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Phobic anxiety symptom scores and incidence of type 2 diabetes in US men and women

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Abstract

Context—Emotional stress may be a risk factor for type 2 diabetes (T2D), but the relation between phobic anxiety symptom scores and risk of T2D is uncertain.

Objective—To evaluate prospectively the association between phobic anxiety symptom scores and incident T2D in three cohorts of US men and women.

Design, Setting and Patients—We followed 30,830 men in the Health Professional's Follow-Up Study (HPFS) (1988–2008), 69,336 women in the Nurses' Health Study (NHS) (1988–2008), and 80,120 women in the Nurses' Health Study II (NHS II) (1993–2011). Phobic anxiety symptom scores, as measured by the Crown-Crisp index (CCI), calculated from 8 questions, was administered at baseline and updated in 2004 for NHS, in 2005 for NHS II, and in 2000 for HPFS. Incident T2D was confirmed by a validated supplementary questionnaire. We used Cox proportional hazards analysis to evaluate associations with incident T2D.

Results—During 3,110,248 person-years of follow-up, we documented 12,876 incident T2D cases. In multivariable Cox regression models with adjustment for major lifestyle and dietary risk factors, the HRs of T2D across categories of increasing levels of CCI (scores= 2-<3, 3-<4, 4-<6, 6), compared with a score of <2, were increased significantly by 6%, 10%, 11% and 13% (P_{trend} =0.0005) for NHS; and by 19%, 11%, 22%, and 29% (P_{trend} <0.0001) for NHS II. Each score increment in CCI was associated with 3% higher risk of T2D in NHS (HRs, 1.03, 95%CI: 1.02-1.04) and 4% higher risk of T2D in NHS II (HRs, 1.04, 95%CI:1.03-1.05). Further adjustment for self-reported depression and antidepressant use did not change the results. In HPFS, the association between CCI and T2D was not significant after adjusting for lifestyle variables.

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Evaluating the association between phobic anxiety symptom scores and incident T2D in three cohorts of US men and women.

Conclusion—Our results suggest that higher phobic anxiety symptom scores are associated with an increased risk of T2D in women.

INTRODUCTION

The prevalence of type 2 diabetes (T2D) is increasing at alarming rates in the US and worldwide (1, 2). In addition to well-known diabetic risk factors such as diet, obesity, physical inactivity, age, race, and a family history of T2D (3, 4), recent studies have suggested a role of emotional stress in the etiology of T2D (5-7). The epidemiological studies support the concept that different forms of emotional stress, particularly depression, general emotional stress, anxiety, anger/hostility and sleeping problems (6), contribute to an elevated risk of T2D. Anxiety disorders are the most prevalent mental disorders and lifetime prevalence of specific phobia and social phobia is over 12% in the U.S. (8, 9).

Emotional stress may influence behavioral factors and thereby increase the risk of T2D through unhealthy dietary intake, excessive alcohol consumption, smoking and low exercise levels (7, 10, 11). Additional evidence also suggests the association between phobic anxiety symptoms and increasing inflammatory biomarkers such as C-reactive protein, tumor necrosis factor α, leptin, soluble E-selectin and soluble intercellular adhesion molecule (12, 13), which are well-known risk factors for T2D (14). Importantly, phobic anxiety is treatable; thus, any potential impacts on T2D incidence may be amendable through early identification and intervention.

An association between phobic anxiety symptoms scores and increased risk of coronary heart disease (CHD) in men and women has been previously reported in our and other cohorts (15-17), to date, however, the relationship between phobic anxiety symptoms scores and T2D incidence has not been directly examined. Therefore, using data from three prospective cohorts, the Nurses' Health Study (NHS), Nurses' Health Study II (NHS II) and Health Professional Follow-up Study (HPFS), we examined the association between phobic anxiety symptoms scores, as measured by Crown-Crisp index (CCI), and T2D incidence in women and men.

