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Brain-derived neurotrophic factor is associated with self-reported quality of sleep in type 2 diabetes patients in Ghana

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Objective: Sleep disturbances are common in Type 2 diabetes (T2DM) patients and this exacerbates the severity of disease and results in poor quality of life. Brain-derived neurotrophic factor (BDNF) has been reported to mediate the association between T2DM and poor sleep health. We investigated the burden of self-reported poor sleep quality and duration in T2DM and their association with serum BDNF levels.
Methods: In a case-control design, the Pittsburgh Sleep Quality Instrument (PSQI) was used to assess self-reported sleep quality and duration in 100 T2DM patients and 80 nondiabetic controls. Sociodemographic data and medical history were collected from case notes and/or using a structured questionnaire. 5 ml of fasting venous blood samples were collected to measure plasma lipid profile and serum BDNF levels.
Results: T2DM patients had low levels of BDNF, poor sleep quality (61.9% vs 27.5%, p<0.001), and shorter sleep duration (6.1±2.2 vs 6.9±1.1 hours, p=0.003). T2DM status was associated with doubling the odds of poor sleep quality [OR (95% CI) = 2.06 (1.07 – 6.43), p=0.039] and 1.6 times the odds of short sleep duration [1.63 (1.03 – 3.79), p=0.028]. There was no association between serum BDNF levels and sleep status in multivariable logistic regression analysis. However, there was a negative biological interaction between T2DM and BDNF levels on poor sleep quality, resulting in 0.28 relative excess risk due to the interaction and a 12% attributable proportion due to the interaction.
Conclusion: T2DM patients in our study population had a high burden of self-reported poor quality of sleep and shorter sleep duration compared to the nondiabetic controls. T2DM interacts negatively with serum BDNF levels to affect sleep quality.

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Brain-derived neurotrophic factor is associated with self-reported quality of sleep in type 2 diabetes patients in Ghana

Short running title: BDNF & Sleep in T2DM patients in Ghana

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Abstract

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Keywords: Type 2 diabetes, sleep quality, sleep duration, brain-derived neurotrophic factor, Ghana

Introduction

Type 2 diabetes (T2DM) is a condition whereby the body tissues are unable to sense and respond to insulin, and this leads to metabolic abnormalities in carbohydrate, lipid and protein homeostasis. It was estimated in 2019 that about 463 million adults were living with diabetes and that number may grow to about 700 million people with diabetes by 2045 [1]. The prevalence of diabetes in the Ghanaian adult population was estimated to be 6.46% by a recent meta-analysis study [2]. T2DM negatively affects sleep quality due to the effect of stress from various diabetic management regimens, as well as the

presence of diabetic complications [3]. There is a bidirectional association between T2DM and insomnia, with some studies reporting that sleep disturbances contribute to the pathogenesis of T2DM, while others report sleep disturbances as a complication of T2DM [4-6]. Sleep adequacy is usually decomposed into sleep duration and quality of sleep, with the two dimensions, usually overlapping in many research reports [7, 8]. Few studies have reported on the relationship between diabetes and sleep disturbances in Africa [9, 10] and no studies have investigated the underlying mechanisms of poor sleep in Africans.

Brain-derived neurotrophic factor (BDNF) is the most common neurotrophic growth factor in medical literature and it is reported to regulate the survival, development, and differentiation of neurons [11]. Several studies have reported that the dysregulation of serum BDNF affects cognitive functions through modulation of neurite outgrowth, neuronal differentiation, survival, and growth [12]. Furthermore, BDNF is reported to regulate tissue metabolism through its central and peripheral influence on various enzymes that regulate intermediary metabolism, with abnormal levels of BDNF resulting in dysglycemia and dyslipidaemia [13]. BDNF levels are generally reported to be reduced in T2DM patients [14] and individuals with poor sleep [15], although some studies have reported contrasting findings [16]. The relationship between diabetes, mental disorders and circulating BDNF levels may imply that serum BDNF may be an important psychophysiological biomarker of metabolic and mental disorders [17]. There is a paucity of data on the levels of BDNF in T2DM patients and sleep quality and duration in the sub-Saharan African population. This study investigated the prevalence of poor sleep quality and short duration in T2DM patients in Ghana and their association

with serum BDNF levels. We hypothesize that serum BDNF levels would be low in patients with T2DM and this would be associated with poor sleep quality and short sleep duration.

