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ORIGINAL RESEARCH

Increased Levels of Serum Glycosylated Hemoglobin are Associated with Depressive Symptoms in a Population with Cancer (≥49 Years): An Antidepressant-Stratified Analysis

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Purpose: Patients with cancer tend to have a high prevalence of depressive symptoms. The direct relationship between serum glycosylated hemoglobin (GHb) levels and depressive symptoms in cancer patients is still uncertain. We aimed to evaluate the association with serum GHb levels with depressive symptoms in the population (aged ≥49 years) with cancer.
Patients and Methods: Longitudinal data in 204 participants with cancer obtained from The Irish LongituDinal Study on Ageing (TILDA) were used to investigate the association of serum GHb levels with depressive symptoms.
Results: Our results suggested a positive and significant association between serum GHb levels and depression score, independent of age, gender, body mass index (BMI), currently married, education, smoking status, drink alcohol, systolic and diastolic blood pressure (BP), physical activity, self-reported cardiovascular diseases and laboratory measurement in participants with cancer (coefficient =0.141, P<0.001; Model 2) at baseline (wave 1). Higher GHb levels did associate with higher prevalence of depressive symptoms in participants with cancer (OR=2.100, 95% CI 1.105–5.036, P=0.004; Model 2) after adjustment for these same confounding factors in wave 1 was made. Stratified analysis further showed that these significant associations were interfered by antidepressants. Sensitivity analysis showed that higher serum GHb levels in subjects with cancer were linked to higher prevalence of depression events during a follow-up of 4 years.
Conclusion: Our results found a significant association between elevated serum GHb levels and increased risk of depressive symptoms in the population aged ≥49 years with cancer after confounding factors were adjusted.

Keywords: glycosylated hemoglobin, depression, cancer, middle-aged and elderly

Introduction

More and more evidence suggested that cancer patients tend to have an increased risk of depressive symptoms which is related to poor treatment adherence,[1,2] as well as a high risk of cancer-related complications, such as cardiovascular diseases (CVDs) and all-cause mortality.[3–6] Patients in the cancer stage can intensify the symptoms of depression. A study pointed out that cancer-related depression risk factors include diagnosed cancer, poor pain control, cancer progression, physical damage or others.[7] These risk factors can promote the occurrence of depressive symptoms in cancer patients. Finding significant risk factors as sensitive markers or

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predictors for detecting depression is of great significance for treating cancer and alleviating the rate of cancer-related complications in patients with cancer.

Mental health comorbidities including depression are also increasing worldwide and worsen outcomes for population with diabetes.[8,9] As one of the important indexes to evaluate blood glucose levels, the association of glycosylated hemoglobin (GHb) levels with depression is still unclear. GHb is a product of the combination of carbohydrates in serum and hemoglobin in red blood cells. Its content depends on the blood glucose concentration and the contact time between blood glucose and hemoglobin, but has nothing to do with blood sampling time, fasting, insulin use and other factors.[10,11] Therefore, GHb can effectively and steadily reflect the blood glucose control of diabetic patients. GHb is usually used as a monitoring index for diabetes control clinically. Although the association between GHb and depression has been investigated in the adult population previously. These results are not consistent and follow-up studies are few.[12] Studies investigating the relationship between serum levels of GHb and depressive symptoms have variably reported positive, negative, or nonexistent relationships.[13–15] Considering the above evidence, we would like to further evaluate the association of serum GHb levels and depressive symptoms in this study.

The Irish Longitudinal Study on Ageing (TILDA) consists of a study population aged ≥49 years with ... information on biochemical detection and depression score. Thus, we can comprehensively investigate the association between GHb levels and depressive symptoms in this study. We would like to investigate the relationship of serum levels of GHb with depression events during a follow-up of 4 years. It was hypothesized that elevated levels of GHb were linked to higher risk of depressive symptoms in subjects with cancer and the association may be modified by antidepressant medications. Our study aimed to assess the association of serum levels of GHb with the risk of depressive symptoms in a middle-aged and elderly population with cancer that was further stratified by those with taking antidepressant medications.