RESEARCH DESIGN AND METHODS

Study Population

We used data from 3 prospective cohort studies: NHS (started in 1976; n=121,704; age range at baseline: 30–55 y, enrolled from 11 US states), NHS II (established in 1989; n=116,643; age range at baseline: 24–43 y; enrolled from 14 US states) and HPFS (initiated in 1986, n=51,529; age range at baseline: 40–75 y; enrolled from 50 US states). In all the 3 cohorts, questionnaires were administered at baseline and biennially thereafter to collect and update information on lifestyle practices and occurrence of chronic diseases. Information on phobic anxiety was first obtained on the 1988 questionnaire in NHS (n=103,614), on the 1993 questionnaire in NHS II (n=87,238) and on the 1988 HPFS questionnaire (n=48,834); this served as the baseline populations for our analyses. Participants were excluded if they had T2D, cancer, CHD or stroke at baseline (n=16,255 in NHS, n=5935 in NHS II and n=7370 in HPFS), missing information on T2D diagnosis date (n=3355 in NHS, n=937 in NHS II, and n=1524 in HPFS), age (n=48 in NHS and n=182 in NHS II), or phobic anxiety symptoms score data (n = 14,620 in NHS, n =64 in NHS II, and n=9110 in HPFS). After exclusions, data from 69,336 women in NHS, 80,120 women in NHS II and 30,830 men in HPFS were available for the analysis. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health (Boston, Massachusetts, United States).

Assessment of T2D

In the three cohorts, participants who reported a new diagnosis of T2D on any of the biennial questionnaires were sent supplementary questionnaires regarding symptoms, diagnostic tests, and hypoglycemic therapy. A case of T2D was considered confirmed if at least one of the following items was reported on the supplementary questionnaire according to the National Diabetes Data Group criteria (18): 1) one or more classic symptoms (excessive thirst, polyuria or frequent urination, weight loss, or hunger) plus fasting plasma glucose concentrations ≥140 mg/dl or random plasma glucose concentrations ≥200 mg/dl; 2) ≥2 elevated plasma glucose concentrations on different occasions (fasting concentrations ≥140 mg/dl, random plasma glucose concentrations ≥200 mg/dl, and/or concentrations ≥200 mg/dl after ≥2 h shown by oral glucose tolerance testing) in the absence of symptoms; or 3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). For cases diagnosed in 1998 and later, the fasting plasma glucose threshold was lowered to 126 mg/dl according to the American Diabetes Association criteria (19). The validity of the supplementary questionnaire has been demonstrated previously in the NHS (20, 21). Only cases confirmed by the supplemental questionnaires were included in the current analysis.

Assessment of Phobic Anxiety symptoms scores: The Crown-Crisp Index (CCI)

The phobic anxiety scale of the CCI measures personality symptoms of phobic anxiety (22). It is a standardized, self-rating inventory of 8 questions on common symptoms of phobic anxiety with two (0, 2) to three (0, 1, 2) levels of possible responses to each question. The scores range from 0 to 16, with higher scores given to higher levels of phobic anxiety symptoms (22). The CCI has been validated in psychiatric outpatient clinic settings and it could discriminate patients with anxiety disorders and agoraphobia from healthy controls and patients with other forms of psychopathology (e.g., depressive, obsessive-compulsive) (22, 23). The validity of the phobic anxiety scale of CCI in the NHS population has been tested through assessing the association with tranquilizer medication (15). For those with missing data on 1 or 2 questions, the total score was divided by the fraction of questions answered and then rounded to the nearest whole number. The CCI was completed by participants in the NHS in 1988, in NHS II in 1993 and HPFS in 1988 and updated in 2004 for NHS, in 2005 for NHSII, and in 2000 for HPFS. The Spearman correlation between 1988 and 2004 (NHS), 1993 and 2005 (NHS II) and 1988 and 2000 (HPFS) were high ($r=0.66$, $p<0.0001$ in NHS and NHS II, $r=0.64$, $p<0.0001$ in HPFS), an indication that scores reliably represent long-term phobic anxiety symptoms levels.

Assessment of covariates

In the biennial follow-up questionnaires, we inquired and updated information on risk factors for chronic diseases, such as body weight, cigarette smoking, physical activity, aspirin use, multivitamin use, family history of diabetes, menopausal status and postmenopausal hormone use (NHS and NHS II only), marital status and routine screening for physical exam. Dietary information (including alcohol) was assessed using a validated semi-quantitative food frequency questionnaire every 4 year starting from 1986 (NHS), 1991 (NHS II) and 1986 (HPFS) (24).