Methods

The study was a case-control design, conducted at Diabetic Clinic, Korle Bu Teaching Hospital in Accra, Ghana from December 2022 to June 2023. T2DM patients were selected using a systematic random sampling as every third eligible patient within the age range of 30 through 65 years was invited to participate in the study. Thereafter, comparable nondiabetic controls were purposively contacted from the communities close to the hospital to participate in the study. T2DM status was determined clinically as patients who were diagnosed with diabetes after age 30 and were managed initially on lifestyle modification or antidiabetic drugs. Patients with type 1 diabetes, infectious disease or terminal illness, a diagnosis of neurological or psychiatric disease, multiple sclerosis, chronic periodontitis, rheumatoid arthritis, coronary heart disease, heart failure, or chronic liver or kidney disease, or being treated with clopidogrel, corticosteroids, antidepressants, statins or aspirin, as well as those on shifting work schedules were excluded from the study.

A structured questionnaire containing elements of sociodemography, lifestyle, and clinical and medical history was administered to all participants. Blood pressure was measured in a seated position after 5 min rest using an automated digital blood pressure monitor (Omron 907XL pro, Healthcare, Inc., Vernon Hills, IL). Body weight

and height were measured with a validated scale (Seca 740 scale) and a stadiometer respectively, and the body mass index (BMI) was calculated as weight in kilogrammes divided by the height in metres squared.

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) which is a validated questionnaire, that was used to measure sleep quality over the past month and has previously been implemented among diabetes patients. The items on the PSQI instrument are categorized into seven different domains (sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication, and daytime dysfunction) with scores ranging from 0 (no difficulty) to 3 (severe difficulty). The scores for the seven domains were summed up to give a final PSQI. A total PSQI score less than 5 was used to define poor sleep quality as per guidelines [9, 18, 19].

Participants were asked about their bedtimes and wake-up times on the weekdays and the weekends. Sleep duration was calculated as the difference between the bedtime and waking time for weekdays and weekends and weighted as 5/7*(weekday sleep duration) + 2/7*(weekend sleep duration). Short sleep was defined as sleeping duration <7 hours based on the recommendation of the National Sleep Foundation [20].

After 8–12 hours of overnight fasting, blood samples were collected into appropriate vacuum tubes, centrifuged at 4000G and the serum/plasma was aliquoted and stored at -70ºC until analysis. Analyses of plasma glucose (FPG), total cholesterol, high-density (HDL) lipoprotein cholesterol and plasma triglyceride levels were performed using a semi-automated biochemistry analyser (Contec BC 400, China) and commercial reagents (Randox Laboratory Reagents, UK).

Serum levels of BDNF were measured by enzyme-linked immunosorbent assay (ELISA) according to the procedures supplied by the manufacturer (DuoSet, R&D Systems, Minneapolis, MN, USA). All samples were assayed in triplicate, and the technician was blind to the group assignment of the samples. The lower detection limit was 5 pg/ml. Concentrations were expressed as nanograms per millilitre (ng/ml). The inter- and intra-assay coefficients of variation were less than 5%.

The ethics of the study protocol was approved by the Ethics and Protocol Review Committee of the College of Health Sciences of the University of Ghana (Protocol ID number: CHS-Et/M24.12/2018-2019) and each participant gave written voluntary informed consent before being included in the study.

Sample size calculation

The sample size required for this study was calculated based on the pilot data of BDNF levels from 20 T2DM patients and 20 nondiabetic controls (23.5±12.1 vs 28.9±11.4 ng/ml). A minimum of 76 participants were required in each group to achieve a power of 80% at a 95% significance level. We, therefore, recruited 100 T2DM patients and 80 nondiabetic controls.

Statistical analysis

Data were analysed using SPSS version 28. Data were presented as mean with standard deviation for continuous variables and as proportions for categorical variables. Differences between the T2DM patients and nondiabetic control with regards to their socio-demographic, clinical and biochemical variables were analyzed using a chi-squared (χ^2) test for the comparison of categorical variables and Student's t-test for

continuous measures. We performed three different binary and multivariable logistics regression models to assess the association between T2DM, serum BDNF and sleep status, ie, poor sleep quality and sleep duration. In the first logistic regression model, serum BDNF was excluded and in the second model, serum BDNF was added to the model while T2DM status was excluded. The third model included both T2DM and serum BDNF, as well as their cross-product term (T2DM×BDNF) to assess multiplicative interaction. The estimation of biological interaction between T2DM and serum BDNF levels was performed using the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (S) as described by Rothman et al [21]. RERI or AP = 0 means no interaction or exactly additivity; RERI or AP > 0 means positive interaction or more than additivity; RERI or AP < 0 means negative interaction or less than additivity. The level of significance was set at $p < 0.05$.

