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, as well as a high risk of cancer-related complications, such as cardiovascular diseases (CVDs) and all-cause mortality. 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. These risk factors can promote the occurrence of depressive symptoms in cancer patients. Finding significant risk factors as sensitive markers or...
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 enough 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 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 postgraduate/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.
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 ≥16) 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/m²); 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...
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 1.105–5.036, \( p=0.004 \), 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.

### 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 factors.
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       | 0.053–0.219     | 0.035  |
| Model 2                                     |                             | 0.052       | 0.038–0.149     | 0.061  |

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.

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) | OR       | Adjusted 95% CI | P value |
|------------------------------------|-----------------------------|----------|-----------------|--------|
| Serum Glycosylated Haemoglobin Levels (per 1-SD Increase) |                             |          |                 |        |
| 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) | OR       | Adjusted 95% CI | P value |
|----------------------------------------------|-----------------------------|----------|-----------------|--------|
| Serum Glycosylated Haemoglobin Levels (per 1-SD Increase) |                             |          |                 |        |
| 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.10-22 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 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).
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) |
|------------------------------------------------|-------------------------------|
|                                                 | HR   | Adjusted 95% CI | P value |
| Serum Glycosylated Haemoglobin Levels (per 1-SD Increase) |       |                 |        |
| 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) |
|------------------------------------------------|-------------------------------|
|                                                 | HR   | Adjusted 95% CI | P value |
| Serum Glycosylated Haemoglobin Levels (per 1-SD Increase) |       |                 |        |
| Crude                                          | 2.608 | 1.150–5.560     | <0.001 |
| Model 1                                        | 2.492 | 1.139–5.381     | <0.001 |
| Model 2                                        | 2.311 | 1.130–4.947     | <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. 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. 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. 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. 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. 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, and common pathological mechanisms including inflammation and oxidative stress. 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. 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 association was unclear. Certainly, some limitations exist in these results. First, some data were lost for some participants in the TILDA study, leading to deviations in our results. Second, several time-varying factors including BMI and physical activity may disturb our results on the association between GHb and depressive symptoms. Third, we did not have enough data about what specific types of cancer are in all subjects, so we could not adjust it in multivariate regression analysis.

Conclusions
Serum GHb levels are positively and significantly associated with depressive symptoms after adjustments of various lifestyle factors in an adult population with cancer were made.

Disclosure
The authors report no conflicts of interest in this work.

References
1. Wang Y-H, Li J-Q, Shi J-F, et al. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. Mol Psychiatry. 2020;25(7):1487–1499. doi:10.1038/s41380-019-0595-x
2. Erim DO, Bensen JT, Mohler JL, et al. Prevalence and predictors of probable depression in prostate cancer survivors. Cancer. 2019;125(19):3418–3427. doi:10.1002/cncr.32338
3. Rajan S, McKee M, Rangarajan S, et al. Association of symptoms of depression with cardiovascular disease and mortality in low-, middle-, and high-income countries. JAMA Psychiatry. 2020;77(3):301–309.
4. Huang Y, Xu Y, Jiang Y, et al. Sex differences in the associations between blood pressure and anxiety and depression scores in a middle-aged and elderly population: The Irish Longitudinal Study on Ageing (TILDA). J Affect Disord. 2020;274:118–125. doi:10.1016/j.jad.2020.05.133
5. Wollersheim BM, Boekhout AH, van der Poel HG, et al. The risk of developing cardiovascular disease is increased for patients with prostate cancer who are pharmacologically treated for depression. BJU Int. 2020;125(3):433–441. doi:10.1111/bju.14961
6. Ohdo S, Koyanagi S, Matsunaga N. Chronopharmacological strategies focused on chrono-drug discovery. Pharmacol Ther. 2019;202:72–90. doi:10.1016/j.pharmthera.2019.05.018
7. Biessels GJ, Verhagen C, Janssen J, et al. Effect of linaglaptin on cognitive performance in patients with type 2 diabetes and cardiovascular comorbidities: the CARMELINA randomized trial. Diabetes Care. 2019;42(10):1930–1938. doi:10.2337/dc19-0783
8. Castro-Costa E, Diniz BS, Firmo JOA, et al. Diabetes, depressive symptoms, and mortality risk in old age: the role of inflammation. Depress Anxiety. 2019;36(10):941–949. doi:10.1002/da.22908
9. Yazdanpanah S, Rabiee M, Tahriiri M, et al. Evaluation of glycated albumin (GA) and GA/HbA1c ratio for diagnosis of diabetes and glycemic control: a comprehensive review. Crit Rev Clin Lab Sci. 2017;54(4):219–232. doi:10.1080/10408363.2017.1299684
10. Mancini GBJ, Maron DJ, Hartigan PM, et al. Lifestyle, glycosylated hemoglobin A1c, and survival among patients with stable ischemic heart disease and diabetes. J Am Coll Cardiol. 2019;73(16):2049–2058. doi:10.1016/j.jacc.2018.11.067
11. Gibbons CH. Treatment-induced neuropathy of diabetes. Curr Diab Rep. 2017;17(12):127. doi:10.1007/s11892-017-0960-6
12. Indelicato L, Calvo V, Dauriz M, et al. Depressive symptoms and glycemic control in adults with type 1 diabetes: an exploratory study on the role of family functioning. Acta Diabetol. 2020;57(1):23–30. doi:10.1007/s00592-019-01356-z
13. Lee S-Y, Wang T-Y, Chen S-L, et al. Combination of dextromethorphan and memantine in treating bipolar spectrum disorder: a 12-week double-blind randomized clinical trial. Int J Bipolar Disord. 2020;8(1):11. doi:10.1186/s40345-019-0174-8
14. Zhu L, Chandran SR, Tan WB, et al. Persistent anxiety is associated with higher glycemia post-transition to adult services in Asian young adults with diabetes. Diabetes Metab J. 2020;15. doi:10.4093/dmj.2019.0226
15. Whelan BJ, Savva GM. Design and methodology of The Irish Longitudinal Study on Ageing. J Am Geriatr Soc. 2013;61:S265–S268. doi:10.1111/jgs.12199
16. Radloff LS. The CES-D Scale. Appl Psychol Meas. 1977;1(3):385–401. doi:10.1177/01466176700100306
17. Karim J, Weisz R, Bibi Z, et al. Validation of the eight-item Center for Epidemiologic Studies Depression Scale (CES-D) among older adults. Curr Psychol. 2015;34(4):681–692. doi:10.1007/s12144-014-9281-y
18. Krull KR, Hardy KK, Kahalley LS, et al. Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. J Clin Oncol. 2018;36(21):2181–2189. doi:10.1200/JCO.2017.76.4696
19. Friend AJ, Felthower RG, Hughes EJ, et al. Mental health of long-term survivors of childhood and young adult cancer: a systematic review. Int J Cancer. 2018;143(6):1279–1286. doi:10.1002/ijc.31337
21. Jacobs LA, Shulman LN. Follow-up care of cancer survivors: challenges and solutions. *Lancet Oncol*. 2017;18(1):e19–e29. doi:10.1016/S1470-2045(16)30386-2

