Anxiety Amplifies Plasma Oxytocin Levels in Older Individuals with type 2 Diabetes. Findings from the Cross-Sectional KORA-Age Study.

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Abstract

Purpose

Beyond its role in parturition, lactation, and emotion regulation, oxytocin (OXT) plays an important role in metabolism and energy homeostasis, although evidence is still limited. We investigated the association between endogenous OXT levels and type 2 diabetes mellitus (T2DM) and whether anxiety may modify its association.

Methods

A cross-sectional analysis was conducted in 1006 participants aged 65-93 years (mean=75.9, SD $\pm$ 6.6) from the population-based KORA-Age study. Multivariable generalized linear regression analyses were performed to examine the association between non-extracted plasma OXT levels and T2DM with adjustments for potential confounders.

Results

Across the OXT tertile groups, no substantial differences between sociodemographic, lifestyle, cardiometabolic or psychosocial factors were found except for multimorbidity. The differences between the OXT tertile groups with respect to obesity status were on the borderline of statistical significance ($P=0.05$). However, a significant statistical interaction between T2DM and anxiety on OXT levels was found ($p = 0.03$). In T2DM individuals with anxiety, substantially higher plasma OXT levels (Least Squares (LS) mean = 340.82 pg/ml, 95% CI 231.12-502.59) were observed compared to those without anxiety (217.08 pg/ml, 95% CI 190.93 – 247.99) ($p=0.02$). No significant association between T2DM and OXT levels in individuals without anxiety was found.

Conclusion

OXT levels were significantly elevated in T2DM subjects, particularly among older individuals with anxiety. The modifying role of anxiety highlights that anxiogenic stimuli may be associated with enhanced OXT signalling, particularly in subjects who suffer from T2DM as a severe pathological feature of dysregulated metabolism.

Introduction

Oxytocin (OXT), a popular hypothalamic neuropeptide known as the “prosocial hormone”, is well recognized for its positive functions in parturition, lactation, mother-infant bonding, sexuality, attachment, interpersonal trust, and emotion regulation [1]. Impairments in psychosocial domains, such as anxiety disorders, schizophrenia, and depression, may also have an impact on endogenous OXT levels [1]. Recently, increasing evidence indicates that OXT may also play a positive role in regulating metabolism by modulating eating behavior, body fat, body weight, energy expenditure, and glucose homeostasis [2].

OXT receptors have been found on pancreatic α and β cells, suggesting a potential link between OXT and type 2 diabetes mellitus (T2DM) [3]. A double-blinded crossover study on 29 healthy men found that intranasal OXT administration could acutely enhance glucose tolerance and β cell responsivity [4]. Another randomized pilot clinical trial with 24 patients reported effectively reversed prediabetic changes over 8 weeks of continuous intranasal OXT treatment [5]. Although these intervention studies showed beneficial effects of OXT on T2DM-related metabolic profiles, how T2DM may affect endogenous OXT levels is still poorly understood. While previous studies in young to middle-aged adults have found an association between lower OXT levels and T2DM [6–11], others have reported conflicting findings with higher levels of OXT in metabolic disorders [12–14]. Furthermore, most studies investigating the association between OXT and T2DM are small-sized and stem from sex-specific young populations. To date, only one study in an older men population has shown an association between elevated OXT levels and metabolic syndrome [14]. In older subjects suffering from metabolic syndrome, a compensatory mechanism of OXT may operate to maintain metabolic homeostasis where aging-related deficits develop [15]. As circulating levels of OXT tend to decline with age in animal models [16], there are possible age-by-sex related differences in circulatory OXT in humans [17], leading to mixed findings. Therefore, further research to explain these conflicting results and how T2DM may impact OXT secretion in old aged are warranted.

Symptoms of anxiety are frequently observed in T2DM individuals with prevalence ranges from 14–41% in various populations [18]. Given that OXT is a profound anxiolytic factor of the brain [19], and anxiety amplifies the progression of prediabetes to T2DM onset [20], it is crucial to find out how anxiety may impact the OXT-T2DM relationship. The potential involvement of anxiety may provide some useful insights into the psychoneuroendocrinological coping mechanism of the body to deal with chronic metabolic disease conditions like T2DM. Therefore, we aimed to examine in a representative elderly population-based study: (i) the association of T2DM and plasma OXT levels and (ii) the potential modifying role of anxiety on this association.