Results

General characteristics of study participants

In this study, compared to nondiabetic controls, T2DM patients were likely to be hypertensive, less educated, and had previously smoked and taken alcohol. The mean levels of BMI, blood pressure, fasting plasma glucose, triglycerides, total, HDL and LDL cholesterols were significantly higher in the T2DM patients compared to the nondiabetic individuals. Serum BDNF levels were lower in T2DM patients compared to the nondiabetic controls (Table 1). The median duration of diabetes in the T2DM patients was 8.1 years (range: 0.1 – 17.6 years), with 46, 37 and 17 patients having a duration of

T2DM with <5 years, 5 – 10 years and >10 years respectively. Concerning diabetes treatment, four patients were on lifestyle management, 61 patients were on oral hypoglycemic agents and 35 patients were on insulin and oral hypoglycemic agents.

Sleep deficits and serum BDNF levels

T2DM patients had higher global PSQI scores and a higher prevalence of poor sleep quality than the nondiabetic controls. T2DM patients had lower mean self-reported sleep duration than the nondiabetic controls and participants who reported short sleep duration (<7 hours sleep) were mostly T2DM patients (Table 2). In T2DM patients, those with poor sleep quality had lower serum BDNF levels compared to patients with good sleep quality. In nondiabetic controls, serum BDNF levels were similar between those with good and poor sleep quality (Figure 1). In T2DM patients and nondiabetic controls, those with short sleep duration had lower BDNF levels compared with participants with normal sleep duration (Figure 2).

Interaction between T2DM, BDNF and sleep status

In the logistic regression models, T2DM status was associated with increased odds of poor sleep quality while an increase in serum BDNF level was associated with decreased odds of poor sleep quality in unadjusted models. In the adjusted model, having T2DM was associated with increased odds of poor sleep quality compared to nondiabetic controls. In the interactive model, the multiplicative interaction between T2DM and serum BDNF levels significantly increased the odds of having poor sleep quality in the unadjusted model but was non-significant in the adjusted models. The was

a negative biological interaction between T2DM and serum BDNF levels as indicated by RERI. In addition, the interaction between T2DM and serum BDNF was associated with 18% and 12% excess risk (AP score) in unadjusted and adjusted models respectively (Table 3, A).

Similarly, T2DM status was associated with increased odds of short sleep duration while an increase in serum BDNF level was associated with decreased odds of short sleep duration in unadjusted models. In the adjusted model, having T2DM was associated with increased odds of short sleep duration compared to nondiabetic controls. In the interactive model, the multiplicative interaction between T2DM and serum BDNF levels significantly increased the odds of having short sleep duration in the unadjusted model, but no association in the adjusted model. There was a negative biological interaction between T2DM and serum BDNF levels in the unadjusted and adjusted models as indicated by RERI values. In addition, the interaction between T2DM and serum BDNF was associated with 19% and 14% excess risk (AP score) in unadjusted and adjusted models respectively (Table 3, B).

Discussion

The main findings of this study were that, compared to nondiabetic controls, T2DM patients had low levels of BDNF and a high prevalence of self-reported poor sleep quality and shorter sleep duration. Increased serum BDNF was associated with decreased odds of poor sleep quality in T2DM patients, as well as decreased odds of short sleep duration in nondiabetic controls.

We have previously reported a high burden of poor sleep in T2DM patients compared to nondiabetic controls and this was associated with reduced HDL cholesterol levels and increased triglyceride levels [22]. We found that T2DM patients had short sleep duration compared to nondiabetic controls, similar to what has been reported in other studies. In the Taiwanese population, those with short sleep duration (≤5 hours) had twice the odds of diabetes compared to those with 7 hours or more sleep duration [18].

