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lncRNA TUG1 transcript levels and psychological disorders: insights into interplay of glycemic index and glycemic load

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Abstract

Background There is an association between obesity and psychological disorders such as depression, anxiety, and stress. Environmental factors and genetics play a crucial role in this regard. Several long non-coding RNAs (lncRNAs) are involved in the pathophysiology of the nervous system. Additionally, we intend to investigate how dietary glycemic index and load relate to psychological disorders in women with obesity and overweight by identifying the possible interaction with metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and taurine upregulated gene 1 (TUG1).

Methods 267 overweight or obese women between the ages of 18 and 48 were recruited for the current study. A reliable and validated food frequency questionnaire (FFQ) consisting of 147 items assessed food consumption, glycemic load (GL), and glycemic index (GI). Depression-Anxiety-Stress Scales (DASS-21) were used to assess mental well-being. A real-time polymerase chain reaction (PCR) was used to assess transcript levels for lncRNAs MALAT1 and TUG1.

Results In obese and overweight women, a positive correlation was found between anxiety and MALAT1 mRNA levels ($P=0.007$, CC = 0.178). Age, energy intake, physical activity, total fat, income, marriage, thyroid, and BMI were adjusted, and GI and TUG1 were positively correlated on DASS-21 ($\beta=0.006$, CI = 0.001, 0.01, $P=0.031$), depression ($\beta=0.002$, CI = 0.001, 0.004, $P=0.019$), Stress ($\beta=0.003$, CI = 0.001, 0.005, $P=0.027$). The interaction of GL and TUG1 on stress was also observed ($\beta=0.03$, CI = 0.001, 0.07, $P=0.048$).

Conclusions The lncRNA TUG1 appears to be associated with depression and stress through interaction with GI and correlated with stress by interaction with GL. To establish this concept, further research is required.

Keywords Long non-coding RNA, Glycemic index, Glycemic load, Diet, Obesity, Psychological disorders

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Introduction

The obesity epidemic is considered a global issue with negative implications for health and economics [1], including type 2 diabetes, cardiovascular diseases, and cancer risk [2–4]. The traditional approach to obesity management has primarily focused on short-term weight loss, with less focus on psychological factors that affect long-term weight maintenance [5]. Obesity is often influenced by psychological factors and may be maintained as a result of them [6]. Data revealed that depression, anxiety, and stress as psychological factors are associated with obesity [7–9]. Beyond genetics, mental disorders can be prevented and treated with nutrition [10–12].

Considerable attention is paid to carbohydrate consumption. Both the quantity and quality of carbohydrates affect the glycemic responses. A high glycemic index (GI) and a high glycemic load (GL) diet increase the risk of psychiatric disorders [13, 14]. The GI compares equal amounts of carbohydrates and provides a measure of the quality rather than the quantity of carbohydrates. The GL is based on GI and predicts human blood glucose response more strongly than GI [15]. The higher the GL, the more noteworthy blood glucose increases, and the insulinogenic impact of the food is anticipated. Diets that contain high levels of Gl and GL are associated with a higher risk of depression in the long term [16, 17]. An association between greater GL and lower mental illness risk has been suggested [17].

Epigenetic mechanisms are considered well-qualified candidates to explain the link between environmental factors like diet in subsequent health outcomes such as obesity and related disorders including psychological disorders [18–21]. Glucose, one of the most important substances in the body, regulates gene expression through epigenetic alteration [22]. Transient episodes of hyperglycemia contribute to the epigenetic process [23]. As obese individuals are more likely to experience transient hyperglycemia, epigenetic alterations may facilitate the progression of metabolic complications [24].

Long non-coding RNAs (lncRNAs), as a class of noncoding RNAs have been observed to regulate gene expression and function in lots of biological processes [25]. In the brain, long noncoding RNAs are highly expressed and play a pivotal role in key neuronal functions [26]. LncRNA dysregulation can induce neurodegenerative, neurodevelopmental, and neuroimmunological disorders, primary brain tumors, and psychiatric disorders [27]. A well-known lncRNA is metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) also known as noncoding nuclear-enriched abundant transcript 2 (NEAT2), that regulates the neurite growth. It is found in a variety of tissues; however, is concentrated in nerve cells. MALAT1 can regulate synaptogenesis-associated gene expression. Data revealed that synaptic density is reduced when MALAT1 is knocked down [28, 29].

The lncRNA Taurine up-regulated 1 (TUG1), found to be associated with human disease, plays various physiological roles, such as regulating gene expression, transcription, post-transcription, translation, and post-translation [30]. TUG1 was found to be elevated in relapsing-remitting multiple sclerosis (MS) patients in comparison with healthy controls [31].

Although there is ample evidence of the close association between obesity and psychological disorders, studies on the association between lncRNAs (MALAT1 and TUG1) with psychological disorders (anxiety, depression, and stress) are scarce. Moreover, the influence of the interaction of these lncRNAs and glycemic index and load on psychological disorders has yet to be investigated. Therefore, more investigation in this area warranted these relationships. To the best of the authors' knowledge, no data were available on the interplay between lncRNAs, (MALAT1 and TUG1), and the dietary glycemic index and load related to psychological disorders. Here, we aimed to evaluate how the lncRNAs and GI and GL interaction affect psychological disorders. In this study, we examined how lncRNAs, GI, and GL interaction affect anxiety, depression, and stress as psychological disorders among overweight and obese women.

