



Short report: Epidemiology

Anxiety boosts progression of prediabetes to type 2 diabetes: findings from the prospective Cooperative Health Research in the Region of Augsburg F4 and FF4 studies

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Abstract

Aim To investigate the association between anxiety symptoms and the progression from prediabetes to type 2 diabetes.

Methods A sample of 1708 participants aged 31–82 years from the population-based Cooperative Health Research in the Region of Augsburg F4 and the follow-up Cooperative Health Research in the Region of Augsburg FF4 studies was included. Prediabetes was defined as impaired fasting glucose and/or impaired glucose tolerance, and anxiety status was measured by the generalized anxiety disorder-7 questionnaire. Newly diagnosed type 2 diabetes cases were identified after 6.5 years (11 102 person-years) and confirmed by medical records. Multivariate logistic regression analyses were employed to estimate the effect of prediabetes and anxiety on the incidence of type 2 diabetes with different levels of adjustments for potential confounders. The population attributable risk of type 2 diabetes in participants with prediabetes and anxiety was estimated.

Results Prediabetes at baseline was prevalent in 247 participants, of whom 77 developed diabetes after follow-up, accounting for a progression rate of 31%. In participants with prediabetes, high anxiety was associated with a 3-fold increased risk of progression to type 2 diabetes in comparison with low anxiety, even after accounting for socio-demographic, lifestyle and metabolic risk factors (OR = 2.82, 95% CI = 0.95–8.37, $P = 0.06$). A significant proportion of incident type 2 diabetes was attributed to having anxiety in addition to prediabetes (attributable risk proportion: 0.52; 95% CI = 0.004–1.04, $P = 0.05$).

Conclusions Anxiety symptoms independently increase the progression risk of prediabetes to type 2 diabetes and should be routinely considered alongside the traditional risk factors in people with prediabetes.

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Introduction

Prediabetes indicates a high-risk state for diabetes development with blood glucose concentrations higher than normal

but lower than the diabetes threshold [1]. Specifically, individuals with prediabetes are faced with a 3–10-fold higher risk of developing type 2 diabetes, with a yearly conversion rate of 5–10%, indicating that up to 70% of people with prediabetes will eventually progress to type 2 diabetes [1].

Thus, identifying predictors of the progression from prediabetes to diabetes can contribute substantially to reducing the incidence of type 2 diabetes. Clinicians often employ variables such as hypertension, BMI, diabetes family history and lifestyle information to prepare a risk profile. However, to

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What's new?

- Although both prediabetes and anxiety are established risk factors for the incidence of type 2 diabetes, the role of anxiety in the progression from prediabetes to diabetes remains inconclusive.
- The current investigation reveals that anxiety, independently of additional risk factors, boosts the progression from prediabetes to type 2 diabetes.
- These findings highlight the significance of screening for anxiety among high-risk people with prediabetes.

date, no risk prediction model enables a precise prediction of those people who will progress to type 2 diabetes.

It is increasingly acknowledged that considering psychosocial predictors of type 2 diabetes is imperative in clinical practice [2,3], although investigations specific to the role of prediabetes in this dynamic remain scarce. It has been shown that individuals having prediabetes with depression or anxiety have a 2.52- and 2.36-fold increased risk of progression to self-reported type 2 diabetes, respectively, although the synergistic effect between anxiety symptoms and prediabetes was not significant following adjustment for covariates [4]. This finding is in line with studies showing an association between anxiety and the incidence of type 2 diabetes [5]; however, this needs to be investigated further, and within the framework of anxiety symptomology, adjusted for that of co-morbid depression.

Hence, in the current investigation, we aim to assess the extent to which anxiety symptoms increase the risk of progression from prediabetes to type 2 diabetes using a prospective population-based study.

Participants and methods

Data were derived from the Cooperative Health Research in the Region of Augsburg (KORA) F4 (N = 3080, 2006–2008, aged 31–81 years) and KORA FF4 studies (N = 2279, 2013–2014), both follow-up examinations of the population-based KORA S4 study (1999–2001, N = 4261, aged 25–74 years). This study was approved by the Ethics Committee of the Bavarian Medical Association.