Patients and Methods

Study Sample

In summary, the anonymized TILDA data are available to scientific research workers who meet the criteria for access from the Interuniversity Consortium for the Irish Science Data Archive at University College Dublin and Political and Social Research at the University of Michigan. TILDA also approves applications for privileged access to the data set by a website called "hot desk" (www.tilda.ie). However, we obtained enough data from the TILDA study through a website (www.icpsr.umich.edu/icpsrweb/ICPSR/) which is a data-sharing platform for researchers to use it for free. All included subjects from TILDA were used for analyses and were performed in a detailed flow chart (Figure 1). The detailed information on the design and method of the study were published elsewhere.[16] In summary, all subjects who have finished the self-completed questionnaire and computer-aided personal interview (CAPI) were invited to take a health examination in one of the health centres. All included subjects finished a CVD assessment in health centres including biochemical examination. Thus, our study had accurate GHb data for analysing the association of serum GHb levels and depression. The Trinity College Research Ethics Committee has approved the TILDA protocol, and all subjects have given informed written consent.

Test for Serum GHb

Technicians collected blood samples from all included subjects on the same day after they finished the self-completed questionnaire and the CAPI. The measurement procedures and methods of serum GHb levels in the cohort subjects were published elsewhere.[16]

Depression Score

Depressive score was calculated by using the Centre for Epidemiological Studies Depression (CES-D) scale.[17] A cut-off score (≥16) was defined as indicative of Depressive symptoms in wave 1 or depression events in wave 3.[18]

Covariates

Sociodemographic characteristics and lifestyle factors were included in this study. Marital status was classified as "currently married" or "not currently married". Education was defined as follows:

> primary [some primary (not complete), primary or equivalent], secondary (an intermediate/junior/group certificate or equivalent or a leaving certificate or equivalent or a diploma/certificate) and high. (primary degree or post-graduate/higher degree)

Smoking was defined as "current smoker", "past smoker", or "never smoker". Drinking was defined as "yes" or "no". Level of physical activity was defined as level 0, level 1 and level 2.

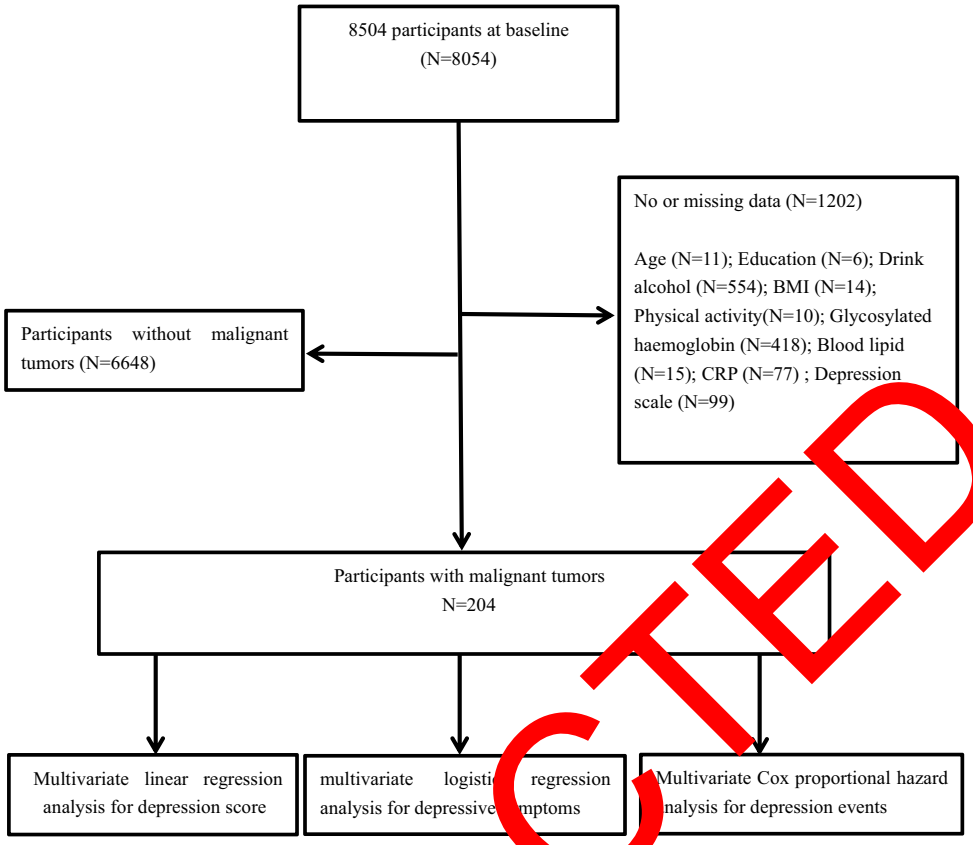

Figure 1 A detailed flow chart of subjects included in the analysis.