22. Rugbjerg K, Olsen JH. Long-term risk of hospitalization for somatic diseases in survivors of adolescent or young adult cancer. *JAMA Oncol*. 2016;2(2):193–200. doi:10.1001/jamaoncol.2015.4393

23. Goodenough CJ, Liang MK, Nguyen MT, et al. Preoperative glycated hemoglobin and postoperative glucose together predict major complications after abdominal surgery. *J Am Coll Surg*. 2015;221(4):854–861.e1. doi:10.1016/j.jamcollsurg.2015.07.013

24. Iwama N, Sugiyama T, Metoki H, et al. Associations between glycated hemoglobin level at less than 24 weeks of gestation and adverse pregnancy outcomes in Japan: the Japan Environment and Children’s Study (JECS). *Diabetes Res Clin Pract*. 2020;169:108377. doi:10.1016/j.diabres.2020.108377

25. Blair JC, McKay A, Ridyard C, et al. Continuous subcutaneous insulin infusion versus multiple daily injection regimens in children and young people at diagnosis of type 1 diabetes: pragmatic randomised controlled trial and economic evaluation. *BMJ*. 2019;365:k1226. doi:10.1136/bmj.k1226

26. Goldstein JM, Hale T, Foster SL, et al. Sex differences in major depression and comorbidity of cardiometabolic disorders: impact of prenatal stress and immune exposures. *Neuropsychopharmacology*. 2019;44:59–70.

27. Chew BH, Vos RC, Metzendorf M-J, et al. Psychological interventions for diabetes-related distress in adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2017;9:CD011469. doi:10.1002/14651858.CD011469.pub2

28. Lim S-M, Park S-H, Sharma N, et al. Blood glucose regulation mechanism in depressive disorder animal model under hyperglycemic states. *Brain Res Bull*. 2016;124:116–122. doi:10.1016/j.brainresbull.2016.03.014

29. Carroll AJ, Huffman MD, Zhao L, et al. Associations between depressive symptoms, cigarette smoking, and cardiovascular health: longitudinal results from CARDIA. *J Affect Disord*. 2020;260:583–591. doi:10.1016/j.jad.2019.09.049

30. Buchberger B, Huppertz H, Krabbe L, et al. Symptoms of depression and anxiety in youth with type 1 diabetes: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2016;70:70–84. doi:10.1016/j.psyneuen.2016.04.019

31. Bekhbat M, Chu K, Le N-A, et al. Glucose and lipid-related biomarkers and the antidepressant response to infliximab in patients with treatment-resistant depression. *Psychoneuroendocrinology*. 2018;98:222–229. doi:10.1016/j.psyneuen.2018.09.004

32. Koene RJ, Prizment AE, Blaes A, et al. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133(11):1104–1114. doi:10.1161/CIRCULATIONAHA.115.204060

33. Mehta LS, Watson KE, Barac A, et al. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American Heart Association. *Circulation*. 2018;137(8):e30–e66. doi:10.1161/CIR.0000000000006556

34. Aune D, Keum N, Giovannucci E, et al. Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies. *Am J Clin Nutr*. 2018;108(5):1069–1091. doi:10.1093/ajcn/nqy097

35. Zuo Z, Prather P, Stetskov S, et al. Inflammaging and oxidative stress in human diseases: from molecular mechanisms to novel treatments. *Int J Mol Sci*. 2019;20(18):4472. doi:10.3390/ijms20184472

36. Ferrucci L, Fabbri E. Inflammaging: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol*. 2018;15:505–522.

37. Lee CW-S, Lin C-L, Sung F-C, et al. Antidepressant treatment and risk of dementia: a population-based, retrospective case-control study. *J Clin Psychiatry*. 2016;77(1):117–122. doi:10.4088/JCP.14m09580

38. Gadzhanova S, Roughhead EE, Pont LG. Antidepressant switching patterns in the elderly. *Int Psychogeriatr*. 2018;30(9):1365–1374. doi:10.1017/S1011364718002964

39. Bocking CLH, Klein NS, Elgersma HJ, et al. Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus tapering antidepressants and preventing relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. *Lancet Psychiatry*. 2018;5(5):401–410. doi:10.1016/S2215-0366(18)30100-7

40. Huang Y, Zhu M. Increased global PSQI score is associated with depressive symptoms in an adult population from the United States. *Nat Sci Sleep*. 2020;12:487–495. doi:10.2147/NSS.S256625