Methods and materials

Population characteristics

The cross-sectional study included 267 women aged 18 to 48 years with BMIs ranging from 25 to 39.9 kg/m². These women, selected from health centers in Tehran, Iran, were healthy but exhibited overweight and obesity. The study's exclusion criteria covered a wide array of conditions, including acute and chronic diseases, as well as, pregnancy, lactation, and menopause. Furthermore, individuals currently using any medicine or weight-loss supplements, and having recently pursued dieting were also ineligible for participation in the study. The details of the study population are available in our previous articles [20, 21]. Before the study, participants were required to provide explicit written consent. The research plan got the approval from Tehran University of Medical Sciences Ethics Committee, following all ethical norms, under code IR.TUMS.MEDICINE.REC.1401.073.

Body composition assessment

To assess the body composition of all participants following the techniques, precautions, and guidelines set out in the manufacturer's protocol [29], we used a bioelectrical impedance analyzer, BIA Inbody 770 Co., Seoul, Korea. Participants removed footwear, excess clothing, and metal accessories before standing on the scale and holding the BIA handles as per protocol. This ensured

accurate measurements within 15 to 20 s. The bioelectrical analyzer effectively evaluated several crucial body composition components, such as weight, trunk fat, body fat mass (BFM), and visceral fat.

Anthropometric indices measurement

We used a calibrated digital scale with minimal measurement error for precise weight measurement, accurate to around 100 g. Participants wore light clothing for accuracy. Height was measured standing up with a non-elastic tape, accurate to 0.5 cm. BMI was calculated using weight (in kg) divided by height squared (in meters). Waist and hip circumferences were measured accurately with a 0.5 cm non-elastic tape, above the iliac crest and at the widest part of the hip, respectively. The waist-to-hip ratio was derived by dividing waist circumference by hip circumference. All measurements were conducted by a qualified expert to ensure precision and minimize errors.

Dietary intake assessment

A validated 147-question semi-quantitative food frequency questionnaire (FFQ) was used to assess participants' dietary intake over the past year [32]. The questionnaire's reliability and accuracy were confirmed in prior assessments for robust data collection on dietary habits. Participants indicated their food consumption frequency (daily, weekly, monthly, or annually), with portion size details discussed during face-to-face interviews. Participants estimated food item frequency using standardized units, converted to grams using FFQ data and a home scale guide. Energy and nutrients were accurately assessed with the NUTRITIONIST 4 food analyzer [33].

Glycemic index and load assessment

Dietary GI and GL were adjusted for total caloric intake using the residuals method. This ensures a more accurate assessment of their impact, independent of overall energy consumption [34]. Participants in the study were tested on 3–5 separate mornings after fasting overnight. On two occasions, they consumed test meals with 50 g of available carbohydrates to assess the impact of specific foods. The remaining occasions involved consuming a reference food like 50 g of glucose, 55 g of dextrose, or 50 g of white bread. After fasting blood sample collection, participants consumed the designated meal. This setup examined physiological responses to various reference foods under controlled fasting conditions. Blood samples were collected at 15, 30, 45, 60, 90, and 120 min after eating, and the Area Under the Curve (AUC) was calculated for each subject. This was expressed as a percentage of the mean AUC from the reference food. The average of these percentages across all subjects determined the GI of the test food. This approach compared glycemic responses to different foods against the reference, revealing their effects on blood glucose levels over time. When white bread was the reference, GI values were adjusted by multiplying them by 0.71 to align with the glucose scale (with a GI of 100). GL values were calculated by multiplying the available carbohydrate content of each food by its GI value, then further adjusted by the amount consumed. The sum of these values across all food items provided the total GL. This standardized method enabled a comprehensive comparison of glycemic responses across different foods relative to the reference food (white bread) and their impact on blood glucose levels [35].

Mental well-being assessment

As part of this study, symptoms of depression, anxiety, and stress were assessed using the Depression-Anxiety-Stress Scale-21 (DASS-21) questionnaire, which consists of 21 items. As developed by Lovibond and Lovibond [36], this valid and reliable questionnaire [37–39] consists of three self-report scales used in various populations to assess depression, anxiety, and stress. To complete the questionnaire, a person needed to specify their symptoms status. As part of the DASS-21, each subscale consisted of 7 questions, and the final score of each subscale was determined by adding the scores of each question. The questions were scored from 0 (not at all: does not apply to me at all) to 3 (very much: applies to me completely). Final scores were categorized based on established thresholds for depression (≥ 10), anxiety (≥ 8), and stress (≥ 15), enabling classification according to each mental health dimension [39].

Assessment of physical activity

The short form of the International Physical Activity Questionnaire (IPAQ) was used to evaluate participants' physical activity (PA) levels. This survey collected information regarding the length and regularity of individuals' daily activity throughout the week within the previous year. The data offered valuable insights into the weekly physical activity of each participant, which was measured in metabolic equivalent hours per week (MET-h/week) [40].

