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Linking glucose swings and mental health to cardiovascular outcomes and mortality in general practice

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The global rise in type 2 diabetes mellitus (T2DM) underscores the importance of early prevention in primary care. This study examined how changes in glucose tolerance and the presence of neuropsychiatric disorders relate to cardiovascular outcomes (CVO) and mortality. In a 10-year longitudinal study, 1,069 general practice patients (mean age 62.9 years; 51% male) underwent standard 2-hour glucose tolerance tests (GTT). Data on lifestyle, cardiovascular risk factors, comorbidities, and neuropsychiatric diagnoses (MINI Interview) were collected. The difference between baseline and follow-up GTT values (GTTdiff) was analyzed in relation to cardiovascular events and mortality. Patients who died had significantly higher GTTdiff (mean 1.37 mmol/L) compared to those with CVO (0.95 mmol/L) or without events (0.81 mmol/L; $p = .002$). Kaplan–Meier analysis showed shorter survival in patients with Major Depressive Episode (MDE) and GTTdiff > 3 mmol/L (7.43 years) versus those without MDE (8.76 years). Greater glucose variability and comorbid depression are associated with increased cardiovascular mortality. Interventions targeting both glucose control and mental health may improve outcomes in non-diabetic primary care populations.

Keywords Glucose fluctuation, Type 2 diabetes mellitus, Primary care cardiovascular outcomes, 10 years follow-up study

Globally, 425 million people have diabetes mellitus (DM), and the prevalence of type 2 diabetes mellitus (T2DM) has now reached pandemic proportions[1,2]. Diabetes-related chronic hyperglycemia is a key risk factor for developing microvascular and macrovascular complications, which substantially worsen the prognosis of affected patients[3].

Recent studies have examined whether glycemic fluctuations are directly related to the incidence of complications, including death[4,5]. Evidence suggests that diabetic complications arise not only from sustained hyperglycemia but also from glucose variability, which influences molecular mechanisms across multiple cells and tissues[6]. Glucose variability, expressed as intraday fluctuations between peaks and nadirs, has emerged as an HbA1c-independent risk factor for vascular complications in type 2 DM[3]. Furthermore, long-term visit-to-visit glycemic variability is considered a better predictor of microvascular and macrovascular complications than mean HbA1c levels[7]. However, real-world data on glucose fluctuation in general practice populations remain scarce. Although care paradigms have evolved from a gluco-centric to a vascular-centric approach, understanding how hyperglycemia and glucose variability affect outcomes remains crucial for improving survival and quality of life[8].

Depression and other neuropsychiatric disorders frequently coexist with diabetes—occurring roughly twice as often as would be expected by chance—yet are often underdiagnosed despite the availability of effective screening tools[9]. Neuropsychiatric conditions are associated with altered cortisol regulation, which can impair glucose metabolism. Zuccoli et al. demonstrated that stress-induced neuronal metabolic shifts, along with the metabolic side effects of psychotropic medications such as antidepressants and neuroleptics, contribute to weight gain, insulin resistance, and increased risk of metabolic syndrome[10,11]. Depression has a multifactorial pathophysiology and is strongly linked to type 2 DM and other cardiometabolic disorders[12]. A meta-analysis found that the prevalence of depression is moderately increased in prediabetes and markedly elevated in diagnosed diabetes compared with normal glucose metabolism[13]. Moreover, diabetes may predispose to other neuropsychiatric disorders, including anxiety[14]. Depression, driven by monoaminergic dysfunction and reduced serotonin levels, is associated with higher body weight, central adiposity, hyperglycemia, insulin resistance, and depressed mood[15].

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Stress and depression are further linked through inflammatory mechanisms. Population-based studies indicate that stress is associated with elevated glucose levels[16], while the inflammatory hypothesis of depression emphasizes the role of pro-inflammatory cytokines and immune activation[16]. These processes likely act bidirectionally[17], contributing to cardiovascular disease through inflammatory and metabolic pathways.

