Risk factors and outcomes of anxiety symptom trajectories in type 2 diabetes: The Fremantle Diabetes Study Phase II

Running head: anxiety and depression trajectories in type 2 diabetes

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Statement of Novelty:

- Screening for anxiety is a recommended part of routine diabetes care, yet the course of anxiety symptoms in this population has not been examined
- A subset of individuals with type 2 diabetes are at risk of elevated anxiety symptoms that do not remit over a 4-year period
- High HbA_{1c}, higher BMI, and a lifetime history of both depression and anxiety disorders are significant predictors of elevated anxiety
- Comorbid depression symptoms are associated with a more persistent pattern of anxiety, and regular screening for both may enable earlier detection and targeted psychological intervention for those at risk.

ABSTRACT

Aims: To identify determinants and outcomes of four-year trajectories of anxiety symptoms in a community-based cohort with type 2 diabetes.

Methods: 1,091 participants in the Fremantle Diabetes Study-Phase II with type 2 diabetes completed the Generalized Anxiety Disorder Scale at baseline and biennially for four years, in addition to psychological, biomedical, and self-management measures. Latent growth mixture modeling identified trajectories of anxiety symptom severity, and regression models determined predictors of trajectory membership and associated outcomes.

Results: Two distinct groups of participants were identified: those with continuously low-no anxiety symptoms (87%) and those with improving but consistently high anxiety symptoms (elevated-anxiety; 13%). Higher HbA_{1c} and BMI, macrovascular complications, and a history of generalized anxiety and/or major depressive disorder increased the risk of elevated-anxiety. Elevated-anxiety did not predict change in health-related outcomes over time. Elevated-anxiety and depression symptoms were highly comorbid and affected individuals displayed the most persistent anxiety symptoms.

Conclusions: A sub-group of individuals with type 2 diabetes are at risk of persistently elevated anxiety symptoms. Routine monitoring of the severity of psychological symptoms over time in this population should facilitate earlier and more intensive mood management.

Key words: anxiety; type 2 diabetes mellitus; longitudinal study; symptoms.

INTRODUCTION

Although depression substantively impacts the management and sequelae of type 2 diabetes mellitus (type 2 diabetes) [1–3], anxiety disorders have received less attention. Generalised anxiety disorder (GAD) is the most common and presents as persistent worry about multiple life areas, accompanied by physiological and behavioural symptoms [4]. In the general population, GAD affects 2-3% of individuals and the lifetime prevalence approaches 5.7% [5]. By contrast, 25-40% of people with type 2 diabetes report anxiety symptoms [6,7] and 14% meet the criteria for GAD [6]. In cross-sectional studies, GAD has been associated with an increased risk of vascular complications [8], worse glycaemic control [1,9], obesity [1] and disability [10]. While routine screening for anxiety in type 2 diabetes is now recommended [11], the long-term development and impact of anxiety symptoms and implications for intervention remain unclear.

General population studies indicate that GAD can be chronic, although less persistent than depression [12], with symptoms improving in some individuals [13]. In type 2 diabetes, one short-term longitudinal study found that the proportion of individuals meeting GAD diagnostic criteria declined over 18 months [14], but the broad spectrum of anxiety symptoms were not examined. The direction and strength of the temporal relationship between anxiety, glycaemia and chronic complications remains uncertain [4,7,9]. Subthreshold anxiety symptoms may be an important GAD precursor [4] and anxiety symptoms may increase as a consequence of poor health.

We recently identified, in a cohort with type 2 diabetes who were followed for five years, discrete groups of individuals who experienced persistent depression symptoms that cycled over

time, and which were associated with a lifetime history of major depression and reduced psychological and health-related function [3]. Based on temporal changes in these symptoms, participants were allocated to sub-groups using latent-class analysis. A similar approach to anxiety symptoms might help identify groups who could benefit from more intensive psychological management. Given the overlap between anxiety and depression [8,10], and the increased likelihood of recurrence of both mood disorders when present together in diabetes [15], exploring the trajectories of both anxiety and depression symptoms would help clarify these comorbid mood disorders.