Biochemical factors assessment

A 10-ml venous blood sample was collected between 8:00 and 10:00 in the morning after fasting overnight. 5 mL of blood was collected, while the rest was divided into tubes. The tubes were stored at -21 °C for one hour, then at -80 °C for gene expression analysis. All methods for measuring biochemical parameters fasting blood glucose (FBG), triglyceride (TG) and total cholesterol (TC), low-density lipoprotein (LDL-c), high-density lipoprotein (HDL-c) cholesterol, homeostasis Model Assessment Insulin Resistance (HOMA-IR), alanine aminotransferase

(ALT), and aspartate aminotransferase (AST) can be seen in our previous articles [20, 41, 42].

Real-time quantitative polymerase chain reaction (PCR)

The details of the real-time qPCR method have been published in our previous article [21]. The primer sequences utilized to investigate the expression of MALAT1, TUG1, and 18s rRNA genes are provided in Table S1.

Statistical evaluation

The Kolmogorov-Smirnov test was utilized to assess the normal distribution of the data. Descriptive analysis, including measures such as the mean and standard deviation, was employed to evaluate the general characteristics of the study participants. Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were employed to compare biochemical variables and body composition among participants, accounting for covariates that might affect results. ANCOVA adjusted for BMI, total fat, energy intake, income, age, marriage, physical activity, and thyroid diseases to enhance result precision by accounting for potential influences on outcomes. We investigated the correlation and association between MALAT1 and TUG1 and psychological disorders using Pearson correlation and linear regression tests, respectively. Additionally, we examined the interaction between GI and GL with TUG1 and MALAT1 on psychological disorders using generalized linear models, while considering various covariates. All statistical analyses were performed using SPSS version 23 software (SPSS, Chicago, IL, USA). Reported *P*-values were two-sided, and statistical significance was considered at a *P*-value less than 0.05. *P*-values below 0.07 were also considered of marginal significance.

Results

General characteristics of study population according to tertiles of DASS-21

Table 1 displays the baseline characteristics of research participants arranged based on DASS-21 tertiles. As indicated in Table 1, in the crude model, there was a marginally significant difference among tertiles of the DASS-21 in terms of MCP-1 ($P=0.067$) and used supplements ($P=0.050$). The PA ($P=0.064$) of participants among tertiles of the DASS-21 became significant after confounders including age, energy intake, physical activity, total fat, income, marriage, thyroid, and BMI were adjusted. Additionally, a significant mean difference in terms of MCP-1 ($P=0.048$) and supplement use ($P=0.035$) was observed among tertiles of the DASS-21.

Dietary intake of study population according to tertiles of DASS-21

As depicted in Table 2, the crude model showed that there was a significant mean difference among the tertiles of the DASS-21 in terms of caffeine ($P=0.001$), fluoride ($P=0.002$), vitamin C ($P=0.036$), and marginally significant for vitamin K ($P=0.053$), vegetables ($P=0.051$); after the energy intake was adjusted, the mean differences in terms of caffeine ($P=0.001$), fluoride ($P=0.001$), and vitamin C ($P=0.035$) remained significant. There were also marginally significant differences among the tertiles of the DASS-21 in terms of vitamin K ($P=0.063$), vegetables ($P=0.067$), pantothenic acid ($P=0.059$), and vitamin B6 ($P=0.057$).

Long non-coding RNAs, GI, and GL of the study population according to tertiles of DASS-21

Table 3 shows the study population's genes, GI, and GL based on DASS-21 tertiles. In both crude and adjusted models, there was no significant mean difference ($P>0.05$) across tertiles of DASS-21 in terms of TUG1 and MALAT1 transcript levels, GI, and GL.

The correlation between long non-coding RNAs and psychological disorders

The relationship between genes and psychological disorders is displayed in Table 4A. In the crude model, anxiety and MALAT1 gene expression in overweight and obese women showed a positive correlation ($P=0.007$, $CC=0.178$). In all other cases, no significant relationship was found between genes and psychological disorders.

The association between transcript level of long non-coding RNAs and psychological disorders

Long non-coding RNAs and the psychological disorders model were associated in Table 4B, where anxiety and MALAT1 gene expression were found to be significantly correlated in obese and overweight women ($B \pm SE=0.11 \pm 0.04$, CI=0.03, 0.19, $P=0.007$). Neither the crude nor adjusted models showed a significant correlation between genes and other psychological interventions.

