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Prediabetes, depressive and anxiety symptoms, and risk of type 2 diabetes: A community-based cohort study

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ABSTRACT

Objective: To examine the potential synergistic associations between prediabetes, depressive and anxiety symptoms, and the risk of incident type 2 diabetes.
Methods: Data were from the Emotional Well-Being, Metabolic Factors and Health Status (EMHS) study and included 2486 adults between 40 and 69 years without diabetes at baseline. Hemoglobin A1c levels and measures of depressive and anxiety symptoms were collected at baseline and mutually exclusive groups were formed based on the presence/absence of prediabetes and high/low depressive and anxiety symptoms. A follow-up telephone interview conducted approximately 4.6 years later inquired about new diabetes diagnoses.
Results: 86 participants developed diabetes during the follow-up period. After accounting for sociodemographic, lifestyle, and metabolic characteristics, participants with prediabetes and elevated depressive symptoms had an increased risk of developing diabetes compared to those without prediabetes and with low depressive symptoms (OR = 10.65, 95% CI = 4.60, 24.66). The joint effect of prediabetes and depressive symptoms on diabetes risk was synergistic (Synergy Index = 2.57, 95% CI = 1.02, 6.49). Similar results were found for participants with prediabetes and high symptoms of anxiety (OR = 8.95, 95% CI = 3.54, 22.63), however the joint effect of prediabetes and anxiety symptoms did not significantly exceed additive risk after adjusting for covariates (Synergy Index = 2.39, 95% CI = 0.83, 6.87).
Conclusion: The combination of prediabetes and depressive or anxiety symptoms was associated with an increased risk of developing diabetes. This study underscores the importance of mental health in the progression from prediabetes to type 2 diabetes.

1. Introduction

Type 2 diabetes is a major public health concern as prevalence rates are rapidly rising [1,2]. Prediabetes, a condition characterized by blood glucose levels that are above the normal range but that do not reach the threshold for a diagnosis of type 2 diabetes, is a well-established risk factor for type 2 diabetes [3] that is also increasing in prevalence [4]. Though not everyone with prediabetes will develop type 2 diabetes, reported rates of progression from prediabetes to type 2 diabetes are as high as 70% [5]. Identifying predictors of the progression from prediabetes to type 2 diabetes could have important implications for reducing the incidence of type 2 diabetes.

Among people with prediabetes, the likelihood of reverting to normal glucose levels can be increased with healthy lifestyle changes [6–8]. Lifestyle behaviours such as smoking, unhealthy eating habits, and physical inactivity are common in people with depressive and anxiety symptoms [9] and these symptoms might increase the risk of progressing from prediabetes to type 2 diabetes. Depressive and anxiety symptoms are also well-documented correlates of type 2 diabetes [10–14]. Though prediabetes and depressive and anxiety symptoms are uniquely associated with an increased risk of diabetes, the combination of prediabetes and depressive or anxiety symptoms might amplify this risk. Only one study to date, to our knowledge, directly examined the associations between prediabetes, depressive and anxiety symptoms, and the risk of incident diabetes [15]. This study found that high psychological distress, assessed with a measure that combined symptoms of depression and anxiety, was associated with approximately double the risk of incident diabetes among participants with advanced prediabetes compared to those with advanced prediabetes and low psychological distress. Psychological distress was not associated with the risk of incident diabetes among those without prediabetes and low metabolic risk. It is unclear, however, whether the joint effect of prediabetes and depressive or anxiety symptoms on the risk of diabetes is synergistic, that is, whether the combined risk exceeds additive risk, and whether the potential risk remains when accounting for other metabolic factors.

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The relative roles of depressive and anxiety symptoms in increasing the risk of progressing from prediabetes to type 2 diabetes are also unclear. Many of the existing longitudinal studies on psychological distress and the risk of type 2 diabetes have focused on depressive symptoms [16]; fewer studies have examined the role of anxiety and the risk of type 2 diabetes. Though some studies have shown that anxiety symptoms specifically are associated with the risk of diabetes [13], it is unclear if depressive symptoms and anxiety symptoms have similar patterns of associations with diabetes. For instance, Meurs and colleagues [17] found different patterns of cross-sectional associations between depressive and anxiety symptoms with diagnosed versus undiagnosed diabetes. They reported that whereas both undiagnosed and diagnosed diabetes were associated with increased odds of concurrent depressive symptoms, only diagnosed diabetes was associated with increased odds of concurrent anxiety symptoms. Therefore, despite the high comorbidity between depressive and anxiety disorders [18], it is unclear whether the patterns of associations with prediabetes and the risk of diabetes are similar for depressive and anxiety symptoms.