Materials And Methods

Study Design and Participants

Data for this study were obtained from the 2008–2009 baseline assessment of the KORA-Age study, a population-based longitudinal study designed to determine the prevalence of multimorbidity, functioning, and successful aging [21].

The KORA-Age study is a follow-up of all participants aged 65 years or older on 31 December 2008, who participated in at least one of the MONICA/KORA (Monitoring of Trends and Determinants in Cardiovascular Diseases/Cooperative Health Research in the Region of Augsburg) Surveys S1-S4 conducted between 1984–2001 among inhabitants of Augsburg and its two surrounding counties in southern Germany.

All eligible participants of the KORA-Age study (n = 5991) who were alive and reachable received a postal health questionnaire (response rate 76.2%, n = 4565), followed by a standardized telephone interview (response rate 68.9%, n = 4127). Furthermore, a gender- and age-stratified random subsample of the KORA-Age cohort (53.8% of eligible participants, n = 1079) underwent an extensive medical examination, including a non-fasting blood draw and a face-to-face interview. After the exclusion of participants with missing information on plasma OXT (n = 66), diabetes status (n = 2) and non-psychosocial covariates (n = 5) in this subsample, our study has a sample size of 1006 participants. A drop-out analysis of the excluded participants revealed no significant age, sex and education level differences.

This study was approved by the Ethics Committee of the Bavarian Medical Association, and written informed consents were provided by all the participants.

Outcome – Plasma OXT Level

Non-extracted plasma OXT level was measured from a non-fasting venous blood sample of each participant during the physical examination at the study centre using OXT Enzyme Immunoassay (Assay Designs, Ann Arbor, MI), as previously described [22]. Samples were collected in chilled EDTA tubes with 500 KIU/ml aprotinin, centrifuged within 30 min, and stored at -80°C to minimize preanalytical sample degradation. All the samples were analyzed within 2 months using the same batch of reagents. The detection limits of the assay range from 15 to 2000 pg/ml. Intra-assay coefficients of variability are below 15%, and inter-assay coefficients of variability are 15.4%, 18.5% and 17.9% at concentrations of 234, 416 and 1930 pg/ml, respectively. The plasma OXT concentrations showed a right-skewed distribution. For the descriptive analyses, the distributions of plasma OXT were split by the tertiles, and subjects were stratified into those with low, medium or high levels.

Exposure – T2DM

T2DM was determined by the participant's report in the self-administered questionnaire, and each case was verified by assessing the participant's medical history, records from physicians, information from previous MONICA/KORA surveys, as well as the use of antidiabetic medication.

Covariates

Low education was defined as less than 12 years of education. A current smoker was defined as someone smoking cigarettes regularly or occasionally. Alcohol consumption was classified into two categories: consuming alcohol more than once per week, or not. Participants were considered as physically active during leisure time if they regularly participated in sports for at least 1 hour/week in either summer or winter, and inactive else. Obesity was defined as Body Mass Index (BMI) greater than 30, where BMI was calculated as weight (kg) / height² (m). Hypertension was defined as blood pressure $\geq 140/90$ mmHg or current use of antihypertensive medication. Dyslipidemia was defined as the ratio of total cholesterol (TC) to high density lipoprotein cholesterol (HDL-C) $TC/HDL-C \geq 5.0$, where TC and HDL-C in mmol/L were measured by enzymatic methods (CHOD-PAP, Boehringer Mannheim, Germany). HbA1c was quantified with a reverse-phase cation-exchange HPLC method using a Menarini–Arkray Analyzer HA-8160 (Menarini Diagnostics, Florence, Italy) in mmol/mol and %. HbA1c levels $\geq 6.5\%$ was considered

as hyperglycemia and < 6.5% as normoglycemia. Multimorbidity was determined by the co-occurrence of > 2 disease conditions according to the Charlson Comorbidity Index [23].