The interaction of GI and GL with the long non-coding RNAs TUG1 and MALAT1 in psychological disorders

In the context of psychological diseases, Table 5 shows the association between GI and GL and the transcript levels of TUG1 and MALAT1. There was a positive interaction between GI and TUG1 transcript levels on DASS-21 ($\beta=0.006$, CI=0.001, 0.01, $P=0.031$), depression ($\beta=0.002$, CI=0.001, 0.004, $P=0.019$), and stress ($\beta=0.003$, CI=0.001, 0.005, $P=0.027$), after adjusting for age, energy intake, physical activity, total fat, income, marriage, thyroid, and BMI. Furthermore, GL and TUG1

Table 1 General characteristics of the study population according to tertiles of DASS-21 in obese and overweight women ($n=267$)

Variables†	DASS-21				
	Mean ± SE			*P*-value*	*P*-value**
	T_1($n=87$)	T_2($n=90$)	T_3($n=90$)		
Age (years)	36.94 ± 0.90	35.50 ± 0.87	37.07 ± 0.89	0.380	0.157
PA (MET-min/week)	924.19 ± 121.98	1384.56 ± 307.01	1229.11 ± 212.32	0.382	**0.064**
Anthropometric measurements					
Weight (kg)	80.16 ± 1.38	81.72 ± 1.18	78.85 ± 0.96	0.228	0.565
WC (cm)	98.32 ± 1.15	99.72 ± 0.97	97.51 ± 0.82	0.278	0.887
WHR	0.92 ± 0.005	0.93 ± 0.005	0.92 ± 0.004	0.431	0.830
BMI (kg/m^2)	30.66 ± 0.44	31.27 ± 0.41	30.44 ± 0.34	0.315	0.142
BF (%)	40.94 ± 0.57	41.52 ± 0.60	41.20 ± 0.52	0.778	0.911
Fat trunk (%)	306.09 ± 7.45	315.73 ± 7.05	307.30 ± 6.06	0.558	0.951
VFL	15.19 ± 0.40	17.97 ± 2.18	15.29 ± 0.32	0.237	0.722
FFMI (kg)	17.94 ± 0.16	19.43 ± 1.46	17.76 ± 0.14	0.321	0.896
FMI (kg)	12.71 ± 0.34	13.20 ± 0.32	12.81 ± 0.29	0.532	0.896
FFM (kg)	47.08 ± 0.62	47.01 ± 0.55	45.97 ± 0.52	0.297	0.923
BFM (kg)	33.37 ± 0.94	34.38 ± 0.81	32.67 ± 0.68	0.332	0.880
Obesity degree (%)	142.63 ± 2.07	143.86 ± 2.07	141.51 ± 1.60	0.684	0.479
Biochemical variables					
FBS (mg/dl)	87.68 ± 1.12	87.19 ± 1.08	86.76 ± 1.09	0.842	0.348
TC (mg/dl)	181.77 ± 3.82	179.54 ± 3.75	189.65 ± 4.48	0.179	0.114
TG (mg/dl)	118.52 ± 6.73	126.62 ± 9.60	119.51 ± 6.77	0.727	0.883
HDL (mg/dl)	47.47 ± 1.12	44.45 ± 1.18	47.42 ± 1.28	0.123	0.535
LDL (mg/dl)	95.15 ± 2.52	90.82 ± 2.58	98.32 ± 2.95	0.140	0.407
GOT (u/l)	18.98 ± 1.08	18.72 ± 0.89	17.03 ± 0.64	0.252	0.213
GPT (u/l)	21.09 ± 1.86	20.01 ± 1.62	18.27 ± 1.26	0.465	0.382
HOMA index	3.40 ± 0.14	3.35 ± 0.14	3.34 ± 0.15	0.953	0.192
hs.CRP (mg/l)	4.14 ± 0.43	5.33 ± 0.56	4.73 ± 0.46	0.236	0.284
MCP-1	65.56 ± 14.76	55.44 ± 10.66	29.67 ± 5.23	**0.067**	**0.048**
TUG1	1.49 ± 0.88	1.81 ± 0.88	2.35 ± 0.66	0.747	0.934
MALAT1	0.99 ± 0.38	1.49 ± 0.67	2.28 ± 0.89	0.411	0.965
Income (n)				0.093	0.484
< 500,000	0	1	4		
500,000–1,000,000	4	5	0		
1,000,000–1,500,000	27	24	24		
1,500,000<	36	35	45		
Marriage (n)				0.636	0.295
Married	71	66	69		
Single	14	21	18		
Away from spouse more than 6 month	1	1	0		
Dead spouse	0	1	0		
Divorce	1	1	3		
Supplementation (n)				**0.050**	**0.035**
Yes	42	44	34		
NO	28	22	39		

BF%; body fat percentage; BFM: body fat mass; BMI: body mass index; FBS: fasting blood sugar; FFM: fat free mass; FMI: Fat Mass Index; FFMI: Fat-Free Mass Index; GOT: Glutamate oxaloacetate transaminase; GPT: glutamate pyruvate transaminase; HDL: high density lipoprotein; HOMA; homeostatic model assessment; hs-CRP: high-sensitivity C-reactive protein; MCP-1: monocyte chemoattractant protein-1; PA: physical activity; SE: standard error; T: tertile; TC: total cholesterol; TG: triglyceride; VFL: visceral fat level; WC: waist circumference; WHR: waist height ratio

* Calculated by analysis of variance (ANOVA)

**: Adjusted for age, energy intake, physical activity, total fat, income, marriage, thyroid, and BMI

P value < 0.05 was considered significant, and 0.05–0.07 was considered marginally significant