We calculated a dietary score composed of quintile values of polyunsaturated fat to saturated fat ratio, trans fat (inverted), cereal fiber, whole grains, and glycemic load (inverted) by standardizing and summarizing the respective continuously scaled dietary variables. This method was described in detail elsewhere (25). In women, we defined depression status (yes/no) as having: Mental Health Index-5 (MHI-5) ≤ 52 [from the Medical Outcomes Short Form-36, scaled from 0 to 100; higher scores indicate better mental health; included on questionnaires in 1992, 1996, and 2000 in the NHS and in 1993, 1997 and 2001 in the NHS II], self-reported regular antidepressant use, and/or self-reported physician-diagnosed

depression. In men, we defined depression status (yes/no) based on self-reported regular antidepressant use and self-reported physician-diagnosed depression.

Statistical analyses

Person-years for each participant were calculated from the return date of the phobic anxiety questionnaire (1988 in NHS, 1993 in NHS II and 1988 in HPFS) to the date of diagnosis of T2D, death, loss to follow-up, or the end of the follow-up period (June 30, 2008 for NHS, June 30, 2011 for NHS II and January 30, 2008 for HPFS), which came first. The CCI score was calculated and categorized into 5 groups as follows: <2 (the reference group); 2-<3; 3-<4; 4-<6; and 6 or above (the highest phobic anxiety symptoms group) (26). We used Cox proportional-hazards models to estimate the hazard ratios (HRs) and 95% confidence intervals (CI) of developing T2D across the 5 categories of the CCI; the comparison group was participants with CCI <2. In addition to adjustment for age, we further adjusted for the following covariates: Model 1: race, marital status, husband education (in NHS and NHS II), family history of diabetes, current aspirin use, menopausal status and hormone use (in NHS and NHS II), smoking status, alcohol intake, physical activity, and Model 2: further adjustment for dietary factors (energy intake, dietary score, coffee). In additional analyses, we further adjusted for body mass index (BMI) to examine the degree to which the association between T2D and CCI was mediated by BMI (Model 3). Due to known high degree of association between anxiety and depression (27) and the relationship between depression and T2D incidence (28), we also conducted a secondary analysis additionally adjusted for depression status. Because phobic anxiety symptoms might affect physical exam screening, we conducted an additional analysis in which we adjusted for routine screening of physical exam.

To better represent the long-term CCI scores and to minimize within-person variation, we created cumulative averages of CCI scores from baseline to second measurement. We stopped updating the CCI scores when the participants reported a diagnosis of stroke, CHD and cancer that might lead to changes in CCI scores. In sensitivity analyses, however, we also examined cumulative average of CCI scores that was continually updated even after the development of stroke, CHD, or cancer.

The above time-varying covariates included in the multivariate analyses were updated every 2 or 4 y. The last value was carried forward for one 2-y cycle to replace missing values. If the last value was also missing, then a missing value indicator was created (29). To examine whether associations between CCI scores and T2D risk were modified by established diabetes risk factors, a cross-product term between CCI scores and risk factor was included in the multivariable model. P values for tests for interactions were obtained from a likelihood ratio test comparing the model with the interactions terms to the model with only the main effects.

SAS macro %MEDIATE (publicly available at http://www.hsph.harvard.edu/faculty/spiegelman/mediate.html) was applied to estimate the proportion of the association between phobic anxiety and diabetes explained by other covariates according to the methods described by Lin et al. (30). For all statistical analyses, two-sided $p<0.05$ was considered to be statistically significant. Data were analyzed with SAS 9.3 (SAS Institute Inc).

RESULTS

During the 3,110,248 person-years of follow-up, a total of 12,876 incident T2D cases (6180 in NHS, 4401 in NHS II and 2304 in HPFS) were documented in these 3 cohorts. The CCI scores ranged from 0 to 16. The means of CCI scores were higher in women than men (NHS: 3.02±2.36, NHS II: 2.56±2.22, and HPFS: 2.04±1.91 ($p<0.0001$)) and a lower

proportion of men than women had scores in the highest group of CCI scores (≥6) (NHS: 14.8%, NHS II: 10.6% and HPFS: 5.8%).