Depressive symptoms were measured by the 15-item German version of the Geriatric Depression Scale (GDS 15), with a score ≥ 10 or taking antidepressants indicating depression [24]. Anxiety symptoms were assessed using the Generalized Anxiety Disorder-7 (GAD-7) Questionnaires, where anxiety was defined by a score of 10 or higher [25]. Perceived stress from a stressful life event experienced in the past year, if any, was assessed in a personal interview rated on 5-point Likert Scale, where scale 4-quite a lot and scale 5-severely were categorized as suffering from heavy/severe stress [22]. Social network was assessed by the Beckman social network index score and classified into high (score 3–4) and low (score 1–2) social network [26].

Statistical Analysis

The plasma OXT concentrations showed a right-skewed distribution and, therefore, were logarithmically transformed to approximate a normal distribution. Descriptive data of sociodemographic, lifestyle, clinical, and psychosocial characteristics were stratified by tertiles of log-transformed plasma OXT levels. The χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables were used to compare the differences across the OXT tertile groups. Categorical variables were expressed as frequencies (n), and age was reported as means with standard deviations ($\pm$ SD). Multivariable generalized linear regression (GLM) models were applied to assess the association between T2DM (exposure) and plasma OXT levels (outcome) with 5 different models adjustment. Model 1 was a crude model adjusted only for age and sex. Model 2 was further adjusted for educational level as a sociodemographic confounder. Model 3 and model 4 were additionally adjusted for established lifestyle (smoking, alcohol consumption, physical activity) and metabolic risk factors (obesity, hypertension, dyslipidemia, multimorbidity) of T2DM. Model 5 was performed on a smaller subgroup of participants (N = 961) with complete information for depression, anxiety, perceived stress, and social network status to consider the influence of psychosocial factors on the association. We also reanalyzed the association of OXT levels and T2DM by an additional adjustment for HbA1c levels in the crude and full model.

Additional sensitivity analyses were performed to consider the interaction effect of sex and T2DM on OXT levels by including the sex X T2DM interaction term in all the models. The influence of anxiety in the association between T2DM and OXT was examined by introducing an interaction term to the crude and fully-adjusted logistic regression model. In the case of significant interaction, the regression analyses were further stratified by anxiety. The influence of obesity or glycemic status was assessed via the introduction of an interaction term of HbA1c levels*T2DM.

Age and sex-adjusted least-square means (LS-means) of log-transformed plasma OXT levels and 95% confidence intervals were calculated from generalized linear models for the total study population and stratified by anxiety status. The model fits were sufficient as indicated by acceptable adjusted R-square and Root MSE statistics values throughout the GLM models. No multicollinearity among covariates was detected as assessed with the Variance Inflation Factor (VIF) with a cut-off of VIF > 2.

All the statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The significance level was set at 0.05. The reporting of this study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.

Results

A total of 1006 participants (489 women and 517 men) of KORA-Age were included in our study, with an age range of 65–93 (mean 75.9, SD $\pm$ 6.6) years. Table 1 presents the study characteristics according to tertiles of the OXT level. No substantial differences between sociodemographic, lifestyle or cardiometabolic factors across the OXT tertile groups were found except for multimorbidity. The differences between the OXT tertile groups with respect to obesity status were on the borderline of statistical significance ($P = 0.05$). Of note, no significant differences between OXT tertile groups and anxiety were observed.

Table 1
Characteristics of study population stratified by tertiles of plasma OXT levels in means ($\pm$ standard deviation) or N (%) (N = 1006)

Plasma OXT level	Low (n = 336, 33.40%)	Middle (n = 334, 33.20%)	High (n = 336, 33.40%)	p
Sociodemographic factors				
Age	75.74 ($\pm$ 6.81)	76.16 ($\pm$ 6.43)	75.86 ($\pm$ 6.68)	0.698
Male	170 (50.60%)	176 (52.69%)	171 (50.89%)	0.841
Low Education	242 (72.02%)	238 (71.26%)	250 (74.40%)	0.635
Lifestyle factors				
Smoking	10 (2.98%)	20 (5.99%)	17 (5.06%)	0.167
High Alcohol Consumption	161 (47.92%)	155 (46.41%)	149 (44.35%)	0.648
Physically inactive	162 (48.21%)	147 (44.01%)	158 (47.02%)	0.532
Clinical factors				
Obesity	100 (29.76%)	115 (34.43%)	87 (25.89%)	0.054
T2DM	46 (26.6%)	65 (37.6%)	62 (35.8%)	0.136
HbA1c (%)	5.72 (0.56)	5.75 (0.58)	5.72 (0.59)	0.750
HbA1c (mmol/mol)	38.99 (6.11)	39.35 (6.37)	38.94 (6.46)	0.755
Hypertension	251 (74.70%)	258 (77.25%)	244 (72.62%)	0.385
Dyslipidaemia	46 (13.69%)	62 (18.56%)	54 (16.07%)	0.230
Multimorbidity	197 (58.63%)	228 (68.26%)	217 (64.58%)	0.032
Psychosocial factors				
Depression	23 (7.17%)	19 (5.90%)	23 (7.17%)	0.761
Anxiety	22 (6.85%)	22 (6.83%)	27 (8.41%)	0.680
Great/Severe Stress	52 (16.20%)	60 (18.63%)	60 (18.69%)	0.642
Low Social Network	209 (65.11%)	204 (63.35%)	208 (64.80%)	0.884
<i>P</i> values: Kruskal-wallis test for continuous variables and χ^2 test for categorical variables.				