Self-reported CVDs were defined as "yes" or "no". "Taking antidepressant medications" was classified as "yes" or "no".

Statistical Analysis

SPSS 24.0 was used for analyzing data. Multivariate linear regression analysis was performed to assess the relationship between depression score and serum GHb levels in wave 1 (baseline). Then, the relationship between serum levels of GHb and depression score was further investigated by stratified analysis by using "taking antidepressant medications" as a covariate. Furthermore, multivariate logistic regression analysis was used to evaluate the association of serum GHb levels with depressive symptoms (CES-D score ≥10) at baseline (wave 1). Stratified analysis by using "taking antidepressant medications" as a covariate was also performed.

Finally, we furthermore analysed the association of GHb levels at baseline with depression events by multivariate Cox proportional hazard analysis. Sensitivity analysis using "taking antidepressant medications" as a confounding variable was also performed. The "$p<0.05$" was considered to be statistically significant in all analyses.

Results

Baseline Characteristics

In order to evaluate the serum GHb levels in cancer patients, 408 age- and gender-matched subjects (1:2), who have undergone physical examination without cancer or any other severe illnesses, were obtained as the healthy control group at baseline. Our results showed that serum GHb levels were significantly higher compared with control subjects in Table 1. The baseline data of all subjects are detailed in Table 2. The age of subjects with cancer was 64.9±9.1 (years) and 68.6% of them were male. BMI of them was 32.36±5.40 (kg/m^2); serum GHb level was 45.79±10.34 mmol/L; rate of taking antidepressant medications was 26.5% and depression score was 6.92±7.12.

The Association Between Serum GHb Levels and CES-D Score at Baseline by Multivariate Linear Regression Analysis

To confirm the relationship of serum GHb levels with depression score, the multivariate linear analysis model was performed. Our study demonstrated that serum GHb

Table 1 Baseline Characteristics of Patients with Cancer and Control Subjects

Variables	Patients with Cancer (N=204)	Control Subjects (N=408)	*P* value
Age (years)	64.9±9.1	65.6±9.5	0.867
Gender (male), n (%)	140 (68.6)	284 (69.6)	0.645
GHb (mmol/L)	45.79±10.34	39.43±6.22	<0.001

Note: Data are presented as mean ± SD for normally distributed data and n (%) for nonnormally distributed data.
Abbreviation: GHb, glycosylated haemoglobin.

was independently and positively linked with CES-D score (coefficient=0.141, $p<0.001$, Model 2) in subjects with cancer (Table 3). The relationship between GHb and CES-D score was affected by using "antidepressant medications" as a confounding variable in stratified analysis (Table 4). Serum GHb was only independently and significantly associated with CES-D score in subjects with cancer who did not have "antidepressant medications".

The Association of Serum GHb with Depressive Symptoms (CES-D Score ≥16) at Baseline by Using Multivariate Logistic Regression Analysis

In order to evaluate the association between GHb levels and depression symptoms, multivariate logistic regression model was used. We found that serum GHb was significantly linked with depressive symptoms (OR=2.100, 95% CI 1.205–5.036, $p=0.004$, Model 2) in subjects with cancer after relevant confounding factors were adjusted in the multivariate model (Table 5). Stratified analysis demonstrated that the relationship between serum GHb and depressive symptoms was also affected by "taking antidepressant medications" (Table 6). Serum GHb was still associated with depressive symptoms in subjects with cancer after the adjustment of related confounding factors was made. These results demonstrated that cancer subjects with elevated serum levels of GHb have an increased risk of depressive symptoms.

