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Generalized Anxiety Disorder and Type 2 Diabetes Onset: Findings from the prospective Cooperative Health Research in the Region of Augsburg F4 and FF4 studies

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Abstract:	Objective To investigate the association between symptoms of generalized anxiety disorder (GAD) on the incidence of type 2 diabetes. Research design & Methods Participants from the prospective KORA F4/FF4 German cohort were followed for a mean of 6.5 years. Generalized Anxiety Disorder scale (GAD-7) was used to assess GAD symptoms and incident type 2 diabetes cases were confirmed using a standard oral glucose tolerance test. Multivariate logistic regression models adjusted for sociodemographic, lifestyle, cardio-metabolic risk factors and psychosocial risk factors were used to estimate the effect of GAD on the incidence of type 2 diabetes. Results The present study included 1,694 participants (51.8% women, 48.2% men) with a mean age of 51.2 years, among whom 113 (6.7%) met GAD criteria. Participants with GAD had more psychosocial impairment and higher levels of high sensitivity C-reactive protein than participants without GAD, although not cardio-metabolic dysregulation. During the follow-up period (11,102 person/years), 113 (6.5%) type 2 diabetes cases were confirmed. Participants with GAD had 2-fold higher incidence of type 2 diabetes than participants without GAD (17.7 vs. 8.7 cases/1000 person-years). Correspondingly, GAD independently increased the risk of type 2 diabetes by an odds ratio of 2.09 [95%CI 1.02-4.32, p=0.04] after adjustment, and had an even larger impact in individuals without prediabetes at baseline 2.79 ([0.95-8.24], P=0.06). Conclusions Although GAD was not associated with cardio-metabolic dysregulation, individuals with GAD suffered from psychological impairment and subclinical inflammation, consequently increasing their incidence of type 2 diabetes by over 2-fold.

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To:
Dr. Jess Fiedorowicz
Editor in Chief, *Journal of Psychosomatic Research*

Munich, October 22, 2020

Submission of Manuscript: "Generalized Anxiety Disorder and Type 2 Diabetes Onset: Findings from the prospective Cooperative Health Research in the Region of Augsburg F4 and FF4 studies'

Dear Dr. Jess Fiedorowicz,

The situation surrounding the COVID-19 pandemic has led to global uncertainty and worry, increasing the symptoms of generalized anxiety not only in individuals at risk but also the general population. Although psychological conditions are increasingly acknowledged as risk factors for the onset of type 2 diabetes, no study to date has convincingly shown that generalised anxiety disorder (GAD) is a significant risk factor.

In the current manuscript, GAD was associated with an increased risk of incident type 2 diabetes in over 1,600 participants from the general population followed for 7 years. Of note, the observed GAD – incident type 2 diabetes association remained significant in a fully adjusted model adjusted for main diabetes risk factors (odds ratio: 2.09 [95%CI 1.02-4.32, p=0.04]), as well as in participants without prediabetes at baseline.

This manuscript has been submitted solely to *Journal of Psychosomatic Research* and is not under consideration at any other journal and it has not been previously published, either in whole or in part, nor have the findings been posted online. All authors have read and approved the manuscript. As a corresponding author, I confirm that I have personal full access to all aspects of the research and writing process and take final responsibility for the paper. All persons designated as authors have qualified for authorship and declare no conflict of interest.

Looking forward to hearing from you.

Yours sincerely,

Karl-Heinz Ladwig
Senior lecturer at TUM Medical Faculty Munich, Germany

Highlights

- The current study shows participants with high symptoms of GAD were more likely to have low-grade inflammation as measured by plasma C-reactive protein levels at baseline, although GAD was not associated with cardiometabolic risk factors including obesity
- Nevertheless, during nearly 7 years of follow-up, participants with high symptoms of GAD developed type 2 diabetes at a 2-fold higher rate than participants without GAD, independently of traditional type 2 diabetes risk factors.