Previously diagnosed type 2 diabetes was self-reported by the participants and validated by the physicians, or as current use of glucose-lowering agents. All participants without diabetes received a standard oral glucose tolerance test to identify new cases according to WHO criteria [6]. Prediabetes was defined as impaired fasting glucose (fasting plasma glucose of 42–48 mmol/mol [6.0–6.5%] and/or impaired glucose tolerance (2 hours of plasma glucose of < 53 mmol/mol [7.0%] after oral glucose tolerance test). Incidence of type 2 diabetes was determined by clinician-validated diagnoses of type 2 diabetes, current use of antidiabetic agents, or

high fasting and/or 2-hour glucose levels in the oral glucose tolerance test. Generalized anxiety disorder was assessed by using the self-reported Generalized Anxiety Disorder-7 scale, whereby high anxiety was defined by a score of 10 or higher [7]. The reliability and validity of the Generalized Anxiety Disorder-7 scale in detecting anxiety has been confirmed by population-based studies [8]. Information on lifestyle and objectively measured metabolic covariates have previously been described elsewhere [9]. After excluding participants with any type of diabetes or unknown diabetes status at baseline (n = 432), unknown status of anxiety (n = 352) and unknown type 2 diabetes status at follow-up (n = 588), the final study population consisted of 1708 participants. A dropout analysis revealed that individuals who were not participants in the KORA-FF4 study were older ($P < 0.001$), and had a higher prevalence of prediabetes ($P = 0.006$) and anxiety ($P = 0.04$).

Descriptive characteristics were summarized according to prediabetes status at baseline. The χ^2 test was used to examine the differences within categorical variables and ANOVA for continuous variables.

Multivariate logistic regression analyses assessed the odds of type 2 diabetes in participants with prediabetes and high anxiety. Model 1 was adjusted for age and sex; model 2 was additionally adjusted for smoking (≥ 1 cigarette/day), alcohol consumption and physical activity; model 3 (primary model) was additionally adjusted for obesity, hypertension and dyslipidaemia; and model 4 was further adjusted for depression, as assessed by the short version of the Patient Health Questionnaire-9. The proportion of incident type 2 diabetes cases attributable to the interaction of exposure to both anxiety and prediabetes was calculated by the Attributable Risk Proportion, where an attributable risk proportion value of > 0 indicates an additive effect of anxiety in individuals with prediabetes [10]. The attributable risk proportion value was calculated using the R package 'epiR' [11]. All statistical analyses were run in RStudio version 1.1.383. An alpha level of 5% was used throughout without any adjustment for multiplicity of statistical tests.

Results

The current study included 1708 participants (48% men, 52% women; mean age 51 years, SD 10), among whom 247 (14%) had prediabetes and 114 (7%) had anxiety symptoms at baseline. According to the baseline characteristics presented in Table 1, participants with prediabetes were more likely to be older, male, non-smokers, less physically active, obese, and have hypertension and dyslipidaemia, as well as higher depression symptoms compared with participants without prediabetes. However, no differences were found in anxiety status between participants with or without prediabetes. On the other hand, participants with anxiety were more likely to be women and less physically active in comparison with those without anxiety at baseline.

Table 1 Baseline characteristics of 1708 study participants from the KORA F4 study, stratified by prediabetes status

Characteristics	No prediabetes N = 1461 (85.54%)		Prediabetes N = 247 (14.56%)		P-value
	N	%	N	%	
Moderate/severe GAD					1.00
No	1364	93	230	93	
Yes	97	7	17	7	
Age (year) (mean ± SD)	50 ± 10		58 ± 9		<0.001
Sex					0.007
Men	683	47	139	56	
Women	778	53	108	44	
Education					0.17
Low	777	53	144	58	
High	680	47	103	42	
Living alone					0.25
No	1150	79	203	82	
Yes	311	21	44	18	
Smoking					0.005
No	1220	84	224	91	
Yes	241	16	23	9	
Alcohol					0.51
No	391	27	64	26	
Moderate	813	56	132	53	
High	257	18	51	21	
Physical activity					0.001
Active	913	62	127	51	
Inactive	548	38	120	49	
Obesity					<0.001
No	1216	83	139	56	
Yes	244	17	108	44	
Hypertension					<0.001
No	1129	77	128	52	
Yes	330	23	119	48	
Dyslipidaemia					<0.001
No	1218	83	167	68	
Yes	243	17	80	32	
Depression					0.01
Mild	1409	96	228	92	
Moderate	38	3	13	5	
Severe	14	1	6	3	

