional hazards models, the association between DM and incident dementia diagnosis was significant among those aged 85–89 years old at baseline in Model 1 (HR = 1.53; 95% CI 1.02, 2.31) (Table 3). In Model 2, excluding participants with history of stroke, the association between DM and incident dementia diagnosis was significant only among those aged 75–79 years old at baseline (HR = 1.75; 95% CI 1.07, 2.87).

4. Discussion

This study examined the association between DM diagnosis and cognitive performance over time, and between DM diagnosis and the risk of developing dementia in a nationally representative sample of Medicare beneficiaries aged 65 years old and older. We found that DM diagnosis at Round 1 was significantly associated with declining cognitive test performance on tests of episodic memory and visuospatial ability and executive functioning over a period of five years. Additionally, we found that DM diagnosis at Round 1 was associated with increased risk of incident dementia diagnosis among those aged 75–79 and 85–89 at baseline.

Models including interaction terms suggested that age was an effect modifier in the association between DM and cognitive outcomes, so we additionally performed age-stratified analyses. We found decline in immediate and delayed word recall was primarily driven by participants aged 65–79 and 85–89 years at baseline, whereas the association between DM and decline in scores on the Clock Drawing Test was primarily driven by those aged 65–69 at baseline. These findings may support the hypothesis that DM starts to affect cognition in later middle age, and later onset of DM may not as strongly affect risk of cognitive decline (Tuligenga et al., 2014). The association between DM and incident dementia was driven by those aged 85–89 years old at baseline among all participants and those aged 75–79 at baseline in analyses excluding participants with history of stroke. This is likely because dementia diagnosis is more common at older ages (Plassman et al., 2007).

In this study we observed the most robust association between DM and word list memory test performance. Word list memory immediate and delayed recall have been shown to have moderate sensitivity and good specificity when distinguishing between clinically normal individuals and individuals with mild cognitive impairment and dementia (Gavett et al., 2009). Past studies have found a similar longitudinal association between DM and cognitive decline (Reijmer, vandenBerg, Ruis, Kappelle, & Biessels, 2010) and dementia (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006; Cheng, Huang, Deng, & Wang, 2012); however, few studies have examined the longitudinal relationship between DM and cognitive outcomes in such a large and current nationally representative cohort (Rawlings et al., 2014).

The present study has a number of strengths, including the large, nationally representative sample of Medicare beneficiaries, five years of longitudinal follow-up, and inclusion of measures of verbal memory, visuospatial ability, executive function, and dementia. However, this study also had limitations. First, medical conditions, including DM and dementia were

self-reported. Studies suggest that both of these conditions are under-diagnosed (American Diabetes Association, 2013; Boustani, Peterson, Hanson, Harris, & Lohr, 2003); yet, misclassification would have biased results toward the null, so our results are likely a conservative estimate of the association between DM and cognitive outcomes. For example, at baseline 4.6% of persons reported a dementia diagnosis, compared to estimates that suggest 14% of community-dwelling adults over 71 have dementia (Plassman et al., 2007). Further, nursing home residents, who have an even higher prevalence of dementia (Gaugler, Yu, Davila, & Shippee, 2014), were excluded from this analysis. Therefore, it is likely the observed relationship would remain if the sample included institutionalized adults.

Although there is a concern of misclassification when using self-report data, evidence from another large cohort study indicates that self-reported DM diagnosis has 84%–97% specificity and 55%–80% sensitivity, and that there is greater than 92% reliability over time (Schneider, Pankow, Heiss, & Selvin, 2012). Additionally, reviewed research suggests that dementia patients, particularly in the earlier stages of the disease, have insight into their disease and symptoms (Frank, Lenderking, Howard, & Cantillon, 2011). It should also be noted that self-reported height and weight correlate well with height and weight measures among older adults (Pasalich, Lee, Burke, Jancey, & Howat, 2014). Second, this study only examined whether DM diagnosis was associated with cognitive outcomes; however, many studies have found that even among people without DM, measures of insulin resistance, blood glucose, and higher glycated hemoglobin (HbA1c) are also associated with poorer cognitive test performance and dementia (Awad, Gagnon, & Messier, 2004; Benedict et al., 2012; Crane et al., 2013). If we were able to use these more sensitive metabolic measures, we may have observed a stronger association between DM-related variables and poor cognitive outcomes. Finally, although the NHATS interviews are detailed and comprehensive, not all potential confounders could be evaluated. For example, a recent randomized controlled trial showed that the physical activity component of a multimodal intervention is strongly linked to improved cognition and lifestyle factors (Ngandu et al., 2015); however, physical activity was not assessed in this sample, and may be a confounder in the observed association.