Table 2 Baseline Characteristics in Patients with Cancer

Variables	Subjects with Cancer (N=204)
Age (years)	64.9±9.1
Gender (male), n (%)	140 (68.6)
BMI (kg/m^2)	32.36±5.40
Currently married, n (%)	144 (70.6)
Education	
Primary, n (%)	70 (34.3)
Secondary, n (%)	119 (58.3)
High, n (%)	15 (7.4)
Smoking status	
Never, n, (%)	88 (43.1)
Past, n (%)	106 (52.0)
Current, n (%)	10 (4.9)
Drink alcohol, n (%)	148 (72.5)
Levels of physical activity	
Level 0	82 (40.2)
Level 1	71 (34.8)
Level 2	51 (25.0)
Systolic BP (mmHg)	138.6±16.7
Diastolic BP (mmHg)	82.7±10.3
Taking antidepressant medications, n (%)	54 (26.5)
Self-reported CVDs	
Hypertension, n (%)	133 (65.2)
[illegible] n (%)	21 (10.3)
Heart failure, n (%)	7 (3.9)
Myocardial infarction or coronary thrombosis, n (%)	31 (14.2)
Stroke, n (%)	10 (4.9)
Laboratory measurement	
GHb (mmol/L)	45.79±10.34
Triglycerides (mmol/L)	1.88±1.12
LDL (mmol/L)	2.46±0.14
HDL (mmol/L)	1.25±0.38
Cholesterol (mmol/L)	4.65±1.10
C-reactive protein (mg/L)	6.37±11.74
Depression score	6.92±7.12

Note: M ±SD for normally distributed data and n (%) for categoric variables.
Abbreviations: BMI, body mass index; BP, blood pressure; CVDs, cardiovascular diseases; GHb, glycosylated haemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Elevated GHb Levels in Wave 1 Were Associated with Higher Risk of Depression Events During a Follow-Up of 4 Years

Our results have suggested that serum levels of GHb were significantly correlated to depressive symptoms in wave 1. Hence, we analysed the relationships between GHb levels at baseline and depression events after 4 years from wave 1 (Table 7). A multivariate Cox proportional hazard model was used for assessing the association of serum GHb levels with depression events. Our results suggested that serum GHb levels were independently and positively associated with depression events (OR=2.103, 95% CI 1.105–4.694, $p=0.006$, Model 2) after the adjustment for confounding

Table 3 Multivariate Linear Regression on Association of GHb Levels with Depression Score at Baseline

Variables	Subjects with Cancer (N=204)		
	Coefficient	Adjusted 95% CI	P value
Crude	0.206	0.104–0.332	<0.001
Model 1	0.183	0.100–0.275	<0.001
Model 2	0.141	0.092–0.258	<0.001

Notes: Crude: adjusted for age and gender. Model 1: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP and physical activity. Model 2: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP, physical activity, self-reported CVDs and laboratory measurement.
Abbreviations: GHb, glycosylated haemoglobin; BMI, body mass index; BP, blood pressure.

Table 4 Multivariate Linear Regression on Association of GHb Levels with Depression Score by Stratified Analysis at Baseline

Variables	Subjects with Cancer (N=204)		
	Coefficient	Adjusted 95% CI	P value
No taking antidepressant medications (N=150)			
Crude	0.235	0.112–0.379	<0.001
Model 1	0.198	0.105–0.304	<0.001
Model 2	0.160	0.100–0.282	<0.001
Taking antidepressant medications (N=54)			
Crude	0.140	0.090–0.245	<0.001
Model 1	0.101	0.013–0.219	0.035
Model 2	0.052	[illegible]	[illegible]

Notes: Crude: adjusted for age and gender. Model 1: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP and physical activity. Model 2: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP, physical activity, self-reported CVDs and laboratory measurement.
Abbreviations: GHb, glycosylated haemoglobin; BMI, body mass index; BP, blood pressure.

factors was made. To exclude the confounding effects of antidepressant therapy (Patients with taking antidepressant medications were excluded), our sensitivity analysis showed that serum GHb was still significantly and independently related to depression events (OR=2.311, 95% CI 1.130–4.947, $p<0.001$, Model 2, Table 8).