This exploratory study aimed to 1) identify distinct trajectories of anxiety symptoms in individuals with type 2 diabetes over time, 2) identify demographic, self-management and clinical predictors of anxiety trajectory membership, 3) assess whether having a lifetime history of anxiety or depression predicts anxiety trajectory membership beyond significant demographic predictors, and 4) examine whether anxiety trajectory membership is associated with important self-management and clinical outcomes, after controlling for these variables at baseline. A further aim was to determine the overlap between anxiety symptom trajectories and previously published depression symptom trajectories.

PARTICIPANTS AND METHODS

Study sample

The Fremantle Diabetes Study Phase II (FDS2) is a longitudinal, observational study of known diabetes conducted in a postcode-defined area surrounding the city of Fremantle in Western Australia [16]. Details of FDS2 recruitment procedures have been published [16]. Briefly, 1,732

individuals were recruited between 2008 and 2011, and followed until 2016 when active surveillance ended [16]. Of these, 1,549 were aged >18 years with clinically diagnosed type 2 diabetes and were included in this study. The Human Research Ethics Committee of the South Metropolitan Area Health Service (07/397) and the University of Western Australia (RA/4/1/5798) approved the study, and all participants gave written, informed consent.

Study procedures

At study entry, participants completed a comprehensive face-to-face interview, clinical examination and questionnaire pack. This was repeated every other year (Year 2, Year 4). In the intervening years, data were collected through a postal questionnaire. Questionnaire data included demographic characteristics and mood measures, and interview data collected by trained diabetes research nurses included diabetes duration, height and weight, current blood glucose-lowering treatment (quantity, dose, frequency, mode of insulin application), frequency of self-monitoring of blood glucose (SMBG; % who endorsed yes, and then the number of times per week), smoking status, and antidepressant use, as well as the number of primary care and hospital clinic visits in the past year [16]. Fasting biochemical tests including serum glucose and HbA_{1c} were carried out via fasting blood test and assayed the same day in a single, nationally-accredited laboratory. Chronic complications (microvascular: peripheral neuropathy, macrovascular: stroke, cardiovascular disease) and BMI were assessed at clinical examination and ascertained using standard criteria **(see Supplemental Table S1).** Anxiety data were part of Year 0, 2 and 4 assessments, with complete anxiety data available for 801 (52%) participants at 3 time points, 290 (19%) at 2 time points, 380 (25%) at Year 0 alone, while 78 (5.0%) had missing

data at all three assessments. Depression symptoms were also assessed in the intervening years as part of a postal questionnaire pack.

Mood assessment

Anxiety symptom severity was assessed using the Generalized Anxiety Disorder Scale (GADS; [17]. Individuals rate the presence of GADS items over the past 6 months from 0=not at all present to 3=present nearly every day, with an item scored positively if endorsed as 2 or 3. The GADS has been validated against the SCID-RV-Anxiety Disorders Module clinical interview and demonstrates good test-retest reliability [17]. Probable GAD diagnosis was classified based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria, if individuals scored positively for excessive worry and difficulty controlling their worry, in addition to 3 or more anxiety symptoms [17]. Total scores range from 0-24 with higher scores indicating more severe anxiety symptoms. To determine an optimal cut-point for clinically significant anxiety symptoms, the GADS was further validated in a stratified sample of 57 individuals from the FDS2 against the SCID-RV-Anxiety Disorders Module. Following previously established guidelines [18], a cut-off of 15 was chosen based on the highest area under the curve (AUC: 0.93), sensitivity (83%) and specificity (92%) values.

The Generalized Anxiety Disorder – Lifetime Scale (GAD-LT) was used to assess lifetime GAD at baseline. This instrument was designed for the FDS2 to parallel the GADS, but with the time criterion set to one month to reflect DSM-IV lifetime criteria. Participants are asked to rate (yes/no) whether they have experienced a period in their lives, for > one month, during which they worried excessively or had difficulty controlling their worries. If either symptom is

endorsed, the participant indicates if they experienced the additional 6 GAD symptoms during that period. The GAD-LT provides a probable diagnosis of lifetime GAD using DSM-IV criteria and has been validated for use in type 2 diabetes [19].