This study is an important addition to the literature because it illustrates the longitudinal association between DM and cognitive outcomes in an older, large, nationally representative sample. Our findings suggest that self-reported DM diagnosis is associated with declining cognitive performance and incident dementia diagnosis. Population attributable risk analyses have estimated that 6 to 10% of dementia cases are directly attributable to DM (Kloppenborg, van den Berg, Kappele, & Biessels, 2008). Because there is no cure for dementia, treating modifiable risk factors may be the most effective way to delay the onset of, or even prevent, cognitive decline and dementia. Of note, recent findings suggest that adherence to a multimodal intervention, which included diet, exercise, cognitive training, and vascular risk monitoring, improved cognition, BMI, diet, and physical activity levels (Ngandu et al., 2015). Future studies should continue to investigate the long-term effects that DM and other similar risks, have on cognitive decline and dementia risk. Further, studies should determine the extent to which the risk of cognitive decline and dementia might be ameliorated through treatments and prevention efforts for DM.

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The findings from this study were presented at the Annual Meeting of the American Association of Geriatric Psychiatry March 27–30, 2015, New Orleans, LA.

This study was conducted in accord with the ethical standards of the Committee on Human Experimentation of Johns Hopkins University. The study protocols were approved by the Johns Hopkins Institutional Review Board. All participants provided written informed consent. This study did not involve experimentation on animals.

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Fig. 1.
Participant follow-up Rounds 1–5.

Table 1

Participant characteristics at Round 1 by DM diagnosis, mean (SE) or %.

Unweighted N	Total Sample (N = 7605)	Diabetes (N = 1925)	No Diabetes (N = 5680)	p
Age category, %				< 0.001
65–69 years old	28.0	26.5	28.4	
70–74 years old	25.0	28.9	23.7	
75–79 years old	19.0	20.3	18.7	
80–84 years old	14.7	14.0	14.9	
85–89 years old	9.1	7.6	9.6	
90+ years old	4.2	2.8	4.7	
Sex, % female	56.6	51.3	58.3	< 0.001
Race, %				< 0.001
White, non-Hispanic	81.5	72.8	84.2	
Black, non-Hispanic	8.2	12.7	6.8	
Hispanic	6.8	9.9	5.8	
Other	3.5	4.6	3.2	
Education level, %				< 0.001
< High school	21.7	27.6	19.9	
High school	27.6	28.7	27.3	
> High school	50.6	43.6	52.8	
BMI	27.6 (0.08)	30.0 (0.16)	26.8 (0.08)	< 0.001
PHQ-2	0.97 (0.02)	1.29 (0.04)	0.87 (0.02)	< 0.001
GAD-2	0.94 (0.02)	1.11 (0.04)	0.88 (0.02)	< 0.001
Heart attack	14.1	21.3	11.8	< 0.001
Heart disease	17.5	25.9	14.8	< 0.001
Hypertension	63.9	78.6	59.3	< 0.001
Stroke	10.1	15.2	8.4	< 0.001

BMI = body mass index (kg/m^2); GAD-2 = Generalized Anxiety Disorder Scale 2-item; PHQ-2 = Patient Health Questionnaire 2-item (higher scores indicate greater depression and anxiety).

Bolded because significant at $p < 0.05$.

Table 2

Association between baseline DM diagnosis and change in cognitive test performance across 5 Rounds.