Table 2 Dietary intake of study population according to tertiles of DASS-21 in obese and overweight women ($n=267$)

Variables†	DASS-21				
	Mean ± SD			*P*-value	*P*-value*
	T_1 ($n=87$)	T_2 ($n=90$)	T_3 ($n=90$)		
Food group					
Whole grains (g/d)	72.42 ± 6.63	54.78 ± 6.43	62.60 ± 5.74	0.144	0.112
Refined grains (g/d)	365.22 ± 20.22	379.14 ± 27.63	351.72 ± 22.32	0.711	0.872
Fruits (g/d)	561.96 ± 38.77	514.99 ± 37.86	454.66 ± 35.78	0.129	0.159
Vegetables (g/d)	416.02 ± 31.32	409.52 ± 26.99	334.75 ± 19.67	**0.051**	**0.067**
Low-fat dairy (ml/d)	289.72 ± 23.55	330.87 ± 25.08	285.49 ± 25.12	0.356	0.417
High-fat dairy (ml/d)	83.91 ± 16.46	86.04 ± 14.39	86.48 ± 13.70	0.992	0.950
Red meat (g/d)	22.58 ± 2.10	24.55 ± 2.10	18.21 ± 1.84	0.073	0.102
Poultry (g/d)	35.16 ± 4.91	37.41 ± 4.11	36.75 ± 4.32	0.936	0.919
Fish (g/d)	12.81 ± 1.67	11.02 ± 1.07	11.24 ± 1.30	0.607	0.607
Nuts (g/d)	17.00 ± 1.89	13.77 ± 1.83	14.59 ± 1.79	0.445	0.362
Egg (g/d)	22.66 ± 1.55	20.79 ± 1.45	22.44 ± 1.70	0.660	0.584
Caffeine (g/d)	604.38 ± 47.36	656.38 ± 48.16	1015.16 ± 122.01	**0.001**	**0.001**
Glucose (g/d)	21.73 ± 1.12	20.96 ± 1.17	18.92 ± 1.41	0.259	0.305
Sucrose (g/d)	32.36 ± 2.12	34.23 ± 2.18	30.22 ± 2.11	0.412	0.555
Fructose (g/d)	26.12 ± 1.33	25.17 ± 1.39	23.32 ± 1.64	0.391	0.463
GI	237.10 ± 4.53	243.93 ± 6.05	244.12 ± 4.14	0.531	0.336
GL per score	4.96 ± 0.34	4.80 ± 0.33	5.27 ± 0.33	0.596	0.453
Nutrient intake					
Energy (kcal/d)	2625.24 ± 80.89	2649.91 ± 79.17	2562.51 ± 78.92	0.722	-
Protein (g/d)	90.42 ± 3.24	90.71 ± 3.11	85.92 ± 2.91	0.463	0.582
Carbohydrate (g/d)	376.96 ± 12.61	377.09 ± 13.99	359.85 ± 12.25	0.553	0.557
Total fat (g/d)	93.25 ± 3.57	95.23 ± 29.66	94.53 ± 33.39	0.920	0.509
MUFA (g/d)	30.60 ± 1.23	31.45 ± 1.14	31.86 ± 1.24	0.758	0.331
PUFA (g/d)	19.71 ± 0.97	20.52 ± 0.94	19.86 ± 0.84	0.804	0.829
SFA (mg/d)	27.77 ± 1.14	28.06 ± 1.08	28.67 ± 1.36	0.863	0.319
Trans fat	0.001 ± 0.0004	0.0008 ± 0.0001	0.001 ± 0.0002	0.670	0.651
Vitamin A (mg/d)	790.83 ± 40.71	804.06 ± 50.84	752.61 ± 43.45	0.702	0.859
Vitamin D (ug/d)	2.14 ± 0.20	1.91 ± 0.15	1.84 ± 0.17	0.460	0.482
Vitamin E (mg/d)	16.97 ± 1.11	17.92 ± 0.94	17.27 ± 0.93	0.792	0.817
Vitamin K (mg/d)	198.17 ± 14.45	255.16 ± 32.74	185.03 ± 11.58	**0.053**	**0.063**
Thiamin (mg/d)	2.07 ± 0.06	2.11 ± 0.07	2.04 ± 0.06	0.782	0.924
Riboflavin (mg/d)	2.20 ± 0.09	2.28 ± 0.08	2.12 ± 0.08	0.409	0.533
Niacin (mg/d)	25.61 ± 1.04	25.84 ± 1.10	24.57 ± 0.85	0.630	0.860
Pantothenic acid (mg/d)	6.67 ± 0.22	6.80 ± 0.33	6.02 ± 0.20	0.074	**0.059**
Vitamin B6 (mg/d)	2.23 ± 0.08	2.24 ± 0.08	2.04 ± 0.06	0.110	**0.057**
Biotin (mg/d)	39.65 ± 1.61	40.01 ± 2.36	35.75 ± 1.47	0.195	0.262
Folate (mcg/d)	668.06 ± 24.86	684.79 ± 25.20	668.04 ± 21.04	0.847	0.806
Vitamin B12 (mcg/d)	4.50 ± 0.28	4.52 ± 0.23	4.12 ± 0.27	0.482	0.637
Vitamin C (mg/d)	218.90 ± 17.25	199.08 ± 11.98	169.72 ± 10.95	**0.036**	**0.035**
Iron (mg/d)	18.96 ± 0.62	19.04 ± 0.72	18.03 ± 0.57	0.459	0.482
Zinc (mg/d)	13.40 ± 0.46	13.21 ± 0.47	12.32 ± 0.43	0.201	0.083
Manganese (mg/d)	7.15 ± 0.25	6.78 ± 0.28	7.28 ± 0.35	0.483	0.132
Copper (mg/d)	2.05 ± 0.07	2.08 ± 0.09	1.87 ± 0.06	0.132	0.082
Fluoride (mg/d)	2271.54 ± 159.21	2337.05 ± 152.67	3515.33 ± 416.04	**0.002**	**0.001**