We recently reported findings from the Emotional Well-Being, Metabolic Factors and Health Status (EMHS) study [19], a community-based cohort study that examines the interactions between mental health and metabolic dysregulations in the development of type 2 diabetes over approximately 4.6 years. This study demonstrated that depressive symptoms in combination with metabolic dysregulations amplified the risk of developing type 2 diabetes by approximately 6 times compared to having low depressive symptoms and good metabolic health. The goals of the present study were to conduct a secondary analysis of the EMHS study to examine the potential synergistic interactions between prediabetes status and depressive and anxiety symptoms with the risk of type 2 diabetes, accounting for traditional risk factors for type 2 diabetes including sociodemographic characteristics, lifestyle behaviours, and other metabolic risk factors. The joint effect of prediabetes and depressive symptoms was expected to be greater than the sum of the individual effects in increasing the risk of incident diabetes, which would indicate a synergistic interaction. Similar results were expected for prediabetes and anxiety symptoms. A sensitivity analysis was also carried-out to examine the potential synergistic interaction between prediabetes and comorbid depressive and anxiety symptoms with the risk of diabetes. A secondary goal of the present study was to estimate the extent to which depressive or anxiety symptoms increase the rate of progression from prediabetes to type 2 diabetes by comparing the risk of diabetes among those with prediabetes only based on the presence or absence of depressive or anxiety symptoms.

2. Method

2.1. Study population

EMHS participants were recruited from the CARTaGENE baseline cohort, a population-based health study of men and women aged between 40 and 69 years without diabetes at baseline and residing in one of four metropolitan areas in the Canadian province of Québec [20]. Blood samples and questionnaire assessments of psychological characteristics were collected by the CARTaGENE research group from August 2009 to October 2010. A subset of participants between 40 and 69 years of age with complete baseline data on depressive symptoms and metabolic abnormalities and who did not have diabetes at baseline participated in EMHS ($N = 2525$). Diabetes at baseline was determined by either a positive response to the question "Has a doctor ever told you that you had diabetes?", the self-reported use of diabetes medication, or hemoglobin A1c (HbA1c) levels of equal or higher than 48 mmol/mol (6.5%) based on blood assessments. The EMHS study consisted of a follow-up telephone interview that took place between October 2014 and March 2015. Stratified sampling was used to recruit participants from the CARTaGENE cohort with varying metabolic and depressive symptom profiles at baseline by including approximately equal proportions of participants with and without metabolic dysregulations and with and without high depressive symptoms. For the stratified sampling procedure, metabolic dysregulations were determined based on having three or more of the following metabolic factors: elevated blood pressure, impaired glycaemic control, low high-density lipoprotein cholesterol, elevated triglycerides, and central obesity. Depressive symptoms were based on a validated cut-off score for mild to severe depression [21] on the Patient Health Questionnaire-9 (PHQ-9) [22], a self-report questionnaire of depressive symptomology. Ethical approval was obtained from institutional research ethics boards by EMHS and CARTaGENE investigators and all participants provided informed consent.

A participant flow chart and further sample and methodological details are described in Schmitz et al. [19]. Briefly, 20,004 residents of Quebec participated in the CARTaGENE study. A total of 7998 CARTaGENE participants who agreed to be re-contacted for future studies during the baseline assessment, did not have diabetes at baseline, and had information on depressive symptoms were invited to take part in the follow-up EMHS telephone interview, of which 2525 agreed to participate. Participants who took part in the EMHS study had similar sociodemographic and clinical characteristics compared to the original CARTaGENE cohort, though EMHS participants had a slightly higher education level [19]. Given that the focus of this secondary analysis of the EMHS cohort was to examine the risk of diabetes based on prediabetes and depressive or anxiety symptom profiles, 39 EMHS participants who did not have complete data on HbA1c and anxiety symptoms were excluded from the present study, making the total study sample $N = 2486$.

2.2. Measures

Incident diabetes was assessed by self-report with the question "Has a doctor ever told you that you had diabetes?" during the follow-up telephone interview.

Baseline prediabetes status was determined by HbA1c levels derived from the collected blood samples being between 39 mmol/mol (5.7%) and 46 mmol/mol (6.4%), according to the American Diabetes Association diagnostic criteria for prediabetes [23]. HbA1c levels within this range are associated with a considerably increased risk of type 2 diabetes [24].

Depressive symptoms were assessed with the PHQ-9, a 9-item measure that assesses symptoms experienced over the past two weeks. Items are rated on a 4-point scale ranging from 0 "*not at all*" to 3 "*nearly every day*". The PHQ-9 has good validity and reliability [22] and good agreement with clinical diagnoses of major depressive disorder [25]. In our sample, internal consistency for the PHQ-9 was $\alpha = 0.84$. In the present study, we were interested in moderate to severe depressive symptoms and thus employed a classification system for high depressive symptoms that was more conservative than the classification used for the EMHS stratified sampling approach. The present study used the cut-off for moderate to severe depressive symptoms indicated by a score of ≥10 [26].

Anxiety symptoms were assessed with the Generalized Anxiety Disorder Scale (GAD-7) [27], a 7-item measure that assesses symptoms of general anxiety experienced over the past two weeks. Items are rated on a 4-point scale ranging from 0 "*not at all*" to 3 "*nearly every day*". The GAD-7 demonstrates good psychometric properties and a cut-off of score of ≥10 has been validated to indicate moderate to severe levels of anxiety [27]. In our sample, internal consistency for the GAD-7 was $\alpha = 0.87$.

2.3. Statistical analysis

All analyses were conducted in Stata version 14.0 (StataCorp, College Station, TX). Binary logistic regression analyses estimated the potential synergistic interaction between prediabetes status and depressive or