Generalized Anxiety Disorder and Type 2 Diabetes Onset: Findings from the prospective Cooperative Health Research in the Region of Augsburg F4 and FF4 studies

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Abstract

Objective To investigate the association between symptoms of generalized anxiety disorder (GAD) on the incidence of type 2 diabetes.

Research design & Methods Participants from the prospective KORA F4/FF4 German cohort were followed for a mean of 6.5 years. Generalized Anxiety Disorder scale (GAD-7) was used to assess GAD symptoms and incident type 2 diabetes cases were confirmed using a standard oral glucose tolerance test. Multivariate logistic regression models adjusted for sociodemographic, lifestyle, cardio-metabolic risk factors and psychosocial risk factors were used to estimate the effect of GAD on the incidence of type 2 diabetes.

Results The present study included 1,694 participants (51.8% women, 48.2% men) with a mean age of 51.2 years, among whom 113 (6.7%) met GAD criteria. Participants with GAD had more psychosocial impairment and higher levels of high sensitivity C-reactive protein than participants without GAD, although not cardio-metabolic dysregulation. During the follow-up period (11,102 person/years), 113 (6.5%) type 2 diabetes cases were confirmed. Participants with GAD had 2-fold higher incidence of type 2 diabetes than participants without GAD (17.7 vs. 8.7 cases/1000 person-years). Correspondingly, GAD independently increased the risk of type 2 diabetes by an odds ratio of 2.09 [95%CI 1.02-4.32, p=0.04] after adjustment, and had an even larger impact in individuals without prediabetes at baseline 2.79 ([0.95-8.24], P=0.06).

Conclusions Although GAD was not associated with cardio-metabolic dysregulation, individuals with GAD suffered from psychological impairment and subclinical inflammation, consequently increasing their incidence of type 2 diabetes by over 2-fold.

Key words: Anxiety, type 2 diabetes, incidence, subclinical inflammation

Introduction

Despite increasing knowledge of the risk factors for type 2 diabetes, recent projections estimate that the prevalence will rise by 51% to 700 million within the next 25 years (1). Although dysregulation of stress-related processes continue to gain significance as an important pathway towards type 2 diabetes (2), the effect of chronic worry in day-to-day life - which can manifest as generalized anxiety disorder (GAD) - has yet to be understood.

GAD is a highly prevalent mental health condition affecting up to 7% of the general population and over 20% of patients within primary care (3, 4). Evolving from the notion of 'free-floating anxiety', individuals suffering from GAD are characterized by dysregulated worrying, often paired with stress induced somatic symptoms (5, 6). The physiological and behavioral effects of GAD can lead to cardiac dysregulation (e.g. lower heart rate variability and higher heart rate) (7), increased arousal at baseline in the absence of threat (8), as well as an increased response to threat stimuli (9, 10). In consequence, the resulting allostatic load is thought to affect the individual's systematic physiology by disturbing the complex balance between the neuroendocrine, immune and metabolic mediators(11), particularly via "glucose allostasis" (12).

In line with this, the umbrella term 'anxiety', encompassing a cluster of conditions and high comorbidity with depression, has been associated with the onset of type 2 diabetes in a healthy population. A meta-analysis of 14 longitudinal studies with nearly 2 million participants confirmed that anxiety increases the odds of type 2 diabetes by 1.47 (1.23-1.75), although GAD as a risk factor remains inconclusive (13).

As it has recently been suggested that GAD significantly amplifies the progression from prediabetes to type 2 diabetes in a healthy population(14), it is further necessary to investigate the independent effect of GAD in a healthy population. In line with this, the present investigation aims to evaluate whether the identification of individuals with symptoms of GAD could be a step towards early intervention and prevention against type 2 diabetes.