GI: glycemic index; GL: glycemic load; MUFA; monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; SFA: saturated fatty acid; T: tertile

Data are mean ± SE

P-value*: ANCOVA was performed to adjust the potential confounding factor (energy intake)

P value < 0.05 was considered significant, and 0.05–0.07 was considered marginally significant

Table 3 The long non-coding RNAs, GI, and GL of the study population according to tertiles of DASS-21 in obese and overweight women ($n=267$)

Variables	DASS-21			*P*-value*	*P*-value **
	Mean ± SE				
	T_1 ($n=87$)	T_2 ($n=90$)	T_3 ($n=90$)		
TUG1	1.49 ± 0.88	1.81 ± 0.88	2.35 ± 0.66	0.747	0.934
MALAT1	0.99 ± 0.38	1.49 ± 0.67	2.28 ± 0.89	0.411	0.965
GI	237.10 ± 4.53	243.93 ± 6.05	244.12 ± 4.14	0.531	0.322
GL per score	4.96 ± 0.34	4.80 ± 0.33	5.27 ± 0.33	0.596	0.180

T: tertile; GI: glycemic index; GL: glycemic load

* Calculated by analysis of variance (ANOVA)

**: Adjusted for age, energy intake, physical activity, total fat, income, marriage, thyroid, and BMI. (ANCOVA)

P value < 0.05 was considered significant, and 0.05–0.07 was considered marginally significant

Table 4A Correlation between long non-coding RNAs and psychological disorders in obese and overweight women ($n=267$)

Variables		TUG1		MALAT1	
		CC	*P*-value	CC	*P*-value
DASS-21	Crude	0.102	0.125	0.115	0.083
	Adjusted	0.103	0.217	**0.002**	0.981
Depression	Crude	0.111	0.096	0.072	0.280
	Adjusted	0.122	0.144	**0.004**	0.964
Stress	Crude	0.089	0.178	**0.065**	0.332
	Adjusted	0.103	0.220	**-0.048**	0.566
Anxiety	Crude	0.060	0.364	0.178	**0.007**
	Adjusted	0.026	0.754	**0.067**	0.428

CC: correlation coefficient

The adjusted model of the significant level after adjustment for the variables of age, energy intake, physical activity, total fat, income, marriage, thyroid, and BMI

P value < 0.05 was considered significant, and 0.05–0.07 was considered marginally significant

Table 4B Association between long non-coding RNAs and psychological disorders in obese and overweight women ($n=267$)

Variables		TUG1			MALAT1		
		B ± SE	95% CI	*P*-value*	B ± SE	95% CI	*P*-value*
DASS-21	Crude	0.17 ± 0.11	-0.48, 0.393	0.125	0.22 ± 0.12	-0.02, 0.48	0.083
	Adjusted	0.13 ± 0.11	-0.0.8, 0.36	0.217	0.004 ± 0.18	-0.35, 0.36	0.981
Depression	Crude	0.07 ± 0.04	-0.01, 0.16	0.096	0.05 ± 0.05	-0.04, 0.15	0.280
	Adjusted	0.06 ± 0.04	-0.02, 0.15	0.144	0.003 ± 0.07	-0.13, 0.14	0.964
Stress	Crude	0.06 ± 0.04	-0.02, 0.15	0.178	0.05 ± 0.05	-0.05, 0.16	0.332
	Adjusted	0.06 ± 0.05	-0.03, 0.16	0.220	-0.04 ± 0.08	-0.20, 0.11	0.566
Anxiety	Crude	0.03 ± 0.03	-0.04, 0.10	0.364	0.11 ± 0.04	0.03, 0.19	**0.007**
	Adjusted	0.01 ± 0.03	-0.06, 0.08	0.754	0.04 ± 0.06	-0.07, 0.16	0.428

CI: confidence interval; SE: standard error

*The significance of the linear regression test

The adjusted model of the significant level after adjustment for the variables of age, energy intake, physical activity, total fat, income, marriage, thyroid, and BMI

P value < 0.05 was considered significant, and 0.05–0.07 was considered marginally significant

gene expression on stress were found to positively interact (β=0.03, CI=0.001, 0.07, $P=0.048$). In contrast, there was no discernible relationship between GI and GL and MALAT1 gene expression in terms of stress, anxiety, depression, or DASS-21.