OXT levels were higher in participants with T2DM (age and sex-adjusted LS-mean = 224.78, 95% CI: 200, 189–211 pg/ml) compared to those without T2DM (199.74, 199–254 pg/ml) ($p = 0.08$). T2DM participants were more likely to be older, have lower education levels, have BMI ≥ 30 kg/m², consume less

alcohol, have hypertension and multimorbidity, and suffer more from stressful life events (Supplementary Table 1).

Multivariable linear regression analyses on the association of plasma OXT levels and T2DM were employed with adjustments for sociodemographic, lifestyle, metabolic, and psychosocial factors, as displayed in Table 2. T2DM was associated with higher levels of plasma OXT; however, only with borderline statistical significance (Model 1: $\beta = 0.13$, $SE = 0.07$, $p = 0.07$). Adjustments for all potential confounders further reduced the strength of association into non-significance (Model 5: $\beta = 0.11$, $SE = 0.07$, $p = 0.13$).

Table 2
 β estimates, standard errors (SE) and P -values for the association between T2DM and plasma OXT levels (pg/ml) of the KORA-Age participants (N = 1006)

	β	SE	p
Model 1	0.13	0.07	0.07
Model 2	0.12	0.07	0.08
Model 3	0.13	0.07	0.09
Model 4	0.12	0.07	0.12
Model 5 (n = 961)	0.11	0.08	0.13
Model 1: generalized linear model adjusted for age and sex			
Model 2: Model 1 + education level			
Model 3: Model 2 + smoking status, alcohol consumption, physical activity			
Model 4: Model 3 + obesity, hypertension, dyslipidemia, multimorbidity			
Model 5: Model 4 + anxiety, depression, perceived stress, social network			

Additional analytical models demonstrated, however, that a significant interaction between T2DM and anxiety on OXT levels was observed in multivariable linear regression models adjusted for age and sex ($p = 0.03$). A significant interaction indicates that the association between T2DM and OXT levels is modified by the presence of anxiety. Therefore, stratified analyses were performed on the study population grouped by individuals having anxiety symptoms. As displayed in Fig. 1, elevated plasma OXT levels were observed in T2DM individuals with anxiety ($p = 0.008$) but not in those without anxiety ($p > 0.05$) (LSMeans for T2DM participants, with anxiety: 340.82 pg/ml, 95% CI 231.12–502.59; without anxiety: 217.08 pg/ml, 95% CI 190.93–247.99). In multivariable linear regression models, neither the strength nor the significance of the association was substantially altered by further adjustments for concurrent risk factors (anxiety: $\beta = 0.62$, $SE = 0.24$, $p = 0.01$; no anxiety: $\beta = 0.05$, $SE = 0.08$, $p = 0.50$) (Table 3). No significant interaction of T2DM by sex on plasma OXT levels ($p > 0.05$) was found.

Table 3
 β estimates, standard errors (SE) and *P*-values of the association between T2DM and plasma OXT levels stratified by anxiety (n = 961).