Reactive hypoglycemia, though less studied, may also contribute to adverse cardiovascular outcomes within the context of glucose variability. Ford et al. (1976) proposed that neuropsychiatric symptoms observed during glucose tolerance testing might sometimes reflect true metabolic disturbances rather than incidental findings[18]. This underscores the need for careful interpretation of glucose tolerance test (GTT) results, especially in psychiatric populations where glucose excursions may confound assessment of cardiovascular risk mechanisms. Subsequent work, including Schwartz et al. (2023), and other recent evidence, indicates that glycemic variability itself is associated with increased cardiovascular events and mortality, independent of mean glucose levels[19,20].

Chronic stress further promotes immune dysfunction via the hypothalamus–pituitary–adrenal (HPA) axis and the sympathetic nervous system, increasing the production of inflammatory cytokines[17]. Both physiological and behavioral mechanisms—including endothelial dysfunction, platelet abnormalities, inflammation, autonomic dysregulation, and poor adherence to healthy behaviors—may link depression to adverse cardiac outcomes[21]. The relationship between diabetes and mental disorders appears reciprocal: hyperglycemia predisposes to inflammatory changes, while mood and anxiety disorders exacerbate abnormal glucose metabolism, together contributing to the shared pathobiology of these progressive diseases and their complications[17,22].

The glucose tolerance test (GTT) is a well-established, simple, and inexpensive method for assessing glucose metabolism patterns[23]. It is routinely used to evaluate diabetes mellitus, insulin resistance, pancreatic beta-cell dysfunction, and reactive hypoglycemia, and occasionally to investigate rarer disorders of carbohydrate metabolism such as acromegaly[24]. Its practicality and reliability make the GTT indispensable in both clinical and research settings[25]. The most common form, the oral glucose tolerance test (OGTT), involves ingestion of a standardized glucose dose followed by measurement of blood glucose levels two hours later[26,27].

This study aimed to evaluate mortality and cardiovascular outcomes (CVO) in relation to changes in 2-hour GTT parameters and the presence of neuropsychiatric disorders among general practice patients. We hypothesized that greater glucose fluctuation and comorbid psychiatric conditions, particularly major depressive episodes, would independently predict long-term cardiovascular outcomes and mortality in primary care populations.

Materials and methods

This study was approved by the Kaunas Regional Bioethics Committee of Lithuania (for the first stage of study No. 6B/2003; for the follow-up No. BE-2-34/2011 and No.PI-22/2013) because initially data was gathered for a doctoral thesis.

Study design. It was a prospective observational population-based cohort study of a permanent population (living in towns and villages) from the Lithuanian 12th district, Raseiniai, Lithuania. Patients were randomly selected to participate in the study in the first stage of 2003 and were evaluated in a 10-year follow-up. The study sample was calculated according to the general 45+-aged population in the Raseiniai district and its proportions by age, sex, and place of residence (town or rural). According to official Lithuanian state statistics, there were 17,668 residents in the Raseiniai district at the beginning of 2003; 41% were male, and 36% were from the town. It was assumed that a 95% confidence level and 3% confidence interval would fit our study best. The calculated sample size was 1006. Important to note that the initial sample size calculation was for establishing a representative cohort with a defined precision for population characteristics, and that subsequent analyses of group differences were conducted within this established, sufficiently powered dataset for the observed effects.

This study was conducted at the Raseiniai Primary Health Care Centre, assuming its clients may represent the district. The cohort was assembled using a postmailing invitation. The sample was created by taking every fourth patient from an alphabetical list. Knowing that not all patients would agree to participate, 60% more invitation letters were sent—that is, 1613 (applying analogical randomisation for the list that was left after the first round). One thousand one hundred fifteen adults agreed (signed informed consent) to participate in the survey (response rate 69.1%) after being motivated by the possibility of getting blood test results free and consulting with the endocrinologist. The sample size analysed in this study was 1069 because 46 patients had DM and were excluded from the study.