The severity of depression symptoms was assessed using the Patient Health Questionnaire-9 item version [20], a self-report measure validated for use in diabetes [21]. Items are rated on the same 4-point Likert scale as the GADS **with the time criterion set to the past two weeks.** PHQ-9 total scores range from 0-27, with higher scores indicating more severe symptoms. This measure was administered annually, and total PHQ-9 scores at each assessment were used to identify trajectories of depression symptoms in our previously published study [3]. The Brief Lifetime Depression Scale (BLDS; [2]) assessed lifetime prevalence of major depressive disorder (lifetime MDD) at baseline. Similar to the GAD-LT, this measure provides a probable diagnosis of lifetime MDD based on the DSM-IV criteria, if more than 5 symptoms are endorsed positively for >2 weeks at any point in their life [2].

Statistical analysis

Anxiety trajectories

Latent growth mixture modeling (LGMM) was used to identify sub-groups of people who displayed a similar trajectory of anxiety symptom severity over time based on temporal changes in GADS total scores, and to estimate the probability of each individual belonging to a particular group [22].

To determine the best single-group representation of change, growth curve models with no growth (intercept only), and with intercept and slope parameters, were estimated for linear and logarithmic fit [22] using: Bayesian Information Criterion (BIC); Akaike Information Criterion (AIC) [23]; Root Mean Square Error of Approximation (RMSEA); Standard Root Mean Square Residual (SRMR); Tucker Lewis Index (TLI); and Comparative Fit Index (CFI) [23]. GADS data were missing completely at random at Year 0 and 4 (Little's MCAR $P>0.05$) and missing at random at Year 2 (Little's MCAR $\chi^2(205)=289.38$, $P<0.001$). There was <5% missingness, so missing values were imputed using expectation maximization [23]. LGMM was performed with 1-3 classes to determine the best fitting number of groups, with variances of the intercept and slope allowed to vary [24]. The Vuong-Lo-Mendell-Rubin (LRM-LRT) and Parametric Bootstrap Likelihood Ratio Tests (BLRT) were used to determine improvement in fit for k+1 groups [25]. High posterior probabilities for each class and high entropy reflect good model precision [24].

Predictors of anxiety group membership were examined using unadjusted bivariate logistic regression models. To delineate the contribution of lifetime GAD and lifetime MDD to group membership, an adjusted logistic regression model was performed with significant bivariate demographic characteristics entered first, followed by lifetime GAD, then lifetime MDD. Anxiety group membership was then used to predict self-management and clinical variables at Year 4 using linear regression models, performed with and without controlling for these variables at baseline.

The degree of overlap between identified anxiety groups, and those with persistent-depression symptoms (as previously identified using Latent Curve Growth Analyses; [3]), was examined. Following our prior publication [3], and to allow comparability, the two identified groups of individuals with persistent-depression symptoms were combined to reflect one "persistent depression group" due to similarities in patterns of symptomatic change and limited clinical differences. The percentage overlap between anxiety group membership and those with persistent-depression symptoms was then explored. χ^2 tests, one-way ANOVA, or Kruskal-Wallis tests for non-normally-distributed data, were used to examine baseline, between-group differences in clinical, self-management and psychological variables for those with and without overlapping anxiety and depression symptom trajectories. Differences in GADS total scores were compared at Years 0, 2 and 4 using separate one-way ANOVA. Analyses were performed using *Mplus* Version 7 and IBM SPSS Statistics Version 23. Alpha was 0.05, two-tailed. Data are presented as proportions, mean±SD, or median [inter-quartile range, IQR] for non-normal variables, with Bonferroni correction to adjust for multiple comparisons.