Methods

Participants and Data Collection

Data were obtained from 2,161 participants who participated in the Cooperative Health Research in the Region of Augsburg (KORA) F4 study (2006–2008) and the KORA FF4 study (2013–2014), both follow-up examinations of the population-based KORA Survey 4 study (1999–2001) conducted in Augsburg (Germany)(14, 15). The inclusion and exclusion criteria leading to the final sample of 1,688 participants are presented in Supplementary Figure 1. A drop-out analysis has revealed that individuals who did not participate in follow-up examination were older ($p<0.001$) and had higher prevalence of prediabetes ($p=0.006$) and GAD ($p=0.04$).

Data were collected in standardized personal interviews conducted by trained medical staff and a self-administered questionnaire. Participants further underwent an extensive medical examination including the collection of a blood sample and anthropometric measurement. All procedures were approved by the ethics committee of the Bavarian Chamber of Physicians.

Assessment of type 2 diabetes

Type 2 diabetes prevalence and incidence was based on physician validated self-report, current use of glucose-lowering agents, and on a standard 75-g oral glucose tolerance test (OGTT) (16). Glucose tolerance categories were defined using fasting and 2-h glucose levels according to WHO diagnostic criteria(17) :normoglycemia (fasting glucose <6.1 mmol/l and 2-h-glucose <7.8 mmol/l), prediabetes (impaired fasting glucose (IFG) [fasting glucose ≥6.1 mmol/l but <7.0 mmol/l, and 2-h-glucose <7.8 mmol/l], impaired glucose tolerance (IGT) [fasting glucose <6.1 mmol/l and 2-h-glucose ≥7.8 mmol/l but <11.1 mmol/l] or combined IFG/IGT), newly diagnosed diabetes (fasting glucose ≥7.0 mmol/l or 2-h-glucose ≥11.1 mmol/l).

Assessment of GAD symptoms

GAD symptoms were assessed using the Generalised Anxiety Disorder-7 (GAD-7) scale (18), which evaluates the severity of seven-items on a 4-point Likert scale with scores ranging from 0–21 points. The presence of GAD symptoms were defined as having a total score ≥10 and no GAD if <10 on GAD-7 scale, based on findings that 89% of 965 patients who underwent diagnostic interviews for the presence of GAD scored 10 or higher on the GAD-7 (18) .

Concurrent sociodemographic, lifestyle and cardiometabolic risk factors

The assessment of lifestyle, anthropometric, and metabolic risk factors were performed as previously reported (16). *Low education* was defined as less than 12 years of education. *Currently*

smoking was defined as smoking at least one cigarette per day. *Alcohol consumption* was measured continuously (g/day) and classified into the binary variable: low (0–39.9 g/day for men, 0–19.9 g/day for women) and high (≥40 g/day for men, ≥20 g/day for women) alcohol intake (19). *Physical activity* was based on the frequency and duration of activity during leisure time in summer and winter for at least <1 hour/week. *Obesity* was defined as having a BMI >30 kg/m^2, and *waist-to-hip ratio* was obtained by dividing the waist circumference by the hip circumference. Total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods (CHOD-PAP, Boehringer Mannheim, Germany). The *TC/HDL-C ratio* was dichotomized into two groups (<5, ≥5). Triglycerides (mg/dl) were measured with the Boehringer GPO-PAP assay (non-fasting in diabetic subjects). *Hypertension* was defined as blood pressure of ≥140/90 mmHg and/or using antihypertensive medication(20). High sensitivity C- reactive protein (*hsCRP*)(mg/L) was used to assess subclinical inflammation. Concentrations of *hs*CRP were measured in EDTA plasma samples using a high-sensitivity latex-enhanced nephelometric assay on a BN II analyser (Siemens, Marburg). Intra- and inter-assay CVs were 4.27% and 6.11%, respectively.

Concurrent psychosocial risk factors

Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9) with a validated cut-off score of 10 (21, 22). *Antidepressant medication* was defined as using selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, monoamine oxidase inhibitors (MAOI) or other antidepressants. *Sleep complaints* included difficulty with initiation and or maintaining sleep. *Somatic symptoms* were based on 8 items from the Van-Zerssen Symptom Checklist and assessed the severity of physical symptoms associated with psychosocial stress.