A self-administered questionnaire was administered to all patients to assess lifestyle and cardiovascular risk factors, including present and former smoking habits, sociodemographic data, general health, and concomitant diseases. The MINI International Neuropsychiatric Interview, to diagnose mental disorders such as Major depressive episode (MDE), Dysthymia, Suicidality, Post-traumatic stress disorder (PTSD), and Generalised anxiety disorder (GAD), was administered during the first visit. All patients were subjected to a standard 2-hour glucose tolerance test. The difference between the results of the second and first GTT (GTTdiff) (Difference = 2-hour Glucose—Fasting Glucose) was calculated. This measure was selected because is a standardized, widely used tool for assessing postprandial glucose handling, insulin sensitivity, and beta-cell function. By comparing baseline and follow-up GTT values over time, GTTdiff quantifies longitudinal glycemic instability—an underexplored but clinically relevant marker of metabolic dysregulation in general practice populations. This approach is particularly valuable because:

- GTTdiff reflects real-world glycemic shifts that may not be captured by fasting glucose or HbA1c alone.
- Visit-to-visit variability in GTT values may signal progressive impairment in glucose regulation, even in non-diabetic individuals.
- Reactive hypoglycemia and exaggerated post-load hyperglycemia, both detectable via GTT, have been linked to autonomic dysfunction and increased cardiovascular risk.

- Neuropsychiatric disorders, such as depression and anxiety, are associated with HPA axis dysregulation, altered cortisol rhythms, and impaired glucose metabolism—factors that may amplify GTT fluctuations and cardiovascular vulnerability.

Patients' cardiovascular events (CVE) (stroke, transient ischemic attack (TIA), myocardial infarction (MI), unstable angina pectoris (UA), deep venous thromboembolism (dVTE) of legs) and/or deaths were assessed as cardiovascular outcomes (CVO) at 10 years follow-up, based on Raseiniai Primary Health Care Centre data. At the end of the study, all patients were divided into three groups: 1st- without CVE, 2nd—with diagnosed CVE, and 3rd—those who died within 10 years.

Baseline data are presented as means (M) and standard deviations (SD). The comparison of the groups was conducted by applying the Student t-test and two-way ANOVA to assess the interaction between the variables. Cox regression analysis was conducted to evaluate predictive values of variables for death outcome. Statistical models were adjusted for demographic, lifestyle, and clinical covariates potentially associated with glucose regulation and cardiovascular outcomes (sex, living environment, smoking status, alcohol use, physical activity, major depressive episode, dysthymia, suicidality, post-traumatic stress disorder, and generalized anxiety disorder, age, body mass index (BMI), waist circumference, GTTdiff). These covariates were selected based on established associations between these factors and both glycemic variability and cardiovascular risk. Including them in the models allowed control for potential confounding effects related to metabolic health, behavioral risk factors, and neuropsychiatric comorbidities. Survival analysis over 10 years was conducted by applying Kaplan-Meier curves. All analyses were conducted using the IBM SPSS Statistics 22 package.

Results

One thousand sixty-nine patients (546 males, 523 females, age M = 62.95 years) had complete information and were subjected to a standard 2-hour GTT procedure. Baseline characteristics of the study population are shown in Table 1.

Cox regression analysis was conducted to evaluate the relationship between GTT, psychiatric diagnoses, and a long-term outcome—death—as time-to-event data was only available for this outcome in the dataset. The analysis revealed that the only significant predictor of mortality was the glucose tolerance difference (GTTdiff), with B = 0.096, Wald = 11.430, $p = .001$, Hazard Ratio [Exp(B)] = 1.101, 95% CI = 1.041–1.164. The model demonstrated a good fit ($F(1) = 10.727$, $p = .001$). No significant associations were observed between the psychiatric variables and the outcome.

GTTdiff remained a significant predictor even after other variables from Table 1 were included in the Cox regression model (the final step of the analysis is shown in Table 2). Therefore, it was considered methodologically appropriate to continue focusing the analysis on the GTTdiff variable, in line with the study's primary objectives.

The objective of our study was to evaluate GTT fluctuations as GTTdiff in patients with various neuropsychiatric disorders. Table 3 presents the results.

The results showed that experienced PTSD and MDE were significantly related to greater glycemic fluctuations by GTTdiff: the GTTdiff reached M = 1.57 in those patients who had PTSD, but it was only M = 0.88 in those who had no PTSD ($p = .006$). Similar results were seen in the MDE assessment: the average result of GTTdiff in those with this disorder was M = 1.48, while in the group of those with no MDE, it was only M = 0.083 ($p = .001$).