We found that serum BDNF levels were significantly lower in T2DM patients compared to their nondiabetes counterparts. This is consistent with a study by Krabbe et al., who reported that plasma BDNF levels were reduced in diabetes patients compared to nondiabetic controls, and even in healthy individuals, hyperglycemia reduces circulating BDNF [14]. Furthermore, Chinese T2DM patients had lower serum levels of BDNF compared to nondiabetic controls [23]. Contrary to our findings, some studies have reported high BDNF levels in patients with T2DM compared to nondiabetic individuals [24, 25]. These conflicting data about the association between BDNF and diabetes may be due to at least in part ethnic differences, duration and severity of diabetes [26]. BDNF has been shown to have an anti-diabetic effect by increasing insulin secretion and sensitivity in peripheral tissues, as well as decreasing blood glucose through insulin-independent mechanisms [27]. For instance, intraventricular administration of BDNF in diabetic mice was reported to mitigate hyperglycemia by reducing hepatic glucose output through the normalization of glucagon secretion and hepatic expression of gluconeogenic enzyme synthesis, without affecting insulin secretion or sensitivity [28].

One interesting finding of our study was that the negative biological interaction between T2DM and serum levels of BDNF was significant concerning poor sleep quality, but the interaction between T2DM and BDNF did not contribute to poor sleep duration in the multivariable model. Therefore, it is reasonable to infer that the quality of sleep, rather than quantity, may be associated with circulating BDNF levels. In T2DM patients, unlike their nondiabetic counterparts, there are a lot of sleep problems that might culminate in poor sleep quality [6], and this may be responsible for the reduction of BDNF. It may be possible that the relationship between the duration of sleep and serum BDNF may be similar to that of a U-shaped pattern as reported in adolescents [29] and, hence, the linear models applied to our analysis of the data from this study might have masked possible biological interaction. We could not test the U-shaped relationship because the number of participants with excess sleep duration (>9 hours) in this study was too small to be analyzed separately. Further studies may be required to investigate whether this observation may be due to metabolic abnormalities from insulin dysfunction or the presence of other comorbidities in T2DM patients. On the other hand, short sleep duration, rather than poor sleep quality, was relevant in maintaining serum BDNF levels in nondiabetic controls. This is consistent with previous studies that reported low levels of BDNF in patients with insomnia [30]. The association between short sleep duration and BDNF has also been demonstrated in preclinical studies [31]. In interventional studies, the reversal of sleep deficits with pharmacological agents [32] or non-pharmacological such as exercise and repetitive transcranial magnetic stimulation [33] was able to increase circulating BDNF levels. In contrast to our findings, studies

conducted in the Japanese population reported no association between subjective sleep quality and serum BDNF levels [34]. Likewise, Mokoteit et al reported an association between serum BDNF and rapid-eye movement sleep, but not objective sleep quality from polysomnography [35]. The underlying mechanism of reduction of BDNF in T2DM and insufficient sleep may be related to stress [5, 36]. Both diabetes and insufficient sleep hypertactivate the dual stress loop; the hypothalamic-pituitary-adrenal and sympatho-adrenomedullary axes [5, 37]. This leads to high-stress levels in patients, which has been shown to reduce the synthesis of mRNA of BDNF in the brain [36].

Limitations of study

The interpretation of the findings of this study has some limitations. The data were collected cross-sectionally in a single facility, limiting the inference of causality and generalisation to the entire Ghanaian population. Quality and duration of sleep in this study were self-reported, which is prone to recall bias. Furthermore, we measured circulating levels of BDNF in the serum, which may differ from plasma and cerebrospinal BDNF levels [12]. The concentration of BDNF in serum has been reported to be 50 times higher than that of plasma. This is due to the capacity of platelets to absorb BDNF produced by the brain and release them into serum during the coagulation process [38]. This may explain the observed moderate correlation between plasma BDNF and hippocampal BDNF in a previous study [11]. In our methodology, we reduced the impact of diurnal variability and storage effect on BDNF levels by taking fasting blood samples early in the morning before 9 am and measuring serum levels within 6 months of storage at -80°C. Indeed, 12 months of storage of samples at that

temperature has been shown to have no significant effect on BDNF levels in a healthy population [39]. However, the Elisa method we used to test serum levels BDNF is reported to capture both mature BDNF and proBDNF forms [40], which could have introduced some errors in our analysis. We, however, expect the effect of this error to be negligible with respect to our sample size and the use of nondiabetic controls.