Statistical analysis

Baseline characteristics were assessed according to GAD status and presented as mean (standard deviation, SD) for continuous variables and frequency (%) for categorical variables. Differences between groups were compared using Kruskal-Wallis test for continuous variables and Chi-squared test for categorical variables.

The absolute incidence of type 2 diabetes associated with GAD was assessed using Poisson regression, whereas the odds of developing type 2 diabetes was assessed using stepwise logistic regression models to obtain odds ratios (OR) and 95% confidence intervals (CI). Model 1 was adjusted

for age, sex and educational level, model 2 also included lifestyle factors (smoking status, alcohol consumption and physical activity), model 3 also included cardio-metabolic factors (BMI, TC/HDL-C ratio, hypertension) and *hs*CRP, whereas model 4 further included depression and antidepressant medication use. As a sensitivity analysis, associations between anxiety and incident type 2 diabetes were assessed after adjustment for as well as exclusion of participants with prediabetes.

A p-value <0.05 was used for all tests to indicate statistical significance. Statistical analysis was performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). The analysis and description of the study followed the STROBE guidelines for observational studies (23).

Results

Baseline characteristics

In the present study including 1,694 participants (51.8% women, 48.2% men) with a mean (±SD) age of 51.2 (10.6) years, a total of 113 (6.7%) participants with GAD were identified. The baseline characteristics shown in Table 1 revealed that participants with GAD were more likely to be women, physically inactive, living alone, have higher *hs*CRP levels and a lower prevalence of hypertension. GAD was additionally associated with substantially worse psychosocial stress by higher levels of depression, somatization and sleep complaints. However, significant differences in smoking status, alcohol intake or cardio-metabolic factors were not observed.

Incident type 2 diabetes by GAD status

During the follow-up period of 6.5 years accounting for 11,102 person-years, 110 participants (6.5%) were diagnosed with type 2 diabetes, of whom 14 (12.7%; 64% women, 36% men) had GAD symptoms at baseline (Table 2). Participants with GAD had a 2-times higher absolute incidence of type 2 diabetes than participants without GAD (17.7 vs 8.7 cases per 1000 person-years, p=.01). Correspondingly, regression analyses confirmed that GAD was independently associated with an increased risk of type 2 diabetes by an odds ratio (OR) of 2.09 [95%CI 1.02-4.32, p=0.04], independently of concurrent risk factors (Table 3). On the other hand, the incidence of prediabetes did not differ between participants with or without GAD (Table 2).

A sensitivity analysis examining GAD-type 2 diabetes association following exclusion of 245 (14.5%) participants with prediabetes at baseline, of whom 17 (6.9%) had GAD, strengthened our main

findings. In the fully adjusted model, the odds of developing type 2 diabetes were 2.79 ([0.95-8.24], p=0.06). Likewise, adjustment for prediabetes in the fully adjusted association between GAD and type 2 diabetes led to increased onset of type 2 diabetes in participants with GAD in comparison to those without GAD (OR 2.68 [1.23-5.88], p=0.01).

Discussion

In the present investigation including 1,694 community-dwelling participants, the prevalence of GAD reached nearly 7%. Participants with GAD concurrently presented a cluster of psychosocial stress conditions, including depression, somatic symptoms, sleep complaints and living alone. The impairment associated with GAD was further reflected by subclinical inflammation, as elucidated by *hs*CRP. Of note, GAD was not associated with metabolic risk factors, including obesity, waist-to-hip ratio, triglycerides and TC/HDL ratio. Nevertheless, participants with GAD had an over 2-fold higher incidence of type 2 diabetes over 6.5 years. In addition, the effect of GAD on type 2 diabetes was further amplified by adjustment, as well as the exclusion of the presence of prediabetes.