The longitudinal study design allowed us to evaluate how the GTTdiff between the first and second measures was related to cardiovascular events and lethal outcomes over 10 years. The results showed that GTTdiff was significantly greater in patients who died before the end of follow-up (M = 1.37, SD = 2.38) than in those who had a major cardiovascular event (M = 0.95, SD = 2.1) or who had no cardiovascular events and were alive at the end of the follow-up period (M = 0.81, SD = 2.05) ($F = 6.086$, $p = .002$).

While there were differences in the neuropsychiatric disorders in 10 years of follow-up outcomes, we decided to evaluate whether there was an interaction between these two variables. The results of the two-way ANOVA are presented in Fig. 1.

The results showed only one statistically significant interaction between MDE and long-term outcomes ($p = .021$), yet the effect size was small ($\eta^2 = 0.007$). GTT fluctuation of the full sample, M = 1.37, was found to increase to M = 2.37 in the group of patients with lethal outcomes who had MDE. The GTTdiff of the full sample, M = 0.095, increased to M = 2.05 in the group of patients with cardiovascular events and MDE. In contrast, the average GTT fluctuation was lower in patients who died, but had no MDE (M = 1.13). Similarly, the average GTT fluctuation in patients with CVE who had no MDE was M = 0.66.

Finally, knowing that those who were alive at the end of the study and those who died had statistically different GTT fluctuations, a Kaplan-Meier survival analysis was conducted. Patients with GTTdiff results were divided into four groups: (1) the GTT fluctuation was negative (the result of the first measurement was higher than the second); (2) the GTT fluctuation range was from 0 to 1 mmol/l; (3) the GTT fluctuation range was from 1 to 3 mmol/l; and (4) the GTT fluctuation range was more than 3 mmol/l.

The results in the full sample showed that the worst survival estimation was for those whose GTT fluctuation was more than 3 mmol/l—the estimated life tenure was 8.49 years (95% CI 8.05- 8,92 years). The best survival estimation was among patients whose GTT fluctuated between 0 and 1 mmol/l, 9.15 years (95% CI 8.86–9.43 years) (Table 4; Fig. 2a). While analysing results in the sample of those who had MDE, the estimated survival of those whose GTT was greater than 3mmol/l was 7.43 years (95% CI 6.33–8.54 years), and only 43.3% of participants in this group survived during the study. In the 2nd group, the survival estimation was 9.45 years (95% CI 9.06–9.83 years) (Fig. 2b). The results of estimated survival in the groups of patients without MDE were more similar to those of the whole group. However, the shortest estimated survival was in study participants with a GTTdiff between 1 and 3 mmol/l, 8.64 years (Fig. 2c).

	N	%
Sex		
Male	546	51.1
Female	523	48.9
Living		
Town	312	29.2
Rural	757	70.8
Smoking		
Yes	357	33.4
No	712	66.6
Alcohol usage		
Yes	954	89.2
No	115	10.8
Physical activity		
Yes	516	48.3
No	553	51.7
Major depressive episode		
Yes	185	17.3
No	884	82.7
Dysthymia		
Yes	94	8.8
No	975	91.2
Suicidality		
Yes	76	7.1
No	993	92.9
Post-traumatic stress disorder		
Yes	102	9.5
No	967	90.5
Generalized anxiety disorder (GAD)		
Yes	253	23.7
No	816	76.3
	M	SD
Age	62.9	9.6
BMI	29.6	5.4
Waist circumference	99.2	13.7
First GTT measure	4.85	0.7
Second GTT measure	5.38	2.15

Table 1. Study population baseline characteristics.

					95.0% CI for Exp(B)	
	B	Wald	*p*	Exp(B)	Lower	Upper
GTTdiff.	0.039	1.770	0.183	1.040	0.982	1.101
Sex	0.464	7.136	0.008	1.590	1.132	2.235
Physical activity	−0.341	4.842	0.028	0.711	0.524	0.963
Smoking	0.461	7.553	0.006	1.585	1.141	2.202
Alcohol usage	−0.424	5.295	0.021	0.655	0.456	0.939
Age	0.062	59.805	0.000	1.064	1.047	1.081

Table 2. Results of final step Cox regression with all study variables.