RESULTS

Of the 1,549 adults with type 2 diabetes, 1,091 (70%) had GADS data for two or more time points and were included in LGMM. Compared to included participants, those with insufficient GADS data were older (64.8±10.8 vs. 66.4±12.2 years, P=0.02), had longer diabetes duration (8.0 [2.0-15.1] vs. 10.6 [4.0-18.0] years, P<0.001), higher HbA_{1c} **(51 [44-58] vs. 53 [45-65] mmol/mol, P<0.001) (6.8% [6.2%-7.5%] vs. 7.0% [6.3%-8.1%])** and were less likely to have received secondary education (91% vs. 77%, P<0.001) or to be of Anglo-Celt ethnicity (58% vs. 40%, P<0.001). Excluded participants were more likely to be female (45% vs. 54%, P <0.001) or

unmarried (12% vs. 44%, $P<0.001$).

At baseline, 6.2% of the final sample reported symptoms indicative of probable diagnosis using DSM-IV criteria for current GAD and 7.1% reported anxiety symptoms above the clinical cut-point of 15. The mean GADS score was 5.6±5.2. DSM-IV criteria for lifetime GAD were met by 27% and 36% for lifetime MDD; and 15% of the sample was taking antidepressant medication, of whom 89% were prescribed antidepressants specifically for depression.

Anxiety trajectories

A linear model provided the best fitting single growth model for GADS data, resulting in the lowest χ^2 (0.19), AIC (17150.95), and parsimony ratio (0.07) **(Supplemental Table S2).** LGMM revealed the GADS data best fit a linear 2-group model (see Figure 1 and Table 1). Group 1 ('no-anxiety'; 87%), the majority of the sample, had low-no anxiety symptoms over time (Baseline GADS total score 4.1±3.2). Group 2 ('elevated-anxiety'; 13%) displayed a pattern of anxiety symptoms that fell above the clinical cut-point at baseline (GADS total score 16.2±3.7), gradually improved to below this cut-off over time, but remained elevated.

Baseline predictors of anxiety groups

Compared with the no-anxiety group, the elevated-anxiety group was younger, more likely to be female, and of non-Anglo-Celt ethnicity (Table 2). The odds of experiencing elevated-anxiety symptoms were higher for those with high HbA_{1c}, higher BMI, less likely to indicate that they self-monitored blood glucose (but with no differences in SMBG frequency), greater insulin and antidepressant use, with more macrovascular complications, and more regularly attending

healthcare appointments. Further analyses indicated that the effect of elevated-anxiety on worse SMBG was restricted to people not prescribed insulin.

In the logistic regression model, age, gender, and Anglo-Celt ethnicity were entered into the first step, with younger age (OR = 0.95, 95% CI = 0.94, 0.97) and female gender (OR = 1.56, 95% CI = 1.07, 2.29) significant predictors. In step two, lifetime GAD was associated with a five-fold increased risk of elevated-anxiety symptoms (OR = 5.51, 95% CI = 3.67, 8.29). This relationship remained significant, but reduced, when lifetime MDD was included in the third step (lifetime GAD: OR = 2.78, 95% CI = 1.74, 4.44; lifetime MDD: OR = 4.09, 95% CI = 2.43, 6.87).

Outcomes of anxiety groups

Relative to the no-anxiety group, membership of the elevated-anxiety group predicted higher BMI (B=1.98, $p<0.001$), more frequent attendance at Primary Care Physician (B=4.50, $P<0.001$) and outpatient appointments (B=1.29, $P=0.046$), and more antidepressant use at Year 4 (B=1.17, OR=3.21, $P<0.001$). However, these relationships became non-significant after accounting for the severity of each variable at baseline (all $p>0.05$). This demonstrates that between-group differences for these variables persisted over the four years of follow-up. Anxiety group was not associated with HbA1c, SMBG, health complications, or any other clinical characteristics at Year 4 (all $P>0.05$).