P-values: ANOVA for continuous variables and χ^2 test for categorical variables
GAD, generalized anxiety disorder

After the follow-up mean of 6.5 years (accounting for 1102 person-years), 112 (7%) participants were diagnosed with type 2 diabetes. Prediabetes at baseline was prevalent in 77 (69%) of these participants, accounting for a progression rate of 31% (average annual rate 5%). By contrast, 14 (12%) participants with anxiety developed type 2 diabetes at follow-up.

Participants with prediabetes (OR = 10.76, 95% CI = 6.52–17.76, $P < 0.001$) or high anxiety (OR = 2.89, 95% CI = 1.09–7.20, $P = 0.03$) experienced increased odds of type 2 diabetes in model 3. The odds of type 2 diabetes incidence in participants with prediabetes and high anxiety, in comparison with low anxiety, is presented in Table 2. In individuals with prediabetes, high vs. low anxiety increased the odds of type 2 diabetes incidence (OR = 2.82, 95% CI = 0.95–8.37, $P = 0.06$). However, this borderline significance was largely attenuated by adjustment for depression ($P = 0.11$).

In comparison with participants without prediabetes and low anxiety, those with anxiety and prediabetes had substantially higher odds of developing type 2 diabetes (OR = 20.90, 95% CI = 6.35–69.00, $P < 0.001$). Based on this, attributable proportion of risk revealed that the joint effect of prediabetes and anxiety attributed a risk of 0.52 in type 2 diabetes incidence (95% CI = 0.004–1.04, $P = 0.05$) in model 3, implying a significant additive effect.

Discussion

In the current investigation, 7% of the 1708 community-dwelling participants developed type 2 diabetes during a mean follow-up period of 6.5 years. Confirming previous studies, prediabetes [1] and anxiety [5] were individually significant predictors of diabetes incidence during this time. Nevertheless, the additional presence of anxiety in participants with prediabetes more than tripled the incidence of

Table 2 Risk of type 2 diabetes in 247 participants with prediabetes from the KORA F4-FF4 study, according to high vs. low anxiety symptoms

Prediabetes	N	Type 2 diabetes	Model 1		Model 2		Model 3		Model 4	
			OR	P-value	OR	P-value	OR	P-value	OR	P-value
low anxiety	230	69	1.00 (reference)	0.00	1.00 (reference)	0.00	1.00 (reference)	0.00	1.00 (reference)	0.00
High anxiety	17	8	3.06 (1.07–8.77)	0.04	2.92 (1.00–8.52)	0.05	2.82 (0.95–8.37)	0.06	2.74 (0.79–9.55)	0.11

P-values are determined by Wald Chi-square tests based on the analysis of maximum likelihood estimates.

Model 1: logistic regression model adjusted for sex and age (continuous)

Model 2: Model 1 + smoking status, alcohol consumption, physical activity

Model 3: Model 2 + obesity, hypertension, dyslipidaemia

Model 4: Model 3 + depression

diabetes. Notably, extended adjustment for concurrent metabolic risk factors and depression only marginally reduced the impact of anxiety in participants with prediabetes on the progression to a diabetes diagnosis, but led to a marginal loss of statistical significance.

Only one population-based study, with a follow-up period of 4.6 years, has evidenced the impact of anxiety in prediabetes on disease progression. Deschenes *et al.* [4] found that participants were 2.36-fold more likely to progress from prediabetes to diabetes if they reported high symptoms of anxiety, although the interaction did not reach statistical significance. Similar to their findings, this association in the current analysis led to 2.82-fold ($P = 0.06$) increased odds of type 2 diabetes diagnoses in individuals with prediabetes in the primary model, and 2.74-fold ($P = 0.11$) when including depression. However, the current study further showed a significant attributable proportion of diabetes risk (0.52) as a result of the interaction between prediabetes and anxiety. This is a more reliable method of analysis for assessing additive interactions using ORs because it is less affected by changes in the type of interaction of baseline risk, as opposed to the Synergy Index used in the previous study [12].