Selected demographic and lifestyle characteristics and potential confounders were compared across levels of CCI scores in the 3 cohorts (Table 1). In these cohorts, men and women with CCI scores ≥6 were older, more likely to have a higher BMI, and to be current smokers. These participants were also more likely to have a family history of diabetes and history of hypertension and hypercholesterolemia. CCI scores were also associated with use of beta-blockers and antidepressant drugs ($p<0.0001$). Participants with high CCI scores also tended to have lower levels of physical activity, lower routine screening of physical exam, and lower dietary score; they also had a higher total energy intake. Women with high CCI scores tended to have lower levels of alcohol consumption but men with higher score of CCI had higher levels of alcohol consumption.

The age-adjusted HRs of T2D across categories of CCI score (2-<3, 3-<4, 4-<6, ≥6), compared with a score of <2, were increased by 11%, 21%, 28% and 48% (P_{trend} <0.0001) for NHS and 30%, 34%, 57% and 101%, (P_{trend} <0.0001) for NHS II. In multivariable Cox regression models with adjustment for demographic, behavior, family history and other biologic factors, relative to reference group, the HRs of T2D across categories of CCI scores were somewhat attenuated but remained significantly increased by 6%, 10%, 11% and 13% (P_{trend} =0.0005) for NHS; and by 19%, 11%, 22%, and 29% (P_{trend} <0.0001) for NHS II (Model 3, Table 2). When CCI score was modeled as a continuous variable, after adjustment for demographic, behavior, family history and other biologic factors the HRs was 3% higher for each CCI score increment in NHS and 4% higher for each CCI score increment in NHS II (Table 2, Model 3). Additional adjustment for depression or routine screening of physical exam did not appreciably attenuate the HR's further (data not shown). The proportion of the association between phobic anxiety and T2D explained by BMI and physical activity were reported in table 3. In NHS, BMI explained 41.7% (30.5-52.8) and physical activity explained 18.1% (13.0-23.2) of the association between phobic anxiety and T2D. In NHS II, BMI explained 43.7% (35.5-51.9) and physical activity explained 13.8% (10.8-16.7) of the association between phobic anxiety and T2D.

In HPFS, the significant association between CCI scores and diabetes incidence in age-adjusted model (P_{trend} =0.001) disappeared after adjustment for potential confounders or mediators in models 1 to 3 (Table 2). However, BMI and physical activity were not significant contributors of phobic anxiety and T2D association (BMI: 114.6%; 95% CI:-40.7-269.9 and physical activity: 65.4%; 95% CI:-22.7-153.5) (Table 3). In addition, results did not differ when we adjusted additionally for depression or routine screening of physical exam (data not shown).

In sensitivity analysis, in all the three cohorts, when we continued updating a participant's CCI scores even after a diagnosis of cancer, stroke or CHD, risk estimates were similar to those obtained when we stopped updating CCI scores at these diagnoses (data not shown).

We also examined whether the association between CCI scores and T2D risk differed by levels of T2D risk factors including smoking, alcohol intake, BMI, physical activity, family history of diabetes, and beta-blocker use. In all three cohorts, none of the P values for interaction were statistically significant (data not shown).

DISCUSSION

In these 3 large prospective cohorts' studies of US men and women, with 18–20 years of follow-up, we observed that a higher phobic anxiety symptoms scores was associated with a

greater risk of developing T2D in women. Associations remained statistically significant after adjustment for depression and numerous potential confounders and appeared to be partly mediated through body weight and physical activity. Age-adjusted associations are evident in men but these are less robust with addition of covariates. Our results do not support a significant role for phobic anxiety symptoms scores in T2D incidence in men independent of known T2D risk factors.