Conclusion

In our study population, we found a high burden of self-reported poor sleep quality and short duration in T2DM patients compared to nondiabetic controls. There was negative interaction between T2DM and serum BDNF in contributing to sleep deficits. This findings emphasize the importance of sleep screening and management as part of diabetes care to minimize the impact of diabetes on factors that regulate the functioning of the nervous system.

Abbreviations:

AP, attributable proportion due to interaction; BDNF, Brain-derived neurotrophic factor; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSQI, Pittsburgh Sleep Quality Instrument; RERI, relative excess risk due to interaction; S, synergy index; T2DM, Type 2 diabetes.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 2021. Geneva, Switzerland: IDF; 2022

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2. Asamoah-Boaheng M, Sarfo-Kantanka O, Tuffour AB et al. Prevalence and risk factors for diabetes mellitus among adults in Ghana: a systematic review and meta-analysis. International Health 2018; 11: 83-92. doi:10.1093/inthealth/ihy067
3. Jackson CL, Redline S, Kawachi I et al. Association Between Sleep Duration and Diabetes in Black and White Adults. Diabetes Care 2013; 36: 3557-3565. doi:10.2337/dc13-0777

4. Beihl DA, Liese AD, Haffner SM. Sleep Duration as a Risk Factor for Incident Type 2 Diabetes in a Multiethnic Cohort. Annals of Epidemiology 2009; 19: 351-357. doi:https://doi.org/10.1016/j.annepidem.2008.12.001
5. Parameswaran G, Ray DW. Sleep, circadian rhythms, and type 2 diabetes mellitus. Clinical Endocrinology 2022; 96: 12-20. doi:https://doi.org/10.1111/cen.14607
6. Plantinga L, Rao MN, Schillinger D. Prevalence of self-reported sleep problems among people with diabetes in the United States, 2005-2008. Prev Chronic Dis 2012; 9: E76
7. Azharuddin M, Kapur P, Adil M et al. The impact of sleep duration and sleep quality on glycaemic control in Asian population with type 2 diabetes mellitus: A systematic literature review and meta-analysis of observational studies. Clinical Epidemiology and Global Health 2020; 8: 967-975. doi:https://doi.org/10.1016/j.cegh.2020.03.006
8. Tan X, Chapman CD, Cedernaes J et al. Association between long sleep duration and increased risk of obesity and type 2 diabetes: A review of possible mechanisms. Sleep Medicine Reviews 2018; 40: 127-134. doi:https://doi.org/10.1016/j.smrv.2017.11.001
9. Jemere T, Mossie A, Berhanu H et al. Poor sleep quality and its predictors among type 2 diabetes mellitus patients attending Jimma University Medical Center, Jimma, Ethiopia. BMC Research Notes 2019; 12: 488. doi:10.1186/s13104-019-4531-6
10. Sokwalla SMR, Joshi MD, Amayo EO et al. Quality of sleep and risk for obstructive sleep apnoea in ambulant individuals with type 2 diabetes mellitus at a tertiary referral hospital in Kenya: a cross-sectional, comparative study. BMC Endocrine Disorders 2017; 17: 7. doi:10.1186/s12902-017-0158-6
11. Klein AB, Williamson R, Santini MA et al. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. International Journal of Neuropsychopharmacology 2011; 14: 347-353. doi:10.1017/s1461145710000738
12. Morichi S, Kashiwagi Y, Takekuma K et al. Expressions of Brain-Derived Neurotrophic Factor (BDNF) in Cerebrospinal Fluid and Plasma of Children With Meningitis and Encephalitis/Encephalopathy. International Journal of Neuroscience 2012; 123: 17-23. doi:10.3109/00207454.2012.721829
13. Wang C-P, Lorenzo C, Habib SL et al. Differential effects of metformin on age related comorbidities in older men with type 2 diabetes. Journal of Diabetes and its Complications 2017; 31: 679-686. doi:https://doi.org/10.1016/j.jdiacomp.2017.01.013
14. Krabbe KS, Nielsen AR, Krogh-Madsen R et al. Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. Diabetologia 2007; 50: 431-438. doi:10.1007/s00125-006-0537-4
15. Ballesio A, Zagaria A, Curti DG et al. Peripheral brain-derived neurotrophic factor (BDNF) in insomnia: A systematic review and meta-analysis. Sleep Medicine Reviews 2023; 67: 101738. doi:https://doi.org/10.1016/j.smrv.2022.101738
16. Wei H, Qu H, Wang H et al. Serum brain-derived neurotrophic factor levels and sleep disorders in Chinese healthy and newly diagnosed type 2 diabetic subjects. Journal of Diabetes 2017; 9: 180-189. doi:https://doi.org/10.1111/1753-0407.12401
17. Iannitelli A, Tirassa P, Fiore M et al. Gender differences in ultradian serum levels of NGF and BDNF correlate with psychophysical traits in healthy humans. Rivista di Psichiatria 2021; 56: 314-320. doi:10.1708/3713.37045
18. Lin C-L, Tsai Y-H, Yeh MC. Associations between sleep duration and type 2 diabetes in Taiwanese adults: A population-based study. Journal of the Formosan Medical Association 2016; 115: 779-785. doi:https://doi.org/10.1016/j.jfma.2016.01.013
19. Lou P, Qin Y, Zhang P et al. Association of sleep quality and quality of life in type 2 diabetes mellitus: A cross-sectional study in China. Diabetes Research and Clinical Practice 2015; 107: 69-76. doi:https://doi.org/10.1016/j.diabres.2014.09.060