Discussion

Our findings indicate a positive association between anxiety and MALAT1 gene expression in women with obesity and overweight. Upon adjusting for potential confounders such as age, energy intake, physical activity, total fat, income, marriage, thyroid, and BMI, a notable positive interaction emerged between GI and TUG1 concerning DASS-21, depression, and stress. Additionally, a positive interaction was identified between GL and TUG1 gene expression specifically related to stress.

Ample evidence showed that lncRNAs may have important regulatory roles in depression and anxiety pathologies [27, 43]. The functional analysis of highly correlated mRNAs in microarray-based analysis of

Table 5 The interaction between GI and GL with TUG1 and MALAT1 on psychological disorders in obese and overweight women (*n* = 267)

Variables	GI	TUG1			MALAT1		
		B	95% CI	*P*-value	B	95% CI	*P*-value
DASS-21		0.006	0.001, 0.01	**0.031**	0.003	-0.009, 0.01	0.610
Depression		0.002	0.001, 0.004	**0.019**	0.002	-0.003, 0.007	0.476
Stress		0.003	0.001, 0.005	**0.027**	0.003	-0.003, 0.008	0.332
Anxiety		0.001	-0.001, 0.002	0.465	-0.001	-0.005, 0.003	0.538
Variables	**GL**	**TUG1**			**MALAT1**		
		B	**95% CI**	***P*-value**	**B**	**95% CI**	***P*-value**
DASS-21		0.05	-0.02, 0.14	0.192	0.031	-0.09, 0.16	0.635
Depression		0.01	-0.01, 0.04	0.365	0.01	-0.03, 0.06	0.652
Stress		0.03	0.001, 0.07	**0.048**	0.02	-0.02, 0.08	0.324
Anxiety		0.003	-0.02, 0.03	0.847	-0.009	-0.05, 0.03	0.666

CI: confidence interval; GI: glycemic index; GL: glycemic load

GLM was performed to identify the interaction between GI and GL with TUG1 and MALAT1 on psychological disorders

P-value = adjusted for potential confounding factors including (age, energy intake, physical activity, total fat, income, marriage, thyroid, and BMI)

P value < 0.05 was considered significant, and 0.05–0.07 was considered marginally significant

rodent hippocampal tissue revealed that the dysregulated lncRNAs play a role in a variety of biological processes and pathways. These lncRNAs appear to contribute to the modulation of rat susceptibility or resilience to stress, depression, or anxiety [44]. LncRNA down-regulation in peripheral blood samples was negatively associated with the risk of suicide in major depressive disorder (MDD) patients [45]. The anterior cingulate cortex of suicide victims showed substantial changes in the expression of many lncRNAs. The data unveiled the potential regulatory effects of these lncRNAs, influencing transcriptome dynamics involved in different depression-associated molecular processes. These processes encompassed the organization of the cytoskeleton, plasma membrane function, cell adhesion, regulation of nucleus, DNA-binding, and the modulation of dendrite morphology and development [46].

Psychological disorders data indicated a significant alteration in the expression of MALAT1. Specifically, individuals with bipolar disorder exhibited downregulation of MALAT1 in their blood compared to controls. This observation suggests the potential utility of MALAT1 as a diagnostic biomarker in the blood of individuals with bipolar disorder [29]. On the other hand, alterations in MALAT1 have been observed in Parkinson's disease [47], and it has been observed that β-asarone by targeting and reducing MALAT1 can serve as a target for therapeutic intervention in Parkinson's disease [48]. In alignment with the current findings, another study focusing on peripheral blood leukocytes reported no significant differences in MALAT1 levels between patients with Major Depressive Disorder (MDD) and healthy subjects [49].

There is inconsistency in the available data related the MALAT1 and obesity and related disorders [50, 51]. Human adipose-tissue stem cells (hADSCs) contain a high level of MALAT1 in their exosomes. The majority of MALAT1 lncRNA is retained by preadipocytes and adipocytes after the differentiation of hADSCs into adipocytes [52]. Moreover, MALAT1 might be a potential regulator of fat deposition; because of increased expression of MALAT1 in porcine adipose tissue, which was dependent on backfat accumulation [53].

In the current study, no discernible differences were noted in MALAT1 expression among the three tertiles of DASS-21 within the studied groups. However, a positive correlation was identified between MALAT1 expression and anxiety within the entire population.