We found a gender difference in the relation between phobic anxiety symptoms scores and T2D risk. Association between phobic anxiety and risk of CHD in men and women has been previously reported in our and other cohorts (15-17). To our knowledge, there have been no prior studies in which the relationship between phobic anxiety and risk of T2D has been directly examined in both genders with similar measures and long-term follow-up. However, gender differences in the relationship between other forms of psychological stress and T2D have been shown. In line with our results, after 11 years follow-up, Norberg et al (31) demonstrated that work stress and low emotional support increased the risk of T2D among middle-aged women, but not in men. In contrast, Kato et al. (5), in a community-based, prospective cohort study, found that the risk of T2D increased with an increasing stress level, among men but not women. They assessed mental stress only based on three levels of response (low, medium and high) to the question, “How much stress do you feel in your daily life?”. In contrast to mental stress, they reported that the association between type A behavior (based on a validated instrument) and incidence of T2D was significant only among women. Also, Eriksson et al (32) found that self-reported psychological distress, measured by five items (anxiety, apathy, depression, fatigue and insomnia) in the questionnaire, was not associated with later onset of T2D in middle-aged women but was related to higher risk of T2D in middle-aged men. Psychological distress was measured by questioning how often during the latest twelve months they had been troubled by anxiety, apathy, depression, fatigue and insomnia. In a cohort study by short term follow-up, Atlantis et al. found higher risk of diabetes in Danish men and women with depression and anxiety (33). However, the results were not reported for men and women separately.

We could not determine why our observed associations between phobic anxiety symptoms scores and T2D were stronger in women than in men. It is possible that the differential association is partly related to the different distribution of phobic anxiety symptoms between men and women. Furthermore, it has been hypothesized that phobic anxiety symptoms may influence T2D risk through inflammation (12, 13) and activation of the hypothalamic–pituitary–adrenal (HPA) axis/hypercortisolism (34). In addition, corticotropin-releasing hormone (CRH) plays an essential role in the HPA axis and the stress response and both estrogen receptor α and β can stimulate CRH gene expression (35). Thus, it is possible that involvement of sex hormones in the regulation of the stress response and the HPA axis may partly determining who is more likely to develop new onset T2D under chronic stress (36), thereby distinguishing effects among men and women.

Similar other emotional stress, phobic anxiety may influence on behavioral factors, such as sedentary lifestyles, smoking, drinking alcohol and overeating that may also help to explain the effects of phobic anxiety on the onset of diabetes (7, 10, 11). In these cohorts, participants with higher phobic anxiety symptoms scores had higher BMI, higher total energy intake, lower levels of physical activity and a lower dietary score and were more likely to smoke. There was a gender difference in alcohol consumption: with higher scores on the phobic anxiety symptoms scale women tended to have lower levels while men had higher levels of alcohol consumption. While risk in women was somewhat attenuated by inactivity, obesity, alcohol and dietary intake, and smoking status, the association was also maintained even after adjusting for these factors. Furthermore, we did not observe the significant interactions with BMI, physical activity, alcohol intake, family history of

diabetes, smoking and antidepressant medication. Nevertheless, in men, we found that adjustment for alcohol intake, BMI and lifestyle factors substantially decreased the HRs, indicating phobic anxiety symptoms scores may be related to diabetes through poor health-related behaviors.

The large sample size and long follow-up provided sufficient power to examine the association with T2D over a wide range of phobic anxiety symptoms scores in men and women. Furthermore, the prospective nature and high rate of follow-up minimize the potential for recall and selection bias compared with other observational study designs because phobic anxiety symptoms were assessed prior to the event (T2D). The detailed, standardized and updated information on diet, physical activity, smoking and BMI in 3 cohorts allowed us to have information on a wide range of health and lifestyle-related confounders and control for them throughout the follow-up. Furthermore, we excluded participants with CHD, stroke and cancer at baseline and also stopped updating CCI scores after developing these diseases during the follow-up that could be associated with mood disorders. However, including these participants in the analysis did not change the results.