20. Hirshkowitz M, Whiton K, Albert SM et al. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health 2015; 1: 233-243. doi:https://doi.org/10.1016/j.sleh.2015.10.004
21. Rothman KJ, Greenland S, Lash TL. Modern epidemiology: Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia; 2008
22. Agyekum JA, Gyamfi T, Yeboah K. Depression, poor sleep quality, and diabetic control in type 2 diabetes patients at Sunyani Regional Hospital, Ghana: a case–control study. Middle East Current Psychiatry 2023; 30: 45. doi:10.1186/s43045-023-00317-1
23. He M, Wang J. Decreased serum brain-derived neurotrophic factor in Chinese patients with type 2 diabetes mellitus. Acta Biochim Biophys Sin 2014; 46: 426-427
24. Berton O, McClung CA, DiLeone RJ et al. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science 2006; 311: 864-868
25. Boyuk B, Degirmencioglu S, Atalay H et al. Relationship between levels of brain-derived neurotrophic factor and metabolic parameters in patients with type 2 diabetes mellitus. Journal of diabetes research 2014; 2014
26. Rozanska O, Uruska A, Zozulinska-Ziolkiewicz D. Brain-Derived Neurotrophic Factor and Diabetes. International Journal of Molecular Sciences 2020; 21: 841
27. Eyileten C, Kaplon-Cieslicka A, Mirowska-Guzel D et al. Antidiabetic Effect of Brain-Derived Neurotrophic Factor and Its Association with Inflammation in Type 2 Diabetes Mellitus. Journal of Diabetes Research 2017; 2017: 2823671. doi:10.1155/2017/2823671
28. Yamanaka M, Itakura Y, Tsuchida A et al. Comparison of the antidiabetic effects of brain-derived neurotrophic factor and thiazolidinediones in obese diabetic mice. Diabetes, Obesity and Metabolism 2007; 9: 879-888. doi:https://doi.org/10.1111/j.1463-1326.2006.00675.x
29. Silva Junior JF, Eckeli AL, Ribeiro CCC et al. Influence of excessive daily sleeping and sleep quality on BDNF and NGF serum levels in adolescents. Sleep Medicine 2021; 84: 415-423. doi:https://doi.org/10.1016/j.sleep.2021.06.024
30. Fan T-T, Chen W-H, Shi L et al. Objective sleep duration is associated with cognitive deficits in primary insomnia: BDNF may play a role. Sleep 2018; 42. doi:10.1093/sleep/zsy192
31. Misrani A, Tabassum S, Wang M et al. Citalopram prevents sleep-deprivation-induced reduction in CaMKII-CREB-BDNF signaling in mouse prefrontal cortex. Brain Research Bulletin 2020; 155: 11-18. doi:https://doi.org/10.1016/j.brainresbull.2019.11.007
32. Giese M, Beck J, Brand S et al. Fast BDNF serum level increase and diurnal BDNF oscillations are associated with therapeutic response after partial sleep deprivation. Journal of Psychiatric Research 2014; 59: 1-7. doi:https://doi.org/10.1016/j.jpsychires.2014.09.005
33. Feng J, Zhang Q, Zhang C et al. The Effect of sequential bilateral low-frequency rTMS over dorsolateral prefrontal cortex on serum level of BDNF and GABA in patients with primary insomnia. Brain and Behavior 2019; 9: e01206. doi:https://doi.org/10.1002/brb3.1206
34. Saitoh K, Furihata R, Kaneko Y et al. Association of serum BDNF levels and the BDNF Val66Met polymorphism with the sleep pattern in healthy young adults. PLOS ONE 2018; 13: e0199765. doi:10.1371/journal.pone.0199765
35. Mikoteit T, Brand S, Eckert A et al. Brain-derived neurotrophic factor is a biomarker for subjective insomnia but not objectively assessable poor sleep continuity. Journal of Psychiatric Research 2019; 110: 103-109. doi:https://doi.org/10.1016/j.jpsychires.2018.12.020
36. Bath KG, Schilit A, Lee FS. Stress effects on BDNF expression: Effects of age, sex, and form of stress. Neuroscience 2013; 239: 149-156. doi:https://doi.org/10.1016/j.neuroscience.2013.01.074