While information on the mechanisms involving MALAT1 is limited, a study conducted on mice with autism spectrum disorder (ASD) has shed some light on this aspect. The investigation revealed an upregulation of caspase-3 (CASP3) and a concurrent downregulation of MALAT1, influencing apoptosis in hippocampal neurons of autistic mice. MALAT1, predominantly located in the nucleus, was found to recruit DNA methyltransferases to the CASP3 promoter region, promoting methylation and consequently inhibiting gene expression. In vitro research suggested that the downregulation of MALAT1 led to increased cellular apoptosis through the upregulation of CASP3 and Bax, along with the downregulation of Bcl-2. These findings contribute additional evidence supporting MALAT1's role in regulating CASP3 promoter methylation to prevent neuronal apoptosis in the hippocampal regions of mice with ASD [54]. On the other hand, Fatty acid binding protein 4 (FABP4) and lipoprotein lipase (LPL) regulatory genes are positively correlated with MALAT1 expression in fat tissue [55]. Also, MALAT1 participates in fatty acid metabolism and adipogenesis at the transcriptional level through the

regulation of peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway [55]. Further investigation is required to elucidate the mechanistic processes involving MALAT1 lncRNA and its impact on downstream miRNA and mRNA pathways.

A study conducted by *Safari et al.* on schizophrenic patients reported the downregulation of h0091 compared to healthy subjects [56]. In patients with Autism Spectrum Disorder (ASD), there was observed up-regulation of TUG1 compared to the healthy control group [57]. There is an inhibitory effect of TUG1 on miR-9, a conserved miRNA related to animal behavioral deficits, and subsequently, this miRNA affects multiple mRNAs [58]. In another investigation, the overexpression of TUG1 dramatically reduces inflammation and improves insulin sensitivity in obesity through the downregulation of miR-204, as well as through the activation of the SIRT1/GLUT4/PPARγ/AKT pathway [59]. MALAT1 and TUG1 might play a pivotal role in obesity because the transcription levels of MALAT1 and TUG1 showed a positive correlation with major lipogenic and adipogenic genes [60]. The data on this matter is inconsistent; however, in this particular investigation, no significant differences in TUG1 were seen between the three tertiles of DASS-21 in overweight and obese women.

Dietary intake plays a pivotal role in epigenetics and psychological disorders. Data from one systematic review among cohort studies revealed a significant positive correlation between dietary GI and depression. Additionally, significant effects of high-GL diet intake on depression have been demonstrated in clinical trials [16]. *Haghighatdoost et al.*. reported that a higher GI diet was linked to a greater risk of depression [17]. On the other hand, data showed a greater GL was associated with a decreased risk of mental disorders, depression, and psychological distress [17]. An investigation among Iranian adults showed that higher GL diet intake was related to lower stress risk; although, no significant association was observed between GI or GL and depression and anxiety risk [61]. Also, our previous study revealed a negative correlation between quality of life and GL, but not GI, among overweight and obese women [62]. Our recent study revealed that MALAT1 positively interacted with the cholesterol/saturated fat index among overweight and obese women, which affects the visceral adiposity index and body adiposity index [21].

Our study revealed a positive interaction between GI and TUG1 gene expression on DASS-21, depression, and stress. Additionally, a positive interaction was identified between GL and TUG1 gene expression specifically related to stress. These findings contribute to a growing body of evidence highlighting the interplay between TUG1 and GI in the context of psychological disorders.

Despite the rapid evolution of the epigenetics field, only a limited number of lncRNAs have been extensively studied through detailed experiments. Predictions about their functions remain scarce, and further research is essential to unravel the signaling pathways and regulatory networks implicated in psychiatric disorders such as depression, anxiety, and stress.

While the present study's results are promising, it is crucial to acknowledge certain limitations. Firstly, because of the cross-sectional design we fail to assess a causal relationship between evaluated components of the investigation. We also intend to emphasize that our research is ongoing, and we plan to conduct follow-up studies to establish longitudinal cohorts in the future. Also, it seems necessitates additional research to delve into the potential mechanisms underlying the observed interactions. Secondly, the reliance on the Food Frequency Questionnaire (FFQ) for dietary assessment introduces the possibility of recall bias. Moreover, the study was confined to overweight/obese women. Future research endeavors should encompass both genders, involve larger populations, and consider diverse obesity phenotypes to provide a more comprehensive understanding of these associations.

Conclusion

Collectively, our findings contribute to the existing body of literature by affirming a positive association between MALAT1 and anxiety in obese and overweight women. Additionally, we observed a positive interaction between GI and TUG1 gene expression concerning DASS-21, depression, and stress. Similarly, a positive interaction was identified between GL and TUG1 gene expression specifically related to stress. However, further studies are imperative to elucidate the intricate interactions between the mentioned lncRNAs and GI and GL in the context of psychological disorders among overweight and obese women.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-024-01976-7.

Supplementary Material 1

Author contributions

NR performed experimental tests. NR and KM participated in the study design and interpreted results. NR and KM conducted sample collection. NR performed biochemical experiments and helped with the methodology. MSY and NR performed the statistical analysis. NR, FE, AKH, and KM wrote the draft of the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol received approval from the ethics committee of the Endocrinology and Metabolism Research Center of Tehran University of Medical Sciences (TUMS) under the identification number IR.TUMS.MEDICINE.REC.1401.073. Before participating in the study, each participant received comprehensive information about the study protocol and willingly provided written and informed consent. All procedures and methodologies adhered to the relevant guidelines, regulations, and principles outlined in the Declaration of Helsinki.

Consent for publication
The final manuscript received approval from all authors, and they provided consent for its publication.

Competing interests
The authors declare no competing interests.

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