		β	SE	<i>p</i>
No Anxiety (N = 891)	Model 1	0.06	0.08	0.43
	Model 2	0.05	0.08	0.47
	Model 3	0.05	0.08	0.50
	Model 4	0.04	0.08	0.58
	Model 5	0.05	0.08	0.50
Anxiety (N = 70)	Model 1	0.58	0.22	0.01
	Model 2	0.59	0.22	0.01
	Model 3	0.58	0.23	0.01
	Model 4	0.56	0.23	0.02
	Model 5	0.62	0.24	0.01
Model 1: generalized linear model adjusted for age and sex.				
Model 2: Model 1 + education level				
Model 3: Model 2 + smoking status, alcohol consumption, physical activity.				
Model 4: Model 3 + obesity, hypertension, dyslipidemia, multimorbidity.				
Model 5: Model 4 + depression, perceived stress, social network.				

Discussion

In a sample of community-dwelling older people of 64–93 years, we found a borderline significant association between T2DM and elevated plasma OXT levels which was further diminished after adjustment for concurrent risk factors. However, driven by a significant interaction between T2DM and anxiety on OXT levels, indicating a potential modifying role of anxiety on the T2DM-OXT link, we revealed a substantially 44% higher mean level of OXT in T2DM subjects with anxiety compared to their non-T2DM counterparts with anxiety. Notably, a significant association between T2DM and OXT levels in subjects without anxiety was not found. While increasing evidence points to positive effects of OXT in attenuating metabolic risks [2, 27] as well as its profound anxiolytic behavioral effect [28], our findings seem to be counterintuitive at first sight.

However, the findings of heightened levels of OXT in T2DM subjects with anxiety do not come unexpectedly: both the impact of OXT on fear and anxiety, and its role in the metabolic regulation has yielded contradictory findings. Concerning human social behavior, OXT is widely acknowledged as a

candidate molecule to facilitate fear extinction and anxiolysis [29] and, thus, is emerging as a target for mood treatment approaches [30]. However, opposing experimental data are available. Grillon et al. (2012) exposed healthy subjects to an electrical startle experiment and evidenced that OXT increased anxiety to unpredictable threat [31]. Likewise, Eckstein et al. subjected 97 healthy male probands to a Pavlovian fear learning experiment and disclosed that OXT enhanced CNS responses to social stimuli during fear conditioning, provoking increased vigilance and heightened alertness to threat [32].

Peters et al. (2014) showed that chronic intra-cerebroventricular infusion of high doses of OXT in male mice induces an anxiogenic phenotype while a low dose of OXT prevents hyperanxiety [33]. Thus, the specific nature, dosage, and timing of OXT are key aspects in orchestrating OXT responses and, instead of acting unidirectional, may result in both anxiolytic and anxiogenic behavioral effects [34]. A low dose of OXT administration is likely to alleviate the effects of stress, while a chronic high dose of OXT may increase anxiety-like behavior [34]. Furthermore, chronic administration of OXT increases adreno-corticotrophic hormone (ACTH) and corticosterone levels, indicating a potentiating effect of OXT on the hypothalamic-pituitary-adrenal (HPA) axis stress reactivity [35, 36].

Of note, the positive association between T2DM and OXT levels in subjects with anxiety remained strong even after adjustment for potentially important influential lifestyle factors (e.g. physical activity, smoking and alcohol consumption). This suggests a robust association of anxiety in T2DM patients independent from unfavorable lifestyle habits and highlights chronic anxiety as a clinically relevant phenotype [37].

Comparable to its role in affect regulation, a functional dichotomy of OXT is also apparent in metabolic regulation: On the one hand, evidence indicated that high OXT levels were positively associated with T2DM and obesity [38, 12, 39, 14, 13], reflecting the role of OXT as a signal of energy availability [3]. High OXT levels may appropriately signal the need to reduce caloric intake and increase energy expenditure [3]. On the other hand, conflicting evidence comes from studies showing low endogenous OXT levels in people with obesity (Fu-Man et al., 2019; Maestrini et al., 2018) or T2DM (Eisenberg et al., 2018; Qian et al., 2014; Yuan et al., 2016). In the present investigation, we assert a weak association between high OXT levels and T2DM. Most studies showing low OXT levels in T2DM subjects were conducted in samples of newly diagnosed or uncontrolled T2DM patients. In the present study, the majority of T2DM subjects (77%, n = 133) were under ongoing treatment. In a sensitivity analysis that considered only T2DM participants under treatment, we found that the results of our analyses remained unaltered (data are not shown).