37. Ortiz R, Kluwe B, Odei JB et al. The association of morning serum cortisol with glucose metabolism and diabetes: The Jackson Heart Study. Psychoneuroendocrinology 2019; 103: 25-32. doi:https://doi.org/10.1016/j.psyneuen.2018.12.237
38. Fujimura H, Altar CA, Chen R et al. Brain-derived Neurotrophic Factor Is Stored in Human Platelets and Released by Agonist Stimulation. Thromb Haemost 2002; 87: 728-734
39. Naegelin Y, Dingsdale H, Säuberli K et al. Measuring and Validating the Levels of Brain-Derived Neurotrophic Factor in Human Serum. eNeuro 2018; 5. doi:10.1523/eneuro.0419-17.2018
40. Michalski B, Fahnestock M. Pro-brain-derived neurotrophic factor is decreased in parietal cortex in Alzheimer's disease. Molecular Brain Research 2003; 111: 148-154. doi:https://doi.org/10.1016/S0169-328X(03)00003-2

Table legends

Table 1. General characteristics of the study participants

Table 2. Comparison of PSQI scores and sleep duration among study participants

Table 3. The interactive effects of T2DM and serum BDNF on sleep quality and duration from logistic regression models.

Figure legends

Figure 1. Comparison of serum BDNF levels in study participants by their quality of sleep status

Figure 2. Comparison of serum BDNF levels in study participants by the duration of sleep

Disclosures

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Authors' contributions: KY conceptualized the study, analysed the data and drafted the manuscript. JAA analyzed the data and made scientific contributions to the manuscript. All authors approved the content of the manuscript.

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Availability of data: The dataset supporting the conclusions of this paper is available and can be requested from the corresponding author.

Ethics approval and consent to participate

All procedures performed in this study involving human participants were conducted in conformity with the Helsinki Declaration on Human Experimentation, 1964, with subsequent revisions, latest Seoul, October 2008. Ethical approval was obtained from the Ethics and Protocol Review Committee of the College of Health Sciences of the University of Ghana (Protocol ID number: CHS-Et/M24.12/20182019) and each patient provided written voluntary informed consent after the rationale and procedure of the study were thoroughly explained.

Table 1. General characteristics of the study participants

	T2DM patients (n=100)	Nondiabetic controls (n=80)	p
Demographical parameters			
Gender, n (%)			0.404
Male	42 (42)	35 (43.8)	
Female	58 (58)	45 (56.2)	
Age, yrs	56±8.4	53.6±10.6	<0.001
Age decades, n (%)			0.001
<40	12 (12)	12 (15)	
40-49	23 (23)	24 (30)	
50-59	45 (45)	32 (40)	
60+	20 (20)	12 (15)	
Married	68 (68)	50 (62.5)	0.363
Educational levels, n (%)			0.005
None	16 (16)	9 (11.3)	
Junior high school	34 (34)	28 (35)	
Senior high school	32 (32)	34 (42.5)	
Tertiary	18 (18)	9 (11.2)	
Employment, n (%)			0.021
Formal	37 (37)	37 (45.6)	
Self-employed	44 (44)	33 (41.3)	
Unemployed	19 (19)	10 (12.5)	
Clinical parameters			
Alcohol intake, n (%)	31 (31)	21 (26.3)	0.005
Previous smoker, n (%)	9 (9)	5 (6.3)	<0.001
Hypertension, n (%)	69 (69)	17 (21.3)	<0.001
BMI, kg/m^2	30.8±7.1	25.9±5.9	<0.001
Systolic BP, mmHg	147±22	138±17	0.003
Diastolic BP, mmHg	89±14	82±18	0.005
Mean BP, mmHg	75±15	69±11	0.002
Pulse BP, mmHg	61±12	52±11	<0.001
Heart rate, beats/min	72±16	67±8	<0.001
Biochemical parameters			