Discussion

Historically, the Verona Diabetes Study raised concerns about maintaining long-term stability in fasting plasma glucose, identifying it as a predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus[28]. Building on this, glucose variability has gained recognition as a surrogate marker for beta-cell

	Yes	No	t	df	*p*
Major depressive episode	*N* = 185	*N* = 884			
	1.48 ± 2.35	0.83 ± 2.08	3.463	247.68	0.001
Dysthymia	*N* = 94	*N* = 975			
	1.18 ± 2.25	0.92 ± 2.13	1.094	109.67	0.276
Suicidality	*N* = 76	*N* = 993			
	0.73 ± 2.06	0.96 ± 2.15	− 0.935	87.93	0.352
Post-traumatic stress disorder	*N* = 102	*N* = 967			
	1.57 ± 2.43	0.88 ± 2.10	2.785	117.47	0.006
Generalized anxiety disorder	*N* = 253	*N* = 816			
	1.18 ± 2.19	0.87 ± 2.12	1.963	408.36	0.050

Table 3. The GTTdiff in participants with different neuropsychiatric disorders by the MINI. GTT, glucose tolerance test; the MINI, the MINI International Neuropsychiatric Interview.

dysfunction, particularly in type 2 diabetes. Kohnert et al. demonstrated that postprandial beta-cell impairment strongly correlates with glycemic excursions[29].

Although lifestyle factors were not directly assessed in our cohort, prior molecular analyses have shown that inconsistent dietary patterns and physical inactivity amplify glucose fluctuations and worsen metabolic outcomes[30]. Systematic reviews by Zhou et al. and Belli et al. further confirm that long-term glycemic variability predicts adverse cardiovascular and microvascular outcomes, independent of mean glucose levels[20,31].

T2DM is a major contributor to macrovascular and microvascular pathology, increasing the risk of myocardial infarction, heart failure, stroke, renal failure, and premature mortality[1,32]. The "ticking clock hypothesis" suggests that macrovascular damage begins long before diabetes is clinically diagnosed, implying that early metabolic instability may silently drive cardiovascular risk[33].

Our study adds to the growing consensus that glycemic variability predicts diabetes-related all-cause mortality[7,34], cardiovascular events[35,36], and renal deterioration[35,37,38], although some conflicting reports remain[34,37,39]. Acute hyperglycemia has been shown to activate the same metabolic and hemodynamic pathways as chronic hyperglycemia, compounding tissue damage[3,7].

Glycemic variability encompasses intraday glucose oscillations, including postprandial spikes and hypoglycemic episodes[40]. While some degree of variability exists even in normoglycemic individuals[41], studies evaluating glucose fluctuations in non-diabetic populations are limited. Importantly, the practical use of GTTdiff has not been widely implemented in primary care, despite its potential to reveal cardiovascular risk.

Oscillating glucose levels exert more deleterious effects than sustained hyperglycemia on endothelial function and oxidative stress, both central to atherosclerosis and cardiovascular pathology[42,43]. Our study employed standard 2-hour glucose tolerance testing to calculate GTTdiff, aiming to prompt a reevaluation of diagnostic interpretation in primary care beyond the conventional binary classification of glucose tolerance.

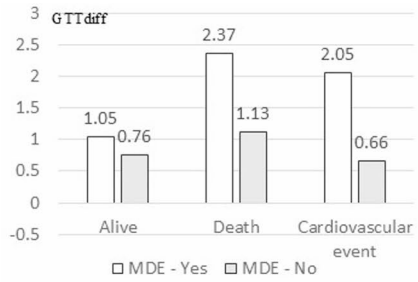
Despite the absence of a universally accepted gold standard for assessing glucose fluctuations, continuous glucose monitoring (CGM)-derived metrics such as the coefficient of variation (CV) have emerged as promising tools. According to the international consensus on time in range, CV values below 36% indicate stable glucose profiles and are increasingly used to quantify intra- and interday variability[44]. CV has demonstrated predictive value for diabetes complications and complements traditional markers like glycated hemoglobin[45]. Breyton et al. emphasized its relevance in evaluating therapeutic interventions and metabolic risk in type 2 diabetes[46], although none of these studies addressed non-diabetic populations.