Discussion

Our study has suggested a significant association between serum GHb levels and depressive symptoms in an adult population aged >49 years. The higher serum levels of GHb in subjects with cancer tended to be significantly linked with higher risk of depression events.

Table 5 Adjusted Association of GHb Levels with Depressive Symptoms by Multivariate Logistic Regression Analysis at Baseline

Variables	Subjects with Cancer (N=204)		
Serum Glycosylated Haemoglobin Levels (per 1-SD Increase)	OR	Adjusted 95% CI	*P* value
Crude	2.504	1.145–5.692	<0.001
Model 1	2.328	1.127–5.257	0.002
Model 2	2.100	1.105–5.036	0.004

Notes: Crude: adjusted for age and gender. Model 1: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP and physical activity. Model 2: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP, physical activity, self-reported CVDs and laboratory measurement.
Abbreviations: GHb, glycosylated haemoglobin; BMI, body mass index; BP, blood pressure.

Table 6 Adjusted Associations of GHb Levels with Depressive Symptoms by Multivariate Logistic Regression Analysis by Stratified Analysis at Baseline

Variables	Subjects with Cancer (N=204)		
Serum Glycosylated Haemoglobin Levels (per 1-SD Increase)	OR	Adjusted 95% CI	*P* value
No taking antidepressant medications (N=150)			
Crude	2.713	1.151–5.898	<0.001
Model 1	2.548	1.145–5.486	<0.001
Model 2	2.386	1.139–5.481	0.002
Taking antidepressant medications (N=54)			
Crude	1.510	1.019–2.639	0.034
Model 1	1.314	1.006–2.210	0.092
Model 2	1.205	1.003–1.993	0.214

Notes: Crude: adjusted for age and gender. Model 1: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP and physical activity. Model 2: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP, physical activity, and laboratory measurement.
Abbreviations: GHb, glycosylated haemoglobin; BMI, body mass index; BP, blood pressure.

Existing evidence suggested that two-thirds of patients diagnosed with an invasive cancer today will live more than 5 years, with a resulting rising population of long-term survivors due to improvements in cancer treatment and detection.[19–22] Although many cancer survivors have adjusted to cancer and its associated treatments, a subgroup still struggles with emotional adjustment in the survivorship period. Early detection of depression has

Table 7 Adjusted Associations of GHb Levels with Depressive Symptoms by Multivariate Cox Proportional Hazard Analysis After a Follow-Up of 4 Years

Variables	Subjects with Cancer (N=204)		
Serum Glycosylated Haemoglobin Levels (per 1-SD Increase)	**HR**	**Adjusted 95% CI**	***P* value**
Crude	2.426	1.142–5.491	<0.001
Model 1	2.285	1.120–5.037	<0.001
Model 2	2.104	1.103–4.694	0.006

Notes: Crude: adjusted for age and gender. Model 1: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP and physical activity. Model 2: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP, physical activity, and laboratory measurement.

Abbreviations: GHb, glycosylated haemoglobin; BMI, body mass index; BP, blood pressure.

Table 8 Adjusted Associations of GHb Levels with Depressive Symptoms by Multivariate Cox Proportional Hazard Analysis by Sensitivity Analysis (Patients with Taking Antidepressant Medications Were Excluded, N=54)

Variables	Subjects with Cancer (N=150)		
Serum Glycosylated Haemoglobin Levels (per 1-SD Increase)	**HR**	**Adjusted 95% CI**	***P* valu**
Crude	2.608	1.150–5.[illegible]0	<0.001
Model 1	2.492	1.13[illegible].381	<0.001
Model 2	2.311	1.030–4.[illegible]17	<0.001

Notes: Crude: adjusted for age and gender. Model 1: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP and physical activity. Model 2: adjusted for age and gender, BMI, currently married, education, smoking status, drink alcohol, systolic BP, diastolic BP, physical activity, and laboratory measurement.

Abbreviations: GHb, glycosylated haemoglobin; BMI, body mass index; BP, blood pressure.

a significant role in improving treatment outcomes and alleviating the rate of cancer-related complications such as CVDs in patients with cancer.