Potential limitations also need to be considered. Because of predominant white educated US adults, we cannot determine whether our findings are generalizable to other race or ethnic groups. Several T2D risk factors such as decreased physical activity and smoking could play the causal role in link between phobic anxiety and T2D risk, thus raising the possibility of statistical over-adjustment and leading to an underestimate of the association between phobic anxiety and T2D incidence. Also, detection bias cannot be ignored because phobic anxiety might affect testing for T2D. Participants with higher score of CCI had lower routine screening of physical exam and avoided seeing doctors. Another limitation of the study is the long interval between two measurements of phobic anxiety symptoms, and therefore, the inability to account for changes in phobic anxiety in short time, which would tend to obscure associations if the effect is of short duration. However, phobic disorders tend to be early in onset and chronic in nature (35). Overall median age-of-onset for phobic disorders is <12 years (9) and are considered to be influenced little during the life. Therefore, mid-life phobic anxiety levels in our participants likely reflected symptoms that had been present for decades, reducing concerns of possible change by changes lifestyle factors. It should be considered that CCI is not a diagnostic tool and association between CCI score and diabetes may not be restricted to phobic anxiety because the symptoms captured by the CCI scale have some overlap with other types of anxiety (22, 36). Despite this limitation, CCI has demonstrated strong relations with diabetes incidence in women.

In summary, our study in prospective cohorts suggest that higher levels of phobic anxiety symptoms are associated with increased risk of T2D in women, independent of other known risk factors; whereas phobic anxiety symptoms is not associated with T2D risk in men. Further studies are needed to elucidate the potential mechanisms underlying these associations and also the differences between men and women. Furthermore, if phobic anxiety symptoms are associated with the T2D incidence, at least in women; then, any potential impacts on T2D incidence may be prevented through early recognition, diagnosis and treatment of these disorders.

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Table 1

Characteristics of participants according to phobic anxiety score in NHS, NHS II and HPFS cohorts. [a]

	CCI Score				
	<2	**2-<3**	**3-<4**	**4-<6**	**6**
Women (NHS)					
Participants (n)	21405	12595	10649	14441	10246
Age (years)	54.0±7.1	53.8±7.1	53.9±7.1	53.8±7.2	54.1±7.1
BMI (kg/m2)	25.0±4.6	25.1±4.6	25.4±4.7	25.5±4.8	25.9±5.0
Physical activity (MET-h/wk)	17.0±23.1	16.0±21.3	15.6±21.9	15.0±22.0	13.2±19.1
Family history of diabetes (%)	27	28	28	29	31
Postmenopausal hormone use (%)	20	20	20	19	19
History of hypertension (%)	21	23	25	27	30
History of hypercholesterolemia (%)	20	22	23	23	25
Current smoker (%)	17	19	19	20	21
Multivitamin supplement use (%)	40	40	38	39	37
Current aspirin use (%)	64	65	65	66	64
Beta-blocker use (%)	7	8	8	9	10
Depression (%)	24	27	27	29	34
Race [white (%)]	98	98	98	98	97
Marital status [married (%)][b]	75	75	75	75	73
Physical exam [routine screening (%)]	86	83	83	81	78
Total calorie intake (kcal/d) [c]	1748±521	1768±521	1775±519	1787±524	1787±540
Alcohol (g/d) [c]	6.4±10.5	6.5±10.6	6.1±10.3	6.4±11.0	6.1±11.3
Diabetes dietary score [c]	12.1±2.4	12.0±2.5	12.0±2.4	11.9±2.4	11.7±2.5
Women (NHS II)					
Participants (n)	31131	15359	11472	13641	8517
Age (years)	38.0±4.7	38.0±4.6	38.0±4.6	38.2±4.6	38.3±4.6
BMI (kg/m2)	24.8±5.2	25.1±5.6	25.2±5.6	25.4±5.8	26.1±6.3
Physical activity (MET-h/wk)[d]	22.3±28.5	21.2±27.8	20.2±25.7	19.9±26.4	18.3±250
Family history of diabetes (%)	33	34	34	36	37
Postmenopausal hormone use (%)	6	6	7	7	8
History of hypertension (%)	6	7	8	8	10
History of hypercholesterolemia (%)	15	16	18	19	22
Current smoker (%)	9	11	11	13	15
Multivitamin supplement use (%)	44	45	45	43	43
Current aspirin use (%)	8	9	10	11	11
Beta-blocker use (%)[e]	4	5	5	6	7
Depression (%)	15	19	23	27	42
Race [white (%)]	97	97	97	96	94