To date, there is no clear understanding of sexual dimorphism related to the OXT regulation. Although sexual dimorphism has been recognized in the OXT system [40], both genders seem to be involved in the OXT-regulated energy homeostasis [41, 42]. The present study adds to the conflicting evidence by showing that neither sex differences nor interaction of T2DM by sex influences OXT levels. Our data also demonstrate that endogenous plasma OXT levels were unaffected by increasing age, supporting a previous report that showed OXT response during the insulin tolerance test had similar patterns and magnitudes in all groups [43]. However, it is also likely that the increase in OXT levels of older T2DM

subjects could be a compensatory mechanism for the maintenance of metabolic homeostasis where age-related metabolic impairments may have already developed.

Study strengths and limitations

This present study was conducted in a large population-based sample of older subjects from the KORA-Age study. The random sampling of the study population, the low loss to follow-up rate, and the strict quality assessment ensured the quality of the data. The substantially larger sample size of this study compared to other relevant studies to date made it easier to draw firm conclusions based on analytical results. The study design involved extensive assessments of psychological tests and biomarkers, providing the possibility to consider potential modifying factors and to produce robust results adjusting for covariates. The current study contributes to the understanding of endogenous OXT-T2DM association in an older population.

Limitations exist in this study. First, due to its cross-sectional design, we could not infer causality on the anxiety driven association between increased OXT levels and T2DM, and the findings from our study may not be generalizable to other populations. Second, the OXT levels of participants were measured from a single blood sample which may not accurately represent the average metabolic status of an individual. However, in this epidemiologic setting, the quality of the data was ensured by highly standardized procedures and a very strict quality assessment. The non-extracted plasma OXT enzyme immunoassay method used in our study may yield levels of higher magnitude than traditional radioimmunoassays because the samples may contain interfering substances [3]. Therefore, we acknowledge that OXT levels from immunoassays are measuring OXT immunoreactive products, not absolute values of OXT, preventing comparisons of absolute OXT levels between studies. However, the optimal method measuring endogenous OXT is still in active development, and “discrepancies between methods (i.e., extracted or unextracted) are not necessarily an indicator that some methods are valid whereas others are not” [44]. Furthermore, previous reports have shown a robust correlation between extracted and unextracted serum oxytocin levels [45], as well as associations between non-extracted OXT levels with body dysmorphic disorder (BDD) [46] or relationship distress [47], providing evidence for biologic relevance in these sample preparations. Therefore, in the current study, we valued the non-extracted plasma OXT enzyme immunoassay for comparing relative levels of peripheral OXT in participants with T2DM without T2DM.

Conclusion

The present investigation demonstrates that both T2DM status and sustained symptoms of anxiety in this old aged population contribute to a strong combined effect leading to a significantly elevated OXT level. Thus, anxiogenic stimuli significantly activate the body's OXT system, however, only in subjects who additionally suffer from T2DM as a severe pathological feature of dysregulated metabolism. The clinical consequences of this finding actually remain unclear, however, it may be speculated that this

particular OXT signaling network may be achieved to influence psychosocial adaptations with an impact on lifestyle behaviors related to energy regulation and metabolism.

Declarations

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Conflict of Interest Statement

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

The informed consent given by KORA study participants does not cover data posting in public databases. However, data are available upon request from KORA/KORA-gen (<https://epi.helmholtz-muenchen.de/>) by means of a project agreement. Requests should be sent to kora.passt@helmholtz-muenchen.de and are subject to approval by the KORA Board.

Code availability

Statistical codes are available from the corresponding author on request.

Author Contributions

KHL and MB designed the study. HJ and LJ conducted literature searches and performed statistical analyses. HJ and LK wrote the first draft of the manuscript. SA and KHL provided critical feedback, proofread and approved the final manuscript. MB and JK proofread and approved the final manuscript.

Ethics approval

The study was approved by the Ethics Committee of the Bavarian Medical Association, and written informed consents were provided by all the participants.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

The authors affirm that human research participants provided informed consent for publication.

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Figures

Figure 1

Age and sex-adjusted least-squares means (LS-means) of log-transformed plasma OXT levels (95% CI) by T2DM status, stratified by anxiety status (N=961).

Supplementary Files

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