GHb is formed by the combination of some special molecular sites of hemoglobin and glucose through a slow and irreversible reaction. The amount of GHb production is closely related to the level of blood glucose, and GHb is much more stable than blood glucose.[10,11] So the determination of GHb can reflect the average blood glucose level in a period of time from 8 to 12 weeks before the blood sampling, which is a good indicator to reflect the good or bad blood glucose control for a long period of time.[23,24] Studies have demonstrated that population with cancer have an increased risk of depressive symptoms. However, studies on the association between serum GHb levels and depression in patients with cancer are few. In our study, we found that serum GHb levels in patients with cancer were associated with higher risk of depressive symptoms. The potential reasons that can be explained are as follows: First of all, diabetes is a long-term chronic disease and there is no complete cure method. Patients must always pay attention to diet management, often monitor blood sugar and take long-term medication. Some patients even need long-term insulin injection, which greatly reduces the quality of life of patients.[25] Some patients believe that the use of insulin indicates a serious condition, so the psychological pressure is greater, and the pessimistic mood is more serious.[26,27] Second, if the blood glucose control is not good, the patients may have complications in 5–10 years, which is a threat to the patients, which will inevitably lead to fear, anxiety and depression.[28–31] Moreover, long-term treatment produces a lot of medical expenses, which brings heavy financial burden to patients and families, and psychological pressure will increase dramatically.

In the present study, our results suggested that GHb levels in patients with cancer were significantly higher than in control subjects. Previous studies have shown that chronic diseases such as cancer, CVDs and type 2 diabetes have common risk factors including age, obesity and excessive alcohol consumption,[32–34] and common pathological mechanisms including inflammation and oxidative stress.[35,36] These results may be partially explained by that more patients with cancer tend to have abnormal blood glucose. Our results further showed that increased serum GHb levels have higher depression scores, which suggested a strong association of GHb levels with depressive symptoms. Indeed, our multifactor logical analysis suggested that increased serum GHb levels were associated with higher risk of depressive symptoms (OR=2.100, 95% CI 1.105–5.036, P=0.004, Model 2) after related confounding factors were adjusted. These results are consistent with previous studies.[19–21] Differently, we further found that these significant associations between GHb and depression were interfered by antidepressants in stratified analysis. In cancer subjects with taking antidepressant medications, the strong relationship was disappeared (OR=1.205, 95% CI 1.003–1.993, P=0.214, Model 2). Obviously, antidepressant therapy led to a change for the depression score, which led to non-significant results. Existing studies have also shown that antidepressant treatment led to

the disappearance of positive results,[37–40] which is consistent with our findings. In addition, our study also found that increased serum GHb was associated with elevated risk of depression events in subjects with cancer (HR=2.104, 95% CI 1.103–4.694, P=0.006, Model 2) after a follow-up of 4 years. In order to eliminate the influence of taking antidepressant medications, Our sensitivity analysis (subjects with taking antidepressant medications were excluded, N=54) showed serum GHb can be considered as an independent prognostic factor or predictor for detecting depression events.

Our study has some strengths. First, our study data were obtained from TILDA, a longitudinal study with a national population of an adult population.[16] Our analysis suggested that elevated serum GHb levels are significantly linked to the high risk of depression events. Second, we showed a positive relationship between GHb levels and depression in the population aged ≥49 years with cancer after controlling for various confounding factors for GHb and depression. This association was strongly significant when adjusted for possible confounders. We confirmed that an elevated GHb levels can predict the occurrence of depression events so that the causality of this association is clear, which further improves the deficiencies of previous studies where the causality of this associati[on] unclear. Certainly, some limitations exist in these results. [F]irst, some data were lost for some participants in th[e] LDA st[udy], leading to deviations in our results. Se[co]nd, sev[e]ral tim[e] varying factors including BMI and phys[ic]al acti[vity] dis[e]turb our results on the association b[e]tween G[Hb] and depressive symptoms. Third, we did not [h]ave enough da[ta] about what specific types of cancer are in all su[b]jects, so we could not adjust it in multivariate [r]egression analys[is].

Conclusions

Serum GH[b] lev[el]s are [p]ositi[ve]ly and significantly associated [w]ith depr[e]ssive symp[t]oms after adjustments of various life[st]yle [f]actors in an adult population with cancer were made.

Disclosure

The authors report no conflicts of interest in this work.

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