Overlap between anxiety and depression groups

Trajectories of PHQ-9 depression symptoms were previously investigated using Latent Curve Growth Analysis [3], and two clinically meaningful sub-groups were found: one with

persistently elevated depression and one without. In the current sample, 14% of individuals had persistent-depression symptoms over the same time period that the anxiety trajectories were examined. Notably, two-thirds of those in the elevated-anxiety group (*n*=87; 64%) experienced persistent-depression symptoms.

Finally, we examined how the overlap between anxiety and depression groups over time impacted anxiety symptom severity (GADS total scores). Out of interest to the reader, the impact on depression symptom severity (PHQ-9 total scores) is included in **Supplemental Table S3.** Figure 2 displays average anxiety symptoms at each time point (Baseline, Year 2 and Year 4) for individuals captured in the following symptom trajectory groups: elevated-anxiety, persistent-depression, comorbid elevated-anxiety and persistent-depression, and neither. At Years 0 and 2, mean anxiety symptoms were higher for those with comorbid anxiety and depression trajectories, compared to elevated-anxiety alone (all $P<0.001$). Notably, by Year 4, those with persistent-depression, and comorbid anxiety and depression, reported more severe anxiety symptoms than those with elevated-anxiety only ($P<0.001$).

Tests of between-group differences at Year 0, revealed that lifetime MDD and lifetime GAD were more prevalent in the comorbid elevated-anxiety and persistent-depression group relative to the elevated-anxiety group alone ($P<0.001$). This group also had higher HbA_{1c} at Year 0 relative to the other two groups ($F(2,192)=3.87$, $P=0.023$), but this relationship became non-significant after Bonferroni adjustment (both $P>0.006$).

DISCUSSION

The present study identified trajectories of anxiety symptoms in a large, community-based cohort with type 2 diabetes. Two distinct groups emerged; individuals with sustained low-to-no anxiety symptoms (Group 1), and those experiencing high anxiety symptoms which reduced over time but remained sub-clinically elevated over four years (Group 2). Membership of this latter group was predicted by younger age, higher HbA_{1c} and BMI, more macrovascular complications, insulin use, and both lifetime GAD and MDD. The presence of comorbid depression and anxiety symptom trajectories conferred the greatest risk of a more severe pattern of anxiety symptoms. These data indicate that screening for and management of anxiety symptoms in diabetes, particularly in those with suboptimal diabetes management, chronic complications and depression, may be beneficial.

Current recommendations are to screen and consider therapies for anxiety at key points in the course of type 2 diabetes, including diagnosis, onset of complications and commencement of insulin [11,26]. The most important finding in this study is that, for a group of individuals with long duration disease and chronic complications (median diabetes duration of 8.9 years in Group 2), less severe anxiety symptoms were more prevalent and persistent than previously recorded and displayed a lifetime course. In the only prior study of the course of GAD in diabetes, there was a reduction in the prevalence of GAD diagnoses from 6.9% to 0.7% over 18 months [14]. By assessing anxiety symptoms over 4 years, we found that a substantially larger proportion (12.6%) continued to experience sub-threshold anxiety symptoms which waned but remained higher than those with low-no anxiety. One explanation for this finding is that GAD presents as residual anxiety symptoms that recur over time, displaying the pattern of relapse and remission observed

in the general population [12,26]. Thus, a single assessment and relying on DSM-IV GAD criteria may under-estimate the impact of psychological issues in people with diabetes. Regular monitoring of anxiety symptoms, especially for those with lifetime history of GAD and/or MDD, may facilitate earlier identification of individuals in need of ongoing mood management.