The current investigation presents evidence that in an apparently healthy population, GAD is associated with an increased onset of type 2 diabetes as confirmed by a glucose tolerance test. Notably, GAD as a risk factor was independent of comprehensive set of diabetes risk factors including lifestyle, cardio-metabolic, psychosocial risk factors, and *hs*CRP. The current investigation extends the existing meta-analysis of the anxiety – type 2 diabetes link, which was restricted to an abstract (24), and an association only in the presence of prediabetes (25).

Analyses of baseline characteristics associated with GAD provided insight into the mechanisms that may contribute to the onset of type 2 diabetes. Given its' detrimental nature, GAD was associated with severe psychosocial stress. For instance, over 35% of participants with GAD had depressive symptoms in comparison to only 2% of participants without GAD, whereas up to 12% of participants with GAD were on antidepressant medication. Similarly, over 50% of participants with GAD additionally had sleep problems and somatic symptoms. Furthermore, GAD was significantly associated with physical inactivity, an established risk factor for type 2 diabetes, particularly when combined with autonomic nervous system dysfunction (26). However, the harmful risk factor profile associated with GAD surprisingly did not include metabolic dysregulation, advocating psychosocial stress pathology that may manifest atypically. This was supported by the current finding that GAD was not associated

with a higher incidence of prediabetes, considered the underlying aetiology of metabolic syndrome, hence more research is needed to elucidate an independent stress-induced phenotype of type 2 diabetes.

Although the present investigation did not aim to investigate the underlying mechanisms of the GAD-type 2 diabetes link, our findings confirm that the brain is a key player in glucose regulation and type 2 diabetes (27). Specifically, the subclinical inflammation observed in participants with GAD is thought to a marker of the neuroendocrine dysregulation between psychosocial stress and type 2 diabetes (28-30). Stress signalling pathways, including the autonomic nervous system and the HPA axis can supress or dysregulate immune system homeostasis by altering cytokine balance and inducing low-grade inflammation (31). GAD, notably when accompanied by somatic symptoms, disrupts the autonomic response (32) via overactivation of the sympathetic nervous system (33) and/or under activation of the parasympathetic nervous system (34). This underlying mechanism has been linked to a number of diseases including type 2 diabetes (35). For instance, the reduced heart rate variability associated with GAD (34) increases glucocorticoids and expression of pro-inflammatory cytokines (36). Consequent glucocorticoid receptor resistance, in turn, further dysregulates HPA axis function and failure to down-regulate inflammatory responses (37). Altogether, these mechanisms may contribute to insulin resistance (38) - which itself is intrinsically connected to low-grade inflammation (39).

The strengths of the current study include its prospective study design, validated diagnosis of type 2 diabetes and OGTT at both time points, the measurement of GAD based on a highly specific and validated instrument, as well as comprehensive adjustments for sociodemographic, metabolic and lifestyle factors, as well as depression and anti-depressive medication. On the other hand, the association could be attenuated by confounders which were not available in the current study. Additionally, although there were not a large sample of participants with GAD, the prevalence in the current population was in line with the literature and the width and magnitude of the 95% confidence intervals were not wide. However, as participants with prediabetes and GAD were less likely to partake in the follow-up, the results reported herein could be an underestimation of the real effect. Lastly, although the current definition of GAD symptoms is limited to the GAD-7(18), the diagnostic validity of this instrument has been shown to be high in the general population (40, 41).

In conclusion, the current study provides preliminary evidence that GAD increases the incidence of type 2 diabetes during 6.5 years of follow-up. Furthermore, the association remains robust despite

adjustment for comprehensive risk factors of type 2 diabetes, as well as exclusion of baseline prediabetes. The implications of these findings are important within a primary care setting because individuals with GAD are likely to suffer from overwhelming stress-related symptoms, driving them to seek health care assistance (4). Most importantly, as the current manuscript has revealed, individuals with GAD may not present several main type 2 diabetes risk factors including increased body weight. Therefore, GAD as an independent and modifiable risk factor for type 2 diabetes must be acknowledged and further studied.