Fasting plasma glucose mmol/l	7.8±3.5	5.4±0.8	<0.001
Total cholesterol, mmol/l	6.1±2.3	5.2±1.4	0.002
Triglycerides, mmol/l	2.8±1.1	2.2±0.9	<0.001
HDL cholesterol, mmol/l	1.2±0.4	1.6±0.5	<0.001
LDL cholesterol, mmol/l	3.2±1.1	2.4±1.2	0.004
BDNF, ng/ml	22.1±8.4	26.1±10.2	0.005

SHS, senior high school; BMI, body mass index; BP, blood pressure; PHQ, Patient's Health Questionnaire; BDNF, brain-derived neurotrophic factor; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 Comparison of PSQI scores and sleep duration among study participants

	T2DM patients	Non-diabetes controls	p
PSQI score	8.8±3.7	5.9±2.8	<0.001
PSQI score > 5	99 (61.9)	22 (27.5)	<0.001
Sleep duration, hours	6.1±2.2	6.9±1.1	0.003
Sleep duration classification			0.01
<7 hours	60 (60)	34 (42.5)	
≥7 hours	40 (40)	46 (57.5)	

Table 3. The interactive effects of T2DM and serum BDNF on sleep quality and duration from logistic regression models.

	Unadjusted model		Adjusted model*	
A. Sleep quality (reference: Total PSQI score < 5)				
	OR (95% CI)	p	OR (95% CI)	p
T2DM	4.28 (2.38 – 7.68)	<0.001	2.06 (1.07 – 6.43)	0.039
BDNF	0.84 (0.62 – 0.97)	0.043	0.93 (0.47 – 1.06)	0.094
Interactive model				
T2DM	3.17 (1.93 – 8.55)	0.002	2.62 (1.11 – 8.2)	0.029
BDNF	0.69 (0.41 – 0.93)	0.009	0.86 (0.58 – 1.12)	0.103
T2DM × BDNF	2.43 (1.07 – 5.09)	0.03	2.21 (1.03 – 4.82)	0.047
Measures of biological interaction				
RERI	-0.44 (-0.19 – -0.75)		-0.28 (-0.09 – -0.88)	
AP	-0.18 (-0.05 – -0.46)		-0.12 (-0.03 – -0.67)	
S	0.77 (0.39 – 0.98)		0.82 0.34 – 1.06)	
B. Sleep duration (reference: sleep duration <7 hours)				
T2DM	2.31 (1.12 – 7.69)	0.01	1.63 (1.03 – 3.79)	0.028
BDNF	0.78 (0.41 – 0.95)	0.017	0.81 (0.59 – 1.01)	0.061
Interactive model				
T2DM	2.68 (1.14 – 4.99)	0.003	1.43 (1.06 – 4.56)	0.014
BDNF	0.74 (0.52 – 1.04)	0.087	0.68 (0.42 – 0.98)	0.008
T2DM × BDNF	2.03 (1.02 – 6.87)	0.034	1.29 (0.81 – 4.66)	0.201
Measures of biological interaction				
RERI	-0.39 (-0.08 – -0.81)		-0.18 (-0.01 – -1.01)	
AP	-0.19 (-0.02 – -0.53)		-0.14 (-0.01 – -1.06)	
S	0.78 (0.35 – 0.92)		2.64 (0.96 – 5.82)	

*Adjusted for age, sex, BMI, diabetes medication, smoking, alcohol, hypertension,. educational level and employment status.

T2DM, type 2 diabetes; BDNF, brain-derived neurotrophic factor; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; S, synergy index.