Recent studies have begun to explore fasting plasma glucose (FPG) variation in non-diabetic individuals. Yu et al. found that long-term FPG variation is independently associated with cardiovascular disease and mortality[47]. Lee et al. reported that increasing FPG was linked to higher risks of myocardial infarction, stroke, and all-cause mortality[48]. Wang et al. confirmed that elevated visit-to-visit FPG variability significantly increased cardiovascular risk, independent of mean FPG and other baseline parameters[49].

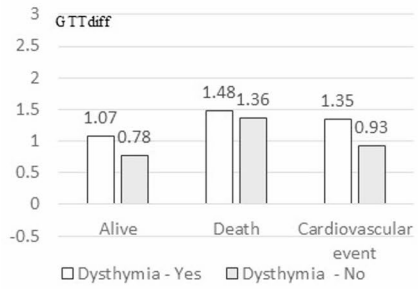
It is well established that subtle elevations in glucose and lipid levels may precede the diagnosis of type 2 diabetes by over 20 years[50]. This suggests that diabetogenic processes operate silently for decades. We propose that mood disorders, alongside glucose fluctuations, may serve as early indicators of accelerated cardiovascular risk—potentially implying causality.

Several studies support the notion that mood disorders are associated with accelerated alterations in glucose metabolism and increased cardiovascular risk. Scott et al. noted that insulin resistance and glucose disturbances may emerge early in the course of mood disorders[51]. Zhang et al. demonstrated that HPA axis dysfunction and glucose metabolism abnormalities were significantly associated with clinical outcomes in bipolar disorder[52]. A recent systematic review indicated that glucose variability may influence mood states in individuals with diabetes, though longitudinal studies are needed to establish directionality[53].

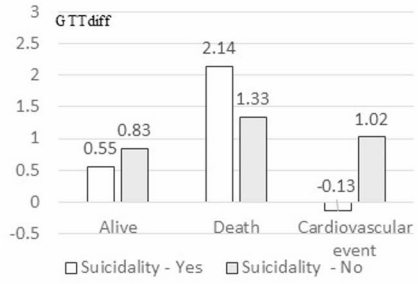
Our findings show that mental disorders—particularly PTSD and depression—are associated with greater GTT fluctuations, which may contribute to the mechanisms linking long-term glucose variability with cardiovascular outcomes. PTSD is known to alter sympathetic nervous system activity, neuroendocrine function, and metabolism in ways that mirror traditional metabolic disorders such as obesity and diabetes[54]. The prevalence of cardiovascular disease is elevated in individuals with PTSD[55], and chronic PTSD has been linked to excessive inflammatory activity[56].



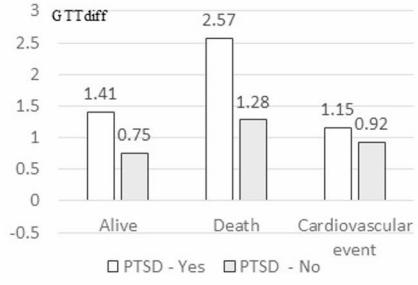
Tests of Between-Subjects Effects	F	p	η^2
Long-term outcome	8.802	**<.001**	.016
MDE	18.877	**<.001**	.017
Long-term outcome x MDE	3.888	**.021**	.007



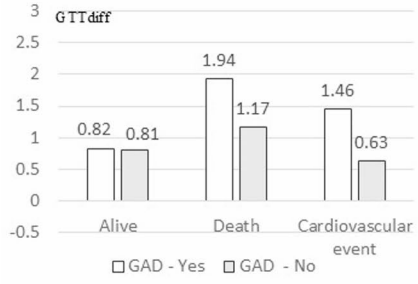
Tests of Between-Subjects Effects	F	p	η^2
Long-term outcome	1.724	.179	.003
Dysthymia	.463	.496	.000
Long-term outcome x Dysthymia	.055	.946	.000



Tests of Between-Subjects Effects	F	p	η^2
Long-term outcome	4.604	**.010**	.009
Suicidality	.295	.587	.000
Long-term outcome x Suicidality	1.758	.173	.003



Tests of Between-Subjects Effects	F	p	η^2
Long-term outcome	4.212	**.015**	.008
PTSD	6.417	.011	.006
Long-term outcome x PTSD	.890	.411	.002



Tests of Between-Subjects Effects	F	p	η^2
Long-term outcome	7.921	**<.001**	.015
GAD	7.740	**.005**	.007
Long-term outcome x GAD	2.856	.058	.005

GTT, glucose tolerance test; MDE, Major depressive episode; PTSD, post-traumatic stress disorder; GAD, generalized anxiety disorder

Fig. 1. Analysis of glucose tolerance test variability expressed as GTTdiff stratified by presence of neuropsychiatric conditions and longitudinal clinical outcomes over a ten year follow up period.