There is debate regarding the directionality of the relationship between less severe generalized anxiety symptoms and health-related outcomes [1,9,14,26]. This study indicates, for the first time, that high HbA_{1c}, less frequent blood-glucose self-monitoring in those not using insulin, and higher BMI were all associated with the risk of elevated-anxiety. However, membership of this elevated-anxiety group did not predict worse self-management or clinical outcomes at Year 4. For BMI, this may be explained by the fact that between-group differences in this variable appeared to persist over the four years of follow-up. For other variables, less severe anxiety symptoms may not significantly impact these outcomes. However, it is possible that elevated-anxiety symptoms are associated with diabetes self-management and clinical outcomes more proximally in time, which was not captured in this study, or could have a more sinister longer-term physiological impact. For example, in community-based samples, sub-threshold anxiety and worry have been associated with heart failure and hypertension in individuals with cardiovascular disease [27] and may increase insulin resistance and mortality [28]. Depression and anxiety disorders can promote production of pro-inflammatory cytokines and hypothalamic-pituitary axis and sympathetic nervous system activation, known risk factors for maladaptive immunological and metabolic changes [28]. Stepped-care treatment of any elevated generalized anxiety symptoms over time in diabetes may, thus, help minimize the long-term impact of

anxiety disorders on physiological and psychological functioning and **warrants further investigation.**

A notable contribution of this study was the identification of significant overlap between anxiety and depression symptoms longitudinally. Both lifetime MDD and GAD were the strongest predictors of membership of the elevated-anxiety group, whilst individuals with persistent-depression symptoms were particularly vulnerable to the development of anxiety symptoms over time. Previous research showing that comorbid anxiety and depression confer greater disability, symptom burden, and severity of diabetes [10] has been extended to a longer duration of follow-up. As the presence of anxiety disorders can make depression harder to treat [15], more intensive monitoring and treatment of anxiety symptoms may be required for individuals with depression, particularly for those who have previously met diagnostic criteria for GAD or MDD. For these individuals, prompt referral for psychotherapy specific to mood and diabetes, for which Cognitive Behaviour Therapy (CBT) currently has the best support, in addition to possible pharmacological intervention [11,29], may be needed.

A key strength of this study was the use of novel methodology in a large representative sample, allowing for the detection of underlying, individual trajectories of anxiety symptoms [24]. Furthermore, while GADS was used instead of the Generalized Anxiety Disorder 7-item scale (GAD-7) (the GAD-7 was not available when the FDS2 was designed), GADS is an improvement on the GAD-7 as it assesses DSM-IV/V criteria for GAD over the past 6 months rather than a partial list of symptoms over the past 2 weeks [17]. GADS has excellent test-retest reliability and concordance with diagnostic interview [17]. However, interpretation of the

overlap between depression and anxiety groups may be limited as the PHQ-9 was administered annually and GADS biennially, **and these measures have different response timeframes (2 weeks for PHQ-9, 6 months for GADS).** Ongoing follow-up of the overlap in, and correlates of, depression and anxiety symptom trajectories over more regular intervals would be valuable, **in addition to the development of instruments with similar timeframes to allow more accurate comparability.** The smaller sample available for GADS ROC curve analysis, and potential for recruitment bias due to not capturing those who withdrew from the study over time, are further limitations. Finally, we did not assess diabetes-specific emotional distress which addresses the complex psychological and behavioural burden associated with having diabetes [14]. Some of the longitudinal inter-relationships observed between anxiety, depression, and glycaemic control may be driven by elevated levels of diabetes distress [14,30].

Conclusion

These data confirm that anxiety is an important comorbidity in type 2 diabetes and suggest that clinicians should actively monitor anxiety symptoms as part of routine care. A sub-group of individuals will experience generalized anxiety symptoms that remain elevated but below clinical cut-points over time, especially in those with comorbid depression. As an extension of current guidelines [11], we recommend frequent screening for anxiety and depression and their severity, and using measures such as the BLDS and GAD-LT, in addition to clinical DSM-IV categorization, to enable earlier detection and targeted psychological intervention.

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Table 1. LGMM fit statistics for GADS latent linear growth model (N = 1091).