Declaration of interest

None

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Table 1. Baseline characteristics of KORA F4 stratified by GAD status in adults between 25 and 74 years old (N=1,694)

Baseline characteristics (%)	**Total N=1,694**	**Low anxiety N=1,581**	**High anxiety N=113**	***p***
Age, mean (SD), years	**51.2 (10.6)**	51.2 (10.6)	52.3 (9.7)	0.25
Female	**878 (51.8)**	802 (50.7)	76 (67.3)	0.001
Male	**816 (48.2)**	779 (49.3)	37 (32.7)	0.001
Low education	**916 (54.1)**	847 (53.6)	69 (61.1)	0.12
Currently smoking	**311 (18.4)**	296 (18.7)	15 (13.3)	0.15
High alcohol intake*	**306 (18.1)**	285 (18.0)	21 (18.6)	0.90
Physically inactive	**657 (38.9)**	597 (37.9)	60 (53.1)	0.001
Hypertension	**446 (26.3)**	415 (26.2)	31 (27.4)	0.78
TC/HDL-C ratio ≥5	**322 (19.0)**	303 (19.2)	19 (16.8)	0.54
Triglycerides (mean (SD),	**117.3(83.8)**	117.3(84.3)	116.3(76.3)	0.90
Obesity†	**351 (20.7)**	325 (20.6)	26 (23.0)	0.53
Waist-to-hip ratio	**0.9(0.09)**	0.9(0.08)	0.8(0.09)	0.09
BMI, mean (SD), kg/m^2	**26.9 (4.6)**	26.9 (4.6)	27.0 (4.4)	0.94
‡*hs*CRP[c], mean (SD), mg/L	**2.0 (3.4)**	1.9 (3.4)	2.4 (2.9)	0.03
Depressive symptoms	**70 (4.1)**	33 (2.1)	37 (32.7)	0.001
Sleep complaints	**406 (24.0)**	342 (21.6)	64 (56.6)	0.001
Living alone	**351 (20.7)**	311 (19.7)	40 (35.4)	0.001
Somatic Symptoms	**370(21.8)**	306(19.4)	64 (56.6)	0.001
Antidepressant medication	**43 (2.5)**	30 (1.9)	13 (11.5)	0.001

Abbreviations: BMI, body mass index; SD, standard deviation; TC/HDL-C, Total cholesterol/High density lipoprotein cholesterol;
*High alcohol intake: ≥40 g/day for men, ≥20 g/day for women
†Obesity: BMI ≥30.0 kg/m^2
‡*hs*CRP levels are presented as geometric means

Table 2. Baseline and follow-up prediabetes and diabetes status according to GAD in adults between 25 and 74 years old (N=1,694)