Anxiety might contribute to the progression of prediabetes to diabetes through a variety of possible mechanisms. Anxiety is one of the potential factors leading to hypothalamic-pituitary-adrenal axis abnormalities, which could cause insulin resistance [13]. People with anxiety are more likely to adopt unhealthy lifestyles, such as smoking, drinking alcohol, an unhealthy diet and physical inactivity, all of which increase the risk of diabetes [14]. Some drugs prescribed for treating mental health disorders were also associated with an increased risk of type 2 diabetes [15]. Further research is needed to better understand the biological mechanisms of anxiety that contribute to the onset of diabetes.

The current study is the first to assess the association of anxiety, prediabetes and type 2 diabetes based on a prospective population-based cohort with objective measurements of prediabetes and diabetes status. Nevertheless, it is estimated that a relevant proportion of participants had developed type 2 diabetes before being lost to follow-up,

potentially underestimating our results. In addition, as only 17 participants presented both prediabetes and anxiety at baseline, the 95% CIs were wide and the study is lacking power to produce a statistically significant difference, particularly within the models where more covariates were included. Hence, larger studies are needed to reliably demonstrate the significant effect of anxiety in the transition from prediabetes to diabetes.

Conclusion

Anxiety symptoms independently boost the progression from prediabetes to type 2 diabetes after accounting for socio-demographic, lifestyle and metabolic risk factors. Physicians are advised to additionally screen for anxiety when treating high-risk patients with an adverse risk factor profile. Further research into the underlying mechanisms and the effectiveness of mental health interventions among high-risk populations are urgently needed.

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Competing interests

Nothing to declare.

REFERENCES

- 1 Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: a high-risk state for diabetes development. *Lancet* 2012; **379**: 2279–2290.
- 2 Hackett RA, Steptoe A. Psychosocial factors in diabetes and cardiovascular risk. *Curr Cardiol Rep* 2016; **18**: 95.
- 3 Naicker K, Manuel D, Overland S, Skogen JC, Johnson JA, Sivertsen B *et al.* Population attributable fractions for Type 2 diabetes: an examination of multiple risk factors including symptoms of depression and anxiety. *Diabetol Metab Syndr* 2018; **10**: 84.
- 4 Deschênes SS, Burns RJ, Graham E, Schmitz N. Prediabetes, depressive and anxiety symptoms, and risk of type 2 diabetes: a community-based cohort study. *J Psychosom Res* 2016; **89**: 85–90.
- 5 Smith KJ, Deschenes SS, Schmitz N. Investigating the longitudinal association between diabetes and anxiety: a systematic review and meta-analysis. *Diabet Med* 2018; **35**: 677–693.
- 6 Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539–553.
- 7 Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; **166**: 1092–1097.
- 8 Loewe B, Decker O, Muller S, Brahler E, Schellberg D, Herzog W *et al.* Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Med Care* 2008; **46**: 266–274.
- 9 Lukaschek K, Baumert J, Kruse J, Emeny RT, Lacruz ME, Huth C *et al.* Relationship between posttraumatic stress disorder and type 2 diabetes in a population-based cross-sectional study with 2970 participants. *J Psychosom Res* 2013; **74**: 340–345.
- 10 Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008.
- 11 Stevenson M, Stevenson MM. Biased Urn I. Package ‘epiR’, 2019.
- 12 Kalilani L, Atashili J. Measuring additive interaction using odds ratios. *Epidemiol Perspect Innov* 2006; **3**: 5.
- 13 Demmer RT, Gelb S, Suglia SF, Keyes KM, Aiello AE, Colombo PC *et al.* Sex differences in the association between depression, anxiety, and type 2 diabetes mellitus. *Psychosom Med* 2015; **77**: 467–477.
- 14 Deschênes SS, Burns RJ, Schmitz N. Associations between diabetes, major depressive disorder and generalized anxiety disorder comorbidity, and disability: findings from the 2012 Canadian Community Health Survey—Mental Health (CCHS-MH). *J Psychosom Res* 2015; **78**: 137–142.
- 15 Wu CS, Gau SS, Lai MS. Long-term antidepressant use and the risk of type 2 diabetes mellitus: a population-based, nested case-control study in Taiwan. *J Clin Psychiatry*. 2014; **75**: 31–38.