	CCI Score				
	<2	**2-<3**	**3-<4**	**4-<6**	**6**
Marital status [married (%)]	79	81	81	81	80
Physical exam [routine screening (%)][f]	74	73	70	69	66
Total calorie intake (kcal/d) [c]	1769±536	1791±537	1800±547	1809±550	1819±572
Alcohol (g/d) [c]	3.2±5.9	3.2±6.0	3.3±6.5	3.2±6.3	2.8±6.1
Diabetes dietary score [c]	12.2±2.7	12.0±2.7	12.0±2.7	11.9±2.7	11.6±2.7
Men (HPFS)					
Participants (n)	14893	5817	4061	4286	1773
Age (years)	54.3±9.4	54.4±9.5	54.9±9.5	55.2±9.5	56.0±9.8
BMI (kg/m2)	25.3±3.0	25.4±3.1	25.5±3.1	25.7±3.2	25.9±3.5
Physical activity (MET-h/wk)	31.1±36.4	29.1±32.3	28.8±32.4	26.9±31.7	24.3±31.2
Family history of diabetes (%)	19	20	22	22	22
History of hypertension (%)	16	18	20	21	26
History of hypercholesterolemia (%)	17	18	20	21	24
Current smoker (%)	8	9	9	9	10
Multivitamin supplement use (%)	40	42	41	42	43
Current aspirin use (%)	35	39	40	39	43
Beta-blocker use (%)	6	6	8	8	9
Depression (%)[g]	14	19	19	22	26
Race [white (%)]	96	96	95	94	92
Marital status [married (%)]	90	90	90	91	89
Physical exam [routine screening (%)]	65	63	63	62	60
Total calorie intake (kcal/d)[c]	1991±609	2017±620	2037±630	2032±626	2039±656
Alcohol (g/d)[c]	11.3±15.0	11.6±15.3	11.7±15.4	11.9±15.9	12.3±17.0
Dietary score[c]	12.0±2.7	11.9±2.7	12.0±2.7	11.8±2.7	11.8±2.7

[a] All characteristics are for 1988 in NHS, 1993 in NHS II and 1988 in HPFS, except if otherwise indicated.

[b] Variables are obtained from 1992 questionnaire.

[c] Variables are obtained from 1986 questionnaire in NHS, 1991 questionnaire in NHS II and 1986 questionnaire in HPFS.

[d] Variables are obtained from 1991 questionnaire.

[e] Variables are obtained from 2001 questionnaire.

[f] Variables are obtained from 1989 questionnaire.

[g] Variables are obtained from 2000 questionnaire.

Table 2

Hazard ratio of type 2 diabetes by phobic anxiety score in NHS, NHS II and HPFS cohorts.

	CCI Score						
	<2	**2-<3**	**3-<4**	**4-<6**	**6**	P_{trend}	
Women (NHS, 1988-2008)							
Cases/Person-yrs	1667/390669	1089/229349	979/190685	1373/254352	1072/173091		
Age-adjusted model	1	1.11 (1.03-1.20)	1.21 (1.12-1.31)	1.28 (1.19-1.38)	1.48 (1.37-1.60)	<0.0001	1.06 (1.05-1.07)
Multivariate-adjusted model 1	1	1.08 (1.00-1.16)	1.14 (1.06-1.24)	1.18 (1.09-1.26)	1.25 (1.16-1.35)	<0.0001	1.04 (1.03-1.05)
Multivariate-adjusted model 2	1	1.07 (0.99-1.16)	1.13 (1.04-1.22)	1.16 (1.08-1.25)	1.23 (1.14-1.33)	<0.0001	1.04 (1.03-1.05)
Multivariate-adjusted model 3	1	1.06 (0.98-1.14)	1.10 (1.01-1.19)	1.11 (1.03-1.19)	1.13 (1.05-1.22)	0.0005	1.03 (1.02-1.04)
Women (NHS II, 1993-2011)							
Cases/Person-yrs	1414/549156	875/262838	627/187203	849/216411	636/128302		
Age-adjusted model	1	1.30 (1.20-1.42)	1.34 (1.21-1.47)	1.57 (1.44-1.71)	2.01 (1.83-2.21)	<0.0001	1.11 (1.09-1.12)
Multivariate-adjusted model 1	1	1.26 (1.15-1.36)	1.22 (1.11-1.34)	1.35 (1.24-1.47)	1.55 (1.41-1.71)	<0.0001	1.07 (1.05-1.08)
Multivariate-adjusted model 2	1	1.24 (1.14-1.35)	1.21 (1.10-1.33)	1.33 (1.22-1.44)	1.52 (1.38-1.67)	<0.0001	1.06 (1.05-1.08)
Multivariate-adjusted model 3	1	1.19 (1.09-1.29)	1.11 (1.01-1.22)	1.22 (1.12-1.32)	1.29 (1.18-1.42)	<0.0001	1.04 (1.03-1.05)
Men (HPFS, 1988-2008)							
Cases/Person-yrs	1065/263488	452/101737	333/67989	317/68364	128/26615		
Age-adjusted model	1	1.10 (0.99-1.23)	1.21(1.07-1.37)	1.15 (1.02-1.31)	1.21 (1.01-1.46)	0.001	1.04 (1.02-1.06)