Model 1		Model 2			
	N	B (95% CI)	p	N	B (95% CI) p
Immediate Word Recall					
All ages	7177	-0.21 (-0.26, -0.15)	<0.001	6349	-0.21 (-0.28, -0.15) <0.001
65-69	1358	-0.23 (-0.35, -0.12)	<0.001	1260	-0.23 (-0.35, -0.11) <0.001
70-74	1509	-0.34 (-0.45, -0.24)	<0.001	1366	-0.33 (-0.45, -0.22) <0.001
75-79	1439	-0.22 (-0.35, -0.09)	<0.001	1292	-0.26 (-0.40, -0.13) <0.001
80-84	1421	0.02 (-0.13, 0.16)	0.825	1215	0.04 (-0.13, 0.22) 0.620
85-89	873	-0.26 (-0.46, -0.07)	0.008	732	-0.31 (-0.54, -0.08) 0.008
90+	577	-0.13 (-0.50, 0.24)	0.490	484	-0.15 (-0.55, 0.25) 0.458
Delayed Word Recall					
All ages	7177	-0.24 (-0.31, -0.16)	<0.001	6349	-0.23 (-0.31, -0.15) <0.001
65-69	1358	-0.21 (-0.36, -0.06)	0.005	1260	-0.20 (-0.35, -0.04) 0.013
70-74	1509	-0.46 (-0.59, -0.32)	<0.001	1366	-0.44 (-0.59, -0.30) <0.001
75-79	1439	-0.21 (-0.37, -0.04)	0.014	1292	-0.24 (-0.41, -0.06) 0.009
80-84	1421	-0.02 (-0.20, 0.15)	0.783	1215	0.02 (-0.17, 0.22) 0.826
85-89	873	-0.22 (-0.46, 0.01)	0.060	732	-0.14 (-0.41, 0.12) 0.280
90+	577	-0.17 (-0.48, 0.13)	0.269	484	-0.31 (-0.63, 0.01) 0.061
Clock Drawing Test					
All ages	7177	-0.11 (-0.18, -0.04)	0.003	6349	-0.10 (-0.18, -0.03) 0.005
65-69	1358	-0.12 (-0.20, -0.04)	0.005	1260	-0.12 (-0.20, -0.04) 0.003
70-74	1509	-0.10 (-0.22, 0.02)	0.110	1366	-0.09 (-0.21, 0.04) 0.175
75-79	1439	-0.11 (-0.25, 0.03)	0.136	1292	-0.12 (-0.27, 0.03) 0.112
80-84	1421	-0.06 (-0.22, 0.11)	0.514	1215	-0.03 (-0.21, 0.15) 0.718
85-89	873	-0.15 (-0.41, 0.11)	0.248	732	-0.17 (-0.45, 0.12) 0.244
90+	577	-0.22 (-0.64, 0.21)	0.316	484	-0.19 (-0.65, 0.28) 0.431

Model 1 adjusted for baseline age, sex, education, race, depression and anxiety symptoms, BMI, and heart attack, heart disease, hypertension, and stroke. Model 2 adjusted for the same covariates as Model 1 and excluding participants with history of stroke.

Bolded because significant at $p < 0.05$.

Table 3

Survival analyses association between baseline DM and risk of dementia.

	Model 1				Model 2			
	N	Events	HR (95% CI)	p	N	Events	HR (95% CI)	p
All ages	7176	1851	1.14 (0.83, 1.57)	0.413	6348	1408	1.21 (0.85, 1.73)	0.288
65–69	1358	79	2.25 (0.81, 6.25)	0.118	1260	60	2.14 (0.65, 7.05)	0.209
70–74	1509	168	1.44 (0.73, 2.83)	0.292	1366	127	1.10 (0.48, 2.55)	0.816
75–79	1439	370	1.34 (0.84, 2.14)	0.214	1292	307	1.75 (1.07, 2.87)	0.024
80–84	1420	454	1.04 (0.67, 1.63)	0.848	1214	321	1.09 (0.64, 1.85)	0.750
85–89	873	464	1.53 (1.02, 2.31)	0.040	732	354	1.29 (0.77, 2.17)	0.333
90+	577	316	0.93 (0.58, 1.50)	0.775	484	239	0.76 (0.44, 1.31)	0.318

Model 1 adjusted for baseline age, sex, education, race, depression and anxiety symptoms, BMI, and heart attack, heart disease, hypertension, and stroke. Model 2 adjusted for the same covariates as Model 1 and excluding participants with history of stroke.

Bolded because significant at $p < 0.05$.