Importantly, our study revealed that PTSD was significantly associated with greater GTTdiff, and to our knowledge, no prior studies have evaluated this relationship in the general population. PTSD is also associated with a wide range of adverse mental and physical health outcomes, including major depression, substance abuse, suicide, and cardiovascular disease[57].

To summarise, key findings and implications of our stydy:

GTT fluctuation	Full sample ($N=971$) ($p=.001$)		With MDE ($N=165$) ($p<.001$)		Without MDE ($N=806$) ($p=.020$)	
	Percent of survived	Estimate (95% CI)	Percent of survived	Estimate (95% CI)	Percent of survived	Estimate (95% CI)
< 0 mmol/l	79.3%	9.12 (8.90–9.34)	80.4%	9.24 (8.63–9.85)	79,1%	9.10 (8.86–9.34)
0–1 mmol/l	82.8%	9.15 (8.86–9.43)	78.9%	9.45 (9.06–9.83)	83,6%	9.09 (8.75–9.42)
1-3mmol/l	72.9%	8.75 (8.45–9.05)	78.4%	9.22 (8.63–9.80)	71,6%	8.64 (8.29–8.98)
> 3 mmol/l	66.4%	8.49 (8.05–8.92)	43.3%	7.43 (6.33–8.54)	72,4%	8.76 (8.30–9.21)

Table 4. Estimated survival in full sample, in groups with MDE and without MDE. GTT-glucose tolerance test; MDE-major depressive episode.