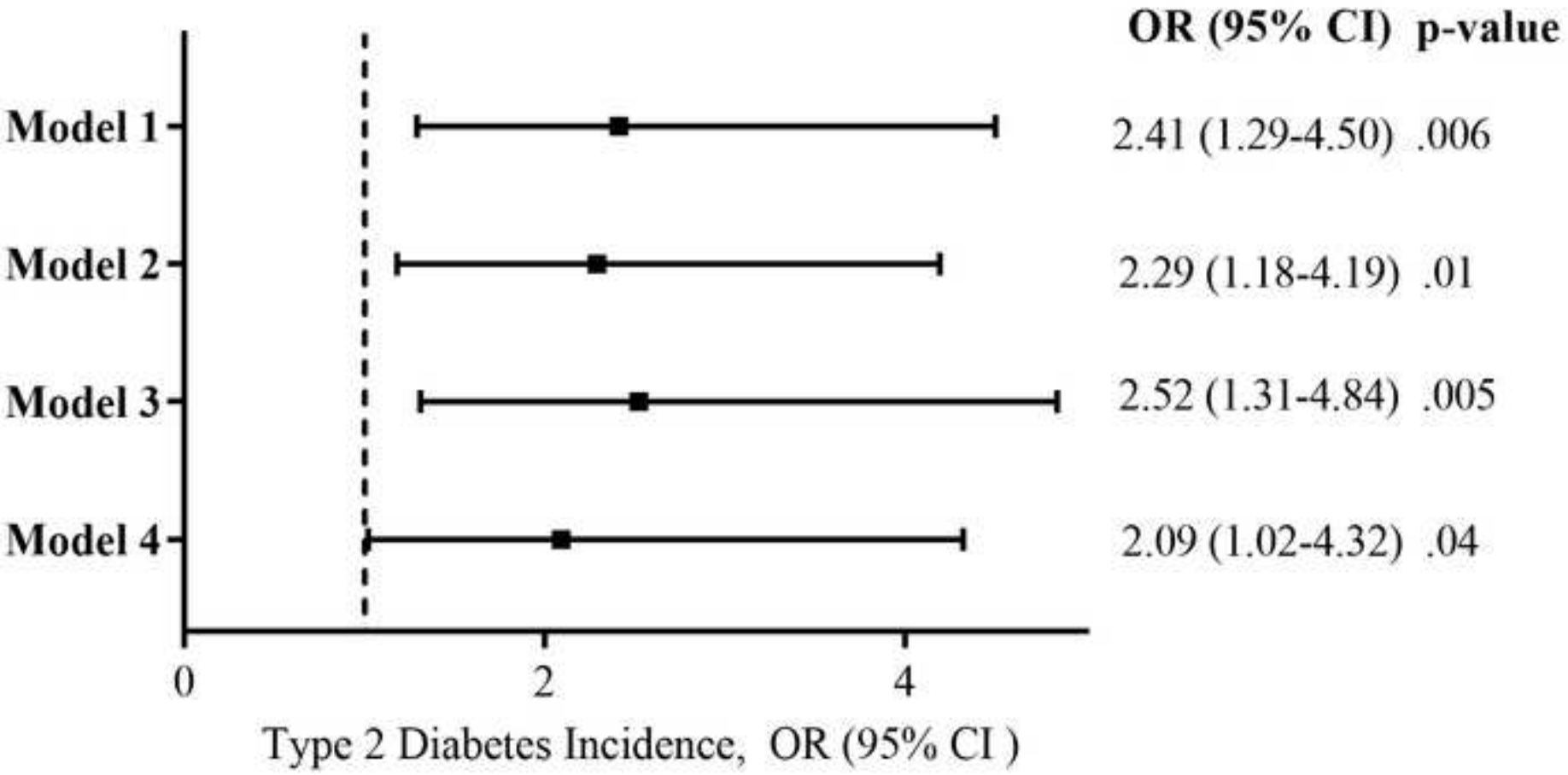
Diabetes status	**Total (N=1694)**	**Low anxiety (N=1581)**	**High anxiety (N=113)**
Baseline			
Prediabetes	245(14.5)	228 (14.4)	17 (15.0)
No diabetes	1449 (85.5)	1353 (85.6)	96 (85.0)
Incidence at follow-up			
Type 2 diabetes	110 (6.5)	96 (6.1)	14 (12.4)
Prediabetes	316 (18.7)	201 (14.9)	13 (13.5)

Figures

Figure 1. Odds ratios (OR) and 95% confidence intervals of type 2 diabetes incidence in participants with generalized anxiety disorder (GAD) in comparison to participants without GAD, adjusted for risk factors (N =1694; type 2 diabetes cases=110).

Model 1: age, sex, educational level
Model 2: Model 1 + smoking status, alcohol intake, physical activity
Model 3: Model 2 + BMI, hypertension, *TC/HDL-C ratio, hs*CRP
Model 4: Model 3 + depression symptoms and use of antidepressants

Figure 1



Supplementary figure 1