	CCI Score						
	<2	**2-<3**	**3-<4**	**4-<6**	**6**	P_{trend}	
Multivariate-adjusted model 1	1	1.04 (0.93-1.16)	1.12 (0.99-1.27)	1.05 (0.93-1.19)	1.02 (0.84-1.22)	0.35	1.01 (0.99 - 1.03)
Multivariate-adjusted model 2	1	1.04 (0.93-1.16)	1.11 (0.98-1.26)	1.03 (0.91-1.17)	0.99 (0.82-1.19)	0.56	1.01 (0.98 - 1.03)
Multivariate-adjusted model 3	1	1.01 (0.90-1.13)	1.09 (0.97-1.24)	0.97 (0.85-1.10)	0.90 (0.75-1.09)	0.49	0.99 (0.97 - 1.01)

Multivariate-adjusted model 1: age (year), race (white/non-white), marital status (married/non-married), family history of diabetes, current aspirin use, smoking status (never, past, current 1-14/d, current 15-24/d, current ≥25), alcohol intake (none, .01-4.9, 5–14.9, ≥15 g/day), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, ≥27 METs/wk). Among women, we also adjusted for menopausal status and hormone use (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users) and husband's education (<high school, some high school, high school grade or collage grade, graduate school, not applicable or missing).

Multivariate-adjusted model 2: model 1 plus energy intake (quintile), diabetes dietary score (quintile), coffee (quintile),

Multivariate-adjusted model 3: model 2 plus BMI (<23, 23-25, 25-29.9, 30-34.9, ≥35 kg/m^2),

*Results for the two cohorts (NHS and NHS II) were pooled by means fixed-effects meta-analyses.

Table 3

The mediation proportion for the effect of phobic anxiety on diabetes risk explained by BMI and physical activity

	HR (95% CI) per 1 score CCI	Mediation proportion (95% CI)
Women (NHS, 1988-2008)		
Base model*	1.04 (1.03-1.05)	
Base model + physical activity	1.03 (1.02-1.04)	18.1% (13.0-23.2%)
Base model + BMI	1.02 (1.01-1.03)	41.7% (30.5-52.8%)
Women (NHS II, 1993-2011)		
Base model*	1.07 (1.06-1.08)	
Base model + physical activity	1.06 (1.05-1.07)	13.8% (10.8-16.7%)
Base model + BMI	1.04 (1.03-1.05)	43.7% (35.5-51.9%)
Men (HPFS, 1988-2008)		
Base model*	1.02 (0.99-1.04)	
Base model + physical activity	1.00 (0.98-1.03)	65.4% (−22.7-153.4%)
Base model + BMI	1.00 (0.98-1.02)	114.6% (−40.7-269.9%)

HR adjusted for age (year), race (white/non-white), marital status (married/non-married), family history of diabetes, current aspirin use, smoking status (never, past, current 1-14/d, current 15-24/d, current ≥25), alcohol intake (none, .01-4.9, 5–14.9, ≥15 g/day), energy intake (quintile), diabetes dietary score (quintile), coffee (quintile), Among women, we also adjusted for menopausal status and hormone use (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users) and husband's education (<high school, some high school, high school grade or collage grade, graduate school, not applicable or missing).