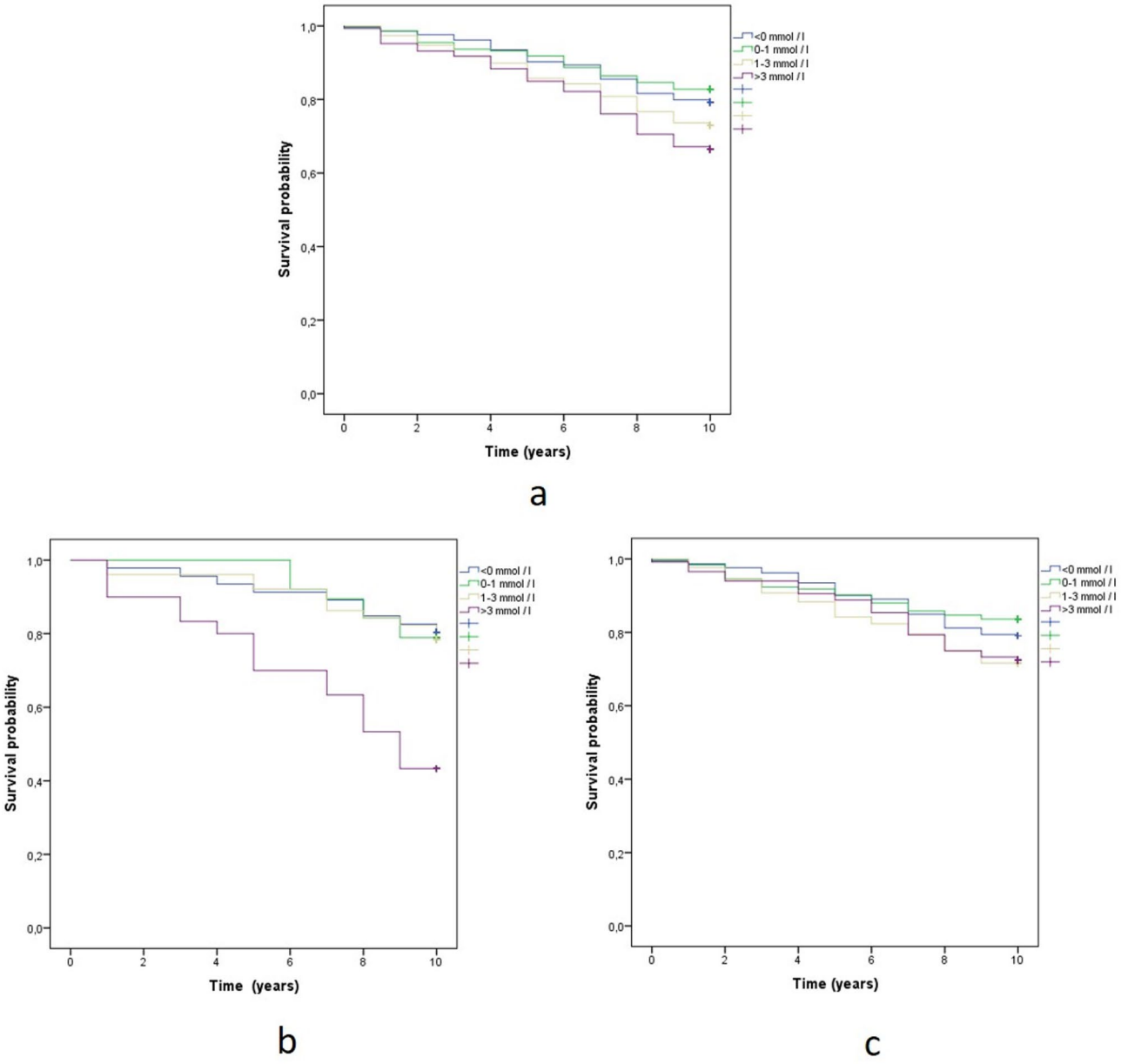


Fig. 2. Estimated survival (**a**) in full sample, (**b**) in participants with MDE and (**c**) in participants without MDE.

- GTTdiff is a novel, practical marker of long-term glycemic instability, applicable in primary care and capable of identifying cardiovascular risk in non-diabetic individuals. Incorporating GTTdiff into routine follow-up of patients with metabolic risk factors could help identify those experiencing emerging glucose dysregulation who might otherwise remain undetected by standard fasting glucose or HbA1c screening.
- Patients with Major Depressive Episode (MDE) and GTTdiff > 3 mmol/L had significantly reduced survival, suggesting a synergistic effect of psychiatric burden and glucose fluctuation on cardiovascular outcomes. Such patients could be prioritized for closer cardiovascular monitoring, lifestyle counseling, and early preventive interventions.
- PTSD was independently associated with elevated GTTdiff, highlighting a previously unexplored link between trauma-related psychopathology and metabolic instability.

These findings suggest that psychiatric comorbidity may accelerate the pathophysiological processes underlying cardiovascular disease, even in the absence of overt diabetes. The integration of mental health screening with metabolic assessment -particularly using GTTdiff—into routine metabolic reviews may enhance early risk stratification, intervention strategies and support comprehensive, patient-centered care in general practice.

Limitations and strengths

This study is limited by its observational design and the potential for residual confounding. Causality between glucose fluctuations and cardiovascular outcomes cannot be definitively established. Glucose variability may reflect underlying comorbidities rather than act as a direct causal factor.

Nonetheless, the strengths of our study include a large representative sample size, a decade-long follow-up, and a focus on non-diabetic individuals—a population often overlooked in cardiovascular risk research. By applying GTTdiff longitudinally, we offer a novel perspective on the metabolic and psychiatric predictors of cardiovascular outcomes in general practice.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity, and are available from the primary investigator and co-author Antanas Norkus upon reasonable request. The data are located in controlled-access data storage at Vilnius University.

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Conceptualization: A.N, J.G., I.Ž. Data curation: I.Ž. Formal analysis: I.Ž. Methodology: J.G., A. N. Project administration: J.G. Supervision: A.N. Validation: J.G., A.N. Visualization: I.Ž. Writing – original draft: J.G., I.Ž. Writing – review & editing: J.G., I.Ž., A.N.

Declarations

Competing interests
The authors declare no competing interests.

Institutional review board statement
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Lithuanian Bioethics Committee (for the first stage of study No. 6B/2003; for the follow-up No. BE-2-34/2011 and No.PI-22/2013).

Informed consent statement
Informed consent was obtained from all subjects involved in the study.

Additional information
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