	1-Class LGMM	2-Class LGMM[1]	3-Class LGMM
Sample size			
N = 1	1091 (100%)	954 (87.4%)	914 (83.8%)
N = 2	-	137 (12.6%)	91 (8.3%)
N = 3	-	-	86 (7.9%)
Fit Statistics			
# of Parameters	8	11	14
AIC	17150.95	16919.72	16784.48
BIC	17190.91	16974.66	16854.41
ABIC	17165.50	16939.73	16809.94
Entropy	na	0.879	0.871
Log likelihood	-8567.48	-8448.86	-8378.24
LRM-LRT p-value	na	<0.001	0.194
BLRT p-value	na	<0.001	<0.001

Note. [1] = preferred model; AIC = Akaike Information Criterion (lower score = better fit); BIC = Bayesian Information Criterion (lower score = better fit); ABIC = Adjusted Bayesian Information Criterion (lower score = better fit); entropy (higher value = better fit); LRM-LRT = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (significant *p* value = improvement in model fit); BLRT = Bootstrap Likelihood Ratio Test (significant *p* value = improvement in model fit). The LRM-LRT *p*-value indicated no improvement in model fit for the 3-class model compared with 2-class model, and entropy reduced for the 3-class model. The 2-class model was therefore chosen as best fit.

Table 2. Bivariate logistic regression models examining baseline predictors of anxiety group membership among 1,091 people with type 2 diabetes.

Baseline characteristics	Group 1: "No anxiety" (87.4%) n = 954	Group 2: "Elevated anxiety" (12.6%) n = 137	Odds Ratio (OR)	*P*-value
Demographic characteristics				
Age (year)	66±11	60±11	0.96	<0.001
Age at diabetes diagnosis (year)	56±11	50±12	0.96	<0.001
Diabetes duration (years)	8 [2,15]	9 [3,15]	0.99	0.625
Gender, % women	44	61	1.59	0.012
Ethnicity, % Anglo-Celt	60	51	0.70	0.050
English fluency, % non-fluent	7.2	9.5	1.35	0.350
Education, % primary or less	9.0	13	1.44	0.196
Marital status, % single	34	36	1.07	0.716
Clinical characteristics				
BMI (kg/m^2)	31.1±5.7	33.6±6.8	1.07	<0.001
HbA_{1c}, mmol/mol	50 [44,28]	55 [44,63]	1.25	<0.001
HbA_{1c}, %	6.7 [6.2,7.5]	7.2 [6.2,7.9]	1.25	<0.001
Fasting serum glucose, mmol/L	7.1 [6.1,8.4]	7.7 [6.3,9.8]	1.12	<0.001
Diabetes treatment, %				
Diet/exercise	27	19	0.63	0.043
Oral glucose lowering medications (OGLMs)	54	47	0.76	0.140
Insulin only	3.7	7.3	2.07	0.050
Insulin + OGLMs	16	27	1.98	0.001

Number of medical visits in past year				
Primary Care Physician	3 [2,4]	4 [2,12]	1.07	<0.001
Diabetes outpatient clinic visit	0 [0,0]	0 [0,1]	1.18	0.002
Diabetes-related outpatient clinic visit	0 [0,0]	0 [0,1]	1.04	0.37
Self-management and health outcomes				
SMBG, number of times per week	6 [2,10]	6 [0,14]	1.01	0.49
SMBG, % yes	87	78	0.52	0.005
Self and/or other monitoring of blood glucose, % yes	88	80	0.52	0.007
Smoking status, % current	7.6	8.8	1.18	0.62
Macrovascular complications, % any	35	52	1.99	<0.001
Peripheral sensory neuropathy, % yes	59	53	0.77	0.16
Psychological characteristics				
Antidepressant use, % current	11	31	3.73	<0.001
Lifetime generalized anxiety, % yes	22	63	6.18	<0.001
Lifetime major depression, % yes	30	78	8.46	<0.001

Note. Reference category = no anxiety; BMI = body mass index; HbA_{1c} = glycated hemoglobin; SMBG = self-monitoring of blood glucose. Data are presented as proportions, means±standard deviations, or medians [interquartile range].

Figure 1. Mean estimated anxiety scores (GADS total scores) for 2-class LGMM over 4 years, including clinical cut-off (GADS ≥ 15).

Figure 2. Mean estimated anxiety scores (GADS total scores) in the total available sample (N=1086) for overlapping elevated-anxiety and persistent-depression groups over 4 years.